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Tiago Castro e Couto

DEPRESSÃO ANTENATAL:

análise clínica e imunológica

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Mabel e Sofia, companheiras de todos os momentos e amores da vida

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"Born to lose, live to win"

Ian "Lemmy" Kilmister

"Existem muitas hipóteses em ciência que estão erradas. Isso é perfeitamente aceitável, elas são a abertura para achar as que estão certas"

Carl Sagan

RESUMO

O estudo dos aspectos clínicos da Depressão Antenatal (DAN) tem sido gradativamente suplantado pelo o estudo dos aspectos biológicos da DAN. Entre os estudos de suas variáveis biológicas, os que envolvem características imunológicas têm recebido cada vez mais atenção. O primeiro objetivo do presente trabalho foi avaliar as alterações clínicas relacionadas à DAN, bem como analisar o comportamento de um provável componente biológico do sistema da ocitocina que pode contribuir para a DAN. Os demais objetivos foram: validar escalas de rastreio depressivo para aplicação na gravidez e estudar dados de suicidalidade na DAN. Utilizou-se entrevista clínica estruturada (MINI-PLUS), assim como instrumentos de rastreamento da depressão. Constatou-se que os dados de prevalência, bem como seu comportamento, e os fatores de risco de DAN da nossa amostra assemelham-se aos encontrados em estudos internacionais prévios. Foram validados e encontrados pontos de corte para rastreio depressivo na gravidez diferentes dos já estabelecidos em não grávidas: *Edinburgh Postnatal Depression Scale* (EPDS) $\geq$ 11, *Beck Depression Iventory* (BDI) $\geq$ 15 e *Hamilton Depression Rating Scale* (HAM-D) $\geq$ 9. Chamou a atenção os dados de suicidalidade, com o elevado risco de suicídio da amostra, e, dentre esses, a elevada composição do alto risco. O estudo do sistema ocitocina evidenciou que os autoanticorpos livres imunoglobulina G antiocitocina estão relacionados à DAN. Também os autoanticorpos livres imunoglobulina M antiocitocina estão relacionados - depressão maior prévia à gravidez atual. O reconhecimento mais acurado da clínica psiquiátrica da DAN e de seus componentes imunológicos pode auxiliar na elaboração de condutas que visem ao adequado diagnóstico e ao correto tratamento desse transtorno.

Palavras-chave: depressão antenatal; inventários; rastreamento; diagnóstico; suicídio; imunologia; autoanticorpo; ocitocina.

ABSTRACT

Studies analyzing Antenatal depression (AD) biological aspects are gradually becoming more common than those addressing AD clinical aspects. Among the studies addressing AD biological features, those involving immunological characteristics have been receiving increasing attention. The first objective of this study was to evaluate clinical changes related to AD, as well as analyze the behavior of a possible biological component of the oxytocin system contributing to AD. The other objectives were to validate depressive symptoms screening scales for use during pregnancy and study the suicidality data of the AD. We used a structured clinical interview (MINI-PLUS), in addition to depression screening instruments. It was found that the AD prevalence data, along with its behavior, and the AD risk factors in our sample are similar to those found in previous international studies. The validated cutoffs found for depression screening in pregnancy were different from those already established in non pregnant: Edinburgh Postnatal Depression Scale (EPDS) $\geq$ 11, Beck Depression Inventory (BDI) $\geq$ 15 e Hamilton Depression Rating Scale (HAM-D) $\geq$ 9. The suicidality data called attention, with the high risk of suicide in the sample, and among these, the elevated composition of higher risk. The study showed that oxytocin free immunoglobulin G autoantibodies are related to AD. Moreover, oxytocin free immunoglobulin M autoantibodies are related to major depression prior to current pregnancy. A more accurate recognition of the AD clinics and its immunological components can assist in the development of conducts aimed at proper diagnosis and treatment of this disorder.

Keywords: antenatal depression; inventories; screening; diagnosis suicidality; immunology; autoantibodies; oxytocin.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS

BDI - *Beck Depression Inventory*
CIDI - *Composite International Diagnostic Interview*
COEP - Comitê de Ética em Pesquisa
CRH - hormônio liberador de corticotrofina
DAN - Depressão Antenatal
DM - Depressão Maior
DPP - Depressão Pós-parto
DSM – *Diagnostic and Statistical Manual of Mental Disorders*
EPDS - *Edinburgh Postnatal Depression Scale*
HAM-D - *Hamilton Depression Rating Scale*
HC - Hospital das Clínicas
HPA - Hipotálamo-Hipófise-Adrenal
MINI - *Mini-International Neuropsychiatric Interview-Plus*
NMDA - N-metil-D-aspartato
SCID - *Structured Clinical Interview*
UFMG - Universidade Federal de Minas Gerais

SUMÁRIO

PREFÁCIO

Nos anos de Faculdade de Medicina, sempre tive a impressão de que eu poderia ter feito “algo a mais”, mas a verdade é que, provavelmente, devido à imaturidade, eu ia blindando esse sentimento e fingindo que a cobrança era infundada. No mais, eu ia sendo aprovado nas disciplinas e cada vez chegava mais perto do que me fez cursar Medicina: ser Psiquiatra. Esse, sim, o objetivo final, por mais que eu me dedicasse aos outros conhecimentos acadêmicos.

Entrei para a Residência de Psiquiatria. Havia chegado lá. Aquela sensação de que “agora sim! Agora, eu vou finalmente estudar o que eu quero para o resto da minha vida”. Na residência, acredito que desenvolvi minhas potencialidades, tudo que eu tinha “conscientemente (ou...inconscientemente)” praticado durante a graduação foi gradualmente sendo corrigido.

Maior dedicação, mais estudo, menos idealização. Importante ressaltar que nesse momento de “lua-de-mel” do início da residência, questões relacionadas a Mestrado e a Doutorado não passavam pela minha mente. O que eu queria mesmo era formar-me um bom Psiquiatra e clinicar, principalmente, se fossem pacientes com transtorno mentais graves.

Foi passando o tempo de residência e aos poucos foi caindo a ficha de que para ser um clínico fora da média, o estudo continuado é necessário. Além do mais, grande parte dos preceptores eram pesquisadores de destaque e, por meio de suas exposições, frequentemente, apontavam para a importância da Ciência. “Pronto! Olha a dívida da graduação assombrando... Lá estou eu de novo cobrando aquele esforço a mais”.

Muitas pessoas foram importantes para a realização deste projeto. O Grupo de Pesquisa em Saúde Mental da Mulher, principalmente Mayra, contemporânea de jornada. O professor Fernando Neves, com sua aula de discussão de artigos. Os professores Rodrigo Nicolato e Maila Neves, com os conselhos e “empurrões”, que, sinceramente, sem os quais eu não teria nem iniciado a Pós-Graduação *stricto senso*. O professor Frederico Garcia, com o aceite para co-orientação e parceria indispensável no momento crítico. O Professor Humberto Corrêa, grande catalisador de ideias, coordenador do Grupo de Pesquisa, facilitador da prática e, sobretudo, orientador.

A proposta do trabalho é apresentar o perfil clínico e o recorte imunológico de gestantes atendidas no Ambulatório de Ginecologia e Obstetrícia do Hospital das Clínicas (HC) da Universidade Federal de Minas Gerais (UFMG).

A tese foi dividida em três partes principais. A primeira parte é constituída por introdução, objetivos e métodos, responsável por situar os leitores no tema, demonstrar relevância, justificar e delinear o estudo. A segunda seção é composta pelos resultados, que foram dispostos em forma de artigos, que se inter-relacionam. Por fim, na terceira parte estão a discussão e a conclusão, que trazem o fechamento do trabalho.

Cabe aqui destacar que os resultados podem, por sua vez, serem divididos em dois *clusters:* os três primeiros artigos fazem parte da análise clínica e o último artigo da análise imunológica. Assim têm-se:

O artigo 1, intitulado *Antenatal depression: Prevalence and risk factor patterns across the gestational period*, publicado na *Journal of Affective Disorders*, apesar de entre os três primeiros artigos ser aquele que cronologicamente foi publicado por último, foi o primeiro a começar a ser escrito. Sua submissão deu-se *a posteriori*, porque, ao permitir durante as análises estatísticas de seus dados e as constatações que propiciaram os outros dois artigos da sequência, acabou sendo superado pela facilidade com que os últimos foram escritos. Entretanto, é o primeiro dos resultados devido a essa importância já explicitada.

O artigo 2, intitulado *What is the best tool for screening antenatal depression?*, também publicado na *Journal of Affective Disorders*, foi inspirado pelo achado no artigo 1 de taxas de prevalência de Depressão Antenatal similares ao resto do mundo. Nele, buscou-se validar, para aplicação no período antenatal, as versões brasileiras das três escalas de sintomas depressivos mais amplamente utilizadas no Brasil: *Beck Depression Iventory* (BDI), *Edinburgh Postnatal Depression Scale* (EPDS) e *Hamilton Depression Rating Scale* (HAM-D) As duas primeiras escalas já haviam sido validadas para uso na gravidez em estudos internacionais. A terceira foi pela primeira vez validada em nosso estudo. Também foi feita uma análise de qual dessas três escalas seria o melhor instrumento de rastreio para Depressão Antenatal no Brasil.

O artigo 3, intitulado *Suicidality among pregnant women in Brazil: prevalence and risk factors*, publicado na *Archives of Women's Mental Health,* também está relacionado às taxas de prevalência observadas no artigo 1. Diante da constatação de quão elevadas eram as taxas de qualquer transtorno mental durante a gravidez, aproximadamente 40%, e da já estabelecida elevada associação entre suicídio e transtornos mentais, procurou-se verificar a suicidalidade da gestantes.

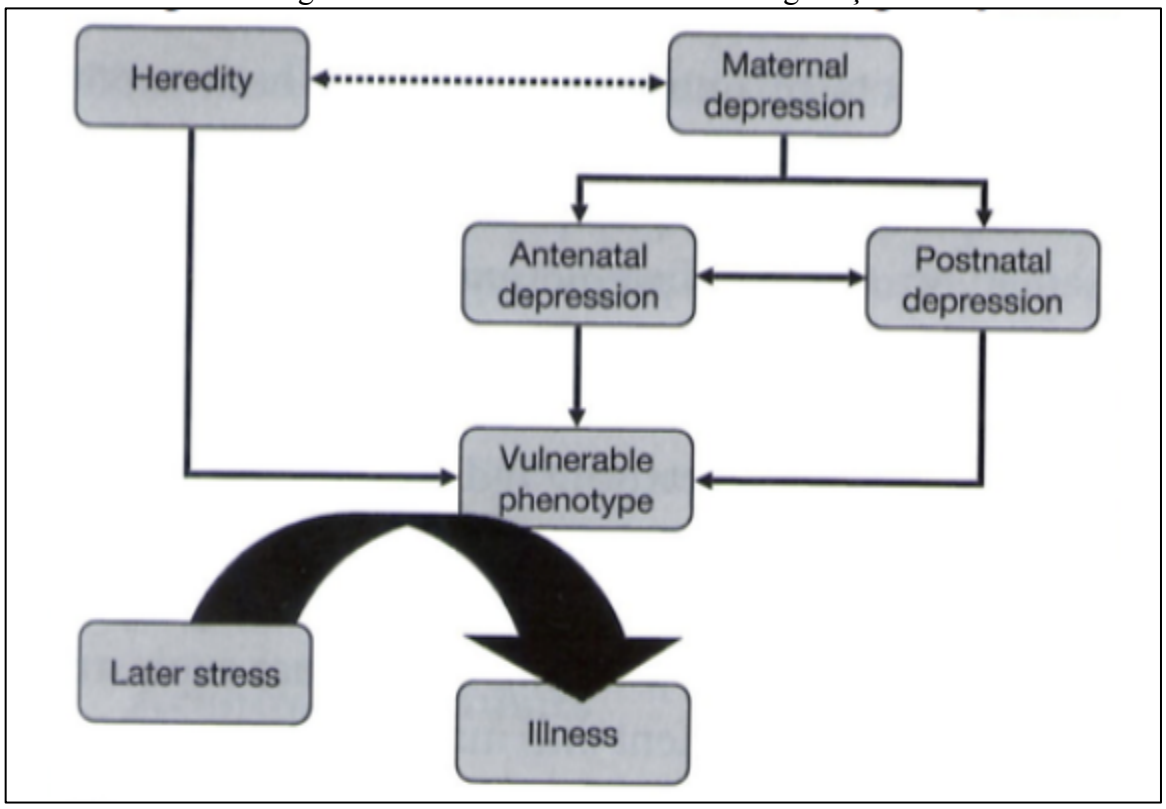
Finalmente, o artigo 4, intitulado *Autoantibodies reacting with oxytocin are associated with antental depression* (em submissão), foi o primeiro no mundo a correlacionar autoanticorpos antiocitocina e Depressão Antenatal.

1 INTRODUÇÃO

1.1 Depressão Antenatal

A primeira descrição de transtornos psiquiátricos perinatais remete ao tempo de Hipócrates, que pode ter encontrado complicações infecciosas pós-parto que ocasionavam *Delirium;* assim como uma das primeiras descrições de Depressão Antenatal (DAN) que foi feita por Esquirol, em 1818, na qual se relatou o caso de uma mulher que desenvolveu depressão em cada uma de suas cinco gestações (BROCKINGTON, 2005). No entanto, de acordo com a atual nosologia psiquiátrica, DAN ainda não é uma entidade diagnóstica válida. DAN ainda carece de validades descritiva, de constructo e de preditiva. Essas validades são necessárias para se ter validade diagnóstica (SPITZER; WILLIAMS, 1985). Postulam Riecher-Rössler e Rohde (2005), que DAN pode ser, nada mais nada menos, que uma variante temporal da Depressão Maior (DM) desencadeada pelo gatilho gravidez com suas alterações biológicas, psicológicas e sociais associadas (Figura 1).

Figura 1 - O modelo estresse diátese na gestação



Fonte: Riecher-Rossler e Rohde (2005)

Estudos recentes reportam que, apesar de a DM permanecer comum durante a gravidez, a sua frequência não é diferente de outros períodos da vida de uma mulher (BENNETT *et al*. 2004a; GAVIN *et al.*, 2005; VESGA-LÓPEZ, 2008). Essa prevalência é variável de acordo com os estudos. Assim, a revisão de 36 artigos que investigaram a prevalência de DAN por meio do uso de diferentes instrumentos (EPDS, BDI, *Structured Clinical Interview* (SCID), *Composite International Diagnostic Interview* (CIDI), *Mini-International Neuropsychiatric Interview-Plus* (MINI), etc.) encontrou média de 20% (intervalo de 8.1% a 56%) em países em desenvolvimento e de 15% (intervalo de 6.4% a 30%) em países desenvolvidos (PEREIRA; LOVISI, 2008).

Os fatores de risco para DAN parecem estar fortemente associados aos estressores sociais, particularmente aqueles associados a eventos de vida (DA-SILVA *et al.*, 1998; LOVISI *et al.,* 2005). Dificuldades financeiras podem ser consideradas como um desses eventos (LOVISI *et al.*, 2005; RICH-EDWARDS *et al*., 2006), assim como a violência contra a mulher, seja ela cometida pelo cônjuge, por um familiar, ou mesmo por um desconhecido (CAMPBELL *et al.,* 1992; LOVISI *et al.,* 2005; FISHER *et al.,* 2012).

No entanto, pobreza e violência parecem ser fatores de risco independentes para a depressão na gestação (LOVISI *et al.,* 2005). Esses fatores estressantes podem permanecer significativos mesmo após a aparente resolução do estresse associado ao evento desencadeante. Assim, tem-se que mulheres que tiveram um aborto ou natimorto em gestação anterior permanecem com risco aumentado para DAN, mesmo após uma gravidez subsequente que resultou em uma criança saudável (BLACKMORE *et al.*, 2011).

Mulheres solteiras ou divorciadas estão entre as que apresentam mais sintomas depressivos no período gestacional (FELICE *et al.,* 2004; LOVISI *et al.,* 2005). A associação entre DAN e percepção de apoio dos parceiros desde o início da gestação tem sido constantemente replicada (O'HARA, 1986; KITAMURA *et al.*, 1993; DUDAS *et al.*, 2012; JEONG *et al.,* 2013). Por sua vez, atitude negativa perante a gravidez, muitas vezes indesejada ou não planejada, também se relaciona com a DAN (KITAMURA *et al.,* 2006; DUDAS *et al.,* 2012; ABAJOBIR *et al.,* 2016).

Fatores obstétricos também podem ser identificados como facilitadores do aparecimento de DAN (DUDAS *et al.*, 2012). Entre eles, destaca-se histórico prévio de aborto (KUMAR; ROBSON, 1984; ARMSTRONG, 2004; FAISAL-CURY; ROSSI MENEZES, 2007; BERGNER *et al.*, 2008). Um estudo nacional mostrou que existia uma tendência à significância positiva quando avaliado histórico prévio de tratamento psiquiátrico e DAN (DA-SILVA *et al.,* 1998).

Essa tendência deixa de ser tendência e atinge significância estatística quando o fator de risco pesquisado é DM prévia (MARCUS *et al.*, 2003; FELICE *et al.*, 2004; CHEE *et al.,* 2005; KIM *et al.*, 2006; DUDAS *et al.,* 2012; JEONG *et al.*, 2013).

Finalmente, em um modelo de DAN, as variáveis biológicas não tiveram efeito direto nos sintomas depressivos. Entretanto, elas agiram indiretamente por meio da significativa influência delas nos estressores psicossociais e nos sintomas ansiosos. Esse modelo demonstrou a importância de testar os fatores de risco individualmente e de se considerar ambas as variáveis biológicas e psicológicas em transtornos complexos, tais como transtornos perinatais do humor (ROSS *et al.,* 2004).

Gestantes com DAN tem maior incidência de complicações obstétricas: aborto espontâneo, sangramentos gestacionais, resistência da artéria uterina aumentada, crescimento intrauterino restrito, parto prematuro, baixo peso do bebê ao nascer, recém-nascidos pequenos para a idade gestacional, baixo *score* de Apgar e admissão pós-parto na unidade neonatal; sendo que, menor adesão as consultas de pré-natal em função da depressão contribui para algumas dessas complicações (BENNETT *et al.,* 2004a; BONARI *et al.,* 2004). Além disso, a DAN está associada à hipertensão gestacional, à pré-eclâmpsia (KURKI *et al.,* 2000) e ao abuso de substâncias lícitas e ilícitas durante a gravidez (BOWEN; MUHAJARINE, 2006; PAJULO *et al.,* 2001; BENNETT *et al*., 2004a).

O transtorno psiquiátrico antenatal também parece ter impacto direto intraútero (BONARI *et al.*, 2004; MATTHEWS; MEANEY, 2005) levando a *déficits* cognitivos e problemas emocionais nas crianças (TALGE; NEAL; GLOVER, 2007; TRONICK; RECK, 2009), assim como alterações da fisiologia neonatal (MATTHEWS, 2002; DIEGO *et al.,* 2004; FIELD; DIEGO; HERNANDEZ-REIF, 2006), morfologia cerebral (UNO *et al.,* 1994) e até expressão genética da prole (OBERLANDER *et al.,* 2008).

Não obstante, todos os achados acima, a DAN é subdiagnosticada e subtratada. Um estudo de Marcus (2009) estabeleceu que apenas 20% das pacientes com DAN recebem tratamento, o que corrobora a percepção de que muitos profissionais ainda não estão atentos a essa possibilidade ou acreditam que um tratamento específico não é necessário ou que tem a relação risco/benefício desfavorável (MARCUS, 2009).

Dada à relevância da DAN, a 5ª edição do Manual Diagnóstico e Estatístico de Transtornos Mentais da Associação Psiquiátrica Americana, ou *Diagnostic and Statistical Manual of Mental Disorders* (DSM 5), recentemente passou a reconhecer o especificador "com início no periparto".

1.2 Imunologia

1.2.1 Gravidez Normal e Imunologia

Há aproximadamente de 55 anos, Medawar (1952) propôs o paradigma do porquê o feto, como um semialoenxerto, não é rejeitado pelo sistema imune materno, tendo, inclusive, a presença de material imune materno na área de implantação do embrião como evidência de suporte (MOR; CARDENAS, 2010). Em consequência, pesquisadores buscaram durante anos os mecanismos que permitiriam ao feto escapar da vigilância imunológica materna e, nas várias hipóteses propostas, a percepção da gravidez como um estado imunossupressor exercia um papel central (LOKE; KING, 2000; AAGAARD-TILLERY; SILVER; DALTON, 2006; MOR; CARDENAS, 2010). A melhora na gestação de doenças autoimunes Th1, tais como artrite reumatoide, e piora daquelas caracterizadas por uma dominância Th2, tais como lúpus, seria visto como uma evidência para essa teoria (LAROCCA *et al.,* 2008). Outro mecanismo de tolerância do feto pode ser devido aos linfócitos T reguladores (T reg), que podem suprimir a imunidade celular (ALUVIHARE; KALLIKOURDIS; BETZ, 2004). Em humanos, ocorre um aumento das células T reguladoras durante o início da gravidez, com o pico no segundo trimestre, e o declínio no pós-parto (SOMERSET *et al.*, 2004).

A resposta Th1, também chamada imunidade celular, é dependente da inflamação fagocitária e está associada à expressão das citocinas pró-inflamatórias, tais como: interleucina-1-beta (IL-1β), IL-2, IL-6, fator de necrose tumoral-alfa (TNF-α), interferon-alfa (IFN- α), interferon-gama (IFN-γ), entre outras. Já a resposta Th2, também chamada imunidade humoral, é fagocitária-independente, proporciona a produção de anticorpos e nela ocorre expressão das citocinas anti-inflamatórias, tais como: IL-4, IL-10, IL-13 e fator transformador de crescimento-beta (TGF-β) (PRETE, 1998; SINGH; MEHROTRA; AGARWAL, 1999; ROMAGNANI, 2000). A resposta Th2 pode ser considerada como parte de um mecanismo de *downregulation* (ou supressor) para resposta Th1 exagerada ou inapropriada (PRETE, 1998).

Entretanto, a noção de que grávidas seriam em grande parte imunossuprimidas é inconsistente com o conceito evolucionário de que, de fato se o feto humano e/ou sua mãe não fossem capazes de sobreviver à investida de agentes infecciosos durante a gestação, a sobrevivência do *Homo Sapiens* como uma espécie estaria ameaçada de extinção (NAHMIAS; KOURTIS, 1997; AAGAARD-TILLERY; SILVER; DALTON, 2006).

Outra forma de verificar a inter-relação imunologia e gestação são os modelos propostos de imunodistrofismo e imunotrofismo. O primeiro, propôs que os eventos reprodutivos normais podem ser afetados adversamente por fatores imunológicos. Na decídua, existiriam uma miríade de células apresentadoras de antígenos e outras células envolvidas na resposta imune, que em resposta a invasão trofoblástica seriam ativadas. Um subproduto dessa ativação seria a secreção por essas células de um perfil de citocinas com perfil Th1 ou Th2. Em casos em que o perfil Th1 predominasse, essas citocinas poderiam direta ou indiretamente serem prejudiciais para o início da diferenciação e do crescimento placentário e, portanto, tóxicas para o desenvolvimento embrionário. Evidências adicionais para essa hipótese viriam de achados de que uma predisposição genética para uma resposta Th1 vigorosa nessas mulheres seria decorrente de um polimorfismo na região promotora da IL-1β (HILL; CHOI, 2000).

Já o segundo, ancora-se nos estudos de Wegmann, iniciados na década de 70, que sugeriam que produtos de macrófagos e linfócitos T ativados atuariam como fatores de crescimento para células placentárias sem causar danos ao embrião, mas promovendo seu crescimento e viabilidade. Células T maternas, reconhecendo aloantígenos fetais presentes na interface materno-fetal, responderiam, secretando citocinas, que desencadeariam uma "inflamação" que promoveria o crescimento do trofoblasto, um melhor desempenho das funções placentárias e, consequentemente, uma gestação normal (WEGMANN, 1988).

A razão dessas percepções contraditórias pode ser uma simplificação demasiada de observações isoladas feitas durante a gestação (MOR; CARDENAS, 2010). Em vários estudos, a gravidez é avaliada como um evento uniforme, quando na verdade ela teria três fases imunológicas distintas (MOR; CARDENAS, 2010). Assim temos que a implantação, a formação da placenta, o primeiro trimestre e início do segundo trimestre da gestação se assemelham a "uma ferida aberta", que requer uma pronta resposta inflamatória. Durante essa primeira fase, o blastocisto tem que romper o revestimento epitelial do útero para implantação e danificar o endométrio para invadi-lo; em seguida, o trofoblasto age sobre o endotélio e o tecido muscular liso dos vasos maternos para garantir adequado suporte sanguíneo placenta-feto (MOR; CARDENAS, 2010).

Todas essas atividades criam um "campo de batalha" de células invadindo, morrendo e sendo reparadas. Um ambiente inflamatório passa a ser necessário para assegurar um reparo adequado do epitélio uterino e remoção dos debris celulares. Esse ambiente levaria a um estado caracterizado por febre, hipersonolência, fadiga, anorexia, enjoo, letargia, diminuição

do comportamento exploratório e atividade sexual diminuída. Essa síndrome comportamental inespecífica recebeu o nome de comportamento-doente (DANTZER, 2004), e pode ser a causadora das manifestações somáticas de primeiro trimestre nas grávidas (MOR; CARDENAS, 2010).

Assim, o primeiro trimestre da gravidez é uma fase pró-inflamatória. A segunda fase imunológica da gravidez é, em muitos modos, um período ótimo para a mãe. É um período de rápido crescimento e desenvolvimento fetal. A mãe, a placenta e o feto são simbióticos, e a característica imunológica predominante é a indução de um estado anti-inflamatório. A mulher não apresenta mais comportamento-doente como ela havia tido durante a primeira fase, em parte porque a resposta inflamatória não é mais a característica predominante (MOR; CARDENAS, 2010).

Finalmente, durante a última fase imunológica da gravidez, o feto completou seu desenvolvimento, todos os órgãos são funcionais e preparados para o mundo externo. Agora, a mãe precisa de parir o bebê e isso é atingido por meio de nova inflamação. O parto é caracterizado por um influxo de células imunes para dentro do miométrio para promover recrudescência de um processo inflamatório. Esse ambiente pró-inflamatório promove a contração do útero, expulsão do bebê e rejeição da placenta (MOR; CARDENAS, 2010).

Concluindo, a gravidez é uma condição pró-inflamatória e anti-inflamatória, dependendo do período da gestação (AAGAARD-TILLERY; SILVER; DALTON, 2006; LAROCCA *et al.,* 2008; MOR; CARDENAS, 2010).

1.2.2 Depressão Maior e Imunologia

A resposta imune inata é iniciada por uma infecção, trauma, doença autoimune, malignidade ou estresse. É de rápida instalação e tem como propósito limitar tanto o dano tecidual quanto a infecção. É orquestrada, principalmente, por meio da síntese e da liberação de citocinas pró-inflamatórias e anti-inflamatórias (WATKINS *et al.,* 1999). A liberação dessas citocinas pró-inflamatórias leva ao já citado comportamento-doente, que em humanos também produz humor deprimido e anedonia (DANTZER, 2004).

Por outro lado, devido ao potencial de uma inflamação desregulada causar efeitos colaterais e danos indesejados no indivíduo, a resposta pró-inflamatória normalmente é controlada pela produção recíproca de citocinas anti-inflamatórias, aqui incluídas IL-4 e IL-10, que inibem a produção de citocina pró-inflamatórias (OPAL; DEPALO, 2000). Ocasionalmente, o equilíbrio entre as citocinas pró e anti-inflamatórias é interrompido,

causando impacto na saúde mental dos indivíduos. Pesquisas sugerem que uma ativação prolongada ou em excesso de uma resposta pró-inflamatória pode ser um mecanismo para DM (RAISON; CAPURON; MILLER, 2006; DANTZER *et al.,* 2008; CAPURON; MILLER, 2011).

Entre as evidências que temos para tal associação está a constatação de que a administração de até concentrações nanomolares de IFN-α em pacientes com doenças infecciosas ou câncer produz o aparecimento de sintomas depressivos (CAPURON; MILLER, 2004; RAISON; CAPURON; MILLER, 2006). Em indivíduos deprimidos, os níveis de citocinas pró-inflamatórias, aqui incluídas IL-1β, IL-6 e TNF-α, estão elevados (SCHIEPERS; WICHERS; MAES, 2005; DOWLATI *et al.*, 2010), enquanto antidepressivos podem reduzir esses níveis (HANNESTAD; DELLAGIOIA; BLOCH, 2011) ou até estimular a produção de citocinas anti-inflamatórias, como a IL-10 (KENIS; MAES, 2002). Essas citocinas pró-inflamatórias podem alterar a via serotoninérgica por meio da ativação da enzima indoleamina-2,3-dioxigenase (IDO), que é catabolizadora de triptofano (SCHIEPERS; WICHERS; MAES, 2005), e até a via dopaminérgica através de disfunção nos gânglios da base (JUENGLING *et al.,* 2000).

Além disso, as citocinas parecem ser responsáveis por hiperativação do eixo hipotálamo-hipófise-adrenal (HPA) por meio da inibição do *feedback* negativo do cortisol no hipotálamo (CHROUSOS, 1995), processo esse que, afinal, é bidirecional e levará em sequência à redução das citocinas pró-inflamatórias e ao aumento das anti-inflamatórias (ELENKOV; CHROUSOS, 2002). Outra possiblidade de desregulação do eixo HPA por fatores imunológicos foi demonstrado por Garcia *et al.* (2011). Esses pesquisadores evidenciaram que autoanticorpos antiocitocina e antivasopressina estavam associados com alterações do humor em pacientes moderadamente deprimidos e que pelo menos os níveis de autoanticorpos antivasopressina estavam associados à secreção de cortisol (GARCIA *et al.*, 2011). Por fim, outros autoanticorpos específicos, por exemplo, antitireoideanos, anti-receptores N-metil-D-aspartato (NMDA), antigliadina, etc., também estão associados à DM em outros estudos (ISEME *et al.*, 2014).

1.2.3 Depressão Antenatal e Imunologia

São cada vez mais frequentes os estudos imunológicos durante episódios de DAN, os quais focam, principalmente, em dois *clusters* de marcadores imunológicos: citocinas e autoanticorpos (OSBORNE; MONK, 2013; DAMA *et al.,* 2016; LEFF-GELMAN *et al.,*

2016) e talvez, não por coincidência, o primeiro estudo de um desses *clusters* evidenciou positividade dessa associação (SCHMEELK *et al.,* 1999), enquanto o primeiro estudo do outro *cluster*, não (ORETTI et al., 1997). Essa condição de achados contraditórios se repete numa análise mais detalhada dos estudos de mesmo cluster.

Oretti *et al.* (1997) não conseguiram estabelecer associação entre grávidas que possuíam autoanticorpos anti-peroxidase (anti-TPO) e DAN. No entanto, a revisão sistemática recente, que abarca esse estudo de Oretti *et al.* (1997), demonstrou o contrário (DAMA *et al.,* 2016); com três (KUIJPENS *et al.,* 2001; POP *et al.*, 2006; GROER; VAUGHAN, 2013) dos cinco estudos que procuraram essa associação encontrando resultados significativos (DAMA *et al.,* 2016). Viés de seleção, de comparabilidade e de desfecho seriam as limitações possíveis nos dois estudos (ORETTI *et al.,* 1997; BUNEVICIUS *et al.,* 2009) que não encontram associação DAN e anti-TPO. A revisão ainda especula que seus resultados sugerem que os anticorpos anti-TPO podem ser, na verdade, marcadores de que o sistema imune materno esteja mantendo um estado pró-inflamatório enquanto a gestação transcorre do primeiro para o segundo trimestre (DAMA *et al.,* 2016). Procurando por estudos de outros autoanticorpos e DAN, percebe-se que esse é um campo que precisa ser mais bem explorado, pois, à exceção dos autoanticorpos tireoideanos, apenas autoanticorpos contra o antígenos Esptein-Barr parecem ter sido pesquisados até o momento (GROER; MORGAN, 2007; HAERI *et al.,* 2011b). Enquanto Haeri *et al* (2011b) encontraram associação positiva significativa, Groer e Morgan (2007) encontraram apenas tendência à significância positiva.

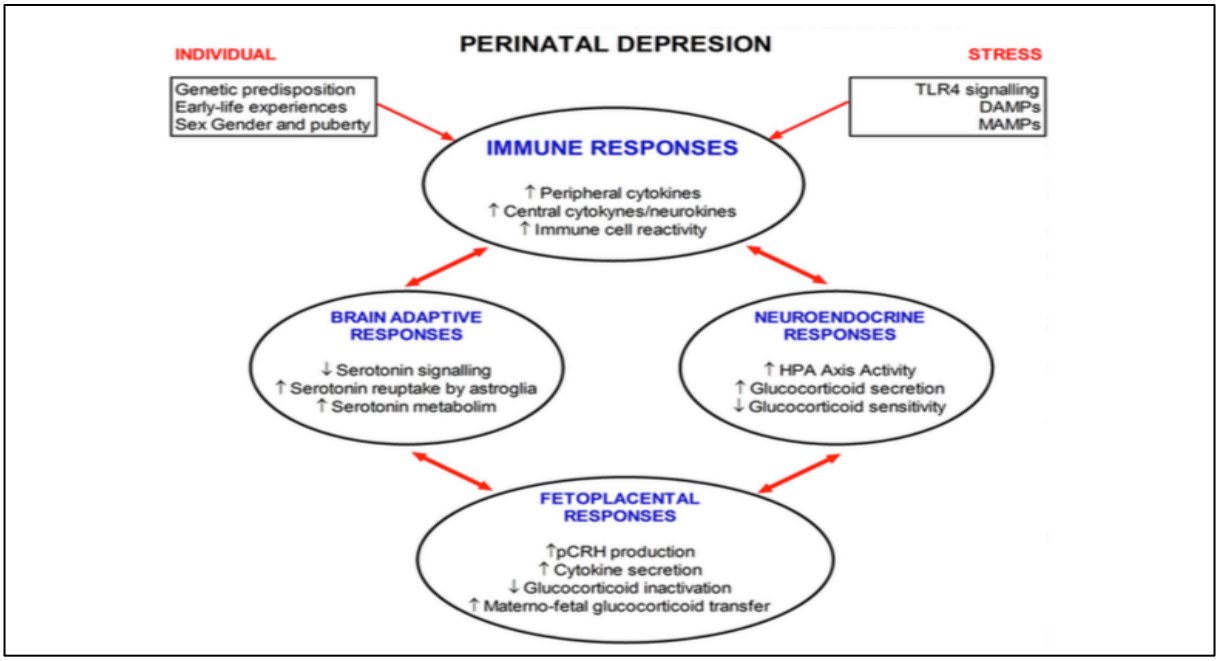
Já Schmeelk *et al.* (1999), apesar de não demonstrarem associação entre DAN e IL-1β, evidenciaram que DAN e o hormônio liberador de corticotrofina (CRH) foram capazes de prever os níveis do antagonista do receptor de IL-1 (IL-1ra) (SCHMEELK *et al.,* 1999). Durante a gravidez, a placenta produz e libera grandes quantidades de CRH na circulação materna e fetal (CHROUSOS; TORPY; GOLD, 1998). Esses níveis de CRH aumentados, por sua vez, foram associados à DAN (RICH-EDWARDS *et al.,* 2008). Hipercortisolemia também estaria associada à DAN (SETH; LEWIS; GALBALLY, 2016). Somada essa constatação de que a gravidez em si pode levar a alterações do eixo HPA e de que essa mesma gravidez também pode levar a uma ruptura no equilíbrio pró/anti-inflamatório das citocinas (item 1.2.1), a hipótese de que esses fatores imunológicos também poderiam ser causadores da DAN fica evidente (OSBORNE; MONK, 2013; GELMAN *et al.,* 2015; LEFF-GELMAN *et al.,* 2016). De fato, IL-6 (CHRISTIAN *et al.,* 2009; HAERI *et al,* 2011a; CASSIDY-BUSHROW *et al.,* 2012), IL-1β (CASSIDY-BUSHROW *et al.,* 2012), TNF-α (HAERI *et al.,* 2011a) e fator inibitório de migração de macrófagos (CHRISTIAN *et al.,* 2010) são algumas

das citocinas que já foram relacionados à DAN. Entretanto, essa associação pode também não existir, por exemplo, em dois estudos não foi possível replicar a associação entre DAN e IL-6 ou TNF-α (BLACKMORE *et al*., 2011; BLACKMORE *et al*., 2014).

Existem ainda evidências em estudos imunológicos de Depressão Pós-parto (DPP), condição muitas vezes vista como análoga à DAN, de que outro *cluster*, no caso um *cluster* celular, também pode estar ligado à manifestação de sintomas depressivos no periparto (HUCKLEBRIDGE *et al.,* 1994). Inclusive, com maiores níveis de linfócitos T – reguladores no pré-natal como marcadores preditivos de DPP (KRAUSE *et al.,* 2014). Aliás, essa abordagem de usar valores pré-natais de moléculas sabidamente associadas a fatores imunológicos como preditores de DPP rendeu outros achados, tais como, neopterina (KRAUSE *et al.*, 2014), leptina (SKALKIDOU *et al.,* 2009), IL-6 e IL-10 (SIMPSON *et al.*, 2016).

Por fim, o estudo de Maes *et al.* (2002) avaliando dados do periparto reforçou o achado de que uma gravidez normal levaria a uma degradação aumentada de triptofano, que, por sua vez, seria, provavelmente, resultante de influência sobre a indolamina 2,3 dioxigenase de alterações imunológicas geradas pela própria gravidez (FUCHS *et al.,* 1996). Sinalizaram ainda que a severidade de sintomas depressivos e ansiosos no puerpério imediato poderia ter sido causada por essa degradação do triptofano (MAES *et al.,* 2002). A Figura 2 pode ser vista como uma síntese dessa introdução.

Figura 2 – O modelo de Depressão Antenatal e suas alterações neuroimunoendócrinas



Fonte: Leff-Gelman *et al.* (2016)

2 OBJETIVOS

2.1 Objetivo geral

Avaliar as características clínicas e imunológicas associadas ao desenvolvimento de depressão antenatal em gestantes atendidas no Ambulatório Jenny de Andrade Faria, de Ginecologia e Obstetrícia, do HC-UFMG.

2.2 Objetivos específicos

1. Analisar se, ao longo da gestação, há diferenças clínicas: prevalência e fatores de risco para DAN. Comparar os resultados da nossa amostra e os dados da literatura mundial;
2. Validar para o período pré-natal, as três escalas de sintomas depressivos mais utilizadas no Brasil - BDI, EPDS e HAM-D - e comparar essas escalas entre si;
3. Avaliar os dados de suicidalidade associados à DAN na nossa amostra
4. Verificar se as interleucinas 6 e 1-β, TNF-α e os autoanticorpos antiocitocina, em semelhança à DM, também estão associadas à DAN.

3 MATERIAIS E MÉTODOS

O presente estudo é um recorte de uma coorte que permanecerá em andamento, existente graças à parceria entre professores dos Departamentos de Saúde Mental e Ginecologia e Obstetrícia do Hospital das Clínicas de Belo Horizonte. O projeto "Investigação clínica e molecular da depressão pós-parto" foi aprovado pelo Comitê de Ética em Pesquisa (COEP) da UFMG, sob o protocolo n.º 227/05.

Artigo 1: De uma população de 318 mulheres em seguimento na coorte, à época que o artigo foi escrito, foram selecionadas aquelas que tinham avaliações do MINI em ambos (segundo e terceiro) trimestres gestacionais avaliados, o que resultou em uma amostra de 148 mulheres. Entrevista semi-estruturada, BDI e EPDS também foram aplicados. Feito estudo sócio-demográfico da amostra. Análises bivariadas e multivariadas foram usadas para determinar a prevalência e os fatores de risco significativos ao longo dos dois trimestres.

Artigo 2: A amostra consistiu nas 247 mulheres consecutivamente inseridas na coorte que estavam no segundo trimestre de gestação. EPDS, BDI, HAM-D e MINI foram aplicados. Análise da curva ROC foi usada para aferir a validade das escalas de sintomas depressivos e determinar qual delas seria o melhor instrumento de rastreamento no diagnóstico de DAN. Também foram calculados os pontos de corte mais acurados, correlações e consistências internas das escalas quando usadas para investigar DAN.

Artigo 3: Feito um recorte da coorte à época da confecção do artigo, em que foram selecionadas 255 pacientes que já haviam tido seus dados de segundo trimestre coletados. Entrevista semi-estruturada, MINI, EPDS e BDI foram aplicadas para avaliar dados sócio-demográficos e identificar fatores significativos de risco para suicídio dessas pacientes, assim como características de suicidalidade das escalas de sintomas depressivos.

Artigo 4: Selecionada um recorte da coorte em que a amostra consistiu em grávidas apresentando DAN e grupo de mulheres com gestações sem complicações, pareadas por idade e selecionadas aleatoriamente na proporção de 1:1 (n=92). Foram aplicados: questionário avaliando características sócio-demográficas e obstétricas, MINI, BDI, EPDS, HAM-D, Childhood Trauma Questionnaire (CTQ). Esses dados foram usados para avaliar a relação entre os níveis plasmáticos de autoanticorpos antiocitocina e o diagnóstico e a severidade de DAN.

4 RESULTADOS

4.1 Artigo 1: Antenatal depression: Prevalence and risk factor patterns across the gestational period

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Research paper

Antenatal depression: Prevalence and risk factor patterns across the gestational period

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ABSTRACT

Background: The prevalence of antenatal depression (AD) among pregnant women varies according to the populations under study and the periods of evaluation. This paper investigated patterns of AD prevalence and risk factors in a Brazilian sample.

Methods: Using semi-structured interviews as well as the Edinburgh Postnatal Depression Scale, the Beck Depression Inventory, and the Mini-International Neuropsychiatric Interview-Plus (MINI), 148 pregnant women were assessed in their second and third trimesters. Bivariate and multivariate analyses were used to determine the prevalence of and the significant risk factors for AD across both trimesters ($p < 0.05$).

Results: The prevalence of AD using the MINI was 13.5% and 10.1% in the second and third trimester, respectively. Prevalence rates using the symptom scales were even higher. In our bivariate analysis, lifetime major depression was the main AD risk factor ($p < 0.001$), along with the number of sons ($p = 0.02$) and intimate partner abuse ($p = 0.01$). After adjustment for confounding factors, only lifetime major depression ($p < 0.001$) and intimate partner abuse ($p = 0.02$) remained as independent risk factors. There were no statistically significant differences in the AD prevalence rates and risk factors found when comparing across trimesters.

Limitations: The study is limited by possible selection bias introduced by the method of recruitment and the number of women lost to follow up.

Conclusion: AD prevalence rates found are close to the worldwide rates. Lifetime major depression was the main risk factor for AD in our study.

1. Introduction

The likelihood of women developing a major depressive disorder is nearly double when compared with men (Silva et al., 2014; Weissman et al., 1993). The highest risk period for women is reported to be during their reproductive years (Weissman et al., 1993). However, recent studies have reported that despite remaining common during pregnancy, depression is not less frequent during other stages of a woman's life (Bennett et al., 2004a, Gavin et al., 2005; Vesga-López, 2008).

Estimates for the prevalence of AD vary widely across different studies. Pereira and Lovisi (2008) reviewed 36 studies, which investigated AD prevalence rates using different instruments (i.e., Edinburgh Postnatal Depression Scale (EPDS), Beck Depression Inventory (BDI), Structured Clinical Interview (SCID), Composite International Diagnostic Interview (CIDI), Mini-International Neuropsychiatric Interview-Plus (MINI), etc.). In developing countries, they calculated the average rate of depressive patients as 20% (with a broad range from 6.4 to 30%). Rates determined in developed countries were lower (15%) and ranged from 8.1% to 56%.

The prevalence of AD could even be altered by the time of evaluation of the gestational period, as demonstrated in two independent studies with conflicting results (Bennett et al., 2004b; Gavin et al., 2005). The first study reported a Gaussian distribution, with prevalence rates of 7.4%, 12.8%, and 12.0% for the first, second, and third trimesters, respectively, while the second study found that the prevalence of AD was 11.0% in the first trimester, but then decreased to 8.5% in the second and third trimesters.

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From the epidemiological and public psychological health views, these differences in reported AD prevalence rates are too vast and multiform data backgrounding is relatively lacking for a disorder with an already well-established impact on the health of the affected woman (Castro e Couto et al., 2015a; Misri et al., 2013; Orr et al., 2007; Fiacentini et al., 2008), her offspring (Barker et al., 2011; Capron et al., 2015; Pawlby et al., 2009; Rice et al., 2007), and the entire family (Escriba-Aguir and Artazcoz, 2011; Mahedy et al., 2014; Paulson and Bazemore, 2010; Wee et al., 2011). Therefore, more studies addressing the matter are needed to afford a better knowledge of AD prevalence rates and patterns. Given this lack, providing more detailed epidemiological information is one of the main purposes of our work; we also address the risk factors for AD and its patterns of presentation.

Risk factors for AD do not seem to be influenced by the gestational period or particular population; in developing countries, they closely mirror those in developed countries, except for some factors associated with unfavorable economic conditions, such as low education, unemployment, financial difficulties, and domestic violence, which predominate in studies in low income countries. Generally, risk factors for AD include a previous history of depression, financial difficulties, low education levels, unemployment, poor social support, substance dependence, and domestic violence (Pereira and Lovisi, 2008). Thus, it appears that pregnancy per se is not associated with an increased risk of psychological disorders (Vesga-López, 2008).

We first describe the prevalence of AD across the gestational period in our sample of pregnant Brazilian women. We then seek to determinate similarities and differences in the risk factors for AD in the second and third trimesters.

2. Methods

The study was conducted at the Clinics Hospital of the Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil. Second trimester pregnant women waiting for their obstetric appointment were invited and all those willing to participate were enrolled. We invited 350 individuals in the waiting room and ended with a sample of 318 acceptances.

After informed consent was obtained, we administered a questionnaire consisting of standardized questions regarding maternal age, education level, marital status, pregnancy planning, history of abortion, intimate partner abuse, and sociodemographic status, among other factors. At the same time, participants were also evaluated using the Brazilian validated version of the EPDS (Santos et al., 2007) and the BDI (Gorenstein and Andrade, 1996). Then, trained psychiatrists (CCT and FCG), blinded to EPDS and BDI scores, re-evaluated each patient using the MINI-Plus (5.0 version) (Amorim, 2000). The application of the rating scales for depressive symptoms and the MINI-Plus were repeated in the third trimester.

Therefore, we sought to establish AD prevalence rates using MINI, EPDS and BDI because these are well-used instruments worldwide and would in theory allow more comparisons. BDI $\geq$ 15 and EPDS $\geq$ 11 were the optimal cut-off points used in this population (Castro e Couto et al., 2015b).

In the end, using the MINI was our gold-standard instrument for AD diagnosis, we had to exclude 167 individuals due to missing MINI in one of the trimesters. Other exclusion criteria were loss due to miscarriage (2) or medical decision to interrupt the pregnancy (1). Those exclusions resulted in a final sample of 148 pregnant women.

Statistical analyses were performed using Stata 13 software (StataCorp LP, College Station, TX, USA). We performed statistical analyses for proportions (MINI-Plus categories included) using the chi-squared test or Fisher's exact test when appropriate. A repeated measures logistic regression mixed model, which accounted for the effects of multiple measures (second and third trimesters) from each subject, was used to assess the independent risk factors for AD. In our bivariate analysis, we searched for associations between AD and sociodemographic (Jesse et al., 2005; Fischer et al., 2012), obstetric (Alami et al., 2006; Dudas et al., 2012) and psychiatric (Andersson et al., 2003; Chee et al., 2005; Rich-Edwards, 2006; Marcus et al., 2003) variables already described within the literature. The multivariate method was used to address which significant variables were independently identified as risk factors. We used the standard 0.05 threshold for statistical significance.

All women diagnosed with any psychiatric disorder and/or showing suicidal potential were referred for treatment. The study was approved by the Research Ethics committee of the UFMG. The data were collected from January 2013 to December 2014.

3. Results

3.1. Sociodemographic data and the prevalence of mental disorders

The average age of the pregnant women participating in this study was 28 (SD = 7.05, range = 13–45) years. Most of the women were non-Caucasian (74.5%), had a lower socio-economic status (64.8%), were married (70.1%), and had > 10 years of education (56.9%). Less than half (50.3%) were primigravid, almost one-fourth had had a previous abortion (24.5%), and a little more than half of the current pregnancies were unplanned (56.5%). Almost one-third (32.8%) had a history of intimate partner abuse and almost all (97.28%) received some support (health professionals not included) during the prenatal period.

Neuropsychiatric comorbidities among the study participants are shown in Table 1, demonstrating a high frequency of lifetime psychiatric disorders, especially mood and anxiety disorders. Note that patients may have more than one diagnosis.

3.2. Prevalence of AD and trends

Differences in the prevalence of AD were obtained according to the methods used to evaluate AD, i.e., MINI-Plus, BDI, or EPDS. We found that BDI and EPDS estimates of the prevalence were higher than MINI estimates.

The prevalences of AD in the second and third trimesters were similar, and we did not find any significant differences between the trimesters (Table 2).

3.3. Risk factors for AD

Lifetime major depression, the number of sons and a history of intimate partner abuse were the only variables that achieved statistical significance as risk factors for AD in the bivariate analysis. We did not find risk factors differences between the trimesters (Table 3).

For the adjusted logistic regression model results, we found that lifetime major depression and a history of intimate partner abuse remained statistically significant (Table 4).

4. Discussion

Notably, there was a high prevalence of current mental disorders among the study participants (43.2% and 37.4% in the second and third trimesters, respectively), which was expected because our study was developed in a high-risk population. These rates were higher than those reported previously in a Swedish

Table 1
Psychiatric disorders according to Mini-International Neuropsychiatric Interview-Plus.

Psychiatric diagnosis	N	2nd trimester	N	3rd trimester
Any mental disorder (current)	64/108	41.3%	50/147	33.6%
Any mental disorder (lifetime)	68/106	46.5%	67/106	45.8%
Any mood disorder (current)	20/108	13.5%	15/108	10.1%
Any mood disorder (lifetime)	40/147	20.8%	38/147	25.8%
Major depression (current)	20/108	13.5%	15/108	10.1%
Major depression (lifetime)	40/147	20.8%	38/108	25.8%
Dysthymia (current)	0/108	0.0	2/108	1.3%
Dysthymia (lifetime)	1/108	0.6%	0/147	0.0
Bipolar disorder (current)	0/108	0.0	0/108	0.0
Bipolar disorder (lifetime)	0/108	0.0	0/108	0.0
Any anxiety disorder	40/108	31.0%	41/147	27.8%
Panic disorder	1/108	0.6%	0/108	0.0
Agoraphobia	5/108	3.1%	9/108	6.0%
Social phobia	9/108	6.0%	6/108	4.0%
Specific phobia	34/108	22.8%	28/108	18.8%
Obsessive compulsive disorder	3/108	2.0%	2/108	1.3%
Mixed anxiety-depression disorder	1/108	0.6%	1/108	0.6%
Post-traumatic stress disorder	1/108	0.6%	0/147	0.0
Generalized anxiety disorder	9/108	6.0%	9/108	6.0%
Psychosis not otherwise specified	2/108	1.3%	0/108	0.0
Anorexia	0/108	0.0	0/108	0.0
Bulimia	0/108	0.0	0/108	0.0
Somatoform disorder	0/108	0.0	0/108	0.0
Hypochondriac disorder	0/108	0.0	0/108	0.0
Body dysmorphic disorder	0/108	0.0	0/108	0.0
Pain disorder	1/108	0.6%	1/108	0.6%
Attention-deficit/hyperactivity disorder	0/108	0.0	0/108	0.0
Adjustment disorder	13/108	8.7%	8/108	5.4%
Premenstrual dysphoric disorder	30/108	20.2%	19/108	12.8%

Table 2
Antenatal depression prevalence and trends.

Instrument	N	2nd trimester	n	3rd trimester	p-values
MINI-Plus	108	13.5% (20)	148	10.1% (15)	0.368
BDI ≥ 15	114	23.8% (12)	111	31.2% (34)	0.268
EPDS ≥ 11	90	33.3% (30)	111	22.5% (21)	0.407

Note: MINI-Plus: Mini-International Neuropsychiatric Interview-Plus, BDI: Beck Depression Inventory, EPDS: Edinburgh Postnatal Depression Scale.

study in the second trimester (Andersson et al., 2006) and in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions in the United States of America (20.2% and 20.3%, respectively) (Vesga-López, 2008). However, our higher rate may have been overestimated because of the study methodology because the MINI-Plus allows for comorbid diagnoses, and the same person may be counted more than once. Moreover, a meta-analysis of the point-prevalence of common non-psychotic mental disorders (including depression, anxiety, adjustment, and somatic disorders) in low-middle income countries reported a prevalence of 15.6% during pregnancy, but with substantially higher and lower rates in specific countries (3.5 to 40.7% range) (Fisher et al., 2012).

In the second and third trimesters, respectively, the prevalence of any mood disorder (13.5% and 10.1%) was lower than that of any anxiety disorder (31.1% and 27.9%). This trend was similar to that of the US cohort, in both currently pregnant women (8.5–12.2%) and past-year pregnant women (13.7–14.9%). Nevertheless, it is important to note that the prevalence of depression and anxiety during pregnancy can be moderate, high, or even overlapping (Heron et al., 2004; Skouteris et al., 2008).

Our cut-off point used for AD screening, EPDS ≥ 11, in spite of being the optimal cut-off point for this population (Castro e Couto et al., 2015b), was lower than the commonly used ≥ 14/15 (Gibson et al., 2009), which could explain why our AD prevalence rates were higher than the usual 10–15% (Adewuya et al., 2006; Felice et al., 2004; Murray and Cox, 1990). For the BDI, the optimal cut-off point used (i.e., ≥ 15; Castro e Couto et al., 2015b) was closer to the ≥ 16 recommended by Holcomb et al. (1996) and produced a prevalence that was closer to the 19% that those authors found in their study. Finally, our AD prevalence rates in the second and third trimesters using the MINI (13.5% and 10.1%, respectively) was close to that reported in previous reviews (i.e., 12.8% and 12%; Bennett et al., 2004b; i.e., 12.7%, Gavin et al., 2005) and to a previous Brazilian study that analyzed AD data in the first trimester also with MINI (15.1%) (Farias et al., 2013). Overall, confirming previous papers, our study showed higher prevalence rates using the symptoms scales than using a semi-structured interview for the diagnosis of AD (Bennett et al., 2004b; Gavin et al., 2005; Kitamura et al., 1993; Kumar and Robson, 1984).

We also found that there was a decrease in the AD prevalence rates as pregnancy drew to its close across all the instruments used (EPDS, BDI, MINI). Nevertheless, despite decreasing these between trimesters, differences in the prevalence of AD did not achieve statistical significance in any of the instruments used; once again, confirming a trend postulated by previous reviews (Bennett et al., 2004a, Gavin et al., 2005).

In a systematic review of the literature on risk factors for AD, Lancaster et al. (2010) suggested that maternal anxiety, life stress, history of depression, lack of social support, unintended pregnancy, Medic-aid insurance, domestic violence, lower income, lower education, smoking, single status, and poor relationship quality were associated with a greater likelihood of AD symptoms by bivariate analysis. Life stresses, lack of social support, and domestic violence have a significant association with the prevalence of AD in multivariate analysis.

Our findings were statistically significant only for lifetime major depression, number of sons and history of intimate partner abuse. Contrary to other studies, we did not find a correlation between AD and previous abortions (Armstrong, 2004; Bergner et al., 2008; Faisal-Cury and Rossi Menezes, 2007), premenstrual mood changes (Jeong et al., 2013; Kitamura et al., 1996), prenatal support (Alami et al., 2006; Dudas et al., 2012; Felice et al., 2004; Jeong et al., 2013; Kleinberg et al., 2013), education (Faisal-Cury and Rossi Menezes, 2007; Jeong et al., 2013; Lovisi et al., 2005; Patel et al., 2002), pregnancy planning (Alami et al., 2006; Chee et al., 2005; Dudas et al., 2012; Rich-Edwards et al., 2006), age (Kitamura et al., 2006), civil status (Adewuya et al., 2007; Andersson et al., 2003; Felice et al., 2004; Jeong et al., 2013) or ethnicity.

Of the risk factors, lifetime major depression was the most important risk variable found because it increased the risk of AD by more than 10-fold in the period, followed by the number of sons and intimate partner abuse, 3 and 2.6 times, respectively.

Lifetime major depression seems to be strongly linked with AD prevalence, as previous papers have demonstrated (Chee et al., 2005; Dudas et al., 2012; Felice et al., 2004; Jeong et al., 2013; Kim et al., 2006; Marcus et al., 2003; Rich-Edwards et al., 2006). On the other hand, few studies have previously correlated the number of sons or intimate partner abuse with AD prevalence. Kitamura et al. (1993) found that the first delivery was most associated with AD, however the same paper may explain our different result because

Table 3
Antenatal depression risk factors.

	2nd trimester AD (%)	3rd trimester AD (%)	OR (CI 95%) *p*-value	Between trimesters difference *p*-value
Age				
≤ 20	1/18 (5.56)	2/18 (11.11)	1.23 (0.71–2.14)	0.258
20–29	30/168 (16.71)	6/168 (3.82)	0.016	
30–39	6/53 (11.32)	4/53 (7.55)		
≥ 40	2/8 (25.00)	2/8 (25.00)		
Ethnicity				
Caucasian	4/38 (10.53)	2/38 (5.26)	1.64 (0.55–4.88)	0.242
Non-caucasian	33/309 (13.76)	12/309 (11.01)	0.366	
Civil status				
Unmarried	6/44 (13.64)	7/44 (15.91)	0.62 (0.26–1.48)	0.252
Married	31/303 (12.62)	7/303 (6.80)	0.281	
Number of sons				
0	4/74 (5.41)	5/74 (6.76)	1.04 (1.30–7.75)	0.245
≥ 1	33/73 (28.55)	9/73 (12.33)	0.038*	
Previous abortion				
No	33/111 (11.71)	11/111 (9.91)	1.38 (1.06–1.05)	0.252
Yes	6/36 (16.67)	3/36 (8.33)	0.714	
Intimate partner abuse				
No	5/93 (5.38)	8/93 (8.60)	2.66 (1.09–1.20)	0.161
Yes	12/65 (26.67)	3/65(6.67)	0.011*	
Prenatal support				
No	1/4 (25.00)	1/4 (25.00)	0.36 (0.05–2.41)	0.257
Yes	38/343 (12.38)	13/343 (8.09)	0.297	
Pregnancy planning				
No	11/83 (13.25)	11/83 (13.25)	0.62 (0.25–1.48)	0.251
Yes	8/64 (12.50)	3/64 (4.69)	0.282	
School years				
Until 10	8/63 (12.70)	11/63 (17.46)	0.52 (0.22–1.21)	0.259
More than 10	11/83 (13.25)	3/83 (3.61)	0.126	
Lifetime major depression				
No	4/100 (3.85)	4/100 (3.85)	11.32 (4.80–26.66)	0.504
Yes	15/44 (34.09%)	11/38 (28.95%)	< 0.001*	
Premenstrual dysphoric disorder				
No	14/118(11.86)	12/120 (11.11)	1.63 (1.67–1.05)	0.308
Yes	6/33 (20.00)	3/39 (15.79)	0.278	

Note: AD: Antenatal depression, OR: Odds ratio, CI: Confidence interval.
* $p < 0.05$.

Table 4
Antenatal depression risk factors and adjusted OR (CI 95%).

Risk factor	N	OR (CI 95%)	*p*-values
Lifetime major depression	138	11.12 (4.38–28.22)	< 0.001*
Intimate partner abuse	138	2.82 (1.19–6.80)	0.020*

Note: OR: Odds ratio, CI: Confidence interval.
* $p < 0.05$.

living in an accommodation with an expectation to be crowded after the forthcoming childbirth was also a risk factor for AD. In addition, another Brazilian study also reported that not being primiparous was a risk factor for AD (Silva et al., 2010). A history of intimate partner abuse also had been previously positively correlated with AD in Brazil and other low-income countries (Fischer et al., 2012; Lovisi et al., 2005; Patel et al., 2002).

After adjustment for confounding factors, lifetime major depression and intimate partner abuse remained as primary risk factors for AD. Notably, maternal abuse may be responsible for epigenetic disturbances, with offspring of the abused mothers presenting with increased and persistent depressive symptoms in adolescence and adulthood (Roberts et al., 2015).

A recent study proposed that the time for evaluation might be one of the reasons for the differences in AD risk factor results among studies. This study reported that several risk factors (unwanted and unplanned pregnancy, high neuroticism) were independent predictors of AD throughout the entire pregnancy, while other risk factors (low education, previous history of depression, the occurrence of psychosocial stressors at the end of pregnancy) were trimester specific (Banoviciun et al., 2009). Nevertheless, in our study we did not find differences in the risk factors between the second and third trimesters. Another possible explanation for our differences in the risk factors is that the magnitude of the relationship between them and AD may vary accordingly to the sample source (Maniglio, 2010). Finally, in a prenatal model of depression, biological variables had no direct effect on depressive symptoms. However, they did act indirectly through their significant effects on psychosocial stressors and symptoms of anxiety. This model demonstrates the importance of testing the risk factors individually and of considering both biological and psychosocial variables in complex health conditions such as perinatal mood disorders (Ross et al., 2004). Taking this into consideration, it could be of interest to evaluate temperaments as risk factors too because they may influence mood disorders (Ferreira et al., 2013).

The study's sample was not randomized and was composed mainly of low-income women who received prenatal care at a public health center, which somewhat limits the external validity of the results. Moreover, as it was a tertiary center, the pregnant women typically came for evaluation when they were already in their mid-pregnancy, making data collection of the first trimester impossible and, therefore, not allowing a full between trimesters comparison. Finally, prevalence of AD in the studied population could be even higher due to the high rate of follow-up losses in our sample. As showed by De Graaf et al. (2000), patients with psychiatric disorders are prone to drop out.

In conclusion, the prevalence of AD among pregnant women in

Brazil is close to the rates found in other parts of the world, despite the Brazilian population being one of the most heterogeneous populations in the world, formed mainly by a mixture of European, African, and Native American populations and with different genetic profiles (Cordeiro et al., 2009). This finding seems to highlight the universal validity of the construct AD. Furthermore, previous history of major depression was once again identified as one of the main risk factors for AD.

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4.2 Artigo 2: What is the best tool for screening antenatal depression?

Tiago Castro e Couto, Mayra Yara M. Brancaglion, Mauro N. Cardoso, Andressa B. Protzner, Frederico D. Garcia, Rodrigo Nicolato, Regina Amélia L. Aguiar, Henrique Vitor Leite, Humberto Corrêa.

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Research report

What is the best tool for screening antenatal depression?

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ABSTRACT

Background: Antenatal depression (AD) can have devastating consequences. No existing scales are specifically designed to measure it. Common practice is to adapt scales originally developed for other circumstances. We designed this study to validate and determine the psychometric values for AD screening in Brazil.

Methods: We collected clinical and socio-demographic data in the second gestational trimester. The following instruments were also administered during that period: MINI-PLUS, EPDS, BDI and HAM-D.

Results: At the time of assessment, 17.34% of the patients were depressed, and 31.08% met the diagnostic criteria for lifetime major depression. All instruments showed an area under the curve in a receiver operating characteristic analysis greater than 0.85, with the BDI achieving a 0.90 and being the best-performing screening instrument. A score ≥11 on the EPDS (81.58% sensitivity, 73.33% specificity), ≥15 on the BDI (82.00% sensitivity, 84.26% specificity) and ≥9 on the HAM-D (87.76% sensitivity, 74.60% specificity) revealed great dichotomy between depressed and non-depressed patients. Spearman's rank correlation coefficients (ρ) among the scales had good values (EPDS vs. BDI 0.79; BDI vs. HAM-D 0.70, and EPDS vs. HAM-D 0.67).

Limitations: This study was transversal, assessing only women in the second gestational trimester. Results may be applicable only to the Brazilian population since psychometric properties may vary with the population under study. Major depression can amplify somatic symptomatology, affecting depressive rating scale data.

Conclusion: AD is highly prevalent in Brazil. To address the problem of under-recognition, physicians can use the EPDS, BDI and HAM-D to identify AD.

1 Introduction

Antenatal depression (AD) has been described as a form of clinical depression that affects women during pregnancy and that may increase the risk of postpartum depression if not properly treated (Milgrom et al., 2008; Norhayati et al., 2015).

Moreover, AD is a highly frequent condition, with prevalence estimated as high as 18% of pregnancies (Gavin et al., 2005). The presence of AD can have multiple deleterious effects, not only on women but also on offspring and the entire family. Depressed pregnant women, for example, are more prone to exhibiting high-risk behaviors. They are more likely to use alcohol, tobacco and illicit drugs; to have unhealthy eating habits; to suffer from sleep disturbances; and to attend fewer prenatal follow-up appointments (Bennett et al., 2004a; Field et al., 2008; Haugen et al., 2012; Marcus et al., 2003; Orr et al., 2007; Zuckerman et al., 1989). These behaviors interact with the intrinsic biological mechanisms of depression to create an increased risk of obstetric complications, such as pre-eclampsia, pre-term birth, restricted fetal growth and/or low birth weight (Bonari et al., 2004; Davalos et al., 2012; Diego et al., 2009; Field et al., 2008; Grote et al., 2010). In addition, an increasingly large body of clinical and experimental evidence suggests that both biological markers and the physiology of the offspring of depressed females can be influenced by maternal hypothalamic–pituitary–adrenal (HPA) axis dysfunction, including increased levels of cortisol and catecholamines (Brummelte and Galea, 2010; Frodl and O'Keane, 2013; Wadhwa et al., 2002). These abnormalities may have life-long implications for the developing brain of the fetus, such as negative consequences for neural circuits, neurotransmitter activities and epigenetic changes (Davis et al., 2011; Field et al., 2006; Frodl and O'Keane, 2013; Oberlander et al., 2008; Weinstock, 2005), rendering the

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offspring more vulnerable to mental health disorders later in life (Halligan et al., 2007; O'Donnel et al. 2014; Pawlby et al., 2009; Pearson et al., 2013, Santos et al., 2014; Talge et al., 2007). Finally, a positive correlation between maternal and paternal depression has been demonstrated, emphasizing that AD is not merely a women's issue but is a problem that affects entire families (Escriba-Agüir and Artazcoz, 2011; Paulson and Bazemore, 2010).

All of these factors illustrate that AD diagnosis and treatment should be considered a public health issue, and all pregnant women should be screened for signs of AD. Unfortunately, the rate of AD under-diagnosis can be as high as 80% (Kelly et al., 2001a) and is likely higher in areas with deficient healthcare infrastructures. Therefore, studying instruments that could be used in primary care settings by non-doctors and non-specialists is critical to enable broad screening for AD among pregnant women.

The most frequent scales used in the assessment of AD, the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Bennett et al., 2004a), were developed for general use with major depression across the life span and during the postpartum period, respectively. Because of the sensitivity of these instruments, however, normal symptoms in pregnancy can sometimes be misconstrued as indicators of depression, and although they may resolve as pregnancy nears completion, such symptoms can lead to higher scores on self-report measures (Matthey and Ross-Harnid, 2012). An additional concern pertains to the psychometric characteristics of these scales with regard to cultural population characteristics and their use in populations in which illiteracy remains a problem. Although scholars have debated the extent to which the psychometric properties of those scales are adequate for use in AD, the EPDS and BDI have been utilized extensively in the antenatal period (Areias et al., 1996; Buist et al., 2006; Chung et al., 2001; Da-Silva et al., 1998; Evans et al., 2001; Josefsson et al., 2001; Gotlib et al. 1989; Manikkam and Burns, 2012; Matthey and Ross-Harnid, 2012; Milgrom et al., 2008; Rochat et al., 2011; Seguin et al., 1995). However, questions remain regarding whether there are major differences between the self-fulfillment scales (EPDS and BDI) and those applied by professionals, such as the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960).

To the best of our knowledge, none of these three depression screening tools have been validated for use in an antenatal population in Brazil. Our aim was to compare the psychometric characteristics of the EPDS, BDI and HAM-D scales to those of a structured interview (MINI-PLUS) (Amorim, 2000), which is the gold standard for AD diagnosis, in second-trimester pregnant women.

2. Methods

2.1. Research protocol

A total of 247 consecutive women who were in their second trimester of pregnancy and were attending antenatal care at a public hospital were enrolled in the study. After a full explanation of the study purpose, written informed consent was obtained from each participant. As part of the study, the patients were evaluated using the Brazilian validated version of the EPDS (Santos et al., 2007) and the BDI (Gorenstein and Andrade, 1996). A trained psychiatrist blinded to the EPDS and BDI scores then re-evaluated each patient using the HAM-D (17-item version) (Hamilton, 1960) and the Mini-International Neuropsychiatric Interview (MINI-Plus 5.0 version) (Amorim, 2000).

All women who were found to meet the criteria for any psychiatric disorder were referred for treatment. This study was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais.

2.2. Statistical analysis

Receiver operating characteristic (ROC) analyses were used to measure the accuracy of the EPDS, BDI and HAM-D in diagnosing major depression according to DSM IV-TR criteria. Youden's Index was used to determinate the best cut-off points for screening (Youden, 1950). Spearman's rank correlation coefficient (ρ) was calculated to examine concordance among the psychometric scales tested. Cronbach's alpha (α) was used as an estimate of scale reliability, resulting in a coefficient of internal consistency and allowing for visualization of item homogeneity. Analyses were performed using Stata version 12 based on a 0.05 significance level.

3. Results

3.1. Depression prevalence and risk factors

A major depressive disorder was diagnosed during the second trimester of pregnancy or during the lifetime in 17.34% and 31.98% of the women, respectively. Table 1 contains the sociodemographic and clinical characteristics of these women diagnosed with AD.

Pregnant women with more than one child ($p=0.004$), those who had experienced a previous abortion ($p=0.026$), those who had a history of suffering aggression ($p<0.001$) and those who had not received support from their family or friends during prenatal care ($p=0.05$) had a statically significant risk of developing AD (see Table 1).

3.2. Psychometric properties of the scales

3.2.1. Validity

The areas under the curve (AUC) in a ROC analysis for the scales were 0.85 (SE=0.03; CI95%=0.78–0.91), 0.90 (SE=0.02; CI95%=0.85–0.94) and 0.86 (SE=0.02; CI95%=0.81–0.91) for EPDS, BDI and HAM-D, respectively (Fig. 1).

3.2.2. Cut-offs

The optimal cut-off points for this sample were chosen after applying Youden's Index. This strategy yielded the following cut-off scores: ≥ 11 for the EPDS (sensibility: 0.81; specificity: 0.73; PPV: 0.75), ≥ 15 for the BDI (sensibility: 0.82; specificity: 0.84; PPV: 0.83) and >9 for the HAM-D (sensibility: 0.87; specificity: 0.74; PPV: 0.77) (Table 2).

3.2.3. Correlation

The strongest correlation between the scales was that between EPDS and BDI (0.7946), followed closely by the correlations between BDI and HAM-D (0.7006) and between EPDS and HAM-D (0.6716) (Fig. 1).

3.2.4. Reliability

Internal consistencies were determined using Cronbach's α. The values obtained were 0.8717, 0.9042 and 0.8179 for the EPDS, BDI and HAM-D instruments, respectively, in the gestational period.

4. Discussion

In our sample, we found an AD prevalence rate of 17.34% in the second trimester based on the structured MINI-Plus interview, which is similar to that obtained by other researchers (Bennett et al., 2004a; Gavin et al., 2005). By contrast, the prevalence rates obtained using the EPDS, BDI and HAM-D were 32.6% (23.7–43.0), 25.0% (17.1–35.0) and 38.0% (28.6–48.5), respectively.

Table 1
Sociodemographic and clinical characteristics of the sample.

	Antenatal depression (N=91)	OR (CI 95%)	p-Value
Age			
≤ 20	2/16 (5.56)	3.9 (0.887–15.438)	0.364
20–29	21/116 (18.42)		
30–39	15/82 (18.29)		
≥ 40	3/11 (23.08)		
Ethnicity			
Caucasian	12/66 (18.18)	0.882 (0.420–1.851)	0.739
Non-Caucasian	29/177 (16.38)		
Marital status			
Without partner	14/73 (19.18)	0.785 (0.385–1.601)	0.445
With partner	27/172 (15.70)		
School years			
Until 10	13/99 (12.17)	0.565 (0.630–1.812)	0.018
11 or more	28/138 (20.87)		
Number of children			
0	31/116 (26.68)	2.891 (1.403–6.063)	0.004*
≥ 1	30/129 (23.26)		
Previous abortion			
No	24/178 (13.48)	2.282 (1.095–4.166)	0.026*
Yes	13/67 (25.37)		
Aggression history			
No	13/154 (8.44)	4.582 (2.199–8.270)	< 0.001*
Yes	22/76 (28.31)		
Prenatal support			
No	5/14 (35.71)	0.332 (0.113–1.001)	0.05*
Yes	30/231 (15.58)		
Pregnancy planning			
Unplanned	30/147 (20.41)	0.481 (0.236–1.029)	0.59
Planned	11/98 (11.22)		

* $p \leq 0.05$.

The results above are consistent with existing variability based on country and study methodology. In high-income countries (HICs), the prevalence of AD closely resembles the rate of postnatal depression (11% vs. 13%) (Gavin et al., 2005), whereas in low-income countries (LICs) such as sub-Saharan Africa, the rates may be higher (11.3% vs. 18.3%) (Sawyer et al., 2010; Woolsong et al. 2014). The depressive symptom rating scales produced higher and broader rates overall relative to that obtained from the structured interview. Specifically, the obtained HIC rates were 8–31% from depressive symptom scales vs. 2–21% from structured interviews, whereas the LIC rates were 20–51% from depressive symptom scales vs. approximately 38% from the structured interviews (Bennett et al. 2004a). In addition to income, the gestational period may also have influenced the estimated prevalence of AD. In a systematic review, Gavin et al.'s (2005) estimates suggested that as many as 18.4% of pregnant women were depressed during their pregnancy (*i.e.*, from conception to birth), with as many as 12.7% experiencing an episode of major depression. Those researchers also found that the point prevalence of AD in the first trimester was 11.0% but that it dropped to 8.5% in the second and third trimesters.

Overall, our data show that all of the scales examined are valid screening tools for AD in Brazil. All three screening tools had narrow confidence intervals and yielded positive predictive values greater than 0.75. Moreover, all scales had good internal consistency (Cronbach's $\alpha = 0.81$). However, the BDI had the highest AUC value (0.90), suggesting that this tool may be the best and most reliable screening instrument. The next highest AUC values were obtained for both the HAM-D and EPDS, with values of 0.86 and 0.85, respectively. The apparent superiority of the BDI can be interpreted in view of evidence suggesting that somatic complaints remain important symptoms of depression even in populations in which non-depression-related physical symptoms are common. For instance, as patients with general medical conditions may present with multiple somatic symptoms, some authors have suggested that is optimal to include rather than exclude somatic items in screening tools for depressive disorders (Mitchell et al., 2012).

To date, the EPDS screening tool has been utilized most frequently in AD validation studies (Adewuya et al., 2006; Felice et al., 2006; Murray and Cox, 1990; Stewart et al., 2013; Tran et al., 2011). To our knowledge, only one previous study validated the BDI (Holcomb et al., 1996), and no previous study has validated the HAM-D for use in AD populations.

Stewart et al. (2013) found that the ROC curve for the EPDS was flat over the part of the curve that was closest to the top left-hand corner of the plot and thus noted that the curve did not indicate clear optimum cut-off scores. Other studies of EPDS have established cut-off points of 12 (Adewuya et al., 2006), 13/14 (Felice et al., 2006) and 14/15 (Murray and Cox, 1990) for probable depression. In contrast to these findings, a Vietnamese study indicated an EPDS cut-off point of 3/4 (Tran et al., 2011) for AD. This finding derives from the fact that the ultimate goal of the study was to measure common mental disorders, including depression, anxiety, adjustment and somatoform disorders, each of which compromises day-to-day functioning and is identifiable in primary health care settings (Goldberg and Huxley, 1992), rather than solely measuring AD.

The only paper that we identified as validating the BDI in a sample of pregnant women stated that the choice of a cutoff value for a screening test depends not only on disease prevalence but also on the consequences of making, mistaking, or missing a diagnosis (Holcomb et al., 1996). Those authors ultimately concluded that a cut-off score of 16 was optimal in their population.

Our analyses yielded cut-off points that differed from those previously identified as more capable of identifying AD in the international literature. The variable findings in the literature demonstrate the importance of assessing instruments' psychometric properties for use with different populations. Our results indicated that cut-offs ≥ 11 for the EPDS, ≥ 15 for the BDI and ≥ 9 for the HAM-D would be the optimal values for determining whether an individual should be referred to a professional for diagnostic confirmation. Differences in the prevalence, methodology, language, culture, diagnostic interviews and decision-making criteria used across study samples could be responsible for the variability in recommended cut-off scores (Hallbreich and Karkun, 2006; Gibson et al., 2009).

Our results may apply only to the second trimester of pregnancy in Brazil and must be interpreted in consideration of certain limitations. First, in this transversal study, we assessed only women in the second gestational trimester. Accordingly, different AD prevalence rates can be found for different gestational trimesters (Bennett et al., 2004b; Gavin et al., 2005), and different trends can be observed when examining the correlation of pregnancy and gestational period. For instance, Gavin et al. (2005) showed that the point prevalence of AD decreases as pregnancy nears its conclusion, from 11% in the first trimester to 8.5% in the second and third trimesters. This trend differs from the 7.4% (CI95: 2.2–12.6), 12.8% (CI95: 10.7–14.8), and 12.0% (CI95: 7.4–16.7) prevalence rates found by Bennett et al. (2004b) for the first, second, and third trimesters, respectively. Nevertheless, in both studies, the 95% CIs overlap substantially; hence, given available evidence, the AD prevalence cannot be said to differ significantly by trimester. Second, major depression can amplify somatic symptomatology, including nausea, vomiting, physical discomfort and fatigue during pregnancy (Kelly et al., 2001b), thus affecting women's responses on depressive rating scales. Nevertheless, a study in rural South Africa found that despite the frequent observation of somatic pregnancy symptoms, rates of depression prevalence were not overestimated (Rochat et al., 2011).

Our study shows that the EPDS, BDI, and HAM-D can be used as screening tools for AD. We have further shown that the BDI has

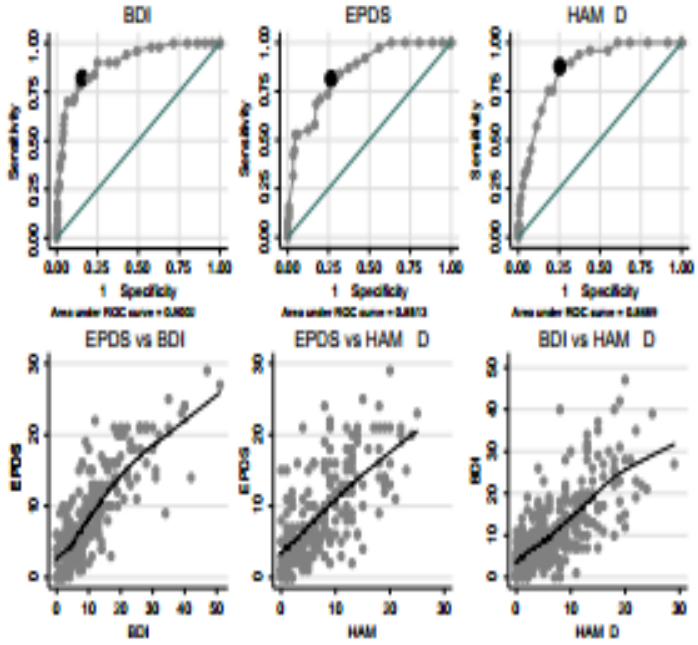

Fig. 1. Receiver operating characteristic (ROC) curves and correlation graphs.

Table 2
Scales' psychometric properties.

	Cut-off	Sensitivity	Specificity	Correctly classified	LR+	LR-	Youden's index
EPDS							
	(≥ 8)	89.47%	58.00%	64.36%	2.1303	0.1815	47.47%
	(≥ 9)	86.84%	62.67%	67.56%	2.3261	0.21	49.51%
	(≥ 10)	84.21%	68.00%	71.35%	2.6316	0.2322	52.21%
	(≥ 11)	81.58%	73.33%	75.68%	3.0592	0.2532	54.91%
	(≥ 12)	73.68%	75.33%	75.00%	2.9872	0.3490	49.01%
	(≥ 13)	71.05%	80.00%	78.38%	3.5526	0.3618	51.05%
	(≥ 14)	68.42%	82.67%	79.73%	3.9474	0.382	51.09%
BDI							
	(≥ 12)	90.00%	75.33%	78.54%	3.6304	0.1333	65.33%
	(≥ 13)	84.00%	79.66%	78.54%	3.9076	0.2007	60.66%
	(≥ 14)	82.00%	80.38%	80.57%	4.1471	0.2244	62.38%
	(≥ 15)	82.00%	84.28%	83.01%	5.211	0.2136	66.28%
	(≥ 16)	78.00%	86.78%	84.62%	5.8911	0.2569	64.78%
	(≥ 17)	72.00%	88.85%	85.43%	6.4478	0.3152	60.85%
	(≥ 18)	70.00%	89.85%	85.83%	6.895	0.3339	59.85%
	(≥ 19)	70.00%	91.40%	88.66%	10.0377	0.3212	61.40%
HAM-D							
	(≥ 6)	89.47%	56.00%	64.19%	2.0342	0.0728	53.00%
	(≥ 7)	89.47%	62.86%	69.33%	2.5167	0.0972	56.84%
	(≥ 8)	89.47%	67.72%	72.27%	2.7632	0.1567	57.52%
	(≥ 9)	87.76%	70.68%	77.31%	3.4934	0.1661	62.36%
	(≥ 10)	75.51%	78.81%	78.15%	3.5679	0.1936	54.33%
	(≥ 11)	75.51%	81.48%	80.25%	4.0776	0.3006	56.99%
	(≥ 12)	65.31%	85.71%	81.51%	4.5714	0.4048	51.02%

Note: EPDS: Edinburgh Postnatal Depression Scale; BDI: Beck Depression Inventory; HAM-D: Hamilton Depression Rating Scale; LR: Likelihood ratio.

better psychometric properties than the more widely used EPDS and should thus be used preferentially. Furthermore, our analyses indicate that cut-off values may be dependent on the population studied, emphasizing the need to validate instruments for use in different populations. We hope that the broad use of these scales as screening tools can be associated with an increase in diagnosis and treatment of the disorder, thus minimizing the harmful effects of AD.

Conflict of interest
We declare that we have no conflicts of interest.

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4.3 Artigo 3: Suicidality among pregnant women in Brazil: prevalence and risk factors

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ORIGINAL ARTICLE

Suicidality among pregnant women in Brazil: prevalence and risk factors

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Abstract Suicide is one of the major causes of preventable death. We evaluated suicidality among pregnant women who participated in prenatal care in Brazil. A total of 255 patients were assessed using semi-structured interviews as well as the Edinburgh Postnatal Depression Scale (EPDS), Beck Depression Inventory (BDI), and Mini-International Neuropsychiatric Interview (MINI) Plus. Thereafter, Stata 12 was used to identify the significant predictors of current suicide risk (CSR) among participants using univariate and multivariate analyses ($p<0.05$). According to MINI Plus module C, the lifetime suicide attempt rate was 12.55 %. The overall CSR was 23.53 %, distributed across risk levels of low (12.55 %), moderate (1.18 %), and high (9.80 %). Our rates approximate those found in another Brazilian study (18.4 %). Antenatal depression (AD), lifetime bipolar disorder, and any current anxiety disorder (as measured using the MINI) as well as BDI scores ≥15 and EPDS scores ≥11 were identified as positive risk factors in a univariate analysis ($p<0.001$). These factors changed after a multivariate analysis was employed, and only years of education [odds ratio (OR) = 0.45; 95 % confidence intervals (CIs) = 0.21–0.99], AD (OR = 3.42; 95 % CIs = 1.37–8.51), and EPDS scores ≥11 (OR = 4.44; 95 % CIs = 1.97–9.9) remained independent risk factors. AD and other psychiatric disorders were the primary risk factors for suicidality, although only the former remained an independent factor after a multivariate analysis. More than 10 years of education and EPDS scores ≥11 were also independent factors; the latter can be used as a screening tool for suicide risk.

Keywords Suicidality · Pregnancy · Antenatal depression · Prenatal screening · Risk factors

Introduction

Suicide is a major cause of premature and preventable death; more than 90 % of suicide victims have a diagnosable mental illness, and approximately 60 % of all suicides occur in people with mood disorders (Beautrais et al. 1996). A diagnosis of major depression dramatically increases the risk for suicide or serious suicide attempts.

Despite the common thought that pregnancy is a period of health among women, studies of pregnant women have indicated that depression is common; furthermore, this condition is no less frequent during pregnancy compared with any other time in a woman's life (Bennett et al. 2004a; Gavin et al. 2005). Pregnancy might trigger the appearance and recurrence of depressive symptoms in vulnerable women. This condition is known as antenatal depression (AD). Previous authors have found that AD affects an estimated 15–20 % of women, although rates vary by country and measurement type (Bennett et al. 2004b; Gavin et al. 2005; Halbreich 2004; Pereira and Lovisi 2008).

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A population-based study of suicide during pregnancy in England and Wales found a suicide rate that was approximately 1/20 of that expected in the general female population [standardized mortality ratio (SMR)=0.05]. This result also applied to pregnant adolescents who showed a significantly lower suicide rate than that found among their counterparts in the general population (SMR=0.28). Nevertheless, pregnant adolescents had a suicide rate that is over five times greater than the overall rate for pregnant adults. In addition, a higher than expected proportion of pregnant women used uncommon but dramatic suicide methods compared with the less violent methods common among non-pregnant women (Appleby 1991). A North American study also reported a lower risk of suicide among pregnant women in New York City from 1990 to 1993 than among non-pregnant controls. The risk was approximately one third of what is expected among the general population of women aged 15–44 (SMR=0.33; Marzuk et al. 1997). In a study of maternal mortality from 1976 to 1986 in rural Bangladesh, Fauveau and Blanchet (1989) found that suicide was the second most frequent cause of mortality, accounting for 20 % of all deaths during pregnancy.

Suicidality, defined as deaths due to suicide, intentional self-harm (with or without intent to die), and thoughts of death and self-harm, is one way to measure the risk of suicide; therefore, it is important in the context of preventing potentially fatal outcomes. Suicide ideation with high intent is a distal predictor of future death due to suicide (Joiner et al. 2000).

We evaluated the prevalence of suicidality during the second trimester of pregnancy. We also sought to ascertain whether certain sociodemographic, obstetric, psychosocial, and clinical risk factors are associated with suicidality.

Methods

All 255 patients were assessed during their second trimesters using a questionnaire that consisted of standard questions regarding maternal age, education, ethnicity, marital status, pregnancy planning, prenatal support, parity, thoughts of abortion, domestic violence, and sociodemographic status. Moreover, participants were evaluated using the Brazilian validated version of the Edinburgh Postnatal Depression Scale (EPDS; Santos et al. 2007) and the Beck Depression Inventory (BDI; Gorenstein and Andrade 1996). Next, a trained psychiatrist blinded to participants' EPDS and BDI scores re-evaluated each patient using the Mini-International Neuropsychiatric Interview (MINI) Plus, version 5.0 (Amorim 2000). Thus, we were able to evaluate AD and suicidality. The data were collected from January 2013 to December 2014.

Lifetime suicide attempts were assessed as previously described by Corrêa et al. (2002). Suicidality was evaluated using the suicide module of the MINI (module C), which consists of six items (0–33 points) that assess the presence and level (1–5=low, 6–9=moderate, ≥9=high) of current suicide risk (CSR). This study confirmed the presence of CSR when patients scored ≥1 point on module C. In addition, the BDI (Gorenstein and Andrade 1996) and EPDS (Santos et al. 2007) were used to quantify depressive symptoms and suicidality, especially EPDS item 9 (suicidal thoughts or wishes: I don't have any thoughts of killing myself; I have thoughts of killing myself, but I would not carry them out; I would like to kill myself; I would kill myself if I had the chance) and BDI item 10 (The thought of harming myself has occurred to me: yes, quite often; sometimes; hardly ever; never).

Statistical analyses were performed using Stata 12. After obtaining the simple frequency of all variables, a gross analysis was conducted using the chi-square test. Then, a logistic regression was used to evaluate the rates of the independent variables associated with the presence of suicidality. After the adjusted analysis, the significance threshold was set at 0.05 (two-tailed). An analysis was performed to determine the significant predictors of suicidal potential among participants.

Women who were diagnosed with psychiatric disorders showed suicidal potential, or both were referred for treatment. The Research Ethics Committee of the Universidade Federal de Minas Gerais approved this study.

Results

The average age of the pregnant women was 27.95 years old (SD=7.12, range=13–45 years). Most of the women were non-Caucasian (73.20 %) and of low socioeconomic status (63.52 %), married (70.63 %), and had more than 10 years of education (56.15 %). Fewer than half (48.41 %) were primigravid, approximately one fourth had received a previous abortion (25.79 %), and the majority of pregnancies were unplanned (60.32 %). Approximately one third (34.33 %) had experienced partner aggression, but nearly all received support during pregnancies from their partners, family members, or friends (92.83 %).

According to the MINI Plus module C, the rate of lifetime suicide attempts was 12.55 %. CSR was present in approximately one fourth of the sample (23.53 %), and these participants showed low, moderate, and high suicide risk rates of 12.55, 1.18, and 9.80 %, respectively.

To evaluate the clinical variables associated with CSR, the sample was divided into two groups: those showing suicide risk (≥1 point on MINI Plus module C) and those without suicidality (0 on MINI Plus module C). Sociodemographics (age, ethnicity, marital and socioeconomic status, and years of education), obstetric (parity, previous abortion, and pregnancy planning), psychosocial (history of partner aggression and prenatal support), and clinical (presence or absence of mental

Table 1 CSR risk factors (univariate analysis)

	CSR (%) (module C score ≥1)	OR (95 % CIs)	*p* value
Age			
<20	10/37 (27.03)		0.857
20–29	27/118 (22.88)		
30–39	19/84 (22.62)		
≥40	3/13 (23.08)		
Ethnicity			
Caucasian	11/67 (16.42)	1.75 (0.85–3.62)	0.124
Non-Caucasian	47/183 (25.68)		
Marital status			
Unmarried	16/74 (21.62)	1.11 (0.58–2.15)	0.735
Married	42/178 (23.60)		
Socioeconomic status			
Upper class	15/89 (16.85)	1.71 (0.88–3.31)	0.107
Lower class	40/155 (25.81)		
School years			
Until 10	30/107 (28.04)	0.63 (0.34–1.14)	0.127
More than 10	27/137 (19.71)		
Parity			
0	24/122 (19.67)	1.44 (0.79–2.61)	0.222
≥1	34/130 (26.15)		
Previous abortion			
No	41/187 (21.93)	1.26 (0.65–2.42)	0.485
Yes	17/65 (26.15)		
History of partner aggression			
No	31/153 (20.26)	1.58 (0.85–2.96)	0.145
Yes	23/80 (28.75)		
Prenatal support			
No	6/18 (33.33)	0.57 (0.20–1.59)	0.285
Yes	52/233 (22.32)		
Pregnancy planning			
No	38/152 (25.00)	0.75 (0.40–1.38)	0.356
Yes	20/100 (20.00)		
AD (MINI)			
No	30/198 (15.15)	5.60 (2.82–11.11)	<0.001*
Yes	20/40 (50.00)		
Lifetime bipolar disorder (MINI)			
No	50/238 (21.01)	5.37 (2.12–13.61)	<0.001*
Yes	10/17 (58.82)		
Any current anxiety disorder (MINI)			
No	24/158 (15.19)	3.40 (1.89–6.11)	<0.001*
Yes	36/95 (37.89)		
Psychosis not otherwise specified (MINI)			
No	58/250 (23.20)	3.31 (0.23–46.24)	0.373
Yes	1/2 (50.00)		
BDI score ≥15			
No	22/167 (13.17)	6.40 (3.46–11.84)	<0.001*
Yes	34/89 (49.28)		
EPDS score ≥11			
No	14/113 (12.39)	7.07 (3.53–14.13)	<0.001*
Yes	34/68 (50.00)		

CSR current suicide risk, *AD* antenatal depression, *MINI* Mini-International Neuropsychiatric Interview, *BDI* Beck Depression Inventory, *EPDS* Edinburgh Postnatal Depression Scale, *OR* odds ratio, *CIs* confidence intervals

*p<0.05

disorder as assessed by the MINI) variables were tested against suicide risk (Table 1).

We found that only AD, lifetime bipolar disorder, and any current anxiety disorder (as measured using the MINI) were positive risk factors for suicide risk. We also found that applying the best BDI and EPDS cutoff points for screening AD in this population (≥15 and ≥11, respectively; Couto et al. 2015) led to positive correlations with CSR.

All the variables used to predict suicidality, BDI item 9, EPDS item 10, MINI Plus module C, and lifetime suicide attempts, were highly correlated with AD in secondary analyses, despite, 26, 80, 17, and 17 participants, respectively, failed to complete these items and were removed from the analyses (Table 2).

Because of the collinearity between the EPDS ≥11 and BDI ≥15 cutoffs, only the former was retained in the multivariate analysis, along with years of education and AD. Years of education were an independent protective factor, and AD and EPDS ≥11 were independent risk factors (Table 3).

Discussion and conclusion

Suicidality risk factors among pregnant women have previously been linked to unwanted/unplanned pregnancies (Frautschi et al. 1994; Newport et al. 2007); unhelpful or unsupportive mothers-in-law or husbands and family preference for a male child (Gausia et al. 2009); women with ≥2 births (Farias et al. 2013); single status (Huang et al. 2012; Newport et al. 2007; Silva et al. 2012); verbal, physical, and sexual abuse (Asad et al. 2010; Gausia et al. 2009; Pinheiro et al. 2012; Stark and Flitcraft 1995); thoughts of or actual abortions (Coleman 2011; Pinheiro et al. 2012; Silva et al. 2012); antenatal psychosocial stress (Gavin et al. 2011); low socioeconomic status, social support, and education levels (Pinheiro et al. 2012; Silva et al. 2012); smoking tobacco (Huang et al. 2012); posttraumatic stress disorder (Eggleston et al. 2009); depressive symptoms or AD (Asad et al. 2010; Farias et al. 2013; Gavin et al. 2011; Huang et al. 2012; Newport et al. 2007; Pinheiro et al. 2012; Silva et al. 2012); and anxiety symptoms or disorders (Asad et al. 2010; Farias et al. 2013; Newport et al. 2007; Pinheiro et al. 2012; Silva et al. 2012).

Table 2 Association between AD and suicidality markers

AD	2nd trimester		
	N	Median±SD	*p* value
# BDI item 9			
No	189	0.11±0.42	<0.001*
Yes	40	0.53±0.68	
# EPDS item 10			
No	146	0.21±0.61	<0.001*
Yes	29	1.28±1.13	
# MINI module C			
No	198	0.24±0.67	<0.001*
Yes	40	1.15±1.35	
# of lifetime suicide attempts (%)			
No	198	17 (8.59)	0.003*
Yes	40	10 (25.00)	

AD antenatal depression, *BDI* Beck Depression Inventory, *EPDS* Edinburgh Postnatal Depression Scale, *MINI* Mini-International Neuropsychiatric Interview, *SD* standard deviation

*$p<0.05$

Table 3 CSR risk factors (multivariate analysis)

CSR	OR (95 % CIs)	*p* value
School years	0.45 (0.21–0.99)	0.049*
AD (MINI)	3.42 (1.37–8.53)	0.008*
EPDS ≥11	4.44 (1.97–9.97)	<0.001*

CSR current suicide risk, *AD* antenatal depression, *MINI* Mini-International Neuropsychiatric Interview, *EPDS* Edinburgh Postnatal Depression Scale, *CIs* confidence intervals, *OR* odds ratio

*$p<0.05$

In our sample, suicidality (as measured using MINI module C) resulted in a CSR of 23.53 % in the second trimester. This value could be subdivided into low, moderate, and high risks of 12.55, 1.18, and 9.80 %, respectively. In other words, nearly dichotomous suicidal behavior was observed. The majority of patients exhibited either low (53.4 %) or high (41.65 %) risks of suicide.

During pregnancy, self-harm ideation is more common than attempts or deaths. Suicidal ideation during pregnancy is not unusual, but the rates have varied greatly across previous samples (Lindahl et al. 2005). Recent studies of pregnant and postpartum women have shown rates of suicidal ideation between 2.7 and 35 % (Eggleston et al. 2009; Gausia et al. 2009; Gavin et al. 2011; Huang et al. 2012; Newport et al. 2007).

The difference between our findings and those mentioned above might be due to different methodologies. The aforementioned studies were based on a single item that pertained to suicidal ideation and originated from the regular psychiatric scales usually employed during symptomatology screenings such as the Addiction Severity Index (ASI; Eggleston et al. 2009), the EPDS (Gausia et al. 2009), the Patient Health Questionnaire (PHQ; Gavin et al. 2011), the Self-Report Questionnaire 20 (SRQ20; Huang et al. 2012), the BDI (Newport et al. 2007), and the Hamilton Rating Scale for Depression (HRSD; Newport et al. 2007). In fact, a Brazilian study also used the MINI to determine CSR among first-trimester pregnant women and found a rate that was close to ours (i.e., 18.4 %; Farias et al. 2013). Sample characteristics might also have influenced the results given that some of the analyses were conducted among women who were already

seeking antenatal treatment for neuropsychiatric or epileptic conditions (Newport et al. 2007) or illicit drug use (Eggleston et al. 2009) and who were likely also at higher CSR. Moreover, this risk might vary by evaluation time. Studies employing the EDPS found decreasing rates from the third (5.4 %) to the sixth (4.1 %) to the eighth (3 %) month of pregnancy (Mauri et al. 2012) and from the third (10.2 %) to the eighth (6.8 %) month (Evans et al. 2001).

We found that AD increases CSR by 5.60 times [95 % confidence intervals (CIs)=2.82–11.11]. Despite the wide range of the confidence interval suggesting that the sample may overlapped, another study from Brazil showed similar results: Depressed pregnant women were 3.83 times more likely to present with suicidality (95 % CIs=2.24–6.56; Silva et al. 2012). A North American study found that AD increased suicidal ideation by 4.12 times (95 % CIs=1.86–9.13; Newport et al. 2007).

During the second trimester, all the examined suicidality markers (BDI item 9, EPDS item 10, MINI module C, and lifetime suicide attempts) were correlated with AD. A positive correlation was also found for CSR and BDI and EPDS best cutoff points for screening AD in this population (≥15 and ≥11, respectively; Couto et al. 2015). These results should have been expected because major depressive disorder is well known to convey one of the highest risks for suicidal ideation (Nock et al. 2008). These positive correlations demonstrate the future importance of these markers for use as suicidality screening tools in primary care settings. The need for this screening is supported by findings showing that only a small number of patients inform their physicians of their suicide plans or attempts (Isometsä et al. 1994).

Anxiety disorders also increased CSR by 3.40 times (95 % CIs=1.89–6.11), repeating the findings of other studies showing a correlation between CSR and anxiety (Farias et al. 2013; Newport et al. 2007; Silva et al. 2012). Finally, bipolar disorder also augmented CSR by 5.37 times (2.12–13.61), but psychosis not otherwise specified did not.

As shown above, our study found that mental disorders (i.e., AD, any current anxiety disorder, and lifetime bipolar disorder), above all the other tested variables, were related to higher rates of suicidality. From a clinical point of view, these results suggest that mental health professionals should focus on the factors that are consistently and strongly associated with suicide attempts across different populations including young people, females, and those with major depression or other psychiatric disorders (Perez-Rodriguez et al. 2008).

After a multivariate analysis, years of education [odds ratio (OR)=0.45; 95 % CIs=0.21–0.99], AD (OR=3.42; 95 % CIs=1.37–8.53), and EPDS scores ≥11 (OR=4.44; 95 % CIs=1.97–9.97) remained independent risk factors for CSR. Pregnant women with more than 10 years of education were 0.45 times less risk of suicide, whereas those with AD and EPDS scores ≥11 were 3 and 4 times more likely to commit suicide, respectively.

The use of the MINI mental health assessment, a validated psychiatric instrument, strengthens our findings. Most studies investigating suicidality during pregnancy have been based on the psychiatric scales usually employed for symptomatology screenings (Eggleston et al. 2009; Gausia et al. 2009; Gavin et al. 2011; Huang et al. 2012; Newport et al. 2007), and it is possible that using a single item to assess suicidal ideation excludes important dimensions of this variable (Lindahl et al. 2005). Nevertheless, we acknowledge that certain limitations are present in the current study. First, as with any cross-sectional study, causality cannot be assessed. Second, our sample contained a small proportion of adolescents that might have overestimated suicidality risk (Appleby 1991; Pinheiro et al. 2012). Finally, the fact that our sample was primarily composed of low-income women who received prenatal care at a public health center might have limited the external validity of our results.

Together, our study supports the view that suicidality is relatively common among pregnant women; however, numerous epidemiological genetic studies have demonstrated that suicidal behavior is at least partially under genetic control and independent of psychiatric disorders (Bondy et al. 2006). Therefore, this finding should also be tested among pregnant women.

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Conflict of interest The authors declare that they have no competing interests.

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4.4 Artigo 4: Autoantibodies reacting with oxytocin are associated with antenatal depression

Original Research Article

Title

Autoantibodies reacting with oxytocin are associated with antenatal depression

Running Header

Anti-OT and antenatal depression

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[1] OT: oxytocin; ATD: antenatal depression; AutoAbs: autoantibodies;

Abstract

Background. Abnormal oxytocin (OT) signaling may contribute to the physiopathology of antenatal depression (ATD). OT-reactive autoantibodies (autoAbs) may interfere with the plasmatic levels of OT and have been associated with major depressive disorder. We hypothesize that, as for major depressive disorder, depressive symptoms and ATD correlate with OT autoAbs levels. In the present study, we compared anti-OT autoAbs levels in pregnant women with and without ATD.

Methods. This is a cross-sectional study with a sample composed of pregnant women with and without antenatal depression. Depression was assessed with MINI diagnostic interview, Edinburgh Postnatal Depression Scale (EPDS), the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS). Plasma levels of total and free OT-reactive IgG and IgM autoAbs were measured by ELISA and analyzed with relation to the depression severity and diagnosis.

Results. The mean level of free anti-OT IgG autoAbs was 10% lower in women with a current depressive episode diagnosis (p=0.041). Free anti-OT IgM autoAbs levels were 20,3% lower in women with a previous depressive episode diagnosis (p=0.05).

Conclusion. These data show that changes in levels of OT-reactive autoAbs can be associated with the altered mood in subjects with ATD.

Keywords: Antenatal depression; mood disorders; oxytocin; behavior; neuropeptides; natural immunity;

1. Introduction

The pathogenesis of antenatal depression (ATD) is still not completely understood (Serati et al., 2016). Research on the neurobiology of ATD is focused on the deregulation of the hypothalamic-pituitary-adrenal axis (HPA) and the imbalances in monoamines and hormones (Brummelte and Galea, 2010; Doornbos et al., 2009; Kammerer et al., 2006; Workman et al., 2012). More recently some authors also assessed genetic (Couto et al., 2015; Serati et al., 2016) and inflammatory mechanisms (Osborne and Monk, 2013; Serati et al., 2016).

In the last ten years, a growing interest has been focused on oxytocin (OT), a neuropeptide not only responsible for intrapartum uterine contractions and milk ejection but also involved in neurocognitive processes and neuropsychiatric disorders (Kim et al., 2014). OT is a neuromodulator and neurotransmitter that acts in the limbic system regulating social behavior, anxiety, stress response and memory formation (Donaldson and Young, 2008; Veenema and Neumann, 2008). Moreover, maternal bonding and behavioral adaptation to motherhood seem to be related to OT (Skrundz et al., 2011). OT may also influence neural plasticity in response to environmental circumstances, and 'for better or for worse' might affect later behavioral and psychological outcomes (Belsky et al., 2009; McQuaid et al., 2014). OT may make positive experiences more salient resulting in increased resilience to stress and the lack of OT may reinforce the adverse events, such as traumas, leading to major depressive disorders (McQuaid et al., 2014).

Higher OT levels have been associated with fewer depressive symptoms. OT probably buffers the stress-induced cortisol response, thereby decreasing vulnerability to depression (Moura et al., 2016). Cox et al. (2015) reported that symptomatic postpartum depressed women experienced a positive correlation between OT and cortisol, instead of the expected negative correlation, suggesting that deregulation of OT secretion and/or response to OT may play a role at least in the pathogenesis of postpartum depression (Cox et al., 2015).

A possible mechanism for this bidirectional behavior is the altered stability of OT in plasma by carrier proteins – i.e. molecules which can reversibly bind these peptides (Avrameas, 1991; Garcia et al., 2011). Immunoglobulins, i.e. naturally occurring autoantibodies (autoAbs), may play such a role as carriers for peptide hormones (Avrameas, 1991; Garcia et al., 2011). In fact, OT-reactive autoAbs have

been correlated with major depressive episodes and the severity of depressive symptoms (Garcia et al., 2011; Iserne et al., 2014).

Finally, OT has inhibitory effects on hypothalamus-pituitary-adrenal (HPA) axis and cytokine activity, and the increase of OT-reactive during episodes of acute stress would limit their prolonged actions (McQuaid et al., 2014). However, under conditions where oxytocin is decreased, as observed among individuals who encountered early-life stressors, the reduction of the inhibitory effects of this peptide could favor elevated cortisol and pro-inflammatory cytokine functioning (McQuaid et al., 2014).

We may though hypothesize that, as for major depressive disorder, depressive symptoms and ATD correlate with OT autoAbs levels. Moreover, OT autoAbs levels could be influenced by early-life trauma events. To address this hypothesis, in the present study, we compared levels anti-OT autoAbs in pregnant women with and without ATD.

2. Methods

2.1 Study subjects and blood sampling

This is a cross-sectional study carried out in the Hospital das Clínicas University Hospital Maternity, an academic tertiary public health center, responsible for near 3000 deliveries/year, which handles low-risk and high-risk pregnancy referrals addressed from primary care facilities and specialized services. The UFMG Research Ethics Board reviewed and approved the study protocol (ETIC 227/2005). All subjects provided written informed consent for study participation. All women diagnosed with psychiatric disorders or presenting suicidal risk were referred for treatment.

The sample of this study was issued from a larger longitudinal study (Castro e Couto et al., 2015). Specifically, for this study, we selected a subsample of pregnant women presenting depressive symptoms in the antenatal period and a group of age-matched, randomly selected women with uncomplicated pregnancies in a proportion of 1:1. as the inclusion criteria included minimum 18 years of age and a second trimester pregnancy (13 to 26 weeks after menses cessation).

All subjects completed a questionnaire assessing sociodemographics [e.g. age, ethnicity, marital status, and economic level (Correa et al., 2002)] and obstetric issues

(e.g. unintended pregnancy status, prenatal support, number of previous children, existence of gestational risk – low or high). High-risk pregnancies were defined as the presence of one or more of the following: past adverse obstetric history, preexisting medical conditions, use of drugs with potential effects on pregnancy, preeclampsia, intrauterine growth restriction, preterm premature rupture of membranes, placenta previa, placenta accrete, fetal anomaly, multiple pregnancy, gestational diabetes, threatened preterm labor, twin–twin transfusion syndrome or others such as preexisting hypertension and cervical incompetence.

All subjects were interviewed and completed the validated Brazilian Portuguese versions of the Edinburgh Postnatal Depression Scale (EPDS) (Castro e Couto et al., 2015), the Beck Depression Inventory (BDI) (Castro e Couto et al., 2015) and the Childhood Trauma Questionnaire (CTQ) (Grassi-Oliveira et al., 2006). Finally, a trained psychiatrist blind to the EPDS and BDI scores interviewed each patient using the validated Brazilian Portuguese versions of the Hamilton Depression Rating Scale (17 items version; HDRS 17) (Castro e Couto et al., 2015) and the Mini-International Neuropsychiatric Interview (MINI-Plus 5.0 version) (Amorim, 2000). Current suicide risk was also assessed through data obtained by the MINI.

Venous blood samples were obtained in the morning after overnight fasting. Plasma was separated by centrifugation and frozen at -80° C until analyzed.

2.2 Serum levels of OT-reactive autoantibodies

Plasma levels of autoAbs (IgG and IgM) reacting with OT were measured using enzyme-linked immunosorbent assay (ELISA) technique previously described (Fetissov, 2011). In brief, OT peptide (Sigma, Saint Louis, MO, USA) was coated on Maxisorp plates (Nunc, Rochester, NY, USA) using 100 µl and a concentration of 2 µg/ml in 100mM $NaHCO_3$ buffer, pH 9.6 for 24 h at 4 °C. Plates were washed (5 min 3×) in phosphate-buffered saline (PBS) with 0.05% Tween 20 (Sigma, Saint Louis, MO, USA), pH 7.4, and then incubated overnight at 4 °C with 100 µl of human plasma diluted 1:200 in PBS to determine free autoAbs levels or diluted 1:200 in dissociating buffer (3M NaCl, 1.5M glycine, pH 8.9) to determine total autoAbs levels. The optimal dilutions of plasma (1:200) were determined by dilution curves (1:50, 1:100, 1:200, 1:400 and 1:800). The plates were washed (3×) and incubated with 100µl of alkaline phosphatase-conjugated goat anti-human IgG and IgM (1:2000) (Sigma, Saint Louis,

MO, USA) for 3 h at room temperature 37°C. Following washing (3×), 100 µl of p-nitrophenyl phosphate solution (Sigma, Saint Louis, MO, USA) was added as alkaline phosphatase substrate. After 40 min of incubation at RT, the reaction was stopped by adding 50 µl of 3 N NaOH. The optical density (OD) was determined at 405 nm using a microplate reader VICTOR Multilabel Plate Reader, (PerkinElmer, Wellesley, MA, USA). Blank OD values resulting from the reading of plates without the addition of human plasma were subtracted from the sample OD values. Each determination was done in duplicate. The variation between duplicate values was less than 5%.

2.3 Statistical analysis

We performed statistical analysis in Stata 12.0 software (StataCorp LP, College Station, TX, USA) and plotted the graphs using the GraphPad Prism 5.01 (GraphPad Software Inc., San Diego, CA). The Kolmogorov-Smirnov test evaluated normality. For our analysis, we grouped women according to the presence or absence of a current depressive episode as assessed by MINI score.

Group differences were assessed using the Mann-Whitney for non-parametric or Student's t-test for parametric variables. Spearman's rank correlation coefficient (ρ) was calculated to examine concordance among OT total and free IgG or IgM autoAbs levels and the severity of depressive symptoms assessed by the EPDS, HDRS, and BDI, childhood trauma based on the total CTQ score, and for suicide risk measure by the MINI-C items, considered as a continuous variable.

For all tests, $p<0.05$ was considered significant, and considering exploratory nature of the present study, the reported p-values were uncorrected for the number of tests performed.

3. Results

3.1 Sample Description

Sociodemographic data is summarized in Table 1. The depressed group differed from the control group because it presented a significantly higher prevalence of unintended pregnancy status ($p=0.026$) and were not primiparous ($p=0.036$).

Table1: Comparison of the depressed and non-depressed groups accordingly to the sociodemographic characteristics.

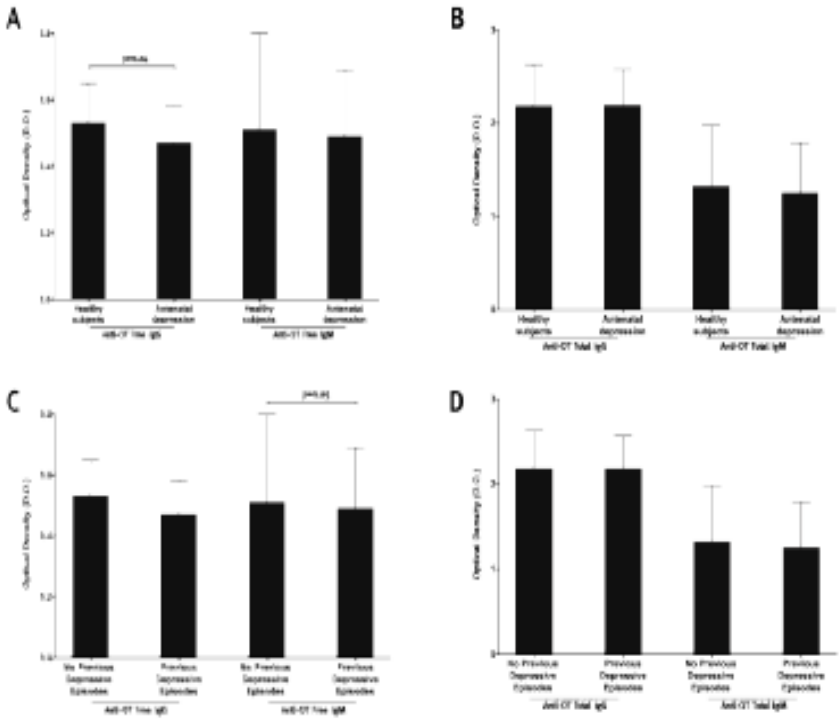
	Depressed n=46		Not-depressed n=46			Total n=92	
	Mean±S.D.		Mean±S.D.		p	Mean±S.D.	
Age	28.9±6.8		27.5±6.4		0.27	28.2±6.6	
School years	10.4±2.6		9.8±2.7		0.29	10.1±2.7	
	n	%		%		n	%
Socioeconomic status							
High	19	42.2	11	25.6	0.1	30	34.1
Low	26	57.8	32	74.4		58	65.9
Ethnicity							
Caucasian	7	15.6	13	28.3	0.14	20	22
Non-caucasian	38	84.4	33	71.7		71	78
Marital status							
Single	7	15.2	14	30.4	0.08	21	22.8
Prenatal support							
Absent	1	2.2	4	8.7	0.16	5	5.4
Unintended pregnancy							
Yes	20	43.5	10	21.7	0.02*	30	32.6
Not primiparous							
Yes	20	43.5	30	65.2	0.03*	50	54.4

S.D.: Standard Deviation; Low economic status: family income lower than $600; *p < 0.05

3.2 Levels of anti-OT autoantibodies and ATD

The mean level of free anti-OT IgG autoAbs was 10% lower in women with a current depressive episode diagnosis (p=0.04). Free anti-OT IgM autoAbs levels were 20.3% lower in women with a previous depressive episode diagnosis (p=0.05) (Figure 1).

Figure 1: Total and free anti-oxytocin IgG and IgM total and Free levels in subjects with a current and previous depressive episode.



3.3 Levels of anti-OT autoantibodies and comorbidities

Free Anti-OT IgG and IgM levels were not associated with other psychiatric comorbidities such as current or previous diagnosis of generalized anxiety disorder (GAD) or the presence of gestational risk (Table 2).

Table 2: Total and free anti-oxytocin IgG and IgM levels in patients according to the presence of current ATD or previous depressive episode, generalized anxiety disorder, suicidality and gestational risk.

		Total anti-OT IgG		Total anti-OT IgM		Free anti-OT IgG		Free Anti-OT IgM	
Condition		Mean±S.D.	p	Mean±S.D.	p	Mean±S.D.	p	Mean±S.D.	p
Current depressive episode	No	2.18±0.45	0.95	1.32±0.66	0.59	0.53±0.12	0.04*	0.51±0.29	0.82
	Yes	2.19±0.39		1.25±0.54		0.47±0.11		0.49±0.20	
Previous depressive episode	No	2.18±0.45	0.96	1.32±0.66	0.83	0.53±0.13	0.11	0.56±0.29	0.05*
	Yes	2.18±0.39		1.25±0.54		0.48±0.11		0.44±0.19	
GAD	No	2.18±0.43	0.94	1.31±0.62	0.41	0.50±0.12	0.91	0.51±0.27	0.93
	Yes	2.19±0.40		1.19±0.54		0.50±0.13		0.47±0.16	
Previous GAD	No	2.18±0.41	0.8	1.28±0.61	0.87	0.50±0.13	0.74	0.51±0.26	0.69
	Yes	2.15±0.44		1.26±0.57		0.51±0.10		0.46±0.17	
Current Suicide risk	No	2.17±0.43	0.78	1.26±0.63	0.42	0.51±0.13	0.23	0.51±0.29	0.74

	Yes	2.20±0.40		1.37±0.59		0.48±0.11		0.48±0.17	
Gestational risk	No	2.19±0.45	0.77	1.30±0.66	0.98	0.51±0.11	0.97	0.52±0.24	0.42

S.D.: Standard deviation; GAD: Generalized Anxiety disorder; *p < 0.05

3.4 Levels of anti-OT autoantibodies and suicide risk

Total and free anti-OT IgG and IgM levels did not differ according to suicide risk, measured by the MINI-C score (Table 2).

3.5 Levels of anti-OT autoantibodies and depressive symptoms

We have not found statistically significant correlations between total and free anti-OT autoAbs and the current depressive symptoms measured by the BDI, HDRS or EPDS (Table 3).

Table 3: Spearman rank correlation between depressive symptoms and childhood trauma scales and anti-OT free and total autoAbs.

	Total anti-OT AutoAbs					
	IgG	IgM	BDI	HDRS	EPDS	Total CTQ
IgG	1					
IgM	0.52	1				
BDI	-0.10	-0.14	1			
HDRS	-0.03	-0.08	0.79*	1		
EPDS	-0.10	-0.04	0.82*	0.73*	1	
Total CTQ	-0.04	-0.13	0.44*	0.34*	0.34*	1
	Free anti-OT autoAbs					
IgG	1					
IgM	0.39	1				
BDI	-0.22	-0.11	1			
HDRS	-0.17	-0.07	0.79*	1		
EPDS	-0.11	-0.02	0.82*	0.73*	1	
Total CTQ	-0.07	-0.04	0.44*	0.34*	0.39*	1

BDI: Beck depression inventory; HDRS: Hamilton Depression Rating Scale; EPDS: Edinburgh Postnatal Depression Scale; CTQ: Childhood Trauma Questionnaire. *p>0.05

3.6 Levels of anti-OT autoantibodies and childhood trauma

No statistically significant correlation was found between total and free anti-OT autoAbs and childhood trauma measured by the total score of CTQ (Table 3).

4. Discussion

In this study, we determined the levels of natural antibodies reactive with OT in patients with and without ATD. To the best of our knowledge, this is the first study assessing anti-OT autoAbs in pregnant women with ATD and the second to assess these autoAbs in depressive disorder (Garcia et al., 2011). We aimed to evaluate if anti-OT autoAbs levels were altered in women with ATD when compared to healthy pregnant women and if childhood trauma influenced these levels.

We found that patients with a current ATD episode presented lower levels of free anti-OT IgG autoAbs and women with a previous depressive episode showed a lower free anti-OT IgM autoAbs. No association was found between anti-OT antibody levels and childhood trauma measured by the CTQ.

These results should be regarded in light of some drawbacks. First, this is a cross-sectional study, and it does not allow us to infer causality. Second, despite our care in sample selection, even using a randomization procedure to assign healthy subjects to patients with ATD, the latter group presented a higher prevalence of unintended pregnancies and were not primiparous. These differences could be only an epiphenomenon as these factors have been previously associated to ATD (Biaggi et al., 2016; Silva et al., 2010). However, unintended pregnancy have been related to an increase in anxiety and may have though influenced stress response and hence the immune system (Biaggi et al., 2016). Third, we have not corrected our results for other factors that can affect the immune system, like body mass index; smoking status; alcohol consumption; use of antidepressant and the duration of the current depressive episode (Joyce et al., 1992; Lopresti et al., 2014; Van Hunsel et al., 1996). Finally, we have not measured blood levels of OT precluding the evaluation of the real impact of autoAbs on the availability of this neuropeptide.

Our results complement previous findings regarding a lower level of anti-OT autoAbs IgG in patients with a major depressive episode (Garcia et al., 2011). However, differently from the previous study, we have not found a statistically significant correlation between depressive symptoms and the levels of total anti-OT autoAbs.

As for other psychiatric disorders, modifications in the levels of anti-neuropeptides autoAbs may influence the action of these neuropeptides. This phenomenon was previously demonstrated for ghrelin and melanocyte-stimulating hormone (MSH) in anorexia nervosa (Coquerel et al., 2012; Terashi et al., 2011) and neuropeptide Y (NPY) in major depression (Garcia et al., 2012).

Anti-OT autoAbs may play a role in stabilization of OT in plasma, decreasing the hydrolysis of this neuropeptide by plasmatic peptidases. In this sense, anti neuropeptide autoAbs may play either agonistic or antagonistic roles depending on their relative affinity, i.e. free fraction of autoAbs represent mainly low-affinity autoAbs which may potentiate peptide signaling by serving as peptide carriers while total autoAbs which are measured after dissociation of immune complexes may have increased affinity and peptide blocking properties (Garcia et al., 2011).

Depressed women are more likely than controls to display a deregulated pattern of peripheral oxytocin levels (Cyranowski et al., 2008; van Londen et al., 1997). Three studies demonstrated that lower levels of OT in plasma increase the risk of ATD development (Cox et al., 2015; Skrundz et al., 2011; Stuebe et al., 2013). The lower levels of free anti-OT IgG found in our study can, however, be associated with decrease in OT levels as observed in the previous studies.

Finally, researchers have reported an association between autoantibodies and altered behaviour in mice independent of pro-inflammatory cytokines and immune complex formation (Huerta et al., 2006; Iseme et al., 2014; Kowal et al., 2006). These study findings suggest that the occurrence of autoantibodies in depressed individuals may represent an independent pathological process contributing to the occurrence of depressive symptoms (Iseme et al., 2014).

5. Conclusion

Our study showed a significant association between lower levels of free anti-OT IgG autoAbs and ATD, suggesting that these autoAbs may have a functional role in stabilization of OT in plasma. Future research assessing the connection between plasma levels of OT and anti-OT autoAbs are warranted.

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Statement of interest

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The other authors have no conflicts to declare.

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5 DISCUSSÃO

As alterações neuropsiquiátricas em gestantes são atualmente um campo prolífico da Psiquiatria. O presente trabalho permitiu estudar diversos aspectos clínicos da DAN, e ainda um recorte imunológico até então inédito.

Os artigos 1 e 3 foram aqueles que avaliaram as características clínicas da coorte mais aprofundadamente. De maneira geral, a idade média das mulheres participantes foi de 28 anos; sendo a maior parte delas: não-caucasianas, de baixo nível sócio-econômico, casadas, com mais de 10 anos de educação, multíparas e com gestações não planejadas. Também foram elevadas as proporções de pacientes que haviam sofrido aborto prévio (1/4 da amostra) ou agressão por parte do parceiro (1/3 da amostra). Entretanto, apesar do resumos dos achados nos artigos 1 e 3 apontarem na mesma direção, cabe aqui a ressalva, assim como nos demais artigos, que as amostras de onde esses resultados foram obtidos não são exatamente as mesmas; e também não correspondem à totalidade da coorte, mas sim, um recorte dessa.

Ao analisar-se os dados de prevalência dos artigos 1 e 2, reforça-se a influência dos instrumentos de avaliação (CASTRO E COUTO *et al.*, 2015; CASTRO E COUTO *et al.*, 2016). Assim, tem-se que, também na nossa amostra, em ambos artigos, quando utilizadas as escalas de sintomas depressivos, sempre se obteve maiores taxas de prevalência de DAN do que quando utilizada a entrevista estruturada MINI (AMORIM, 2000). Nos dois artigos, as prevalências de DAN obtidas utilizando o MINI ficaram entre 10% – 17%, ou seja, taxas muito próximas dos valores internacionais (BENNETT *et al.*, 2004a; GAVIN *et al.*, 2005) e de estudo nacional, que usou o mesmo instrumento de avaliação (FARIAS *et al.,* 2013). Apontou, ainda, o artigo 1 que do segundo para o terceiro trimestres existiu um declínio das taxas de prevalência de DAN em todos os instrumentos (MINI, BDI, EPDS), mas sem que essa redução fosse estatisticamente significativa (BENNETT *et al.,* 2004b; GAVIN *et al.,* 2005).

O artigo 1 também procurou avaliar se os fatores de risco para DAN eram diferentes entre os trimestres, haja vista a profusão de fatores associados ao transtorno (PEREIRA; LOVISI, 2008; LANCASTER *et al.,* 2010). Não foi encontrada diferença estatística significativa entre os trimestres para os fatores de risco testados: idade, etnia, anos de estudo, estado civil, número de filhos, aborto prévio, agressão pelo companheiro, apoio no pré-natal, planejamento da gravidez, DM prévia e transtorno disfórico pré-menstrual. Entretanto, entre os fatores que se mostraram associados à DAN na nossa amostra - número de filhos, agressão pelo companheiro e DM prévia - apenas os dois últimos permaneceram como fatores de risco

independentes; sendo que DM prévia aumentava em 11 vezes o risco de DAN na nossa amostra. Mais uma vez, comprovou-se achados anteriores, que já davam a DM prévia como um dos principais fatores de risco para DAN (LANCASTER *et al.,* 2010).

Vale frisar que a proximidade dos resultados de prevalência e dos resultados de fatores de risco obtidos nos artigos 1 e 2 com os resultados encontrados em estudos internacionais parece apontar para a validade do constructo DAN (CASTRO E COUTO *et al.,* 2016).

Ao concluir que entre as três escalas de sintomas depressivos que validamos para uso durante a gestação - BDI, EPDS e HAM-D - a primeira era o instrumento com maior validade e acurácia das três para rastreio de DAN, o artigo 2 produziu resultado talvez inesperado. Por ser uma escala de sintomas depressivos que tem maior peso de sintomas somáticos, era de se esperar que o BDI fosse aquela que tivesse pior acurácia quando comparada com o MINI, uma vez que DAN amplificaria os sintomas somáticos presentes na gestação, como enjoo, vômito, desconforto físico, fadiga e cansaço, acarretando uma maior pontuação (KELLY; RUSSO; KATON, 2001). Tal possibilidade já havia sido evidenciada por Bennet *et al.* (2004b), que encontraram diferença entre as prevalências de DAN medidas por entrevistas estruturadas e BDI, mas não com EPDS. Entretanto, um estudo de pacientes com câncer também já havia destacado que queixas somáticas permanecem como importantes sintomas de DM mesmo em populações nas quais sintomas físicos não relacionados à DM são comuns. Daí, a proposta de ser melhor incluir do que excluir itens somáticos em instrumentos de rastreio depressivo (MITCHELL; LORD; SYMONDS, 2012).

Estudos prévios de DAN haviam encontrado 16 como ponto de corte para BDI (HOLCOMB *et al.,* 1996) e de 14/15 para EPDS (GIBSON *et al.,* 2009) e nenhum estudo até então havia validado HAM-D na DAN. O artigo 2, por sua vez, identificou como melhores pontos de corte para DAN os valores: EPDS $\geq$ 11, BDI $\geq$ 15 e HAM-D $\geq$ 9. Destaca-se, aqui, a importância da validação desses instrumentos para uma amostra brasileira, uma vez que o uso dos valores internacionais poderia levar a subdiagnósticos e, por sua vez, dificultar a obtenção de tratamento por essas gestantes.

Verificando o perfil de nossa amostra, onde aproximadamente 40% das participantes tinham algum transtorno mental atual durante a gestação (CASTRO E COUTO *et al.*, 2016) e tendo em mente que um dos maiores fatores de risco para suicídio é justamente essa presença de algum transtorno mental (BEAUTRAIS *et al.,* 1996), procurou-se estudar a suicidalidade dessas gestantes no artigo 3. Destacou-se, assim, a importância da avaliação do suicídio no exame neuropsiquiátrico da gravidez, condição essa frequentemente ignorada nessa fase do ciclo de vida das mulheres. Foi elevada a frequência de risco de suicídio (23.5%) e de

pacientes que haviam tentado suicídio alguma vez na vida (12.5%). Especial gravidade pôde ser constatada em 9.8% das participantes que apresentavam alto risco de suicídio.

A DAN não só exerce um grande impacto negativo sobre a qualidade de vida, como também foi a principal variável ligada ao risco de suicídio na gravidez, mesmo quando consideradas outras variáveis clínicas. Em análises bivariadas, a DAN elevou em aproximadamente seis vezes o risco de suicídio das gestantes, enquanto o transtorno bipolar (prévio) e qualquer transtorno ansioso (atual) elevaram esse risco em cinco e três vezes, respectivamente. Além do mais, BDI $\geq$ 15 e EPDS $\geq$ 11, valores estabelecidos para rastreio de DAN na nossa amostra (CASTRO E COUTO, *et al.,* 2015) também elevaram significativamente o risco de suicídio: seis e sete vezes, respectivamente. Numa análise multivariada, DAN e EPDS $\geq$ 11 permaneceram como fatores de risco independentes para suicídio. A importância desse achado também reside na facilidade de aplicação do EPDS, podendo auxiliar obstetras, outros clínicos e profissionais de saúde na identificação do risco de suicídio na gravidez.

Até o século passado, revisões sobre a DAN mostravam que ela era abordada nos estudos, principalmente, por dois grandes grupos: aqueles que pesquisavam os fatores de risco para depressão na gravidez e os que buscavam associar a depressão como fator de risco para certos desfechos obstétricos (ZUCCHI, 1999). Entretanto, nos últimos anos, esse panorama tem mudado com cada vez mais revisões abordando aspectos biológicos da DAN (OSBORNE; MONK, 2013; FIGUEIREDO *et al.*, 2015; DAMA *et al.*, 2016; LEFF-GELMAN *et al.,* 2016; MOURA; CANAVARRO; FIGUEIREDO-BRAGA, 2016; SERATI *et al.,* 2016).

Não foram encontrados achados significativos correlacionando DAN e IL-6 ou IL-1-β ou TNF-α. No entanto, encontramos associação significativa com autoanticorpos antiocitocina; marcador biológico até então inédito na literatura da DAN (artigo 4).

A proximidade da ocitocina (trabalho de parto e lactação) com a gravidez e o pós-parto provavelmente foi o que fez com que esse peptídeo fosse cada vez mais avaliado quanto a sua participação nos transtornos mentais do periparto (MOURA; CANAVARRO; FIGUEIREDO-BRAGA, 2016). Sendo que, na maioria desses estudos do sistema ocitocinérgico, o foco estava em alterações dos níveis bioquímicos e até genética; não imunológicas (MOURA; CANAVARRO; FIGUEIREDO-BRAGA, 2016; SERATI *et al.,* 2016). Entretanto, um estudo prévio de autoanticorpos contra ocitocina já havia evidenciado associação desses com depressão maior (GARCIA *et al.,* 2011). Segundo esses pesquisadores, pessoas que tinham depressão maior moderada tinham níveis reduzidos de autoanticorpos

totais antiocitocina Imunoglobulina (Ig)-G em comparação com quem tinha depressão maior leve ou não tinha depressão. Daí, a proposta do artigo 4, de avaliar a possível influência de autoanticorpos antiocitocina na DAN.

No nosso estudo, não foi encontrado associação entre DAN e autoanticorpos totais contra ocitocina. Entretanto, verificou-se que existe uma associação positiva com baixos níveis de autoanticorpos livres antiocitocina Ig-G e DAN. Também baixos níveis de autoanticorpos livres antiocitocina Ig-M foram correlacionados a depressão maior prévia à gravidez atual.

Os autoanticorpos livres são em, sua maioria, autoanticorpos com baixa afinidade que podem potencializar a sinalização dos peptídeos ao agir como carreadores. Daí, a importância de considerar-se que esses autoanticorpos antiocitocina poderiam, portanto, ser os responsáveis por ativar/potencializar mecanismos/redes imunoneuroregulatórias que ocasionariam DAN em pessoas com vulnerabilidade. Entre os exemplos de mecanismos imunoreguláveis possíveis, tem-se a alteração do eixo HPA (GELMAN *et al.,* 2015; LEFF-GELMAN *et al.,* 2016), que frequentemente é associada à depressão maior.

Os níveis reduzidos de autoanticorpos livres antiocitocina IgG podem ainda ser associados à redução da ocitocina na DAN evidenciada em estudos prévios (MOURA; CANAVARRO; FIGUEIREDO-BRAGA, 2016). O que destaca uma das principais limitações desse artigo 4 que foi não ter dosado a ocitocina. Tal fato impediu de se ter uma noção se essa alteração de autoanticorpos livres antiocitocina IgG poderia influenciar nos níveis plasmáticos do peptídeo.

Esse aspecto imunológico da DAN, após reprodução e melhor elucidação dos mecanismos, deverá entrar para o rol de biomarcadores para DAN (SERATI *et al.,* 2016).

6 CONCLUSÃO

O presente estudo corrobora a diversidade psicopatológica encontrada na DAN. A análise da DAN por meio de instrumentos validados e padronizados, como o BDI, HAM-D e o EPDS, permitem a melhor descrição e o estudo desse transtorno. Sobretudo, a utilização dos resultados aqui descritos pode facilitar o diagnóstico da DAN em sua fase inicial, podendo minimizar a morbidade, o impacto na qualidade de vida e a mortalidade das pessoas com o transtorno. Estes achados são originais e podem contribuir no delineamento de pesquisas futuras e também para aprimorar o diagnóstico e tratamento da DAN.

Por fim, o achado desses autoanticorpos também permite especular que terapias imunológicas como vacinas possam ser efetivas na depressão e mereceriam melhor exploração de pesquisas futuras (ROOK; RAISON; LOWRY, 2012).

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APÊNDICE 1 – ENTREVISTA DO PROJETO DE DEPRESSÃO PERIPARTO

DADOS DE IDENTIFICAÇÃO DA PACIENTE – Número do Prontuário:			
Nome:			Data de nascimento:
Anos de estudo:	Escolaridade: ☐0 – fundamental ☐ 1 – médio incompl. ☐ 2 – médio compl. ☐3 - superior incompl. ☐4 – superior ☐5 – pós-graduada		
Ocupação atual: ☐0 – trabalhando 1 –☐desempregada 2 – aposentada 3 –afastada☐ 4 – do lar ☐5- estudante ☐			Profissão:
Estado civil: ☐0 – solteira ☐1 – casada 2 ☐viúva 3 –☐separada 4 – d☐orciada 5 - am☐iada			
Número de filhos:	Etnia: ☐0– branca ☐1–negra 2☐amarela 3–☐parda/mulata 999 -☐utra		
Anos de estudo do parceiro:	Escolaridade do parceiro: ☐0– fundamental ☐1 – médio incompl. ☐ 2 – médio completo ☐3 – superior incompl. ☐4 – superior 5 –☐pós-graduado		
Classificação socioeconômica: 0☐A1 1 ☐A2 2 –☐B1 3 –☐B2 4 – C☐ 5 – C☐ 6 – D ☐7 – E ☐			
Informações de contato:			
Rua:		N°:	Compl:
Bairro:	Cidade:		Estado:
Telefone residencial:	Celular:		Trabalho:

DADOS DO PRIMEIRO ATENDIMENTO PRÉ-NATAL		
Data:	Período da gestação (semanas):	
Fargestron:	Cage:	TCI:
BDI:	Hamilton:	

Entrevista:

1 - Você trabalha fora de casa?

☐ Sim Quantos turnos? _____

☐ Não

2 – A sua gestação foi planejada?

☐ Sim Você conhece métodos contraceptivos? _____

☐ Não Quais?_____

3 – Você tem recebido apoio de alguém durante o pré-natal?

☐ Sim De quem? _____

☐ Não

4 – Em algum momento você pensou em não prosseguir com a gestação?

☐ Sim

☐ Não

5 – Você já passou por um aborto anteriormente?

☐ Sim Foi espontâneo? _____

☐ Não Quantos abortos? _____

6 – Você e o pai da criança estão juntos?

☐ Sim

☐ Não

7 – Quanto tempo tem o relacionamento de vocês? _____anos_____meses

8 – No relacionamento de vocês existem desentendimentos e brigas frequentes:

☐ Sim Com qual a frequência elas ocorrem? _____

☐ Não

9 – Você alguma vez foi verbalmente ofendida por seu companheiro?
☐ Sim Com qual frequência esses episódios acontecem? _____
☐ Não

10 – Alguma vez você foi agredida fisicamente pelo seu companheiro?
☐ Sim Com qual frequência esses episódios acontecem? _____
☐ Não

11 – Como você está com relação ao seu relacionamento?
☐ Completamente satisfeita
☐ Satisfeita
☐ Nem satisfeita, nem insatisfeita
☐ Insatisfeita
☐ Completamente insatisfeita

12 – Em algum momento da sua vida você apresentou quadro de depressão?
☐ Sim Quando? _____
☐ Não Foi diagnosticada por médico? _____

13 – Em algum momento de sua vida você desenvolveu algum outro quadro psiquiátrico?
☐ Sim Qual? _____
☐ Não

14 – Você já apresentou depressão pós-parto em gestações anteriores?
☐ Sim Quando / Quantas vezes? _____
☐ Não

15 – Durante os seus períodos menstruais, você apresentava algum sintoma depressivo ou ansioso?
☐ Sim Depressivo ou Ansioso?_____
☐ Não

16 – Alguém da sua família possui algum quadro psiquiátrico?
☐ Sim Quem? Qual quadro?_____
☐ Não

17 – A sua gestação é considerada de risco (pressão alta, diabetes, hipotiroidismo, algum outro problema de saúde?)?
☐ Sim Qual foi a complicação? _____
☐ Não

18 – Fez uso de alguma medicação durante o pré-natal?
☐ Sim Quais medicamentos utilizou? _____
☐ Não

19 – Qual a previsão para o parto?
☐ Parto normal
☐ Cesariana

20 – Alguém vai te acompanhar durante o parto?
☐ Sim Quem? _____
☐ Não

21 – Você tem religião? _____ Qual? _____

22 – Onde pretende realizar o acompanhamento pediátrico do bebê?

ANEXO 1 – PARECER DO COEP

Universidade Federal de Minas Gerais
Comitê de Ética em Pesquisa da UFMG - COEP

Parecer nº. ETIC 227/05

Interesse: Prof. Marco Aurélio Romano Silva
ICB - UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP, aprovou no dia 23 de novembro de 2005, o projeto de pesquisa intitulado « **Investigação clínica e molecular da depressão pós-parto** » bem como o Termo de Consentimento Livre e Esclarecido do referido projeto.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Dra. Maria Elena de Lima Perez Garcia
Presidente do COEP/UFMG

Av. Presidente Antonio Carlos, 6627, Prédio da Reitoria, 7º andar sala 7018 - 31.270-901 - BH - MG
(31) 3499-4592 - FAX: (31) 3499-4027 - coep@prpq.ufmg.br

ANEXO 2 – DOCUMENTAÇÃO DA SUBMISSÃO DO ARTIGO 4

Manuscript Details

Manuscript number	PNP_2016_194
Title	Autoantibodies reacting with oxytocin is associated with antenatal depression.
Article type	Research Paper

Abstract

Background. Abnormal oxytocin (OT) signaling may contribute to the physiopathology of antenatal depression (ATD). OT-reactive autoantibodies (autoAbs) may interfere with the plasmatic levels of OT and have been associated with major depressive disorder. We hypothesize that, as for major depressive disorder, depressive symptoms and ATD correlate with OT autoAbs levels. In the present study, we compared anti-OT autoAbs levels in pregnant women with and without ATD. Methods. This is a cross-sectional study with a sample composed of pregnant women with and without antenatal depression. Depression was assessed with MINI diagnostic interview, Edinburgh Postnatal Depression Scale (EPDS), the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS). Plasma levels of total and free OT-reactive IgG and IgM autoAbs were measured by ELISA and analyzed with relation to the depression severity and diagnosis. Results. The mean level of free anti-OT IgG autoAbs was 10% lower in women with a current depressive episode diagnosis (p=0.041). Free anti-OT IgM autoAbs levels were 20,3% lower in women with a previous depressive episode diagnosis (p=0.05). Conclusion. These data show that changes in levels of OT-reactive autoAbs can be associated with the altered mood in subjects with ATD.

Keywords	Antenatal depression; mood disorders; oxytocin; neuropeptides;
Taxonomy	Adaptive Immunity, Clinical Neuroimmunology, Psychoneuroimmunology, Antenatal Depression
Corresponding Author	Frederico Garcia
Corresponding Author's Institution	Universidade Federal de Minas Gerais
Order of Authors	Tiago Couto, Mayra Yara Brancaglion, Raíssa Lima Gonçalves Pereira, Sordaini Caligiorni, Maila de Castro, Humberto Correa, Frederico Garcia
Suggested reviewers	Serguei Fetissov, Evelyn Kiive, Florence Thibaut, Tomas Hökfelt, Elisabeth Cox

Submission Files Included in this PDF

File Name [File Type]

Copy-of-Oficio 64-2016 - Cover Letter.pdf [Cover Letter]

Oficio 65-2016 - Ethics Statment.pdf [Ethical Statement]

Autoantibodies reacting with oxytocin and antenatal depression Submited.docx [Manuscript File]

Figure 1 - AutoAbs in antenatal drepression.tiff [Figure]

Highlights 08-11-2016.docx [Highlights]

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O Profissional

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ANEXO 3 – ATA DA DEFESA DA TESE

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA MOLECULAR

ATA DA DEFESA DE TESE DO ALUNO

TIAGO CASTRO E COUTO

Realizou-se, no dia 02 de dezembro de 2016, às 11:00 horas, sala 526, 5º andar da Faculdade de Medicina, da Universidade Federal de Minas Gerais, a defesa de tese, intitulada *Depressão Antenatal: análise clínica e imunológica*, apresentada por TIAGO CASTRO E COUTO, número de registro 2014706287, graduado no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em MEDICINA MOLECULAR, à seguinte Comissão Examinadora: Prof(a). Humberto Correa da Silva Filho - Orientador (UFMG), Prof(a). Frederico Duarte Garcia - Coorientador (UFMG), Prof(a). Henrique Vitor Leite (UFMG), Prof(a). Rodrigo Nicolato (UFMG), Prof(a). Rodrigo Grassi de Oliveira (UFRGS), Prof(a). Joel Renó Junior (USP).

A Comissão considerou a tese:

(X) Aprovada

( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 02 de dezembro de 2016.

Prof(a). Humberto Correa da Silva Filho (Doutor)

Prof(a). Frederico Duarte Garcia (Doutor)

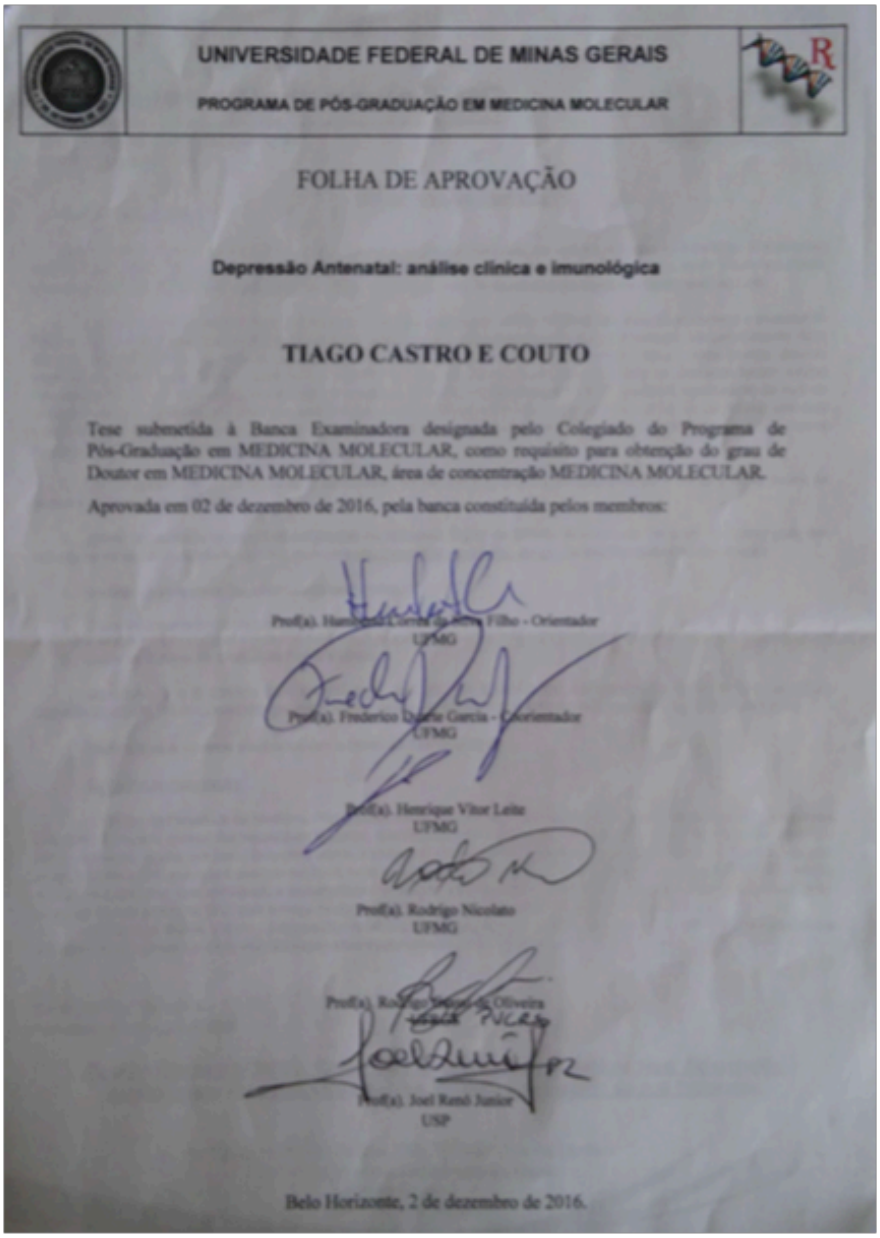
Prof(a). Henrique Vitor Leite (Doutor)

Prof(a). Rodrigo Nicolato (Doutor)

Prof(a). Rodrigo Grassi de Oliveira (Doutor)

Prof(a). Joel Renó Junior (Doutor)

ANEXO 4 – DECLARAÇÃO DE APROVAÇÃO



UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA MOLECULAR

FOLHA DE APROVAÇÃO

Depressão Antenatal: análise clínica e imunológica

TIAGO CASTRO E COUTO

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em MEDICINA MOLECULAR, como requisito para obtenção do grau de Doutor em MEDICINA MOLECULAR, área de concentração MEDICINA MOLECULAR.

Aprovada em 02 de dezembro de 2016, pela banca constituída pelos membros:

Prof(a). Humberto Correa da Mota Filho - Orientador
UFMG

Prof(a). Frederico Duarte Garcia - Coorientador
UFMG

Prof(a). Henrique Vitor Leite
UFMG

Prof(a). Rodrigo Nicolato
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Prof(a). Rodrigo Machado Oliveira
UFMG

Prof(a). Joel Renó Junior
USP

Belo Horizonte, 2 de dezembro de 2016.