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Geschlechtsspezifische Aspekte der Migräne

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von

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Inhaltsverzeichnis

Abkürzungen

CGRP = Calcitonin Gene-Related Peptid

DMKG = Deutsche Migräne- und Kopfschmerzgesellschaft

EHF = European Headache Federation

ELISA = Enzyme-Linked ImmunoSorbent Assay

ICHD = International Classification of Headache Disorders

MRT = Magnetresonanztomographie

PRES = Posteriores Reversibles Enzephalopathiesyndrom

YLD = Years Lived with Disability

1. Einleitung

1.1 Migräne: Epidemiologie, Diagnostik und Pathophysiologie

Migräne ist eine primäre Kopfschmerzerkrankung, die etwa 15% der Weltbevölkerung betrifft (Ashina et al., 2021). Während Jungen und Mädchen in ähnlichem Maße von Migräne betroffen sind, entwickeln sich ab der Pubertät geschlechtsabhängige Unterschiede (Vetvik & MacGregor, 2017). Bei erwachsenen Frauen tritt Migräne zwei- bis dreimal häufiger auf als bei Männern (Vetvik & MacGregor, 2017). Zudem ist Migräne mit einer hohen Krankheitslast assoziiert und verursacht eine deutliche Beeinträchtigung der Lebensqualität (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Tatsächlich steht Migräne weltweit an zweiter Stelle bei den Erkrankungen, die zu "Years lived with disability" (YLD - Jahre, die mit Behinderung gelebt werden) führen (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Bei Frauen im Alter von 15 bis 49 Jahren belegt Migräne sogar den ersten Platz in dieser Rangliste (Steiner et al., 2020).

Migräne zeichnet sich durch wiederkehrende Kopfschmerzattacken aus und wird anhand der Kriterien der International Classification of Headache Disorders (ICHD-3) diagnostiziert (Headache Classification Committee of the International Headache Society, 2018). Die Kopfschmerzattacken dauern unbehandelt in der Regel zwischen 4 und 72 Stunden. Der Kopfschmerz ist typischerweise einseitig, pulsierend, von mittelstarker bis starker Intensität und verstärkt sich durch körperliche Aktivität. Zusätzlich treten Begleitsymptome wie Übelkeit, Erbrechen oder Phono- und Photophobie auf (Headache Classification Committee of the International Headache Society, 2018).
Bei bis zu einem Drittel der Patienten liegt zusätzlich eine Aura vor, definiert als neurologische Symptome wie visuelle Phänomene und Sensibilitätsstörungen, die in der Regel vor den Kopfschmerzen auftreten, sich langsam entwickeln und innerhalb einer Stunde remittieren (Headache Classification Committee of the International Headache Society, 2018).
Je nach Häufigkeit der Kopfschmerzattacken wird zwischen episodischer und chronischer Migräne unterschieden. Bei episodischer Migräne treten die Migräneattacken an höchstens 14 Tagen im Monat auf. Chronische Migräne hingegen ist definiert durch ≥15 Kopfschmerztage im Monat, wobei an mindestens acht dieser Tage die Migränekriterien erfüllt sein müssen (Headache Classification Committee of the International Headache Society, 2018).

Die genaue Pathophysiologie der Migräne ist noch nicht vollständig geklärt. Das

trigeminovaskuläre System gilt als pathoanatomisches Substrat für den Migränekopfschmerz (Ashina, 2020). Aktuellen pathophysiologischen Modellen zufolge wird eine Migräneattacke durch die Aktivierung von trigeminalen Neuronen erster Ordnung ausgelöst, was zur Freisetzung von vasoaktiven und pro-nozizeptiven Neuropeptiden führt (Ashina, 2020). Unter den pro-nozizeptiven Neuropeptiden spielt Calcitonin Gene-Related Peptide (CGRP) eine bedeutende Rolle. CGRP ist einer der potentesten Vasodilatatoren im menschlichen Körper und wird während der Migräneattacken in hohen Konzentrationen freigesetzt (Goadsby et al., 1990). Dies führt wiederum zu einer Sensibilisierung und Aktivierung von trigeminalen Neuronen zweiter Ordnung im Hirnstamm und dritter Ordnung im Thalamus, bis die nozizeptiven Impulse den somatosensorischen Kortex erreichen (Ashina, 2020). Die Mechanismen, die der initialen Aktivierung zugrunde liegen, sind Gegenstand aktueller Forschung, wobei sowohl zentrale als auch periphere Mechanismen beteiligt sein können (Do et al., 2023).

1.2 Migräne: Geschlechtsspezifische Unterschiede

Neben den oben genannten Geschlechtsunterschieden hinsichtlich der Migräneprävalenz dauern Migräneattacken bei Frauen im Durchschnitt länger und gehen häufiger mit einem Wiederkehrkopfschmerz nach der Akutbehandlung einher (Verhagen et al., 2023A). Einige Untersuchungen haben zudem eine erhöhte Rate von Begleitsymptomen wie Phono- und Photophobie sowie eine höhere Schmerzintensität bei Frauen gezeigt (Chalmer et al., 2023). Diese Unterschiede sind das Ergebnis einer komplexen Interaktion von biopsychosozialen Faktoren, die bisher nur teilweise untersucht wurden und verstanden sind.

1.2.1 Biologische Unterschiede

Sexualhormone, insbesondere das Östrogen, modulieren die Schmerzwahrnehmung auf komplexe Weise und können den Migräneverlauf beeinflussen (Martin, 2009; Nappi et al., 2022). Unterschiedliche Hormonkonzentrationen bzw. deren Fluktuationen tragen zumindest teilweise zur Erklärung der geschlechtsspezifischen Unterschiede in der Prävalenz und den klinischen Erscheinungsformen von Migräne bei.

Die Östrogenentzugshypothese und die menstruelle Migräne

Die gängigste Hypothese, um den Einfluss von Östrogenschwankungen auf Migräne zu erklären, ist die sogenannte Östrogenentzugshypothese, die im Jahr 1972 vom australischen Neurologen Brian W. Somerville entwickelt wurde (Somerville, 1972). Diese Hypothese besagt, dass ein rascher Abfall der Östrogenkonzentrationen Migräneattacken auslösen kann

(Somerville, 1972).

Ein prominentes Beispiel hierfür ist der abrupte Östrogenabfall in der prämenstruellen Phase, der zu vermehrten perimenstruellen Migräneattacken beitragen könnte (Vetvik & MacGregor, 2021). Die Menstruation ist der am häufigsten selbstberichtete Triggerfaktor für Migräne bei Frauen (van Casteren et al., 2021) und es ist bekannt, dass es bei Frauen zyklusabhängige Schwankungen in der Häufigkeit von Migräneattacken gibt, wobei eine Zunahme in der perimenstruellen Phase beobachtet wird (Verhagen et al., 2023B).

Diese Erkenntnisse führten zur Einführung der Diagnose „menstruelle Migräne“, die im Appendix der ICHD-3 aufgeführt ist (Headache Classification Committee of the International Headache Society, 2018). Dabei unterscheidet die ICHD-3 zwischen einer rein menstruellen Migräne und einer menstruationsassoziierten Migräne. Bei der rein menstruellen Migräne treten Attacken ausschließlich in der perimenstruellen Phase auf, d.h. zwischen Tag -2 und Tag 3 des Menstruationszyklus, wobei Tag 1 der erste Tag der Menstruation ist. Bei der menstruationsassoziierten Migräne sind auch Attacken zu anderen Zykluszeitpunkten möglich (Headache Classification Committee of the International Headache Society, 2018). Populationsbasierte Studien haben gezeigt, dass die rein menstruelle Migräne sehr selten ist, wohingegen die menstruationsassoziierte Migräne bis zu 6% aller Frauen betrifft (Couturier et al., 2003; Vetvik et al., 2014).

Trotz des eindeutigen zeitlichen Zusammenhangs zwischen dem Östrogenabfall und der Zunahme der Attackenfrequenz bleibt es dennoch unklar, wie genau Östrogen die Schmerzwahrnehmung im trigeminovaskulären System moduliert. Sowohl tierexperimentelle als auch humane Studien lieferten widersprüchliche Ergebnisse, wobei Östrogen in einigen Untersuchungen pro-nozizeptiv und in anderen anti-nozizeptiv wirkte (Martin, 2009; Nappi et al., 2022). Spezifisch bei Patientinnen mit Migräne deuten einige Studien auf eine perimenstruelle Änderung der kortikalen Schmerzverarbeitung hin (De Icco et al., 2016; Varlibas & Erdemoglu, 2009), die jedoch in größeren und besser definierten Kohorten weiter untersucht werden sollte.

Die Rolle von CGRP

Eine mögliche Erklärung für hormonell bedingte Veränderungen in der Häufigkeit und Schwere von Migräneattacken liegt in der Modulation des CGRP-Signalwegs durch Sexualhormone. Tatsächlich können Sexualhormone die CGRP-Synthese und Freisetzung beeinflussen (Labastida-Ramírez et al., 2019). Die bisherige Literatur fokussiert sich auch hier vorranging auf Östrogen. Es zeigt sich ein komplexes Wechselspiel zwischen CGRP und Östrogen mit

variablen Effekten, abhängig vom untersuchten Gehirnareal, der Spezies und dem genauen hormonellen Zustand (Labastida-Ramírez et al., 2019).

Ältere Untersuchungen wiesen auf höhere CGRP-Konzentrationen bei Personen mit erhöhten Östrogenspiegeln hin. Beispielsweise zeigte Valdemarsson et al., dass Frauen im Vergleich zu Männern höhere CGRP-Konzentrationen aufwiesen – bei Frauen, die hormonelle Kontrazeptiva einnahmen, waren diese Konzentrationen am höchsten (Valdemarsson et al., 1990). Es ist jedoch zu beachten, dass es sich in diesen Studien um Untersuchungen mit kleinen Fallzahlen handelte, und die genaue hormonelle Phase nicht berücksichtigt wurde.

Aktuellere Untersuchungen suggerieren dagegen eine vermehrte Freisetzung von CGRP in Phasen mit niedrigen Östrogenspiegeln. Zum Beispiel wurde nach der Anwendung von Capsaicin auf der Stirn eine deutlichere Zunahme des CGRP-abhängigen dermalen Blutflusses während der Menstruation im Vergleich zur Lutealphase beobachtet (Gazerani et al., 2005).

Die Zusammenhänge zwischen CGRP-Konzentrationen und verschiedenen hormonellen Zuständen bei Patientinnen mit Migräne wurden bis zu der hier vorgestellten Arbeit (**Originalarbeit 1**, Raffaelli et al., 2023) nicht erforscht. Solche Erkenntnisse könnten dazu beitragen, die Mechanismen hinter hormonell bedingten Migräneattacken besser zu verstehen und personalisierte therapeutische Ansätze zu entwickeln.

Endometriose als wichtige Komorbidität

Geschlechtsspezifische Unterschiede manifestieren sich auch in einem unterschiedlichen Spektrum an Komorbiditäten (Burch et al., 2019; Vetvik & MacGregor, 2017). Eine besonders bedeutsame Komorbidität, die ausschließlich Frauen betrifft, stellt die Endometriose dar (Bulun, 2009). Diese ist eine chronische entzündliche gynäkologische Erkrankung, die über 10% aller Frauen weltweit betrifft (Bulun, 2009). Die Endometriose ist gekennzeichnet durch das Vorkommen von endometrium-ähnlichem Gewebe außerhalb des Endometriums. Typische Symptome sind Dysmenorrhoe, aber auch Dyspareunie, Miktions- und Defäkationsbeschwerden sowie Infertilität (Bulun, 2009).

Epidemiologische Studien ergaben, dass Frauen mit Migräne doppelt so häufig an Endometriose leiden wie Frauen ohne Migräne (Tietjen et al., 2006). Umgekehrt besteht bei Frauen mit einer Endometriose häufiger gleichzeitig eine Migräne (Ferrero et al., 2004).

Diese Komorbidität könnte auf pathophysiologische Gemeinsamkeiten zurückzuführen sein. Es ist möglich, dass eine Fehlregulation von entzündlichen Signalwegen oder deren hormonelle Modulation sowohl bei der Endometriose als auch bei Migräne pathophysiologisch bedeutsam ist (Adewuyi et al., 2020). Unter anderem scheint bei der Endometriose, wie auch bei der

Migräne, der CGRP-Signalweg involviert zu sein. Histologische Untersuchungen zeigten eine erhöhte Dichte an CGRP-positiven Nervenfasern in Endometrioseherden und CGRP ist an der neurogenen Inflammation im Endometriosegewebe beteiligt (Gupta et al., 2016; Yan et al., 2019).

Bis zu dieser Arbeit (**Originalarbeit 2**, Raffaelli et al., 2021A) wurden CGRP-Konzentrationen bei Frauen mit komorbider Migräne und Endometriose nicht untersucht. Dies könnte die Relevanz einer Veränderung des CGRP-Signalweges bei komorbiden Frauen untermauern und zur Aufklärung der zugrunde liegenden pathophysiologischen Gemeinsamkeiten beitragen.

Die Rolle exogener Sexualhormone

Nicht nur die natürlichen hormonellen Fluktuationen können den Migräneverlauf beeinflussen, sondern auch die Zufuhr von exogenen Hormonen. Dazu gehören beispielsweise hormonelle Kontrazeptiva, die Hormonersatztherapie während der Perimenopause sowie geschlechtsangleichende Therapien bei transgender Personen (Hranilovich & Millington, 2023; MacGregor, 2018; Sacco et al., 2018).

Der Einfluss exogener Hormone auf Migräne ist äußerst variabel und hängt von der genauen Formulierung, Dosierung, dem Applikationsweg und der Behandlungsdauer ab (Sacco et al., 2018).

Bezüglich einer hormonellen Kontrazeption zeigen etwa ein Drittel der Frauen mit Migräne eine Besserung der Migränefrequenz, während sich bei einem Drittel die Migräne verschlechtert und bei einem Drittel unverändert bleibt (Delaruelle et al., 2018). Wenn es zu einer vermehrten Häufung von Migräneattacken kommt, tritt dies am häufigsten bei einer kombinierten Kontrazeption während des sogenannten hormonfreien Intervalls auf (Delaruelle et al., 2018). Sofern sich die Migräne innerhalb von fünf Tagen nach der letzten Einnahme von Östrogen entwickelt und maximal drei Tage anhält, wird diese von der Internationalen Kopfschmerzklassifikation als "Östrogenentzugskopfschmerz" klassifiziert (Headache Classification Committee of the International Headache Society, 2018).

Präparate, die kontinuierlich ohne Pause eingenommen werden, wie beispielsweise eine kombinierte Langzeit-Kontrazeption oder eine Gestagen-Monotherapie, sind hingegen häufiger mit einer Verbesserung der Migräne assoziiert. Insbesondere bei einer menstruationsassoziierten Migräne können hormonelle Therapien, die die natürlichen hormonellen Fluktuationen ausschalten, erfolgsversprechende Therapieoptionen darstellen (Allais et al., 2017).

Bei östrogenhaltigen Präparaten ist zusätzlich das erhöhte Risiko für kardiovaskuläre

Erkrankungen zu beachten (Sacco et al., 2018). Migräne, vor allem mit Aura, stellt einen eigenständigen Risikofaktor für kardiovaskuläre Erkrankungen dar, insbesondere ischämische Schlaganfälle (Øie et al., 2020). Frauen mit Migräne mit Aura, die eine hormonelle Kontrazeption einnehmen, haben ein signifikant erhöhtes Schlaganfallrisiko (Øie et al., 2020). Das absolute Risiko steigt von 2,5/100.000 bei Frauen ohne Migräne und ohne hormonelle Kontrazeption auf 36,9/100.000 bei Frauen mit Migräne mit Aura und einer hormonellen Kontrazeption (Sacco et al., 2018). Dieses steigt weiter, wenn zusätzliche Risikofaktoren wie Adipositas oder Rauchen vorhanden sind. Das Risiko ist am höchsten bei Präparaten mit hohen Östrogendosen, während eine Gestagen-Monotherapie kein zusätzliches Risiko darstellt (Sacco et al., 2018).

Die Empfehlungen zur Verwendung hormoneller Kontrazeption bei Patientinnen mit Migräne sind weltweit nicht einheitlich. Die Europäische Kopfschmerzgesellschaft (European Headache Federation, EHF) empfiehlt die Verwendung einer Gestagen-Monotherapie oder nicht-hormoneller Methoden bei Patientinnen mit Migräne mit Aura. Bei Migräne ohne Aura werden niedrig dosierte Östrogenpräparate als mögliche Option betrachtet, sofern keine zusätzlichen Risikofaktoren vorliegen (Sacco et al., 2018). Die Deutsche Migräne- und Kopfschmerzgesellschaft (DMKG) ist in ihren Empfehlungen etwas permissiver und erlaubt die Verwendung von östrogenhaltigen Kontrazeptiva auch bei Patientinnen mit Migräne mit Aura, sofern keine weiteren Risikofaktoren vorhanden sind (Deutsche Migräne- und Kopfschmezgesellschaft, 2012).

In Deutschland erfolgt die Verschreibung hormoneller Kontrazeptiva in der Regel durch niedergelassene Gynäkolog:innen. Bis vor dieser Arbeit (**Originalarbeit 3**, Fitzek et al., 2023) war jedoch unbekannt, in welchem Maße bei der Verschreibung hormoneller Kontrazeption nach dem Vorliegen einer Migräne gefragt wurde und wie die oben genannten Empfehlungen tatsächlich berücksichtigt wurden. Die Erforschung dieses Aspekts ist von Bedeutung, da sie Einblicke in die Umsetzung klinischer Leitlinien bietet und Möglichkeiten zur Verbesserung der Aufklärung und der Versorgung von Frauen mit Migräne aufzeigen kann.

Migräne in der Schwangerschaft

Die Schwangerschaft zeichnet sich durch ausgeprägte hormonelle Veränderungen aus, die erheblichen Einfluss auf den Migräneverlauf haben können (Negro et al., 2017).

In den meisten Fällen kommt es während der Schwangerschaft zu einer Abnahme der Migränefrequenz bis hin zum vollständigen Sistieren (Melhado et al., 2007). Diese Verbesserung wird den in der Schwangerschaft hohen Östrogenspiegeln zugeschrieben. Eine

Verschlechterung einer bekannten Migräne oder ein Neuauftreten sind jedoch auch möglich. Falls Migräne in der Schwangerschaft neu auftritt, ist das am häufigsten eine Migräne mit Aura (Burch, 2020).

Falls sich eine bekannte Migräne während der Schwangerschaft bedeutsam verändert, sollten sekundäre Kopfschmerzursachen ausgeschlossen werden. Sekundäre Kopfschmerzen sind Kopfschmerzen, die als Symptom einer anderen zugrunde liegenden medizinischen Ursache auftreten. Anders ausgedrückt sind sie keine eigenständige Erkrankung, sondern treten als Begleiterscheinung einer anderen gesundheitlichen Störung auf (Do et al., 2019). Die präzise Identifikation und adäquate Behandlung der Ursachen von sekundären Kopfschmerzen sind wichtig, um potenziell schwerwiegende gesundheitliche Probleme rechtzeitig zu erkennen, Komplikationen zu verhindern und eine angemessene Versorgung sicherzustellen (Do et al., 2019). Die Schwangerschaft ist ein Risikofaktor für zahlreiche sekundäre Kopfschmerzen, insbesondere hypertensiver Ursache (Contag et al., 2009; Robbins et al., 2015). Die Veränderung eines bereits bekannten Kopfschmerzes zählt zu den sogenannten "Red Flags" für sekundäre Kopfschmerzen während der Schwangerschaft. Weitere Charakteristika sind ein plötzlicher Beginn, begleitende fokal-neurologische Defizite, Vigilanzminderung oder ein begleitender epileptischer Anfall, aber auch Fieber oder eine Blutdruckentgleisung (Robbins et al., 2015). Besonders im akuten Setting, beispielsweise in einer Notaufnahme, ist es von entscheidender Bedeutung, auf diese "Red Flags" zu achten und bei Vorkommen eine angemessene Diagnostik einzuleiten.

Eine bereits bestehende Migräne stellt einen Risikofaktor für einige sekundäre Kopfschmerzen in der Schwangerschaft dar, darunter Präeklampsie und ischämische Schlaganfälle (Allais et al., 2010; Facchinetti et al., 2009). Dies unterstreicht die Notwendigkeit, bei schwangeren Frauen mit Migräne besonders auf Hinweise für sekundäre Kopfschmerzerkrankungen zu achten, um Komplikationen während der Schwangerschaft zu verhindern und die Gesundheit von Mutter und Kind zu schützen.

Studien aus den USA legen nahe, dass über ein Drittel der schwangeren Frauen, die aufgrund von Kopfschmerzen die Notaufnahme aufsuchen, letztendlich an sekundären Kopfschmerzen leiden (Robbins et al., 2015). Bis vor dieser Arbeit (**Originalarbeit 4**, Raffaelli et al., 2017) wurden die Kopfschmerzursachen schwangerer Frauen in Deutschland jedoch nicht systematisch untersucht. Die Erhebung solcher Daten in Deutschland ist von Bedeutung, da das deutsche Gesundheitssystem und die klinische Praxis sich von denen in anderen Ländern unterscheiden. Die Untersuchung der Ursachen von Kopfschmerzen bei schwangeren Frauen in einer deutschen Rettungsstelle ermöglicht es, die spezifischen Herausforderungen und

Bedürfnisse dieses Patientenkollektivs im nationalen Kontext zu verstehen und maßgeschneiderte Empfehlungen zu entwickeln.

1.2.2 Psychosoziale Unterschiede und die Rolle der Medien

Die bisherige Evidenz zeigt, dass Mädchen und Frauen mit Migräne eine höhere psychosoziale Belastung erfahren als gleichaltrige Männer (Chalmer et al., 2023). Dies äußert sich beispielsweise darin, dass Frauen häufiger über Probleme in ihrem Liebesleben aufgrund der Migräne berichten, größere Schwierigkeiten haben, Akzeptanz bei Freunden und Familienmitgliedern zu finden, und Ängste vor bevorstehenden Attacken hegen (Neumeier et al., 2021). Zudem tendieren Frauen häufiger dazu, ihre Erkrankung zu verbergen, möglicherweise aus Angst, nicht ernstgenommen zu werden (Neumeier et al., 2021).

Obwohl sowohl Männer als auch Frauen unter erheblichen Belastungen aufgrund von Migräne leiden, wird Migräne oft bagatellisiert und die Beschwerden der Patient:innen nicht ernst genommen. Kommentare wie „Jeder hat mal Kopfschmerzen“ oder „Es ist nur Stress“ sind allgegenwärtig im Leben von Patient:innen mit Migräne (Pearson et al., 2019). Die Unsichtbarkeit der Erkrankung scheint das Stigma noch weiter zu erhöhen, insbesondere bei Frauen, bei denen Schmerz (oder Schmerzerkrankungen) im Allgemeinen weniger ernst genommen werden (Hoffmann & Tarzian, 2001; Samulowitz et al., 2018). Der sogenannte Geschlechterbias in der Wahrnehmung und Behandlung von Schmerzerkrankungen wurde bereits ausgiebig dokumentiert. Frauen bekommen beispielsweise seltener Schmerzmedikamente verschrieben, stattdessen werden psychologische Behandlungen häufiger empfohlen (Hirsh et al., 2014).

Die derzeitige mediale Darstellung von Migräneattacken scheint dieses Stigma weiter zu verstärken. In den Medien wird Migräne häufig als Leiden einer jungen, gutaussehenden Frau dargestellt, die sich mit schmerzverzerrtem Gesicht die Schläfen hält (Gvantseladze et al., 2020). Diese einseitige Darstellung entspricht jedoch nicht der vielfältigen Realität von Patient:innen mit Migräne (Gvantseladze et al., 2020). Gerade in der heutigen Zeit, in der die digitalen Medien einen großen Einfluss auf unsere Wahrnehmung der Welt ausüben, kann eine solche pauschale Darstellung das Stigma weiter verstärken. Bis zu dieser Arbeit (**Originalarbeit 5**, Raffaelli et al., 2021B) wurde allerdings nicht untersucht, wie Patient:innen mit Migräne diese Darstellung wahrnehmen und/oder ob sie sich damit identifizieren können. Dies kann dazu beitragen, die Sensibilität und das Bewusstsein für die Belange von Menschen mit Migräne zu schärfen und die mediale Darstellung dieser Erkrankung zu verbessern.

1.3 Fragestellung

Die vorliegende Arbeit beleuchtet verschiedene geschlechtsspezifische Aspekte der Migräne. Dabei umfasst die Arbeit sowohl frauenspezifische pathophysiologische Faktoren, diagnostische und therapeutische Strategien als auch soziale Aspekte wie die Wahrnehmung von typischen Migränebildern in den Medien.

Im Einzelnen werden durch diese Arbeit folgende wissenschaftliche Fragen beantwortet:

- Welchen Einfluss haben weibliche Sexualhormone auf die CGRP-Konzentrationen bei Frauen mit Migräne im Vergleich zu gesunden Kontrollprobandinnen? (**Originalarbeit 1**)
- Wie sind die systemischen CGRP-Konzentrationen bei Frauen mit Migräne, die an einer komorbiden Endometriose leiden? (**Originalarbeit 2**)
- Wie ist das Verschreibungsverhalten deutscher Gynäkolog:innen in Bezug auf hormonelle Kontrazeption, wenn Patientinnen eine Migräne haben? (**Originalarbeit 3**)
- Welche sind die häufigsten Kopfschmerzursachen für eine Vorstellung in der Rettungsstelle eines deutschen Maximalversorgers während der Schwangerschaft? (**Originalarbeit 4**)
- Wie nehmen Patient:innen mit Migräne die Darstellung von Migräneattacken in den Medien wahr? (**Originalarbeit 5**)

2. Eigene Arbeiten

2.1 Einfluss von Sexualhormonen auf die CGRP-Konzentrationen im Blutplasma und in der Tränenflüssigkeit (Originalarbeit 1)

CGRP ist ein relevantes Neuropeptid in der Initiierung von Migräneattacken (Edvinsson et al., 2018; Goadsby et al., 1990). Frühere Erkenntnisse aus in vitro-Studien und tierexperimenteller Forschung deuten darauf hin, dass Sexualhormone die Synthese und Freisetzung von CGRP beeinflussen können (Labastida-Ramírez et al., 2019). Diese Erkenntnisse werfen die Frage auf, ob der Zusammenhang zwischen hormonellen Schwankungen und Migräneattacken durch die Modulation von CGRP vermittelt wird (Labastida-Ramírez et al., 2019). Die Daten aus der humanen Forschung sind jedoch uneinheitlich und konzentrieren sich weitgehend auf Probandengruppen ohne Migräne (Stevenson et al., 1986; Valdemarsson et al., 1990).
Ein weiteres limitierendes Element besteht darin, dass CGRP-Konzentrationen in diesen Studien ausschließlich im Blutplasma gemessen wurden, was zwar wichtige Informationen über systemische Konzentrationen liefert, jedoch nicht spezifisch für die Freisetzung von CGRP im trigeminovaskulären System ist (Kamm, 2022). Weitere Biomaterialien, wie die Tränenflüssigkeit, können wertvolle Einblicke liefern, da sie wahrscheinlich stärker von der trigeminalen Freisetzung von CGRP beeinflusst werden (Kamm et al., 2019).
Im Rahmen meiner Arbeit habe ich die CGRP-Konzentrationen sowohl im Blutplasma als auch in der Tränenflüssigkeit bei Frauen mit Migräne und gesunden Kontrollprobandinnen in unterschiedlichen hormonellen Zuständen untersucht. Das Hauptziel meiner Forschung war es, zu klären, ob unterschiedliche Sexualhormonprofile die CGRP-Konzentrationen beeinflussen können.

Der nachfolgende Text entspricht dem Abstract der Arbeit:

Raffaelli B, Storch E, Overeem LH, Terhart M, Fitzek MP, Lange KS, Reuter U. Sex Hormones and Calcitonin Gene-Related Peptide in Women With Migraine: A Cross-sectional, Matched Cohort Study. Neurology 2023 Apr 25;100(17):e1825-e1835. doi: 10.1212/WNL.0000000000207114.

*"**Background and objectives**: Sex hormones may modulate calcitonin gene-related peptide (CGRP) release in the trigeminovascular system. We studied CGRP concentrations in plasma and tear fluid in female participants with episodic migraine (EM) and a regular menstrual cycle (RMC), female participants with EM and combined oral contraception (COC), and female*

participants with EM in the postmenopause. For control, we analyzed 3 corresponding groups of age-matched female participants without EM.

***Methods**: Participants with an RMC had 2 visits: during menstruation on menstrual cycle day 2 ± 2 and in the periovulatory period on day 13 ± 2. Participants with COC were examined at day 4 ± 2 of the hormone-free interval (HFI) and between days 7 and 14 of hormone intake (HI). Postmenopausal participants were assessed once at a random time point. Plasma and tear fluid samples were collected at each visit for determination of CGRP levels with an ELISA.*

***Results**: A total of 180 female participants (n = 30 per group) completed the study. Participants with migraine and an RMC showed statistically significantly higher CGRP concentrations in plasma and tear fluid during menstruation compared with female participants without migraine (plasma: 5.95 pg/mL [IQR 4.37-10.44] vs 4.61 pg/mL [IQR 2.83-6.92], p = 0.020 [Mann-Whitney U test]; tear fluid: 1.20 ng/mL [IQR 0.36-2.52] vs 0.4 ng/mL [IQR 0.14-1.22], p = 0.005 [Mann-Whitney U test]). In contrast, female participants with COC and in the postmenopause had similar CGRP levels in the migraine and the control groups. In migraine participants with an RMC, tear fluid but not plasma CGRP concentrations during menstruation were statistically significantly higher compared with migraine participants under COC (p = 0.015 vs HFI and p = 0.029 vs HI, Mann-Whitney U test).*

***Discussion**: Different sex hormone profiles may influence CGRP concentrations in people, with current or past capacity to menstruate, with migraine. Measurement of CGRP in tear fluid was feasible and warrants further investigation."*

RESEARCH ARTICLE OPEN ACCESS

Sex Hormones and Calcitonin Gene–Related Peptide in Women With Migraine

A Cross-sectional, Matched Cohort Study

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Neurology® 2023;100:e1825-e1835. doi:10.1212/WNL.0000000000207114

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Page e1849

Abstract

Background and Objectives

Sex hormones may modulate calcitonin gene-related peptide (CGRP) release in the trigeminovascular system. We studied CGRP concentrations in plasma and tear fluid in female participants with episodic migraine (EM) and a regular menstrual cycle (RMC), female participants with EM and combined oral contraception (COC), and female participants with EM in the postmenopause. For control, we analyzed 3 corresponding groups of age-matched female participants without EM.

Methods

Participants with an RMC had 2 visits: during menstruation on menstrual cycle day 2 ± 2 and in the periovulatory period on day 13 ± 2. Participants with COC were examined at day 4 ± 2 of the hormone-free interval (HFI) and between days 7 and 14 of hormone intake (HI). Postmenopausal participants were assessed once at a random time point. Plasma and tear fluid samples were collected at each visit for determination of CGRP levels with an ELISA.

Results

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Discussion

Different sex hormone profiles may influence CGRP concentrations in people, with current or past capacity to menstruate, with migraine. Measurement of CGRP in tear fluid was feasible and warrants further investigation.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

C-COC = without EM–treatment with a COC; **CGRP** = calcitonin gene-related peptide; **COC** = combined oral contraceptive; **C-PM** = without EM–postmenopause; **C-RMC** = without EM–regular menstrual cycle; **EM** = episodic migraine; **FSH** = follicle-stimulating hormone; **HFI** = hormone-free interval; **HI** = hormone intake; **IQR** = interquartile range; **LH** = luteinizing hormone; **M-COC** = with EM–treatment with a COC; **M-PM** = with EM–postmenopause; **M-RMC** = with EM–regular menstrual cycle.

The prevalence of migraine is 3 times higher in women than in men.[1] Fluctuations of sex hormones play a crucial role in the pathophysiology of the disease.[2] The estrogen withdrawal hypothesis suggests that a drop in estrogen plasma concentrations can trigger migraine attacks.[3] In line with this hypothesis, migraine frequency and pain severity are higher during the perimenstrual phase of the menstrual cycle but also in the perimenopausal period before hormonal stabilization at an older age.[2,4] Migraine prevalence gradually declines after natural menopause.[5]

Hormonal contraception leads to the suppression of physiologic hormonal fluctuations with variable effects on migraine.[6] The most common hormonal contraception in Europe and North America are combined estrogen-progesterone oral compounds (combined oral contraceptives [COCs]).[7] Although some patients experience an improvement of migraine with COC, others experience worsening, with migraine attacks occurring most frequently during the 7-day hormone-free interval (HFI).[6]

The pathophysiologic mechanisms leading from hormonal changes to the development of migraine attacks are complex. The neuropeptide calcitonin gene-related peptide (CGRP) has a key role in migraine initiation[8] and is likely to have a relevant function in the processes initiated by sex hormone changes. During a migraine attack, CGRP is released from trigeminal afferents and triggers an inflammatory response.[9] Preclinical research suggests that sex hormone fluctuations can lead to activation of the trigeminovascular system and subsequent release of CGRP, which may contribute to the high prevalence of migraine in female persons of childbearing age.[10] However, the clinical evidence in humans is inconclusive. Although older investigations suggest a direct relationship between estrogen and CGRP concentrations,[11,12] newer studies imply a higher CGRP release in low estrogen phases.[13,14]

The accurate measurement of CGRP in peripheral blood is challenging due to its very short half-life time, degradation, and dilution effects after release.[15] A recent pilot study detected increased CGRP concentrations in tear fluid in participants with migraine compared with control participants without migraine.[16] This exploratory method is non-invasive and could provide a more direct measurement of the trigeminal CGRP release due to its spatial proximity to the trigeminal nerve.

Here, we studied CGRP concentrations in both plasma and tear fluid of female participants with migraine and female participants without migraine under different hormonal conditions. We aimed to assess the relationship between sex hormones and CGRP levels and whether the presence of migraine affects this relationship. It was our hypothesis that (1) female persons with migraine display higher CGRP concentrations than female persons without migraine during the physiologic menstrual cycle and (2) that the suppression of naturally occurring sex hormones through COC or after menopause is associated with changes in the CGRP concentrations.

Methods

Study Design and Participants

This is a cross-sectional, matched-cohort study at the Headache Center, Department of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany. The study cohort consisted of 3 groups of female participants with episodic migraine (EM): (1) with a regular menstrual cycle (M-RMC); (2) under contraceptive treatment with a COC (M-COC); and (3) during the postmenopause (M-PM). For control, we studied 3 respective groups of age-matched control female participants without EM (C-RMC, C-COC, and C-PM).

Participants with migraine were recruited from our outpatient headache clinic. For the recruitment of participants without migraine, we contacted hospital and university staff via announcements in mailing lists or direct approach.

Inclusion and Exclusion Criteria

EM was defined according to the International Classification of Headache Disorders 3.[17] All female participants with migraine should have had at least 3 days with migraine in the 4 weeks before screening, as documented in a headache diary.

An RMC was defined as the cycle duration of 28 ± 2 days in the 3 months before screening. In this group, the diagnosis of menstrually related migraine[17] was required for study participation. For inclusion in the COC groups, female participants should confirm the regular use of the same contraceptive drug in a 21/7 regimen (i.e., 21 days of hormone intake [HI] followed by a 7-day HFI), beginning at least 3 months before screening. For the postmenopausal groups, the last menstruation should have occurred at least 5 years before inclusion in the study.

Exclusion criteria were any other diagnosed primary headache disorder except tension-type headache on less than 2 days in the month before screening; concurrent migraine preventive drug treatment; any gynecologic or other neurologic diseases; ophthalmologic conditions interfering with lacrimation; any other relevant diseases requiring regular medication; hormonal treatment with indications other than contraception; pregnancy; lactation; and poststerilization. For participants with migraine and an RMC, the diagnosis of pure menstrual migraine[17] led to exclusion from the study.

Study Procedures

Before the beginning of experimental procedures, potential participants were screened for eligibility. Eligible individuals had an initial interview to record their medical history and a physical examination. In participants with migraine, we reviewed their headache calendars of the month before screening.

The study protocol for female participants with an RMC consisted of 2 study visits. The first visit was scheduled at day 2 ± 2 of the menstrual cycle (during menstruation), whereas the second visit took place at day 13 ± 2 of the menstrual cycle (periovulatory period). These time intervals were selected because estrogen levels are at their lowest during menstruation and at their highest during ovulation.

Female participants with COC were assessed twice: at day 4 ± 2 of the HFI and between days 7–14 of HI. Postmenopausal female participants had only 1 visit at a variable time point.

All visits in participants with migraine were performed in the interictal period, defined as a state free of any migraine symptoms and free of acute pain medication for 12 hours before and after each visit. Participants were instructed to call and reschedule the appointment in case of migraine or acute medication intake within 12 hours before the scheduled visit. We also contacted all participants by phone the day after each visit and asked about any migraine symptoms or medication intake in the 12 hours after the study visit. If this was the case, the visit was repeated at the next possible time point.

Sample Preparation and Analytical Procedures

Each visit took place between 9 AM and 5 PM in a nonfasting condition. Blood and tear fluid samples were collected following standardized protocols.[16,18]

For CGRP measurement, blood was collected in precooled 4 mL EDTA tubes (BD Vacutainer), which were previously prepared with 150 μL aprotinin (3–7 trypsin inhibitor unit (TIU)/mL) (Sigma Aldrich, Munich, Germany). The tubes were immediately centrifuged for 15 minutes at −6°C and 2,000 rpm. Plasma was then transferred in 1.5 mL polypropylene tubes (Eppendorf, Hamburg, Germany). We collected tear fluid from the lateral canthus of 1 eye with a 10-μL glass capillary (Brand, Wertheim, Germany). In participants with migraine, we selected the eye on the side on which migraine occurred most frequently. If there was no side preference and in participants without migraine, the right side was chosen by default. The capillary was removed after reaching the maximal volume of 10 μL or after 60 seconds at the latest. If the eye showed signs of irritation, such as redness or pruritus, the procedure was stopped immediately. A lack of tear production after 1 minute led to exclusion from the study. The volume of tear fluid collected was determined (range: 1.4–10.0 μL), and tear fluid was then transferred in a 1.5-mL tube containing 500 μL of tissue protein extractor solution (Pierce, Rockford, IL). Both plasma and tear fluid samples were stored at −80°C. We measured CGRP concentrations in plasma and tear fluid with a commercial sandwich ELISA kit (CUSABIO, Wuhan, China), following the manufacturer's instructions. The detection range of this kit is 1.56–100 pg/mL, and the minimal detectable dose was 0.39 pg/mL. However, the company does not disclose the specific recognition site of the ELISA antibodies. The kit has high intra-assay and interassay precision (coefficients of variation < 8% and <10%, respectively). Using this kit, mean CGRP concentrations in previous cohorts without migraine range from 4.2 to 6.6 pg/mL in plasma[16,19-21] and between 0.7 and 0.8 ng/mL in the tear fluid.[16,19]

In addition, blood was collected in 5-mL serum tubes (BD Vacutainer) at room temperature and sent to our partner laboratory (Labor Berlin, Charité Vivantes GmbH) for the analysis of sex hormones. The following hormones were assessed via electrochemiluminescence immunoassay: estradiol, progesterone, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

End Points

The primary end point of the study was the difference in CGRP concentrations in plasma (pg/mL) between M-RMC and C-RMC. Secondary end points were the differences in CGRP plasma concentrations between M-COC and C-COC and between M-PM and C-PM.

The differences in tear fluid CGRP concentrations (ng/mL) between the migraine and the control groups were considered exploratory endpoints. As further exploratory end points, we analyzed correlations between CGRP levels at both study visits in participants who were measured twice and assessed the differences in CGRP plasma and tear fluid concentrations among the 3 migraine and the 3 control groups. We also analyzed correlations between the estrogen and progesterone levels and the CGRP concentrations in tear fluid and plasma. In addition, the total cohort of participants with migraine was compared with the cohort of participants without migraine.

Statistical Analysis

Sample size calculation was performed using the software G*Power.[22] Based on a previous study on interictal CGRP plasma levels in patients with migraine compared with controls without migraine,[23] we assumed a large effect size of d = 0.8 for the primary end point. A sample size of 30 participants

per group was therefore sufficient to detect an effect of similar magnitude with a statistical power of 0.80 at a significance level of $\alpha = 0.05$ (2 tailed) using the Mann-Whitney *U* test. Similar statistical considerations apply for differences in tear fluid concentrations.[16] We therefore aimed at 30 participants per group with complete data sets.

We summarized demographic, anamnestic, and laboratory data using descriptive statistics with median and interquartile ranges (IQRs) for numerical variables and frequencies and percentages for categorical variables. Given the non-normal data distribution, we compared outcomes between groups using the Mann-Whitney *U* test or the Kruskal-Wallis analysis of variance, as appropriate. Correlations were tested using Spearman rank correlations.

Statistical analysis was performed with SPSS Statistics 27 (IBM Corp., Armonk, NY). No adjustment for multiple comparisons was made for the exploratory outcome measures.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the Charité Ethical Committee (EA1/004/20). All participants provided written informed consent following study information.

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Between August 2020 and May 2022, n = 196 persons who self-identified as women participated in the study. The study protocol was completed by n = 180 female participants, n = 30 per group. Reasons for dropout were no sufficient lacrimation (n = 11), occurrence of migraine in the 12 hours after study visits with no possible rescheduling (n = 4), and lost to follow-up (n = 1).

Demographic characteristics were similar between the migraine groups and the respective control groups. Table 1 shows the demographics across all groups and key migraine features in the 3 migraine groups. All female participants with migraine and an RMC reported migraine attacks within the perimenstrual period during most months.[17]

Female Participants With a Regular Menstrual Cycle

M-RMC and C-RMC presented physiologic hormonal levels at the 2 study visits with low estrogen concentrations during

Table 1 Description of the Study Population

	M-RMC	C-RMC	M-COC	C-COC	M-PM	C-PM
Age (y)	26.50 (24.00–30.00)	26.00 (24.00–31.00)	25.00 (22.75–30.00)	27.00 (22.75–31.00)	57.50 (55.75–60.00)	58.50 (55.75–61.25)
Height (m)	1.69 (1.63–1.74)	1.70 (1.63–1.72)	1.68 (1.65–1.71)	1.69 (1.63–1.74)	1.70 (1.63–1.72)	1.63 (1.60–1.67)
Weight (kg)	63.00 (53.75–73.43)	59.00 (55.00–70.75)	62.00 (56.75–70.25)	59.00 (55.00–70.75)	70.00 (60.75–77.25)	73.50 (62.00–80.50)
Cycle length (d)	28 (27–30)	28 (26–30)				
Estradiol dose in COC (mg)			0.03 (0.03–0.03)	0.03 (0.03–0.03)		
Progesterone dose in COC (mg)			2.00 (0.15–2.00)	2.00 (0.15–2.00)		
Age at menopause (y)					50.00 (48.87–51.00)	50.00 (48.75–52.00)
Age at migraine onset (y)	16.75 (12.37–22.50)		20.00 (17.75–22.13)		20.50 (15.62–31.25)	
Aura (n, %)	11, 36.7%		17, 43.3%		9, 30.0%	
Monthly migraine d	4.00 (3.87–6.25)		5.80 (4.0–7.0)		5.25 (4.00–9.00)	
Pain intensity (0–10 NAS)	7.5 (7.0–8.0)		8.0 (6.0–9.0)		7.0 (6.0–10.0)	
Attack duration (h)	24.00 (12.00–36.00)		27.00 (9.25–48.00)		36.25 (15.75–63.00)	
Positive family history (n, %)	22, 73.3%		18, 60.0%		22, 73.3%	

Abbreviations: C = control female participants without migraine; COC = combined oral contraception; IQR = interquartile range; M = female participants with migraine; NAS = numeric analog scale; PM = postmenopause; RMC = regular menstrual cycle.
Values are median (IQR) or n, %.

Table 2 Concentrations of Sex Hormones in Participants With Migraine and Control Participants With a Regular Menstrual Cycle

	Menstrual		Periovulatory	
	M-RMC	C-RMC	M-RMC	C-RMC
Day of the menstrual cycle	3 (2–4)	2.5 (2–3)	14 (13–15)	14 (12.75–15)
Estradiol (pmol/L)	136.50 (118.75–175.75)	135.00 (99.92–169.25)	576.50 (303.00–961.25)	607.50 (320.75–1019.75)
Progesterone (nmol/L)	0.80 (0.40–1.12)	0.85 (0.50–1.32)	0.85 (0.40–2.42)	0.95 (0.47–2.72)
Testosterone (µg/L)	0.27 (0.18–0.36)	0.24 (0.14–0.34)	0.34 (0.24–0.44)	0.35 (0.21–0.47)
LH (U/L)	5.60 (4.20–6.45)	5.55 (4.00–7.30)	12.35 (7.45–31.95)	15.40 (10.67–30.72)
FSH (U/L)	5.80 (4.72–6.92)	5.80 (4.47–7.22)	6.15 (4.27–9.00)	6.45 (4.57–9.60)

Abbreviations: C = control female participants without migraine; FSH = follicle-stimulating hormone; IQR = interquartile range; LH = luteinizing hormone; M = female participants with migraine; RMC = regular menstrual cycle.
Values are median (IQR).

menstruation and high estrogen concentrations in the periovulatory period (Table 2). Progesterone levels were low at both time points because both visits occurred before the luteal progesterone increase (Table 2).

During menstruation, CGRP concentrations in both plasma and tear fluid were statistically significantly higher in interictal participants with migraine compared with female participants without migraine (plasma: 5.95 pg/mL [IQR 4.37–10.44 pg/mL] vs 4.61 pg/mL [IQR 2.83–6.92 pg/mL], $p = 0.020$; tear fluid: 1.20 ng/mL [IQR 0.36–2.52 ng/mL] vs 0.4 ng/mL [IQR 0.14–1.22 ng/mL], $p = 0.005$) (Figure 1).

CGRP levels in the periovulatory period were numerically higher in female participants with migraine compared with participants without migraine but failed to reach statistical significance (plasma: 6.28 pg/mL [IQR 3.56–9.48 pg/mL] vs 4.87 pg/mL [IQR 2.95–6.41 pg/mL], $p = 0.089$; tear fluid: 0.70 ng/mL [IQR 0.18–2.29 ng/mL] vs 0.63 ng/mL [IQR 0.14–1.22 ng/mL], $p = 0.225$). There was a strong intraindividual correlation between the CGRP concentrations in the menstrual and the periovulatory visits, both in plasma (rho = 0.809, $p < 0.001$) and tear fluid (rho = 0.635, $p < 0.001$).

Female Participants With Combined Oral Contraception

Both M-COC and C-COC showed suppressed concentrations of naturally occurring sex hormones. CGRP concentrations in plasma and tear fluid were similar between participants with migraine and controls without migraine during the HFI and during HI (Table 3). There was a strong intraindividual correlation between the CGRP concentrations at both visits (plasma: rho = 0.797, $p < 0.001$; tear fluid: rho = 0.615, $p < 0.001$).

Postmenopausal Female Participants

Both postmenopausal groups showed physiologic hormonal profiles with high concentrations of LH and FSH and low concentrations of estrogen, progesterone, and testosterone. There was no statistically significant difference in CGRP concentrations in plasma and tear fluid between M-PM and C-PM (Table 4).

Comparison of CGRP Levels in Female Participants With Migraine in Different Hormonal States

Among all participants with migraine, CGRP plasma concentrations were similar among all groups and visits ($p = 0.195$ among all groups). In the tear fluid, female participants with an RMC had statistically significantly higher CGRP concentrations during menstruation compared with female participants under COC ($p = 0.015$ vs HFI and $p = 0.029$ vs HI) (Figure 2). There was no correlation between the absolute estrogen and progesterone concentrations and the CGRP concentrations in plasma and tear fluid ($p > 0.17$ for all analyses).

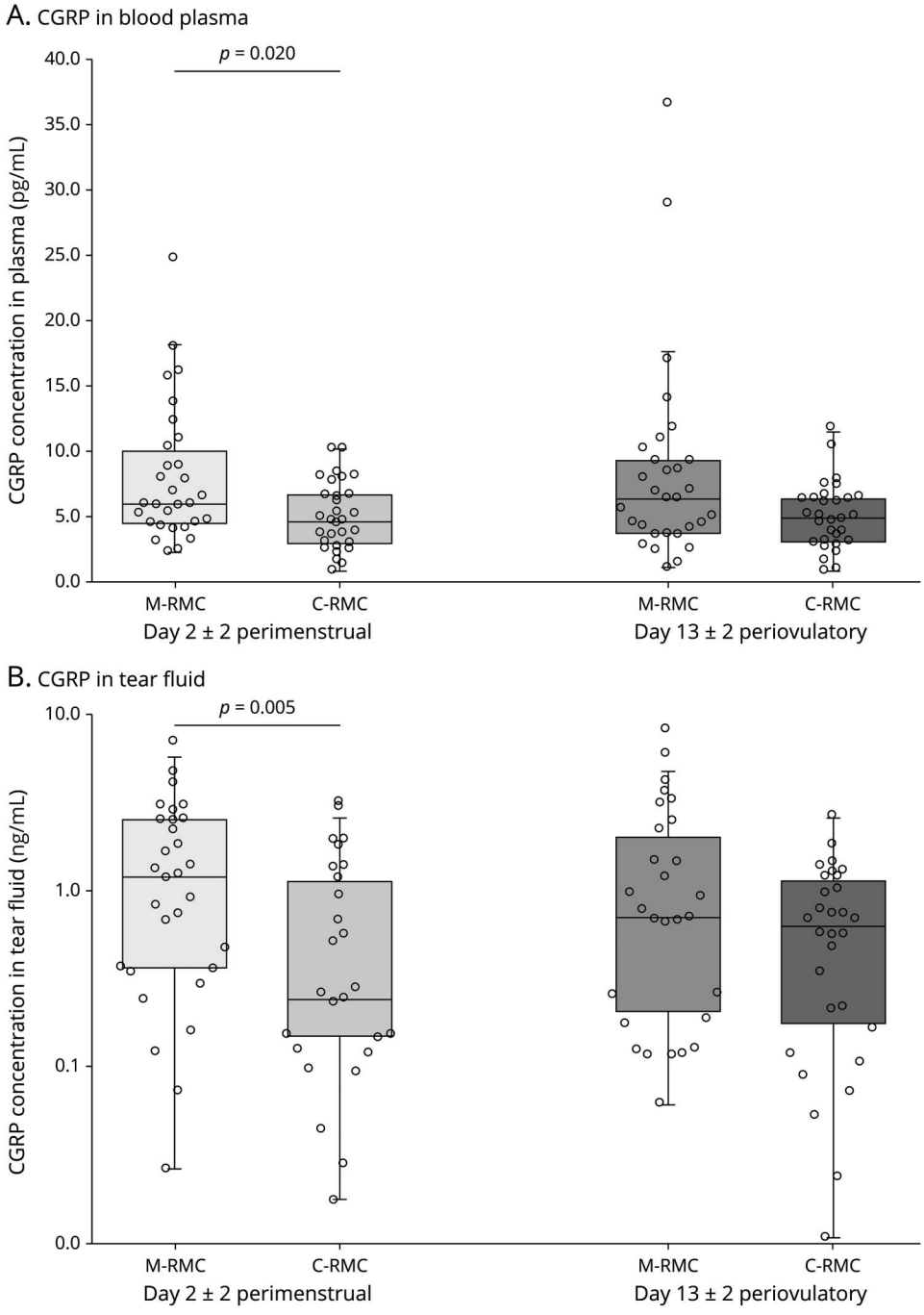
Comparison of CGRP Levels in Female Participants Without Migraine in Different Hormonal States

In plasma, CGRP concentrations of control female participants with an RMC were lower than those of female participants under COC treatment and postmenopausal female participants (menstruation vs HI: $p = 0.035$; ovulation vs HI: $p = 0.030$; menstruation vs postmenopause: $p = 0.015$; ovulation vs postmenopause: $p = 0.013$) (Figure 3). No statistically significant correlation between absolute sex hormone concentrations and CGRP concentrations could be detected ($p > 0.17$ for all analyses). CGRP levels in the tear fluid were similar across all groups and all visits of control female participants ($p = 0.622$ among all groups).

CGRP Plasma vs Tear Fluid Measurements

Across all participants (n = 180) and study visits (n = 300), CGRP concentrations were 5.48 pg/mL (3.98–7.82) in plasma and 0.51 ng/mL (0.16–1.22) in tear fluid. Tear fluid concentrations were 80.5× higher than in plasma (IQR 27.8–260.7).

Figure 1 CGRP Concentrations in Tear Fluid (A) and Plasma (B) in Participants With Migraine and Control Participants With a Regular Menstrual Cycle (RMC)



M = female participants with migraine; C = control female participants.

Overall, participants with migraine had statistically significantly higher CGRP levels in tear fluid compared with participants without migraine (migraine groups: 0.67 ng/mL [IQR 0.17–1.59 ng/mL] vs control groups: 0.41 ng/mL [IQR 0.15–0.80 ng/mL], $p = 0.013$). Plasma concentrations were similar with 5.22 pg/mL (IQR 4.03–7.97 pg/mL) in the migraine groups vs 5.95 pg/mL (IQR 3.73–7.79 pg/mL) in the control groups ($p = 0.965$).

Discussion

CGRP levels in plasma and tear fluid in this large cohort of female participants varied depending on the presence of migraine and the hormonal status. Female participants with EM had higher interictal CGRP concentrations in plasma and the tear fluid during menstruation than female participants without migraine. This finding did not apply to female

Table 3 Concentrations of Sex Hormones and CGRP in Participants With Migraine and Control Participants With COC Treatment

	HFI		HI	
	M-COC	C-COC	M-COC	C-COC
Day of the HFI/HI	3 (2–4.25)	3 (3–4)	10 (8–12)	10 (9.75–12)
Estradiol (pmol/L)	47.65 (20.27–99.70)	21.90 (18.40–58.00)	38.00 (18.40–65.15)	21.30 (18.40–46.03)
Progesterone (nmol/L)	0.30 (0.20–0.50)	0.25 (0.20–0.62)	0.35 (0.20–0.45)	0.40 (0.20–0.70)
Testosterone (µg/L)	0.15 (0.10–0.31)	0.20 (0.13–0.28)	0.14 (0.10–0.23)	0.19 (0.12–0.28)
LH (U/L)	3.20 (0.40–5.32)	1.70 (0.30–4.20)	2.60 (1.20–4.52)	2.15 (0.30–4.90)
FSH (U/L)	3.80 (1.27–7.95)	2.80 (0.30–6.07)	2.55 (1.75–4.12)	1.75 (0.30–4.52)
CGRP in plasma (pg/mL)	4.87 (4.22–6.15)	6.67 (3.76–8.56)	4.92 (3.89–6.24)	6.03 (4.40–9.42)
	$p = 0.165$		$p = 0.099$	
CGRP in tear fluid (ng/mL)	0.46 (0.10–1.01)	0.36 (0.14–0.59)	0.32 (0.09–1.44)	0.40 (0.13–0.82)
	$p = 0.574$		$p = 0.690$	

Abbreviations: C = control female participants without migraine; COC = combined oral contraception; FSH = follicle-stimulating hormone; HFI = hormone-free interval; HI = hormone intake; IQR = interquartile range; LH = luteinizing hormone; M = female participants with migraine.
Values are median (IQR).

participants with COC and during the postmenopause. In female participants with migraine, the suppression of the hormonal fluctuations through COC treatment was associated with lower CGRP tear fluid levels than during physiologic menstruation.

Our findings suggest a link between sex hormones and CGRP in migraine pathophysiology in humans. The influence of sex hormones—in particular estrogen—on intracranial CGRP release has been studied mainly in vitro or animal research. Estrogen receptors are highly expressed in CGRP-positive neurons in the trigeminovascular system,[24] and hormonal fluctuations can modulate their excitability.[10,25] In animal models, deficiency of female sex hormones increases CGRP expression in various brain regions.[26-28] Also in the trigeminal ganglion, the fall of endogenous estrogen levels in ovariectomized rats led to a significant increase in CGRP expression, which decreased following estrogen replacement treatment.[29] These observations are in line with our results in female patients with migraine: the physiologic estrogen drop in the perimenstrual period was associated with higher CGRP concentrations than under hormonal contraceptive treatment.

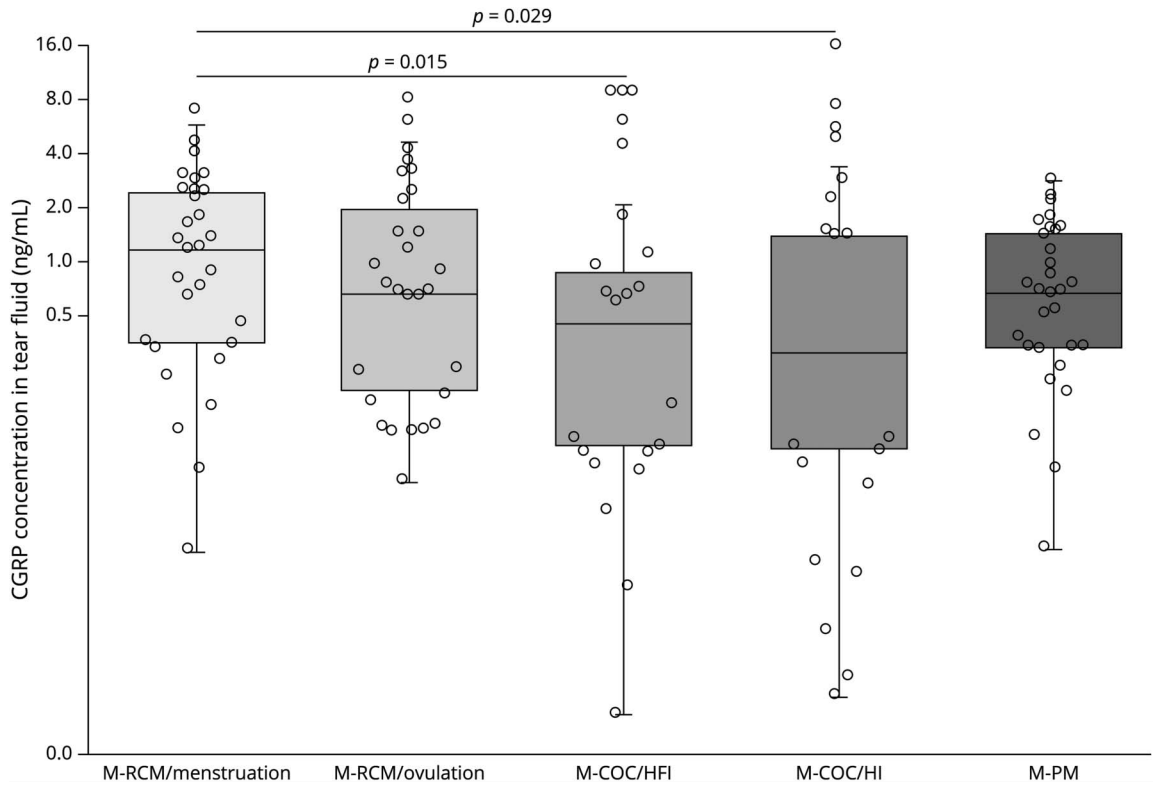
Table 4 Concentrations of Sex Hormones and CGRP in Participants With Migraine and Control Participants Without Migraine During the Postmenopause

	M-PM	C-PM
Estradiol (pmol/L)	22.80 (18.40–52.30)	28.30 (18.40–47.32)
Progesterone (nmol/L)	0.20 (0.20–0.32)	0.20 (0.20–0.20)
Testosterone (µg/L)	0.11 (0.10–0.19)	0.10 (0.03–0.13)
LH (U/L)	36.10 (28.65–49.77)	37.40 (30.40–44.73)
FSH (U/L)	69.05 (58.70–97.25)	75.70 (61.42–104.25)
CGRP in plasma (pg/mL)	5.24 (3.89–7.14)	6.70 (5.48–8.02)
	$p = 0.060$	
CGRP in tear fluid (ng/mL)	0.70 (0.34–1.50)	0.43 (0.21–1.01)
	$p = 0.280$	

Abbreviations: C = control female participants without migraine; FSH = follicle-stimulating hormone; IQR = interquartile range; LH = luteinizing hormone; M = female participants with migraine; PM = postmenopause.
Values are median (IQR).

A higher CGRP release during menstruation could help to explain the biological predisposition for more frequent, severe, and long-lasting migraine attacks in this period.[30] In line with this hypothesis, menstrual migraine attacks were more frequent and severe than nonmenstrual attacks even in female persons treated with the CGRP receptor antibody erenumab.[31] A recent review hypothesized that a decline in estrogen levels may lead to an increased CGRP signaling and generate a promigraine state with an increased susceptibility for migraine attacks.[25] Of note, this seems to apply only for a decrease in naturally occurring estrogen concentrations coming from a previously higher level but not for stable low concentrations during the postmenopause. In addition, the absolute hormone concentrations do not seem to play a relevant role, but rather the changes in hormonal levels. Accordingly, all correlation analyses between estrogen or progesterone levels and CGRP concentrations did not reveal any statistically significant result.

Figure 2 CGRP Tear Fluid Concentrations in Female Participants With Migraine in Different Hormonal States



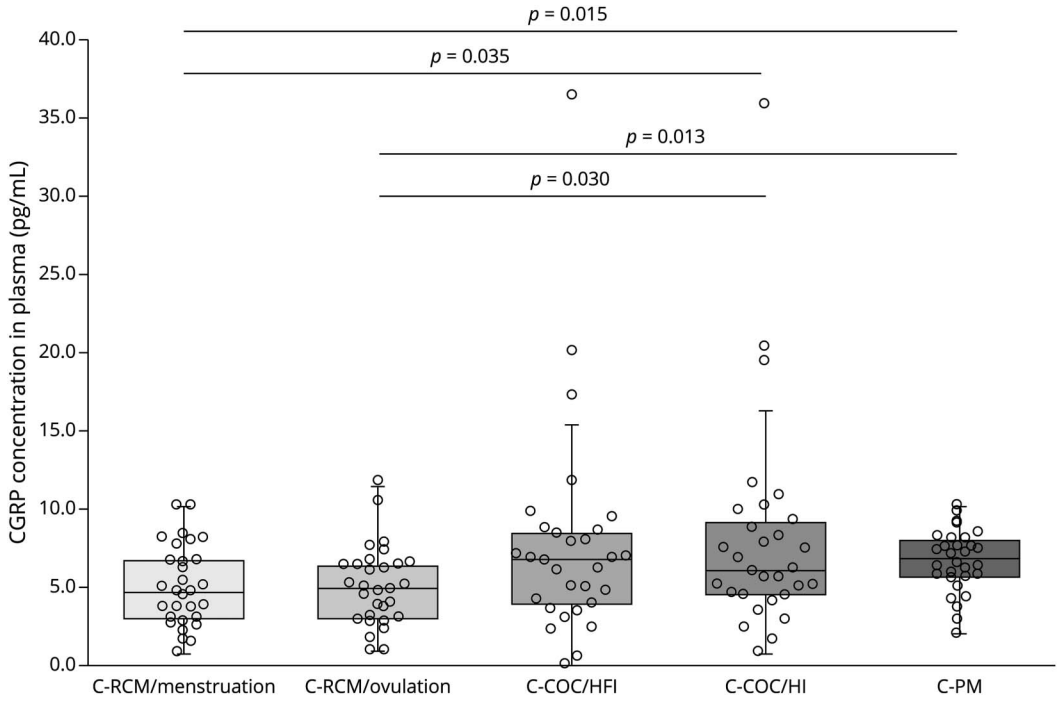
COC = combined oral contraception; HFI = hormone-free interval; HI = hormone intake; PM = postmenopause; RMC = regular menstrual cycle.

A few older studies showed that sex hormones might affect CGRP concentrations also in individuals without migraine. A study from 1986 detected increased concentrations of immunoreactive CGRP in plasma during pregnancy, which decreased after delivery.[11] In another older investigation, CGRP plasma levels were CGRP plasma levels were significantly higher in 11 female participants taking an oral contraception than in 12 female participants without hormonal treatment.[12] The study did not provide data on the day of the menstrual cycle or the regimen of hormonal intake.[12] In accordance with these results, in our study, oral contraception in female participants without migraine was associated with higher levels of CGRP in plasma but not in the tear fluid compared to fertile female participants without contraception. The intake of exogenous hormones seems to induce systemic changes in CGRP concentrations,[10] whereas intracranial CGRP levels as indirectly measured in the tear fluid seem to be not affected. Indeed, high estrogen states like pregnancy have been demonstrated to increase CGRP concentrations in other anatomical regions such as the spinal cord.[32] Estrogen substitution in rats led to a CGRP increase in the mesenteric arterioles, dorsal root ganglia,[33,34] and in the gastric tract.[35] Progesterone treatment induced an increased expression of CGRP receptors in the murine uterus and mesenteric arteries.[36,37] The postmenopause is also associated with an increase in systemic CGRP levels,[38] a finding which we could reproduce in our cohort of control female participants. The cardiovascular system has been proposed as the source of the elevated CGRP concentrations, as postmenopausal female persons with vasomotor symptoms appear particularly affected.[39,40] Taken together, hormone-dependent CGRP changes in plasma of female persons without migraine seem to originate from sources other than the trigeminovascular system.

CGRP concentrations in plasma are influenced by a multitude of factors and allow limited conclusions about the release from the trigeminal nerve system.[15] It is estimated that only one-fifth of CGRP in peripheral blood derives from trigeminal sources.[16] Although the crucial role of CGRP in migraine pathophysiology is indisputable, the feasibility of plasma CGRP as a biomarker of migraine remains a matter of debate.[15] Previous research reported controversial results regarding interictal plasma CGRP levels in patients with EM: although some studies detected higher CGRP levels in cubital vein blood outside of acute migraine attacks, others observed no difference to controls without migraine.[23,41-43] Our results provide a differentiated view depending on the hormonal status of the patients. Female participants with EM during menstruation had higher interictal plasma CGRP concentrations than female participants without EM, whereas this was not the case in the other hormonal conditions examined.

Biomaterials closer to the trigeminal CGRP source such as tear fluid may represent a more direct and suitable approach.[16]

Figure 3 CGRP Plasma Concentrations in Female Participants Without Migraine in Different Hormonal States



COC = combined oral contraception; HFI = hormone-free interval; HI = hormone intake; PM = postmenopause; RMC = regular menstrual cycle.

A recent study reported, in n = 30 interictal mix-sexed patients with EM, higher CGRP concentrations than in n = 48 controls without EM.[16] In the current analysis, we could confirm and expand these findings to a significantly larger cohort. Similar to this previous study, CGRP levels in the tear fluid were much higher than in plasma possibly due to lower proteolytic activity in this liquid than in plasma. In fact, in individuals without ophthalmologic conditions, the levels of peptidases are generally low in the tear fluid.[44-46] On the contrary, CGRP in plasma is quickly sheared into shorter fragments by endopeptidases,[47] which may in part explain the lower CGRP concentrations detected with a commercial ELISA. More complex methods such as high-performance liquid chromatography are able to detect and differentiate between different peptide fragments.[47]

CGRP in the tear fluid originates mainly from trigeminal nerve fibers in the cornea and conjunctiva, whereas ocular autonomic nerve fibers and the lacrimal and meibomian glands express only little or no CGRP.[48,49] Averaged over the whole cohort, the median CGRP concentrations in the tear fluid of interictal patients with migraine were higher than in controls without migraine. This corroborates the hypothesis of an increased activation of the trigeminovascular system even outside the acute attacks. However, in the analysis by subgroups, statistical significance was confirmed only in menstruating persons. Future studies should therefore take the hormonal status of the participants into account when examining CGRP in migraine. Despite these promising findings, CGRP determination in the tear fluid lacks validation and should be considered an exploratory procedure. For further use, a thorough validation study needs to be performed to compare the performance characteristics of CGPR levels in the tear fluid with the current standard measurement in plasma.

This is a comprehensive analysis of sex hormones and CGRP concentrations in female persons with migraine. The 3 groups of female participants with migraine were similar regarding migraine frequency and intensity. The selection of age-matched female participants without migraine and without other significant diseases or regular medication represents a key strength of this investigation. The measurement of sex hormone concentrations at each visit ensured that participants were in the predefined hormonal phase. Without a continuous hormonal measurement, however, we cannot determine whether the periovulatory visits took place exactly on the day of ovulation or rather in the few days before or after. Of note, we excluded female persons with a pure menstrual migraine, who might possibly have an even stronger influence of hormonal fluctuations on migraine-inducing mechanisms. Moreover, we included only cisgender women. Therefore, the findings do not generalize to all women (e.g., transgender women). One further limitation is the definition of the interictal state, that is, at least 12 hours free of migraine and acute medication before and after each visit. This is shorter than in other similar investigations.[16] We rationalized that the shortening of this period reduces organizational visit

changes and thereby dropouts. Twelve hours is more than 2 elimination half-lives of most triptans and NSAIDs, and we did not expect any relevant residual efficacy after this time.[50] CGRP measurement requires strict preanalytical sample handling, and CGRP concentrations may vary between studies depending on the exact methodology. In this study, we followed the protocol by Kamm et al. (2019) with the most sensitive commercial ELISA kit that is available. Indeed, we found similar concentrations of CGRP in both plasma and tear fluid as described in this previous study and other studies with the same commercial kit.[16,19-21] The detection of a strong correlation of CGRP levels between study visits in participants that were assessed twice proves a high interindividual consistency. Importantly, multiple physiologic and pathologic processes can influence both CGRP and sex hormone concentrations. Despite careful selection of subjects and standardized visits, we could not control for all possible confounding factors. This study is intended as a pilot study. It provides evidence of an association between CGRP and different sex hormone profiles in humans and sets the context for further studies with larger sample sizes and adequate power to correct for multiple testing and confounders.

In conclusion, our data suggest hormone-dependent changes in CGRP concentrations in female patients with EM. The elevated CGRP release from the trigeminovascular system following hormonal fluctuations could help to explain a higher susceptibility for migraine in female people who menstruate. The lower CGRP tear fluid concentrations under hormonal contraception in patients with migraine could be associated with an altered migraine susceptibility under hormonal therapy and should be further investigated in a longitudinal design.

Editors' Note

Neurology recognizes that sex and gender are not interchangeable. *Neurology* editors aim to ensure that papers accurately describe and report which of these variables was evaluated in a study. In this case, the authors included only female participants, and this is the terminology used throughout the paper. We were unable to find an equivalent term to use in the title, as style guidelines suggest against using "females" as a noun. Since all the participants also identified as women, we made an editorial decision to use women in the title. *Neurology* strives to affirm persons of all genders and recognizes that the findings of this article may not pertain to all persons who identify as women.

Rebecca Burch, MD; Roy H. Hamilton, MD, MS; Holly E. Hinson, MD, MCR

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Appendix Authors

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Elisabeth Storch	Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
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Maria Terhart	Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Mira Pauline Fitzek, MD	Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Kristin Sophie Lange, MD	Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Uwe Reuter, MD	Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany; Universitätsmedizin Greifswald, Greifswald, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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2.2 CGRP-Konzentrationen bei Patientinnen mit Migräne und Endometriose (Originalarbeit 2)

Endometriose ist eine häufige Komorbidität bei Frauen mit Migräne (Ferrero et al., 2004; Neumeier et al., 2023; Pasquini et al., 2023; Tietjen et al., 2006; Wu et al., 2021). Trotz des vielfältigen Forschungsinteresses in beiden Bereichen gibt es immer noch viele ungeklärte Fragen über die zugrunde liegenden Mechanismen, die die Verbindung zwischen Endometriose und Migräne erklären könnten. Die Identifikation gemeinsamer pathophysiologischer Mechanismen kann einen wichtigen Schritt zur besseren Behandlung und Prävention dieser beiden Erkrankungen darstellen.

In der Literatur wurden bereits einige gemeinsame pathophysiologische Mechanismen diskutiert, die möglicherweise Migräne und Endometriose verknüpfen, darunter eine Fehlregulation inflammatorischer Signalwege (Adewuyi et al., 2020). In diesem Zusammenhang könnte CGRP eine wichtige Rolle spielen. Die Bedeutung von CGRP bei der Entstehung von Migräne ist unbestritten und auch bei der Endometriose zeigten histologische Studien erhöhte Konzentrationen in Erkrankungsherden (Yan et al., 2019).

In meiner Arbeit habe ich die systemischen CGRP-Konzentrationen bei Patientinnen mit Migräne und Endometriose gemessen und sie mit denen von gesunden Frauen und Frauen verglichen, die nur eine der beiden Erkrankungen haben. Dies soll dazu beitragen, die Zusammenhänge zwischen CGRP, Migräne und Endometriose besser zu charakterisieren.

Der nachfolgende Text entspricht dem Abstract der Arbeit:

Raffaelli B, Overeem LH, Mecklenburg J, Hofacker MD, Knoth H, Nowak CP, Neeb L, Ebert AD, Sehouli J, Mechsner S, Reuter U. Plasma calcitonin gene-related peptide (CGRP) in migraine and endometriosis during the menstrual cycle. Ann Clin Transl Neurol 2021 Jun;8(6):1251-1259. doi: 10.1002/acn3.51360.

"***Objective**: Migraine, endometriosis, and the comorbidity of both are frequent pain disorders of special relevance for women. The neuropeptide calcitonin gene-related peptide (CGRP) is critically involved in migraine, and circumstantial evidence suggests a role in endometriosis. We assessed CGRP levels at different times of menstrual cycle in four groups: healthy women, women with migraine or endometriosis and with the comorbidity of both.*

***Methods**: Women with episodic migraine and women with a histologically confirmed*

endometriosis were recruited from specialized centers. For CGRP determination with a commercial enzyme immunoassay kit, cubital vein blood samples were collected on menstrual cycle day 2 ± 2 (during menstruation) and on day 15 ± 2 (periovulatory period). The primary endpoint of the study was the absolute difference of CGRP plasma levels between the menstrual and the periovulatory phase of all study groups. Groups were compared using nonparametric test procedures.

***Results**: A total of 124 women were included in the study. The change of CGRP plasma levels between menstruation and the periovulatory period was different between groups (p = 0.007). Women with comorbid migraine and endometriosis showed an increase of CGRP in the menstrual phase of +6.32 (interquartile range, IQR -3.64-13.60) compared to the periovulatory time, while healthy controls had a decrease of -10.14 (-22.54-0.91, p = 0.004). CGRP levels were different in the periovulatory phase among groups (p = 0.008), with highest values in healthy controls.*

***Interpretation**: CGRP levels change significantly during the menstrual cycle. Different patterns in women with the comorbidity point to a deviant regulation of CGRP release.*“

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RESEARCH ARTICLE

Plasma calcitonin gene-related peptide (CGRP) in migraine and endometriosis during the menstrual cycle

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Abstract

Objective: Migraine, endometriosis, and the comorbidity of both are frequent pain disorders of special relevance for women. The neuropeptide calcitonin gene-related peptide (CGRP) is critically involved in migraine, and circumstantial evidence suggests a role in endometriosis. We assessed CGRP levels at different times of menstrual cycle in four groups: healthy women, women with migraine or endometriosis and with the comorbidity of both. **Methods**: Women with episodic migraine and women with a histologically confirmed endometriosis were recruited from specialized centers. For CGRP determination with a commercial enzyme immunoassay kit, cubital vein blood samples were collected on menstrual cycle day 2 ± 2 (during menstruation) and on day 15 ± 2 (periovulatory period). The primary endpoint of the study was the absolute difference of CGRP plasma levels between the menstrual and the periovulatory phase of all study groups. Groups were compared using nonparametric test procedures. **Results**: A total of 124 women were included in the study. The change of CGRP plasma levels between menstruation and the periovulatory period was different between groups ($p = 0.007$). Women with comorbid migraine and endometriosis showed an increase of CGRP in the menstrual phase of +6.32 (interquartile range, IQR −3.64–13.60) compared to the periovulatory time, while healthy controls had a decrease of −10.14 (−22.54–0.91, $p = 0.004$). CGRP levels were different in the periovulatory phase among groups ($p = 0.008$), with highest values in healthy controls. **Interpretation**: CGRP levels change significantly during the menstrual cycle. Different patterns in women with the comorbidity point to a deviant regulation of CGRP release.

Introduction

Women's health remains a significant challenge across the globe. Endometriosis and migraine are both listed among the most prevalent diseases in women and share pain as their most predominant clinical feature. Endometriosis is a chronic inflammatory gynecological disorder affecting over 10% of women worldwide with a significant therapeutic need and so is migraine.[1,2] Each of them leads to an impairment of quality of life and exhibits detrimental effects on the physical and mental health in affected women.[2,3]

Epidemiological studies report a significant comorbidity of migraine and endometriosis, and the presence of one of the two disorders also increases the chance to suffer from the other.[4,5] In migraine and in endometriosis, severe pain attacks occur often during the menstrual period.[1,2] Impaired regulation of inflammatory signaling pathways and neurotransmitter release, such as calcitonin gene-related peptide (CGRP), may contribute to the development of acute pain episodes.[6,7]

Acute migraine is clearly linked to CGRP release from trigeminal afferent neurons.[6] Hormonal fluctuations

contribute to the generation of attacks,[8] but CGRP levels in women have yet to be determined during the menstrual cycle.

The increased density of CGRP-positive sensory nerve fibers in affected tissues indicates a role of this neuropeptide in endometriosis.[7] Along with the proliferation and growth of endometriosis cells, CGRP seems to promote neurogenic inflammation in this tissue.[9] Despite these findings, CGRP- and CGRP-related mechanisms have not been studied to date in vivo in women with endometriosis.

We therefore studied CGRP levels in women during the menstrual cycle at two predefined timepoints, that is, during menstruation and in the periovulatory period (PO). It was our hypothesis that CGRP levels increase during menstruation in parallel to the perimenstrual (PM) estrogen drop with a difference between women with the comorbidity of migraine and endometriosis, women with migraine and women with endometriosis. We assumed that women with the comorbidity of migraine and endometriosis have most pronounced CGRP level changes based on the assumption that both conditions are CGRP-related.

Methods

Study design and participants

This was a single-center, longitudinal, observational cohort trial conducted at the Headache Center, Department of Neurology, Charité—Universitätsmedizin Berlin, Germany. The approved Endometriosis Center, Department of Gynecology, Charité and an outpatient Endometriosis Center (ADE) recruited patients with endometriosis. Healthy female controls were recruited from hospital staff not related to the study team and medical students through direct approach or announcements in mailing lists.

The study consisted of four study groups: women with episodic migraine, women with endometriosis, women with endometriosis and migraine, and female healthy controls.

For inclusion, all females had to have a regular menstrual cycle, defined as menstrual cycle duration between 25 and 35 days in the 3 months prior to screening.

Patients with migraine had to fulfill the criteria of episodic migraine according to the International Classification of Headache Disorders 3rd Edition (ICHD-3)[10] and to have had at least one migraine attack in the 4 weeks prior to screening. The use of migraine prophylactic medications was not allowed.

For enrollment into one of the endometriosis study groups, a histologically confirmed diagnosis of endometriosis was required, in addition to existing pelvic pain (self-classified as endometriosis-related) at least once in the four weeks prior to screening.

The exclusion criteria have been: use of hormonal contraception, treatment with sex hormones or sex hormone modulators, any other suspected or present gynecological or neurological disease, and diagnosis of chronic migraine or any other diagnosed primary headache disorder except tension-type headache on less than 2 days in the month prior to screening.

For healthy controls, further exclusion criteria applied: Females were excluded if they had a history of primary headache apart from tension-type headache on less than 2 days per month and/or if they reported strong pelvic pain or cramps during menstruation.

The Charité Ethical Committee (EA1/165/18) approved the study. All participants gave written informed consent following study information. The study was registered in the German Clinical Trial Register (DRKS00020744).

Study procedures

The study consisted of three on-site visits, lasting approximately 1 hour each: a screening visit, a visit during menstruation at day 2 $\pm$ 2 (perimenstrual visit = PM), and a visit in the intermenstrual period at day 15 $\pm$ 2 of the menstrual cycle (periovulatory visits = PO). The first day of menstrual bleeding is defined as day 1 of the menstrual cycle.

The patient's medical history with a focus on migraine and/or endometriosis-related symptoms and treatment was taken at screening, followed by a physical examination. A headache-experienced neurologist confirmed the diagnosis of migraine in both migraine groups and classified all reported headache attacks in the month prior to screening as migraine or tension-type headache, in order to assess the inclusion and exclusion criteria. For the grading of endometriosis severity we used the revised classifications of the American Society for Reproductive Medicine (rASRM),[11] as documented in the patient's gynecologic record: stage I corresponds to a minimal severity, stage II mild, stage III moderate, and stage IV severe.

At screening, patients with migraine completed the Headache Impact Test-6 (HIT-6)[12] and patients with endometriosis the Endometriosis Health Profile-30 (EHP-30).[13] The HIT-6 is a standardized, validated questionnaire to assess negative effects of headache on daily life[12] and comprises of six questions. Each question is answered on a 5-point scale. The total global score ranges from 36 to 78, and a score >60 indicates a severe impact of headache on quality of life.

The EHP-30 is a validated, 30-item questionnaire assessing the health-related quality of life in patients with

endometriosis.[13] The items are divided in five dimensions: pain (11 items), control and powerlessness (6), social support (4), emotional well-being (6), and self-image (3). For each dimension, a percentage score (0–100) is built. Lower scores indicate a better health status.

At study visits PM and PO, participants reported the first day of their current menstrual cycle, the date of their last migraine attack and/or endometriosis-related pain episode, and the last intake of acute pain medication. Blood samples for the analysis of CGRP were drawn between 8–12 AM on each visit from the antecubital vein but only when patients were free of any migraine symptoms since more than 12 hours and at least 12 hours after the last intake of any acute pain medication.

We collected the blood samples in precooled 10 ml EDTA tubes (BD Vacutainer®), prepared with 500 µl aprotinin (5–10 trypsin inhibitor unit (TIU)/ml) (Sigma Aldrich, Munich, Germany). Immediately afterwards, the tubes were centrifuged at −6°C and 2000 rpm, for 15 minutes. Plasma was transferred into 1.5 ml polypropylene tubes (Eppendorf, Hamburg, Germany) and stored at −80°C. CGRP concentrations were measured via a commercial enzyme immunoassay-KIT (EIA) (Bertin Bioreagent, Montigny le Bretonneux, France), following manufacturer's instructions. This two-site immunometric assay combines an anti-N terminus antibody with an anti-C terminus antibody and is equally sensitive for all human CGRP isoforms.[14] The limit of detection is 2 pg/ml.[14] All samples of one patient were analyzed in the same kit, and each kit contained samples of all four study groups in similar proportions. Two samples from the first kit were measured in each of the following kits and served as additional quality control and reference standard.

We aimed to schedule PM and PO within the same menstrual cycle, but if not possible, the missing visit was scheduled up to 2 months later.

Outcomes

The primary endpoint of the study was the absolute difference of CGRP concentrations in pg/ml from the menstrual to the PO period (i.e., PM − PO) between all study groups. Secondary endpoints were the relative difference in CGRP concentrations [100 − (PO*100/PM)] as well as the absolute CGRP concentrations at each of the two time points.

Statistical analysis

Based on a previous study of CGRP levels in patients with chronic migraine,[15] we assumed a large effect size of $d = 0.9$ for the primary endpoint. A sample size of 25 patients per group was therefore sufficient to detect an effect of similar magnitude with a statistical power of 0.85 at a significance level of $\alpha = 0.05$ (two-tailed) using the Kruskal–Wallis analysis of variance (ANOVA). Assuming a dropout rate of 15%, we planned to enroll at least 30 patients per group. The power analysis was conducted with G*Power.[16]

Data at screening were summarized with descriptive statistics, using means ± standard error for numerical variables and frequencies and percentages for categorical variables. Only participants who completed study protocol were included in the analysis of primary and secondary endpoints. We tested the primary and secondary outcome measures for normal distribution using the Shapiro–Wilks test. Because data were not normally distributed, we compared outcomes between groups using the Kruskal–Wallis (ANOVA) with post hoc Mann–Whitney U tests. Within-group analyses were performed using the Wilcoxon test. Due to the influence of older age and obesity on CGRP release,[17,18] we examined the effects of age and BMI on the primary outcome usingsemi-parametric probabilistic index models.[19] Correlations between CGRP concentrations and migraine and endometriosis features were explored using Kendall's nonparametric correlation coefficient τ. Kendall's τ can assume values between −1 and 1: The closer the value comes to 0, the weaker the correlation.[20]

All statistical analyses were performed using R (version 3.6.2; The R Foundation for Statistical Computing, Vienna, Austria. Primary and secondary outcomes are reported as median and interquartile range (IQR). In line with common recommendations, p values are reported only for the primary and secondary endpoints. The significance level was corrected for multiple comparisons in post hoc tests using Bonferroni's correction.

Results

Between 8 January 2019 and 18 November 2019, we screened 134 individuals and enrolled 122 females in the study ($n = 31$ in group MM, $n = 30$ in group EE, $n = 30$ in group ME, and $n = 31$ in group HC). The study was completed by 110 participants (90.2%); reasons for noncompletion are shown in Figure 1. All study visits were performed during the same menstrual cycle in 89 patients (80.9%).

All groups were similar in age and BMI (Table 1). Migraine characteristics were similar between the two migraine groups. Patients with migraine only treated their attacks more frequently with triptans than comorbid patients, who had higher use of nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with migraine and endometriosis patients reported a higher number of days

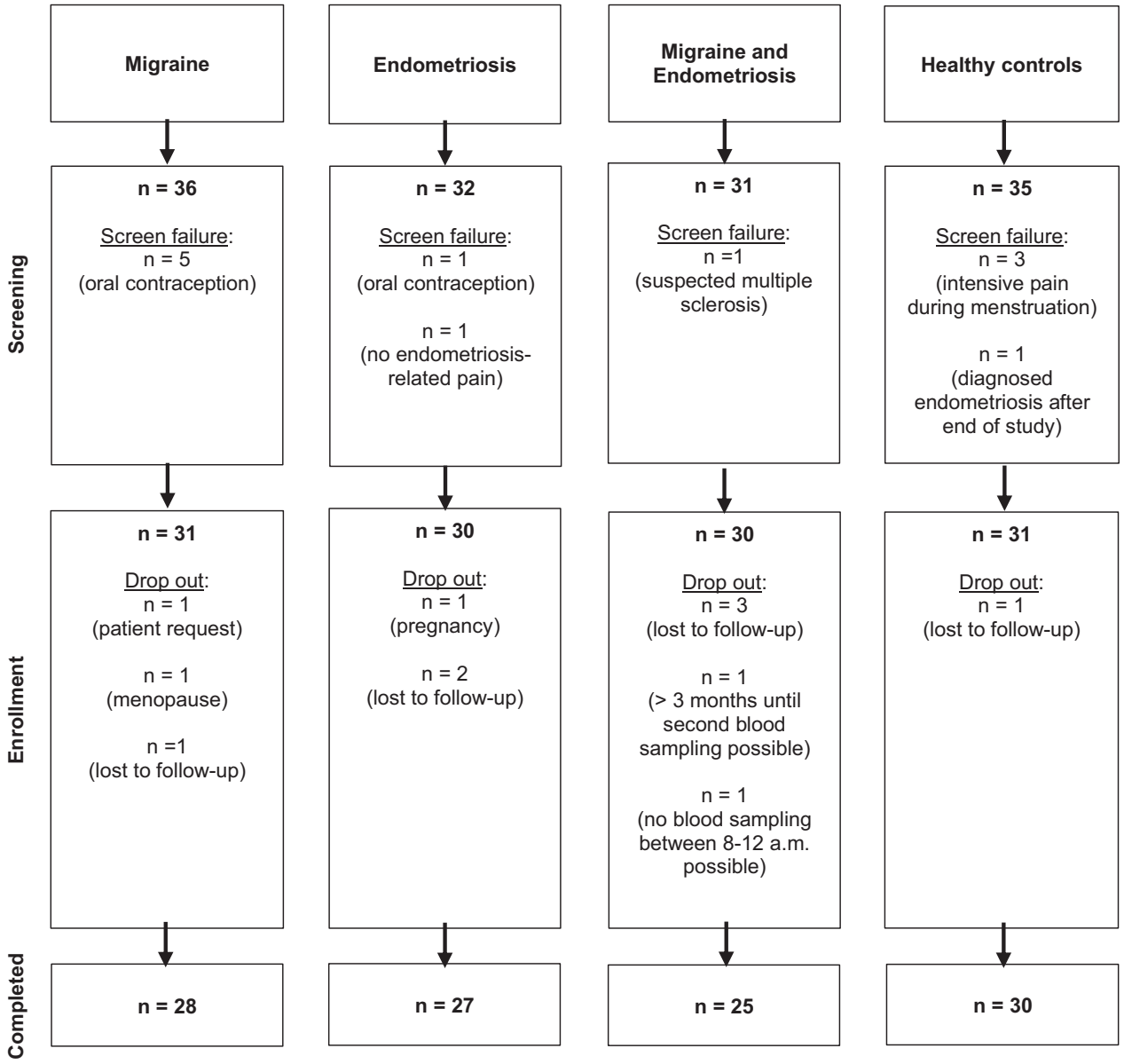

Figure 1. Flowchart of participant selection.

with endometriosis-related pain, pain intensity, and attack duration than patients with endometriosis only. However, rASRM disease scores were similar between the two groups.

Patients in both migraine groups reported a severe impact of headache on their quality of life with HIT-6 scores of 63.45 ± 0.90 (migraine only) and 60.73 ± 1.19 (migraine and endometriosis). The EHP-30 scores were higher in almost every domain in comorbid patients than in patients with endometriosis only, indicating a stronger impact of endometriosis symptoms in patients with migraine and endometriosis on their perceived health status (Figure 2). The difference was particularly evident in the domain "Pain" with an average score of 35.99 ± 4.42 (endometriosis only) and 53.28 ± 3.76 (migraine and endometriosis). This shows a greater influence of endometriosis-related pain on quality of life in comorbid women.

Changes in plasma CGRP levels during the menstrual cycle

The absolute difference in CGRP levels from the PM to the PO was different between all groups ($p = 0.007$).

Table 1. Demographic, anamnestic, and clinical features of study participants.

	Patient characteristics			
	Healthy controls	Migraine	Endometriosis	Migraine and endometriosis
Age	31.55 ± 1.71	32.74 ± 1.31	31.90 ± 1.02	35.70 ± 1.32
BMI	22.76 ± 3.09	24.11 ± 3.73	24.29 ± 4.13	23.76 ± 4.22

	Migraine characteristics			Endometriosis characteristics	
	Migraine	Migraine and endometriosis		Endometriosis	Migraine and endometriosis
Years since migraine diagnosis	16.16 ± 1.63	17.13 ± 2.06	Years since endometriosis diagnosis	3.03 ± 0.66	4.90 ± 1.09
Monthly migraine days	5.48 ± 0.57	4.53 ± 0.75	Monthly days with endometriosis pain	4.27 ± 0.77	5.48 ± 0.87
Pain intensity	7.19 ± 0.22	7.00 ± 0.29	Pain intensity	5.77 ± 0.46	6.43 ± 0.44
Attack duration (h)	28.92 ± 3.94	29.13 ± 4.94	Attack duration (h)	17.50 ± 3.27	26.77 ± 4.36
Aura	5 (17.9%)	2 (8.0%)	rASRM score	2.13 ± 0.22	2.08 ± 0.29
Positive family history	20 (71.4%)	16 (64.0%)	Positive family history	9 (33.3%)	4 (16.0%)

Note: All values are reported as means (±standard error) or *n* (%).

Abbreviations: BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drugs; rASRM, revised classifications of the American Society for Reproductive Medicine.

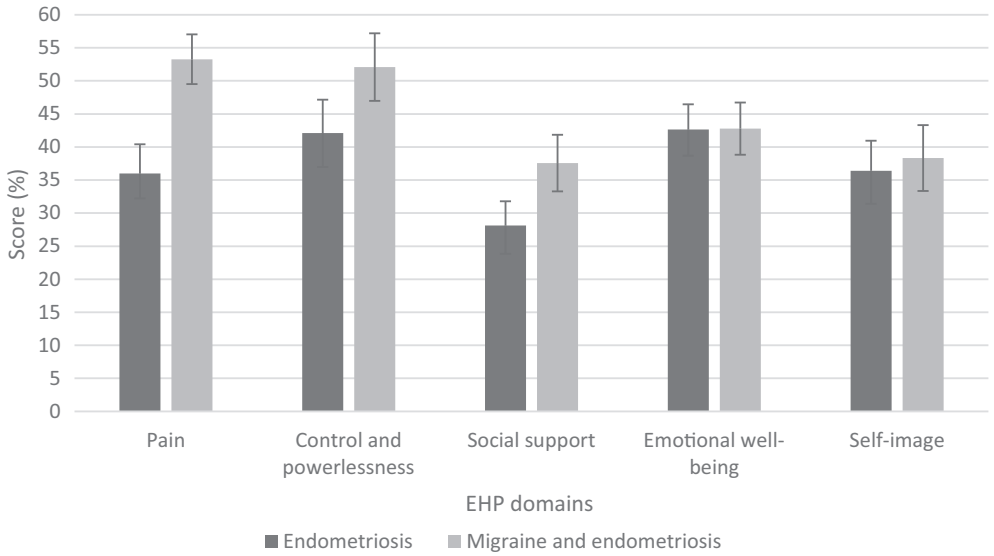

Figure 2. Endometriosis Health Profile-30 (EHP-30) scores (mean ± standard error) in five domains in women with endometriosis (dark gray bars) and women with migraine and endometriosis (light gray bars). Higher scores indicate a worse perceived endometriosis-related health status in the respective domain.

Statistical analyses revealed that comorbid patients had an increase of +6.32 pg/ml (IQR −3.64 to 13.60) during menstruation compared to the PO, while healthy female controls showed a decrease of −10.14 (IQR −22.54 to 0.91, $p = 0.004$), as shown in Table 2. The relative change of CGRP concentrations from PM to PO was also significantly different between comorbid patients and healthy controls (12.5%, IQR −8.6 to 31.0 in comorbid women vs. −11.3%, IQR −29.9 to 1.6 in healthy controls, $p = 0.022$). Adjusting for the covariates age and BMI did not affect the results ($p = 0.001$ in the adjusted model).

Absolute plasma CGRP levels during the menstrual cycle

All groups showed similar plasma CGRP concentrations during menstruation (PM) with 47.70 pg/ml (IQR 33.67–73.31) in patients with migraine, 46.35 pg/ml (IQR

Table 2. Absolute and relative changes in CGRP plasma concentrations from PM to PO in the four analyzed study groups (median and IQR).

	Absolute difference (pg/ml) PM - PO	Relative difference (%) PM - PO
Migraine	−2.44	−3.3
	IQR −18.37 to −2.45	IQR −31.4 to 17.5
Endometriosis	−1.24	−3.4
	IQR −12.46 to 9.22	IQR −29.2 to 17.8
Migraine and endometriosis	6.32	12.5
	IQR −3.64 to 13.60	IQR −8.6 to 31.0
Healthy controls	−10.14	−11.3
	IQR −22.54 to 0.91	IQR −29.9 to 1.6
P value (all groups)	0.007*	0.037*
P value (pairwise)	M – E: >0.999	M – E: >0.999
	M – ME: 0.245	M – ME: 0.549
	E – ME: >0.999	E – ME: 0.676
	M – HC: >0.999	M – HC: >0.999
	E – HC: 0.198	E – HC: >0.999
	ME – HC: 0.004*	ME – HC: 0.022*

Abbreviations: CGRP, calcitonin gene-related peptide; E, endometriosis; HC; healthy controls; IQR, interquartile range; M, migraine; ME, migraine and endometriosis; PM, perimenstrual; PO, periovulatory.
*Statistically significant.

32.48–64.11) in patients with endometriosis, 52.59 pg/ml (IQR 35.08–72.41) in comorbid patients and 55.01 pg/ml (IQR 42.78–130.08) in healthy controls ($p = 0.324$ across all groups).

In the PO, CGRP concentrations were significantly different between all groups ($p = 0.011$). Post hoc analyses revealed that healthy female controls had higher CGRP levels (67.34 pg/ml, IQR 49.60–134.06) when compared to women with migraine and endometriosis (46.21 pg/ml, IQR 34.10–59.56, $p = 0.016$). Women with migraine (47.39 pg/ml, IQR 34.45–104.33) and women with endometriosis (47.85 pg/ml, IQR 33.96–69.99) did not differ significantly from the other groups.

The analyses within groups showed that women with migraine ($p = 0.210$) or endometriosis ($p = 0.962$) had similar CGRP concentrations in PM and PO measurements. Comorbid women showed numerically higher CGRP concentrations at PM, but without statistical significance ($p = 0.078$). Healthy controls had higher concentrations at PO ($p = 0.003$).

Figure 3 illustrates CGRP concentrations at PM and PO for each group.

Data analysis did not reveal any correlation between CGRP levels and migraine headache or endometriosis pain frequency. The time interval since the last migraine or endometriosis-related pain attack or the last intake of pain medication also showed no correlation to CGRP levels (Table 3).

Discussion

This study shows that CGRP levels change during the menstrual cycle. In women with the comorbidity of migraine and endometriosis CGRP levels rise during menstruation. In contrast, healthy females display a decrease of CGRP during the menstrual period, while changes in women with only migraine and women with only endometriosis do not reach statistical significance. PO CGRP concentrations are lower in comorbid women than in healthy controls. The fluctuation of CGRP levels during the female cycle in healthy women is consistent with a possible influence of female sex hormones on CGRP release. The diversion of this pattern in women with migraine and endometriosis points to disease-specific pathophysiological events, which may be explained by a different regulation of CGRP release in females with this comorbidity.

The multitude of factors that influence CGRP homeostasis include ovarian sex hormones.[21] In 1986, Stevenson et al. observed increased CGRP plasma levels during pregnancy, which returned to normal after delivery.[22] Women of reproductive age displayed higher CGRP plasma levels than men.[23] These studies suggest a direct relationship between estrogen levels and CGRP concentrations in blood, which is in line with our observations in healthy females.

In contrast, patients with the comorbidity of migraine and endometriosis display an increase of CGRP in parallel to the perimenstrual estrogen drop. The cause might be found in genetically determined differences underlying this comorbidity, as shared molecular genetic mechanism has been recently proposed by Adewuyi et al.[24] In fact, with *TRIM32 and SLC35G6*, two loci have been identified in a genome wide association study to be associated with this comorbidity. These loci are enriched for mitogen-activated protein kinase (MAPK) and TNF-a signaling, which may lead to a different hormone-dependent CGRP release than in healthy women.[24]

It is unlikely that high menstrual CGRP concentrations in comorbid females are merely a consequence of acute migraine or endometriosis pain. The study visits occurred after a similar time interval from the last acute pain attack in all patient groups, and analyses did not find a correlation between CGRP concentrations and the number of days from the last pain attack.

This study shows that CGRP plasma levels do not differ in the menstrual period and at a later time point in the menstrual cycle between women with migraine and healthy female controls. Previous research showed mixed results on plasma CGRP levels in patients with episodic migraine.[15,25-27] Our results may also differ from these observations as previous studies included mixed-sex

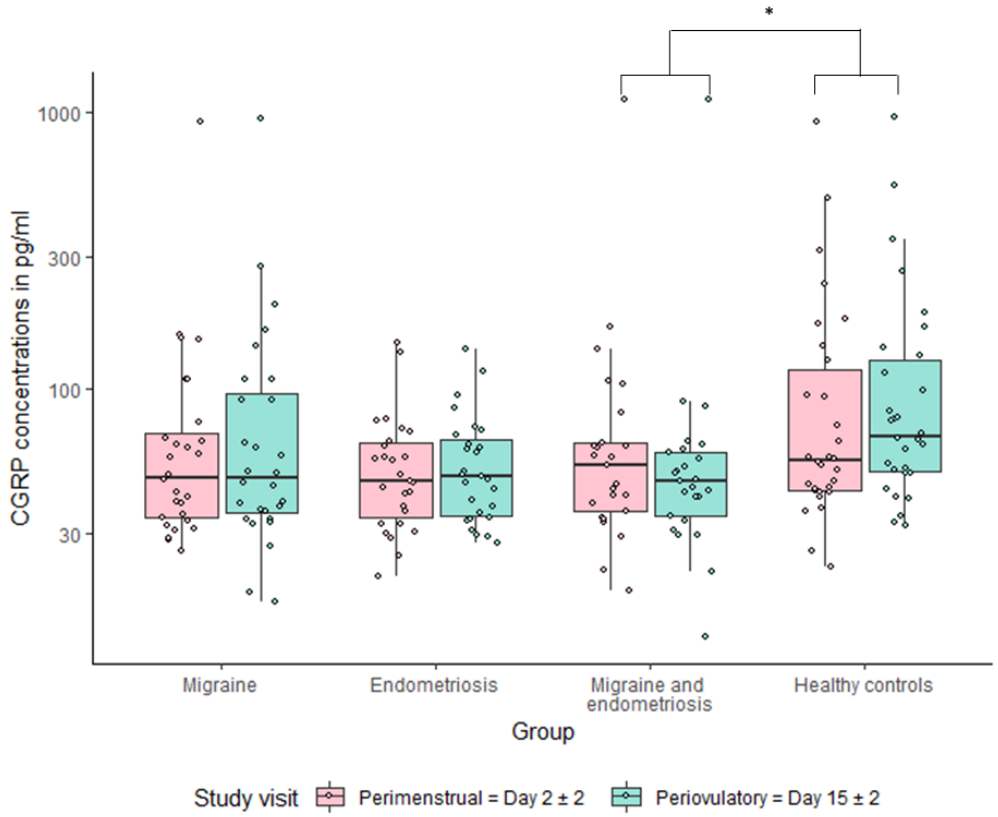

Figure 3. Boxplot and jitter plot for calcitonin gene-related peptide (CGRP) plasma concentrations at the perimenstrual (PM) and periovulatory (PO) visit for each study group. The boxes are drawn from the 25% to 75% quartiles, the horizontal line represents the median. The whiskers are drawn out to 1.5*interquartile range. The dots represent single data points. [a]$p = 0.078$ between PM and PO. *$p = 0.003$ between PM and PO. **$p = 0.004$ for the changes from PM and PO between groups.

Table 3. Kendall's τ correlation coefficient between CGRP levels and time since the last migraine or endometriosis-related pain attacks or the last intake of acute pain medication.

	Perimenstrual CGRP concentrations (PM)	Periovulatory CGRP concentrations (PO)
Migraine frequency	−0.07	−0.10
Endometriosis frequency	0.00	−0.06
Days since last migraine attack	0.03	0.06
Days since intake of acute migraine medication	0.00	0.08
Days since last endometriosis-related pain	0.04	−0.05
Days since last intake of acute pain medication (endometriosis)	−0.17	0.05

Note: A value < 0.2 or > −0.2 indicates a weak correlation.
Abbreviations: CGRP, calcitonin gene-related peptide; PM, perimenstrual; PO, periovulatory.

cohorts and did not consider the influence of the menstrual cycle and hormonal therapies.

We expected higher CGRP plasma levels in women with endometriosis based on intense CGRP staining in endometriotic lesions,[9] which may translate into enhanced CGRP release into the blood. While similar CGRP concentrations in women with endometriosis and healthy controls are unexpected, they do not exclude a role of CGRP in the pathophysiology of endometriosis. Numerous inflammatory signaling pathways are involved in the pathogenesis of endometriosis.[2] The interactions between the individual pathways and regulatory mechanisms are highly complex and were not within the scope of this study. Moreover, CGRP may only accumulate near endometriosis lesions and dilution in cubital vein blood does not allow the detection of local activity changes and fluctuations.

Absolute CGRP plasma concentrations in the literature vary based on EIA or radioimmunoassay (RIA) laboratory methodology. Mean CGRP values range from ~10–140 pg/ml for healthy controls to ~20–250 pg/ml for

migraine patients with large deviations in each case.[28,29] Our median values of ~50 pg/ml fit well into this range. Some outliers were detected in the control group, in which four women had values >200 pg/ml at both time points, leading to higher median values. The reason for these observations remains to be determined. All women in the control group had been carefully selected and had no pre-existing conditions and normal vitals, minimizing the risk of systematic errors.

Migraine and endometriosis are relevant women's health issues.[2,3] The disease burden increases when both condition occur together, and comorbid patients suffer more often from depression and anxiety.[30] In line with this observation, the EHP-30 scores in our study revealed a stronger impact of endometriosis on the perceived health status in comorbid patients. In particular, endometriosis-related pain had a more negative effect on patients' life.

The careful selection of women with the confirmed histological diagnosis of endometriosis and the migraine diagnosis according to ICHD-3 criteria by experienced headache specialists represent a strength of this study. CGRP determination in cubital vein blood can be affected by dilution.[31] Nevertheless, this is a standard method to determine neuropeptide levels in headache disorders. Based on the evidence in the literature, we focused this research on CGRP as the most obvious common underlying molecule of migraine and endometriosis. Other possible targets of interest (e.g., Substance P or Prostaglandin E2) are lacking of strong evidence in one or the other disease and were therefore not within the scope of this investigation. For example, Substance P antagonists are not effective in the therapy of migraine.[32]

All samples were collected under standardized conditions across all groups. The pre-analytical processing with the addition of a protease inhibitor in the vials, immediate centrifugation, and consistent maintenance of the cooling chain minimized CGRP degradation.

In conclusion, our data provide first evidence for a cycle-dependent CGRP release in healthy women and in women with the comorbidity of migraine and endometriosis albeit in a different pattern. Women with only migraine or endometriosis showed similar CGRP concentrations across the menstrual cycle. The findings support the hypothesis of a distinct pathophysiological background in comorbid patients probably due to a specific underlying genetic profile.

Acknowledgments

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Author Contributions

BR and UR designed the study. BR, LHO, JM, MDH, HK, and LN contributed to collection of data. ADE, JS, and SM contributed to the recruitment of study participants. BR, LHO, CPN, and UR analyzed the data. BR and UR wrote the first draft of the manuscript. All authors were involved in the interpretation of the data. All authors critically reviewed and edited the manuscript.

Conflicts of Interest

BR reports grants from Novartis, during the conduct of the study, personal fees from Novartis, Teva, and Allergan, all outside the submitted work. LHO has nothing to disclose. JM reports personal fees from Novartis, outside the submitted work. MDH has nothing to disclose. HK has nothing to disclose. CPN has nothing to disclose. LN reports personal fees from Novartis, Allergan, TEVA, BIAL, Hormosan, and Eli Lilly, all outside the submitted work. ADE has nothing to disclose. JS reports personal fees from Roche, grants and personal fees from Eli Lilly, personal fees from Johnson and Johnson, all outside the submitted work. SM has nothing to disclose. UR reports personal fees from Abbvie, Allergan, Amgen, Eli Lilly, Medscape, Novartis, StreaMedUp, and Teva; institutional fees from Amgen, Eli Lilly, Novartis, Teva, and Alder, and grants from Novartis, all outside the submitted work.

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2.3 Migräne und hormonelle Kontrazeption in der gynäkologischen Praxis (Originalarbeit 3)

Exogene Hormone, wie sie in der hormonellen Kontrazeption eingesetzt werden, können einen vielfältigen Einfluss auf den Migräneverlauf haben (MacGregor, 2013). Manche Patientinnen können von einer hormonellen Therapie profitieren, insbesondere wenn die Behandlung im Langzyklus (also ohne hormonfreie Zeit) erfolgt (Delaruelle et al., 2018). Patientinnen mit Migräne, insbesondere mit Aura, die östrogenhaltige Kontrazeptiva einnehmen, weisen jedoch ein erhöhtes kardiovaskuläres Risiko auf (Øie et al., 2020). Angesichts dieser Herausforderungen gibt es unterschiedliche Leitlinien mit mehr oder weniger restriktiven Empfehlungen zur Verschreibung hormoneller Kontrazeptiva für Patientinnen mit Migräne (Sacco et al., 2018).

In Deutschland wird die Verschreibung hormoneller Kontrazeption in der Regel von niedergelassenen Gynäkolog:innen durchgeführt. In dieser Arbeit untersuchte ich daher, inwiefern die Diagnose einer Migräne in der gynäkologischen Praxis bei der Verschreibung einer hormonellen Kontrazeption berücksichtigt wird und welche Konsequenzen sich ergeben, wenn Patientinnen Migräne mit oder ohne Aura haben. Meine Arbeit zielt darauf ab, einen Einblick in die Praxis und die Umsetzung von Empfehlungen und Richtlinien bezüglich der hormonellen Kontrazeption bei Migränepatientinnen zu gewinnen. Dies könnte dazu beitragen, die Versorgung und Beratung von Frauen mit Migräne und ihren spezifischen Bedürfnissen zu verbessern.

Der nachfolgende Text entspricht dem Abstract der Arbeit:

Fitzek MP, Storch E, Overeem LH, Kull P, Terhart M, Lange KS, Reuter U, **Raffaelli B**. Migraine and Hormonal Contraception in Gynecological Outpatient Care-Cross-Sectional Study among Practicing Gynecologists in Germany. J Clin Med 2023 Feb 10;12(4):1434. doi: 10.3390/jcm12041434.

"*Hormonal contraception (HC) can influence the migraine burden and should be considered in the comprehensive management of women with migraine. In this study, we aim to investigate the influence of migraine and migraine aura on the prescribing behavior of combined oral contraception (COC) and progestogen monotherapy (PM) in gynecological outpatient care. From October 2021 to March 2022, we performed an observational, cross-sectional study using a self-administered online-based survey. The questionnaire was distributed by mail and e-mail*

among 11,834 practicing gynecologists in Germany using the publicly available contact information. A total of 851 gynecologists responded to the questionnaire, of whom 12% never prescribe COC in the presence of migraine. Further 75% prescribe COC depending on the presence of limiting factors such as cardiovascular risk factors and comorbidities. When deciding to start PM, migraine appears to be less relevant, as 82% prescribe PM without restrictions. In the presence of aura, 90% of gynecologists do not prescribe COC at all, while PM is prescribed in 53% without restrictions. Almost all gynecologists reported to be actively involved in migraine therapy by having already initiated (80%), discontinued (96%), or changed (99%) HC due to migraine. Our results reveal that participating gynecologists actively consider migraine and migraine aura before and while prescribing HC. Gynecologists appear cautious in prescribing HC in patients with migraine aura."

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Migraine and Hormonal Contraception in Gynecological Outpatient Care—Cross-Sectional Study among Practicing Gynecologists in Germany

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Abstract: Hormonal contraception (HC) can influence the migraine burden and should be considered in the comprehensive management of women with migraine. In this study, we aim to investigate the influence of migraine and migraine aura on the prescribing behavior of combined oral contraception (COC) and progestogen monotherapy (PM) in gynecological outpatient care. From October 2021 to March 2022, we performed an observational, cross-sectional study using a self-administered online-based survey. The questionnaire was distributed by mail and e-mail among 11,834 practicing gynecologists in Germany using the publicly available contact information. A total of 851 gynecologists responded to the questionnaire, of whom 12% never prescribe COC in the presence of migraine. Further 75% prescribe COC depending on the presence of limiting factors such as cardiovascular risk factors and comorbidities. When deciding to start PM, migraine appears to be less relevant, as 82% prescribe PM without restrictions. In the presence of aura, 90% of gynecologists do not prescribe COC at all, while PM is prescribed in 53% without restrictions. Almost all gynecologists reported to be actively involved in migraine therapy by having already initiated (80%), discontinued (96%), or changed (99%) HC due to migraine. Our results reveal that participating gynecologists actively consider migraine and migraine aura before and while prescribing HC. Gynecologists appear cautious in prescribing HC in patients with migraine aura.

Keywords: migraine; migraine aura; contraception; women's health

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1. Introduction

Migraine is a frequent neurological disease with a prevalence peak in women of childbearing age [1,2]. It ranks second among causes of disability worldwide and is the leading cause of disability in young women [3,4]. In the western population, the majority of women aged 15–49 use contraception, with hormonal contraception (HC) being one of the most commonly used methods [5].

Estrogen-containing contraception [6,7] and migraine, especially migraine with aura [8–12], are both independently associated with an increased risk of ischemic stroke. Therefore, the safety of HC in women with migraine remains controversial, and gynecologists are often faced with the challenge of selecting appropriate contraception. The risk of ischemic stroke with the use of estrogen depends on the dose, with high-dose formulations having the highest risk [13]. Ultra-low-dose formulations, containing less than 20 µg of ethinyl estradiol, do not pose an increased risk of stroke in healthy nonsmokers [6]. Progestogen monotherapy (PM) carries no additional risk of cardiovascular events [14].

Apart from the associated cardiovascular risks, the use of HC can also have preventive potential in migraine, especially in patients with a perimenstrual increase in migraine frequency and severity. Selected preparations can lead to a reduction of the migraine

burden by eliminating the physiological fluctuations in sex hormones [15,16]. Treatment schemes that aim to keep estrogen concentrations stable, such as combined hormonal contraception (COC) used in continuous or extended cycles (shortened hormone free interval) or PM, can reduce menstrual-related migraine by up to 80% [17].

The European Headache Federation (EHF) and European Society of Contraception and Reproductive Health (ESC) consensus statement from 2017 recommends the use of PM or non-hormonal contraception for migraine with aura [11]. In migraine without aura, low-dose estrogen-containing contraception may be used in the absence of additional risk factors [6,11]. In clinical practice, HC is predominantly prescribed by gynecologists, while the prescription of migraine prophylaxis mainly belongs to the field of neurology. In this study, we aimed to investigate if the presence of migraine and migraine aura has an impact on the prescription of HC among German gynecologists and examined potential factors influencing the decision-making process.

2. Materials and Methods

2.1. Study Design, Setting and Procedure

This was an observational, cross-sectional study among practicing gynecologists in Germany. Data were collected between October 2021 and March 2022 using a standardized online questionnaire. The questionnaire was distributed as a link generated through RED Cap application (REDCap 12.0.33-© 2022 Vanderbilt University, Nashville, TN, USA) via e-mail and letter among all practicing gynecologists in non-university outpatient clinics in Germany (n = 11,881). In order to strengthen the response rate, we additionally sent out three reminder e-mails after the first invitation to participate. Contact information was publicly available through the corresponding Association of Statutory Health Insurance ("Kassenärztliche Vereinigung").

2.2. Survey

The survey was a dynamic branching questionnaire that was purpose-built designed by the authors, containing up to 29 questions. The questionnaire was not validated. It was divided into five subunits, which are designed to collect information on the following topics: 1. Demographics; 2. Prescription of COC in the presence of migraine; 3. Prescription of PM in the presence of migraine; 4. Modification (initiation, discontinuation, change) of hormonal contraceptive treatment due to migraine; and 5. Management of patients suffering from migraine (e.g., referral to primary care physicians/neurologists) (see Supplementary Material File S1 for full survey). In questions about migraine, we first asked about migraine in general without sub-specification (hereafter referred to as migraine) and then specifically about migraine with aura. In some questions about the prescription of COCs, we distinguish between a classic cycle (21 days of hormone use +7 days of hormone-free interval) and an extended cycle (shortened or no hormone-free interval). Force-response validation was included in every section. Questions on the primary endpoint (prescription of hormonal contraction in migraine/migraine aura) were designed to be mandatory to complete before proceeding to the next section to minimize missing values. Information on descriptive characteristics and secondary endpoints such as modification of hormonal treatment due to migraine or further treatment of migraine patients was voluntary. Accordingly, number of participants for different questions may vary.

2.3. Statistical Analysis

For statistical analysis, we used IBM SPSS Statistics (IBM SPSS Statistics ©; 23.0, for Mac). For questions with the option not to answer, we classified non-answering as missing values. The total number of respondents per question (n) is indicated in parentheses in each case. We conducted descriptive analyses for sociodemographic characteristics and questions about prescribing behavior of hormonal contraceptives. Categorial variables are presented as absolute numbers (n) and relative frequencies (%), whereas means, min.-max., and standard deviations are used for continuous variables. To examine differences in the

frequency of obtaining migraine anamnesis before starting therapy with COC vs. PM, we performed a chi-square test. In cases with the option to give multiple answers, relative frequencies may exceed 100%. For the comparison of age between subgroups, we used the Mann–Whitney U test, due to the non-normal distribution of data (assessed with the Shapiro–Wilk test). Figures were generated using PRISM software for Mac. (GraphPad Prism ©; version 8.4.3 (471), for Mac, GraphPad Software, Boston, MA, USA).

3. Results

Out of n = 11,834 contacted gynecologists, n = 913 answered the questionnaire over the 6 months (October 2021–March 2022) in which the survey was available. Due to missing informed consent, n = 53 participants had to be excluded. Another nine participants did not answer a single question after giving informed consent and were, therefore, also excluded from the analysis. Accordingly, we analyzed the questionnaires of a total of n = 851 participants (Figure 1), of which n = 841 completed the questionnaire. This corresponds to a response rate of 7.2% for the entirety of practicing gynecologists in Germany. Response rates varied considerably depending on the federal state, with 20% for Thuringia and only 5% for Hesse.

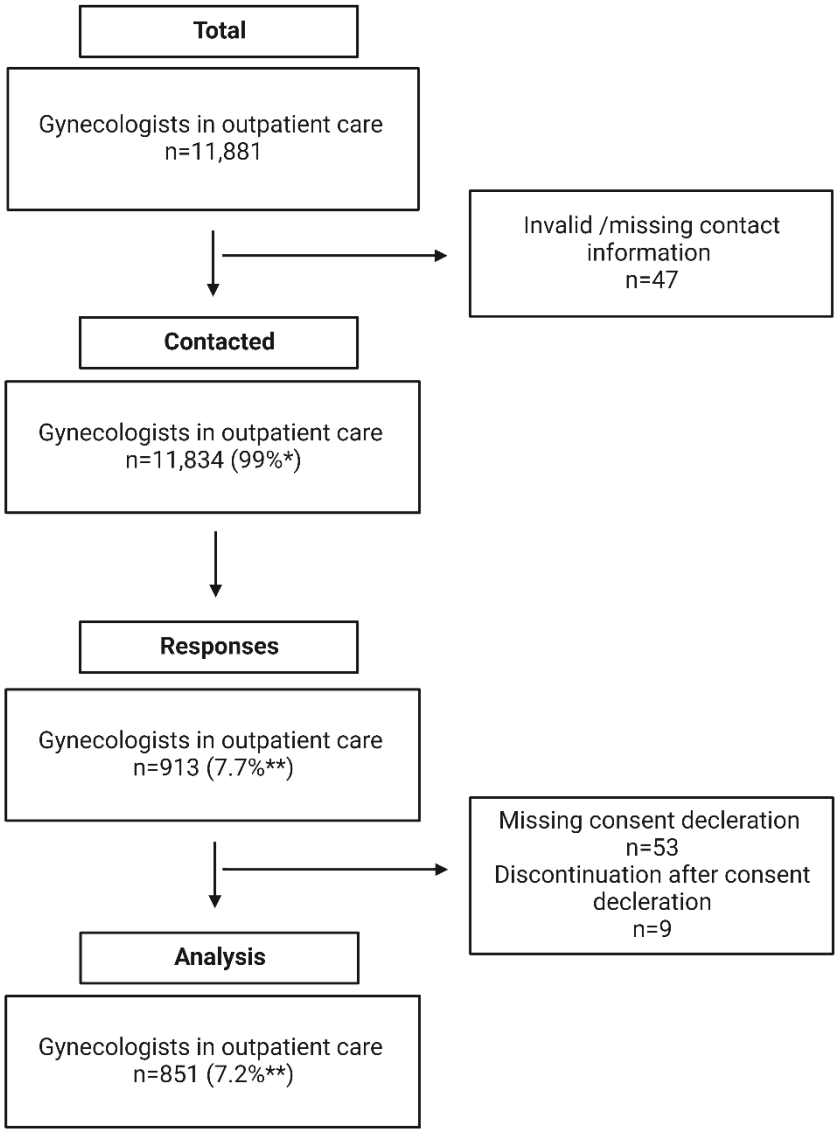

Figure 1. Recruitment; * percent of total population, ** percent of contacted gynecologists.

3.1. Demographics

Table 1 shows the key demographic characteristics of study participants. The average age of respondents was 52 ± 8 (range: 33–78) years. The majority were women (79%; n = 669/845), with a clinical focus in general gynecology (96%; n = 811/842) and a work experience of over 10 years (64%; n = 542/847). Most participants (70%; n = 594/844) reported to have 50 to 150 patient visits weekly. Participating gynecological clinics were located in both low-population regions and large cities and were fairly evenly distributed in terms of population density: rural (20%; n = 170/846); small town (<100,000 inhabitants; 37%; n = 317/846); large city (100,000–500,000 inhabitants; 22%; n = 185/846); and large city (>500,000 inhabitants; 21%; n = 174/846).

Table 1. Demographic characteristics.

Age in Years, Mean ± SD (Min–Max; *n*)	**52 ± 8 (33–78; 775)**
Sex, *n* (%)	845
Male	175 (21)
Female	669 (79)
Divers	1 (0.1)
Work location, *n* (%)	846
Rural	170 (20)
Small town (<100,000 residents)	317 (37)
City (100,000–500,000 residents)	185 (22)
Large city (>500,000 residents)	174 (21)
Work experience in years, *n* (%)	847
<5	144 (17)
5–10	161 (19)
11–20	276 (33)
>20	266 (31)
Clinical focus, *n* (MC)	842
General gynecology, *n* (% of cases)	811 (96)
Oncology, *n* (% of cases)	34 (4)
Endocrinology, *n* (% of cases)	37 (4)
Reproductive medicine, *n* (% of cases)	14 (2)
Other focus, *n* (% of cases)	31 (4)
Weekly number of patients, *n* (%) (MC)	844
<50	41 (5)
50–100	256 (30)
101–150	338 (40)
151–200	149 (18)
>200	60 (7)

SD = standard deviation of the means, MC = multiple choice allowed.

3.2. Hormonal Contraception and Migraine in General

Participating gynecologists reported to ask regularly about migraine prior to beginning any HC (Figure 2). A migraine history is obtained significantly more often before COC than PM treatment ($\chi^2(1) = 103.97$, $p < 0.001$, $\varphi = 0.25/\chi^2(1) = 47$, $p < 0.001$, $\varphi = 0.21$). Gynecologists who regularly (always or frequently) asked about migraine before starting a COC (n = 727/767) tend to be younger than gynecologists who reported to do so only rarely or sometimes (n = 40/767) (52 ± 0.3 age in years [SEM] vs. 55 ± 1.5 age in years [SEM], respectively; U = 12,090, $z = -1.797$, $p = 0.072$, Mann–Whitney-U). Regarding the frequency of obtaining a migraine history prior to prescribing a PM, no age-related differences could be observed (U = 43,387, $z = -1.275$, $p = 0.202$, Mann–Whitney-U).

The presence of migraine influences gynecologists in their decision whether to prescribe COC (Figure 2): 12% (n = 100/844) of participants never prescribed COC for women suffering from migraine. Another 75% (n = 633/844) would do so only to a limited extent. The proportion of gynecologists who prescribed COC without restrictions in patients suffering from migraine (n = 104/190) was significantly younger than those who never prescribed a COC in migraine patients (n = 86/190) (50 ± 0.8 age in years [SEM] vs. 54 ± 0.9 age in

years [SEM], respectively; U = 3115.5, $z = -3.598$, $p < 0.001$, Mann–Whitney-U). When asked about potential factors influencing their decision (multiple answers allowed), the presence of cardiovascular risk factors (not further specified) (78%, $n = 494/633$) and other comorbidities (71%, $n = 447/633$) were listed most frequently (Table 2).

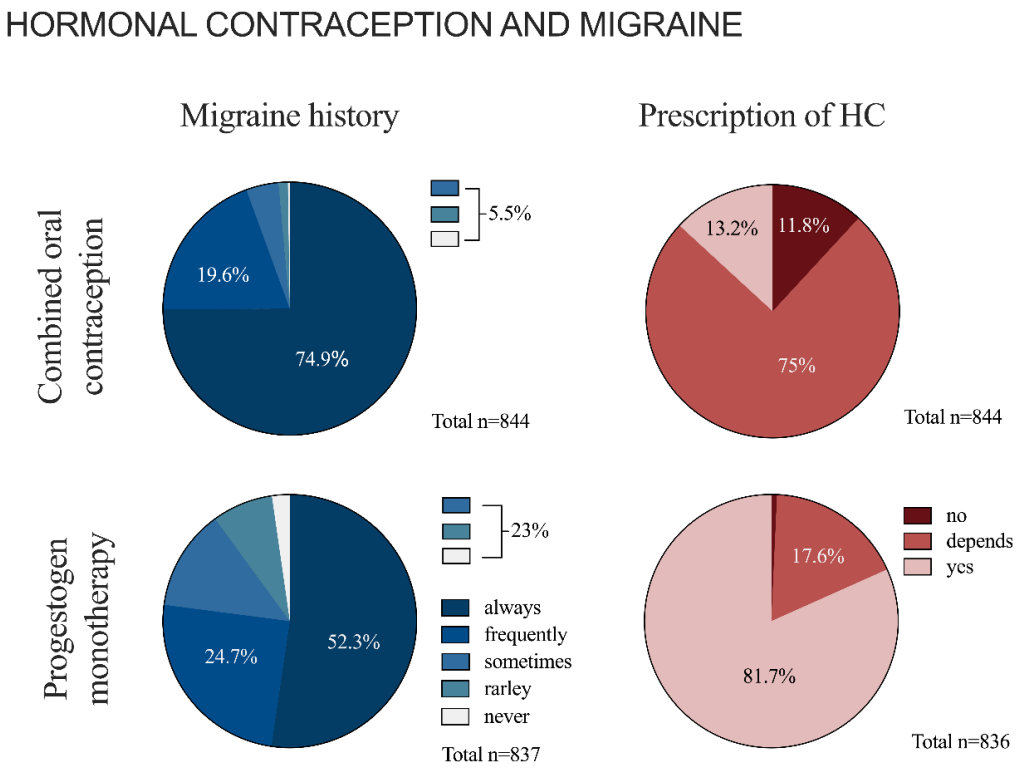

Figure 2. Hormonal contraception and migraine. The figure shows the absolute frequencies of asking about migraine (including migraine with and without aura) before initiating treatment with COC or PM, as well as prescribing patterns of COC and PM in the case of concomitant migraine.

Table 2. Factors limiting HC prescription in concomitant migraine.

Influencing Factors	HC with COC % (*n*/Total *)	HC with PM % (*n*/Total *)
Cardiovascular risk	78 (494/633)	66 (97/147)
Migraine severity	60 (373/633)	53 (78/147)
Migraine frequency	61 (383/633)	50 (73/147)
Other comorbidities	71 (447/633)	N/A
Migraine treatment	26 (163/633)	29 (43/147)
others	23 (143/633)	39 (57/147)

* total = subgroup of gynecologists responding "depends on" when asking for prescription of hormonal contraception in migraine. N/A—not available.

The presence of migraine appears to be less relevant when deciding to start HC with PM: Most participants (82%; $n = 683/836$) prescribed PM regardless of a potential migraine diagnosis (Figure 2). The remaining 18% ($n = 147/836$) prescribed PM only conditionally, naming cardiovascular risk factors (66%, $n = 97/147$) as the prime influencing factors (Table 2).

3.3. Hormonal Contraception and Migraine with Aura

The analyzed cohort of gynecologists often asks specifically about migraine aura before prescribing HC (Figure 3). Questions about migraine aura are asked more frequently prior to COC than PM treatment ($\chi^2(1) = 47$, $p < 0.001$, $\varphi = 0.21$). Gynecologists

who regularly (always or frequently) asked for migraine aura prior to prescribing COC (n = 708/763) are significantly younger than gynecologists who asked only rarely or sometimes (n = 55/763) (52 ± 0.3 age in years [SEM] vs. 56 ± 1.2 age in years [SEM], respectively; U = 14,076, z = −3.428, p = 0.001, Mann–Whitney-U). Regarding the frequency of obtaining a migraine aura history prior prescribing a PM, no age-related differences could be observed (U = 44,964, z = −0.523, p = 0.6, Mann–Whitney-U).

The majority of gynecologists (92%, n = 773/841) never prescribed COC for women with migraine with aura. Another 8% (n = 64/841) only prescribed COC under certain conditions (Table 3).

Regarding PM, more than half of the participating gynecologists (n = 442/835; 53%) prescribed this kind of HC without reservations in migraine with aura. Another 40% (n = 336/835) would do so only after taking certain factors into account (Table 3). A proportion of 7% (n = 57/332) never prescribed PM in migraine with aura. Gynecologists who prescribed PM in migraine aura without restriction (n = 408/453) appear to be significantly younger than those who would never prescribe PM for migraine with aura (n = 45/453) (51 ± 0.4 age in years [SEM] vs. 54 ± 1.4 age in years [SEM], respectively; U = 6840.5, z = −2.809, p = 0.005, Mann–Whitney-U).

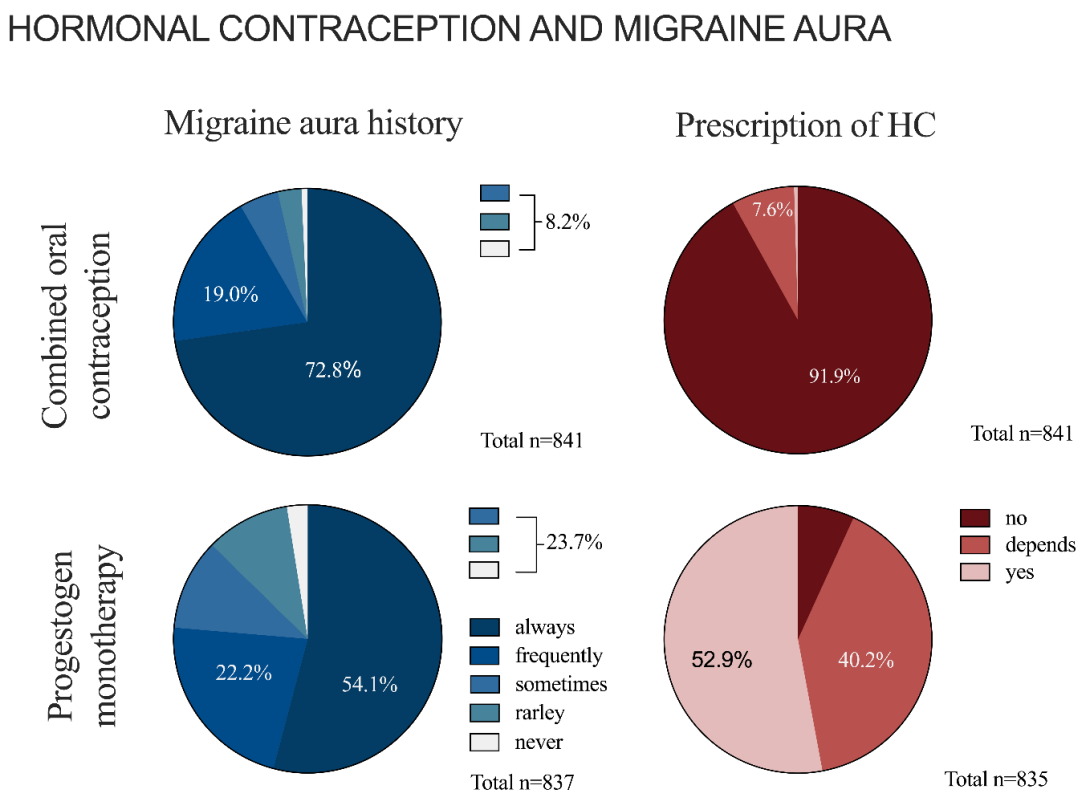

Figure 3. Hormonal contraception and migraine aura. The figure shows the absolute frequencies of asking about migraine aura before initiating treatment with COC or PM, as well as prescribing patterns of COC and PM in the case of concomitant migraine aura.

3.4. Modification of Hormonal Treatment due to Migraine

Almost all participating gynecologists initiated (80%; n = 661/826), discontinued (96%; n = 791/826), and/or changed (99%; n = 820/827) a HC due to migraine. Figure 4 shows the type of modification in hormonal therapy and the respective frequencies. When asked how gynecologists would proceed with patients with migraine (multiple choices), the majority said they would refer them to a neurologist (92%, n = 736/826), followed by a referral to a primary care physician (28%, n = 229/826). Only 10% (n = 83/826) of respondents said they would treat migraine patients regarding the migraine themselves.

Table 3. Factors limiting HC prescription in concomitant migraine with aura.

Influencing Factors	HC with COC % (*n*/Total *)	HC with PM % (*n*/Total *)
Cardiovascular risk	57 (36/63)	68 (224/332)
Migraine severity	57 (36/63)	51 (69/332)
Migraine frequency	56 (35/63)	49 (161/332)
Migraine aura severity	46 (29/63)	42 (140/332)
Migraine aura frequency	46 (29/63)	44 (147/332)
Other comorbidities	54 (34/63)	N/A
Migraine treatment	41 (26/63)	39 (129/332)
Others	38 (24/63)	28 (93/332)

* total = subgroup of gynecologists responding "depends on" when asking for prescription of hormonal contraception in migraineaura. N/A—not available.

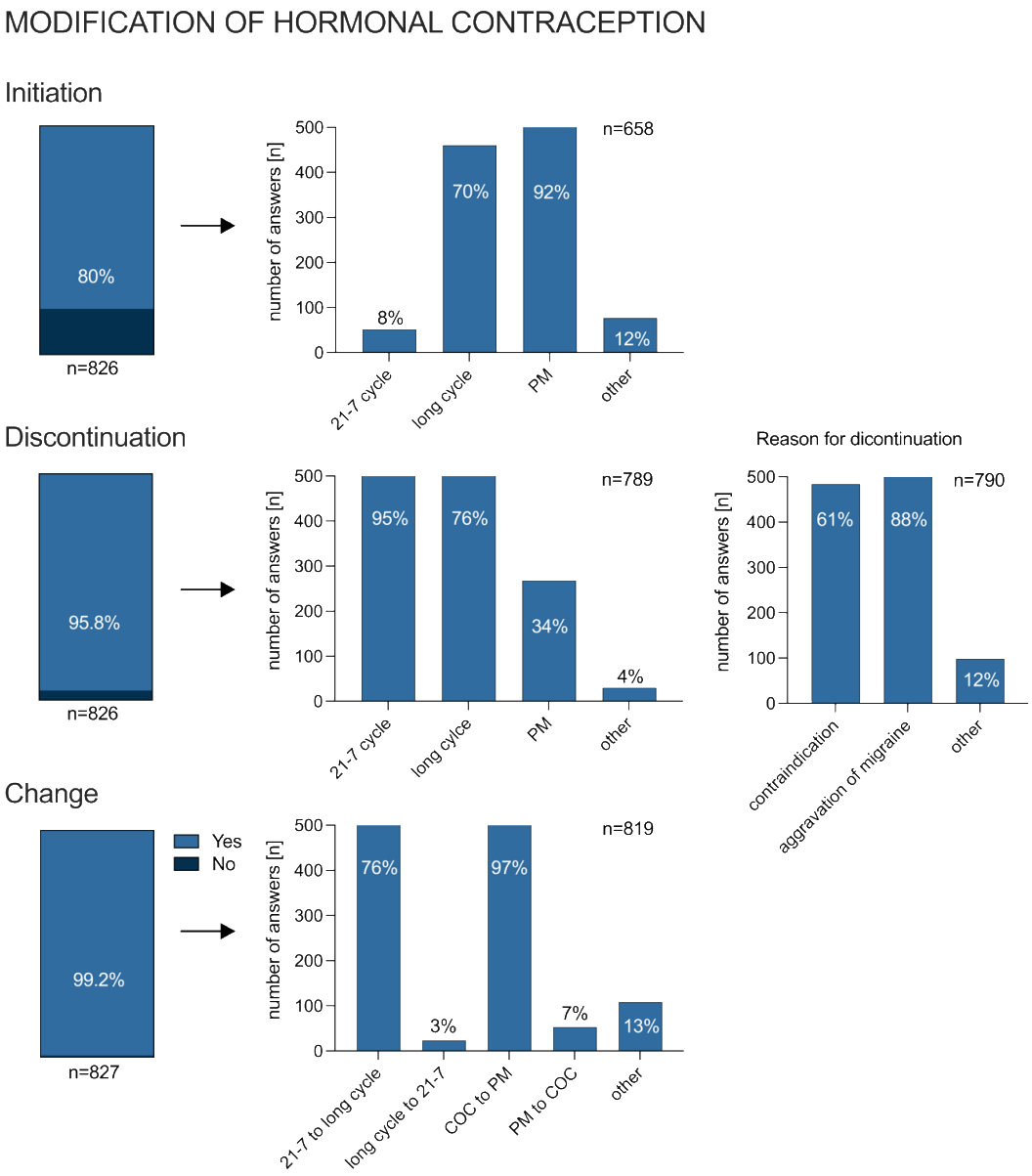

Figure 4. Modification of hormonal contraception due to migraine categorized into initiation, discontinuation and change, as well as reasons in the case of discontinuation of hormonal therapy.

4. Discussion

In this observational study, we analyzed the influence of migraine and migraine aura on the prescription of hormonal contraception in gynecologist outpatient care. Our results reveal that gynecologists actively consider the presence of migraine in general and migraine with aura before prescribing hormonal contraception (HC). In women with migraine, gynecologists tend to prescribe progesterone monotherapy (PM) more often than combined oral contraception (COC), which is in line with currently valid guidelines [11]. This cohort of gynecologists, and especially the older participants, seems to be somewhat cautious in prescribing HC in patients with migraine, especially with aura, because of existing limiting factors like cardiovascular risk factors.

Without HC, the absolute risk of an ischemic stroke in women aged 20 to 44 with migraine without and with aura amounts to 4/100,000 and 5.9/100,000, respectively, and increases to 10/100,000 and 14.5/100,000 under the use of HC [11]. The risk of a stroke increases only with estrogen-containing contraception and remains unchanged with estrogen-free compounds [6–8,11,18]. In line with this, participating gynecologists are very reluctant in prescribing COC for migraine with aura and are more likely to resort to contraception without estrogen using PM. However, concerns about cardiovascular events appear to cause a significant proportion of gynecologists to hesitate even in prescribing PM. After all, 40% of participants prescribed PM in migraine with aura only with reservations, naming cardiovascular risk factors to be influencing factors, even though there are no contraindications to the use of PM in women with migraine and aura, as it is not associated with any additional stroke risk [14]. In fact, current guidelines recommend PM in migraine with aura when HC is desired. A restrictive prescription may unnecessarily impede access to HC for young women with migraine with aura. Interestingly, gynecologists' prescribing behavior differed between age groups in two specific scenarios: prescription of COC in migraine and of PM in migraine aura. In detail, gynecologists who reported to prescribe COC in migraine without restrictions were significantly younger than those who reported to never prescribe COC in migraine. The same was observed for the prescription of PM in migraine aura. At least in the context of COC, one could speculate that this reflects changes in treatment recommendations over recent years that have softened the previous recommended strong advice against the use of COC for any patients suffering from migraine.

The use of hormonal contraception can influence the burden of migraine in both ways. Among women with migraine using HC, 18–50% notice a worsening of migraine, 3–35% report an improvement, and 39–65% experience no change in migraine frequency under hormonal treatment [19]. A worsening of migraine appears to be more often with the use of COC in the classical 21-7 cycle, whereas progestogen-only treatment schemes, as well as COC used in the long-term cycle, are associated with an improvement in migraine burden [17,20–22]. As part of the treatment of a migraine patient with oral contraceptives, an adjustment of the hormonal strategy may be necessary over time. Accordingly, almost all participating gynecologists answered to have already changed and/or discontinued HC due to migraine. Interestingly, more than 3/4 of participants stated to have already started HC due to migraine and thus were actively involved in the prophylactic migraine treatment. However, for further migraine treatment the majority of gynecologists would refer to a neurologist. This highlights the close overlap between the specialties of neurology and gynecology with regard to the patient collective of young women suffering from migraine. The reality of everyday clinical practice indicates that one often works past each other. In a survey among 115 women's healthcare providers in Connecticut, only 6% reported to be aware of migraine treatment guidelines and only 37% ever received headache-specific education [23]. A closer cooperation between neurologists and gynecologists would certainly be in the patients' best interests and should definitely be strived for.

Despite comparable response rates in other surveys within the German outpatients setting [24,25], a limitation of the present study is the overall low response rate of 7.2%. Considering this low response rate, our results must be interpreted with caution when transferred to the entirety of practicing gynecologists in Germany. Potential motives

for the low participation rate might include: 1. Lack of approachability—many of the contact addresses used were functional e-mail addresses, which in some cases are only rudimentarily read. In addition, a referral to the physician could not be guaranteed, even if this was actively requested in the cover letter; 2. Lack of time capacities—gynecologists having up to 150 patients per week and, correspondingly, up to 30 patients per day implies a lack of time for additional commitments, such as participation in a survey; 3. Request from non-gynecologists may be read with less interest; 4. Lack of scientific interest in migraine. Taking these factors into account, the population described in this study likely consists of gynecologists with a generally high interest in research and/or those with a particular interest in the topic of hormonal treatment for migraine, which could have led to a selection bias. In addition, the gender ratio of practicing gynecologists in Germany is approximately 1/3 men and 2/3 women. In our study cohort, the ratio is somewhat more pronounced, with 20% to 80% women. Possibly, female gynecologists are more willing to participate in a questionnaire study and may have a greater interest in migraine due to the higher prevalence of migraine in women.

Moreover, the design of an observational study based on a self-report questionnaire and the nature of the questions asked may have led to responses that are socially desired. However, anonymity should have reduced social desirability bias. In addition, participants were asked to answer truthfully and not to modify their answers to the recommendations of the current guidelines. Finally, it should be noted that the questionnaire was newly developed and not validated.

To overcome the obstacle of low response rates, future studies could investigate the actual intake of hormonal contraception in female patients with migraine of childbearing age. Bypassing the obstacle of practitioner's feedback, this approach might yield more representative, albeit indirect, insight into HC prescribing behavior of gynecologists in patients suffering migraine. Yet such an approach would lack valuable information on the motives of drug selection, which were included in the presented study. Therefore, it should complement rather than replace questionnaire-based studies.

5. Conclusions

Our findings show that German gynecologists who responded to our questionnaire actively consider migraine before and while prescribing hormonal contraceptives, and that the diagnosis of migraine influences their prescribing behavior. Although PM is not associated with additional stroke risk, investigated gynecologists remained reluctant to prescribe this estrogen-free contraception for migraine with aura. Future studies could show whether prescription behavior differs in neurologists treating migraine in women taking hormonal contraception. Ultimately, improved interdisciplinary collaboration between gynecologists and neurologists might improve migraine treatment in in young female patients suffering migraine of childbearing age.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12041434/s1, File S1—questionnaire.

Author Contributions: Conceptualization: M.P.F. and B.R. Methodology: M.P.F. and B.R. Formal Analysis: M.P.F. Investigation: M.P.F., E.S., L.H.O., P.K., M.T., K.S.L. and B.R. Data Curation: M.P.F., L.H.O. and B.R. Writing—Original Draft Preparation: M.P.F. and B.R. Writing—Review & Editing: E.S., L.H.O., P.K., M.T., K.S.L. and U.R. Visualization: M.P.F. Supervision: U.R. and B.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by our institution's ethics committee (Charité Universitätsmedizin Berlin EA1/262/21).

Informed Consent Statement: Prior to participation, interested gynecologists were asked to agree to a free and informed electronic consent statement. Data were kept confidential and were not disclosed unless for study purposes.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: M.P.F. reports personal fees from Teva. E.S. has nothing to disclose. L.H.O. has nothing to disclose. P.K. has nothing to disclose. M.T. reports personal fees from TEVA. K.S.L. reports personal fees from Teva. U.R. received honoraria for consulting and lectures from Amgen, Allergan, Abbvie, Eli Lilly, Lundbeck, Novartis, electroCore, Medscape, StreaMedUp, and Teva. U.R. received research funding from the German Federal Ministry of Education and Research and Novartis. B.R. reports research grants from Novartis and personal fees from Abbvie/Allergan, Eli Lilly, Hormosan, Novartis, and Teva.

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2.4 Eigenschaften und Diagnosen akuter Kopfschmerzen in der Schwangerschaft (Originalarbeit 4)

Die Schwangerschaft ist eine bemerkenswerte Phase in Bezug auf den Verlauf und die Entwicklung von Kopfschmerzerkrankungen (Negro et al., 2017). Einerseits kann sie zu einer deutlichen Verbesserung bestehender Kopfschmerzerkrankungen führen, insbesondere bei Migräne. Andererseits steigt das Risiko für viele sekundäre Kopfschmerzerkrankungen wie hypertensive Störungen (Negro et al., 2017).

Während der Schwangerschaft ist Migräne die häufigste Ursache für die Vorstellung von Frauen in der Notaufnahme wegen Kopfschmerzen (Robbins et al., 2015). Es ist jedoch von entscheidender Bedeutung, potenziell lebensbedrohliche Ursachen auszuschließen (Robbins et al., 2015). Die Identifizierung von demografischen, klinischen und diagnostischen Prädiktoren für sekundäre Kopfschmerzen kann dazu beitragen, den Behandlungsalgorithmus im Akutsetting angemessen zu lenken und die Diagnosestellung zu verbessern.

Bisherige Arbeiten auf diesem Gebiet sind vorwiegend auf US-amerikanische Kohorten beschränkt (Ramchandren et al., 2007; Robbins et al., 2015). In der vorliegenden Arbeit habe ich die Eigenschaften und Diagnosen von akuten Kopfschmerzen in der Notaufnahme der Charité in Berlin untersucht und aus diesen Daten prädiktive Faktoren für sekundäre Kopfschmerzen abgeleitet. Diese Studie zielt darauf ab, Einblicke in die spezifischen Merkmale und diagnostischen Muster von Kopfschmerzen im nationalen Kontext zu gewinnen und damit zur Verbesserung der Identifikation und Behandlung sekundärer Kopfschmerzen während der Schwangerschaft beizutragen.

Der nachfolgende Text entspricht dem Abstract der Arbeit:

Raffaelli B*, Siebert E*, Körner J, Liman T, Reuter U, Neeb L. Characteristics and diagnoses of acute headache in pregnant women - a retrospective cross-sectional study. J Headache Pain 2017 Dec 4;18(1):114. doi: 10.1186/s10194-017-0823-1. * = geteilte Erstautorenschaft.

"***Background**: Acute headache is one of the most frequent neurological symptoms in pregnant women. The early diagnosis of underlying secondary conditions has a major influence on patient outcome, especially in emergency settings. However, at the time being no well-established guideline for diagnostic evaluation of acute headache during pregnancy exists. In this study, we aimed to characterize acute headache in pregnant women concerning demographic, clinical, and diagnostic features, and to determine predictors of secondary*

headache.

***Methods**: We analysed retrospectively the data of 151 pregnant women receiving neurological consultation due to acute headache at the Charité Berlin between 2010 and 2016. To assess risk factors for secondary headache in these patients we compared multiple anamnestic and clinical features of the primary and secondary headache group.*

***Results**: 57.6% of the patients were diagnosed with primary headache, most common migraine and tension type headache. Concerning secondary headaches, the most common aetiologies were infections (29.7%) and hypertensive disorders (22.0%). The primary and secondary headache group were similar in most anamnestic and clinical features. In multivariate logistic regression analysis, secondary headache history [OR 6.6; 95% CI 1.3-33.1], elevated blood pressure [OR 7.2; 95% CI 2.3-22.6], fever [OR 12.1; 95% CI 1.3-111.0] and abnormal neurological examination [OR 9.9; 95% CI 2.7-36.3] represented independent predictors for secondary headache. Regarding additional diagnostic procedures, abnormal thrombocytes, GOT, GPT and CRP, proteinuria, pathologic results of lumbar puncture and neuroimaging were associated with secondary headache.*

***Conclusions**: Secondary headache disorders are common during pregnancy, occurring in over one third of acute headache cases receiving neurological consultation. Most anamnestic and clinical features may not allow a clear distinction between primary and secondary headaches. Clinicians should pay attention to the presence of secondary headache history, elevated blood pressure, fever and abnormal findings in the neurological examination. Additional investigations, including laboratory tests and neuroimaging, are essential for the diagnostic process.*"

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Characteristics and diagnoses of acute headache in pregnant women – a retrospective cross-sectional study

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Abstract

Background: Acute headache is one of the most frequent neurological symptoms in pregnant women. The early diagnosis of underlying secondary conditions has a major influence on patient outcome, especially in emergency settings. However, at the time being no well-established guideline for diagnostic evaluation of acute headache during pregnancy exists. In this study, we aimed to characterize acute headache in pregnant women concerning demographic, clinical, and diagnostic features, and to determine predictors of secondary headache.

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Results: 57.6% of the patients were diagnosed with primary headache, most common migraine and tension type headache. Concerning secondary headaches, the most common aetiologies were infections (29.7%) and hypertensive disorders (22.0%). The primary and secondary headache group were similar in most anamnestic and clinical features. In multivariate logistic regression analysis, secondary headache history [OR 6.6; 95% CI 1.3–33.1], elevated blood pressure [OR 7.2; 95% CI 2.3–22.6], fever [OR 12.1; 95% CI 1.3–111.0] and abnormal neurological examination [OR 9.9; 95% CI 2.7–36.3] represented independent predictors for secondary headache. Regarding additional diagnostic procedures, abnormal thrombocytes, GOT, GPT and CRP, proteinuria, pathologic results of lumbar puncture and neuroimaging were associated with secondary headache.

Conclusions: Secondary headache disorders are common during pregnancy, occurring in over one third of acute headache cases receiving neurological consultation. Most anamnestic and clinical features may not allow a clear distinction between primary and secondary headaches. Clinicians should pay attention to the presence of secondary headache history, elevated blood pressure, fever and abnormal findings in the neurological examination. Additional investigations, including laboratory tests and neuroimaging, are essential for the diagnostic process.

Keywords: Headache, Pregnancy, Secondary headache, Red flags, Clinical features

Background

Primary headache disorders reach a prevalence peak among women of childbearing age due to hormonal influence and particularly oestrogen fluctuations [1, 2]. The prevalence of headache in gravid women has been described to be as high as 35% [3]. At least 5% of pregnancies are affected by de novo headache, meaning either new onset or new type of headache [4]. The most common headache conditions reported during pregnancy are primary headaches such as migraine without aura, followed by tension-type headache and migraine with aura [5]. Primary headache may frequently change its dynamics during pregnancy. Up to three fourth of female patients with tension type headache and migraine with or without aura experience a significant improvement or remission during pregnancy [3, 6]. However, a new onset of primary headache during pregnancy is also

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possible [7], with a beginning of migraine without aura occurring in 1 to 10% and migraine with aura in up to 14% of the cases [3, 6].

There are many causes of secondary headaches that need to be considered in pregnant women: Pregnancy increases the risk of cerebral venous thrombosis, ischaemic and haemorrhagic stroke, arterial dissection and probably subarachnoid haemorrhage [8, 9]. Furthermore, hypertensive disorders including preeclampsia represent common health issues affecting approximately 5% of the pregnancies worldwide [10]. Pre-existing migraine is associated with a higher possibility of developing preeclampsia [11, 12] and might have an impact on the risk of ischemic stroke during pregnancy [13].

Due to its etiological variety, headache as a symptom challenges physicians in the diagnostic process. Especially in emergency settings, the early diagnosis of underlying secondary conditions has a major influence on patient outcome [9]. However, at the time being no well-established guideline for diagnostic evaluation of acute headache during pregnancy exists [5, 14]. Several "red flags" have been developed for assessing the risk of secondary headache in the normal population, including sudden pain onset, changes in a known headache pattern or focal neurological deficits [5, 15, 16]. Yet there are only few studies addressing these factors in pregnant women of mostly Afro-American or Hispanic ethnicity [17, 18].

To extend the results of the preceding studies, we aimed to characterize in detail acute headache in pregnant women in a German urban population. We focused on a variety of clinical features, diagnostic procedures, as well as final diagnoses. Based on our data, we intend to identify predictors of secondary headaches in pregnant women.

Methods

Patients

We analysed retrospectively the medical records of pregnant patients receiving neurological consultation due to acute headache from January 1, 2010 to December 31, 2016 at the Charité hospital in Berlin, Germany. Acute headache was defined as the presence of a new or known headache beginning during the current pregnancy in a previously respectively interictally pain free patient that led to medical consultation. We included women older than 18 years with acute headache as a major symptom who presented to the emergency department or received neurological consultation during an in-patient stay. We excluded consultations of women who left the hospital against their physicians' advice before completing recommended diagnostic procedures. We did not include women in the post-partum period.

Clinical evaluation

Using the clinical electronic documentation system, we reviewed the data of these patients in detail per chart review.

The collected data included details of the present pregnancy as well as prior pregnancies and potential complications within both. We also gathered information about prior headache diagnoses and other pre-existing neurological, psychiatric, and further medical conditions. We further assessed family (specifically headache) and smoking history. We characterized the current headache based on following features: altered characteristics compared to possible prior headache diagnoses, duration, localization, sudden onset, subjective intensity of the pain (on a verbal rating scale 1–10), pain quality, and dynamics of the pain before the diagnostic procedure.

Associated symptoms included vegetative symptoms, neurological and further autonomic symptoms. Vegetative symptoms were nausea, vomiting, photophobia, and phonophobia. Further autonomic symptoms included conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhoea, eyelid oedema, miosis and/or ptosis. Neurological symptoms included visual and sensory disturbance, dizziness and/or vertigo, language and motor impairment, and changes of consciousness both quantitative and qualitative. Furthermore, we documented epistaxis and facial paralysis.

We included neurological examination findings in our data compilation and added information given by other departments like gynaecology, internal medicine and otolaryngology. Possible abnormalities documented in the report were further classified based on their causal association to the acute headache. For example, ptosis would be classified as an abnormal finding in neurological examination not related to the acute symptoms when the patient stated that the condition has been preexisting in this way.

Other physical examination findings included fever and elevated blood pressure. Fever was defined as a body temperature ≥ 38.5 °C or subjective statements of patients about fever. Elevated blood pressure was defined by a single measurement of the systolic blood pressure ≥ 140 mmHg or of the diastolic blood pressure ≥ 90 mmHg.

Diagnostic means were analysed and included laboratory findings, medical imaging and lumbar puncture. A headache expert (LN) confirmed final headache diagnosis after reviewing the collected data based on the classification of the International Headache Society [19].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 24. Subgroup proportions were compared using χ^2. Using unpaired t test, we stratified results

according to the trimester of pregnancy. Logistic regression was used to assessed the correlation between clinical features with a p value ≤0.02 in univariate analyses as independent variables and the dependant variable being the final diagnosis secondary headache. Multivariable analyses were restricted to patients without missing values in the respective category; variables were eliminated using a backward elimination procedure. Threshold for statistical significance was defined as a p value ≤0,05 for all analyses. The confidence interval was defined as 95%.

Results

Demographics, pregnancy details and final headache diagnosis

Over the 6-year period investigated, we evaluated the clinical features and diagnostic process of acute headache in 151 pregnant women. Diagnoses for acute headache were divided into primary headache (57.6%) and secondary headache (42.4%) (Fig. 1). Within the primary headache group, 41.3% of the women had migraine with aura, 33.3% migraine without aura and 21.8% tension type headache. Secondary headaches were most frequently related to infections, including common viral infections (17.2%) as well as acute sinusitis (12.5%). Other recurrent causes of secondary headache were hypertensive disorders of pregnancy (22.0%), including preeclampsia (9.4%), PRES (6.3%) and HELLP syndrome (4.7%).

In the primary headache group, 50.0% of patients diagnosed with a migraine with aura were in the third trimester (vs. 22.2% in the first and 27.8% in the second trimester). 58.6% of patients diagnosed with a migraine without aura were in the second trimester (vs. 13.8% in the first and 27.6% in the third trimester). However, these differences were not significant. Tension type headache was distributed uniformly during pregnancy with 33.3% in the first, 33.3% in the second and 33.3% in the third trimester.

In the secondary headache group, sinusitis and intercurrent infections were more common in the second trimester (72.7% and 75.0% respectively, not significant), whereas hypertensive disorders occurred more frequently in the last trimester (66.7%, not significant).

The primary and secondary headache groups did not differ by age, number of prior pregnancies, prior deliveries or gestational age. Pregnancy complications occurred significantly more often within the secondary headache group (28.1% vs. 12.6%, $p = 0.017$) (Table 1). The most frequent pregnancy complications were hyperemesis gravidarum (34.5%), followed by recurring hypertensive derailments (17.2%), premature contractions (6.9%), and sickle cell crisis (6.9%).

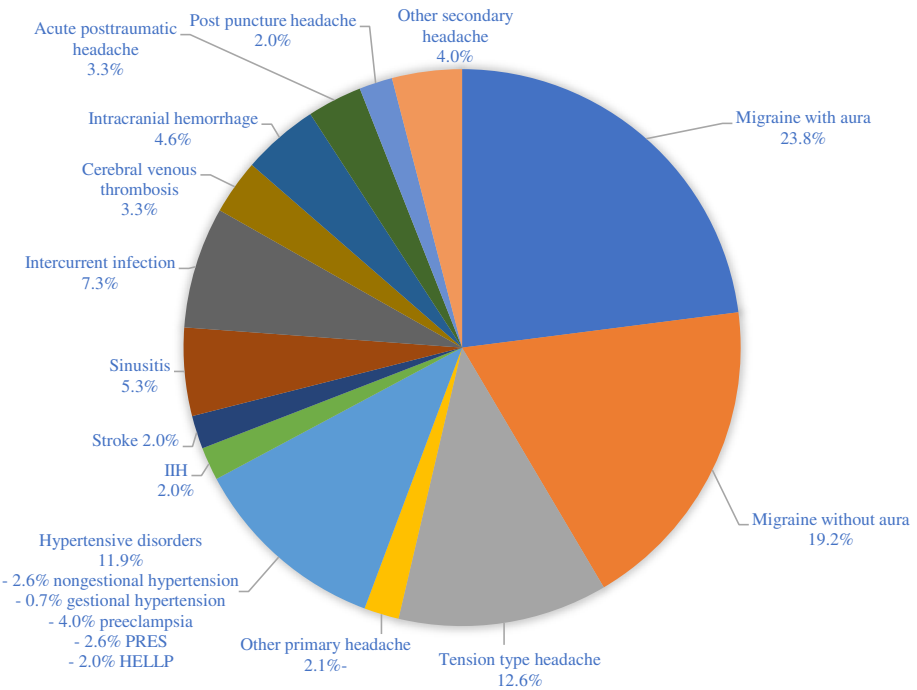

Fig. 1 Final headache diagnoses in pregnant women receiving neurological consultation due to acute headache. Percentages may summate to greater than 100% because some patients were given multiple diagnoses. The denominator for all percentages is the size of the total sample ($n = 151$). PRES = posterior reversible encephalopathy syndrome; HELLP = hemolysis, elevated liver enzymes, and low platelet count; IIH = idiopathic intracranial hypertension

Table 1 Demographics, pregnancy characteristics and medical history of pregnant women receiving neurological consultation due to acute headache

Characteristic	All headache	Primary headache	Secondary headache	*p* value
No.	151	87 (57.6%)	64 (42.4%)	–
Age,years	30.1 (±6.5)	30.4 (±6.3)	29.6 (±6.7)	0.977
Gestations	2.1 (±1.7)	2.3 (±1.9)	1.7 (±1.2)	0.389
Deliveries	0.7 (±1.2)	0.9 (±1.3)	0.5 (±0.9)	0.424
Gestational age, weeks	22.2 (±10.1)	22.5 (±10.3)	21.8 (±9.9)	0.861
Trimester				
First	32 (21.2%)	19 (21.8%)	13 (20.3%)	0.821
Second	63 (41.7%)	35 (40.2%)	28 (43.8%)	0.665
Third	56 (37.1%)	33 (37.9%)	23 (35.9%)	0.802
Complications during current pregnancy	29 (19.2%)	11 (12.6%)	18 (28.1%)	0.017*
Any medical history	51 (33.8%)	27 (31%)	24 (37.5%)	0.406
History of hypertension	5 (3.3%)	2 (2.3%)	3 (4.7%)	0.418
History of venous thromboembolism	3 (2.0%)	2 (2.3%)	1 (1.6%)	0.749
History of autoimmune disease	22 (14.6%)	14 (16.1%)	8 (12.5%)	0.536
History of preeclampsia	4 (2.6%)	2 (2.3%)	2 (3.1%)	0.775
History of gestational diabetes	2 (1.3%)	1 (1.1%)	1 (1.6%)	0.826
Any neurological history	8 (5.3%)	3 (3.4%)	5 (7.8%)	0.237
Any headache history	57 (37.7%)	39 (44.8%)	18 (28.1%)	0.036*
Any primary headache history	51 (33.8%)	39 (44.8%)	12 (18.8%)	0.001*
History of migraine without aura	29 (19.2%)	21 (24.1%)	8 (12.5%)	0.076
History of migraine with aura	14 (9.3%)	12 (13.8%)	2 (3.1%)	0.026*
History of tension type headache	8 (5.3%)	6 (6.9%)	2 (3.1%)	0.307
Any secondary headache history	12 (7.9%)	3 (3.4%)	9 (14.1%)	0.017*

* = statistical significant ($p < 0.05$). Subgroup proportions were compared using χ^2 test

In the stratified analysis by trimester, pregnancy complications were significantly associated with a secondary headache only in the third trimester ($p < 0.001$).

Medical history

33.8% of the women reported any medical condition, excluding neurological and psychiatric conditions. Autoimmune diseases, most frequently Hashimoto's thyroiditis, were the most common medical comorbidity (14.6%), followed by respiratory diseases (3.3%) and non gestional hypertension (3.3%). Rates of all reported conditions were similarly present in primary and secondary headache groups.

History of any psychiatric condition was reported in 5.3% of the patients, referring in all cases to depression, in one case combined with an eating disorder (0.7%), in another case with an anxiety disorder (0.7%). Psychiatric comorbidities were more common in patients with primary headache (8.0%) vs. secondary headache (1.6%) but the difference was not significant ($p = 0.079$).

Prior neurological conditions, excluding headache disorders, were reported in 5.3% of the patients. The most frequent condition was polyneuropathy (1.3%). There was no significant difference between the primary and the secondary headache group ($p = 0.237$) (Table 1).

In the stratified analysis by pregnancy trimester, no significant differences emerged.

Headache history

Any history of headache, both primary and secondary, was present in 37.7% of the patients. 33.8% of the women suffered of a primary headache disorder, most common migraine without aura (19.2%), migraine with aura (9.3%) and tension type headache (5.3%). 7.9% reported a prior secondary headache, most frequently caused by sinusitis (4.0%). Any history of headache was more common in patients with primary headache (44.8% vs. 28.1%, $p = 0.036$). Women with primary headache reported significantly more often a history of primary headache (44.8% vs. 18.8%, $p = 0.001$) and especially of migraine with aura (13.8% vs. 3.1%, $p = 0.026$). Women with secondary headache reported significantly more frequently a history of secondary headache (14.1% vs. 3.4%, $p = 0.017$).

In the stratified analysis by pregnancy trimester, a prior primary headache correlated significantly with a current primary headache during first trimester (p = 0.033), while a prior secondary headache was significantly associated with a current secondary headache during third trimester (p = 0.033).

In cases with a positive headache history, 86% of the patients stated that the current attack was different from the known headache pattern. Differences were reported in associated symptoms (38.6%), increased attack severity (37.5%), localisation (26.8%), duration (23.2%) and frequency (8.9%).

48.8% of patients with a known migraine without aura were diagnosed with the same diagnosis ($p < 0.001$), while 20.7% developed an aura. 71.4% of patients with a known migraine with aura, received the same diagnosis in the current attack (p < 0.001), while 14.2% reported no aura in the index headache. However, most commonly patients with a diagnosed migraine with aura experience attacks with and without aura. De novo migraine without aura was diagnosed in 15 patients (9.9%). A new onset of a migraine with aura was diagnosed in 26 patients (17.2%).

Further details about headache history are given in Table 1.

Acute headache attack features

A detailed overview of the headache characteristics investigated here is shown in Table 2. In short, patients with primary headache were more likely to report a side predominance of the pain (39.1% vs. 18.8%, $p = 0.007$). A dynamic pain progression was more common in patients with secondary headache (37.2% vs. 19.3%, $p = 0.046$). Visual and sensory disturbance were significantly more often reported within the primary headache group (40.2% vs. 20.3%, $p = 0.009$; 31.0% vs. 10.9%, $p = 0.003$).

The most common visual disturbance was a scintillating scotoma (58.3%), followed by blurred vision (31.3%). Sensory disturbance referred mostly to unilateral slowly spreading numbness (73.5%) or paresthesia (17.6%).

Seizures were present in 4.7% of the patients with secondary headache compared to none in the primary headache group ($p = 0.041$).

Considering only patients presenting during the first trimester, subjective pain ≥8/10 and progressive pain dynamics were significantly associated with a secondary headache diagnosis (p = 0.041 and $p = 0.037$, respectively). In the second trimester, side predominance and sensory disturbance correlated significantly with a primary headache ($p = 0.025$ and $p = 0.032$, respectively). In the third trimester, progressive pain dynamics occurred

Table 2 Acute headache attack features in pregnant women receiving neurological consultation due to acute headache

Feature	Missing	All headache	Primary headache	Secondary headache	p value
Pain duration >24 h	21 (13.9%)	74 (56.9%)	37 (50.7%)	37 (64.9%)	0.104
Sudden onset	–	8 (5.3%)	2 (2.3%)	6 (9.4%)	0.055
Side predominance	–	46 (30.5%)	34 (39.1%)	12 (18.8%)	0.007*
Throbbing character	58 (38.4%)	36 (38.7%)	24 (44.4%)	12 (30.8%)	0.182
Subjective pain ≥8/10	56 (37.1%)	33 (34.7%)	16 (28.1%)	17 (44.7%)	0.095
Progressive dynamic	51 (33.8%)	27 (27.0%)	11 (19.3%)	16 (37.2%)	0.046*
Any vegetative symptoms	–	93 (61.6%)	55 (63.2%)	38 (59.4%)	0.631
Nausea/Vomiting	–	81 (53.6%)	48 (55.2%)	33 (51.6%)	0.660
Phonophobia	–	25 (16.6%)	18 (20.7%)	7 (10.9%)	0.111
Photophobia	–	32 (21.2%)	22 (25.3%)	10 (15.6%)	0.151
Syncope	–	9 (6.0%)	7 (8.0%)	2 (3.1%)	0.207
Visual disturbance[a]	–	48 (31.8%)	35 (40.2%)	13 (20.3%)	0.009*
Sensory disturbance[b]	–	34 (22.5%)	27 (31.0%)	7 (10.9%)	0.003*
Language impairment	–	17 (11.3%)	12 (13.8%)	5 (7.8%)	0.251
Vertigo or dizziness	–	16 (10.6%)	7 (8.0%)	9 (14.1%)	0.235
Motoric impairment	–	10 (6.6%)	6 (6.9%)	4 (6.3%)	0.875
Change of consciousness	–	5 (3.3%)	1 (1.1%)	4 (6.3%)	0.083
Seizures	–	3 (2.0%)	0 (0.0%)	3 (4.7%)	0.041*
Autonomic symptoms	–	6 (4.0%)	3 (3.4%)	3 (4.7%)	0.700

* = statistical significant ($p < 0.05$). Subgroup proportions were compared using χ^2 test

[a] = 58.3% scintillating scotoma, 31.3% blurred vision

[b] = 73.8% unilateral hypoesthesia, 17.6% unilateral paresthesia

more often in secondary headache ($p = 0.014$), while nausea and visual disturbance were more frequent in primary headache ($p = 0.035$ in both cases).

Clinical examination

The physical examination was abnormal in 9.6% of the cases, significantly more often within the secondary headache group (15.9% vs. 4.8%, p = 0.025). Patients with secondary headache had significantly more frequently elevated blood pressure (31.7% vs. 8.4%, $p < 0.001$) and fever (14.1% vs. 1.1%, $p = 0.002$). Pathological neurological examination findings were detected significantly more often within the secondary headache group (35.9% vs. 11.5%, p < 0.001) (Table 3).

In the stratified analysis by pregnancy trimester, no significant differences emerged during the first trimester. During the second trimester, fever and pathological results in the neurological examination correlated significantly with a secondary headache ($p = 0.020$ and $p = 0.018$, respectively). During the third trimester, an abnormal physical examination ($p = 0.006$), elevated blood pressure ($p = 0.001$), and abnormal results in the neurological examination ($p = 0.003$) were significantly associated with a secondary headache.

Clinical variables independently associated with secondary headache

Using binomial logistic regression, we analyzed the independent associations of demographic and clinical variables that differed significantly between both headache groups. Secondary headaches were associated with known prior secondary headache, elevated blood pressure, fever and neurologic examination abnormalities. Primary headaches were more likely in patients with reported visual disturbance (Table 4).

Additional diagnostic procedures

Any additional diagnostic procedure was performed in 96.0% of the cases: Blood tests were conducted in 94.7%, urine analysis in 57.0%, neuroimaging in 50.3% and lumbar puncture in 13.2% of the cases with no differences between the primary and secondary headache group.

Any blood value outside the reference range was found in 88.8% of the cases. Abnormal thrombocytes (16.4% vs. 5.0%, $p = 0.025$), abnormal GOT (35.3% vs. 2.3%, $p < 0.001$), abnormal GPT (17.5% vs. 2.0%, $p = 0.006$) and abnormal CRP (58.9% vs. 30.4%, $p = 0.001$) were found significantly more often in the secondary headache group.

Proteinuria was detected in 16.3% of the patients, significantly more frequently in patients with secondary headache (25.6% vs. 8.5%, $p = 0.032$). All other findings did not differ significantly between both headache groups (Table 5).

Pathological results of lumbar puncture were detected in 20.0% of the performed analyses and only in patients with secondary headache (36.4% vs. 0.0%, $p = 0.043$).

Of the 76 patients who underwent neuroimaging, 38.2% had pathologic results, significantly more frequently in the secondary headache group (66.7% vs. 12.5%, $p < 0.001$). All patients undergoing neuroimaging received a magnetic resonance imaging (MRI), 2 (2.6%) both a computed tomography scan and a MRI. Most frequent pathological findings were intracranial bleeding (28.6%), cerebral venous thrombosis (23.8%), and PRES (19.0%).

In the stratified analysis by pregnancy trimester, an abnormal CRP correlated significantly with a secondary headache in the first and second trimester ($p = 0.017$ and $p = 0.009$, respectively). In the second trimester, also abnormal thrombocytes had a significant association with a secondary headache ($p = 0.019$). During the third trimester, abnormal GOT ($p < 0.001$), abnormal GPT ($p = 0.019$), and proteinuria ($p = 0.049$) correlated significantly with a secondary headache.

In every trimester, there was a strong correlation between pathologic neuroimaging results and secondary headache diagnosis (p < 0.001 in first and second trimester, $p = 0.004$ in third trimester).

Discussion

We reviewed the neurological consultations of 151 pregnant women who presented with acute headache, most of them during second and third trimester. The majority

Table 3 Clinical examination findings in pregnant women receiving neurological consultation due to acute headache

Feature	Missing	All headache	Primary headache	Secondary headache	*p* value
Abnormal medical examination	5 (3.3%)	14 (9.6%)	4 (4.8%)	10 (15.9%)	0.025*
Elevated blood pressure	5 (3.3%)	27 (18.5%)	7 (8.4%)	20 (31.7%)	0.000*
Fever	–	10 (6.6%)	1 (1.1%)	9 (14.1%)	0.002*
Abnormal neurological examination	–	33 (21.9%)	10 (11.5%)	23 (35.9%)	0.000*
Abnormal neurological examination referable to acute symptoms	–	26 (17.2%)	6 (6.9%)	20 (31.3%)	0.000*

* = statistical significant ($p < 0.05$). Subgroup proportions were compared using χ^2 test

Table 4 Multivariate logistic regression analysis of clinical and demographics variables associated with secondary headache in pregnant women

Variable	OR (95% CI)	*p* value
Complications during current pregnancy	2.2 (0.7–6.8)	0.155
Prior primary headache	0.5 (0.2–1.3)	0.147
Prior secondary headache	6.6 (1.3–33.1)	0.021*
Side predominance	0.5 (0.2–1.3)	0.141
Visual disturbance[a]	0.3 (0.1–1.0)	0.048*
Sensory disturbance[b]	0.4 (0.1–1.4)	0.154
Elevated blood pressure	7.2 (2.3–22.6)	0.001*
Fever	12.1 (1.3–111.0)	0.028*
Abnormal neurological examination referable to acute symptoms	9.9 (2.7–36.3)	0.001*

* = statistical significant ($p < 0.05$)
[a] = 58.3% scintillating scotoma, 31.3% blurred vision
[b] = 73.8% unilateral hypoesthesia, 17.6% unilateral paresthesia

of our sample was diagnosed with primary headache disorders, most frequently migraine with aura, without aura and tension type headache. However, 42% of the women were found to have a secondary headache, most commonly headache attributed to infections and hypertensive disorders of pregnancy. Infectious diseases occurred more frequently during the second trimester of pregnancy, while hypertensive disorders were more common during the third.

Pregnant women with secondary headache presented more often with pregnancy complications, positive secondary headache history, progressive pain dynamic, seizures, abnormal medical examination, elevated blood pressure, fever and abnormal neurological examination. In blood lab tests, abnormal thrombocytes, elevated transaminases and CRP were associated with a secondary headache diagnosis. Furthermore, proteinuria, pathologic findings in the cerebrospinal fluid and pathologic neuroimaging results correlated with a secondary headache. In multivariate logistic regression analysis, secondary headache history, elevated blood pressure, fever and an abnormal neurological examination resulted as independent risk factors for secondary headache.

Pregnant women with primary headache reported more frequently a history of primary headache, a side predominance of pain as well as visual and sensory disturbance, likely driven by migraine and migraine aura [20]. In fact, the most commonly described visual and sensory deficits were typical aura symptoms, such as scintillating scotoma and slowly spreading unilateral hypoesthesia.

Table 5 Additional diagnostic performed in pregnant women presenting with acute headache

Feature	Missing	All headache	Primary headache	Secondary headache	*p* value
Any additive diagnostic	–	145 (96.0%)	82 (94.3%)	63 (98.4%)	0.193
Additive blood test	–	143 (94.7%)	81 (93.1%)	62 (96.9%)	0.307
Abnormal blood test	8 (5.3%)	127 (88.8%)	69 (85.2%)	58 (93.5%)	0.116
Abnormal Hb	10 (6.6%)	72 (51.1%)	43 (53.8%)	29 (47.5%)	0.465
Abnormal Erythrocytes	10 (6.6%)	46 (32.6%)	27 (33.8%)	19 (31.1%)	0.774
Abnormal Leucocytes	10 (6.6%)	64 (45.4%)	33 (41.3%)	31 (50.8%)	0.258
Abnormal Thrombocytes	10 (6.6%)	14 (9.9%)	4 (5.0%)	10 (16.4%)	0.025*
Abnormal Quick	35 (23.2%)	2 (1.7%)	2 (3.1%)	0 (0.0%)	0.198
Abnormal PTT	35 (23.2%)	3 (2.6%)	1 (1.5%)	2 (3.9%)	0.422
Abnormal D-Dimers	103 (68.2%)	33 (68.8%)	17 (60.7%)	16 (80.0%)	0.155
Abnormal Creatinin	25 (16.6%)	13 (10.3%)	7 (9.9%)	6 (10.9%)	0.848
Abnormal Na	44 (29.1%)	12 (11.2%)	5 (8.5%)	7 (14.6%)	0.319
Abnormal K	44 (29.1%)	9 (8.4%)	4 (6.8%)	5 (10.4%)	0.500
Abnormal GOT	73 (48.3%)	13 (16.7%)	1 (2.3%)	12 (35.3%)	0.000*
Abnormal GPT	60 (39.7%)	7 (7.7%)	1 (2.0%)	7 (17.5%)	0.006*
Abnormal CRP	26 (17.2%)	54 (43.2%)	21 (30.4%)	33 (58.9%)	0.001*
Proteinuria	65 (43.0%)	14 (16.3%)	4 (8.5%)	10 (25.6%)	0.032*
Additive lumbar punction	–	20 (13.2%)	9 (10.3%)	11 (17.2%)	0.220
Pathologic LP results	131 (86.8%)	4 (20.0%)	0 (0.0%)	4 (36.4%)	0.043*
Neuroimaging	–	76 (50.3%)	40 (46.0%)	36 (56.3%)	0.212
Pathologic neuroimaging results	75 (49.7%)	29 (38.2%)	5 (12.5%)	24 (66.7%)	0.000*

* = statistical significant ($p < 0.05$). Subgroup proportions were compared using χ^2 test

Only few previous studies focused on the clinical evaluation of headache in pregnant women. Robbins et al. characterized demographic and clinical features of pregnant women presenting with acute headache in a predominantly Hispanic and Afro-American population [17]. Ramchandren et al. evaluated medical imaging results in pregnant women with emergent headache. Multiparous Afro-American women constituted the majority of their cohort [18]. However, to the best of our knowledge, this is the first study to assess headache features in pregnancy in a primarily Caucasian population.

Besides the differences in ethnicity, the study group assessed by Robbins et al. had more prior pregnancies and live births. The number of final secondary headache diagnosis was slightly lower than in our study. The most common primary headache disorders coincided with our reported results, namely migraine and tension type headache [17]. Within the secondary headache group, the authors found a higher number of hypertensive disorders of pregnancies. This is probably due to the fact that Afro-American ethnicity is a known risk factor for the development of hypertensive disorders [17, 19]. In the study by Ribbins et al., final diagnosis of primary headache correlated with history of headache [17]. Our results extend this finding by showing that only a previous primary headache correlated with a primary headache diagnosis, whereas a known secondary headache could be considered as a risk factor for a current secondary headache. A detailed differentiation of previous headache history could lead to a better differential diagnostic assessment.

MR imaging is the preferred imaging method for evaluating headache in pregnant women, as it involves no exposure to ionizing radiation [1]. In the study of Robbins et al., neuroimaging was performed in almost 90% of the cases, with a 18% rate of pathological imaging findings [17]. In the analysis of Ramchandren et al., only pregnant women receiving neuroimaging were considered and an underlying headache etiology was revealed in 27% of pregnant women suffering from acute headache [18]. In our study, only 50% of the patients had neuroimaging and 38% of them had pathologic results. The higher rate of pathologic results despite lower neuroimaging incidence could indicate a more detailed clinical preselection of cases. Considering the limited assess to 24 h MRI-imaging in some areas and the economic costs, further research should examine which anamnestic and clinical aspects are crucial in determining the decision to order neuroimaging procedures in pregnant women.

Our study is the first one to demonstrate a possible association between laboratory findings and secondary headache during pregnancy. Low thrombocytes and elevated transaminases, especially during the third trimester, were significantly associated with secondary headache. Such laboratory abnormalities are common in pregnancy-associated hypertension und increase with disease severity [21]. Multiple abnormal values, as occurring in HELLP syndrome, are also associated with maternal and perinatal morbidity and mortality [21]. Furthermore, abnormal CRP values as marker for infections were also more common within the secondary headache group.

One of the main strengths of our study is the large sample size, the broad variety of analyzed clinical details and confirmation of headache diagnosis by a headache specialist. However, our study has some limitations. We characterized cases of acute headaches in a mainly Caucasian sample, yet we cannot provide specific information about the ethnic background of our patients since this information is not routinely acquired in our institutional records. Still, we can assume that our study provides adequate information about an urban population in Europe. About 70% of Berlin's population are ethnic German, other ethnic influences come mainly from Southern Europe and the Middle East [22]. Further limitations include the retrospective character of the study and, due to that, some missing details of headache features. Moreover, the study was underpowered to detect differences between groups in rarely occurring features, e.g. pregnancy complications. As we analyzed only headaches, we did not consider isolated auras, which may also represent an issue in pregnant women. In fact, migraine aura is the most frequent condition leading to a focal neurological deficit during pregnancy and visual deficits during pregnancy are almost in two third of the cases related to a migraine aura [20]. Due the cross-sectional nature of the study, we were not able to follow up the headache development during the remaining pregnancy. We cannot exclude that some headache diagnosed as a primary form over the course revealed as a secondary headache, especially in those women without additional diagnostic procedures. Furthermore, we were not able to provide information about delivery and child outcome, as most women did not give birth at our hospital. The index headache was the first headache attack during pregnancy that led to a neurological consultation in our hospital. We cannot completely exclude previous consultations at other hospitals and cannot provide additional information about previous attacks in the same pregnancy.

Conclusions

Headache is a common complaint in pregnant woman. Distinguishing benign headache from ominous secondary changes is of great importance, and can be challenging especially in an emergency setting. We could show that secondary headaches are common during pregnancy, occurring in over one third of pregnant women

presenting to the hospital with acute headache. Our findings show that clinical features of secondary and primary headache do not necessarily differ and are in many cases not sufficient to rule out a possible threat to the mother or unborn child.

Diagnostic vigilance should be highlighted in presence of previous history of secondary headache, progressive pain, seizures, fever, high blood pressure and pathological findings in neurological examination. These symptoms can be considered as predictors for secondary headache in pregnant women. However, attack features alone cannot adequately discriminate between primary and secondary headache. Additional diagnostic tests leading to final diagnosis include blood, urine and cerebrospinal fluid examination as well as neuroimaging. In presence of the above mentioned "red flags", low thresholds for additional diagnostic procedures are justified.

Abbreviations

CI: Confidence interval; CRP: C-reactive protein; GOT: Glutamic oxaloacetic transaminase; GPT: Glutamate-pyruvate transaminase; Hb: Hemoglobin; HELLP: Hemolysis, elevated liver enzymes, and low platelet count; IIH: Idiopathic intracranial hypertension; K: Potassium; LP: Lumbar puncture; MRI: Magnetic resonance imaging; Na: Sodium; OR: Odds ratio; PRES: Posterior reversible encephalopathy syndrome; PTT: Partial thromboplastin time

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Availability of data and materials

Further data from the underlying research material can be obtained upon request to the corresponding author.

Authors' contributions

BR collected data, performed statistical analysis and drafted the manuscript. ES conceptualized and designed the study. JK contributed to data acquisition and statistical analysis. TL made substantial contribution to statistical analysis and interpretation of data. UR revised the manuscript critically for important intellectual content. LN conceptualized and designed the study, interpreted the data, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Authors' information

None.

Ethics approval and consent to participate

The local ethics committee approved the study before initiation (EA1/275/15). Informed consent from patients was not required due to the retrospective character of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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2.5 Wahrnehmung von Migräne in den Medien (Originalarbeit 5)

Nachdem in meinen vorherigen Arbeiten geschlechtsspezifische Aspekte in pathophysiologischen, diagnostischen und therapeutischen Bereichen beleuchtet wurden, liegt der Schwerpunkt dieser letzten Arbeit auf psychosozialen Aspekten, insbesondere auf der gesellschaftlichen Wahrnehmung von Patient:innen mit Migräne.

Die Darstellung von Migräne in den Medien ermöglicht es, zu analysieren, wie die Gesellschaft die Erkrankung und vor allem die Betroffenen wahrnimmt. Eine Untersuchung gängiger Suchportale ergab, dass die meisten Bilder von Menschen mit Migräne junge, attraktive Frauen zeigen, die sich beide Schläfen halten (Gvantseladze et al., 2020). Diese stereotypische und verharmlosende Darstellung kann dazu führen, dass Migräne als schwere neurologische Erkrankung nicht ernst genommen wird und viele der damit verbundenen Symptome und psychosozialen Beeinträchtigungen unbeachtet bleiben (Gross et al., 2023; Seng et al., 2022).

In dieser Arbeit habe ich untersucht, inwieweit Menschen mit Migräne diese stereotype mediale Darstellung als realistisch und repräsentativ für ihre eigene Migräne empfinden und wie sich diese Wahrnehmung von der Wahrnehmung von Gesundheitsfachkräften ohne Migräne unterscheidet. Ein besonderer Schwerpunkt lag auf geschlechtsspezifischen Unterschieden, d.h. auf möglichen Unterschieden in der Wahrnehmung von männlichen und weiblichen Darsteller:innen in den Medien. Diese Forschung zielt darauf ab, das Verständnis für den Einfluss medialer Darstellungen von Migräne auf die gesellschaftliche Wahrnehmung und das Bewusstsein für die Realität von Migränebetroffenen zu vertiefen.

Der nachfolgende Text entspricht dem Abstract der Arbeit:

Raffaelli B, Kull P, Mecklenburg J, Overeem LH, Storch E, Terhart M, Neeb L, Reuter U. Patients' and Health Care Workers' Perception of Migraine Images on the Internet: Cross-sectional Survey Study. J Med Internet Res 2021 Nov 12;23(11):e32707. doi: 10.2196/32707.

"***Background**: The representation of migraine in the media is stereotypical. Standard images of migraine attacks display stylish young women holding their head in a pain pose. This representation may contribute to the social stigmatization of patients with migraine.*

***Objective**: We aimed to analyze how patients with migraine and health care workers perceive online images of migraine.*

***Methods**: The study consisted of an anonymous web-based survey of patients with migraine at the Headache Center of Charité - Universitätsmedizin Berlin (migraine group) and employees and students at our university (health care group). A total of 10 frequently used Adobe Stock photos of migraine attacks were presented to the participants. Each photo was rated on a scale of 0% to 100% based on how closely it resembled a realistic migraine attack (realism score). Patients with migraine also indicated how much each photo corresponded to their own experience of migraine as a percentage (representation score). We calculated the mean realism and representation scores for all photos and conducted further analyses using the categories male or female models, younger or older models, and unilateral or bilateral pain pose.*

***Results**: A total of 367 patients with migraine and 331 health care employees and students completed the survey. In both groups, the mean realism score was <50% (migraine group: 47.8%, SD 18.3%; health care group: 46.0%, SD 16.2%). Patients with migraine identified their own migraine experience in these photos to a lesser degree (mean representation score 44.4%, SD 19.8%; P<.001 when compared to the realism score). Patients and health care workers considered photos with male models to be more realistic than photos with females (P<.001) and photos with older models to be more realistic than those with younger people (P<.001). In the health care group only, a bilateral pain posture was deemed more realistic than a unilateral pose (P<.001).*

***Conclusions**: Standard images of migraine attacks are considered only slightly or moderately realistic by patients and health care workers. Some characteristics perceived as more realistic such as male sex or older age are in contrast with migraine epidemiology. A more accurate representation of migraine in the media could help to raise awareness for migraine and reduce the associated stigma.*"

Original Paper

Patients' and Health Care Workers' Perception of Migraine Images on the Internet: Cross-sectional Survey Study

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Abstract

Background: The representation of migraine in the media is stereotypical. Standard images of migraine attacks display stylish young women holding their head in a pain pose. This representation may contribute to the social stigmatization of patients with migraine.

Objective: We aimed to analyze how patients with migraine and health care workers perceive online images of migraine.

Methods: The study consisted of an anonymous web-based survey of patients with migraine at the Headache Center of Charité – Universitätsmedizin Berlin (migraine group) and employees and students at our university (health care group). A total of 10 frequently used Adobe Stock photos of migraine attacks were presented to the participants. Each photo was rated on a scale of 0% to 100% based on how closely it resembled a realistic migraine attack (realism score). Patients with migraine also indicated how much each photo corresponded to their own experience of migraine as a percentage (representation score). We calculated the mean realism and representation scores for all photos and conducted further analyses using the categories male or female models, younger or older models, and unilateral or bilateral pain pose.

Results: A total of 367 patients with migraine and 331 health care employees and students completed the survey. In both groups, the mean realism score was <50% (migraine group: 47.8%, SD 18.3%; health care group: 46.0%, SD 16.2%). Patients with migraine identified their own migraine experience in these photos to a lesser degree (mean representation score 44.4%, SD 19.8%; P<.001 when compared to the realism score). Patients and health care workers considered photos with male models to be more realistic than photos with females (P<.001) and photos with older models to be more realistic than those with younger people (P<.001). In the health care group only, a bilateral pain posture was deemed more realistic than a unilateral pose (P<.001).

Conclusions: Standard images of migraine attacks are considered only slightly or moderately realistic by patients and health care workers. Some characteristics perceived as more realistic such as male sex or older age are in contrast with migraine epidemiology. A more accurate representation of migraine in the media could help to raise awareness for migraine and reduce the associated stigma.

(J Med Internet Res 2021;23(11):e32707) doi: 10.2196/32707

KEYWORDS

migraine; stigma; mass media; stock photos; advocacy; internet; perception; headache; pain; cross-sectional; survey; stereotype; media; awareness

Introduction

Migraine is one of the most common neurological diseases, with a prevalence of 15% in the general population and rising to over 25% in women of childbearing age [1-3]. Migraine causes significant limitations in quality of life and functioning [4]. It is the second most common cause of health impairment among nonfatal diseases worldwide, as shown by the years lived with disability measure [4]. Among individuals aged 15 and 49 years, migraine ranks first among the most disabling of diseases [5].

Despite the substantial impact on patients' lives, migraine burden is often underestimated [6]. Many patients feel that their symptoms are dismissed as insignificant [7,8]. Platitudes such as "everybody has headaches" or "it's just stress" are omnipresent in the lives of patients with migraine [7,8]. In a survey by Buse et al [9] , almost half of patients with chronic migraine had the impression that their partner did not believe in their disease. The invisibility of migraine can lead to frustration and stigmatization [7]. Out of fear of being doubted, some patients even hide their symptoms and do not seek treatment, which in turn can have a negative impact on the course of the disease [10,11].

The lack of acceptance of migraine as a real disease has historical roots. Until recently, patients with migraine were portrayed as frail women with weak nerves [12]. Although this representation originates from a cultural background different from the present times, these stereotypes continue to shape the common view of patients with this disease [12].

Currently, digital media, and especially the internet, have become an important source of information on health topics [13]. Portrayals of people with migraine in the media can provide an overview on how society currently sees these patients [14]. Most images resulting from the search term "migraine" show slim and stylish young women holding their temples with an expression of pain on their faces [14]. This trivializing and one-sided portrayal could contribute to the insufficient recognition of migraine-related burden and the growth of social stigma [14].

While this stereotypical representation has already raised concerns among experts [14], no study has assessed how the public perceives such images of migraine. In this study, we aimed to investigate the following questions: (1) do patients with migraine and nonaffected health care workers perceive such photos as realistic? and (2) can patients with migraine relate to these portrayals?

Methods

Study Design

This anonymous web-based survey was performed on the REDCap (Research Electronic Data Capture) platform. The link to participate in the survey was distributed among the following two groups:

1. The migraine group: patients at the Headache Center, Charité – Universitätsmedizin Berlin, with a diagnosis of migraine in 2020 per International Classification of Headache Disorders–3 (ICHD-3) criteria [15];
2. The health care group: employees and students at the medical school of Charité – Universitätsmedizin Berlin without migraine.

Patients with migraine received the link to participate via a letter in order to comply with data protection law, while the health care group was invited via email distribution lists and social media groups.

The survey structure is illustrated in Table 1. After the assessment of demographic, occupational, and migraine characteristics, 10 different photos of migraine attacks were presented to the participants on the screen. The participants were instructed to rate on a scale between 0% and 100% how much each picture corresponded to a realistic migraine attack. We defined this percentage value as the realism score. Patients with migraine then indicated how closely each image resembled their own migraine experience on the same 0%-to-100% scale. This score was named the representation score.

Table 1. Structure of the survey.

Section	Description
Study information	Written information about the study design and aim, as well as the data protection statement agreement. Subjects could download the study information to keep for their records.
Written consent form	In order to access the other questionnaires, participants must confirm that they are ≥18 years of age, that they are voluntarily participating in the survey, and that they agree to the publication of the study results in an anonymous form. Participants could download a consent form to keep for their records.
Demographic characteristics	Participants are asked about their gender, age, ethnic background, height, weight, and highest level of education.
Migraine information	Participants are asked whether they experienced migraine, if they have close family members or friends with migraine, and how they assess the impairment caused by migraine in the general population and in their own migraine experience (on a numerical analog scale from 0% to 100%).
Occupational characteristics	Participants are asked whether they work or study at the Charité – Universitätsmedizin Berlin, in which field, and if they have regular contact with patients with migraine at work.
Photos 1-10	Participants are asked to look at 10 photos of migraine attacks and rate how realistic each photo is. Patients with migraine are also asked how representative of their own migraine experience these photos are.

The photos with models were obtained from the stock photo website Adobe Stock (Adobe Inc) [16]. We purchased a commercial license for the use of the 10 photos in the survey. Image selection was based on the following criteria:

- Result of the search term "migraine";
- Sorting by the number of times the photos were downloaded;
- 7 females and 3 males (to match the epidemiological sex distribution of migraine);
- Only 1 person in the photo;
- No black-and-white images;
- No heavy editing or heavy filters and effects;
- Face is visible;
- Only 1 photo of each model;
- Person in the foreground (ie, the background does not take more than half of the image).

Outcomes and Objective

The primary outcomes of the study were the mean realism score for all photos in both groups and the mean representation score for all photos in patients with migraine.

The secondary outcomes were the mean realism and representation scores for the following categories of photos:

- Photos with female models (n=7);
- Photos with male models (n=3);
- Photos with a unilateral pain posture (ie, models holding one side of the head, n=6);
- Photos with a bilateral pain posture (ie, models holding both sides of the head, n=3);
- Photos with younger models (n=5);
- Photos with older models (n=4).

The allocation of the photos into each category was agreed upon unanimously by all authors of this paper. To differentiate between younger and older models, we focused on physical characteristics such as face wrinkles or hair color (ie, white or gray).

Statistical Analysis

The analysis comprises all participants who rated all 10 photos. Employees or students with self-reported migraine were excluded from the health care group.

Demographic and occupational characteristics, as well as realism and representation scores, were summarized with descriptive statistics (absolute frequencies and percentages for categorical variables and mean (SD) values for numerical variables).

We compared the primary and secondary outcome measures between the migraine and health care groups using independent *t* tests. The realism and representation scores were compared within the migraine group using paired-sample *t* tests.

We further assessed the correlation of the primary and secondary outcomes with sex, age, ethnicity, highest level of education, and occurrence of migraine among family and friends using Pearson correlation analyses. A 2-tailed *P* value ≤.05 was considered statistically significant. *P* values were corrected for multiple comparisons with the Bonferroni method.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (EA1/213/20). Participants were required to provide electronic consent prior to completing the survey.

Results

Population

Between October 27, 2020, and January 15, 2021, 367 patients with migraine and 331 Charité employees and medical students completed the survey. The participant selection process is illustrated in Figure 1.

The majority of patients were female (n=318, 86.6%), with an average age of 45.3 (SD 12.7) years. Participants in the health care group were younger (mean 32.1, SD 11.1 years), but their gender and ethnic distribution was similar to that of the migraine group (Table 2).

Figure 1. Flowchart of participant selection in both groups.

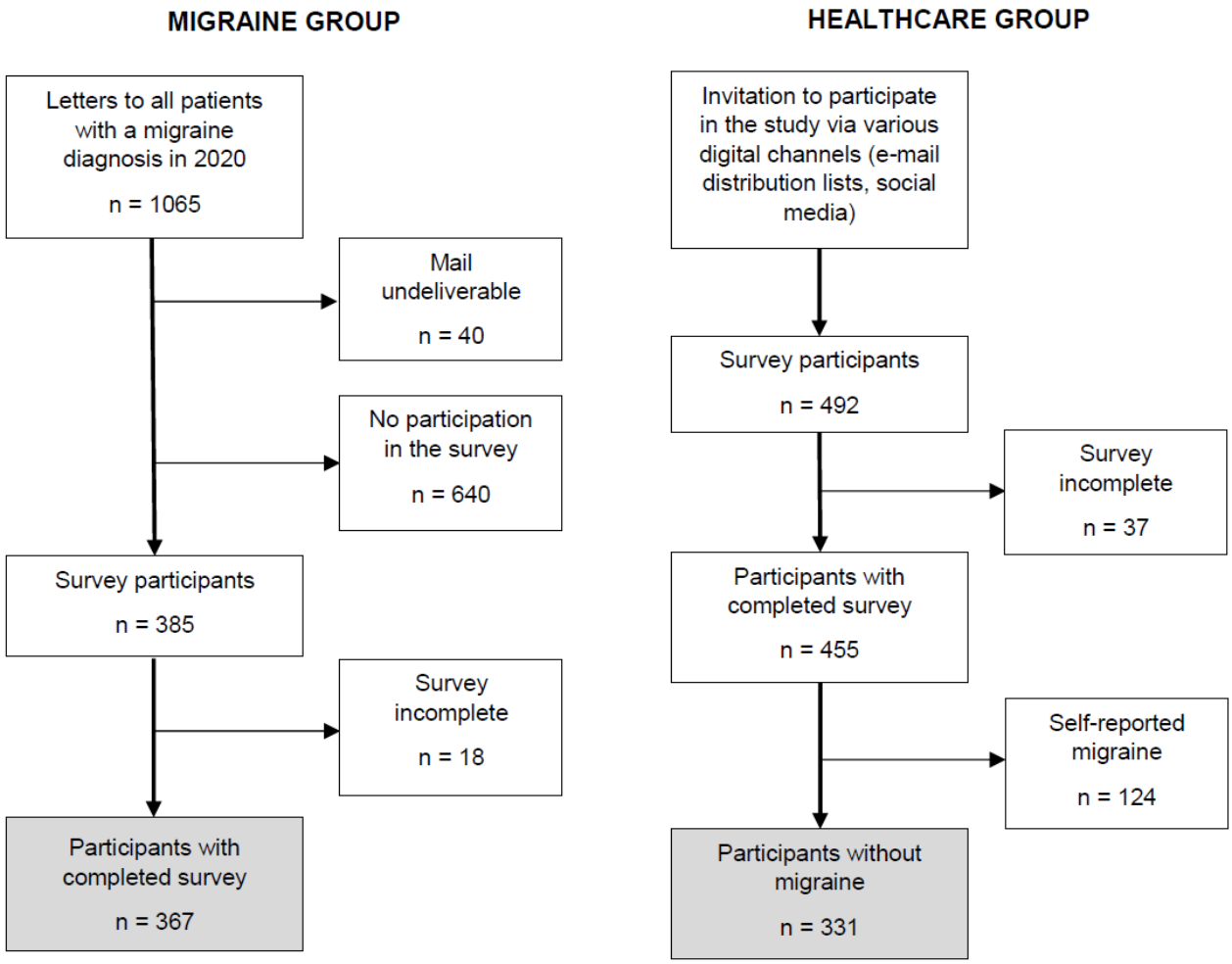


Table 2. Demographic and occupational characteristics of the survey participants.

Characteristic	Migraine group	Health care group
Age (years), mean (SD)	45.3 (12.7)	32.1 (11.1)
Female sex, n (%)	318 (86.6)	245 (73.9)
Northern or Central European descent, n (%)	314 (85.6)	283 (85.6)
Height (cm), mean (SD)	168.9 (8.1)	171.5 (9.7)
Weight (kg), mean (SD)	69.4 (14.6)	68.3 (13.3)
Highest level of education, n (%)		
University degree	154 (42.1)	118 (35.6)
High school diploma	63 (17.2)	155 (46.8)
Technical baccalaureate	29 (7.9)	8 (2.4)
Apprenticeship	60 (16.4)	20 (6.0)
Intermediate secondary school diploma (Realschulabschluss)	38 (10.4)	13 (3.9)
General secondary school diploma (Hauptschlussabschluss)	4 (1.1)	2 (0.6)
Other	19 (4.9)	15 (4.5)
Close friends or family members with migraine, n (%)	196 (53.4)	104 (31.4)
Health care workers' occupation, n (%)	—[a]	167 (50.5)
Physician	—	42 (25.1)
Nurse	—	33 (19.8)
Other medical professionals	—	27 (16.2)
Other nonmedical professionals	—	65 (38.9)
Health care students' study subject, n (%)	—	164 (49.5)
Human medicine	—	122 (74.4)
Dentistry	—	11 (6.7)
Other	—	31 (18.9)
Regular professional contact with patients with migraine, n (%)	—	68 (20.5)

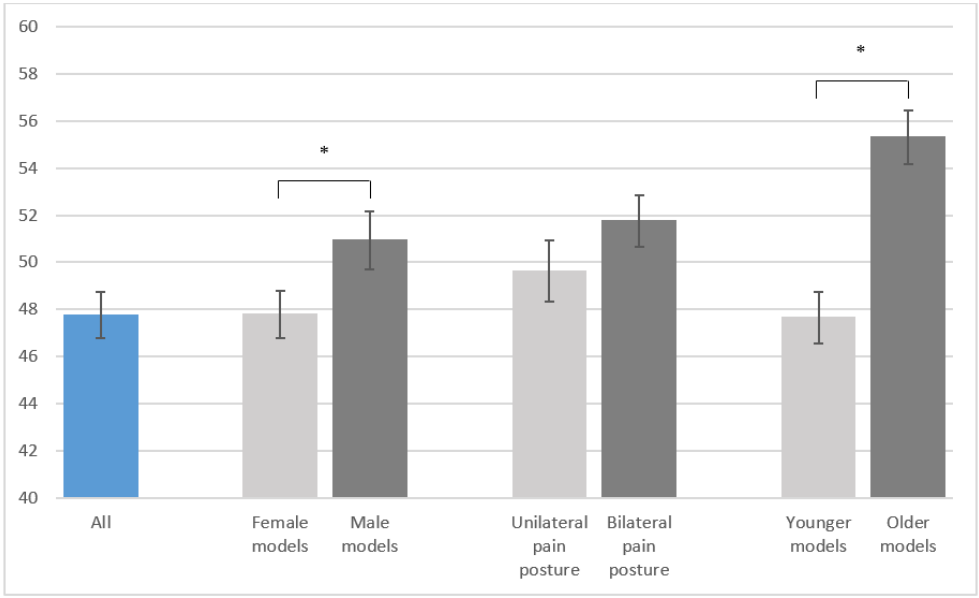
[a]Not applicable.

Patients With Migraine

Realism Scores

Among patients with migraine, the mean realism score for the 10 photos was 47.8% (SD 18.3%). Only 3 out of 10 photos had a mean realism score >50%. Photos with male models were considered more realistic than photos with female models (mean 51.0%, SD 22.4% vs mean 47.8%, SD 18.3%; *P*=.002). Patients rated images with older models as more realistic than those with younger models (mean 55.3%, SD 21.0% vs mean 47.7%, SD 20.1%; *P*<.001). Photos with unilateral and bilateral pain postures had similar realism scores (*P*>.99, Figure 2).

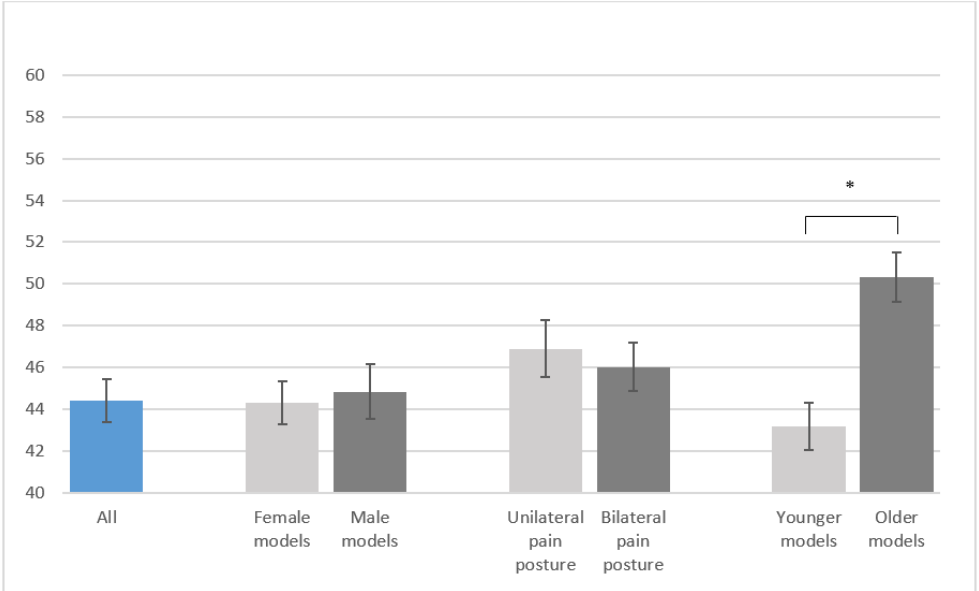
Figure 2. Realism scores of patients with migraine for all photos and different categories. Values are mean (SD), and the asterisk indicates *P*<.001.



Representation Scores

When asked how much the images corresponded to their own experience of migraine, the patients answered with a mean representation score of 44.4% (SD 19.8%). Photos with older models were considered more representative than photos with younger models (mean 50.3%, SD 22.7% vs mean 43.2%, SD 21.9%; *P*<.001). The gender of the models did not lead to significant rating differences in the representation score (*P*>.99). Photos with a unilateral pain posture had similar scores as did photos with a bilateral pain posture (*P*>.99, Figure 3).

Figure 3. Representation scores of patients with migraine for all photos and different categories. Values are mean (SD), and the asterisk indicates *P*<.001.



The mean representation score for all photos and in each category was significantly lower than the corresponding realism score (*P*<.001 for all categories).

There was a negative correlation between the highest level of education and both realism and representation scores: the higher the degree, the less realistic (*P*<.001, *r*=0.26) and representative (*P*<.001, *r*=0.29) the images were rated in all categories. Further analyses revealed a positive correlation between the patients' age and the realism (*P*=.047, *r*=0.11) and representation scores (*P*=.04, *r*=0.12) of images with older models. There was no correlation with the gender or ethnicity or with the occurrence of migraine among close friends or family members.

Health Care Workers and Students

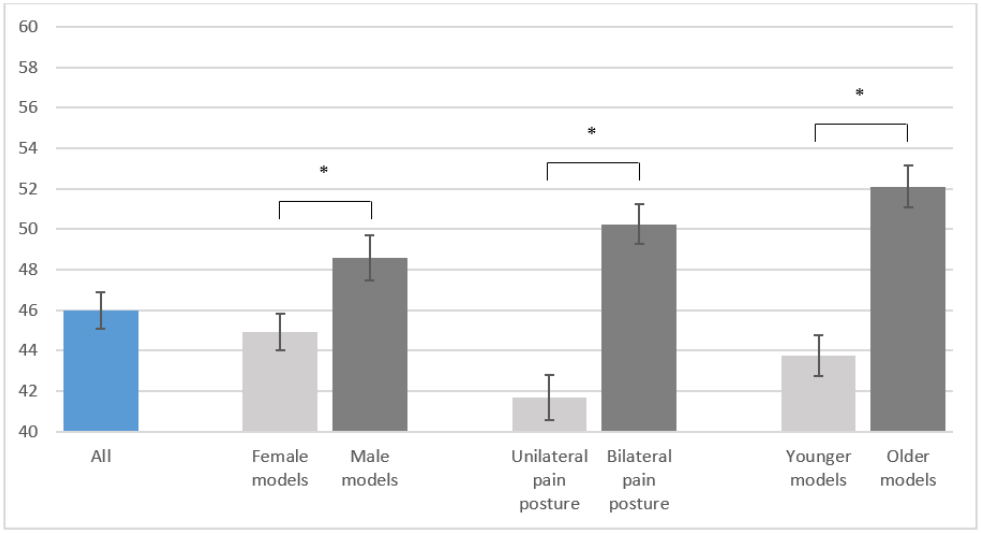
Realism Scores

In the health care group, the 10 photos had a mean realism score of 46.0% (SD 16.2%). Similar to the migraine group, only 3 photos were rated as >50% for realism. Photos with male models received higher scores than photos with female models (mean 48.6%, SD 20.2% vs mean 44.9%, SD 16.4%; *P*<.001). A bilateral pain posture was considered more realistic than a

unilateral pain posture (mean 50.2%, SD 18.1% vs mean 41.7%, SD 20.0%; *P*<.001). Photos with older models were rated higher than photos with younger models (mean 52.1%, SD 18.8% vs mean 43.8%, SD 18.3%; *P*<.001). Figure 4 shows the mean realism scores in the different categories.

There was no correlation to the gender, ethnicity, or age of the participant nor to regular contact with people with migraine (*P*>.99). Further, we detected a negative correlation with the highest level of education in this group (*P*=.004, *r*=0.16).

Figure 4. Realism scores of health care workers and students for all photos and different categories. Values are mean (SD), and the asterisk indicates *P*<.001.



Comparison Between Patients With Migraine and Health Care Workers and Students

Patients with migraine rated photos with a unilateral pain posture as significantly more realistic than the health care group (*P*<.001). Overall, the mean realism score for all photos did not differ between the two groups (*P*=.23). Both groups rated photos with male and older models as more realistic than photos with female and younger models. The mean realism scores for photos with females (*P*=.20), males (*P*>.99), younger models (*P*=.14), and older models (*P*=.53) were similar between groups.

Discussion

Patients with migraine and health care workers perceived commonly used stock photos of migraine attacks as slightly or moderately realistic. Patients identified their own migraine experience in these photos to an even lesser degree. Both groups rated photos with male and older models as more realistic than photos with female or younger ones. Among health care workers, a bilateral pain representation was considered more realistic than a unilateral pose.

The differences between media-based representations and the clinical reality have been described by Gvantseladze et al [14]. An analysis of the top 200 images under the search term “migraine” in 2 popular image-searching websites revealed that the majority of these images represented slim White females in a classic pain pose holding one or both temples [14]. The authors argued that this overrepresentation of ectomorph body types and stereotypical pain behaviors may contribute to the social stigmatization of patients with migraine [14]. Our results confirmed that not only experts but also patients doubt the realism of these images. In line with these findings, the Coalition for Headache and Migraine Patients (CHAMP) stated that media representation is often unrealistic and unlikely to display the severity of migraine [17]. The difference between the standard migraine representation and actual migraine behavior may result in the minimization of symptoms and misunderstanding of people living with this disease.

Such an example was illustrated by a social media trend from 2018, in which models and influencers published photos of themselves in the so-called “migraine pose,” touching one side of their face [18]. The fashion magazine *Elle USA* stated that this “flattering” pose “tightens the face, makes your cheekbones look more prominent, and lifts the brows” [18]. The use of the term migraine to name a glamorous pose indicates a lack of public acceptance for migraine as an extremely burdening condition. In line with the CHAMP Image Guide [17], our results support the need for a more accurate portrayal of migraine attacks. A better representation could include migraine symptoms other than headache, such as photophobia, nausea, or cognitive impairment [17]. A more diverse depiction could also help to move away from the classic temporal headache as the only accepted form of migraine pain. For example, a large proportion of migraine patients also have neck pain during attacks [19], which is almost never displayed as a feature of migraine [20].

Hospital employees and medical students shared the patients’ critical view of these images. This selected population was able to recognize that this stereotypical representation does not substantially correspond to reality. A more realistic representation of migraine attacks could also have a positive impact on patients’ treatment. The process toward effective migraine therapy is often lengthy and difficult [10]. The inaccurate, yet commonly accepted, representation of attacks could lead to a delay in the recognition and diagnosis of migraine, if patients experiencing an attack do not resemble

these common depictions [10]. Giving visibility to migraine in all its facets could therefore alleviate not only social stigmatization but also the therapeutic burden.

Migraine patients and the health care group rated the laterality of the headache pose differently. A unilateral representation was perceived as more realistic by the patients. Unilaterality is one of the key migraine characteristics according to the ICHD-3 but is not a mandatory criterion for migraine diagnosis [15]. Bilateral pain occurs frequently and, in older patients, it is even more common than strict unilateral attacks [21]. Patients with migraine at a tertiary headache center like ours might be better educated about the typical characteristics of migraine and therefore rate unilaterality as a more realistic migraine feature than the nonaffected group.

Migraine prevalence is 3 times higher in women than in men [3]. However, photos with male models were considered significantly more realistic than those with female models in this analysis, regardless of the rater's gender. This observation fits in well with the literature on gender bias, according to which pain disorders in women are taken less seriously than in men [22,23]. Pain expressions of females with chronic pain are underestimated compared to males, and women's pain is considered less severe [24]. In the health care system, women are less likely to receive pain medication than men [25]. On the contrary, psychosocial treatments are more often recommended to female patients experiencing pain [26]. Women with pain diseases are frequently met with skepticism and have to struggle to be believed, which might lead to shame and frustration [27]. If the woman is physically attractive, the credibility of her pain is even lower, which might be applicable to our photo models [28].

Similar considerations may apply to younger patients, especially if female. Young people with pain are often perceived as less ill, based on their healthy physical appearance [29]. This might explain why photos with older models were perceived as more realistic in our survey. This is in contrast with the epidemiology of migraine, which shows a prevalence peak during young adulthood [30].

Finally, our analysis showed that less educated people rated migraine stock images as more realistic than participants with a high level of education. People with a lower education are more likely to be influenced by the media [31,32]. Therefore, it is possible that they are accustomed to this type of migraine representation and do not question its realism. This high receptivity to the media could be useful for educational programs and campaigns to raise awareness for migraine and convey a more accurate and realistic representation.

This is the first study to analyze the perception of commonly used migraine images in a large cohort of patients with migraine and health care workers. Patients with migraine were selected directly from our Headache Center, which ensured a correct diagnosis. Due to data protection regulations, patients could not be contacted by email or telephone. Given that the only possible way to contact the patient was via mail, the response rate of over 30% is within the normal range of response.

A limitation of the study is that participants completed the survey anonymously online without supervision, which might have a negative impact on data reliability. Some biases may have affected our findings: people with a pre-existing awareness of this topic might have participated to a higher extent in the survey; this applies to younger people who are frequent users of the internet as well. We also divided the photos in six categories, but not all image characteristics were taken into account. For example, the outfit of the models, the surrounding environment, or the severity of the expression of pain were not considered and may represent confounding factors. In addition, only health care workers and students were enrolled in the comparison group, which might not be entirely representative of the general population. The extension of the survey to other members of the public might provide further insights on the perception of migraine.

To conclude, the media representation of migraine was considered at best moderately realistic in our large cohort of patients with migraine and health care workers. The rating of male and older models as more realistic contradicts migraine epidemiology. A more truthful representation of migraine is needed in order to raise awareness of the burden of this disease and to reduce migraine-related social stigma.

Conflicts of Interest

None declared.

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Abbreviations

CHAMP: Coalition for Headache and Migraine Patients
ICHD-3: International Classification of Headache Disorders–3
REDCap: Research Electronic Data Capture

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3. Diskussion

Die in der vorliegenden Habilitationsschrift zusammengefassten Arbeiten explorierten relevante geschlechtsspezifische Aspekte in der Pathophysiologie, Behandlung, Differentialdiagnostik und gesellschaftlichen Wahrnehmung der Migräne. Mit einem breiten Spektrum an Schwerpunktthemen verfolgt diese Arbeit das Ziel, die Besonderheiten der Migräne bei Frauen in den Mittelpunkt zu stellen und damit unbeantwortete Fragen zu identifizieren, die zukünftige Forschungsbemühungen leiten können.

3.1 Geschlechtsspezifische Aspekte im CGRP-Signalweg

Die ersten beiden Arbeiten dieser Habilitationsschrift legten ihren Schwerpunkt auf das Neuropeptid CGRP. CGRP hat in der Migräneforschung der letzten Jahre eine zentrale Bedeutung erlangt (Edvinsson et al., 2018), und diese Studien tragen dazu bei, unser Verständnis für die komplexen Zusammenhänge zwischen CGRP, Sexualhormonen und Migräne zu vertiefen.

In der ersten vorgestellten Arbeit lag der Fokus auf Unterschiede in den CGRP-Konzentrationen in Abhängigkeit vom hormonellen Status weiblicher Patientinnen mit Migräne und Probandinnen ohne Migräne (Raffaelli et al., 2023). Die Ergebnisse dieser Arbeit zeigten, dass Patientinnen mit Migräne und einem regulären Menstruationszyklus während der Menstruation höhere CGRP-Konzentrationen im Blutplasma und der Tränenflüssigkeit aufwiesen als gesunde Frauen ohne Migräne. Darüber hinaus wurden niedrigere CGRP-Konzentrationen in der Tränenflüssigkeit bei Patientinnen beobachtet, die eine kombinierte orale Kontrazeption einnahmen, im Vergleich zur physiologischen Menstruation.
Diese Ergebnisse bestätigen die Verbindung zwischen Sexualhormonen und CGRP in der Pathophysiologie der Migräne, die bisher hauptsächlich im Tiermodell erforscht wurde (Krause et al., 2021; Labastida-Ramírez et al., 2019). Verschiedene Tierstudien konnten zeigen, dass ein Abfall von Östrogenkonzentrationen zu einer vermehrten CGRP-Freisetzung führen kann (Herbison & Spratt, 1995; Wang et al., 2014; Yang et al., 1998). Spezifisch im Ganglion trigeminale zeigte sich bei ovariektomierten Ratten eine Erhöhung der CGRP-Expression, welche sich nach Östrogensubstitution wieder normalisierte (Aggarwal et al., 2012). Auch in unserer Kohorte von Migränepatientinnen mit einem regulären Menstruationszyklus zeigten sich höhere CGRP-Konzentrationen während der Menstruation – eine Phase mit niedrigen Östrogenkonzentrationen – im Vergleich zu Patientinnen, die eine östrogenhaltige

Kontrazeption einnahmen.
Interessanterweise traten diese Unterschiede nicht bei gesunden Probandinnen mit regelmäßigem Menstruationszyklus auf, was auf eine mögliche Modulationsstörung des CGRP-Signalwegs bei Frauen mit Migräne hinweisen kann. Die verstärkte perimenstruelle CGRP-Freisetzung bei Frauen mit Migräne könnte die erhöhte Suszeptibilität für Migräneanfälle während der Menstruation erklären (Krause et al., 2021). Ein Abfall der Östrogenspiegel könnte zur Hochregulation des CGRP-Signalwegs führen und einen prädisponierenden Zustand für Migräneattacken schaffen (Krause et al., 2021).
Sofern zukünftige Studien diese Ergebnisse bestätigen, könnte die gezielte Modulation des CGRP-Signalwegs eine Strategie in der spezifischen Behandlung der menstruellen Migräne darstellen. Aktuelle Untersuchungen deuten darauf hin, dass CGRP-gerichtete Therapien, wie monoklonale Antikörper gegen CGRP und den CGRP-Rezeptor, sowohl perimenstruelle als auch nicht-perimenstruelle Migräneattacken reduzieren können (Silvestro et al., 2021; Verhagen et al., 2023C). Spezifische Untersuchungen zur menstruellen Migräne wurden zum Zeitpunkt dieser Habilitation nicht durchgeführt. Gezielte Untersuchungen, die den CGRP-Signalweg bei der menstruellen Migräne genauer explorieren, könnten klinische Implikationen für die Behandlung und Prävention dieser speziellen Form der Migräne liefern.

CGRP spielt aber nicht nur in der Migränepathophysiologie eine Rolle, sondern ist ubiquitär im Körper vorhanden und in verschiedenen physiologischen und pathologischen Prozessen involviert (Deen et al., 2017). Im Kontext geschlechtsspezifischer Komorbiditäten lag der Schwerpunkt der zweiten vorgestellten Arbeit auf der Messung von CGRP im Plasma bei Patientinnen mit Endometriose, einer häufigen Komorbidität bei Frauen mit Migräne (Raffaelli et al., 2021A).
In dieser Arbeit wurden die systemischen CGRP-Konzentrationen bei Patientinnen mit ausschließlich Migräne, ausschließlich Endometriose, komorbider Migräne und Endometriose sowie gesunden Kontrollprobandinnen gemessen. Trotz der Beteiligung von CGRP an beiden Erkrankungen (Gupta et al., 2016; Yan et al., 2019) zeigten die CGRP-Konzentrationen bei komorbiden Patientinnen keine signifikante Erhöhung im Vergleich zu den anderen Gruppen. Interessanterweise wurde jedoch ein Anstieg der CGRP-Konzentrationen in der perimenstruellen Phase bei komorbiden Patientinnen im Vergleich zur periovulatorischen Phase beobachtet, während bei gesunden Kontrollprobandinnen das Gegenteil der Fall war. Dies legt nahe, dass eine hormonbedingte Fehlregulation des CGRP-Signalwegs bei beiden Erkrankungen eine Rolle spielen und zu den verstärkten perimenstruellen Schmerzttacken bei

diesen Patientinnen beitragen könnte. Übereinstimmend wurden in genetischen Studien spezifische gemeinsame genetische Varianten bei Migräne und Endometriose identifiziert, die zu einer hormonbedingten Fehlregulation inflammatorischer Signalwege führen können (Adewuyi et al., 2020; van der Vaart & Merki-Feld, 2022). Zukünftige Studien sollten den Zusammenhang zwischen CGRP, Migräne und Endometriose vertieft untersuchen, um letztendlich die Behandlungsmöglichkeiten für betroffene Patientinnen zu verbessern. In diesem Zusammenhang sollte auch der Einfluss von CGRP-gerichteten Therapien auf die Schmerzen bei Endometriose untersucht werden. Gerade bei komorbiden Patientinnen könnte dies ein vielversprechender Ansatz sein, um beide Erkrankungen gegebenenfalls mit einem Medikament zu behandeln.

Es ist jedoch wichtig zu beachten, dass die Rolle von CGRP als Biomarker für Migräne kritisch diskutiert wird. Obwohl die Bedeutung von CGRP in der Pathophysiologie der Migräne unumstritten ist, gestaltet sich die exakte Messung von CGRP in unterschiedlichen Biomaterialien als herausfordernd (Kamm, 2022; Lee et al., 2018). Eine wesentliche Herausforderung besteht in der kurzen Halbwertszeit von CGRP, die lediglich etwa 7 Minuten beträgt und somit eine äußerst rasche Verarbeitung der Proben erfordert. Darüber hinaus sind zahlreiche kommerzielle Enzyme-linked Immunosorbent Assay (ELISA)-Kits verfügbar, die an verschiedene CGRP-Isotope binden und unterschiedliche Messbereiche aufweisen, was die Vergleichbarkeit von Studienergebnissen einschränken kann (Kamm, 2022).
Insbesondere die Messung der CGRP-Konzentrationen im Blutplasma gestaltet sich als komplex, da sie von einer Vielzahl von verschiedenen Faktoren beeinflusst wird. Es wird angenommen, dass lediglich etwa ein Fünftel des im Blutplasma nachweisbaren CGRP aus dem trigeminovaskulären System stammt, wodurch eine systemische Messung nicht spezifisch für Migräne ist. Alternativ bieten sich andere Biomaterialien wie Speichel (Alpuente et al., 2022) oder Tränenflüssigkeit an, wie in Arbeit 1 beschrieben (Raffaelli et al., 2023). Diese können aufgrund ihrer räumlichen Nähe zum trigeminovaskulären System aufschlussreicher und präziser sein. Tränenflüssigkeit enthält hauptsächlich CGRP, das aus den Trigeminalfasern in der Hornhaut und Bindehaut stammt (Kamm et al., 2019). Unsere Arbeit konnte bestätigen, dass die Konzentration von CGRP in der Tränenflüssigkeit 80x höher ist als im Plasma und allgemein höher bei Migränepatientinnen als bei Kontrollpersonen ohne Migräne. Die Messung von CGRP in der Tränenflüssigkeit stellt somit eine vielversprechende, nicht-invasive Methode dar, die jedoch in künftigen Studien weiter validiert werden sollte.

3.2 Hormonelle Kontrazeption bei Patientinnen mit Migräne

Die dritte vorgestellte Arbeit, die auf einer deutschlandweiten Befragung niedergelassener Gynäkolog:innen basierte, hatte die Verschreibung hormoneller Kontrazeption bei Patientinnen mit Migräne zum Thema (Fitzek et al., 2023). Die Ergebnisse dieser Studie zeigten, dass die teilnehmenden Gynäkolog:innen das Vorliegen einer Migräne vor Verschreibung einer hormonellen Kontrazeption berücksichtigen. Insbesondere bei Patientinnen mit Migräne mit Aura zeigte sich eine deutliche Zurückhaltung hinsichtlich der Verschreibung einer kombinierten Kontrazeption, während eine Progesteronmonotherapie vorsichtig erwogen wurde.

Das Verhalten bezüglich der Verschreibung einer kombinierten oralen Kontrazeption entspricht im Wesentlichen den europäischen Richtlinien, die vor der Verwendung hormoneller Kontrazeptiva bei Migräne mit Aura warnen (Sacco et al., 2018). Dieser Ansatz basiert auf der Erkenntnis, dass das kumulierte kardiovaskuläre Risiko bei Migräne mit Aura sowie bei der Einnahme von östrogenhaltigen Präparaten signifikant erhöht ist (Øie et al., 2020). Frauen mit Migräne und Aura, die gleichzeitig hormonelle Kontrazeptiva verwenden, haben ein erheblich höheres Risiko für die Entwicklung eines ischämischen Schlaganfalls im Vergleich zu Frauen ohne diese Risikofaktoren in ähnlichem Alter (Øie et al., 2020).

Die zurückhaltende Verschreibung einer Progesteronmonotherapie ist hingegen schwieriger zu erklären, da diese Therapie nicht mit einem erhöhten kardiovaskulären Risiko assoziiert ist (Sacco et al., 2018). Tatsächlich legen aktuelle Richtlinien sogar nahe, dass eine Progesteronmonotherapie eine sichere Alternative für Migränepatientinnen mit Aura darstellen kann, die eine hormonelle Kontrazeption in Erwägung ziehen (Sacco et al., 2018).

Ein weiteres Ergebnis der Befragung war die Tatsache, dass nahezu alle teilnehmenden Gynäkolog:innen aufgrund von Migräne bereits eine hormonelle Kontrazeption bei ihren Patientinnen initiiert, beendet oder geändert hatten. Dies unterstreicht die Rolle der Gynäkolog:innen als wichtige Akteure in der ganzheitlichen Versorgung von Migränepatientinnen.

Allerdings ist anzumerken, dass die geringe Beteiligung an der Umfrage, bei der lediglich 7% der angeschriebenen Gynäkolog:innen teilnahmen, Auswirkungen auf die Repräsentativität haben kann. Dies könnte auf den hektischen Praxisalltag, die mangelnde Weiterleitung unserer Briefe und E-Mails an das ärztliche Personal oder ein generelles Desinteresse an diesem Thema zurückzuführen sein. In den Vereinigten Staaten sind beispielsweise nur 6% der Gynäkolog:innen mit den aktuellen Migräneleitlinien vertraut, und weniger als ein Drittel hat eine spezielle Weiterbildung im Bereich Kopfschmerzmedizin absolviert (Verhaak et al., 2021).

Obwohl vergleichbare Zahlen für Deutschland bisher nicht erfasst wurden, betont dies die Notwendigkeit einer verstärkten interdisziplinären Zusammenarbeit zwischen den medizinischen Fachgebieten, um die Versorgung und Beratung von Patientinnen mit Migräne zu optimieren.

3.3 Kopfschmerzen in der Schwangerschaft: Red flags für sekundäre Ursachen

In der vierten vorgestellten Arbeit standen die Diagnosen und die klinischen Merkmale von akuten Kopfschmerzen in der Schwangerschaft im Fokus (Raffaelli et al., 2017). Insgesamt wurden Daten von 151 schwangeren Frauen erfasst, die sich aufgrund akuter Kopfschmerzen in der Rettungsstelle der Charité vorstellten. Während bei der Mehrheit von ihnen die Diagnose einer primären Kopfschmerzerkrankung gestellt werden konnte, ergab sich bei 42% der Fälle die Diagnose eines sekundären Kopfschmerzes, am häufigsten infektiöser und hypertensiver Ursache.

Die Ergebnisse dieser Studie unterstreichen die Wichtigkeit einer detaillierten Anamneseerhebung und zumindest einer ausführlichen klinischen Diagnostik in der Schwangerschaft, da diese einen Risikofaktor für sekundäre Kopfschmerzen darstellt. Besonders bei Frauen mit einer vorherigen Migräneerkrankung sollte eine erhöhte Wachsamkeit gelten, da sie ein erhöhtes Risiko für bestimmte Schwangerschaftskomplikationen haben, die mit Kopfschmerzen einhergehen können (Adeney et al., 2005; Contag et al., 2009; Wabnitz & Bushnell, 2015).

In der untersuchten Kohorte waren insbesondere erhöhter Blutdruck, Fieber, neurologische Auffälligkeiten und eine Vorgeschichte von sekundären Kopfschmerzen prädiktiv für eine sekundäre Kopfschmerzursache. Hingegen waren auratypische visuelle Symptome, wie Flimmerskotome, mit primären Kopfschmerzursachen assoziiert.

Eine vorherige US-amerikanische Studie, bei der eine Mehrheit der Probandinnen People of Color waren, ergab ähnliche Ergebnisse: Etwa ein Drittel der schwangeren Frauen, die sich mit akuten Kopfschmerzen vorstellten, hatten eine sekundäre Kopfschmerzursache (Robbins et al., 2015). In dieser Untersuchung zeigte sich, dass ein hoher Blutdruck und das Fehlen einer bekannten Kopfschmerzerkrankung prädiktiv für sekundäre Kopfschmerzen waren (Robbins et al., 2015).

Die Ursachen sekundärer Kopfschmerzen unterschieden sich leicht zwischen unserer vorwiegend weißen Kohorte und der US-amerikanischen Kohorte. Während hypertensive Erkrankungen in der US-amerikanischen Kohorte häufiger waren, stellten infektiöse Ursachen

in unserer Kohorte die häufigste Ursache dar (Robbins et al., 2015). Interessanterweise zeigten sich in beiden Kohorten keine spezifischen klinischen Kopfschmerzeigenschaften, die eindeutig auf sekundäre Kopfschmerzen hinwiesen. Zwar wies unsere Analyse auf eine Assoziation zwischen einseitigen Kopfschmerzen und primären Kopfschmerzen hin, aber diese verlor in der multivariaten Analyse die statistische Signifikanz.

Diese Daten verdeutlichen eindrücklich, dass eine ausschließliche Berücksichtigung der anamnestischen Angaben der Patiten:innen nicht ausreicht. Stattdessen sollten in jedem Fall mindestens eine Messung der Vitalparameter und eine klinische sowie neurologische Untersuchung durchgeführt werden. Bei Verdacht auf eine sekundäre Kopfschmerzursache sollte eine umfassendere Diagnostik erfolgen, da sekundäre Kopfschmerzerkrankungen in der Schwangerschaft lebensgefährlich sowohl für die Mutter als auch für das ungeborene Kind sein können (Negro et al., 2017).

In einer anschließenden Studie analysierte ich die durchgeführte bildgebende Diagnostik in dieser Kohorte (Raffaelli et al., 2018). Von den teilnehmenden Frauen unterzog sich die Hälfte einer bildgebenden Untersuchung, hauptsächlich in Form einer Magnetresonanztomographie (MRT). Bei 27,6% der Patientinnen mit durchgeführter Bildgebung wurden symptomatische pathologische Befunde festgestellt, wobei intrakranielle Blutungen, Sinusthrombosen, akute ischämische Hirninfarkte, das posteriore reversible Enzephalopathiesyndrom (PRES) und akute Sinusitis die häufigsten Befunde waren. Besonders Frauen im ersten Trimenon der Schwangerschaft wiesen in unserer Kohorte ein erhöhtes Risiko für symptomatische Bildgebungsbefunde auf. Klinische Symptome, die mit solchen Befunden assoziiert waren, umfassten starke Schmerzintensität, Bewusstseinsänderungen und epileptische Anfälle (Raffaelli et al., 2018). Es ist jedoch zu beachten, dass in unserer und anderen Studien auch Frauen ohne weitere neurologische Symptome symptomatische Befunde aufwiesen, was darauf hinweist, dass allein auf die klinische Symptomatik kein uneingeschränkter Verlass ist (Raffaelli et al., 2018; Ramchandren et al., 2007).

Die Durchführung von bildgebenden Untersuchungen bei schwangeren Frauen erfordert besondere Vorsicht (Ray et al., 2016), kann aber gerade bei Kopfschmerzen sinnvoll sein und ist bei Verdacht auf gewisse sekundäre Kopfschmerzursachen obligat. Gleichzeitig ist zu bedenken, dass nicht alle sekundären Kopfschmerzerkrankungen in der Schwangerschaft durch bildgebende Verfahren diagnostiziert werden können. Zum Beispiel gehen hypertensive Schwangerschaftserkrankungen in der Regel mit normalen bildgebenden Befunden einher.

Zusammenfassend sind bei akuten Kopfschmerzen in der Schwangerschaft eine gründliche Anamneseerhebung und klinische Untersuchung unerlässlich. Gegebenenfalls sollten

weiterführende apparative Untersuchungen in Erwägung gezogen werden. Bei Patientinnen mit einer bereits bekannten Migräneerkrankung ist es wichtig, bei einer Veränderung der bekannten Kopfschmerzeigenschaften während der Schwangerschaft, eine ausführlichere Diagnostik durchzuführen und eine zerebrale Bildgebung zu erwägen.

3.4 Gender Bias in der Darstellung von Migräne

Die fünfte präsentierte Arbeit konzentrierte sich auf die mediale Darstellung von Migräneattacken (Raffaelli et al., 2021B). Vorangegangene Studien konnten zeigen, dass die am häufigsten dargestellte Migränesituation die einer "Business-Frau" ist, die sich beide Schläfen hält (Gvantseladze et al., 2020). Die Autor:innen wiesen darauf hin, dass eine solche Darstellung zu einer Verzerrung der gesellschaftlichen Wahrnehmung von Migräneattacken führen und die Stigmatisierung fördern kann (Gvantseladze et al., 2020).

In unserer Untersuchung wurden zehn verschiedene Bilder, die im Internet unter dem Schlagwort "Migräne" abrufbar sind, sowohl Patient:innen mit Migräne als auch Mitarbeitenden aus dem Gesundheitswesen gezeigt. Sie sollten bewerten, ob diese Bilder realistischen Darstellungen einer Migräneattacke oder ihrer eigenen Migräne entsprechen. Die Ergebnisse zeigten, dass diese Bilder weder als sehr realistisch noch besonders repräsentativ wahrgenommen wurden. Besonders bedenklich ist, dass diese Bilder ausgewählt wurden, weil sie zu den am häufigsten heruntergeladenen Bildern im Zusammenhang mit Migräne gehören. Daher weisen diese Ergebnisse auf ein erhebliches Verbesserungspotenzial bei der Darstellung von Migräne hin.

Interessanterweise wurden Bilder mit älteren männlichen Darstellern als realistischer wahrgenommen, obwohl dies nicht der epidemiologischen Verteilung von Migräne entspricht (Allais et al., 2020). Dies könnte zum einen darauf hinweisen, dass gerade Frauen mit Migräne stereotyp und unrealistisch dargestellt werden. Andererseits könnte dies auch darauf hindeuten, dass der Schmerz bei den in den Bildern gezeigten jungen, hübschen Frauen nicht ernst genommen wird. Tatsächlich berichten vor allem Frauen über eine mangelnde Anerkennung ihrer Migräne als echte neurologische Erkrankung und über die Schwierigkeiten, mit denen sie im Alltag konfrontiert werden, um ernst genommen zu werden (Neumeier et al., 2021). In beiden Fällen erscheint eine Überarbeitung der klassischen Migränebilder in Richtung einer inklusiveren und vielfältigeren Darstellung erstrebenswert.

Die Befragung von Patient:innen in Berlin wurde kürzlich in einer Patient:innenkohorte aus Rostock wiederholt (Hamann et al., 2023). Auch in dieser neuen Kohorte ergaben sich ähnliche Ergebnisse, wobei die Bewertung der Bilder in Rostock insgesamt realistischer ausfiel als in

Berlin. Dies kann möglicherweise auf den niedrigeren Bildungsstand der Rostocker Kohorte zurückzuführen sein (Hamann et al., 2023). Es ist bekannt, dass Menschen mit niedrigerem Bildungsgrad stärker von Medieninhalten beeinflusst werden (Fareed et al., 2021; Jilani et al., 2018; McKay et al., 2006). Eine stärkere Beeinflussung durch die üblichen Migränebilder in den Medien könnte daher zu ihrer als realistischer wahrgenommenen Beurteilung beigetragen haben. Interessanterweise zeigten sich in der gesamten Rostocker Kohorte keine signifikanten Unterschiede zwischen Bildern mit weiblichen und männlichen Darsteller:innen. Lediglich männliche Patienten gaben an, dass die Bilder mit männlichen Darstellern repräsentativer für ihre eigene Migräne waren. Im Gegensatz dazu fühlten sich weibliche Migränepatientinnen gleichermaßen von Bildern mit weiblichen und männlichen Darstellern repräsentiert (Hamann et al., 2023). Dies könnte auf eine höhere Empathiefähigkeit von weiblichen Patientinnen hindeuten oder ihre allgemeine Gewöhnung an Medieninhalte, die nicht auf sie zugeschnitten sind.

Die Erkenntnisse aus beiden Studien verdeutlichen den Bedarf an einer realistischen Darstellung von Migräne. Realistische Bilder könnten beispielsweise in Aufklärungskampagnen verwendet werden, um auf die Vielfältigkeit der Migränesymptome hinzuweisen und somit zur Verringerung des Stigmas beizutragen. Es wäre wünschenswert, Bilder zu verwenden, die diversere Patient:innen darstellen und eine breitere Palette von Migränesymptomen sowie die allgemeine Beeinträchtigung durch die Erkrankung berücksichtigen.

4. Zusammenfassung

Migräne tritt bei Frauen zwei- bis dreimal häufiger auf als bei Männern. Zudem sind Migräneattacken bei Frauen länger und schwerer, was insgesamt zu einer stärkeren Beeinträchtigung im Vergleich zu Männern führt. Die Ursachen für solche geschlechtsabhängigen Unterschiede sind vielschichtig und betreffen sowohl psychosoziale als auch biologische Aspekte. Ein tiefergehendes Verständnis geschlechtsabhängiger Mechanismen ist notwendig, um die Versorgung von Migränepatient:innen zu verbessern, spezifische therapeutische Ansätze zu entwickeln und die Lebensqualität der Betroffenen zu steigern.

Die in dieser Habilitationsschrift vorgestellten Studien tragen dazu bei, wichtige geschlechtsspezifische Aspekte in der Pathophysiologie, Diagnostik, Behandlung und sozialer Wahrnehmung von Migräne zu charakterisieren.

Ein zentrales Neuropeptid in der Migränepathophysiologie ist Calcitonin Gene-Related Peptid (CGRP). In einer prospektiven Kohortenstudie konnten wir erstmalig unterschiedliche CGRP-Konzentrationen bei Frauen mit Migräne und gesunden Kontrollprobandinnen, basierend auf ihren Sexualhormonprofilen, nachweisen. Höhere perimenstruelle CGRP-Konzentrationen bei Migränepatientinnen im Vergleich zu gesunden Frauen weisen auf eine verstärkte perimenstruelle Freisetzung von CGRP hin. Diese Ergebnisse bieten somit eine mögliche pathophysiologische Erklärung für die erhöhte Anfälligkeit für Migräneattacken in dieser Zyklusphase.

CGRP spielt auch in der Pathophysiologie der Endometriose, einer häufigen Komorbidität bei Frauen mit Migräne, eine bedeutende Rolle. In einer weiteren Kohortenstudie konnten wir die Hypothese einer hormonbedingten Fehlregulation des CGRP-Signalweges bei komorbiden Patientinnen bestätigen. Obwohl keine signifikanten Unterschiede in den absoluten CGRP-Spiegeln festgestellt wurden, zeigte sich, dass Frauen mit beiden Erkrankungen während der Menstruation einen Anstieg der CGRP-Konzentrationen aufwiesen, was auf eine besondere pathophysiologische Relevanz von CGRP bei komorbiden Patientinnen hinweist.

Ein weiterer geschlechtsspezifischer Aspekt in der Behandlung von Frauen mit Migräne betrifft die Verwendung von hormonhaltigen Kontrazeptiva, die den Migräneverlauf beeinflussen können. Eine deutschlandweite Umfrage unter Gynäkolog:innen ergab, dass diese nahezu immer das Vorhandensein von Migräne vor einer Verschreibung von Kontrazeptiva berücksichtigen. Die Zurückhaltung bei der Verschreibung von östrogenhaltigen Kontrazeptiva bei Migräne mit Aura entspricht den gültigen Leitlinien. Angesichts der Tatsache, dass Gynäkolog:innen ebenfalls therapeutische Entscheidungen für Patientinnen mit Migräne

treffen, betont diese Studie die Notwendigkeit einer guten Zusammenarbeit zwischen beiden Disziplinen.
Veränderungen des hormonellen Zustandes während der Schwangerschaft können zu Änderungen von Kopfschmerzeigenschaften führen. Unsere klinische Datenerhebung zeigte, dass Migräne die häufigste Ursache für kopfschmerzbedingte Vorstellungen in der Rettungsstelle der Charité während der Schwangerschaft ist. Dennoch wurde bei über 40% der Patientinnen eine sekundäre Kopfschmerzursache diagnostiziert. Diese Ergebnisse unterstreichen die Notwendigkeit einer gründlichen Anamnese, klinischen und neurologischen Untersuchung sowie gegebenenfalls weiterer Diagnostik, um potenziell lebensbedrohliche Kopfschmerzursachen nicht zu übersehen.
Abschließend konzentrierte sich eine prospektive Befragung auf die Wahrnehmung von stereotypen Migränebildern in den Medien. Die Ergebnisse zeigen, dass solche Bilder von Patient:innen mit Migräne und Mitarbeitenden im Gesundheitswesen als nur mäßig realistisch wahrgenommen werden. Insbesondere Bilder mit jungen Frauen wurden als am wenigsten realistisch empfunden, was die dringende Notwendigkeit einer Überarbeitung und Verbesserung solcher Darstellungen verdeutlicht.

Die vorgestellten Arbeiten tragen neue Erkenntnisse zu zahlreichen geschlechtsabhängigen Unterschieden in der Pathophysiologie, Diagnostik und gesellschaftlichen Wahrnehmung von Migräne bei. Sexualhormone sind entscheidend an der Migränepathophysiologie beteiligt, und künftige Arbeiten werden sich darauf konzentrieren, hormonabhängige entzündliche, vaskuläre und neuronale Prozesse der Migränepathophysiologie genauer zu charakterisieren. Die Berücksichtigung geschlechtsspezifischer Aspekte im biopsychosozialen Modell der Migräne ist von herausragender Bedeutung, um dieses komplexe Krankheitsbild gründlicher zu verstehen und eine optimale Versorgung von Patient:innen aller Geschlechter in jeder Lebensphase zu gewährleisten.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass
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Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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