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VÂNIA MEIRA E SIQUEIRA CAMPOS

Vínculo parental, saúde mental e catastrofização em mulheres com dor pélvica crônica

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UNIVERSIDADE FEDERAL DE GOIÁS
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VÂNIA MEIRA E SIQUEIRA CAMPOS

Vínculo parental, saúde mental e catastrofização em mulheres com dor pélvica crônica

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde, da Faculdade de Medicina, da Universidade Federal de Goiás (UFG), como requisito para obtenção do título de Doutor em Ciências da Saúde
Área de concentração: Dinâmica do processo saúde-doença

Orientador: Prof. Dr. Délio Marques Conde
Coorientador: Prof. Dr. José Miguel de Deus

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UNIVERSIDADE FEDERAL DE GOIÁS

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ATA DE DEFESA DE TESE

Ata nº **40/2022** da sessão de Defesa de Tese de **Vânia Meira e Siqueira Campos,** que confere o título de Doutora em **Ciências da Saúde**, na área de concentração em **Dinâmica do Processo Saúde-Doença.**

Aos **trinta dias do mês de novembro de dois mil e vinte e dois,** a partir das **08:00h**, **na Faculdade de Medicina da UFG**, realizou-se a sessão pública de Defesa de Tese intitulada **"VÍNCULO PARENTAL, SAÚDE MENTAL E CATASTROFIZAÇÃO EM MULHERES COM DOR PÉLVICA CRÔNICA"**. Os trabalhos foram instalados pelo Orientador, Professor Doutor **Délio Marques Conde (FM/UFG)** com a participação dos demais membros da Banca Examinadora: Professora Doutora **Keila Correia de Alcântara (FF/UFG)**, membro titular externo; Professora Doutora **Marília Oliveira Ribeiro (SES)**, membro titular externo, Professora Doutora **Marta Curado Carvalho Franco Finotti (FM/UFG),** membro titular externo; Professor Doutor **Nílzio Antonio da Silva**, membro titular interno. Durante a arguição os membros da banca **fizeram** sugestão de alteração do título do trabalho. A Banca Examinadora reuniu-se em sessão secreta a fim de concluir o julgamento da Tese, tendo sido a candidata **aprovada** pelos seus membros. Proclamados os resultados pelo Professor Doutor **Délio Marques Conde**, Presidente da Banca Examinadora, foram encerrados os trabalhos e, para constar, lavrou-se a presente ata que é assinada pelos Membros da Banca Examinadora, aos **trinta dias do mês de novembro de dois mil e vinte e dois.**

TÍTULO SUGERIDO PELA BANCA

INFLUÊNCIA DO VÍNCULO PARENTAL NA SAÚDE MENTAL E NA CATASTROFIZAÇÃO EM MULHERES COM DOR PÉLVICA CRÔNICA

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Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Goiás

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DATA: 30/11/2022

DEDICATÓRIA

Dedico esta tese...

À minha filha muito amada MARIANA SIQUEIRA CAMPOS DE DEUS, que concordou em participar comigo da grande aventura de sermos mãe e filha nesta existência. Quisera eu, minha querida, ter, à sua chegada, o conhecimento que adquiri ao estudar e pesquisar sobre vínculos parentais. Talvez eu tivesse sido capaz de proporcionar-lhe uma parentalidade ótima, como lhe era direito. Resta-me o consolo de que este material possa ser-lhe útil, quando for a sua vez de ocupar o papel de mãe.

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“Somente quando a fruta madura cai à terra,
libera aquilo que serve ao futuro.”
(Bert Hellinger)

ESTRUTURA DA TESE

Esta tese foi elaborada em formato de artigo, de acordo com as normas do Programa de Pós-graduação em Ciências da Saúde da Universidade Federal de Goiás. Inclui capa, contracapa com catalogação bibliográfica, página com relação dos membros da banca examinadora, dedicatória, agradecimentos, sumário, relação de tabelas e figuras, relação símbolos, siglas e abreviaturas, resumo, *abstract*, introdução, objetivos, metodologia, um artigo de revisão narrativa e um artigo original escritos em língua inglesa. Os dois artigos já foram publicados. A análise estatística, os resultados e a discussão foram apresentados no artigo original. A tese foi finalizada com as conclusões, referências bibliográficas, apêndices e anexos.

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ARTIGO 2

SÍMBOLOS, SIGLAS E ABREVIATURAS

ACE	*Adverse Childhood Events*
ACOG	*American College of Obstetricians and Gynecologists*
BMI	*Body Mass Index*
BPS	*Bladder Pain Syndrome*
CA-125	*Cancer Antigen 125*
CDC	*Centers for Disease Control and Prevention*
CI	*Confidence interval*
CNS	*Central Nervous System*
COC	*Combined Oral Contraceptive*
COPCs	*Chronic Overlapping Pain Conditions*
CPP	*Chronic Pelvic Pain*
CS	*Central Sensitization*
CSI	*Central Sensitization Inventory*
CSS	*Central Sensitivity Syndrome*
DSM-IV	*Manual Diagnostic and Statistical of Mental Disorders Fourth Edition*
DPC	Dor Pélvica Crônica
DRGS	*Dorsal Root Ganglion Stimulation*
EBSERH	Empresa Brasileira de Serviços Hospitalares
EFIC	*European Federation of IASP Chapters*
EUA	Estados Unidos da América
GAD-7	*Generalized Anxiety Disorder-7*
GnRH	*Gonadotropin-Releasing Hormone*
HAD-A	*Hospital Anxiety and Depression – Anxiety*
HAD-D	*Hospital Anxiety and Depression - Depression*
HADS	*Hospital Anxiety and Depression Scale*
HC	Hospital das Clínicas
HPA	*Hypothalamic-Pituitary-Adrenal*
IASP	*International Association for the Study of Pain*
IBS	*Irritable Bowel Syndrome*
IC	Intervalo de confiança
ICD-10	*International Classification of Diseases, 10th revision*

IMC	Índice de Massa Corporal
MRI	*Magnetic Resonance Imaging*
NHI	*National Institutes of Health*
NSAIDs	*Non-steroidal Anti-inflammatory Drugs*
OR	*Odds Ratio*
p-value	*Probability value*
p-valor	Valor de probabilidade
PBI	*Parental Bonding Instrument*
PCS	*Pain Catastrophizing Scale*
PHQ-9	*Patient Health Questionnaire-9*
PNE	*Pain Neuroscience Education*
PP	*Perineal Pain*
PFP	*Pelvic Floor Physiotherapy*
PSCEBSM	*Pain mechanisms, Somatic, Cognitive, Emotional, Behavioral, Motivation*
QST	*Quantitative Sensory Testing*
r	Coeficiente de correlação de Spearman *(Spearman's correlation coefficient)*
RCT	*Randomized Clinical Trials*
RP	Razão de probabilidade
SciELO	*Scientific Electronic Library Online*
SCS	*Spinal Cord Stimulation*
SD	*Standard Deviation*
SPSS	*Statistical Package for the Social Science*
SUS	Sistema Único de Saúde
THC	*Tetrahydrocannabinol*
TRAILS	*Tracking Adolescents' Individual Lives Survey*
TVUS	*Transvaginal Ultrasonography*
UFG	Universidade Federal de Goiás
USA	*United States of America*
VAS	*Visual Analogue Scale*
vs	*Versus*
WHO	World *Health Organization*

RESUMO

Introdução: A experiência de dor e suas estratégias de enfrentamento, transtornos mentais, como ansiedade e depressão, e traços mal-adaptativos de personalidade, como a catastrofização, têm sido associados a estilos parentais na infância. Por sua vez, catastrofização tem sido considerado um fator preditivo importante dos desfechos de diferentes tipos de dor, incluindo a dor pélvica crônica (DPC) em mulheres, que é uma condição de saúde comum e de difícil tratamento. **Objetivos:** Realizar uma revisão narrativa da literatura disponível sobre DPC em mulheres. Verificar a frequência de vínculos parentais em mulheres com e sem DPC, avaliar a associação entre estilo de vínculo parental e DPC em mulheres e examinar a relação entre catastrofização, intensidade da dor, ansiedade, depressão e estilo de vínculo parental em mulheres com DPC. **Métodos:** Conduziu-se uma revisão narrativa sobre DPC em mulheres, com data limite até 15 de outubro de 2021, nos seguintes bancos de dados: Medline, Embase e SciELO. Foram utilizados os seguintes termos: *chronic pelvic pain, central sensitization, hyperalgesia, chronic pain, neuromodulation, women, somatic pain, visceral pain, nociplastic pain and neuropathic pain*. Realizou-se, também, um estudo de caso-controle, de maio de 2018 a agosto de 2021, envolvendo 123 mulheres com DPC e 123 mulheres sem DPC. Foram investigadas características sociodemográficas, clínicas e comportamentais. O *Parental Bonding Instrument* foi usado para avaliar os estilos de vinculação parental. Para avaliação de ansiedade e de depressão, foram usados *Generalized Anxiety Disorder-7* e *9-item Patient Health Questionnaire*, respectivamente. No grupo com DPC, investigou-se, também, a intensidade da dor através da escala numérica de classificação, e a catastrofização, através da *Pain Catastrophizing Scale*. Os testes Mann-Whitney U e

Qui-quadrado foram usados para comparar as características entre os grupos. Regressão logística múltipla e *odds ratio* (OR), com respectivos intervalos de confiança (IC) de 95%, foram usados para verificar a associação entre vinculação parental e DPC. A correlação entre catastrofização, intensidade da dor, tempo de dor, ansiedade, depressão e vinculação parental em mulheres com DPC foi estimada por meio do coeficiente de correlação de Spearman (r). **Resultados:** Em relação ao grupo controle, o grupo com DPC apresentou maior frequência de baixo cuidado da mãe (60,7% *vs* 45,2%; p=0,026), ansiedade (79,7% *vs* 56,9%; p<0,001), depressão (73,2% *vs* 56,1%; p=0,008), violência física (31,7% *vs* 14,6%; p=0,003), dificuldade de relacionamento (39,8% *vs* 19,5%; p=0,001) e cirurgia abdominal/pélvica (78,0% *vs* 63,4%; p=0,017). Em análise ajustada por possíveis variáveis confundidoras, não houve associação independente entre estilos parentais e DPC em mulheres. No grupo com DPC, houve uma frequência de 77,2% de catastrofização. Identificou-se uma correlação positiva entre catastrofização e intensidade da dor (r=0,342; p<0,001), ansiedade (r=0,271; p=0,002), depressão (r=0,272; p=0,002) e superproteção materna (r=0,185; p=0,046). Entre as participantes com DPC, observou-se uma correlação negativa entre ansiedade e cuidado materno (r=-0,184; p=0,047), ansiedade e cuidado paterno (r=-0,286; p=0,006), depressão e cuidado materno (r=-0,219; p=0,018), depressão e cuidado paterno (r=-0,234; p=0,026). **Conclusões:** DPC é uma condição de saúde desafiadora, nem sempre associada a uma causa evidente. A investigação e o tratamento de comorbidades são recomendados. A identificação clínica de fenótipo de sensibilização central pode nortear o manejo de mulheres com DPC, que deve ser interdisciplinar e envolver aspectos biopsicossociais. Baixo cuidado materno foi mais frequente nas mulheres com dor que nas sem DPC. Não houve associação

independente entre estilo de vínculo parental e DPC. Catastrofização foi muito frequente nas mulheres com DPC e relacionou-se fraca e positivamente com superproteção materna, intensidade da dor, ansiedade e depressão. Houve correlação negativa, porém fraca, entre cuidado materno e ansiedade, cuidado materno e depressão, cuidado paterno e ansiedade, cuidado paterno e depressão nas mulheres com DPC. Nossos achados sugerem estudos mais aprofundados sobre o papel das famílias, particularmente de pai e de mãe, no desenvolvimento emocional e das estratégias de enfrentamento da dor de mulheres com DPC. Também indicam a necessidade de uma abordagem personalizada de mulheres com DPC, buscando melhores resultados terapêuticos.

Palavras-chave: dor pélvica crônica; estilos parentais; saúde da mulher; ansiedade; depressão; habilidades de enfrentamento; regulação emocional

ABSTRACT

Introduction: The experience of pain and its coping strategies, mental disorders such as anxiety and depression, and maladaptive personality traits such as catastrophizing have been associated with parenting styles in childhood. In turn, catastrophizing has been considered an important predictor of outcomes for different types of pain, including chronic pelvic pain (CPP) in women, which is a common and difficult-to-treat health condition. **Aims:** To perform a narrative review of the available literature on CPP in women. To identify the frequency of parental styles in women with and without CPP, to evaluate the association between parenting style and CPP in women, and to investigate the association between catastrophizing, pain intensity, anxiety, depression, and parenting style in women with CPP. **Methods:** A search was conducted of the Medline, Embase and SciELO (Scientific Electronic Library Online) databases up to the cut-off date of October 15, 2021. The following terms were used: chronic pelvic pain, central sensitization, hyperalgesia, chronic pain, neuromodulation, women, somatic pain, visceral pain, nociplastic pain and neuropathic pain. A case-control study was also conducted between May 2018 and August 2021 with 123 women with CPP and 123 pain-free controls. Sociodemographic, clinical, and behavioral data were investigated. Parental Bonding Instrument was used to assess parenting styles. Generalized Anxiety Disorder-7 e 9-item Patient Health Questionnaire were used to evaluate anxiety and depression, respectively. Pain intensity and catastrophizing were investigated in the CPP group using, respectively, a 10-cm numerical pain rating scale and the Pain Catastrophizing Scale. Yates's chi-square test and the Mann-Whitney test were used to compare characteristics between the groups. Multiple logistic regression analyses were

conducted to determine possible associations between each parenting style and CPP in women, and the odds ratios (OR) and their respective 95% confidence intervals (95%CI) were calculated. Spearman's correlation coefficient (r) was used to verify possible correlations between catastrophizing, pain intensity, the duration of pain, anxiety, depression, and parental bonding style (maternal and paternal care and overprotection) in the group of women with CPP. **Results:** A higher frequency of low maternal care (60.7% versus 45.2%; p=0.026), anxiety (79.7% versus 56.9%; p<0.001), depression (73.2% versus 56.1%; p=0.008), physical violence (31.7% versus 14.6%; *p*=0.003), relationship difficulties (39.8% versus 19.5%; p=0.001), and abdominal/pelvic surgery (78.0% versus 63.4%; p=0.017) were found in the CPP group compared to the control group. The domains of parental bonding were not independently associated with CPP in women. Catastrophizing was identified in 77.2% of women in the CPP group. A positive correlation was found between catastrophizing and pain intensity (r=0.342; p<0.001), anxiety (r=0.271; p=0.002), depression (r=0.272; p=0.002), and maternal overprotection (r=0.185; p=0.046). A negative correlation was found between anxiety and maternal (r=-0.184; p=0.047) and paternal (r=-0.286; p=0.006) care and between depression and maternal (r=-0.219; p=0.018) and paternal (r=-0.234; p=0.026) care in the CPP group. **Conclusions:** CPP is an challenger condition that may not be associated with an obvious cause. A timely scheme of investigation and treatment of associated comorbidities is recommended. The clinical identification of a central sensitization phenotype can guide the management of women with CPP, which must be interdisciplinary and involve biopsychosocial aspects. Low maternal care was more common in women with CPP compared to the pain-free controls, with no independent association between parental bonding and CPP. Catastrophizing was very common

and positively, but weakly, correlated with the intensity of pain, anxiety, depression, and maternal overprotection in the CPP group. Maternal and paternal care was negatively and weakly correlated with anxiety and depression in women with CPP. Our findings suggest further studies on the role of families, particularly fathers and mothers, in the emotional development and pain coping strategies of women with CPP. They also indicate the need for a personalized approach to women with CPP, seeking better therapeutic outcomes.

Keywords: chronic pelvic pain; parenting styles; women's health; anxiety, depression; coping skills; emotional regulation.

1 INTRODUÇÃO

1.1 Dor

1.1.1 Conceito

A *International Association for the Study of Pain* (IASP) define dor como “uma experiência sensorial e emocional desagradável, associada com, ou semelhante àquela associada a, um dano tecidual real ou em potencial” (IASP, 27/04/22). Destaca, ainda, os seguintes pontos:

> A dor é sempre uma experiência pessoal, que é influenciada em graus variados por fatores biológicos, psicológicos e sociais.
> Dor e nocicepção são fenômenos diferentes. A dor não pode ser inferida apenas pela atividade nos neurônios sensoriais.
> Através de suas experiências de vida, os indivíduos aprendem o conceito de dor.
> O relato de uma pessoa de uma experiência como dor deve ser respeitado.
> Embora a dor geralmente tenha um papel adaptativo, ela pode ter efeitos adversos na função e no bem-estar social e psicológico.
> A descrição verbal é apenas um dos vários comportamentos para expressar dor; a incapacidade de se comunicar não nega a possibilidade de um animal humano ou não humano sentir dor (IASP, 27/04/22).

Apesar de as definições variarem, a dor é habitualmente classificada em aguda e crônica. A *European Federation of IASP Chapters* (EFIC) sugere que a dor aguda é um fenômeno natural e, até certo ponto, desejável para a sobrevivência do ser humano, seja afastando-o reflexamente de situações de risco, seja avisando-o de que algo não está bem e que deve ser investigado/tratado (IASP, 2022). Considerada como sintoma de uma doença ou de uma lesão traumática ou cirúrgica, a dor aguda é, para alguns, aquela de resolução inferior a 30 dias e, para outros, inferior a três ou seis meses (EFIC, 2022). Por sua vez, as dores crônicas são aquelas com duração maior do que

três ou seis meses, geralmente multifatoriais, que se estendem além do período esperado de cura de uma lesão, podendo mesmo existir na ausência de qualquer lesão, e que podem envolver aspectos psicossociais complexos (EFIC 2022).

Por considerar que ainda há uma relativa negligência governamental no trato da dor, a IASP tem promovido a campanha global “o alívio da dor deveria ser um direito humano” (IASP, 2022). Esta campanha vem ao encontro do que aquela associação declarou em 2004: “a falha no tratamento da dor é vista em todo o mundo como medicina ruim, prática antiética e uma revogação de um direito humano fundamental” (EFIC, 2022).

1.1.2 Impacto econômico

Com reconhecido impacto negativo para seus portadores, para a sociedade, para o sistema de saúde e para a economia como um todo, a dor é uma questão de saúde pública em todo o mundo (EFIC, 2022).

Em 2010, o *National Institute of Health* (NIH) estimou entre 560 e 635 bilhões de dólares o custo anual com dores persistentes em adultos nos Estados Unidos da América (EUA). Este valor seria maior do que os gastos, naquele país, com doenças cardiovasculares, cânceres, traumas/envenenamentos, doenças respiratórias, doenças gastrointestinais e doenças endócrinas/metabólicas/nutricionais, isoladamente (GASKIN & RICHARD, 2012). Por sua vez, em 2016, o custo anual da dor crônica foi superior a 441 bilhões de euros para a União Europeia (SIP, 2017). Vale salientar que estes valores continuam a aumentar (SONG et al., 2021).

Esta sobrecarga financeira envolve fatores associados direta ou indiretamente à dor, como absenteísmo, diminuição de produtividade, aposentadoria precoce, uso excessivo de recursos dos sistemas de saúde, gasto com medicações, entre outros (HENSCHKE; KAMPER; MAHER, 2015).

1.1.3 Epidemiologia

A análise dos diversos estudos epidemiológicos sobre a dor permite verificar a inexistência de uma padronização das variáveis investigadas. Dentre as diferenças observadas nas pesquisas, citam-se os dados sociodemográficos da população avaliada, as características do sintoma álgico, bem como os fatores a ele associados. Isto acaba resultando em estimativas não tão precisas sobre a dor (HENSCHKE; KAMPER; MAHER, 2015).

Cerca de um quarto (24,8%) das pessoas com idade superior ou igual a 18 anos nos Estados Unidos (MURPHY et al., 2017), e um quinto (20,3%) na União Europeia (LANGLEY, 2011), queixam-se de algum tipo de dor. Por sua vez, no Brasil, em estudo de base populacional com pessoas entre 18 e 65 anos, Zimmermann et al. (2017) identificaram 33,8% e 3,1% de dor moderada e grave, respectivamente.

A dor aguda é de ocorrência quase universal (BALIKI & APKARIAN, 2015). Por sua vez, a prevalência global de dores crônicas em adultos também é alta e independe das condições socioeconômicas da população avaliada. Variações de 13% a 49,4% em países de baixa e média renda (JACKSON et al., 2016), e de 35% a 51,3% no Reino Unido (FAYAZ et al., 2016), foram identificadas. Nos EUA, dados apontam para a presença de dor crônica em uma a cada cinco pessoas (21,9%) com idade superior a 18 anos (MILLER & CANO, 2009); em pacientes da atenção básica de saúde, esta frequência mais do que dobra (45,1%) (ARNOW et al., 2006). No Brasil, foi descrita uma prevalência de 45,59% de dores crônicas em adolescentes e adultos em geral (AGUIAR et al., 2021), e de 61,4% em adultos profissionalmente ativos (KRELING; CRUZ; PIMENTA, 2006).

A frequência, a intensidade e a duração da dor costumam ser maiores nas mulheres do que nos homens (EFIC, 2022; HENSCHKE; KAMPER; MAHER, 2015; LANGLEY, 2011). Além disso, as mulheres são mais predispostas a síndromes dolorosas regionais complexas e a dores crônicas (AGUIAR et al., 2021; KRELING; CRUZ; PIMENTA, 2006; MURPHY et al., 2017; SOUZA et al., 2017). Entre as dores crônicas mais frequentes e não relacionadas ao câncer, constam a lombalgia, dores neuropáticas, artralgias, fibromialgia, cefaleias, dores associadas a cirurgias ou a traumas e dores generalizadas (EFIC, 2022; GOREN et al., 2012; JACKSON et al., 2016; KRELING; CRUZ, PIMENTA, 2006; LANGLEY, 2011; MURPHY et al., 2017).

Entre as mulheres, a dor pélvica crônica (DPC) merece destaque por ser uma queixa globalmente frequente em qualquer fase da vida adulta (AYORINDE et al., 2017; LOU et al., 2017), principalmente na idade reprodutiva (AYORINDE et al., 2017; COELHO et al., 2014). O Colégio Americano de Obstetras e Ginecologistas (ACOG) define a DPC como sendo

> “a presença de dor percebida como originária de órgãos/estruturas pélvicas, tipicamente com duração maior que 6 meses. Está frequentemente associada a consequências negativas do ponto de vista cognitivo, comportamental, sexual e emocional, bem como a sintomas sugestivos de disfunção do trato urinário inferior, sexual, intestinal, assoalho pélvico, miofascial ou ginecológico” (ACOG, 2020).

A prevalência mundial de DPC em mulheres varia entre 2% e 27%, sendo próxima de 4% nos países desenvolvidos ((AHANGARI, 2014; LATTHE et al., 2006). No Brasil, a frequência de DPC em mulheres foi reportada em 19% (COELHO et al., 2014).

A etiologia da DPC não é clara e parece ser multifatorial, sendo que 60% das mulheres com esta condição de saúde apresentam afecções ginecológicas e não

ginecológicas superpostas (ACOG, 2020). Além disso, nenhuma doença pélvica é identificada em aproximadamente um terço das pacientes (WARREN; MOROZOV; HOWARD, 2011). Vale salientar que, mesmo após o diagnóstico etiológico, quando possível, e o tratamento adequado, as taxas de recorrência dos sintomas podem ser superiores a um terço (ZONDERVAN et al., 2001).

1.1.4 Modelo biopsicossocial da dor

A experiência de dor é multidimensional e vivenciada a partir de uma matriz de níveis hierárquicos de circuitos neurais. Estes níveis são responsáveis tanto pela codificação do estímulo nociceptivo em modulação consciente, quanto pela formação da memória emocional de tal experiência (BALIKI & APKARIAN, 2015; BASTUJI et al., 2016; GARCIA-LARREA & PEYRON, 2013; HOOTEN, 2016).

Diferentes autores tentam explicar a experiência de dor, particularmente da dor persistente, através de modelos biopsicossociais que envolvem a teoria do apego (BOWLBY, 1977; PORGES, 2003) e sistemas complexos de autorregulação (CHAPMAN; TUCKETT; SONG, 2008; EDWARDS et al., 2016; KAROLY, 2020; REISZ; DUSCHINSKY; SIEGEL, 2018). A teoria do apego é uma maneira de conceituar a propensão dos seres humanos a estabelecer fortes laços afetivos entre si, bem como de explicar as muitas formas de sofrimento emocional e de transtornos de personalidade originados por separação involuntária e perdas (BOWLBY, 1977; PORGES, 2003). Estes modelos biopsicossociais levam em consideração a evolução filogenética do sistema nervoso com foco na sobrevivência do ser humano. Neste sentido, são consideradas como necessidades básicas de todo indivíduo: adaptação ao seu meio ambiente, vínculos e segurança (CHAPMAN; TUCKETT; SONG, 2008; PORGES 2003). Para que estas necessidades sejam atendidas,

diferentes estruturas e circuitos neurais se superpõem em suas funções, por meio de processos fisiológicos (alostase), emocionais, comportamentais e sociais. Os objetivos destes processos são: garantia da estabilidade interna do organismo (homeostase) (MCEWEN et al., 2012), identificação de sinais de segurança ou de perigo, respostas de aproximação ou de defesa do tipo luta-fuga-congelamento, criação de vínculos e convivência social (BOWLBY, 1977; PORGES, 2003).

1.1.4.1 Sistema neuroimunoendócrino

Para o alcance dos objetivos anteriormente citados, o sistema nervoso opera intrínseca e continuamente conectado com os sistemas imunológico e endócrino, como uma entidade funcional única: o sistema neuroimunoendócrino. A comunicação entre eles acontece através de uma linguagem química que envolve catecolaminas, cortisol, neurotransmissores, citocinas pró-inflamatórias, ocitocina, vasopressina, opioides endógenos e endocanabinoides, em ciclos de retroalimentação positivos e negativos constantes (CHAPMAN; TUCKETT; SONG, 2008).

Neurônios nociceptores, periféricos ou centrais, são encarregados da transdução e codificação de estímulos de dano real ou potencial aos tecidos, processo denominado de nocicepção (IASP, 2022). Além disso, algumas partes do sistema nervoso humano, como, por exemplo, a amígdala e o córtex temporal, são responsáveis pela propriedade de neurocepção, que se caracteriza pela captação contínua de sinais de segurança ou de perigo, sem a participação da consciência (PORGES, 2003). Destaca-se, ainda, um sistema de engajamento social, que ajuda

na percepção de segurança, favorecendo comportamentos pró-sociais ou defensivos. Este sistema tem origem no tronco cerebral e é formado por:

- componentes somatomotores: os pares de nervos cranianos trigêmeo (V), facial (VII), glossofaríngeo (IX) e acessório (XI). Eles regulam os músculos da face e da cabeça e são responsáveis por expressões faciais, orientação da cabeça, deglutição, vocalização, fixação do olhar e modulação da captação da voz humana;
- componente visceromotor: o ramo ventral do nervo craniano vago (X), com atuação sobre o coração e os brônquios (PORGES, 2003).

As reações agudas de defesa a ameaças internas ou externas são necessárias e apropriadas, enquanto estas ameaças persistirem, quer elas sejam dor, doenças ou, por exemplo, violência doméstica. Na dor aguda, diferentes áreas do cérebro podem ser ativadas, não tendo sido ainda identificados uma área ou padrões específicos em sua percepção (BALIKI & APKARIAN, 2015). É fundamental que o sistema neuroimunoendócrino seja capaz de modular a resposta de defesa; cessado o perigo, que o referido sistema seja capaz de inibir esta resposta, para que o organismo possa recuperar-se (KOLACZ & PORGES, 2018). Entretanto, uma capacidade comprometida de avaliação de risco pode exacerbar ou prolongar as respostas ao estresse do eixo hipotálamo-pituitária-adrenal (HPA), interferindo na homeostase e nos estados emocionais do indivíduo (DANESE & MCEWEN, 2012). Em decorrência desta falha adaptativa, alterações estruturais no cérebro acontecem, com a participação do sistema límbico exposto à linguagem química previamente citada (CASTRO et al., 2011; CHAPMAN; TUCKETT; SONG, 2008; MCEWEN et al., 2012). O hipocampo, a amígdala, o córtex pré-frontal e o núcleo *accumbens*, principalmente, podem sofrer remodelação de seus dendritos e sinapses, a partir de processos de neuroplasticidade adaptativa (BALIKI & APKARIAN, 2015; HOOTEN,

2016). As consequências, a longo prazo, podem ser cronificação e sinalização alterada da dor, como, por exemplo, hiperalgesia e alodínia, além de processos inflamatórios e infecciosos frequentes, doenças cardiovasculares, distúrbios metabólicos (DANESE & MCEWEN, 2012), dificuldade na formação de vínculos e nas interações sociais (SANDKÜHLER, 2009; PORGES, 2003).

É importante ressaltar que, assim como os sistemas imunológico e endócrino, parte do sistema nervoso dos seres humanos é imaturo estrutural e/ou funcionalmente ao nascimento (SCHORE, 2003). É o caso, por exemplo, dos já citados amígdala, hipocampo e córtex pré-frontal, fundamentais para a resposta emocional e a alostase (DANESE E MCEWEN, 2012), assim como para a categorização e a hierarquização emocional das memórias dos eventos (BALIKI & APKARIAN, 2015; HOOTEN, 2016). A amígdala continua a crescer na infância e é altamente reativa às experiências de medo desta época. Por sua vez, o hipocampo e o córtex pré-frontal médio atuarão como reguladores da amígdala; porém, só estarão maduros para esta função no final da adolescência e início da vida adulta (CALLAGHAN & TOTTENHAM, 2016).

1.1.4.2 Parentalidade e os sistemas de autorregulação das crianças

A fase de amadurecimento dos sistemas de autorregulação é uma época bastante sensível à influência do ambiente socioafetivo (CALLAGHAN & TOTTENHAM, 2016). Durante este período, é indispensável a presença de outros seres humanos adultos que sirvam como correguladores das crianças (PORGES, 2003). Este papel é exercido principalmente pela mãe e pelo pai, ou por outros cuidadores, na ausência ou indisponibilidade dos pais. Ressalta-se que é a qualidade da relação cuidador-criança que fornecerá a base para a modelagem e

expressão fenotípica destes sistemas de autorregulação (ABRAHAM; ZAGOORY-SHARON; FELDMAN, 2021; CALLAGHAN & TOTTENHAM, 2016; DANESE & MCEWEN, 2012; DONNELLY & JAANISTE, 2016; SCHORE, 2003).

O período de plasticidade do circuito amígdala-córtex pré-frontal médio pode ser precoce e inadequadamente encerrado, por exemplo, em crianças que vivenciaram uma privação parental ou uma independência prematura, como, por exemplo, em caso de institucionalização por negligência parental (CALLAGHAN & TOTTENHAM, 2016). Há relatos na literatura de diminuição do volume da amígdala e do hipocampo, de níveis basais elevados de biomarcadores inflamatórios e de respostas inflamatórias exacerbadas em adultos que sofreram maus tratos quando eram crianças (DANESE & MCEWEN, 2012). Além disso, existem indícios de que a qualidade do cuidado materno na infância pode afetar áreas do cérebro que regulam as respostas emocionais das mulheres aos seus filhos, quando elas próprias se tornam mães. Por exemplo, uma hiper-reatividade do hipocampo foi identificada em mães que receberam um baixo cuidado materno quando crianças, como resposta ao choro dos seus próprios bebês (KIM et al., 2010).

Assim, segundo a teoria do apego, para um desenvolvimento saudável, toda criança necessita de uma base segura de cuidado e de estímulo a uma autonomia progressiva (BOWLBY, 1977). A observância destes aspectos é considerada uma parentalidade ótima (PARKER; TUPLING; BROWN, 1979), com repercussões positivas por toda a vida dos filhos (CALLAGHAN & TOTTENHAM, 2016). Por outro lado, falta de cuidado e/ou superproteção/controle caracterizam uma parentalidade disfuncional (PARKER; TUPLING; BROWN, 1979), frequentemente associada a desempenho inadequado dos sistemas de autorregulação dos filhos a longo prazo (ABRAHAM; ZAGOORY-SHARON; FELDMAN, 2021).

Vale, ainda, salientar que as crianças constroem modelos internos positivos ou negativos de si mesmas e dos outros a partir da responsividade, consistência e sensibilidade a elas oferecidas pela mãe e pelo pai, principalmente quando elas estão doentes, com medo ou com dor (BOWLBY, 1977; OTANI et al., 2016). As doenças, e particularmente a dor, podem servir de gatilho para uma necessidade crescente de segurança, proximidade e cuidado (DONNELLY & JAANISTE, 2016). A partir destas interações no início da vida, segundo as atitudes e comportamentos parentais percebidos pelas crianças (PARKER; TUPLING; BROWN, 1979), é que elas desenvolvem padrões seguros ou inseguros de apego (AINSWORTH, 1979). Estes padrões tendem a ter repercussão, ao longo da vida, em sua avaliação cognitiva de ameaças, na expressão e nas estratégias de enfrentamento da dor, na expressão das emoções, nos relacionamentos interpessoais (SHIBATA et al., 2020; FAILO; GIANNOTTI; VENUTI, 2019), na autoestima e na satisfação profissional (MEREDITH; OWNSWORTH; STRONG, 2008).

Sob a influência da teoria do apego, Parker et al. (1979) desenvolveram um questionário, o *Parental Bonding Instrument* (*PBI*), com o intuito de avaliar as duas dimensões que, para eles, mais contribuiriam para a formação do vínculo parental. Uma destas dimensões foi definida como *care* e abordada por 12 questões sobre afeto/cuidado versus indiferença/rejeição. A outra dimensão foi definida como *overprotection* e abordada por 13 questões sobre controle/superproteção versus permissão para autonomia/independência. Estas 25 questões consideram as lembranças que uma pessoa tem dos comportamentos e atitudes de sua mãe e de seu pai até os seus 16 anos de idade. As mesmas questões são respondidas separadamente para cada progenitor. Os escores variam de 0 a 3 para cada item, sendo as categorias baixo e alto definidas pelos seguintes pontos de corte: 27/24 para

cuidado materno/paterno e 14,5/12,5 para controle materno/paterno, respectivamente. Existe a possibilidade de avaliar cada dimensão separadamente ou de agrupá-las em quatro quadrantes, que resultam nos seguintes estilos parentais: parentalidade ótima (alto cuidado + baixo controle); controle sem carinho (baixo cuidado + alto controle); restrição carinhosa (alto cuidado + alto controle) e parentalidade negligente (baixo cuidado + baixo controle) (PARKER; TUPLING; BROWN, 1979). O PBI foi validado transculturalmente para vários idiomas, inclusive para o português do Brasil (HAUCK et al., 2006). Sua consistência e estabilidade a longo prazo também foram validadas (MURPHY; WICKRAMARATNE; WEISSMAN, 2010).

Em pesquisas que usaram o PBI, baixo cuidado e excesso de controle/superproteção maternos e/ou paternos têm sido associados à dor crônica na adolescência (EVANS et al., 2018) e na vida adulta (ANNO et al., 2015; SHIBATA et al., 2020). Às vezes, esta associação é mediada por depressão (AVAGINOU et al., 2010; ANNO et al., 2015; EVANS et al., 2018) e/ou ansiedade (SHIBATA et al., 2020). Em mulheres com dismenorreia primária, um excesso de controle materno se mostrou relacionado à exacerbação de sintomas emocionais e de sintomas funcionais, como, por exemplo, dificuldade de realização das tarefas diárias e de participação em reuniões sociais (XU et al., 2016). Além disso, há dados, na literatura, da associação entre ambiente familiar controlador e piores desfechos de fibromialgia em adolescentes (SIL et al., 2013). Acrescente-se que pesquisadores identificaram a superproteção materna como fator preditor do desenvolvimento de sintomas somáticos funcionais, tais como dores, vômitos, náuseas, problemas de pele e nos olhos em filhas (JANSSENS; OLDEHINKEL; ROSMALEN 2009). Finalmente, a enxaqueca, outro tipo comum de dor crônica, já se mostrou mais

frequente, mais intensa e mais associada à ansiedade e à depressão em jovens com estilo inseguro de apego (TARANTINO et al., 2017).

Por sua vez, uma associação entre parentalidade disfuncional, transtornos mentais e traços de personalidade tem sido relatada por diversos autores em populações e culturas diferentes (EUN et al., 2018; GROTMOL et al., 2010; KAWAI et al., 2017; SHIMURA et al., 2017; SIQUEIRA-CAMPOS et al., 2021). Baixo cuidado e alta superproteção por parte de pai e/ou de mãe têm sido associados à ansiedade e à depressão em adolescentes (EUN et al., 2018) e em jovens adultos (KAWAI et al., 2017). Além disso, há relatos de associação entre parentalidade disfuncional e baixa autoestima em adultos (GROTMOL et al., 2010; SHIMURA et al., 2017). Ainda, quando comparados aos filhos de mães de parentalidade ótima, filhos de mães do tipo controle sem carinho têm apresentado maior prevalência de ansiedade, depressão, baixa autoeficácia (SIQUEIRA-CAMPOS et al., 2021) e neuroticismo, que é uma tendência a emoções negativas (TAKAHASHI et al., 2017).

Além disso, merece destaque a catastrofização da dor, um traço de personalidade (SEMINOWICZ & DAVIS, 2006) que tem sido associado a padrões inseguros de apego (CIECHANOWSKI et al., 2003; DONNELLY & JAANISTE, 2016) e ao comportamento do pai e/ou da mãe como resposta à experiência de dor de suas crianças (CUNNINGHAM et al., 2014).

1.1.4.3 Catastrofização da dor

A catastrofização tem sido descrita como uma tendência à magnificação negativa da experiência álgica (SULLIVAN; BISHOP; PIVIK, 1995; SULLIVAN et al., 2001). Este termo refere-se a um construto psicossocial composto por processos

cognitivos e emocionais, que incluem ruminação, pessimismo e desamparo em situações de dor (EDWARDS et al., 2016; SULLIVAN; BISHOP; PIVIK, 1995; SULLIVAN et al., 2001). Foi inicialmente concebido para descrever estratégias mal-adaptativas de pacientes em relação à ansiedade e depressão (BECK et al., 1979). Posteriormente, a catastrofização passou a ser associada a comportamentos referentes a doenças em geral, como, por exemplo, maior número de visitas a profissionais de saúde, maior frequência e duração de hospitalização e mais automedicação (SULLIVAN et al., 2001). Ao longo do tempo, ganhou lugar de destaque como fator psicológico a ser considerado na experiência da dor (GRUNDSTRÖM et al., 2020; MARTIN et al., 2011; SEWELL et al., 2018; SULLIVAN et al., 2001).

O desenvolvimento deste traço de personalidade inicia-se precocemente, no ambiente familiar (SULLIVAN et al., 2001). Alguns exemplos de comportamentos dos pais (principalmente das mães) do estilo superprotetor/controlador em relação às suas crianças, quando elas estão com dor, são: monitorização constante dos sintomas, excesso de atenção e desvelo, proibição da prática de atividades corriqueiras, entre outros. Estas atitudes podem tornar as crianças mais vigilantes, ansiosas, inseguras e com medo dos seus sintomas, com repercussão negativa a longo prazo nos seus sistemas de autorregulação e nas suas estratégias de enfrentamento álgico, como a catastrofização da dor (CUNNINGHAM et al., 2014; DONNELLY & JAANISTE, 2016; EDWARDS et al., 2016). Vale salientar que a catastrofização é mais frequente nas mulheres, o que pode estar relacionado a questões culturais. Os adultos ainda oferecem mais conforto às mulheres em situações de estresse do que aos homens, o que pode favorecer o desenvolvimento nelas de reações mais alarmistas e catastróficas em relação à dor (SULLIVAN et al., 2001).

Em 1995, Sullivan et al. desenvolveram e validaram a *Pain Catastrophizing Scale* (*PCS*), um questionário autoaplicável capaz de fornecer um índice válido da catastrofização da dor. Esta escala se baseia nos pensamentos e sentimentos das pessoas quando estão com dor. Ela é composta por 13 questões assim distribuídas entre três domínios: 04 sobre ruminação, como, por exemplo, “o sentimento de não conseguir tirar a dor do pensamento”; 03 sobre magnificação, como, por exemplo, “o medo de que a dor pode se tornar ainda pior”, e 06 sobre desamparo, como, por exemplo, “o pensamento de que não há nada para fazer para diminuir a intensidade da dor”. A pontuação para cada questão varia de 0 a 4, com um escore total de 0 a 52. Um ponto de corte ≥ 30 tem sido considerado para catastrofização clinicamente relevante (WIJMA et al., 2016). A escala de catastrofização da dor foi traduzida e validada para o português do Brasil (SEHN et al., 2012).

Há relato na literatura de uma associação independente entre catastrofização e a atividade neural envolvida na percepção da dor (SEMINOWICZ & DAVIS, 2006). Imagens de ressonância magnética funcional têm evidenciado uma correlação positiva entre os escores de catastrofização e a ativação de áreas do cérebro envolvidas com aspectos afetivos, motores e de atenção da dor, tais como a ínsula e os córtex pré-frontal dorsolateral, cingulado anterior rostral, pré-motor e parietal. Por sua vez, a ativação de áreas do córtex pré-frontal, encarregadas da modulação descendente da dor, parece correlacionar-se negativamente com os escores de catastrofização (SEMINOWICZ & DAVIS, 2006). Ademais, uma associação independente entre catastrofização e aumento da interleucina-6, uma citocina pró-inflamatória, já foi identificada em pacientes com dor aguda (EDWARDS et al., 2008) e dor crônica (LAZARIDOU et al., 2018). Estes dados sugerem um importante meio pelo qual a catastrofização pode moldar a experiência da dor, particularmente da dor persistente.

Assim, a catastrofização associa-se a quadros mais intensos de dor e de incapacidade correlata mais grave, por exemplo, em dor abdominal funcional (CUNNINGHAM et al., 2014), fibromialgia (CLAUW, 2015) e osteoartrite (UÇKUN et al., 2020). Em estudo de base populacional numa ilha da Croácia, alguns autores identificaram um efeito mediador da catastrofização entre intensidade de dor e neuroticismo (BANOZIC et al., 2018). Também é digna de nota a alta prevalência de catastrofização em mulheres com DPC, bem como a sua correlação positiva com a intensidade da dor e a sua correlação negativa com a qualidade de vida nesta população (SEWELL et al., 2018). Além disso, a catastrofização tem sido associada a limiares mais baixos de dor para frio, calor e pressão em mulheres com DPC, e pode ser investigada como indício de hipersensibilidade nesta condição de saúde (GRUNDSTRÖM et al., 2020).

Ademais, a catastrofização tem sido considerada como um dos mais importantes preditores dos desfechos de tratamentos em diferentes tipos de dor (ALLAIRE et al., 2018; MARTIN et al., 2011; SEWELL et al., 2018; SULLIVAN et al., 2001; TURNER et al., 2016; UÇKUN et al., 2020). No seguimento de um ano, por exemplo, níveis mais elevados de catastrofização associaram-se a piores resultados dos tratamentos oferecidos a mulheres com DPC, na presença ou ausência de endometriose (ALLAIRE et al., 2018; MARTIN et al., 2011). Por outro lado, a introdução de intervenções interdisciplinares, como programas de atenção plena (*mindfulness*) e terapia cognitiva comportamental, voltadas para a redução de níveis de catastrofização, associou-se à redução da intensidade da dor, à melhora da qualidade de vida e à otimização do uso dos serviços de saúde nos casos de DPC em mulheres (ALLAIRE et al., 2018) e de dor lombar crônica em adultos (TURNER et al., 2016).

Assim, o desenvolvimento e a manutenção de dores crônicas envolvem uma rede intricada e superposta de processos psicossociais e neurobiológicos, que sempre devem ser investigados e abordados nos tratamentos propostos. Entre os transtornos mentais mais associados à DPC em mulheres, estão a ansiedade e a depressão (SIQUEIRA-CAMPOS et al., 2019). Diferentes instrumentos têm sido usados para a investigação destas condições, como a *Hospitalar Anxiety and Depression Scale (HADS)* (ZIGMOND & SNAITH, 1983), a *Generalized Anxiety Disorder-7 scale* (*GAD-7*) (SPTIZER et al., 2006) e o *Patient Health Questionnaire-9* (*PHQ-9*) (KROENKE; SPITZER; WILLIAMS, 2001). Tanto o *GAD-7* quanto o *PHQ-9* são instrumentos curtos, autoaplicáveis, que indicam a presença de ansiedade e de depressão, respectivamente, nas últimas duas semanas.

Nas mulheres, a DPC tem-se revelado desafiadora, merecendo uma revisão ampla e aprofundada quanto à sua caracterização, aos seus mecanismos fisiopatológicos, à sua avaliação e ao seu manejo. Também é importante avançarmos, buscando preencher lacunas ainda existentes na compreensão de tão instigante condição de saúde, com fins preventivo e terapêutico.

2 OBJETIVOS

2.1 Objetivo geral

- Revisar os principais aspectos relacionados à dor pélvica crônica em mulheres, avaliar o estilo de vínculo parental e a saúde mental em mulheres com e sem dor pélvica crônica, e a catastrofização em mulheres com dor pélvica crônica.

2.2 Objetivos específicos

2.2.1 Artigo 1

- Revisar o conceito, prevalência, etiologia, fisiopatologia, abordagens diagnóstica e terapêutica da dor pélvica crônica em mulheres;

2.2.2 Artigo 2

- Analisar a frequência do estilo de vínculo parental em mulheres com e sem dor pélvica crônica;
- Investigar a associação entre estilo de vínculo parental e dor pélvica crônica em mulheres;
- Verificar a correlação do estilo de vínculo parental com ansiedade e depressão em mulheres com dor pélvica crônica;
- Examinar a correlação da catastrofização com intensidade da dor, tempo de dor, ansiedade, depressão e vínculo parental em mulheres com dor pélvica crônica.

3 MATERIAL E MÉTODOS

Os dois artigos produzidos tiveram metodologias diferentes.

3.1 ARTIGO 1

3.1.1 Tipo de estudo

Revisão narrativa

3.1.2 Bancos de dados pesquisados

Medline, Embase e SciELO (*Scientific Electronic Library Online*).

3.1.3 Data limite de busca

15 de outubro de 2021.

3.1.4 Termos de busca

Chronic pelvic pain, central sensitization, hyperalgesia, chronic pain, neuromodulation, women, somatic pain, visceral pain, nociplastic pain, neuropathic pain.

3.1.5 Critérios de inclusão

Artigos originais, revisões sistemáticas, metanálise e consenso de sociedades médicas, publicados em inglês.

3.1.6 Procedimento

As referências dos artigos foram examinadas para identificar os mais relevantes e mais estritamente associados ao tema abordado. Todos os artigos recuperados foram meticulosamente examinados, antes de serem incluídos na presente revisão narrativa.

3.2 ARTIGO 2

3.2.1 Tipo do estudo

Estudo de caso-controle.

3.2.2 Local do estudo

O presente estudo foi conduzido entre maio de 2018 e agosto de 2021, nos ambulatórios de DPC e de Planejamento Familiar do Departamento de Ginecologia e Obstetrícia do Hospital das Clínicas da Universidade Federal de Goiás/Empresa Brasileira de Serviços Hospitalares (HC-UFG/EBSERH), Goiânia, Goiás, Brasil. Esta instituição presta atendimento especializado no âmbito do Sistema Único de Saúde (SUS) e é regulado pelo Gestor da Secretaria Municipal de Saúde de Goiânia, cidade em que se situa.

Referência no atendimento de mulheres com DPC, este serviço recebe mulheres encaminhadas das Unidades Básicas de Saúde de Goiânia, de outras cidades do estado de Goiás, bem como de cidades de outros estados das Regiões Centro-Oeste, Norte e Nordeste do Brasil.

Além disso, essa instituição hospitalar é responsável pela formação de alunos de graduação e pós-graduação dos cursos de medicina, enfermagem, fisioterapia, psicologia, nutrição, serviço social, entre outros.

3.2.3 População do estudo

A população deste estudo foi composta por 246 mulheres consecutivas, distribuídas em dois grupos: 123 mulheres no grupo com DPC (casos), e 123, no grupo sem DPC (controles), que estavam em seguimento no Ambulatório de DPC e no Ambulatório de Planejamento Familiar do HC-UFG/EBSERH, respectivamente, durante o período de coleta dos dados.

3.2.4 Critérios de inclusão

- Idade ≥ 18 anos e ≤ 50 anos;
- Grupo com DPC: presença de dor no baixo ventre, com início há pelo menos seis meses, sem caráter exclusivamente cíclico ou relacionado ao coito;
- Grupo sem DPC: ausência de queixa de dor no baixo ventre nos três meses anteriores.

3.2.5 Critérios de exclusão

- Antecedente de gravidez nos últimos 12 meses;
- Suspeita ou confirmação de gravidez atual;
- Estar na pós-menopausa;
- Antecedente de cirurgia há menos de três meses;
- Antecedente de tratamento de neoplasia maligna.

Uma ficha de verificação dos critérios de inclusão e exclusão para o estudo (Apêndice I) foi preenchida, registrando-se a seleção ou não das mulheres para a pesquisa.

3.2.6 Tamanho amostral

Um tamanho amostral para estudos de caso-controle foi calculado (FLEIS; LEVIN; PAIK; 2013), objetivando verificar associação entre estilo parental, como principal variável independente, e DPC, por meio da comparação da proporção do estilo parental entre casos e controles. Os parâmetros utilizados foram um nível de significância igual a 0,05 (α=0,05), poder estatístico de 0,80 (β=0,20), razão de casos para controles de 1 (k=1), razão de probabilidade (RP) de 2,5 (RP=2,5) e uma proporção de estilo parental disfuncional de 54,4% em mulheres do DCP segundo um estudo piloto anterior (LEITHNER-DZIUBAS et al., 2010). Foi assumido, desta forma, 21,8% de proporção de estilo parental disfuncional no grupo controle, para encontrar uma prevalência da variável independente 2,5 vezes maior nas mulheres

com DCP. Assim, o tamanho amostral necessário foi estimado em pelo menos 202 mulheres, sendo 101 com DCP, e 101, sem DCP.

3.2.7 Aspectos éticos

Este estudo foi apreciado e aprovado pelo Comitê de Ética em Pesquisa Médica Humana e Animal do HC-UFG/EBSERH (Anexo A) e obedeceu aos critérios estabelecidos pela Resolução 466/2012 do Conselho Nacional de Saúde, que regulamenta pesquisa envolvendo seres humanos no Brasil (BRASIL, 2012).

O primeiro contato com as participantes em potencial foi estabelecido na sala de espera dos referidos ambulatórios, enquanto as mesmas aguardavam sua consulta ou logo após o término do seu atendimento. As mulheres foram convidadas para uma sala reservada, com o intuito de garantir sua privacidade. Então, a pesquisadora se apresentou, explicou oralmente os objetivos do estudo e leu para elas algumas informações relevantes: que a sua participação seria voluntária e gratuita; que o anonimato das informações dadas seria garantido; que elas poderiam retirar seu consentimento a qualquer momento que desejassem, sem prejuízo à continuidade do seu atendimento no referido ambulatório. As participantes acompanharam a leitura de todas estas informações.

O Termo de Consentimento Livre e Esclarecido (TCLE) (Apêndice II) foi, então, apresentado para aquelas mulheres que se mostraram dispostas a contribuir com o estudo. O TCLE foi assinado pela pesquisadora e pela participante em duas vias: uma foi entregue à participante e a outra permaneceu arquivada com a pesquisadora.

Os dados coletados estão arquivados pela pesquisadora e ficarão em seu poder por cinco anos, para eventual aprofundamento da análise dos mesmos. Também poderão ser usados para responder eventuais questionamentos que surjam, em caso de sua publicação. Após esse período, os dados serão incinerados.

3.2.8 Coleta de dados

Os dados foram coletados diretamente junto às participantes, em forma de entrevista, através dos seguintes instrumentos:

- Ficha de coleta de dados sobre características sociodemográficas, hábitos de vida e aspectos clínicos das participantes, além de dados sobre a caracterização da dor pélvica para o grupo com DPC (Apêndice III). As seguintes variáveis foram investigadas para ambos os grupos: idade, índice de massa corpórea, renda *per capita* mensal, cor da pele, escolaridade, estado empregatício, estado marital, tabagismo, consumo de álcool, atividade física, abuso físico, abuso sexual, dificuldades de relacionamento, paridade, doenças crônicas e cirurgia abdominal/pélvica. Para o grupo com DPC, ainda foram investigados: intensidade da dor, tempo de dor e consumo de medicação para dor no mês anterior.
- Instrumento de Vinculação Parental (*Parental Bonding Instrument / PBI*) (PARKER; TUPLING; BROWN, 1979) - (Anexo B);
- Escala de Catastrofização da Dor (*Pain Catastrophizing Scale / PCS*) (SULLIVAN et al., 1995) – (Anexo C). Apenas as participantes do grupo com DPC responderam este instrumento.

- Escala de Distúrbio de Ansiedade Generalizada (*Generalized Anxiety Disorder-7 / GAD-7 scale*) (MORENO et al., 2016) – (Anexo D);
- Questionário sobre a Saúde do Paciente (*9-item Patient Health Questionnaire / PHQ-9)* (SANTOS et al., 2013) - (Anexo E).

4 PUBLICAÇÕES

4.1 ARTIGO 1

Current challenges in the management of chronic pelvic pain in women: from bench to bedside

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Current challenges in the management of chronic pelvic pain in women: from bench to bedside

Shortened title: Current challenges in the management of chronic pelvic pain in women

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Abstract

Chronic pelvic pain (CPP) affects a significant proportion of women worldwide and has a negative impact on several aspects of these women's lives including mental health, work, relationships and sexual function, among others. This set of factors ultimately reflects negatively on quality of life. The physiopathology of CPP is complex and remains to be fully clarified; however, recent advances have increased understanding of the mechanisms involved in chronic pain in general, and more specifically, CPP. Nonetheless, even when a detailed clinical history is obtained, meticulous physical examination is performed and imaging resources are appropriately used, the organic cause of the pain may still fail to be identified in a substantial number of women with CPP. Management of CPP may therefore be challenging. This narrative review was aimed at adding to the available literature on the subject, presenting and discussing the principal characteristics of CPP in women. The paper highlights gaps in the literature while providing the most up-to-date evidence associated with the physiopathology and classification of pain, its diagnosis and treatment. In addition, current challenges in the management of women with CPP are discussed.

Keywords: central sensitization; chronic pain; neuropathic pain; nociplastic pain; pain neuroscience education.

Introduction

Chronic pelvic pain (CPP) is a common condition that can affect women at any time during their adult lives. Although more frequent during the reproductive years, it may originate in or extend beyond the menopause. CPP may be the result of an underlying condition that has developed, or it could be associated with different conditions or even with other clinical complaints such as sexual dysfunction, mood swings, abnormal uterine bleeding or urinary and bowel complaints, among others. CPP affects a significant proportion of women and exerts a negative impact on their life course, being frequently associated with a reduced quality of life, symptoms of anxiety and depression, reduced work capacity and a decrease in sexual satisfaction[1,2]. In addition, CPP in women is associated with high direct and indirect medical costs, estimated at 4.9 billion dollars annually in the USA[3,4], and with reduced productivity in women[3]. Therefore, in addition to representing a problem relevant to the patient herself, CPP also appears to represent an economic burden on the healthcare system worldwide[5,6]. Although symptoms can be treated and sometimes suppressed, recurrence is common, leading to frustration, both for patients and for healthcare professionals. Adequate clinical characterization and greater understanding of the physiopathological events involved will result in advances towards more effective treatment, particularly over the long term.

The relevance of this subject prompted us to conduct this narrative review in which the principal aspects of CPP in women are presented and discussed. Gaps in knowledge are highlighted, and the most up-to-date evidence in the literature is presented. In addition, the paper discusses current challenges in the treatment of women with CPP.

Search Methods

A search was conducted of the Medline, Embase and SciELO (Scientific Electronic Library Online) databases up to the cut-off date of October 15, 2021, using the terms *chronic pelvic*

pain, *central sensitization*, *hyperalgesia*, *chronic pain*, *neuromodulation*, *women*, *somatic pain*, *visceral pain*, *nociplastic pain* and *neuropathic pain*.

Original articles, systematic reviews, meta-analyses and consensus reports from medical societies, published in English, were evaluated. Article references were also scrutinized to identify those most relevant and most closely associated with the subject matter. All the articles retrieved were meticulously examined before being included in the present narrative review.

Definition

There are various definitions of CPP in the literature, with differences sometimes being subtle and at other times less so. The American College of Obstetricians and Gynecologists (ACOG) defines CPP as *"pain symptoms perceived to originate from pelvic organs/structures typically lasting more than 6 months. It is often associated with negative cognitive, behavioral, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor, myofascial, or gynecological dysfunction."* Cyclic pelvic pain is also considered a form of CPP if there are significant cognitive, behavioral, sexual and emotional consequences involved. Pain triggered by coitus is a controversial issue, but one that has been discussed as a component symptom of CPP[7,8].

CPP may or may not be associated with other medical conditions. When an association is established, it is reasonable to hypothesize that the pain is due to some physiopathological mechanism of the underlying disease such as inflammation, vascular or mechanical alterations. However, CPP may sometimes be completely dissociated from any other medical condition or may persist even after the woman has undergone adequate treatment for the underlying disease. Consequently, distinguishing between states of chronic secondary pain and states of chronic primary pain, as proposed by the International Association for the Study

of Pain (IASP), also seems to be important[9,10]. Although CPP can also occur in men, that aspect is not within the scope of this review.

Prevalence

The prevalence of CPP worldwide ranges from 2% to 27%, with rates of around 4% in developed countries[11,12]. Gynecological and non-gynecological conditions frequently overlap in up to 60% of cases of CPP[8]. On the other hand, in approximately one-third of patients, no pelvic disease is identified[13]. Around 60-80% of patients present with complaints that fulfill the International Classification of Diseases, 10th revision (ICD-10) criteria for somatoform disorder[14]. Indeed, the condition is responsible for 10-20% of gynecological visits, 20% of hysterectomies and 40% of gynecological laparoscopies[3]. Even after an etiological diagnosis has been reached, when that is possible, and appropriate treatment has been given, symptoms may recur in over a third of cases[15].

Etiology

CPP is a multifactorial condition for which differential diagnosis requires a thorough panel work-up[8]. The most appropriate approach may be to establish an adequate association between the clinical symptoms and the possible physiopathological mechanisms involved, as shown in Figure 1. In addition to providing an idea with respect to the systems that are affected, this approach facilitates the implementation of more effective measures to control the pain or flare-ups.

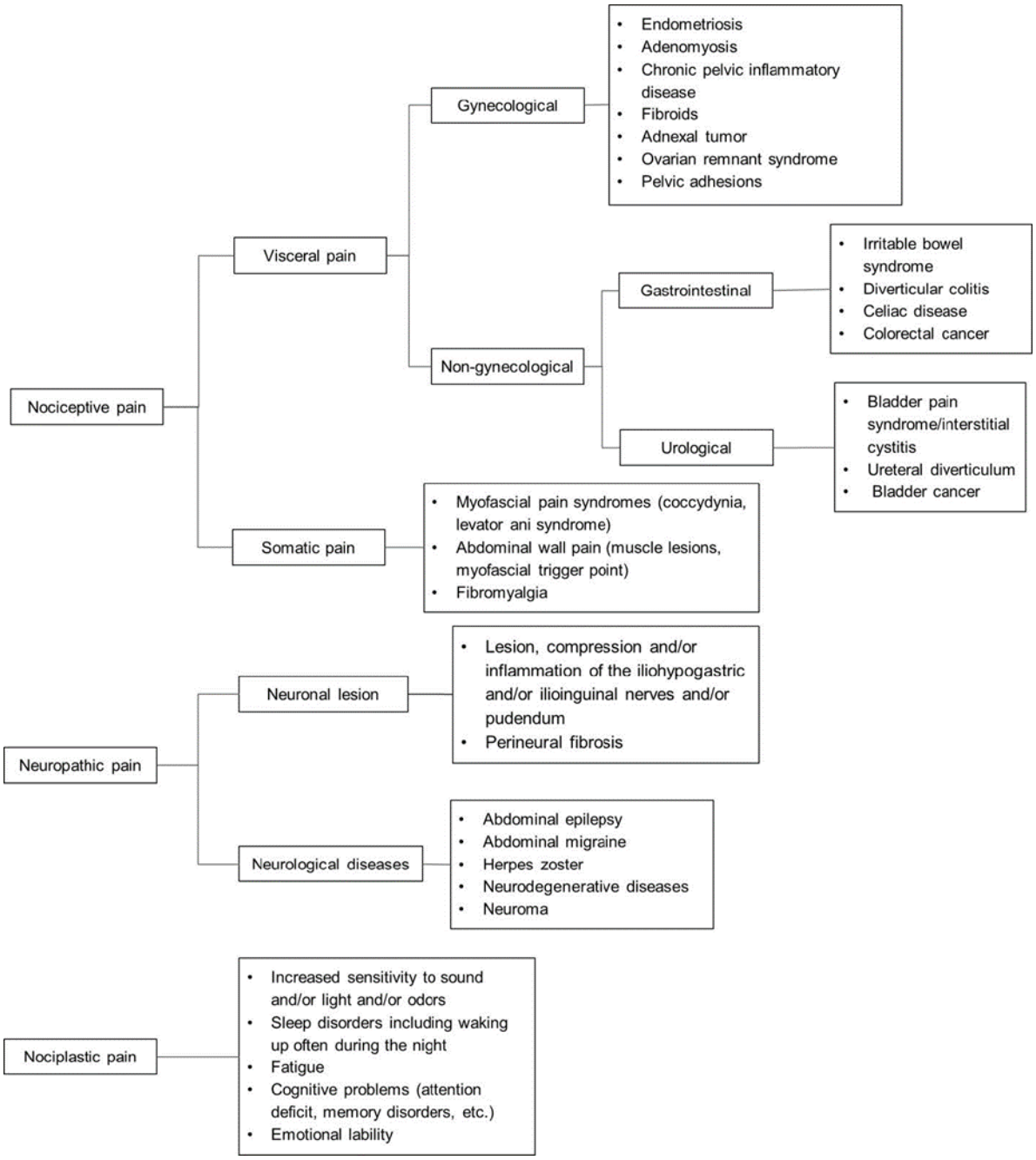

Figure 1. Classification of the mechanisms of pain and the causes of chronic pelvic pain in women

Footnote: NB: Psychosocial factors such as adverse childhood events (physical, sexual, emotional abuse), physical and/or sexual abuse in adult life, depressive disorders, anxiety disorders, pain catastrophizing and other mental disorders can be associated with chronic pelvic pain in women. The nervous system, endocrine system and immune system are involved in the different types of chronic pelvic pain.

Physiopathology

Since this is a condition that can have numerous primary causes and can be associated with many other disturbances, the physiopathology of the disease is complex and remains to be completely clarified. Discussing the specific physiopathology associated with each cause would result in this review being excessively long and of very little clinical use. Nevertheless, some points should be highlighted.

Nociception is normally an important process in detecting a potentially harmful stimulus. In physiological circumstances, nociception is protective and useful in preventing lesions, either by inducing a nociceptive withdrawal reflex or by promoting an unpleasant feeling that leads to complex emotional and behavioral strategies resulting in the avoidance of that stimulus. Finally, pain, in general, is a phenomenon that is to a certain extent "normal" and "desirable"[16]. To this end, the body uses specialized peripheral and central sensory neurons (nociceptors) capable of encoding noxious stimuli[17,18]; however, poorly adapted changes to these physiological mechanisms can result in chronic pain[17].

Therefore, nociceptive pain is pain that "*arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors*"[18]. Nociceptive pain can be visceral or somatic depending on the origin of the nociceptive stimulus and may involve different transmission pathways, entailing different clinical characteristics. Visceral forms of pain are the result of afferent stimuli that travel through the nociceptors located in the visceral walls and reach the spinal cord through afferent nerve fibers, predominantly C-nerve fibers, which is why their location is characteristically imprecise. In the majority of cases, they are triggered through a process of distension, inflammation or by increased contractility of the structure[19]. Somatic pain originates in the fascia, muscles, tendons and other structures that are not specifically nervous structures. Although somatic pain also arises from peripheral nerve terminals, similar to visceral nociceptors, afference is achieved predominantly through A-delta fibers, giving this form of pain the characteristic of being "more precisely located". The

triggers are normally the same as those involved in pain of visceral origin, with direct trauma and chronic inflammatory processes being the most common[20,21].

Neuropathic pain results from demonstrable neurological damage "*or a disease that satisfies established neurological diagnostic criteria*." It may be central or peripheral depending on the site of the somatosensory nervous system affected[18]. This type of pain is associated with deregulated mechanisms of neuronal excitability and is triggered by an inflammatory or compressive process applied directly onto the neuronal fiber. As these neuronal fibers are clustered and carry different stimuli in addition to the nociceptive stimuli, other symptoms such as hypoesthesia, dysesthesia, paresthesia or even anesthesia are often present in the corresponding dermatome[22].

Under certain circumstances, when the stimulus is persistent or intense enough, the nociceptive system becomes sensitized, as characterized by a reduction in the threshold at which the nociceptor is activated and in which the response to subsequent inputs may be amplified. This sensitization is usually also protective and, although it can last for a considerable time, the phenomenon is reversible, not permanent, and the pain thresholds return to baseline values after a period of time without the painful stimulus. A process of peripheral sensitization characterizes this potentially temporary situation, the maintenance of which requires the presence of an ongoing sustained disorder or peripheral stimulus[23]. Each disease involves its own mechanism or set of mechanisms that lead to these alterations. These mechanisms may be repeated in different conditions, since there are abnormalities that are common to women with CPP such as, for example, an increase in the number of nerve fibers in the endometrium irrespective of whether the woman has endometriosis, adenomyosis and/or uterine fibroids[24].

Furthermore, some clinical syndromes such as CPP involve perception of persistent pain, often with no obvious protective nature. Under these conditions, the pain may not only be amplified for a prolonged period of time by a stimulus (hyperalgesia) but may also spread to

other unaffected sites distant from the zone of injury (secondary hyperalgesia). It can also be triggered by apparently innocuous stimuli such as touch (allodynia) and may even appear spontaneously with no obvious triggering factor or after an initial stimulus has disappeared or been eliminated such as following the clinical and/or surgical treatment of endometriosis[25]. One of the key events associated with these conditions is central sensitization (CS). This consists of a series of dysfunctions in the central nervous system (CNS), including alterations in afferent sensory processing and changes in excitatory and inhibitory mechanisms. In women with CPP, a series of morphological and functional changes occurs in the CNS that favors the occurrence of these events[25]. From a clinical point of view, as first described in the 1980s, CS represents an increase in the neural signaling of the nociceptive pathways within the CNS[26]. Unlike peripheral sensitization, CS is the result of phenotypic changes in the neurons of the CNS so that pain is no longer obligatorily dependent on peripheral stimulus, i.e. it becomes capable of maintaining and perpetuating itself, thus supporting some allegations that in these conditions the pain itself is a disease and no longer merely a symptom[10,27].

Early recognition of the symptoms of CS in patients with chronic pain facilitates the implementation of better-targeted treatments with possibly better outcomes. Therefore, in 2017, the IASP introduced a third mechanistic pain descriptor with the term *nociplastic pain* defined as "*pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain*". The IASP also adds that "*patients can have a combination of nociceptive and nociplastic pain*"[18]. From a practical viewpoint, nociplastic pain is pain experienced by patients whose clinical condition is dominated by symptoms associated with CS including "bad feelings" such as sleep disturbance, fatigue, anxiety, dizziness, nausea, emotional lability and cognitive problems[28]. Nonetheless, there is an urgent need to establish precise clinical and psychometric criteria[29].

There is also a group of patients with chronic pain and significant psychiatric symptoms who do not fit into the classifications of nociceptive, neuropathic or nociplastic pain[28]. In clinical practice, these conditions are often labeled as psychogenic, but this can lead to even more confusion and reinforce a pejorative idea in patients, particularly women with CPP. The terminology is not homogenous and even less is known with respect to the physiopathology of these causes of pain. Potentially, they originate from damage to the functioning of the suprathalamic structures. Although this type of pain is indeed of neurological origin, it also has characteristic signs and symptoms[30]. Using exclusion criteria, it could be classified as pain of unknown origin or idiopathic pain[28].

There is evidence of a reciprocal and intertwined network of interaction between the CNS, the immune system and the endocrine system, which may contribute, peripherally and centrally, to pain modulation[31–33]. Accordingly, a complex interaction has been reported between the glia (microglia, astrocytes and oligodendrocytes), endothelial cells, perivascular macrophages and T cells[34,35]. Indeed, one hypothesis for the maintenance of CS is deregulation of the glial function within the CNS[36]. Some authors agree that, after an initial immune challenge, the microglia are able to maintain increased transcriptional activity or epigenetic changes that confer a potentiated response to subsequent challenges that could include stress, lesions, diseases and aging[37]. Moreover, various immune cells (mast cells, macrophages, neutrophils, T and B cells), both those residing locally in the tissues and those recruited peripherally, contain inflammatory mediators and precursors stored in cytoplasmic granules that can be released or activated under certain circumstances, possibly leading to hyperalgesia. These cells appear crucial in the physiopathology of various diseases associated with CPP such as endometriosis[38–42], interstitial cystitis/bladder pain syndrome (BPS)[43–46] and irritable bowel syndrome (IBS)[47–51]. Recent studies have shown that immune cells are also involved in neuropathic pain[52–54]. Additionally, in women, glial reactivity modulated by sex hormones,

particularly estrogen, could contribute to a predominance of persistent pain and be associated with conditions such as endometriosis, inflammatory bowel disease and BPS[55]. Finally, the nervous system, endocrine system and immune system have constant connectivity, which makes them react in an extremely orchestrated manner to the different stressors involved in the different types of chronic pain[33].

Diagnostic evaluation

The diagnostic evaluation of women with CPP is difficult, both because of its multifactorial etiology and because of the overlapping symptoms. This may explain the fact that around 60% of these women never receive an exact diagnosis and approximately 20% are not even submitted to any investigation to explore the cause of their pain[56].

The National Institutes of Health (NIH) recognize a group of chronic overlapping pain conditions (COPCs) that have CS as the common mechanism. These include fibromyalgia, IBS and BPS, among others[57]. One of these conditions could function as a triggering factor for another, even if one was of visceral origin and the other of somatic origin[58]. There appears to be a phenotype for CS that is clinically characterized in individuals who present with unpleasant sensory experiences disproportionate to any observable peripheral cause[57]. As discussed in this review, CPP, which is associated with a frequency of psychosomatic symptoms that is up to eight times greater than in asymptomatic controls, could be included in this group of COPCs and could be considered a functional somatic syndrome together with these other conditions[13].

Identifying potential peripheral and organic causes of CPP through anamnesis, physical examination and supplementary tests remains an important goal. Nevertheless, maintaining an exclusive focus on these aspects could delay treatment and prolong the pain[59]. Therefore, recognizing the phenotypic clinical conditions of CS both when taking the patient's history and at physical examination should be part of the diagnostic work-up of women with CPP[60–

[62]. This approach could have an impact on the relevant treatment[63,64] and could save time, effort and resources with diagnostic tests and surgical procedures that are often unnecessary[61,65].

Anamnesis

Considering that these are women who have generally suffered pain over several years and who often feel frustrated with the results of their treatment, careful listening through a meticulous initial anamnesis and a physical examination that should be more detailed than a normal gynecological examination are recommended[66]. Furthermore, there appears to be a consensus that psychosocial aspects associated with women with CPP should be evaluated[60,65]. The collection of these data should be systematized, taking possible physiopathological mechanisms into consideration. Not doing so can result in further confusion, failed treatment and discouragement, both for the patients and for the healthcare professionals[60,66].

The characteristics of the pain should be addressed during anamnesis, including its duration, frequency, quality, location, irradiation and intensity. Likewise, clinical markers that improve and/or worsen the pain such as nausea, vomiting, fever, urinary and bowel symptoms should be investigated, as well as the relationship between the pain and the menstrual cycle and the pain and sexual activity[66]. This may shed light on possible etiologic factors, comorbidities and the severity of the clinical condition. If the pain worsens cyclically, this is important information, since it identifies a group of women who could benefit from the induction of amenorrhea[67,68].

The way in which the patient describes the site of the pain can be extremely helpful. Visceral pain should be suspected if the patient runs her finger over a site instead of pointing to a specific spot or if she uses various fingers instead of just one to indicate the site of pain. On the other hand, in clinical practice, when the patient points a finger repeated times to a

specific site, this is suggestive of somatic pain. Neuropathic pain is suspected when the site indicated by the patient corresponds to a specific dermatome[69,70].

Alternatively, the patient could point out the site of pain on a body chart[69]. Although these are not diagnostic criteria, particularly because of the frequent overlapping of symptoms in cases of CPP, the positions indicated on body charts may serve as a guide during investigation. In clinical practice, a check mark or an X at a specific point may indicate typically somatic pain, while shadowed areas below the umbilicus may suggest visceral pain, and marks outlining a dermatome may be a sign of neuropathic pain. However, there can be a combination of more than one type of pain.

The intensity of the pain at the time of the clinical visit and in the preceding two weeks can be determined using a 10-cm visual analogue scale (VAS) in which 0 represents the absence of pain and 10 the worst pain experienced by the patient[66]. Nevertheless, pain has psycho-affective components and in many cases the true extent of suffering experienced by a woman with CPP is not registered if only the VAS is used[71]. Graphic representation of pain using either shapes or colors can be a strategy for registering its psycho-affective component. Drawings illustrating negative feelings, harmful instruments and a predominance of cold colors (those from the blue-green spectrum, neutral colors and the grey spectrum) have been described in the literature[71]. The McGill Pain Questionnaire, although extensive, could be particularly useful in certain situations, since the descriptors of pain help legitimize the symptom experienced by the women[72].

In relation to CS, the Central Sensitization Inventory (CSI)[62], a two-part self-report scale, can be extremely useful. Part A of the CSI contains 25 items on current symptoms, with a cut-off score of 40 on a total score that ranges from 0 to 100 representing a strong possibility of the presence of a central sensitivity syndrome (CSS)[61]. Part B of this inventory consists of 10 items that question whether a doctor has already diagnosed the individual with one or more of the seven specific disorders comprising the CSS family and/or certain associated conditions

such as anxiety and depression[62]. More recently, a short version of the CSI containing nine items (CSI-9) was proposed for patients with musculoskeletal pain[73], with 20 being the cut-off point in this version for symptoms of CS[74]. In view of the shorter time required to complete the instrument, future studies using the CSI-9 for other health conditions such as CPP could encourage its use in a clinical setting.

Considering the lack of any simple means of identifying CS in chronic pelvic and perineal pain (PP), a clinical evaluation tool referred to as the Clinical Criteria of Central Sensitization in Chronic Pelvic and Perineal Pain (*Convergences PP Criteria*) was elaborated, based on an expert consensus[60]. Factors taken into consideration include questions on the relationship between the pain and urination, defecation and sexual activity, variability in the intensity and distribution of the pain, and the presence of comorbidities such as migraine, fibromyalgia, multiple chemical sensitivity and others. Although this instrument is unable to establish a diagnosis, it constitutes an excellent guide in clinical practice, with more than 5 positive answers out of a total of 10 being suggestive of CS[60].

The presence of pain hypersensitivity (sensitivity to touch and/or to pressure and/or to motion and/or to hot or cold temperatures) and at least one of the following comorbidities: heightened sensitivity to sound and/or light and/or odors, sleep disorders including waking frequently during the night, fatigue, and cognitive problems such as difficulty concentrating, memory abnormalities, etc. can be considered suggestive of nociplastic pain[28]. Although the IASP guidelines do not directly propose use of the CSI, many of its items were taken into consideration in the investigation of allodynia and of the comorbidities mentioned, with its application for the identification of CS being more practical for day-to-day use[29].

Figure 2 consists of a flowchart listing the clinical criteria suggestive of CS in women with CPP. Nociplastic pain can be associated with neuropathic pain and with non-neuropathic pain.

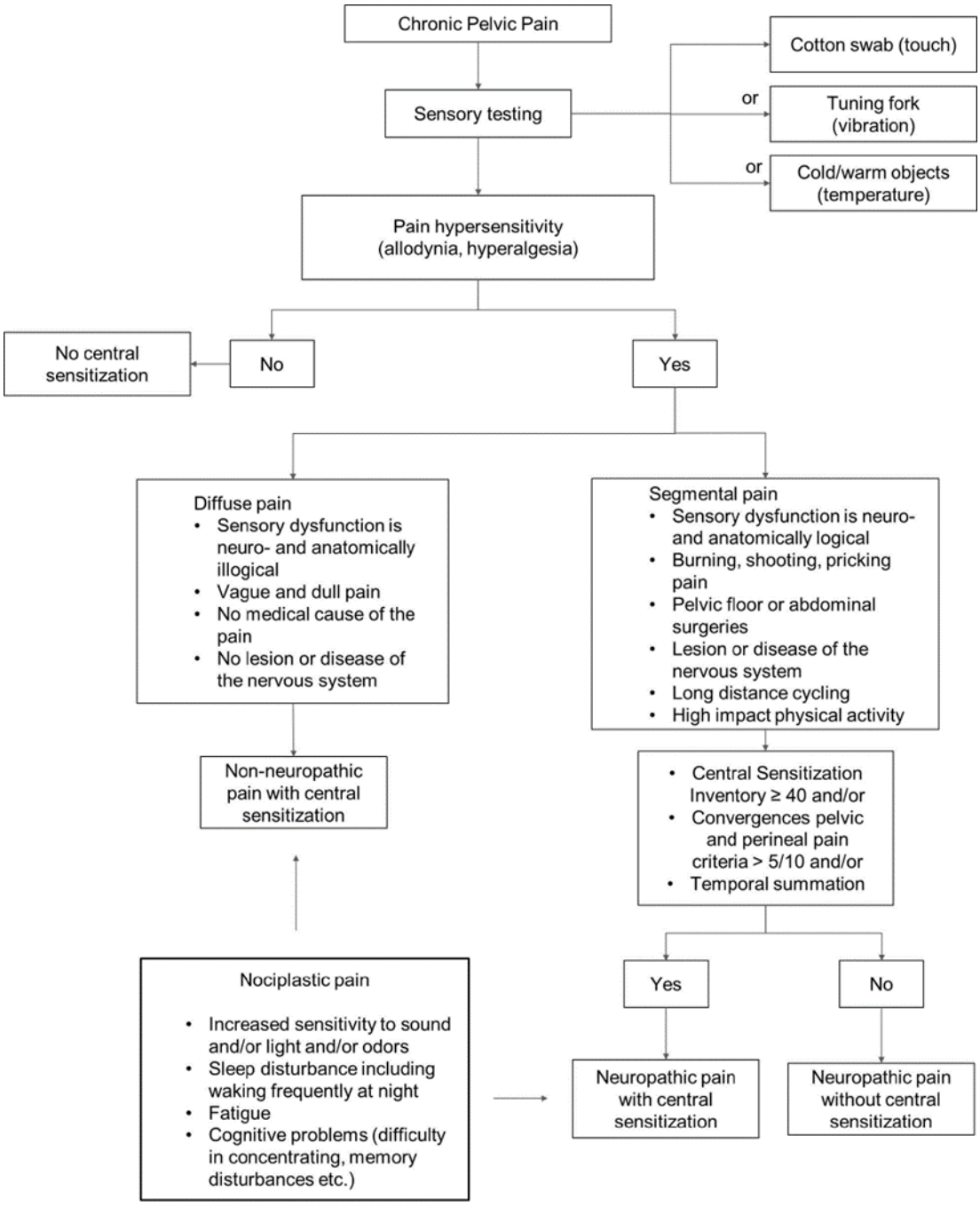

Figure 2. Flowchart of the clinical criteria suggestive of central sensitization in women with chronic pelvic pain.

Psychosocial evaluation

The experience of pain in general is currently understood as an interdependent sum of biological, psychological and social factors[75]. In the case of CPP, there is strong evidence on the role of psychosocial factors[8,65,76].

Coexistence between chronic pain and mental disorders has been widely reported in the literature, with these conditions being more prevalent in women[77–79]. There is increasingly robust biological evidence on the bidirectional relationship of these conditions, with each condition tending to exacerbate the other. Functional magnetic resonance imaging (MRI) shows an overlap in the neural circuits that are activated in situations of pain and in negative mood states[77,78]. The neurotransmitters involved in these conditions, including serotonin, gamma-aminobutyric acid, glutamate, noradrenaline, dopamine, etc., are also shared[80]. Trait anxiety, trait sensory hypersensitivity and the defensive high anxious personality type have been associated with the extent of symptoms in CS in individuals with chronic low back pain[81] and these findings could possibly be extrapolated in the future to women with CPP. Trait anxiety has already been associated with chronic pain following Cesarean section[82]. Despite the limitations involved in determining the order in which the manifestations begin and in establishing a cause-effect relationship, the prognosis of patients with CPP is guarded when these aspects are not taken into consideration in conjunction[79,83,84].

The three emotional conditions most commonly found in individuals with chronic pain in general are anxiety, depression and anger[57]. A high frequency of anxiety, depression[79,83,85] and of mixed anxiety and depressive disorder[85] has been described in women with CPP. The prevalence of adverse childhood events (ACE), including sexual, physical[85–87] and emotional abuse[86,87], is also high in these women. Furthermore, the association between ACE and mental disorders in women with CPP is consistent[76,79,87] and should be taken into consideration in clinical practice. Physical or sexual abuse in adult life has also been associated with CPP as well as with anxiety, depressive mood, somatization, posttraumatic stress disorders[88] and pain-related disability[76]. In addition, women with CPP and a history of sexual abuse are reported to experience more severe pain[89] and efforts to reduce the intensity of pain tend to be less successful[67].

Other social stressors such as the death or illness of family members[67,88], poor education level[76,88] and unemployment[87] are also factors that have been associated with CPP. In fact, over 70% of women with CPP report some event that coincides with the onset of the pain, with a history of marital and/or family conflicts, traumas and obstetric events often being mentioned[67]. A poorer prognosis in the case of women with CPP has been associated with maladaptive thinking, beliefs about pain (catastrophic thinking)[83,89], and lower pain self-efficacy[83], either due to magnification of the pain symptom, poorer compliance with the proposed treatment or fewer coping behaviors. On the other hand, religiosity has been positively associated with quality of life in women with CPP[90]. Further studies are necessary to investigate psychological variables[65,83], religiosity and spirituality[90] in women with CPP.

In general, women with CPP have a poorer perception of their quality of life[91], precisely because CPP involves negative repercussions in the emotional, sexual, behavioral, relational, cognitive and professional spheres. Therefore, the investigation of psychosocial factors in women with CPP has been recommended in the guidelines of several associations such as the ACOG (2020)[8], the Society of Obstetricians and Gynaecologists of Canada[66], the International Society of Psychosomatic Obstetrics and Gynaecology[88], the Royal College of Obstetricians and Gynaecologists[92] and the European Association of Urology[93]. The use of self-administered questionnaires to be completed by the patients in the waiting room prior to medical consultation or even during consultation has been suggested[8,65,66].

Of the various instruments aimed at investigating anxiety, the Generalized Anxiety Disorder-7 (GAD-7) has often been used in studies. It is a short, 7-item self-report questionnaire that indicates the presence of symptoms of anxiety in the preceding two weeks[94]. One option for the investigation of depression is the 9-item Patient Health Questionnaire (PHQ-9), which investigates the presence of depressive symptoms in the preceding two weeks and is based on the diagnostic criteria for major depression listed in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[95]. Another option is the Hospital Anxiety and

Depression Scale (HADS), a 14-item self-report scale in which seven of the items deal with anxiety (HAD-A) and seven with depression (HAD-D)[96]. The choice of the most appropriate instrument for women with CPP should be guided by, among other factors, the objectives behind the investigation (research or clinical practice), the characteristics of the population, and the existence of translated, culturally adapted and validated versions of the instrument.

The Pain Catastrophizing Scale (PCS) is the instrument suggested to identify catastrophizing. PCS is a 13-item tool with three different domains: rumination, magnification and helplessness[97]. A cut-off score ≥ 30 is considered indicative of catastrophizing behavior[98]. Attention should be paid to sexual function when conducting an anamnesis of women with CPP[66], since, according to a previous report, 81% may present with sexual dysfunction[68].

In relation to CS, psychological aspects were not included in Part A of the CSI[62], perhaps because the sensitivity and specificity of this instrument are poor in relation to this condition[69]. Nevertheless, the authors appear to recognize the importance of these issues by having included anxiety/panic attacks and depression in Part B of the CSI[62].

The psychometric instruments mentioned, as well as many others reported in the literature, can be used both at the initial medical consultation to enable diagnosis to be reached and sporadically thereafter during the follow-up of women with CPP to monitor prognosis and outcome[89].

Another option is to investigate, within the scope of the clinical interview, topics such as quality of life, sexual function, beliefs regarding pain, strategies for dealing with pain, family, social and religious support networks, and the impact of pain on an individual's professional life[8,65,66,90]. The most important factor for a woman with CPP may be feeling that her complaints are being taken seriously and that she is being listened to, not necessarily through the use of previously validated instruments. Because CPP is a condition that requires long term monitoring[99], more delicate subjects such as sexual function and a history of sexual

abuse can be gradually addressed at future consultations when the relationship of trust between the healthcare professional and the patient has already been established[65].

Physical examination

Since the physical examination should be more detailed than a routine gynecological examination, it has been suggested that it should be performed at a second appointment, giving the patient plenty of time to report the history of her pain during the first consultation[66].

With the possible primary causes and comorbidities associated with CPP in mind, the examiner should evaluate visceral, musculoskeletal and neurological aspects using visualization, bimanual palpation, mobilization of structures, speculum examination, and digital vaginal and/or rectal examination[65]. Pain at abdominal palpation that is exacerbated when the rectus abdominis muscles are contracted is suggestive of somatic pain, while visceral pain tends to decrease or remain unchanged when the head or the lower limbs are raised[8]. Notwithstanding, the physical examination tends to be normal in the majority of women with CPP, with the patient referring only discomfort during examination. This subjective finding is expected, since the patient is already in pain prior to palpation. More specific findings at physical examination are most commonly related to endometriosis[67]. Endometriosis can be identified as nodules on the abdominal wall in the proximity of a Cesarean scar or as the cause of reduced mobility of the uterus and adnexa, as ovarian cysts, or as lesions on the uterosacral ligaments and rectovaginal septum[100,101].

Signs of CS can be identified at physical examination without the use of any sophisticated devices or methods. The presence of allodynia is simple to detect by gently stroking a brush or cotton swab (Q-tip) or a metal object at room temperature over the area where the patient reports pain and asking the patient about the resulting experience[28]. Abdominal and perineal cutaneous allodynia may discriminate visceral pain from somatic pain[102]. Some authors have

suggested routine investigation of hypersensitivity (pressure hyperalgesia) of the pelvic floor in women with CPP as indicative of CS by performing an internal single digit exam at the bilateral pubococcygeus, iliococcygeus and coccygeus muscles[103]. More sensitive quantitative tests can be used in cases in which CS is not so obvious. In this respect, temporal summation, a marker of CS, can be investigated using a bedside test in which a cotton swab (Q-tip) is successively stroked down the abdomen from the infracostal margin in the midclavicular line to the groin. The test is considered positive if the pain worsens significantly with successive stimuli[63,104]. Hypersensitivity at sites that are distant from the clinical site of pain can be investigated using Quantitative Sensory Testing (QST)[105] and appears to be a sign of CS that is typically present in nociplastic pain[28]. In women with CPP, non-pelvic pressure pain sensitivity can be evaluated using an algometer on the non-dominant thumbnail, as previously reported[103].

Supplementary tests

The use of laboratory and imaging tests is limited in CPP and tests should be requested on an individualized basis, taking into consideration the symptoms of each individual patient and the findings at physical examination[8,65]. Consequently, the parsimonious use of diagnostic tests to identify coexisting diseases appears to be a consensus among groups of specialists in CPP[8,66], with screening for vaginitis and sexually transmitted infections, for instance, being performed if risk factors for these diseases are present[8], and urinalysis and urine culture being requested only in the presence of urinary symptoms[65].

The presence of pelvic tumors can be investigated using transvaginal ultrasonography (TVUS), a simple, inexpensive test with sensitivity and specificity similar to those of pelvic MRI when performed by experienced professionals[106]. Even deep endometriosis, endometriosis of the rectovaginal septum, and retrocervical, bowel and bladder endometriosis can be diagnosed using TVUS, with or without prior bowel preparation[107]. Neither MRI nor the cancer antigen 125 (CA-125) test should be used as routine for the purpose of diagnosing endometriosis[108].

Colonoscopy should be requested only when there is a history suggestive of bowel disease[8] or when the patient is ≥ 45 years old[109]. Diagnostic laparoscopy is increasingly considered second-line for the investigation of CPP in women and should only be requested for cases involving organ abnormalities such as, for example, ovarian cysts, hydrosalpinx, etc.[92]. In close to 40% of patients, no verifiable abnormality is found at laparoscopy and when adhesions and/or endometriosis are detected, and surgical interventions are performed, the outcome tends to be unsatisfactory[65,110,111].

Although its applicability remains impractical, it is worth mentioning that orthostatic intolerance to the tilt-table test is compatible with central hypervigilance and is suggestive of CS, and perhaps of catastrophizing in women with CPP[112].

Treatment

The treatment of CPP is challenging and not always effective, with most of the available guidance being based on other forms of chronic pain and lacking the endorsement of strong scientific evidence[8,65,66,92,100,113]. The treatment of potentially pain-causing conditions is imperative. In relation to COPCs, it has been shown that the treatment of pain of visceral origin can alleviate another form of pain even if it is of somatic origin, reinforcing the need to treat comorbidities in women with CPP[58]. Nevertheless, therapies aimed at reducing the perception of pain or at treating the events associated with the chronification of pain as a disease (CS for example) should be considered[66]. Different society guidelines recommend a multimodal treatment regimen aimed at maximizing the risk-benefit ratio[8,66,92].

Non-pharmacological treatment

Pain neuroscience education

Patients naturally tend to worry about uterine and ovarian diseases that are not necessarily the cause of CPP[65,67]. Therefore, physician-patient communication should be effective in making

it clear that the woman's concerns are being taken seriously and that the biological aspect is not being neglected; that the pain they experience is real and not imaginary, ruling out a primary mental disorder[114]; that their emotions and thoughts in relation to the pain affect the way in which they deal psychologically with the problem and which, biologically, can influence pain-excitatory pathways[98]; and finally, that adverse life experiences and psychological and/or relational conflicts matter, since they can predispose, precipitate and/or perpetuate the pain, particularly pain involving CS[114].

Pain neuroscience education (PNE) has been added to the usual forms of treatment, contributing towards reducing the intensity and catastrophizing of pain[8,65,66,98,115]. Some authors have suggested a practical guide for PNE when dealing with women with CPP that includes an explanation on pain mechanisms (P) and on the different factors associated with pain: somatic (S), cognitive (C), emotional (E), behavioral (B) and social (S), as well as a discussion with the patient on motivation (M) for treatment (the PSCEBSM model)[98]. Effective physician-patient communication should highlight the fact that the management of chronic pain requires long-term treatment, that the condition involves an important biopsychosocial cornerstone and requires changes in lifestyle, meaning that the woman has to play an active role in her treatment[65,98].

Psychotherapy

Although it is already recognized that the approach required in cases of CPP has to be interdisciplinary and must include psychosocial aspects[8,65], randomized clinical trials involving psychological interventions in women with this condition remain scarce. Mindfulness-based stress reduction and cognitive-behavioral therapy has been suggested for other types of chronic pain[116,117] as well as for CPP in women[89]. The outcomes, however, appear to be better when these treatments are aimed at training individuals to change their

way of thinking and their attitudes towards pain, particularly when the objective is decreasing pain catastrophizing[89,117] and increasing patient self-efficacy at managing pain[117].

Considering the high prevalence of ACE and mental disorders in women with CPP[85–87], family constellation[118] could be an interesting option for these patients, since a significant reduction in the intensity of CPP in women has already been shown with this approach[67].

Neuromodulation

The central and neurosensorial mechanisms of pain have been studied as approaches for the management of chronic pain refractory to conventional treatments, with spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) appearing the most promising[119–123]. Different studies have reported a reduction in pain, an improvement in quality of life and a reduction in the use of opioids in patients with chronic pain and CPP submitted to treatments involving DRGS and SCS (Table 1). Nevertheless, small sample sizes and the poor quality of scientific evidence have limited conclusions regarding the actual efficacy of these approaches in the treatment of CPP and other forms of chronic pain[124]. Therefore, despite studies showing the important role of CS in the physiopathology of CPP, intervention strategies based on these mechanisms are not yet well established in the scientific community.

Table 1: Studies on neuromodulation in the management of chronic pain

Authors, year	Country	Design	N	Type of pain	Treatment	Main results
Hunter & Yang, 2019[119]	USA	Case series	7	Chronic pelvic pain	DRGS[a]	Reduction of opioid use and pain relief in all patients.
Schu et al., 2015[120]	Europe	Retrospective	29	Groin pain	DRGS[a]	Mean reduction in pain of 71.4 ± 5.6%, with 82.6% of the participants reporting a reduction in pain of >50% at the last follow-up visit.
Levine et al., 2016[121]	Canada	Prospective	15	Chronic groin, pelvic and abdominal pain	SCS[b]	Reduction in pain intensity from 7.3±1.3 to 3.1±2.8, 3.8±2.4 and 4.2±3.2 at 3, 6 and 12 months, respectively.
Bridger et al., 2021[122]	USA	Prospective	55	Neuropathic pelvic pain	DRGS[a] and SCS[b]	Satisfactory response in 45.5% of 11 patients in the neuromodulation group versus 26.6% of 44 patients in the clinical treatment group after 25 and 33 months, respectively.
Deer et al., 2017[123]	USA	Randomized clinical trial	152	Complex regional pain syndrome and causalgia	DRGS[a] and SCS[b]	Reduction of ≥50% in pain in 81.2% of the DRGS[a] group versus 55.7% of the SCS[b] group after 3 months ($p<0.001$).

DRGS[a]: dorsal root ganglion stimulation; SCS[b]: spinal cord stimulation.

Dietary measures and physical activity

Changes in diet can prevent symptoms from becoming worse, particularly in patients with IBS or BPS. Lactose and/or fructose intolerance can be associated with IBS, and recommendations include controlling consumption of these substances[66]. In addition, fermentable oligosaccharides, disaccharides, monosaccharides, polyols, caffeine, alcohol and gluten should be temporarily avoided, particularly when associated with the aggravation of IBS symptoms, and the benefits of this restriction should be evaluated on an individualized basis[66,125]. In patients with BPS, recommendations include monitoring the dietary consumption of tomatoes, soya, condiments, pepper, caffeine, foodstuffs rich in sodium and citric fruits[126].

The World Health Organization (WHO) recommends aerobic physical activity of moderate intensity for at least 150 minutes/week, which has been shown to provide general health benefits and can reduce anxiety and depression, relevant comorbidities associated with CPP[127]. Nevertheless, there is still no strong scientific evidence confirming the effectiveness of exercise on chronic pain in adults or on endometriosis-related pain[128,129].

Pharmacological treatment

Pharmacological recommendations for CPP are based more on expert opinions than on randomized clinical trials[8,66,92,100,113]. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used empirically as the first-line treatment of CPP[5,68,100], particularly during flare-ups involving increasing pain levels, in view of their accessibility, tolerability, low cost and familiarity to patients.

The uninterrupted use of progestogens or of combined oral contraceptive (COC) pills to induce amenorrhea can be initiated early in cases when pain tends to worsen cyclically, which occurs in 81% of cases of CPP[15]. The benefit achieved with this treatment is expected, irrespective of whether or not there are signs of endometriosis present[66–68]. The progestogens most commonly used in clinical practice are norethisterone, desogestrel, dienogest and the

levonorgestrel-releasing intrauterine system[100,130,131]. The efficacy of the various progestogens is similar and the satisfaction rates of patients with CPP and endometriosis are around 70%; however, norethisterone may be the progestogen of choice in view of its lower cost[130]. Medroxyprogesterone acetate is also an option, preferentially in the form of the three-monthly injection[131]. Conversely, use of GnRH agonists is limited, since they cannot be used over the long term because of their high cost and side effects (hot flashes, vaginal dryness and osteoporosis), in addition to the fact that they need to be combined with add-back hormone replacement therapy[66,132]. A Cochrane review failed to find any reliable evidence on the use of COCs for the treatment of endometriosis-related pain[133]. Nevertheless, various medical societies and different experts in CPP argue that COCs are effective in two-thirds of patients with CPP, particularly when used continuously, irrespective of whether endometriosis has been confirmed by laparoscopy or not[66,92,100,113].

The tricyclic antidepressant amitriptyline has long been used in the treatment of fibromyalgia, BPS, IBS and CPP, particularly when associated with neuropathic pain, and anxiety and/or depression, despite a lack of robust scientific evidence[8,67,92,134–138]. On the other hand, nortriptyline, imipramine and desipramine appear to be ineffective for the treatment of neuropathic pain[139–141].

Antidepressants such as noradrenaline and serotonin reuptake inhibitors have been shown to have a positive effect on pain and on quality of life; however, their effect on depression is minimal and they have no effect at all on anxiety in patients with various types of neuropathic pain, as shown in a recent systematic review with meta-analysis that included 32 studies[142]. Of this class of drugs, duloxetine at the dose of 60 mg/day is able to reduce pain in patients with diabetic neuropathy and/or fibromyalgia[143] and, although no studies have yet been conducted in women with CPP, duloxetine could be tried by inference when this pain is neuropathic[8].

The indication of opioids for the treatment of women with CPP is controversial. On the one hand, their use may result in a return to normal activities for patients who have failed to respond to routine painkillers[66]. On the other hand, the chronic use of opioids is associated with a greater risk of adverse events, tolerance, overdose and dependence, which led the Centers for Disease Control and Prevention (CDC) to recommend that their use should be avoided as first-line treatment or as routine therapy[8]. In addition, evidence suggests more benefits with non-pharmacological treatment and with non-opioid pharmacological treatment when compared to the chronic use of opioids, including fewer side effects[144].

A systematic review that included four randomized controlled trials and 469 participants showed that the anticonvulsant gabapentin reduced CPP in women after six months of use, with the principal side effects being dizziness and somnolence[145]. In a Cochrane review that included 45 studies and 11,906 participants, pregabalin reduced pain by at least 30% in patients with diabetic and post-herpetic neuropathy at a dose of 300 mg/day and in patients with post-traumatic neuropathic pain, whether classified as mixed or not, at a dose of 600 mg/day, with similar side effects to those found with gabapentin[146]. Extrapolating these data, pregabalin could be recommended for the treatment of CPP[8].

The use of delta-9-tetrahydrocannabinol (THC), the active ingredient in *Cannabis sativa*, is controversial. Although the possibility of using it to manage chronic pain has motivated an increasing number of studies into its effects on the modulation of pain perception, different systematic reviews found poor quality evidence in support of the use of medicinal cannabis in the treatment of chronic non-cancer pain[147–150]. In fact, these studies come with the recommendation to use cannabinoids as the third or fourth line of treatment when other analgesics and opioids have failed and warn of a lack of studies with better scientific evidence.

The different approaches to the treatment of CPP mentioned above could be applied to the conditions specified hereafter. Since they are conditions more commonly associated with target organs, some of the characteristics of their treatment will be presented in detail.

In a randomized study in which participants and pain evaluators were blinded to allocation group, performing laparoscopic adhesiolysis of pelvic and abdominal adhesions failed to result in any difference in pain scores and improvement to quality of life over one year of follow-up compared to not performing the procedure[110]. Over a 12-year follow-up period, the group submitted to adhesiolysis had a poorer outcome in terms of pain-free time, the use of analgesics, number of medical consultations and the need for subsequent surgery[111]. Therefore, no benefit is attributed to performing adhesiolysis in women with CPP.

In the therapeutic approach to endometriosis, inducing amenorrhea through the use of progestogens or COCs has been recommended[130,131,151], particularly for women who do not wish to become pregnant. Surgery may be recommended for cases that prove refractory to clinical treatment, in particular when ovarian endometriomas, endometrioma of the abdominal wall, bowel obstruction and/or ureteral obstruction are present[152]. Hysterectomy with bilateral salpingo-oophorectomy is the most effective treatment for endometriosis-associated CPP[66]; however, this procedure is the exception when all other options have failed. A Cochrane review that included 14 clinical trials and 1,563 participants was unable to conclude whether laparoscopic surgery for minimal to severe endometriosis improves pain in women with CPP. Further studies are required to compare laparoscopic interventions with clinical and lifestyle interventions; nonetheless, data on the safety of these surgeries remain insufficient[153]. Both the aromatase inhibitors and the promising oral gonadotropin-releasing hormone (GnRH) receptor antagonists are possible treatment options[100,113].

Trigger points on the abdominal wall are painful points in the musculature of this region. Although it has been suggested that the injection of local anesthetics, with or without corticoids, at these trigger points may be beneficial, the evidence in favor of their use is as yet

insufficient[8,66,92]. A double-blind, randomized clinical trial with 80 women showed a beneficial effect of injections of a local anesthetic after 1-4 applications; however, no benefit was obtained with the addition of botulinum toxin after 60 days[154].

Myofascial physical therapy, a pelvic floor-focused treatment, was found to result in a reduction in psychological distress and in pain intensity over a 9-month follow-up time in women with CPP associated with BPS and provoked vestibulodynia in a non-randomized prospective study without a true control group and with a small sample size[155]. A systematic review covering the period from 2000 to 2019 included four randomized clinical trials (RCTs), although three were considered of only poor to moderate quality[156]. According to the results, physiotherapy for pelvic floor muscle spasms was shown to be beneficial in women with CPP except in patients with BPS. Therefore, although partially discordant, the data available up to the present moment suggest that pelvic floor physiotherapy (PFP) is another option to be offered as treatment for these women while we await the results of more robust studies on the subject.

The treatment of IBS depends on its clinical presentation, with symptoms consisting predominantly of constipation, diarrhea or mixed symptoms[157]. In an overview of Cochrane systematic reviews, taking the poor quality of the primary studies into consideration, only antispasmodics and antidepressants appear to be beneficial of all the pharmacological treatments proposed, while psychological therapy would be the only beneficial treatment among the non-pharmacological interventions[158].

According to a Cochrane review, there is insufficient evidence to endorse any of the 65 different treatments for BPS, which involve medication, behavioral therapy and physiotherapy[159]. Nevertheless, despite the fact that the proposed treatments for this condition are far from ideal, measures involving neuroeducation and dietary measures are considered first-line[160]. Amitriptyline, which is widely used and inexpensive, is a second-line option,

with some analgesic, anticholinergic, sedative, anxiolytic and antidepressant effects, which could improve urinary frequency if the patient is able to tolerate at least 50 mg/day[135].

Figure 3 provides a summary of the principal aspects to be taken into consideration in the management of women with CPP.

Figure 3. Management of women with chronic pelvic pain.

Footnote: [a]VAS: visual analogue pain scale (0-10). VAS>3 (quarterly), VAS≤3 (biannual; if stable over ≥ one year, end of follow-up); [b]experience of the surgeon or multidisciplinary team. CSI: Central Sensitization Inventory; CS: Central sensitization; TVUS: Transvaginal ultrasonography; pMRI: Pelvic magnetic resonance imaging; USG: Ultrasonography; IBS: Irritable bowel syndrome; BPS: Bladder pain syndrome; NSAIDs: Non-steroidal anti-inflammatory drugs; SCS: Spinal cord stimulation; DRGS: Dorsal root ganglion stimulation; CBT: Cognitive behavioral therapy; FC: Family constellation; ART: Assisted reproductive techniques.

Conclusions

CPP is an intriguing condition that may not be associated with an obvious cause and, even when a cause is identified, the extent of the disease is not always proportional to the intensity of the pain. The treatment of the peripheral disease only occasionally results in the cure or prolonged remission of the symptoms. Even so, a timely scheme of investigation and treatment of associated comorbidities is still recommended, with surgery being limited to extremely specific circumstances. Increasing efforts have been dedicated to understanding the physiopathological mechanisms involved in the cause and/or perception of pain and in the clinical recognition of CPP with the aim of offering physiopathology-based targeted therapies that will be effective over the long term. In this respect, early clinical identification of a phenotype for CS is possible and should be an aim, while perhaps relinquishing expensive tests and those of little clinical utility. The treatment of refractory chronic pain with neuromodulation appears promising; however, studies involving women with CPP are still sparse. Furthermore, it is vital that the team providing the treatment validates the patient's pain as a real symptom, establishing a relationship of trust with women who have often consulted with many doctors without feeling that they have been heard. PNE has proven extremely important in enabling patients to understand the various factors associated with pain and encouraging them to participate more actively in their treatment. PFP offers one more treatment option for women with CPP. The psychosocial approach is an important part of the treatment of women with CPP. Therapeutic techniques aimed principally at altering pain-related thoughts and behaviors, and those dealing with emotions associated with adverse life experiences and relationship conflicts, have been described in the literature. Results have been positive, even in relation to CS, and should encourage further in-depth studies. In view of the aforementioned factors, the treatment of CPP in women is challenging and personalized care within an interdisciplinary perspective is the best option.

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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4.2 ARTIGO 2

Parenting Styles, Mental Health, and Catastrophizing in Women with Chronic Pelvic Pain: A Case-Control Study

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Parenting styles, mental health, and catastrophizing in women with chronic pelvic pain: a case-control study

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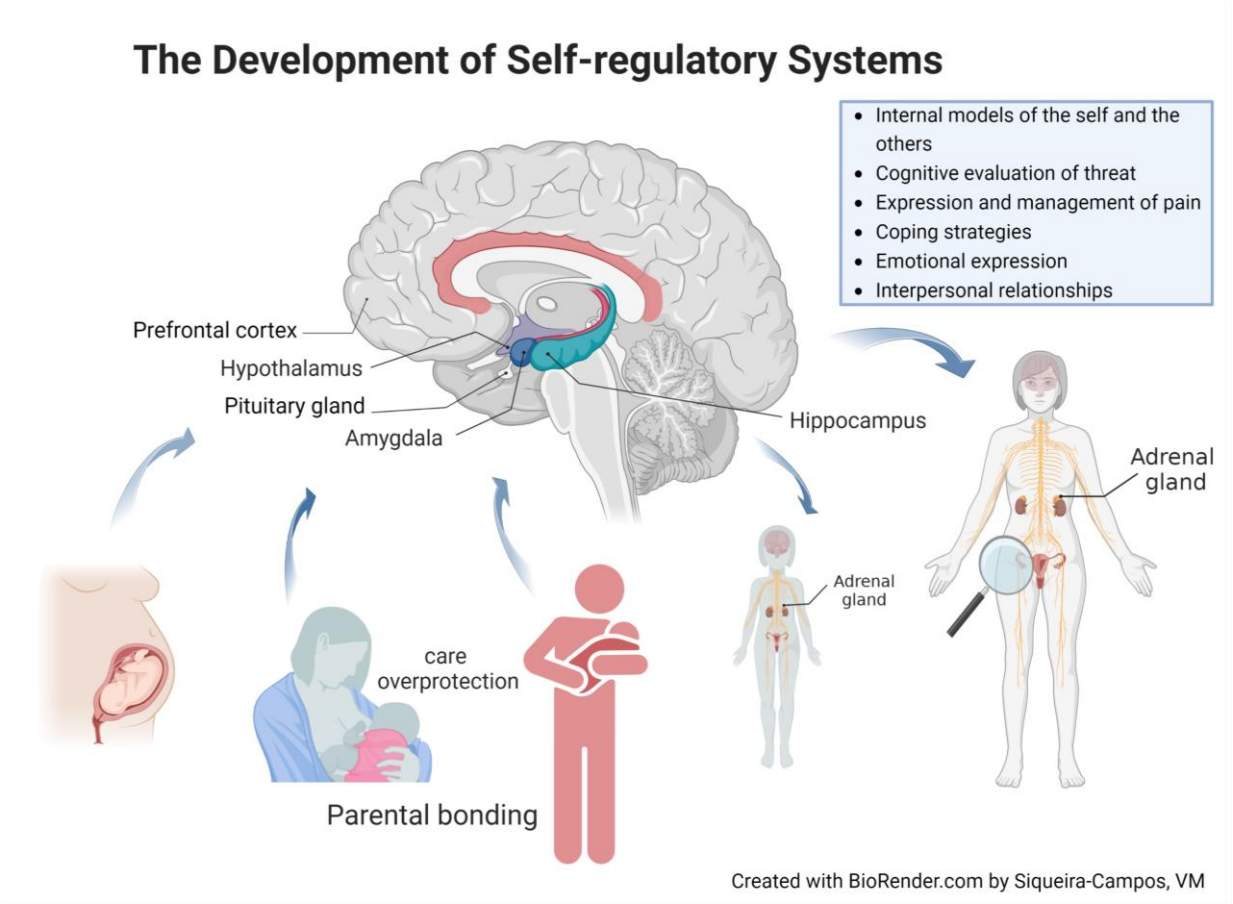
Abstract: Chronic pelvic pain (CPP) in women is a highly prevalent condition worldwide and requires multimodal treatment. Adverse childhood experiences have been associated with CPP in women, while allodynia and poor outcomes have been linked to pain catastrophizing in these patients. Pain perception has been associated with parenting style during childhood. The objective of this study was to investigate the association between parenting style, pain catastrophizing, anxiety, depression and CPP in women. A case–control study was conducted between May 2018 and August 2021 with 123 women with CPP and 123 pain-free controls. Questionnaires were used to collect participants' data. The association between parenting style and CPP was assessed using multiple logistic regression, with odds ratios (OR) and 95% confidence intervals (CI) being calculated. The correlation between catastrophizing, pain intensity, pain duration, anxiety, depression, and parenting style in women with CPP was assessed using Spearman's rank correlation coefficient (r). A higher frequency of low maternal care (60.7% versus 45.2%; $p = 0.026$), anxiety (79.7% versus 56.9%; $p < 0.001$), depression (73.2% versus 56.1%; $p = 0.008$) and physical violence (31.7% versus 14.6%; $p = 0.003$) was found in the CPP group compared to the controls. There was no association between parenting style and CPP in the adjusted analysis. A positive correlation was found between catastrophizing and pain intensity ($r = 0.342$; $p < 0.001$), anxiety ($r = 0.271$; $p = 0.002$), depression ($r = 0.272$; $p = 0.002$), and maternal overprotection ($r = 0.185$; $p = 0.046$). A negative correlation was found between anxiety and maternal ($r = -0.184$; $p = 0.047$) and paternal ($r = -0.286$; $p = 0.006$) care and between depression and maternal ($r = -0.219$; $p = 0.018$) and paternal ($r = -0.234$; $p = 0.026$) care. The present results suggest a significant but weak association of parenting style with pain catastrophizing, the mental health of women with CPP, and the way in which they experience pain.

Keywords: parenting styles; women's health; anxiety; depression; coping skills; emotional regulation

Graphical abstract



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1. Introduction

Chronic pelvic pain (CPP) is a highly prevalent condition in women worldwide, particularly during the reproductive years [1]. In around 35% of patients, no visible lesions are present [2]. CPP exerts negative effects on women that include poor mental health [3], poor quality of life, sexual dysfunction [4], relationship difficulties and impaired work capacity [5]. Since this condition requires complex treatment, and positive outcomes are limited, it has been associated with a heavy economic and social burden [6]. A multimodal, interdisciplinary approach in which the different physiological and pathological mechanisms involved are taken into consideration has been recommended to improve outcomes [7].

Pain is an inherently personal experience [8] involving a multidimensional process that encompasses biological, psychological [9], behavioral [10] and socio-environmental [11] factors, as well as different individual perceptions [12]. Consequently, biopsychosocial models involving self-regulatory systems [13–15] and the attachment theory [16] have been proposed in an attempt to explain the experience of pain, particularly persistent pain. These models take the phylogenetic evolution of the nervous system into consideration, with the focus being on human survival. In this respect, the basic needs of each individual are considered to be adaptation to the environment, bonding and security [13,17]. Through physiological (allostasis), emotional, behavioral, and social processes, the functions of different structures and neural circuits overlap to guarantee the internal stability of the body (homeostasis) [18], identify safety or danger signs, respond to conflict or fight situations, trigger the flight or freeze response, and create bonds of attachment and social coexistence [16,17]. Therefore, the nervous system works in conjunction with the endocrine and immune systems as a single functional entity, modulating the defense response against internal and external threats [19]. However, an impaired ability to assess risk can exacerbate or prolong defense responses, interfering with homeostasis and influencing the individual's emotional states. This can generate body dysfunctions, altered pain signaling such as hyperalgesia and allodynia, and may interfere with social bonding and interactions [17].

Part of the human nervous system is structurally and/or functionally immature at birth [20], with the development of self-regulatory systems being increasingly modeled both by genetic aspects and by the socio-affective environment [11,20,21]. In this respect, human adults (in general the parents, or in their absence, other caregivers) play an essential role in

acting as co-regulators of the developing child [17]. Caregivers are expected to provide a safe basis of affection and to stimulate progressive autonomy in the child [16]. On the other hand, children gradually construct positive or negative internal models of the self and of others based on the responsivity, consistency and sensitivity provided by their caregivers, allowing their needs, particularly when they are ill, afraid or in pain, to be satisfactorily met [16]. During these initial interactions, perceptions of parental care and overprotection [22] lead children to develop secure or insecure attachment patterns [23]. These patterns can have long term repercussions on their cognitive evaluation of threat, expression, and management of pain, coping strategies, emotional expression, and interpersonal relationships [24,25]. Ultimately, this leads to the finding that optimal parenting essentially consists of high care and low overprotection [22].

Dysfunctional parenting styles during childhood have been associated with chronic pain in adolescence [26] and in adulthood [24,27], with this association sometimes being mediated by depression [26–28]. Pain catastrophizing, a psychological tendency to negatively magnify the experience of pain, has been associated with insecure attachment patterns [29] as well as with parental support and the way pain symptoms, particularly in early childhood, are monitored [10]. Catastrophizing, as a pain coping response, has also been associated with a greater intensity of pain [30], allodynia [12] and poor outcomes [31] in women with CPP. Furthermore, adverse childhood experiences (ACEs) such as physical and emotional abuse have been associated with CPP in women [32].

Therefore, the current study aimed to analyze the frequency of parental bonding styles in women with CPP compared to a control group of pain-free women, to investigate the association between parental bonding and CPP, and to examine the association between pain catastrophizing and the intensity and duration of the pain, anxiety, depression, and parental bonding in CPP patients. Our initial hypotheses were that women with CPP would perceive the quality of their parental bonding in childhood as more dysfunctional than pain-free women, that anxiety and depression would be associated with dysfunctional parenting styles in women with CPP, and that pain catastrophizing would be associated with greater pain intensity, a higher consumption of pain medication, longer duration of pain, anxiety, depression and adverse parenting styles.

2. Materials and Methods

2.1. Study Design

An observational, case–control study was conducted between May 2018 and August 2021 at the CPP outpatient clinic and family planning outpatient clinic in the Department of Obstetrics and Gynecology, Teaching Hospital of the Federal University of Goiás, Goiânia, Goiás, Brazil.

2.2. Sample Size

The sample size requirements for case–control study designs [33] were taken into consideration. Sample size calculation was based on the following parameters: significance level of 0.05 ($\alpha = 0.05$), statistical power of 0.80 ($\beta = 0.20$), ratio of cases to controls of 1 ($k = 1$), odds ratio of 2.5 (OR = 2.5), and an expected proportion of dysfunctional parenting style of 54.4% in women with CPP, as previously found in a pilot study [34]. The minimum number of women needed for the total sample was estimated at 202, 101 women with CPP and 101 pain-free controls.

2.3. Participants

Women attending the CPP outpatient clinic, or the family planning outpatient clinic (women without CPP/control group) were consecutively invited to participate in the study. The criteria for inclusion in the CPP group were age ≥ 18 years and ≤50 years, and having experienced lower abdominal pain during the preceding three months that had begun at least six months previously and was not exclusively cyclical or coitus-related, irrespective of whether the woman was receiving treatment for CPP or the cause of CPP. The criteria for inclusion in the control group were age ≥ 18 years and ≤50 years and not having experienced lower abdominal pain in the preceding three months. The range of age defined for both groups was ≥18 and ≤50 years, taking into consideration the legal age of consent and the end of the reproductive years, respectively. Pregnancy, either current or in the preceding 12 months,

post-menopause, surgery in the previous three months and a history of cancer were considered exclusion criteria for both groups. Providing signed informed consent to participate in the study was part of the inclusion criteria in both groups. Table 1 describes the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria.

	Inclusion Criteria	Exclusion Criteria
Both groups	• Age ≥ 18 and ≤50 years • Signed informed consent	• Being currently pregnant or having been pregnant in the preceding 12 months • Being postmenopausal • Having undergone any surgery in the previous 3 months • History of cancer
CPP group	• Lower abdominal pain for ≥6 months, not exclusively cyclical or coitus-related	
Pain-free group	• No lower abdominal pain in the preceding 3 months	

CPP: chronic pelvic pain.

2.4. Procedure

Individual interviews were conducted to obtain sociodemographic, behavioral, and clinical data, and specific instruments were used to assess parental bonding, anxiety, and depression. In the group of women with CPP, further investigation was conducted to assess pain catastrophizing. Data collection was performed in a private room to guarantee participants' privacy.

2.5. Measures

2.5.1. Demographic Data

The following sociodemographic, behavioral and clinical characteristics were investigated in both groups: age, skin color (white/non-white), body mass index (BMI; kg/m^2), years of schooling (<12 years/≥12 years), marital status (partner/no partner), monthly per capita income (Brazilian real, R$), employment status (employed, in paid work/unemployed, retired, homemaker), whether physically active (≥150 min/week) in the preceding month (yes/no), smoker (yes/no), alcohol consumption in the previous three months

(yes/no), parity (0/≥1) and a history of abdominal and/or pelvic surgery (yes/no). Women who currently smoked or who had stopped smoking within the previous year were considered smokers, while those who had never smoked or who had stopped smoking more than a year previously were considered non-smokers. Physical abuse was investigated from the question: "Have you ever suffered physical abuse?" (yes/no). Sexual abuse was investigated by asking: "Have you ever suffered sexual abuse?" (yes/no). Difficulty relating to others was identified from answers to the question: "Are you having difficulties in your relationship with someone or are you in conflict with anyone?" (yes/no). A history of chronic disease was investigated based on answers to the following question: "Do you have any chronic disease such as hypertension, diabetes, hypothyroidism or migraine?" (yes/no).

The participants of the CPP group were asked about the duration of their pain. Pain intensity in the two weeks preceding the interview was investigated using a 10 cm (0–10 points) numerical rating scale in which 0 represents the complete absence of pain and 10 the worst pain imaginable. Participants in this group were also asked whether they had used any medication to manage their pain in the preceding month (yes/no).

2.5.2. Assessment of Parental Bonding

The Parental Bonding Instrument (PBI) was used to determine parenting styles as perceived by the participants based on memories of their parents over the first sixteen years of their life [22]. This 25-item questionnaire consists of two domains: care (12 items) and overprotection (13 items). The "care" domain comprises items such as: "Spoke to me in a warm and friendly voice" and "Made me feel I wasn't wanted". Items in the "overprotection" domain include: "Invaded my privacy" and "Let me decide things for myself". Specific scoring instructions for the PBI are based on a 4-point, Likert-type scale (very like, moderately like, moderately unlike and very unlike), with scores that range from 0 to 3; however, not all the items are scored in the same direction [22]. This instrument is completed with regard to both mothers and fathers separately, using separate cut-off points established for each domain. A care score of 27.0 and a protection score of 13.5 for mothers and a care score of 24.0 and a protection score of 12.5 for fathers have been established as the cut-off points for assigning individuals to "high" or "low" categories of parental bonding [22]. The

PBI has been validated cross-culturally for use in a variety of languages, including Brazilian Portuguese [35].

2.5.3. Assessment of Anxiety

Symptoms of anxiety were investigated using a version of the Generalized Anxiety Disorder-7 (GAD-7) scale that has been translated into Brazilian Portuguese and validated for use in Brazil [36]. This is a 7-item, self-report questionnaire referring to the preceding two weeks, with questions such as: "How often have you been bothered by becoming easily annoyed or irritated" or "How often have you been bothered by not being able to stop or control worrying." Scores range from 0 to 3 for each item (0 = not at all; 1 = several days; 2 = more than half the days; and 3 = nearly every day). Total scores range from 0 to 21, with ≥10 being the cut-off score for anxiety [37].

2.5.4. Assessment of Depression

The 9-item Patient Health Questionnaire (PHQ-9), translated and validated for use in Brazilian Portuguese [38], was used to identify symptoms of depression over the preceding two weeks. This self-administered questionnaire is based on the diagnostic criteria for major depression outlined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and includes the question: "Over the last two weeks, how often have you been bothered by any of the following problems?", e.g., "feeling down, depressed or hopeless." Scores range from 0 to 3 for each item, with 0 meaning "not at all"; 1 "several days"; 2 "more than half the days" and 3 "nearly every day". A score ≥10/27 is considered indicative of depression [37].

2.5.5. Assessment of Pain Catastrophizing

The Pain Catastrophizing Scale (PCS), translated and validated for use in Brazilian Portuguese [39], was used to identify catastrophizing [40] in the CPP group. This self-report questionnaire consists of 13 items distributed across three domains: helplessness,

magnification and rumination. The instrument asks patients to reflect on past painful experiences and to indicate the degree to which they experienced each of the 13 thoughts or feelings when experiencing pain, such as: “It’s terrible and I think it’s never going to get any better.” The total score for the PCS ranges from 0 to 52, with scores for each item being based on a 5-point, Likert-type scale ranging from 0 (not at all) to 4 (all the time). A score ≥30 is considered indicative of a clinically relevant level of catastrophizing [41].

2.6. Statistical Analysis

In the descriptive analysis, absolute and relative frequencies were calculated for the qualitative or categorical variables, and means and standard deviations (SD) were calculated for the continuous quantitative variables. Yates’s chi-square test and the Mann–Whitney test were used to compare characteristics between the groups. The frequency of parenting styles was compared between the two groups using Yates’s chi-square test. Univariate and multiple logistic regression analyses were conducted to determine possible associations between each parenting style and CPP in women, and the odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated in the initial unadjusted form and then after adjustment for the following potential confounders in addition to parenting style: age, alcohol consumption, physical abuse, sexual abuse, relationship difficulties, abdominal/pelvic surgery, anxiety and depression. Spearman’s correlation coefficient (r) was used to verify possible correlations between catastrophizing, pain intensity, the duration of pain, anxiety, depression, and parental bonding style (maternal and paternal care and overprotection) in the group of women with CPP. The strength of the correlation was described as zero (0), weak (0–0.3), moderate (0.4–0.6), strong (0.7–0.9) and perfect (1), including the respective direction: positive (+) or negative (-) [42]. The SPSS software package, version 20, was used throughout the statistical analysis. Significance level was set at 0.05 [43].

2.7. Ethics

All the procedures performed complied with the requirements established in the Declaration of Helsinki. The internal review board of the Federal University of Goiás

Teaching Hospital reviewed and approved the study protocol under reference number 2631464. All the participants signed a written informed consent form.

3. Results

Overall, 294 women were invited to participate in the study. Since 28 women with CPP and 20 potential controls were excluded, the final sample consisted of 246 women, 123 recruited to the CPP group and 123 to the control group of women without CPP, as shown in

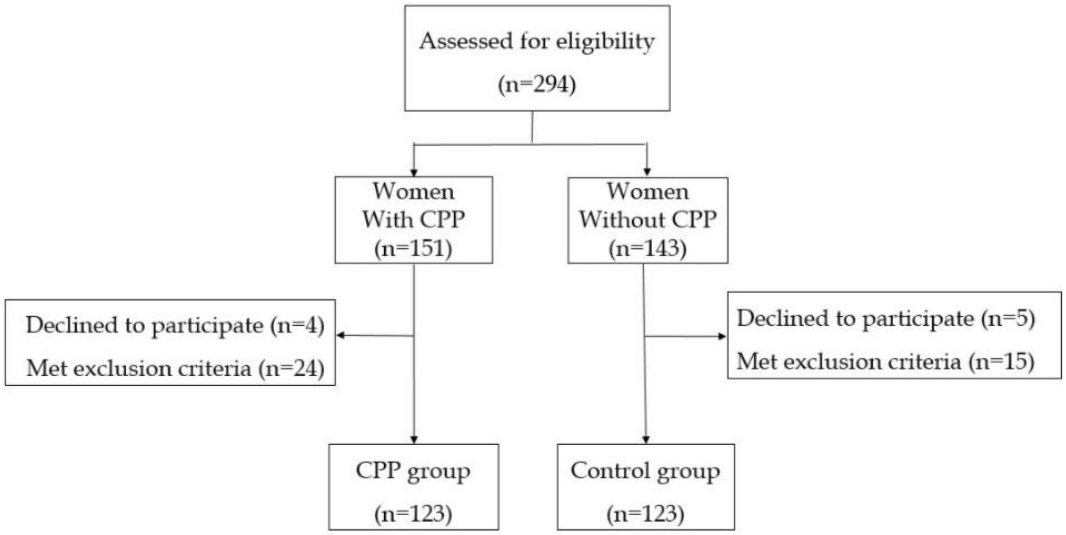

Figure 1. Flowchart of the study population. CPP: Chronic Pelvic Pain.

Table 2 describes the characteristics of the participants. The mean age of the women in the CPP group was 37.0 ± 6.9 years (± SD) compared to 31.9 ± 7.2 years for those in the control group ($p < 0.001$). Relationship difficulties were more common in the women with CPP (39.8% in the CPP group vs. 19.5% in the control group; $p = 0.001$). In the CPP group, 79.7% of the women were found to have anxiety compared to 56.9% in the control group ($p < 0.001$), while depression was identified in 73.2% of women in the CPP group and in 56.1% of the controls ($p = 0.008$).

Table 2. Characteristics of the study participants.

Characteristics	CPP Group (n = 123)	Control Group (n = 123)	*p*-Value
Age (mean ± SD; years) [1]	37.0 ± 6.9	31.9 ± 7.2	<0.001 [c]
Body mass index (mean ± SD; kg/m^2) [1]	27.5 ± 5.4	27.1 ± 5.8	0.310
Monthly per capita income (mean ± SD; R$) [1]	743.28 ± 496.68	748.08 ± 645.27	0.926
	n (%)	n (%)	
Skin color [2]			0.447
White	31 (25.2)	25 (20.3)	
Non-white	92 (74.8)	98 (79.7)	
Years of schooling [2]			0.347
<12 years	46 (37.4)	38 (30.9)	
≥12 years	77 (62.6)	85 (69.1)	
Employment status [2]			0.797
Employed/in paid work	67 (54.5)	70 (56.9)	
Unemployed/retired/homemaker	56 (45.5)	53 (43.1)	
Marital status [2]			0.893
With a partner	82 (66.7)	80 (65.0)	
No partner	41 (33.3)	43 (35.0)	
Smoking [2]			0.055
Smoker	10 (8.1)	21 (17.1)	
Non-smoker	113 (91.9)	102 (82.9)	
Alcohol consumption [2]			0.002 [b]
Yes	48 (39.0)	73 (59.3)	
No	75 (61.0)	50 (40.7)	
Physically active [2]			0.517
Yes	26 (21.1)	21 (17.1)	
No	97 (78.9)	102 (82.9)	
Physical abuse [2]			0.003 [b]
Yes	39 (31.7)	18 (14.6)	
No	84 (68.3)	105 (85.4)	
Sexual abuse [2]			0.062
Yes	27 (22.0)	15 (12.2)	
No	96 (78.0)	108 (87.8)	
Relationship difficulties [2]			0.001 [b]
Yes	49 (39.8)	24 (19.5)	
No	74 (60.2)	99 (80.5)	
Parity [2]			0.148
0	29 (23.6)	19 (15.4)	
≥1	94 (76.4)	104 (84.6)	
Chronic disease [2]			0.071
Yes	93 (75.6)	79 (64.2)	
No	30 (24.4)	44 (35.8)	
Abdominal/pelvic surgery [2]			0.017 [a]
Yes	96 (78.0)	78 (63.4)	
No	27 (22.0)	45 (36.6)	
Anxiety [2]			<0.001 [c]
Yes	98 (79.7)	70 (56.9)	
No	25 (20.3)	53 (43.1)	
Depression [2]			0.008 [b]
Yes	90 (73.2)	69 (56.1)	
No	33 (26.8)	54 (43.9)	

CPP: Chronic pelvic pain. SD: standard deviation. [1] Mann–Whitney U test. [2] Yates chi-square test. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

Perceived low maternal care was significantly more common in women with CPP (60.7% vs. 45.2%; $p = 0.026$). There was no statistically significant difference between the groups insofar as the other parental bonding styles were concerned (Table 3). Six women with CPP and eight controls had had no contact with their mothers during childhood and/or adolescence, while 24.8% of the study population (32 women with CPP and 29 controls) reported having had no contact with their fathers during that period (data not shown as table).

Table 3. Parenting styles in women with chronic pelvic pain (CPP) compared to pain-free controls.

Parenting Styles	CPP Group		Pain-Free Controls		*p*-Value
	n	%	n	%	
Maternal	117		115		
Care					
Low	71	60.7	52	45.2	0.026 [a]
High	46	39.3	63	54.8	
Overprotection					
Low	35	29.9	34	29.6	>0.999
High	82	70.1	81	70.4	
Paternal	91		94		
Care					
Low	45	49.5	46	48.9	>0.999
High	46	50.5	48	51.1	
Overprotection					
Low	22	24.2	30	31.9	0.314
High	69	75.8	64	68.1	

Yates chi-Square test. [a] $p < 0.05$.

In the unadjusted analysis, low maternal care was significantly associated with CPP (OR = 1.87; 95%CI: 1.11–3.15; $p = 0.019$). This association disappeared in the multiple regression analysis following adjustment for potential confounders (Table 4).

Table 4. Association between parenting styles and chronic pelvic pain in women.

Parenting Styles	Chronic Pelvic Pain			
	Unadjusted		Adjusted [1]	
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Maternal				
Care				
High	1.0 (reference)		1.0 (reference)	
Low	1.87 (1.11–3.15)	0.019 [a]	1.38 (0.74–2.57)	0.315
Overprotection				
Low	1.0 (reference)		1.0 (reference)	
High	0.98 (0.56–1.73)	0.954	0.65 (0.33–1.28)	0.212
Paternal				
Care				
High	1.0 (reference)		1.0 (reference)	
Low	1.02 (0.57–1.82)	0.944	0.91 (0.46–1.81)	0.799
Overprotection				
Low	1.0 (reference)		1.0 (reference)	
High	1.47 (0.77–2.81)	0.243	1.12 (0.51–2.43)	0.782

OR: odds ratio. CI: confidence interval. [1] Multiple logistic regression adjusted for age, alcohol consumption, physical abuse, sexual abuse, relationship difficulties, abdominal/pelvic surgery, anxiety, and depression. [a] $p < 0.05$.

In the CPP group, mean values were as follows: duration of pain 7.1 ± 6.5 years, and intensity of pain 7.2 ± 2.4. Catastrophizing was identified in 77.2% of women in the CPP group (data not shown as table). The monthly consumption of pain medication was higher among catastrophizing women compared to non-catastrophizing women (94.7% vs. 78.6%; $p = 0.024$) (data not shown in table). There was a positive and weak correlation between catastrophizing and the intensity of the pain ($r = 0.342$; $p < 0.001$), anxiety ($r = 0.271$; $p = 0.002$), depression ($r = 0.272$; $p = 0.002$) and maternal overprotection ($r = 0.185$; $p = 0.046$). A negative and weak correlation was found between maternal care and anxiety ($r = -0.184$; $p = 0.047$), maternal care and depression ($r = -0.219$; $p = 0.018$), paternal care and anxiety ($r = -0.286$; $p = 0.006$) and paternal care and depression ($r = -0.234$; $p = 0.026$). Other correlations are shown in Table 5.

Table 5. Spearman correlation between characteristics evaluated in women with chronic pelvic pain.

	Pain Intensity	Duration of Pain	Catastrophizing	Anxiety	Depression	Maternal Care	Maternal Overprotection	Paternal Care	Paternal Overprotection
Pain intensity	1.0	−0.051	0.342 [c]	0.208 [a]	0.165	−0.101	−0.098	0.087	−0.153
Duration of pain		1.0	0.028	−0.172	−0.130	0.040	−0.157	0.080	−0.058
Catastrophizing			1.0	0.271 [b]	0.272 [b]	−0.128	0.185 [a]	−0.175	0.102
Anxiety				1.0	0.717 [c]	−0.184 [a]	0.025	−0.286 [b]	−0.003
Depression					1.0	−0.219 [a]	−0.040	−0.234 [a]	−0.003
Maternal care						1.0	−0.183 [a]	0.224 [a]	0.140
Maternal overprotection							1.0	−0.146	0.368 [c]
Paternal care								1.0	−0.079
Paternal overprotection									1.0

[a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

4. Discussion

To the best of our knowledge, this is the first study to investigate the association between perceived parenting styles and CPP in women, and the relationship between catastrophizing and parenting styles in women with this condition. In the current study, low maternal care was more common in women with CPP. In addition, low maternal care was significantly associated with CPP; however, following adjustment for possible confounders, this association was no longer present. Lower maternal and paternal care was also associated with higher anxiety and depression in women with CPP. Catastrophizing correlated positively and weakly with maternal overprotection, the intensity of pain, anxiety, and depression in women with CPP.

The frequency of low maternal care was significantly higher in women with CPP compared to that found in the control group. Previously, a pilot study with a small sample size and without a control group had identified 68.2% of low maternal care in women with CPP [34]. This percentage is slightly higher than that found in the current study (60.7%). Furthermore, the association that was initially found between low maternal care and CPP in women in the unadjusted analysis corroborates other reports involving parenting styles and other types of persistent pain. Indeed, lack of maternal sensitivity in childhood has already been associated with intense chronic pain in adulthood [28] and an association has also been found between low maternal care and chronic pain in adolescents [26]. In addition to the association with the development of chronic pain, parental low care was found to be

associated with the patient's need for psychosomatic treatment in adulthood [24]. This suggests that maternal care in childhood may have an effect on individuals' experiences of pain at different stages of their lives.

Nevertheless, in the current study, the association between low maternal care and CPP disappeared following adjustment for potential confounders. Likewise, a previous study reported that an association between low maternal care in childhood and chronic pain in a general adult population was no longer present following adjustment for depression [27]. In addition, other studies have shown the role of depression as a mediator in the association between low maternal care and chronic pain in adolescents [26] and in adults [28]. In this respect, the impact of the quality of maternal care in childhood on the structural and functional development of parts of the nervous system linked to emotional regulation was demonstrated in a study conducted using magnetic resonance imaging [44]. A better quality of maternal care was associated with a greater volume and greater activation of the middle frontal cortex [44], an important structure in the top-down control over amygdala reactivity to stressors [45]. Conversely, poorer quality of maternal care was associated with a decreased volume and increased activation of the hippocampus [44], with a long-term effect on the negative feedback system of the hypothalamic-pituitary-adrenal (HPA) axis stress response [46].

A negative association was found between maternal care and anxiety and depression in the group of women with CPP in the present study. Notwithstanding, although significant, this association was weak. As already reported in other studies [47], these emotional disorders were significantly more common in women with CPP compared to pain-free control. There is increasingly robust evidence in the literature of a bidirectional association between anxiety, depression and chronic pain through shared neural circuits [48,49] and neurotransmitters [50,51] in the expression of these conditions. Since the relationship between children and their mothers is of a biological and deeply emotional nature, the quality of this bond may be affected by sociocultural changes in the women's role within their families. Therefore, maternal care in childhood, as well as the different family compositions and the roles of each member of the family, merit further investigation regarding their possible direct or indirect effects on CPP in women.

No association was found in the present study between paternal bonding styles in childhood and CPP in women. Conversely, in other clinical settings, some authors have found higher paternal overprotection in childhood to be associated with other types of chronic pain in adolescents [26] and in adults [24,27]. Paternal bonding is predominantly shaped by sociocultural aspects, which may explain, at least in part, the differences between the findings of the present study and those of other authors whose studies involved fathers of other nationalities. Interestingly, in the present study, a negative correlation was found between paternal care and anxiety and depression in women with CPP. This finding is in agreement with the results of a recent study that reported an effect of paternal as well as maternal parenting on the maturation of the HPA axis and the child's immune system [11]. This may be due to the increasingly common transformations in the father's role as caregiver in modern society, and merits further investigation in future studies. In the present study, however, 24.8% of the sample population had had no contact with their father for a variety of different reasons, which may have affected the results obtained in relation to paternal bonding and its possible association with CPP in women.

A high frequency of catastrophizing (77.2%) was found in the group of women with CPP. Albeit lower, a considerable frequency of catastrophizing (53.1%) was found in another study involving women with CPP [30]. In the present study, catastrophizing women were found to use significantly more pain medication compared to non-catastrophizing women, highlighting the clinical and economic impact of this coping strategy. The present results showed a positive and significant association between catastrophizing and pain intensity, anxiety, and depression. Other authors have reported not only a greater intensity of pain [30] but also pain hypersensitivity [12], anxiety, depression, and poorer quality of life associated with catastrophizing in women with CPP [30]. Furthermore, outcomes were found to be poor in catastrophizing women with CPP associated with endometriosis [52] or other causes [31], thus highlighting the relevance of including catastrophizing in the approach used to treat this health condition. It is important to mention that the association found between catastrophizing and pain intensity, anxiety and depression, albeit significant, was weak, and this has to be taken into account when considering the clinical and social interpretation of these findings. The presence of other caregivers and their role in the experience of pain experienced by women with CPP were not investigated further in this study and could have affected its results.

The finding of a positive and weak, although significant, correlation between maternal overprotection and catastrophizing in the women with CPP in the present study is also noteworthy. Since, to the best of our knowledge, this finding is novel, comparison with other studies had necessarily to involve research into other types of pain. A previous study found that maternal overprotection acted as a mediator in the catastrophizing responses of children with functional abdominal pain [10]. Conversely, an unpredictable maternal care model has been associated with an insecure attachment type and migraine in children and adolescents [9,53] and migraine is a common comorbidity in women with CPP [54]. Stressful parent bonding, particularly maternal dominance, has been associated with an increase in the functional and emotional disturbances of primary dysmenorrhea [55]. Results from the Tracking Adolescents' Individual Lives Survey (TRAILS), a prospective cohort study involving 2230 adolescents in the Netherlands, are also of interest [56]. In that study, parental overprotection was found to be predictive of the development of functional somatic symptoms such as aches/pain, with this association being stronger in relation to the maternal overprotection of daughters [56]. Furthermore, a controlling family environment contributes to poorer long term psychosocial functioning in young adults with fibromyalgia [57], a condition that often overlaps CPP in women [54]. Although each one of these studies evaluated different types of pain in different populations, their findings and those of the present study appear to be aligned. In-depth research into the role of families, particularly parents, in the emotional development and in the development of pain coping strategies in children may have a preventive and therapeutic effect on CPP in women.

Furthermore, the history of the participants in the present study suggests a significantly higher frequency of physical abuse and relationship difficulties in the women in the CPP group compared to the controls. In agreement with the present findings, women with CPP have been described as having a history significantly associated with ACEs, particularly physical abuse, sexual abuse and emotional abuse, and of having witnessed domestic violence [32], with a high rate of co-occurrence of anxiety and depression [32,47]. Therefore, irrespective of a cause-effect relationship, these issues must be properly addressed in women with CPP.

The importance of an interdisciplinary approach involving psychosocial aspects in the treatment of CPP in women has already been well-established [7]. Mindfulness-based stress reduction and cognitive behavioral therapy have proven useful in reducing pain

catastrophizing [31]. The present findings support the need for further, more specific research that would produce robust evidence on the role of the early parent–child relationship in the development of emotional self-regulation and coping skills in women with CPP. Therefore, therapeutic approaches with an emphasis on redefining family history and relationships, including family constellation [58], as well as other forms of therapy that encourage experiences of self-discovery and self-regulation such as Identity-Oriented Psychotrauma Therapy [59] could perhaps be included in studies into this intriguing health condition that is CPP in women.

Finally, the management of CPP continues to represent a challenge to healthcare professionals and patients. This study could serve as a starting point for future research into other aspects of interpersonal relationships, parenting and attachment styles, and CPP in women. This could lead to improvements in the prevention and treatment of this important health condition.

Strengths and Limitations

Some limitations need to be taken into consideration when interpreting the findings of the present study. The use of self-report questionnaires may have generated subjectivity in the responses obtained. A history of physical abuse, sexual abuse and relationship difficulties was investigated through single questions requiring yes/no answers. Validated questionnaires on these topics were not used. Only maternal and paternal bonding was considered objects of interest, with the role of other figures of affection when the parents were unavailable not being investigated. Moreover, a quarter of the population evaluated here had had no contact with their father; therefore, this finding cannot be extrapolated. Attachment styles, i.e., the patterns of interpersonal relationships in adulthood based on early life experiences [23], were not evaluated in the present study and should be the focus of future studies. Although there was a difference in the frequency of anxiety, depression and physical abuse between the groups, the analysis was adjusted for these variables, which may have minimized their impact on the results.

Strongpoints include the fact that all the instruments used here have been transculturally validated for use in Brazilian Portuguese. Although the PBI accesses information from memories of the individual’s perceptions on their mother or father in childhood, the stability

and consistency of this instrument have been validated over the long-term [60]. In addition, the fact that this was one of the largest studies in terms of sample size to evaluate women with CPP is also worthy of mention.

5. Conclusions

The frequency of low maternal care was found to be greater in the CPP group compared to the pain-free controls. The domains of parental bonding were not independently associated with CPP, while maternal and paternal care was negatively associated with anxiety and depression in women with CPP. Catastrophizing was very common and positively associated with the intensity of pain, anxiety, depression, and maternal overprotection in the CPP group. These associations, albeit significant, were weak. The findings of the current study should be interpreted taking the psychosocial context of the study population into consideration. Furthermore, these data should be taken into account when planning future studies on the subject and particularly with respect to the clinical management of women with CPP.

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5 CONCLUSÕES

- A dor pélvica crônica é uma condição intrigante de saúde, nem sempre associada a uma causa evidente. Pode superpor-se a várias comorbidades, que devem ser devidamente investigadas e tratadas. A identificação clínica de fenótipo de sensibilização central pode nortear o manejo de mulheres com dor pélvica crônica, que deve ser interdisciplinar e envolver aspectos biopsicossociais.
- A frequência de baixo cuidado materno foi maior em mulheres com dor pélvica crônica do que em mulheres sem dor pélvica crônica.
- Os estilos de vinculação parental não se associaram independentemente à dor pélvica crônica em mulheres.
- Cuidado materno e cuidado paterno correlacionaram-se fraca e negativamente à ansiedade e à depressão em mulheres com dor pélvica crônica.
- Catastrofização correlacionou-se fraca e positivamente com intensidade da dor, ansiedade, depressão e superproteção materna em mulheres com DPC.

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APÊNDICES

Apêndice I - Ficha de verificação de critérios

Grupo: |____| 1. Com DPC 2. Sem DPC Nº no estudo _____

Nome da pesquisadora: _____

	Aceita	Rejeita
1. Qual a sua idade?	| 1 | ≥ 18 e ≤ 50	| 2 | < 18 ou > 50
2. A Sra. está ou suspeita estar grávida?	| 1 | Não	| 2 | Sim
3. A Sra. já fez tratamento para câncer?	| 1 | Não	| 2 | Sim
4. A Sra. esteve grávida nos últimos 12 meses?	| 1 | Não	| 2 | Sim
5. A Sra. está na menopausa?	| 1 | Não	| 2 | Sim
6. A Sra. se submeteu a alguma cirurgia há menos de 03 meses?	| 1 | Não	| 2 | Sim
***Selecionada**	| | Sim	| | Não

*Se a resposta for | 2 | em alguma das questões, a mulher não será aceita para o estudo.

Apêndice II - Termo de consentimento livre e esclarecido

Você está sendo convidada para participar, como voluntária, em uma pesquisa. Meu nome é Vânia Meira e Siqueira Campos. Sou a pesquisadora responsável e minha área de atuação é a Medicina.

Após ler com atenção este documento, ser esclarecida sobre as informações a seguir, no caso de aceitar fazer parte do estudo, *assine em todas as folhas e no final deste documento*, que está em duas vias e também será assinado por mim, pesquisadora, em todas as folhas (uma das vias é sua e a outra é da pesquisadora responsável). Em caso de dúvida sobre a pesquisa, você poderá entrar em contato com a pesquisadora, Vânia Meira e Siqueira Campos, nos telefones: (62)98156-8779 (Tim) e (62)3251-1661. Em caso de dúvida sobre os seus direitos como participante nesta pesquisa, você poderá entrar em contato com o Comitê de Ética em pesquisa no Hospital das Clínicas da Universidade Federal de Goiás da Empresa Brasileira de Serviços Hospitalares (HC-UFG/EBSERH), nos telefones: (62) 3269-8338 e 3269-8426 ou no endereço: Primeira Avenida s/nº Setor Leste Universitário, Unidade de Pesquisa Clínica, segundo andar. Horário de funcionamento: 2ª a 6ª das 07h às 17h.

Informações importantes que você precisa saber sobre a pesquisa:

- Título: Vinculação Parental, Pensamentos Catastróficos sobre a Dor, Ansiedade e Depressão em Mulheres com Dor Pélvica Crônica;
- Quem está aplicando este termo de consentimento: a própria pesquisadora responsável, médica matriculada no Programa de Mestrado em Ciências da Saúde da UFG;
- Objetivo: avaliar vinculação parental (percepção sobre ligação com o pai e com a mãe), pensamentos/sentimentos sobre a dor, ansiedade e depressão em mulheres com dor pélvica crônica, para compreender mais suas dificuldades, com a perspectiva de melhorar as terapias a elas oferecidas;

- Como se dará sua participação: você responderá a cinco questionários: um formulário, preenchido sob forma de entrevista, sobre características sociodemográficos e reprodutiva, bem como sobre aspectos clínicos da dor (se você for do grupo que tem dor pélvica crônica); um questionário sobre ansiedade, um sobre depressão, um sobre pensamentos/sentimentos de quando você está com dor e outro, sobre sua percepção da relação com seu pai e sua mãe (estes quatro você responderá sozinha ou com ajuda de uma pessoa treinada, caso ache necessário);
- A sua participação nesta pesquisa não lhe trará riscos nem prejuízos. Caso surjam reações emocionais, como choro por exemplo, por responder a questões de sua história pessoal, você será atendida pelo Serviço de Psicologia do Ambulatório de Ginecologia do HC-UFG/EBSERH, se assim o desejar;
- Mesmo não tendo benefícios diretos, você estará contribuindo indiretamente para a compreensão da doença estudada e para a produção de conhecimento científico;
- Você não terá gastos nem vantagens financeiras por sua participação neste estudo;
- Sua privacidade e anonimato serão preservados, ou seja, seu nome ou qualquer outro dado ou elemento que possam de alguma forma identificá-la serão mantidos em sigilo;
- Você pode se recusar a participar do estudo ou retirar seu consentimento a qualquer momento, sem precisar se justificar, e por isso não sofrerá qualquer prejuízo à assistência que vem recebendo no Ambulatório de Ginecologia do HC-UFG/EBSERH;
- Os dados coletados serão utilizados apenas nesta pesquisa e ficarão arquivados pela pesquisadora durante cinco anos, com o propósito de esclarecimento ou aprofundamento da análise dos mesmos. Após esse período, os dados coletados serão incinerados.

CONSENTIMENTO DA PARTICIPAÇÃO DA PESSOA COMO SUJEITO DA PESQUISA

Eu, _____

RG nº _____ nº de prontuário_____

abaixo assinado, concordo em participar do estudo Vinculação Parental, Pensamentos Catastróficos sobre a Dor, Ansiedade e Depressão em Mulheres com Dor Pélvica Crônica como sujeito voluntário. Fui devidamente informada e esclarecida pela pesquisadora Vânia Meira e Siqueira Campos sobre a pesquisa, os procedimentos nela envolvidos, assim como os possíveis riscos e benefícios decorrentes da minha participação. Foi-me garantido que posso retirar meu consentimento a qualquer momento, sem que isso leve a qualquer penalidade ou interrupção do meu acompanhamento/assistência/tratamento.

Goiânia, ____/____/____

Nome e assinatura do sujeito ou responsável_____

Assinatura dactiloscópica:

Nome e assinatura da pesquisadora responsável _____

_____

Presenciamos a solicitação de consentimento, esclarecimento sobre a pesquisa e aceite do sujeito em participar.

Testemunhas

Nome: _____ Assinatura: _____

Nome: _____ Assinatura: _____

Apêndice III - Ficha de coleta de dados

FICHA DE COLETA DE DADOS

Identificação da Participante

Grupo: |___| **1. Com DPC** **2. Sem DPC**		Nº no estudo |___|___|___|
Nome:		
Nº do Prontuário: |___|___|___|___|___|___|___|		
End:		Nº
Bairro:	Cidade:	Est.:
Fone:		

*Data da entrevista: |__|__| |__|__| |__|__|__|__|

dia mês ano

**Início da entrevista: _____

Seção I – Características Sociodemográficas

"Gostaria de fazer algumas perguntas sobre a senhora":

1.1. Qual a sua idade? |___|___| anos

1.2. Qual sua data de nascimento? |___|___|_____|

1.3. A senhora considera que a sua cor ou raça é:

(1) branca (2) preta

(3) parda (4) amarela

(5) indígena (6) Outra Qual? _____

1.4. Qual a renda mensal per capita da sua família (soma de todos os membros da família/número de membros da família)? R$_____

1.5. A senhora estudou, frequentou a escola formal?

(1) Sim (2) Não >>>> Passe para a 1.7

1.6. A senhora estudou por quantos anos? |___|___| anos

1.7. Atualmente a senhora é:

(1) Empregada/exerce algum trabalho pelo qual recebe pagamento

(2) Desempregada

(3) Aposentada

(4) Dona de casa

1.8. Com relação ao cigarro, a senhora:

(1) Fuma atualmente

(2) Já fumou e parou >>>> Passe para a 1.11

(3) Nunca fumou >>>> Passe para a 1.13

1.9. Há quanto tempo a senhora fuma?

|___|___| meses e/ou |___|___| anos

1.10. Quantos cigarros a senhora fuma por dia?

|___|___| cigarros

1.11. Por quanto tempo a senhora fumou?

|___|___| meses e/ou |___|___| anos

1.12. Há quanto tempo a senhora parou de fumar?

|___|___| meses e/ou |___|___| anos

1.13. Nos últimos 03 meses, a senhora tem tomado alguma bebida alcoólica (cachaça, cerveja, vinho, uísque etc.)?

(1) Sim (2) Não >>>> Passe para a 1.16

1.14. A senhora toma bebida alcoólica todo dia?

(1) Sim (2) Não >>>> Passe para a 1.16

1.15. Qual a quantidade de álcool que a senhora toma por dia?

(1) Até 02 tulipas de cerveja/chopp ou 02 cálices de vinho ou 02copos de destilados

(2) 02-04 tulipas de cerveja/chopp ou 02-04 cálices de vinho ou 02-04 copos de destilados

(3) > 4 tulipas de cerveja/chopp ou > 4 cálices de vinho ou > 4 copos de destilados

1.16. No último mês, a senhora tem praticado atividades físicas (caminhadas, natação, musculação,

hidroginástica etc.)?

(1) Sim (2) Não >>>> Passe para a 1.18

1.17. No último mês, em média, com que frequência tem praticado esta(s) atividade(s) física(s)?

(1) Menos que 150 minutos por semana

(2) Mais que 150 minutos por semana

1.18. A senhora já sofreu violência física?

(1) Sim (2) Não >>>> Passe para 1.21

1.19. A violência física foi:

(1) na infância/adolescência (≤ 19 anos)

(2) na vida adulta

1.20. Por quem foi a violência ? _____

1.21. A senhora tem religião?

(1) Sim (2) Não

1.22. Atualmente a senhora é?

(1) Solteira

(2) Casada/Amasiada/Vive junto

(3) Separada/Desquitada/Divorciada

(4) Viúva

Seção II – Aspectos familiares

"Agora vou fazer algumas perguntas sobre sua família":

2.1. A senhora conhece(u) sua mãe?

(1) Sim (2) Não

2.2. A sua mãe é viva?

(1) Sim >>> Passe para a 2.6

(2) Não

(3) Não sei >>> Passe para a 2.6

2.3. A senhora sabe qual era a sua idade quando a sua mãe morreu?

(1) Sim Qual? _____

(2) Não sei

2.4. Como sua mãe morreu?

(1) Morte brusca

(2) Doença arrastada >>> Passe para a 2.6

(3) Não sei >>> Passe para a 2.6

2.5. Qual foi o tipo de morte da sua mãe?

(1) Natural (infarto fulminante, AVC hemorrágico, aneurisma etc.)

(2) Não natural/violenta (homicídio, suicídio, acidente etc.)

2.6. A senhora conhece(u) seu pai?

(1) Sim (2) Não

2.7. O seu pai é vivo?

(1) Sim >>> Passe para a 2.11

(2) Não

(3) Não sei >>> Passe para a 2.11

2.8. A senhora sabe qual era a sua idade quando seu pai morreu?

(1) Sim Qual? _____

(2) Não sei

2.9. Como seu pai morreu?

(1) Morte brusca

(2) Doença arrastada >>>> Passe para a 2.11

(3) Não sei >>>> Passe para a 2.11

2.10. Qual foi o tipo de morte do seu pai?

(1) Natural (infarto fulminante, AVC hemorrágico, aneurisma etc.)

(2) Não natural/violenta (homicídio, suicídio, acidente etc.)

2.11. Seus pais:

(1) São (foram) casados/amasiados/ vivem (viveram) juntos

(2) Tiveram um encontro casual >>> Passe para a 2.14

(3) Outro. Qual? _____ >>> Passe para a 2.14

2.12. Os seus pais se separaram?

(1) Sim (2) Não >>> Passe para a 2.14

2.13. A senhora sabe qual era a sua idade na época da separação?

(1) Sim Qual? _____

(2) Não sei

2.14. Antes de a senhora nascer, sua mãe teve filho(s) com outro(s) parceiro(s) que não o seu pai?

(1) Sim (2) Não (3) Não sei

2.15. Antes de a senhora nascer, seu pai teve filho(s) com outra(s) parceira(s) que não a sua mãe?

(1) Sim (2) Não (3) Não sei

2.16. A senhora foi criada por:

(1) Mãe e pai

(2) Mãe

(3) Pai

(4) Avós/outros parentes

(5) Pais adotivos

(6) Orfanato

(7) Outros Quem? _____

2.17. A senhora tem/teve irmãos? (considerar vivos e mortos)

(1) Sim

(2) Não >>>> Passe para a 2.20

(3) Não sei >>>> Passe para a 2.20

2.18. Quantos irmãos a senhora tem/teve? _____

2.19. Dos seus irmãos, a senhora é:

(1) Mais velha (2) Caçula (3) Nem mais velha nem caçula

2.20. A senhora conheceu seus avós por parte de mãe?

(1) Sim >>>> Passe para 2.23

(2) Só um dos dois

(3) Não

2.21. Algum dos seus avós por parte de mãe morreu quando sua mãe era criança?

(1) Sim

(2) Não >>>> Passe para a 2.23

(3) Não sei >>>> Passe para a 2.23

2.22. Quem morreu quando sua mãe era criança?

(1) A mãe dela

(2) O pai dela

2.23. A senhora conheceu seus avós por parte de pai?

(1) Sim >>>> Passe para 2.26

(2) Só um dos dois

(3) Não

2.24. Algum dos seus avós por parte de pai morreu quando seu pai era criança?

(1) Sim

(2) Não >>>> Passe para 2.26

(3) Não sei >>>> Passe para 2.26

2.25. Quem morreu quando seu pai era criança?

(1) A mãe dele

(2) O pai dele

2.26. A senhora tem dificuldades de relacionamento com:

(1) Parceiro (2) Filho (3) Mãe (4) Pai (5) Irmã(o) (6) Genro/nora

(7) Outros Quem? _____

(8) Ninguém

Seção III–Aspectos Reprodutivos

"Eu gostaria de fazer algumas perguntas sobre sua menstruação e seus partos":

3.1. Quantos anos a senhora tinha, quando teve sua primeira menstruação? |___|___| anos

3.2. A senhora já ficou grávida?

(1) Sim (2) Não >>>> Passe a 3.11

3.3. A senhora teve filhos?

(1) Sim (2) Não >>>> Passe a 3.8

3.4. Quantos anos à senhora tinha quando teve seu primeiro filho? |___|___| anos

3.5. Quantos partos a senhora teve? |___|___| partos

3.6. Quantos partos vaginais? |___|___|

3.7. Quantas cesarianas? |___|___|

3.8. A senhora já teve aborto?

(1) Sim (2) Não >>>> Passe a 3.11

3.9. Aborto(s) espontâneo(s)?

(1) Sim (2) Não

3.10. Aborto(s) provocado(s)?

(1) Sim (2) Não

3.11. A senhora já sofreu violência sexual?

(1) Sim (2) Não >>>> Passe para a 3.14

3.12. Por quem?_____

3.13. A violência sexual que sofreu foi:

(1) Na infância/adolescência (≤ 19 anos)

(2) Na vida adulta

3.14. A senhora passou por cirurgia para retirar o útero?

(1) Sim (2) Não >>> Passe para a 3.16

3.15. A senhora sabe qual era a sua idade quando passou por essa cirurgia?

(1) Sim Qual? _____

(2) Não sei

3.16. Os dois ovários da senhora foram retirados?

(1) Sim (2) Não

3.17. A senhora sabe qual era a sua idade quando se submeteu a essa cirurgia?

(1) Sim Qual? _____

(2) Não sei

Seção IV – Aspectos Clínicos

4.1. Peso: |___|___|___| Kg

4.2. Altura: |___|___|___| metros

4.3. Índice de massa corpórea: |___|___|___| Kg/m²

4.4. A senhora tem alguma(s) dessa(s) doença(s) que vou ler?

(1) Pressão alta

(2) Diabetes

(3) Hipotireoidismo

(4) Enxaqueca

(5) Fibromialgia

(6) Síndrome do intestino irritável

(7) Cistite intersticial (síndrome da bexiga dolorosa)

(8) Outra(s) Qual(is)?_____

(9) Não

4.5. A senhora se submeteu a cirurgias abdominais e/ou pélvicas (não considerar a cirurgia para tratamento da dor pélvica crônica)?

(1) Laqueadura tubária (cirurgia para não criar)

(2) Cisto de ovário

(3) Retirada de mioma uterino

(4) Apendicectomia

(5)Outras Qual(is)? _____

(6) Nenhuma

Seção V – Caracterização da dor pélvica crônica (perguntas exclusivas para mulheres com dor pélvica crônica)

5.1. Há quanto tempo a senhora apresenta dor pélvica (região abaixo do umbigo)?

|___|___| meses e/ou |___|___| anos

5.2. Quanto tempo demorou entre o início da dor pélvica e o início do tratamento?

|___|___| meses e/ou |___|___| anos

5.3. Quanto tempo demorou entre o início da dor pélvica e a sua chegada ao ambulatório de dor pélvica crônica do Hospital das Clínicas?

|___|___| meses e/ou |___|___| anos

5.4. Durante o período pré e/ou menstrual, a intensidade da dor pélvica se altera?

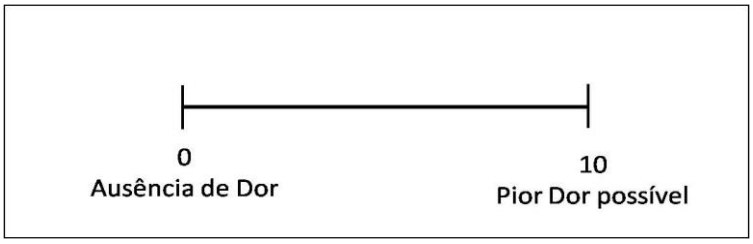
(1) Sim (2) Não >>>> Passe para a 5.6

5.5. Como a dor pélvica se altera?

(1) Aumenta

(2) Diminui

5.6. Em uma escala de 0 a 10, como a senhora classifica a intesidade da dor na região pélvica/abaixo do umbigo (a escala visual analógica é apresentada e explicada à participante)?



Resposta:_____

5.7. A senhora já se submeteu à cirurgia para investigação/tratamento da dor pélvica?

(1) Sim (2) Não >>>> Passe a 5.10

5.8. Quantas cirurgias? _____

5.9. Qual foi o tipo de cirurgia?

(1) Laparoscopia (2) Laparotomia

5.10. No último mês, está usando algum medicamento para tratamento da dor pélvica?

(1) Sim (2) Não >>> Passe para a 5.12

5.11. Qual(is) medicamento(s) para dor pélvica está usando?

(1) Hormonal (Anticoncepcional, Progestágeno)

(2) AINES (Diclofenaco, Ibuprofeno, Piroxicam etc.)

(3) Analgésicos (Dipirona, Paracetamol etc.)

(4) Antidepressivos (Amitriptilina, Fluoxetina, Sertralina etc.)

(5) Opioide (Tramadol, Codeína, Tylex, Paco etc.)

5.12. A senhora está ou esteve em psicoterapia nos últimos 06 meses?

(1) Sim (2) Não

ANEXOS

Anexo A - Parecer do comitê de ética

UFG - HOSPITAL DAS CLÍNICAS DA UNIVERSIDADE FEDERAL DE GOIÁS

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Vinculação Parental, Pensamentos Catastróficos sobre a Dor, Ansiedade e Depressão em Mulheres com Dor Pélvica Crônica

Pesquisador: VANIA MEIRA E SIQUEIRA CAMPOS

Área Temática:

Versão: 3

CAAE: 66461217.5.0000.5078

Instituição Proponente: Hospital das Clínicas Universidade Federal de Goiás - GO

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.631.464

Apresentação do Projeto:

A dor pélvica crônica (DPC) é uma"dor não cíclica, de pelo menos seis meses de duração, que aparece em localizações como a pelve, parede abdominal anterior inferior, região lombar ou glúteos, e que é sério o suficiente para provocar incapacidade ou requerer cuidados médicos". 2 – Epidemiologia A DPC é um problema ginecológico comum, cuja estimativa de prevalência mundial é de 3,8% em mulheres entre 15 e 73 anos (HOWARD, 2003), e de 14-24% em mulheres na idade reprodutiva
(AHANGARI, 2014). O Real Colégio de Obstetras e Ginecologistas britânico (RCOG, 2012) sugere que a DPC pode acometer uma em cada seis mulheres adultas. Silva et al. (2011) relataram uma prevalência de 11,5% de DPC em mulheres acima de 14 anos, e de 15,1% em mulheres em idade reprodutiva, na cidade de Ribeirão Preto, São Paulo (Brasil). Estudo transversal analítico, que compara os escores de ansiedade, depressão e vinculação parental em 100 mulheres com e 100 mulheres sem
dor pélvica crônica, pacientes do Ambulatório de Ginecologia do Hospital das Clínicas-UFG/EBSERH. Serão utilizados os seguintes instrumentos:
Escala de Ansiedade e Depressão Hospitalar, segundo Botega et al. (1995), e Instrumento de Vinculação Parental (Parental Bonding Instrument – PBI), segundo Parker et al. (1979). A população deste estudo será composta por mulheres com e sem DPC, que estejam em seguimento no Ambulatório de Ginecologia do HC da UFG durante o período de coleta dos dados. A amostra será

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composta por 200 mulheres, distribuídas em dois grupos: 100 mulheres no grupo com, e 100, no grupo sem DPC.

Os dados serão coletados diretamente pela pesquisadora junto às participantes, através de três instrumentos:

Formulário sobre características sociodemográficas e reprodutivas das participantes, bem como aspectos clínicos da DPC (Apêndice III), preenchido sob forma de entrevista;

Escala de Ansiedade e Depressão (Hospital Anxiety and Depression Scale – HAD), segundo Botega et al. (1995) - (Anexo A), que é um questionário autoaplicável;

Parental Bonding Instrument – PBI, segundo Parker et al. (1979) - (Anexo B), que também é um instrumento autoaplicável.

Critério de Inclusão:

•Idade 18 anos;•Para inclusão no grupo com DPC: presença de dor no baixo ventre nos últimos três meses, com início há pelo menos seis meses, sem caráter exclusivamente cíclico ou relacionado ao coito;•Para inclusão no grupo sem DPC: ausência de

queixa de dor no baixo ventre nos últimos três meses.

Critério de Exclusão:

•Antecedente de gravidez nos últimos 12 meses;•Suspeita ou confirmação de gravidez atual;•Antecedente de tratamento de neoplasia maligna, com exceção de câncer de pele não melanoma.

Metodologia de Análise de Dados:

Inicialmente, os dados serão registrados e codificados em um banco de dados do programa Microsoft Office Excel, versão 2007 e exportados,

posteriormente, para o programa Statistical Package for Social Science para Personal Computer (SPSSPC).

Serão utilizados os seguintes testes para análise dos dados:•Qui-quadrado (Bussab & Morettin, 1987) para verificar a associação entre duas variáveis;•Exato de Fisher (Bussab & Morettin, 1987) para verificar a associação entre duas variáveis;•t –

Student (Bussab & Morettin, 1987) para comparação de médias entre os dois grupos;•Regressão linear (Draper & Smith, 1981) para identificar fatores associados. O nível de significância estatística adotado será igual a 0,05.

Objetivo da Pesquisa:

Objetivo Primário:

Comparar os escores de ansiedade, depressão e vinculação parental em mulheres com e sem DPC.

Objetivo Secundário:

- Analisar a associação entre as variáveis sociodemográficas, ansiedade, depressão e vinculação parental em mulheres com DPC.- Analisar a associação entre a intensidade da dor pélvica e ansiedade, depressão e vinculação parental.

Avaliação dos Riscos e Benefícios:

Riscos:

Reações emocionais durante a entrevista e preenchimento dos questionários, tais como choro e inibição para falar de acontecimentos da vida pessoal, estão entre os possíveis riscos relacionados a este estudo. Em caso de alguma alteração emocional, as entrevistadas poderão ser encaminhadas para atendimento no serviço de psicologia do HCUFG/ EBSERH, se sentirem essa necessidade.

Benefícios:

Mesmo não tendo benefícios diretos, as participantes estarão contribuindo indiretamente para a compreensão da doença estudada e para a produção de conhecimento científico.

Comentários e Considerações sobre a Pesquisa:

A emenda justifica-se pela inclusão da ESCALA DE PENSAMENTO CATASTRÓFICO SOBRE A DOR (B-PCS), segundo Sullivan et al. (1995), com 13 itens, instrumento já validado para o português do Brasil. Assim, a pesquisa passaria a ser intitulada de VINCULAÇÃO PARENTAL, PENSAMENTO CATASTRÓFICO SOBRE A DOR, ANSIEDADE E DEPRESSÃO EM MULHERES COM DOR PÉLVICA CRÔNICA. Esse trabalho pode ser enriquecido com o acréscimo de dois questionários breves, também já validados transculturalmente para o nosso país, quais sejam: TRIAGEM DE TRANSTORNO DE ANSIEDADE GENERALIZADA (GDA-7), segundo Spitzer et al. (2006), com sete itens, e QUESTIONÁRIO SOBRE A SAÚDE DO PACIENTE (PHQ-9), segundo Spitzer et al (1999), com nove itens. Foram realizadas as adequações necessárias ao Termo de Consentimento Livre e Esclarecido, bem como acrescentadas algumas perguntas sobre aspectos familiares na Ficha de Coleta de Dados, que poderão ser úteis com relação à vinculação parental.

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos foram anexados e apresentados ao CEP conforme recomenda a Resolução 466/12 do Conselho Nacinal de Saúde e suas complementares.

Recomendações:

Não se aplica.

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Conclusões ou Pendências e Lista de Inadequações:

EMENDA 01

A presente emenda apresenta versões atualizadas do protocolo de pesquisa e do TCLE; também solicita inclusão da ESCALA DE PENSAMENTO CATASTRÓFICO SOBRE A DOR e a intitulação da pesquisa para VINCULAÇÃO PARENTERAL, PENSAMENTO CATASTRÓFICO SOBRE SOBRE A DOR, ANSIEDADE E DEPRESSÃO EM MULHERES COM DOR PÉLVICA CRÔNICA.

Os seguintes documentos foram submetidos e analisados:

- Informações básicas;
- Folha de rosto;
- Lista para o estudo;
- Ficha de coleta de dados;
- TCLE;
- GAD7;
- Escala pensamento catastrófico sobre a dor;
- PHQ9;
- Orçamento;
- Cronograma;
- Parecer chefe de serviço.

Considerações Finais a critério do CEP:

Diante do exposto, a Comissão de Ética em Pesquisa do Hospital das Clínicas da Universidade Federal de Goiás, de acordo com as atribuições definidas na Resolução CNS nº 466 de 2012 e na Norma Operacional nº 001 de 2013 do CNS, manifesta-se pela aprovação da emenda proposta ao projeto de pesquisa.

Situação: Emenda aprovada.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1083505_E1.pdf	09/03/2018 15:07:07		Aceito
Folha de Rosto	Folha_de_rosto.pdf	09/03/2018 15:05:14	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Outros	Lista_para_o_estudo.pdf	07/03/2018	VANIA MEIRA E	Aceito

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Outros	Lista_para_o_estudo.pdf	00:15:16	SIQUEIRA CAMPOS	Aceito
Outros	Ficha_de_coleta_de_dados.pdf	07/03/2018 00:13:26	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	07/03/2018 00:12:59	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Outros	GAD7.pdf	27/02/2018 10:29:45	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Outros	Pensamento_catastrofico_sobre_a_dor.pdf	27/02/2018 10:28:51	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Outros	PHQ9.pdf	27/02/2018 10:26:18	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DE_MESTRADO.pdf	10/03/2017 19:59:20	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Orçamento	orcamento2.pdf	07/03/2017 17:31:26	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Cronograma	cronograma.pdf	07/03/2017 17:27:41	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Declaração de Instituição e Infraestrutura	parecer_chefe_de_servico.pdf	07/03/2017 17:11:06	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito
Orçamento	orcamento.pdf	07/03/2017 17:00:27	VANIA MEIRA E SIQUEIRA CAMPOS	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

GOIANIA, 02 de Maio de 2018

Assinado por:
JOSE MARIO COELHO MORAES
(Coordenador)

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Anexo B - Instrumento de Vinculação Parental

Instruções: este questionário lista várias atitudes e comportamentos dos pais. Conforme você se lembra da sua MÃE até os seus 16 anos, faça uma marca no parêntese mais apropriado ao lado de cada afirmativa.

	Muito parecido	Modera-damente parecido	Modera-damente diferente	Muito diferente
Falava comigo com uma voz meiga e amigável	( )	( )	( )	( )
Não me ajudava tanto quanto eu necessitava	( )	( )	( )	( )
Deixava-me fazer as coisas que eu gostava de fazer	( )	( )	( )	( )
Parecia emocionalmente fria comigo	( )	( )	( )	( )
Parecia compreender meus problemas e preocupações	( )	( )	( )	( )
Era carinhosa comigo	( )	( )	( )	( )
Gostava que eu tomasse minhas próprias decisões	( )	( )	( )	( )
Não queria que eu crescesse	( )	( )	( )	( )
Tentava controlar todas as coisas que eu fazia	( )	( )	( )	( )
Invadia minha privacidade	( )	( )	( )	( )
Gostava de conversar sobre as coisas comigo	( )	( )	( )	( )
Frequentemente sorria para mim	( )	( )	( )	( )
Tendia a me tratar como bebê	( )	( )	( )	( )
Parecia não entender o que eu necessitava ou queria	( )	( )	( )	( )
Deixava que eu decidisse coisas por mim mesma	( )	( )	( )	( )
Fazia com que eu sentisse que não era querida	( )	( )	( )	( )
Podia me fazer sentir melhor quando eu estava chateada	( )	( )	( )	( )
Não conversava muito comigo	( )	( )	( )	( )
Tentava me fazer dependente dela	( )	( )	( )	( )
Ela sentia que eu não poderia cuidar de mim mesma, a menos que ela estivesse por perto	( )	( )	( )	( )
Dava-me tanta liberdade quanto eu queria	( )	( )	( )	( )
Deixava-me sair tão frequentemente quanto eu queria	( )	( )	( )	( )
Era superprotetora comigo	( )	( )	( )	( )
Não me elogiava	( )	( )	( )	( )
Deixava-me vestir de qualquer jeito que eu desejasse	( )	( )	( )	( )

Anexo C - Escala de Catastrofização da Dor

Instruções: listamos 13 declarações que descrevem diferentes pensamentos e sentimentos que podem lhe aparecer na cabeça quando sente dor. Indique o GRAU destes pensamentos e sentimentos quando está com dor

	Mínima	**Leve**	**Moderada**	**Intensa**	**Muito intensa**
1. A preocupação durante todo o tempo com a duração da dor é	0	1	2	3	4
2. O sentimento de não poder prosseguir (continuar) é	0	1	2	3	4
3. O sentimento que a dor é terrível e que não vai melhorar é	0	1	2	3	4
4. O sentimento que a dor é horrível e que você não vai resistir é	0	1	2	3	4
5. O pensamento de não poder mais estar com alguém é	0	1	2	3	4
6. O medo que a dor pode se tornar ainda pior é	0	1	2	3	4
7. O pensamento sobre outros episódios de dor é	0	1	2	3	4
8. O desejo profundo que a dor desapareça é	0	1	2	3	4
9. O sentimento de não conseguir tirar a dor do pensamento é	0	1	2	3	4
10. O pensamento que ainda poderá doer mais é	0	1	2	3	4
11. O pensamento que a dor é grave porque ela não quer parar é	0	1	2	3	4
12. O pensamento de que não há nada para fazer para diminuir a intensidade da dor é	0	1	2	3	4
13. A preocupação que alguma coisa ruim pode acontecer por causa da dor é	0	1	2	3	4
	0	**1**	**2**	**3**	**4**

Anexo D - Escala de Distúrbio de Ansiedade Generalizada (GAD-7)

GAD-7

Durante as <u>últimas 2 semanas</u>, com que freqüência você foi incomodado/a pelos problemas abaixo? *(Marque sua resposta com "✔")*	**Nenhuma vez**	**Vários dias**	**Mais da metade dos dias**	**Quase todos os dias**
1. Sentir-se nervoso/a, ansioso/a ou muito tenso/a	0	1	2	3
2. Não ser capaz de impedir ou de controlar as preocupações	0	1	2	3
3. Preocupar-se muito com diversas coisas	0	1	2	3
4. Dificuldade para relaxar	0	1	2	3
5. Ficar tão agitado/a que se torna difícil permanecer sentado/a	0	1	2	3
6. Ficar facilmente aborrecido/a ou irritado/a	0	1	2	3
7. Sentir medo como se algo horrível fosse acontecer	0	1	2	3

(*For office coding: Total Score T*____ = ____ + ____ + ____)

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Anexo E - Questionário sobre a Saúde do(a) Paciente (PHQ-9)

QUESTIONÁRIO SOBRE A SAÚDE DO/A PACIENTE- (PHQ-9)

Durante as <u>últimas 2 semanas</u>, com que freqüência você foi incomodado/a por qualquer um dos problemas abaixo? *(Marque sua resposta com "✔")*	**Nenhuma vez**	**Vários dias**	**Mais da metade dos dias**	**Quase todos os dias**
1. Pouco interesse ou pouco prazer em fazer as coisas	0	1	2	3
2. Se sentir "para baixo", deprimido/a ou sem perspectiva	0	1	2	3
3. Dificuldade para pegar no sono ou permanecer dormindo, ou dormir mais do que de costume	0	1	2	3
4. Se sentir cansado/a ou com pouca energia	0	1	2	3
5. Falta de apetite ou comendo demais	0	1	2	3
6. Se sentir mal consigo mesmo/a — ou achar que você é um fracasso ou que decepcionou sua família ou você mesmo/a	0	1	2	3
7. Dificuldade para se concentrar nas coisas, como ler o jornal ou ver televisão	0	1	2	3
8. Lentidão para se movimentar ou falar, a ponto das outras pessoas perceberem? Ou o oposto – estar tão agitado/a ou irrequieto/a que você fica andando de um lado para o outro muito mais do que de costume	0	1	2	3
9. Pensar em se ferir de alguma maneira ou que seria melhor estar morto/a	0	1	2	3

FOR OFFICE CODING __0__ + _____ + _____ + _____

=Total Score: _____

Se você assinalou <u>qualquer</u> um dos problemas, indique o grau de <u>dificuldade</u> que os mesmos lhe causaram para realizar seu trabalho, tomar conta das coisas em casa ou para se relacionar com as pessoas?

Nenhuma dificuldade	**Alguma dificuldade**	**Muita dificuldade**	**Extrema dificuldade**
☐	☐	☐	☐

Anexo F - Normas de publicação do *International Journal of Women's Health*

- While the editors fully understand the extra challenges posed to authors whose native language is not English, we must ask that all manuscripts be reviewed and edited by a native speaker of English with expertise in that area prior to submission
- Double-spacing
- 3-cm margins
- Page numbers
- Line numbers
- Clear concise language
- American spelling (all components of a manuscript must be in English)
- Ensure tables and figures are cited
- Manuscripts should be submitted in Microsoft Word format
- Use International Systems of Units (SI) symbols and recognized abbreviations for units of measurement
- Do not punctuate abbreviations eg, et al, ie
- Spell out acronyms in the first instance in the abstract and paper
- Word counts are not specified. In general, shorter items range from 1000 to 3000 words and reviews from 3000 to 7,500
- Generic drug names are used in title, text, tables, and figures
- Suppliers of drugs, equipment, and other brand-name material are credited in parentheses (company, name, city, state, country)
- If molecular sequences are used, provide a statement that the data have been deposited in a publicly accessible database, eg, GenBank, and indicate the database accession number
- Depositing laboratory protocols on protocols.io is encouraged, where a DOI can be assigned to the protocol. To include a link to a protocol in your manuscript:

  1) Describe your step-by-step protocol on protocols.io

  2) Select "Get DOI" to issue your protocol with a unique DOI (digital object identifier)

  3) Include the DOI link in the Methods section of your manuscript using the format

provided by protocols.io: http://dx.doi.org/10.17504/protocols.io.xxxxxxx (where xxxxxxx is the unique DOI)

At this stage, your protocol is only visible to those with the link. This allows editors and reviewers to consult your protocol when evaluating the manuscript. You can make your protocols public at any time by selecting "Publish" on the protocols.io website. Any referenced protocols will automatically be made public when your article is published.

Anexo G - Normas de publicação do *International Journal of Environmental Research and Public Health*

Journal Impact Factor: 4.614

Instructions for Authors

Submission Checklist

Please:

1. Read the **Aims & Scope** to gain an overview and assess if your manuscript is suitable for this journal;
2. Use the **Microsoft Word template** or **LaTeX template** or **Free Format Submission** to prepare your manuscript;
3. Make sure that issues about **publication ethics**, **research ethics**, **copyright**, **authorship**, **figure formats**, **data** and **references format** have been appropriately considered;
4. Ensure that all authors have approved the content of the submitted manuscript.
5. Authors are encouraged to add a **biography** (optional) to the submission and post it to **SciProfiles**.

Manuscript Submission Overview

Types of Publications

IJERPH has no restrictions on the length of manuscripts, provided that the text is concise and comprehensive. Full experimental details must be provided so that the results can be reproduced. *IJERPH* requires that authors publish all experimental controls and make full datasets available where possible (see the guidelines on **Supplementary Materials** and references to unpublished data).

Manuscripts submitted to *IJERPH* should neither be published previously nor be under consideration for publication in another journal. The main article types are as follows:

- *Articles:* Original research manuscripts. The journal considers all original research manuscripts provided that the work reports scientifically sound experiments and provides a substantial amount of new information. Authors should not unnecessarily divide their work into several related manuscripts, although short *Communications* of preliminary, but significant, results will be considered. The quality and impact of the study will be considered during peer review. Articles should have a main text of around 3000 words at minimum.
- *Reviews:* These provide concise and precise updates on the latest progress made in a given area of research. Systematic reviews should follow the PRISMA **guidelines.** The main text of review papers should be around 4000 words at minimum.
- *Case reports:* Case reports present detailed information on the symptoms, signs, diagnosis, treatment (including all types of interventions), and outcomes of an individual patient.

Case reports usually describe new or uncommon conditions that serve to enhance medical care or highlight diagnostic approaches.

Submission Process

Manuscripts for *IJERPH* should be submitted online at **susy.mdpi.com**. The submitting author, who is generally the corresponding author, is responsible for the manuscript during the submission and peer-review process. The submitting author must ensure that all eligible co-authors have been included in the author list (read the **criteria to qualify for authorship**) and that they have all read and approved the submitted version of the manuscript. To submit your manuscript, register and log in to the **submission website**. Once you have registered, **click here to go to the submission form for *IJERPH***. All co-authors can see the manuscript details in the submission system, if they register and log in using the e-mail address provided during manuscript submission.

Accepted File Formats

Authors are encouraged to use the **Microsoft Word template** or **LaTeX template** to prepare their manuscript. Using the template file will substantially shorten the time to complete copy-editing and publication of accepted manuscripts. The total amount of data for all files must not exceed 120 MB. If this is a problem, please contact the Editorial Office **ijerph@mdpi.com**. Accepted file formats are:

- *Microsoft Word:* Manuscripts prepared in Microsoft Word must be converted into a single file before submission. When preparing manuscripts in Microsoft Word, we encourage you to use the ***IJERPH* Microsoft Word template file**. Please insert your graphics (schemes, figures, *etc.*) in the main text after the paragraph of its first citation.
- *LaTeX:* Manuscripts prepared in LaTeX must be collated into one ZIP folder (including all source files and images, so that the Editorial Office can recompile the submitted PDF). When preparing manuscripts in LaTeX, we encourage you to use the ***IJERPH* LaTeX template files**. You can now also use the online application **writeLaTeX** to submit articles directly to *IJERPH*. The MDPI LaTeX template file should be selected from the **writeLaTeX template gallery**.
- *Supplementary files:* May be any format, but it is recommended that you use common, non-proprietary formats where possible (see **below** for further details).

Disclaimer: Usage of these templates is exclusively intended for submission to the journal for peer-review, and strictly limited to this purpose and it cannot be used for posting online on preprint servers or other websites.

Free Format Submission

IJERPH now accepts free format submission:

- We do not have strict formatting requirements, but all manuscripts must contain the required sections: Author Information, Abstract, Keywords, Introduction, Materials & Methods, Results, Conclusions, Figures and Tables with Captions, Funding Information,

Author Contributions, Conflict of Interest and other Ethics Statements. Check the Journal ***Instructions for Authors*** for more details.

- Your references may be in any style, provided that you use the consistent formatting throughout. It is essential to include author(s) name(s), journal or book title, article or chapter title (where required), year of publication, volume and issue (where appropriate) and pagination. DOI numbers (Digital Object Identifier) are not mandatory but highly encouraged. The bibliography software package *EndNote*, ***Zotero***, *Mendeley*, *Reference Manager* are recommended.
- When your manuscript reaches the revision stage, you will be requested to format the manuscript according to the journal guidelines.

Cover Letter

A cover letter must be included with each manuscript submission. It should be concise and explain why the content of the paper is significant, placing the findings in the context of existing work. It should explain why the manuscript fits the scope of the journal.

Any prior submissions of the manuscript to MDPI journals must be acknowledged. If this is the case, it is strongly recommended that the previous manuscript ID is provided in the submission system, which will ease your current submission process. The names of proposed and excluded reviewers should be provided in the submission system, not in the cover letter.

All cover letters are required to include the statements:

- We confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal.
- All authors have approved the manuscript and agree with its submission to (journal name).

Author Biography

Authors are encouraged to add a biography (maximum 150 words) to the submission and post it to **SciProfiles**. This should be a single paragraph and should contain the following points:

1. Authors' full names followed by current positions;
2. Education background including institution information and year of graduation (type and level of degree received);
3. Work experience;
4. Current and previous research interests;
5. Memberships of professional societies and awards received.

Note for Authors Funded by the National Institutes of Health (NIH)

This journal automatically deposits papers to PubMed Central after publication of an issue. Authors do not need to separately submit their papers through the NIH Manuscript Submission System (NIHMS, **http://nihms.nih.gov/**).

- **Graphical Abstract:**

A graphical abstract (GA) is an image that appears alongside the text abstract in the Table of Contents. In addition to summarizing the content, it should represent the topic of the article in an attention-grabbing way. Moreover, it should not be exactly the same as the Figure in the paper or just a simple superposition of several subfigures. Note that the GA must be original and unpublished artwork. Any postage stamps, currency from any country, or trademarked items should not be included in it.

The GA should be a high-quality illustration or diagram in any of the following formats: PNG, JPEG, TIFF, or SVG. Written text in a GA should be clear and easy to read, using one of the following fonts: Times, Arial, Courier, Helvetica, Ubuntu or Calibri.

The minimum required size for the GA is 560 × 1100 pixels (height × width). The size should be of high quality in order to reproduce well.

Front Matter

These sections should appear in all manuscript types

- **Title:** The title of your manuscript should be concise, specific and relevant. It should identify if the study reports (human or animal) trial data, or is a systematic review, meta-analysis or replication study. When gene or protein names are included, the abbreviated name rather than full name should be used. Please do not include abbreviated or short forms of the title, such as a running title or head. These will be removed by our Editorial Office.
- **Author List and Affiliations:** Authors' full first and last names must be provided. The initials of any middle names can be added. The PubMed/MEDLINE standard format is used for affiliations: complete address information including city, zip code, state/province, and country. At least one author should be designated as corresponding author, and his or her email address and other details should be included at the end of the affiliation section. Please read the **criteria to qualify for authorship**.
- **Abstract:** The abstract should be a total of about 200 words maximum. The abstract should be a single paragraph and should follow the style of structured abstracts, but without headings: 1) Background: Place the question addressed in a broad context and highlight the purpose of the study; 2) Methods: Describe briefly the main methods or treatments applied. Include any relevant preregistration numbers, and species and strains of any animals used. 3) Results: Summarize the article's main findings; and 4) Conclusion: Indicate the main conclusions or interpretations. The abstract should be an objective representation of the article: it must not contain results which are not presented and substantiated in the main text and should not exaggerate the main conclusions.
- **Keywords:** Three to ten pertinent keywords need to be added after the abstract. We recommend that the keywords are specific to the article, yet reasonably common within the subject discipline.

Research Manuscript Sections

- **Introduction:** The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance,

including specific hypotheses being tested. The current state of the research field should be reviewed carefully and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the main conclusions. Keep the introduction comprehensible to scientists working outside the topic of the paper.

- **Materials and Methods:** They should be described with sufficient detail to allow others to replicate and build on published results. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited. Give the name and version of any software used and make clear whether computer code used is available. Include any pre-registration codes.
- **Results:** Provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.
- **Discussion:** Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible and limitations of the work highlighted. Future research directions may also be mentioned. This section may be combined with Results.
- **Conclusions:** This section is mandatory.
- **Patents:** This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

Back Matter

- **Supplementary Materials:** Describe any supplementary material published online alongside the manuscript (figure, tables, video, spreadsheets, etc.). Please indicate the name and title of each element as follows Figure S1: title, Table S1: title, etc.
- **Funding:** All sources of funding of the study should be disclosed. Clearly indicate grants that you have received in support of your research work and if you received funds to cover publication costs. Note that some funders will not refund article processing charges (APC) if the funder and grant number are not clearly and correctly identified in the paper. Funding information can be entered separately into the submission system by the authors during submission of their manuscript. Such funding information, if available, will be deposited to FundRef if the manuscript is finally published.
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journal staff that involves the author's contribution to the study); AND agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature. For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; Methodology, X.X.; Software, X.X.; Validation, X.X., Y.Y. and Z.Z.; Formal Analysis, X.X.; Investigation, X.X.; Resources, X.X.; Data Curation, X.X.; Writing – Original Draft Preparation, X.X.; Writing – Review & Editing, X.X.; Visualization, X.X.; Supervision, X.X.; Project Administration, X.X.; Funding Acquisition, Y.Y.", please turn to the **CRediT taxonomy** for the term explanation. For more background on CRediT, see **here**. "**Authorship must include and be limited to those who have contributed substantially to the work. Please read the section concerning the criteria to qualify for authorship carefully**".

- **Institutional Review Board Statement:** In this section, please add the Institutional Review Board Statement and approval number for studies involving humans or animals. Please note that the Editorial Office might ask you for further information. Please add "The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code XXX and date of approval)." OR "Ethical review and approval were waived for this study, due to REASON (please provide a detailed justification)." OR "Not applicable" for studies not involving humans or animals. You might also choose to exclude this statement if the study did not involve humans or animals.

- **Informed Consent Statement:** Any research article describing a study involving humans should contain this statement. Please add "Informed consent was obtained from all subjects involved in the study." OR "Patient consent was waived due to REASON (please provide a detailed justification)." OR "Not applicable" for studies not involving humans. You might also choose to exclude this statement if the study did not involve humans. Written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Please state "Written informed consent has been obtained from the patient(s) to publish this paper" if applicable.

- **Data Availability Statement:** In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section "**MDPI Research Data Policies**". You might choose to exclude this statement if the study did not report any data.

- **Conflicts of Interest:** Authors must identify and declare any personal circumstances or interest that may be perceived as influencing the representation or interpretation of reported research results. If there is no conflict of interest, please state "The authors declare no conflict of interest." Any role of the funding sponsors in the choice of research project; design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript; or in the decision to publish the results must be declared in this section. Any projects funded by industry must pay special attention to the full declaration of funder involvement. If there is no role, please state "The sponsors had no role in the design, execution, interpretation, or writing of the study". For more details please see **Conflict of Interest**.

- **References:** References must be numbered in order of appearance in the text (including table captions and figure legends) and listed individually at the end of the manuscript. We recommend preparing the references with a bibliography software package, such as **EndNote**, **ReferenceManager** or **Zotero** to avoid typing mistakes and duplicated references. We encourage citations to data, computer code and other citable research material. If available online, you may use reference style 9. below.
- Citations and References in Supplementary files are permitted provided that they also appear in the main text and in the reference list.

In the text, reference numbers should be placed in square brackets [ ], and placed before the punctuation; for example [1], [1–3] or [1,3]. For embedded citations in the text with pagination, use both parentheses and brackets to indicate the reference number and page numbers; for example [5] (p. 10). or [6] (pp. 101–105).

The reference list should include the full title, as recommended by the ACS style guide. Style files for **Endnote** and **Zotero** are available.

References should be described as follows, depending on the type of work:

Journal Articles:
1. Author 1, A.B.; Author 2, C.D. Title of the article. *Abbreviated Journal Name* **Year**, *Volume*, page range.

Books and Book Chapters:
2. Author 1, A.; Author 2, B. *Book Title*, 3rd ed.; Publisher: Publisher Location, Country, Year; pp. 154–196.
3. Author 1, A.; Author 2, B. Title of the chapter. In *Book Title*, 2nd ed.; Editor 1, A., Editor 2, B., Eds.; Publisher: Publisher Location, Country, Year; Volume 3, pp. 154–196.

Unpublished materials intended for publication:
4. Author 1, A.B.; Author 2, C. Title of Unpublished Work (optional). Correspondence Affiliation, City, State, Country. year, *status* (*manuscript in preparation*; *to be submitted*).
5. Author 1, A.B.; Author 2, C. Title of Unpublished Work. *Abbreviated Journal Name* year, *phrase indicating stage of publication* (*submitted*; *accepted*; *in press*).

Unpublished materials not intended for publication:
6. Author 1, A.B. (Affiliation, City, State, Country); Author 2, C. (Affiliation, City, State, Country). Phase describing the material, year. (phase: Personal communication; Private communication; Unpublished work; etc.)

Conference Proceedings:
7. Author 1, A.B.; Author 2, C.D.; Author 3, E.F. Title of Presentation. In *Title of the Collected Work* (if available), Proceedings of the Name of the Conference, Location of Conference, Country, Date of Conference; Editor 1, Editor 2, Eds. (if available); Publisher: City, Country, Year (if available); Abstract Number (optional), Pagination (optional).

Thesis:
8. Author 1, A.B. Title of Thesis. Level of Thesis, Degree-Granting University, Location of University, Date of Completion.

Websites:
9. Title of Site. Available online: URL (accessed on Day Month Year).
Unlike published works, websites may change over time or disappear, so we encourage you create an archive of the cited website using a service such as **WebCite**. Archived websites

should be cited using the link provided as follows:
10. Title of Site. URL (archived on Day Month Year).
See the **Reference List and Citations Guide** for more detailed information.

Preparing Figures, Schemes and Tables

- File for Figures and Schemes must be provided during submission in a single zip archive and at a sufficiently high resolution (minimum 1000 pixels width/height, or a resolution of 300 dpi or higher). Common formats are accepted, however, TIFF, JPEG, EPS and PDF are preferred.
- *IJERPH* can publish multimedia files in articles or as supplementary materials. Please contact the editorial office for further information.
- All Figures, Schemes and Tables should be inserted into the main text close to their first citation and must be numbered following their number of appearance (Figure 1, Scheme I, Figure 2, Scheme II, Table 1, *etc.*).
- All Figures, Schemes and Tables should have a short explanatory title and caption.
- All table columns should have an explanatory heading. To facilitate the copy-editing of larger tables, smaller fonts may be used, but no less than 8 pt. in size. Authors should use the Table option of Microsoft Word to create tables.
- Authors are encouraged to prepare figures and schemes in color (RGB at 8-bit per channel). There is no additional cost for publishing full color graphics.

Research and Publication Ethics

Research Ethics

Research Involving Human Subjects

When reporting on research that involves human subjects, human material, human tissues, or human data, authors must declare that the investigations were carried out following the rules of the Declaration of Helsinki of 1975 (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**), revised in 2013. According to point 23 of this declaration, an approval from the local institutional review board (IRB) or other appropriate ethics committee must be obtained before undertaking the research to confirm the study meets national and international guidelines. As a minimum, a statement including the project identification code, date of approval, and name of the ethics committee or institutional review board must be stated in Section ‘Institutional Review Board Statement’ of the article.

Example of an ethical statement: "All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of XXX (Project identification code)."

For non-interventional studies (e.g. surveys, questionnaires, social media research), all participants must be fully informed if the anonymity is assured, why the research is being conducted, how their data will be used and if there are any risks associated. As with all research involving humans, ethical approval from an appropriate ethics committee must be obtained prior to conducting the study. If ethical approval is not required, authors must either

provide an exemption from the ethics committee or are encouraged to cite the local or national legislation that indicates ethics approval is not required for this type of study. Where a study has been granted exemption, the name of the ethics committee which provided this should be stated in Section 'Institutional Review Board Statement' with a full explanation regarding why ethical approval was not required.

A written informed consent for publication must be obtained from participating patients. Data relating to individual participants must be described in detail, but private information identifying participants need not be included unless the identifiable materials are of relevance to the research (for example, photographs of participants' faces that show a particular symptom). Patients' initials or other personal identifiers must not appear in any images. For manuscripts that include any case details, personal information, and/or images of patients, authors must obtain signed informed consent for publication from patients (or their relatives/guardians) before submitting to an MDPI journal. Patient details must be anonymized as far as possible, e.g., do not mention specific age, ethnicity, or occupation where they are not relevant to the conclusions. A **template permission form** is available to download. A blank version of the form used to obtain permission (without the patient names or signature) must be uploaded with your submission. Editors reserve the right to reject any submission that does not meet these requirements.

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If the study reports research involving vulnerable groups, an additional check may be performed. The submitted manuscript will be scrutinized by the editorial office and upon request, documentary evidence (blank consent forms and any related discussion documents from the ethics board) must be supplied. Additionally, when studies describe groups by race, ethnicity, gender, disability, disease, etc., explanation regarding why such categorization was needed must be clearly stated in the article.

Sex and Gender in Research

We encourage our authors to follow the **'Sex and Gender Equity in Research – SAGER – guidelines'** and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Article titles and/or abstracts should indicate clearly what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We suggest that our authors consult the full **guidelines** before submission.

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The editors of this journal enforce a rigorous peer-review process together with strict ethical policies and standards to ensure to add high quality scientific works to the field of scholarly publication. Unfortunately, cases of plagiarism, data falsification, image manipulation, inappropriate authorship credit, and the like, do arise. The editors of *IJERPH* take such publishing ethics issues very seriously and are trained to proceed in such cases with a zero tolerance policy.

Authors wishing to publish their papers in *IJERPH* must abide to the following:

- Any facts that might be perceived as a possible conflict of interest of the author(s) must be disclosed in the paper prior to submission.
- Authors should accurately present their research findings and include an objective discussion of the significance of their findings.
- Data and methods used in the research need to be presented in sufficient detail in the paper, so that other researchers can replicate the work.
- Raw data should preferably be publicly deposited by the authors before submission of their manuscript. Authors need to at least have the raw data readily available for presentation to the referees and the editors of the journal, if requested. Authors need to ensure appropriate measures are taken so that raw data is retained in full for a reasonable time after publication.
- Simultaneous submission of manuscripts to more than one journal is not tolerated.
- The journal accepts exact translations of previously published work. All submissions of translations must conform with our **policies on translations**.
- If errors and inaccuracies are found by the authors after publication of their paper, they need to be promptly communicated to the editors of this journal so that appropriate actions can be taken. Please refer to our **policy regarding Updating Published Papers**.
- Your manuscript should not contain any information that has already been published. If you include already published figures or images, please obtain the necessary permission from the copyright holder to publish under the CC-BY license. For further information, see the **Rights and Permissions** page.
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Reuse of text that is copied from another source must be between quotes and the original source must be cited. If a study's design or the manuscript's structure or language has been inspired by previous works, these works must be explicitly cited.

All MDPI submissions are checked for plagiarism using the industry standard software iThenticate. If plagiarism is detected during the peer review process, the manuscript may be rejected. If plagiarism is detected after publication, an investigation will take place and action taken in accordance with our policies.

- **Image files must not be manipulated or adjusted in any way** that could lead to misinterpretation of the information provided by the original image.

Irregular manipulation includes: 1) introduction, enhancement, moving, or removing features from the original image; 2) grouping of images that should obviously be presented separately (e.g., from different parts of the same gel, or from different gels); or 3) modifying the contrast, brightness or color balance to obscure, eliminate or enhance some information.

If irregular image manipulation is identified and confirmed during the peer review process, we may reject the manuscript. If irregular image manipulation is identified and confirmed after publication, we may correct or retract the paper.

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