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Role of genetics and lifestyle in dysmenorrhea

El rol de la genética y estilo de vida en dismenorrea

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Abstract

The aim of this systematic review was to identify the current state of knowledge on the association between susceptibility genes associated with this disorder and the lifestyle of patients (including diet, habits and stress levels). It also highlighted the advances made in this field of study, from a constructive point of view, and pointed out the perspectives for research into this disorder. Dysmenorrhoea, as a primary and secondary disorder, is one of the main causes of partial or total disability in the life cycle of women, both in reproductive age and later. It is recognised as a painful and disabling disorder which, depending on the cultural context, may or may not be cured by medical care, physiotherapy and the use of pain-relieving drugs, from an unknown aetiology (primary dysmenorrhoea) or concomitantly to surgical intervention (secondary dysmenorrhoea). Lifestyle, habits and diet have been identified as related to the intensity of pain and the disability it causes (active or passive use of cigarettes, consumption of alcohol, etc.), and genes related to the interpretation of pain generated by the patient from the morphology of the hypothalamus and the associative function of pain (BNDF Val66Met polymorphism) have been identified, as well as alterations in cytokines (in primary dysmenorrhoea), prostaglandins and an influence of the Cyp1A1 gene (in passive smokers). The study perspective is usually non-integrative and limited to the site studied, as well as to professional, laboratory, imaging (gynaecological and genetic) and/or molecular resources, which can only in a few cases be of an integral approach. Limitations are compounded by the fact that not all the populations studied are usually educated about menstruation, which also limits compatibility and comparability among studies.

Resumen

El objetivo de esta revisión sistemática fue identificar el estado actual de los conocimientos sobre la asociación entre los genes de susceptibilidad asociados a este trastorno y el estilo de vida de los pacientes (incluyendo dieta, hábitos y niveles de estrés). También se destacaron los avances realizados en este campo de estudio, desde un punto de vista constructivo y se señalaron las perspectivas para la investigación de este trastorno. La dismenorrea como trastorno primario y secundario, es una de las principales causas de incapacidad parcial o total en el ciclo vital de la mujer, tanto en edad reproductiva como posteriormente. Se reconoce como un trastorno doloroso e incapacitante que, dependiendo del contexto cultural, puede curarse o no con atención médica, fisioterapia y el uso de fármacos analgésicos, de etiología desconocida (dismenorrea primaria) o concomitante a una intervención quirúrgica (dismenorrea secundaria). Se ha identificado que el estilo de vida, los hábitos y la dieta están relacionados con la intensidad del dolor y la discapacidad que provoca (uso activo o pasivo de cigarrillos, consumo de alcohol, etc.), y se han identificado genes relacionados con la interpretación del dolor generado por el paciente a partir de la morfología del hipotálamo y la función asociativa del dolor (polimorfismo BNDF Val66Met), así como alteraciones en citoquinas (en dismenorrea primaria), prostaglandinas y una influencia del gen Cyp1A1 (en fumadores pasivos). La perspectiva del estudio suele ser no integradora y limitada al lugar estudiado, así como a los recursos profesionales, de laboratorio, de imagen (ginecológicos y genéticos) y/o moleculares, que sólo en unos pocos casos pueden tener un enfoque integral. A las limitaciones se suma el hecho de que no todas las poblaciones estudiadas suelen estar educadas sobre la menstruación, lo que también limita la compatibilidad y comparabilidad entre estudios.

Introduction

Menstruation is a normal physiological process, which occurs approximately every month in women and can generate some level of discomfort and pain, without being disabling or affecting their daily activities [1]. In contrast, painful dysmenorrhea, or painful menstruation, is a common reason for gynecological consultation among adolescents and women, affecting about 90% of reproductive age [2 - 4].

Despite its high prevalence rate and effect on daily life, 76.1% of women still believe that dysmenorrhea is a natural part of the menstrual cycle and only 14.8%, consider medical treatment necessary [5]. In definition, dysmenorrhea as a debilitating syndrome [6], is known as the presence of painful cramping of uterine origin occurring during menstruation and represents one of the most common causes of pelvic pain and menstrual disorder [7]. It usually occurs during the first 1 to 3 years after menarche and is accompanied by sweating, lack of appetite, headache, distractibility, nausea, vomiting, and dizziness [8].

It is not a recognized gynecological disorder [9] and is associated with decreased self-rated general health [10], in combination with depressive [11, 12] and anxious symptoms [13,14]. Dysmenorrhea as a condition of public health concern that can be classified into two distinct types: primary and secondary. Primary dysmenorrhea (PDM) [15] is defined as painful menses in women with normal pelvic anatomy, usually beginning during adolescence [16-18]. It is attributed to excessive pathological uterine contractions, without any other changes in the lesser pelvic area [19] and is recognized as being caused by increased or unbalanced endometrial prostanoid production during menstruation [20]. Secondary dysmenorrhea, is recognized as menstrual pain associated with an underlying pathology [21, 22], and is associated with a prevalence of acquired changes, as well as anatomical and functional abnormalities of the generative organs [6, 23].

Onset can be years after menarche [18], but can also occur as a new symptom in a woman in her 40s or 50s after the onset of an underlying condition [18,24]. It can be caused by a dozen conditions including endometriosis, pelvic inflammatory disease, intrauterine devices, irregular cycles, infertility, ovarian cysts, adenomyosis, fibroids, polyps, intrauterine adhesions or cervical stenosis [25].

The burden of dysmenorrhea is greater than any other gynecologic ailment [26], being the leading cause of morbidity in women of reproductive age, regardless of age, nationality, and economic status [27-31]. The effects extend beyond individuals resulting annually in a significant loss of productivity in society [32,33]. According to the World Health Organization (WHO) , it is the most important cause of chronic pelvic pain [21], affecting between 1.7% and 97% of women [21]. In the U.S., it is responsible for the loss of 600 million work hours and two million dollars each year [28]. It appears to be associated, to a lesser extent with late menarche [12, 34-36] and to a greater extent with early menarche [12, 27, 37-39], as well as with menstrual cycle irregularity [12,40], prolonged [38] and heavier than normal menstrual flow [41], low weight and body mass index [42], inadequate physical exercise [21, 43], genetic predisposition [44], active and passive smoking [41,45-50], alcohol consumption [49, 50], low socioeconomic status, dietary habits [35, 51,52], stress and mental illness [42, 48]. According to authors such as Barcikowska et al. [53], although there are various reports about the factors that may predispose to its occurrence, the results are often contradictory [41,54, 55].

With regard to the underlying causes of dysmenorrhoea, various studies point to a complexity of biochemical reactions between the endocrine, vascular and immune systems, as well as the role of prostaglandins in its pathological mechanism [56]; they increase tone, uterine contractions and cause pain [20]. The excessive release of prostaglandins also explains the coexistence of other symptoms such as nausea and headache [57-59], and in particular their hyperproduction (at the uterine level) is associated with the prostaglandins PGF2 and PGF2a [60]. Unfortunately, cytokines and other pro-inflammatory factors (in PDM) have been less studied [31].

From the structural perspective of the central nervous system, recurrent menstrual pain is associated with central sensitisation, which in turn is associated with structural and functional changes [19,60]. In recent years, studies have developed with brain-derived neurotrophic factor (BDNF), associated with stress regulation [61], with higher expression in the hippocampus [15,62]. According to Duman & Monteggia [63], stress decreases BDNF expression through gamma-aminobutyric acid (GABA)-inhibitory interneurons in limbic structures particularly in the hippocampus as well as that anxiety levels in subjects with the Met/Met

polymorphism (MMP) exceed those of subjects carrying the Val polymorphism (MMP) [14].

Lee et al. [14] reported that genetic factors, such as this polymorphism [64] and OPRM1 A118G55, may influence the genotype-specific process, functional connectivity dynamics of the DPMS (descending pain modulatory system) in female with PDM, and Hirata et al. [65] reported that several genome-wide association studies (GWAS) have successfully identified genomic loci associated with age at menarche [66,67], menopause, dysmenorrhoea [15,68], endometriosis [69-72] and breast size [65,73].

The aim of this systematic review is to characterise a possible association between susceptibility genes in this painful disorder and lifestyle, including diet, general habits and stress levels, and to establish their direct incidence in this condition. It will also identify methodological breakthroughs and/or conceptual gaps in order to clarify the current state of knowledge about the causes and factors involved in dysmenorrhoea, as well as the limitations of the studies developed so far and the perspectives of this field of research.

Methods

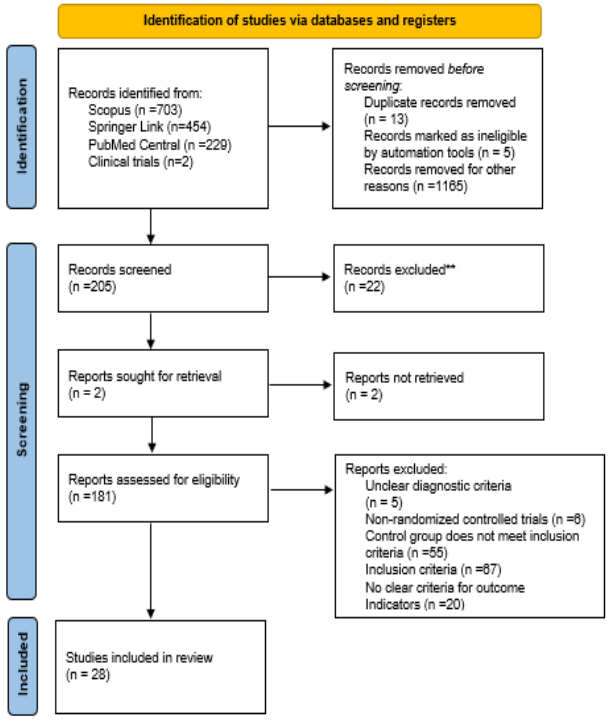
This review was conducted following the recommendations of Cochrane et al. [74] and PRISMA [75]. The NCBI and Science Direct databases were searched between the months of January and October 2022 using the search terms "Dysmenorrhoea" AND "Genes"; "Dysmenorrhoea" AND "lifestyle" in different combinations in Spanish and English. Effective information was obtained from the year 2007 to 2022, with a total of 28 articles selected for the headings lifestyle and multidisciplinary studies with occupational, molecular and imaging (including RMN) components (see figure 1).

Results

Role of lifestyle in dysmenorrhea

Dysmenorrhoea as a painful disorder has been studied from the realities of the environments of interest to the researchers (isolated populations with little education or populations of university and/or health workers with academic training in their condition) and taking into account the demographic characteristics of the population, including the influence of their phenotype in harmful habits or that have been considered, in the literature, as influencing the onset, incidence or worsening of symptoms. In many cases, the studies are limited to the analysis of vocative questionnaires of the self-assessment survey type, as well as a few studies that can combine the gynaecological assessment by imaging and physical examinations, biochemical, molecular studies and, in specific cases, genetic imaging, analysis of the central nervous system.

Figure 1. Flowchart of study selection for systematic review



From this literature review and meta-analysis, it emerged that the studies associating lifestyle and the severity of dysmenorrhoea were usually limited in scope to various factors, including the patient's knowledge of menstruation, the cultural education of the population studied, the bleeding, pain and functional limitations caused by menstruation, as well as the environment and resources in which it can develop. In order to present the information analysed in a systematic way and thus facilitate its interpretation, the information collected has been classified under two subheadings. The first describes the methodology used in the different types of studies reviewed (from the allocation of the sample analysed

to the design of the questionnaires and their subsequent statistical analysis), and a second reports on the factors associated with lifestyle and their incidence on the severity of dysmenorrhoea, mostly associated with primary dysmenorrhoea, the stage chosen by most researchers, depending on the exclusion factors applied to the selected population.

Experimental methodology

The research methodology on this subject has tended to evolve towards the use of mixed questionnaires that include questions on the patient's lifestyle before, during and after the menstrual period, as well as their design with heterogeneous objectives, including causality and risk factors in dysmenorrhoea. They evaluate: the prevalence of dysmenorrhoea and the study of its impact on the quality of life of patients [17]; the relationship between lifestyle and primary dysmenorrhoea [20]; the determination of its frequency according to different definitions in female, in order to identify its associated factors [42]. Similarly, we seek to determine its prevalence and associated factors in particular age groups (Ethiopia - high school students, Muluneh et al. [76]; Spain- university students [1], describe their menstrual characteristics, lifestyle habits, as well as evaluate the impact of specific professions on the risk of the condition, as is the case of health care workers (nurses) considered to be at high risk, based on demographic information, attitudes about menstruation and their influencing factors [12].

These studies are generally mostly prevalent in Taiwan [12], Japan [65], Iran [20], Turkey [25], Italy [42], Spain [1], Poland [56] and Ethiopia [76]. They are usually conducted in one-month point sampling efforts [12, 17, 20, 42] and very few studies evaluate and compare cohorts in different years, or follow them up (e.g. in genetic imaging studies) [14]. The sample size is usually calculated based on the size of the population addressed and the power of the statistical test to be performed [12], or from the total population found in the randomly evaluated institution, course or subsection [76].

In terms of effective sample size (n), groups smaller than 70 individuals (59 with primary dysmenorrhea and 68 as control, [14]) or larger than 200 (250 individuals, [20]; 258 individuals [1]; 408 individuals [42]; 420 individuals; nurses [12], 539 individuals [76]; 623 individuals [17], with prevalence by larger sample sizes. Likewise, it has been differentiated among educational levels, including middle or high schools [17, 76], universities such as Dumlupinar University [17], Sari University of Medical Sciences [20], specific Institutes or faculties in Universities or hospitals (Department of Pediatrics, Gynecology and Obstetrics, University Polyclinic Hospital of Modena [42]; Faculty of Nursing of Ciudad Real, University of Castilla-La-Mancha [1], and medical or care staff (nurses) [12].

The cohorts analyzed are usually delimited to female as their target population (aged at least 18 years [12], aged 18-25 years [20]) and the studies are generally of pre-set order, based on self-assessed questionnaires with a variable number of questions as well as inclusion or not of subsections, where participants are informed that their completion is optional [25, 76], with variable duration between 10 to 40 minutes per session (10-15min [1]; 35-40 min [17]). Response sessions are generally single [17] or split, within the same questionnaire and conducted in the presence of the principal investigator [17] or with supervision of school staff (e.g., volunteer teachers [76]. Only in some cases, such as Muluneh et al. [76], theoretical sessions are conducted about the base concepts, which are to be worked with the participants, in order to give clarity to the questionnaire (e.g. concept of dysmenorrhea, physical activity, non-academic homework, sugar consumption); which are usually based on indices such as the HRQoL (from High Rate Quality of Life [17]) or are pre-established, by the same authors such as Muluneh et al. [76] and/or by referenced authors, such as Chiou et al. [12], Chiou & Wang [77], Mahmoodi et al. [78], Potur et al. [14], Aktaş [2], Habibi et al. [79] and Tomás-Rodríguez et al. [80]. Likewise, they are usually based on international standards, such as the SF-36 (The Short Form-36) or the IPAQ (International Physical Activity Questionnaire [20]).

Scales for the assessment of emotional states and physiological affect are usually instrumented from standard scales such as the scales: *i*) VAS (Visual Analogue Scale) [1,17,42], McGill (McGill pain index

or MPQ) [15,20] or NPRS (Numeric Pain Rating Scale [20]), to stratify menstrual pain (including analgesic effect and interference with social or academic activities [42]; *ii*) MSS (Multidimensional scoring system) [17], *iii*) DKS (Dysmenorrhoea Knowledge Scale) [12] and *iv*) MAS (Menstrual Attitude Scale) [12]. In some cases, patients who reported pain were subjected to additional questionnaires, seeking to establish the characteristics of the pain and its influence on their ability to perform their daily activities [1] and in others, the presence of chronic diseases such as diabetes, high blood pressure, underlying heart disease or infectious diseases, as well as not having self-reported symptoms such as vaginal burning, itching or abnormal discharge, and not having a history of gynecological surgeries were considered as exclusion factors for participants [20].

Some very specific studies that seek to assess the influence of dysmenorrhea pain on brain function and plasticity [14] are accompanied by imaging (MRI) to investigate global, regional, modular structure metrics of resting-state brain functional networks (in female with PDM) [14] and generally, they usually examine and diagnose patients using the same clinical gynecological management, as a control and baseline [14]. In these types of studies, exclusion criteria are more restrictive, such as: *i*) the use of oral contraceptives, hormonal supplements, Chinese herbal medicines, or any centrally acting medications (e.g., opioids, antiepileptics) in the 6 months prior to the study; *ii*) pathological disease of the pituitary gland; *iii*) organic pelvic disease; *iv*) any psychiatric or neurological disorder (e.g., premenstrual dysphoric disorder); *v*) any head injury with loss of consciousness or brain surgery; *vi*) immediate plans for pregnancy or a positive pregnancy test; *vii*) history of childbirth; and *viii*) having a metal implant/pacemaker, claustrophobia, or any contraindications regarding MRI [14]. Multidisciplinary assessment of psychological status throughout the menstrual cycle, including the Spielberger State Trait Anxiety Inventory, Beck Anxiety and Depressive Scales, and pain catastrophization scales during the menstrual (MENS) and postovulatory (POV) phases. The McGill pain questionnaire was also applied in order to assess their respective general and current (MENS and POV) experiences of menstrual pain and serum biochemical, gonadal serum hormone measurements were performed during the two phases examined, seeking to establish a correlation between all the factors examined [14].

Studies such as that of Hirata et al. [65], which evaluate traits related to primary and secondary sexual characteristics with a high impact on dysmenorrhea, during puberty and daily life in adulthood, address methodologies such as genome wide studies (GWAS, eQTL signals), related QTLs identified with phenotypic variables, significant associations for breast size, pain severity and menstrual fever [65]. In these cases, data is collected through specific databases or web pages (voluntary participation of users of the MTI women's health information website and applications) (http://www.mti.co.jp/eng/).

Population samples larger than 10000 individuals are usually included (11379) [14] and the study is conducted by constructing gynaecologically related phenotypes for the analysis of breast size and pain severity [65].

In general terms, statistical analysis of studies is usually performed in regression terms for categorical [20,42], linear [65], bivariate [76] and multivariate [12, 65]. Sociodemographic variables [17,41,76], such as personal, educational, physical, gynecological [1, 20,41], nutritional [17,20,42,76] and self-care factors [20], are included. In other cases, factors are divided into demographic [12], lifestyle and behavioral (including physical activity) [41,42,76], sugar consumption [17,42,76], coffee consumption [42,76], tea [76] and alcohol [42,76], cigarette use [42,76], chewing habits [76], salt consumption [17,42], fish intake [42], reproductive issues (age at menarche), [12] and menstrual patterns [1,76].

Muluneh et al. [76] argue that some experimental approaches, consider it necessary to assess the presence of a sentimental relationship or marital status [42], the use of oral contraceptives, gynecological pathologies and surgeries and associated risk factors [1,42]. From the ethical and regulatory point of view, these studies usually include informed consents [12,42], guaranteeing the anonymity of the participants [1,12,42] or confidentiality [76] and others even report, as an incidence, the obligatory nature presented at the time of their execution, contradicting precisely this premise [76].

Another valid approach to researching this disorder is presented in the literature, namely systematic reviews. In this group of research, Latthe & Champaneira [18] sought to establish the effects of pharmacological treatments on primary dysmenorrhea, including published studies of the Randomized Controlled Trial

(RCT) type and systematic reviews in English language, single-blinded, with 20 or more individuals (10 in each arm) and with a follow-up of more than 80%. Likewise, the authors valued including studies in women with primary dysmenorrhea or where a subgroup analysis was performed in women with primary dysmenorrhea [18]. Similarly, Petraglia et al. [31], conducted a systematic study in function of establishing how pain associated with dysmenorrhea is caused by prostaglandin hypersecretion and an increase in uterine contractility. These authors found that in primary dysmenorrhea, it is quite frequent in female and remains with good prognosis, although it is associated with low quality of life, in contrast to the secondary form of dysmenorrhea, where it is associated with endometriosis and adenomyosis, and where it may represent a key symptom of these conditions. Like the previous authors, it is noted that treatment alternatives include nonsteroidal anti-inflammatory drugs (NSAIDs), alone or combined with oral contraceptives or progestogens [31].

Habits, lifestyle and their influence on the disorder

In 2010, Unsal et al. [17] conducted a study to assess the prevalence of dysmenorrhoea and its impact on health-related quality of life (HRQoL) in a group of female undergraduate students at Dumlupinar University School of Health in western Turkey. Eight domains were assessed using a self-administered questionnaire. Physical functioning, social functioning, role limitations due to emotional problems (role-emotional), role limitations due to physical problems (role-physical), bodily pain, vitality, mental health and general health perception (Turkish version of the SF-36) were included. As a result, the prevalence of dysmenorrhoea was found to be 72.7% and was significantly higher in coffee drinkers, women with a long duration of menstrual bleeding (± 7 days) and those with a positive family history of dysmenorrhoea compared to the others (P<0.05). No statistically significant differences were found between the groups with and without dysmenorrhoea [17].

According to multivariate analysis, coffee consumption (OR 2.084), duration of menstrual bleeding ±7 days (OR 1.590) and positive family history of dysmenorrhea (OR 3.043), were significant risk factors for the disorder. For the domains assessed, except for social functioning, emotional role and mental health, the SF-36 points received in others were higher in women with dysmenorrhea (P <0.05), thus interpreted as configuring a common health problem that has negative effects on health-related quality of life (HRQoL) among female university students. Statistically, there were no differences between the habits and medical characteristics of female students with dysmenorrhea, with the exception of coffee consumption (P <0.001), the mean age at menarche was 13.38 ± 1.20, with a range of 10 to 18 and about 80% reported experiencing regular menstruation (79.8%) [17]. The mean menstrual cycle length of the female students in the study group was 28.73 ± 7.25 days (minimum 10, maximum 90) and the mean duration of menstrual bleeding was 5.73 ± 1.34 days, with a range between 3 and 10. Only 8.3% of the students reported using medications that regulate menstruation and approximately 50% of the students (47.4%) reported having a family history of dysmenorrhea, as well as no differences were revealed between menstrual characteristics and dysmenorrhea status, except for duration of menstrual bleeding and family history [17].

In contrast, Grandi et al. [42], conducted a study that aimed to determine the frequency of dysmenorrhea, identified by different definitions, in a population of female and to investigate factors associated with this complaint. 84.1% of the women reported menstrual pain, 43.1% reported that the pain occurred during all periods and 41% reported that it occurred during some periods. Women with menstrual pain had earlier menarche (P = 0.0002) and longer menstrual flow (P = 0.006), and the group was characterized by a higher prevalence of smokers (P = 0.031) and a lower prevalence of hormonal contraceptive users (P= 0.015). Pain intensity correlated (r= 0.302, P= 0.0001) positively with menstrual flow length (HR = 0.336), history of abortion (HR=3.640) and gynecologic pathologies (HR= 0.948), as well as negatively with age at menarche (HR=-0.225), hormonal contraceptive use (HR=-0.787) and history of gynecologic surgery (HR = -2.115) [42].

Considering the parameters of menstrual pain, need for medication and inability to function normally (absenteeism from the study or social activities) alone or together, the prevalence of dysmenorrhoea was 84.1% when considering menstrual pain alone, 55.2% when considering the association between menstrual pain and need for medication; 31.9% when considering the association between menstrual pain and absenteeism, and 25.3% when considering the association between menstrual pain, need for

medication and absenteeism (*P*=0.0001). Pain intensity by VAS (Visual Analog Scale), was independently (r =0.302, *P*=0.0001) and directly related to menstrual flow length (HR = 0.336), history of miscarriage (HR = 3, 640) and gynecologic pathologies (HR = 0.948) and inversely related to age at menarche (HR=-0.225), use of hormonal contraceptives (HR=-0.787) and history of gynecologic surgery (HR=-2.115). Stratification according to VAS score did not coincide with the figures representing the need for medication and absenteeism. In fact, only 58% of those with severe menstrual pain had a disorder that required concomitant treatment and affected quality of life to the point of inducing absenteeism [42]. Therefore, the authors consider the likelihood of having more severe dysmenorrhea to be directly related to, but not coincident with, pain intensity as measured by a visual analog scale, although at least one in four women experience distressing menstrual pain characterized by the need for medication and absenteeism from study or social activities [42].

In 2018, Muluneh et al. [76] conducted a study on the school-aged population in Ethiopia, given the scarcity of demographic information, and sought to determine the prevalence and associated factors of dysmenorrhoea among high school students. Methodologically, they relied on an institution-based cross-sectional survey of middle and high school students in the city of Debremarkos. As a result, the prevalence of dysmenorrhea was 69.3%, the adjusted odds ratio with respect to age was AOR (95% CI) = 1.38 (1.15,1.65), family history of dysmenorrhea, AOR (95% CI) = 9.79 (4.99, 19.20); physical activity, AOR (95% CI) = 0.39 (0.13, 0.82), sugar intake, AOR (95% CI) = 2. 94 (1.54, 5.61); early menarche, AOR (95% CI) = 4.10 (1.21, 13.09); late menarche, AOR (95% CI) = 0.50 (0.27, 0.91); heavy menstrual periods AOR (95% CI) = 2.91 (1. 59, 5.35) and sexual intercourse AOR (95%CI)=0.24 (0.10,0.55,), presented a statistically significant association with the occurrence of this disorder [76]. It was found that more than half (54.2%) of the students surveyed did not do any physical activity, although 70% of the students were involved in simple non-academic tasks at home and none of them had smoked.

Likewise, it was determined that the mean age at menarche was 13.16 ± 1.76 years with a range of 9-17 years and that 7.6% of the individuals had a history of sexual intercourse, of which 48.7%, had a history of contraceptive use. Only 1 (2.6%) had a history of pregnancy and 75% of the total respondents had regular menstrual cycles, with a normal duration (21-35 days), in 94.0% of the cases. Of the total 511 respondents, 354 (69.3%) had dysmenorrhea and for 168 (47.5%) and 144 (40.7%) the pain started 1-2 days before and just after the onset of menstruation respectively, as well as 76.8% of the total experienced dysmenorrhea during each menstrual period [76]. In conclusion, age, positive family history of dysmenorrhea, physical activity, excessive sugar intake, early menarche, late menarche, sexual intercourse and heavy menstrual periods had a statistically significant association with the occurrence of dysmenorrhea in the evaluated population [76].

In a cross-sectional study conducted by Fernández-Martínez et al. [1] in female from the nursing faculty of Ciudad Real at the University of Castilla - la Mancha, the aim was to determine the prevalence of primary dysmenorrhea and to describe their menstrual characteristics, lifestyle habits and associated risk factors; this included sociodemographic characteristics, lifestyle habits, personal and gynecologic history and pain severity, using the visual analog scale. As a result, the prevalence of dysmenorrhea was 74.8% (n = 193) with a mean pain intensity of 6.88 (±1.71); 38.3% of the students described their menstrual pain as severe and 58% as moderate. In addition to menstrual pain, the most frequently reported symptoms were edema (92.7%), irritability (81.9%) and fatigue (79.3%) [1]. Bivariate analysis showed statistically significant differences between students with and without dysmenorrhea: a higher proportion of women with dysmenorrhea had longer duration of menstrual flow (p = .003), longer duration of menstrual cycle (p= .046), when they were not using the oral contraceptive pill (p = .026) and had a family history of dysmenorrhea (p = .001) [1].

Binary logistic regression analysis (backward stepwise) showed that the risk factors: drinking cola soft drinks, duration of menstrual flow, eating meat and having a first-degree relative with dysmenorrhoea had an influence on the disorder [1]. About 80% of students with dysmenorrhoea had menstrual bleeding lasting more than five days, with a menstrual cycle frequency of more than 29 days (79.9%) [1]. In addition, of the sample with dysmenorrhoea, 75.6% of students reported that their daily activities were affected, and a total of 91.2% of students with dysmenorrhoea were taking analgesics, of whom 77.7% were self-medicating, mainly when they reported worsening symptoms [1]. In the group with dysmenorrhoea, 26% drank alcohol, compared to

32.31% in the group without dysmenorrhoea. Regarding smoking, only 15% of the group with dysmenorrhoea smoked, compared to 23.08% of the group without dysmenorrhoea. Among the factors that were statistically significant, there was a difference in the consumption of tea, cola, simple sugars, meat and fruit three times a day and cooking food with olive oil [1].

According to their findings, Fernández-Martínez et al. [1] indicate that dysmenorrhea affects a large part of the Spanish university population and is configured as a problem that affects the daily life of female students. Likewise, they point out that there are known non-modifiable risk factors in the literature that increase the likelihood of suffering from dysmenorrhoea, such as having a first-degree relative who suffers from the problem. However, in terms of lifestyle and eating habits, and based on their previous findings, they state that further studies are needed to provide or confirm recommendations on the most advisable diets or lifestyle habits to reduce the risk of suffering from dysmenorrhoea [1].

In 2016, Abadi et al. [20] conducted a study to examine the relationship between lifestyle and primary dysmenorrhea in students of Sari University of Medical Sciences to facilitate lifestyle interventions among female. From the scores obtained on the lifestyle questionnaire, significant differences were observed between the groups with and without dysmenorrhea in terms of eating behavior (p = 0.008), physical activity (p = 0.011), stress (p = 0.041), and social relationships (p = 0.000). No differences were observed in terms of self-care (p= 0.115) vs. smoking, and drinking vs. drug use (p = .355). According to logistic regression analysis, age (OR = 1.208, p = 0.014), physical activity (OR = 1.008, p = 0.040) and social relationship (OR = 0.952, p = 0.002), were different in the two groups, in terms of age (p = 0.001) and degree of schooling (p = 0.011), but not in terms of BMI (p = 0.296), age at menarche (P = 0.0374), duration of menstruation (P = 0.54), menstrual cycle (P = 0.54), diet (P = 0.233), socioeconomic status (P = 0.346), grouped as eating behavior, self-care and stress [20].

The results showed that for each unit increase in the social relationship score, the odds of experiencing dysmenorrhoea decreased by 0.05. In other words, according to the authors, people with better social relationships were less likely to have dysmenorrhoea. In addition, a one-unit increase in physical activity score reduced the odds of experiencing dysmenorrhoea by 0.01; therefore, more physically active women are less likely to experience dysmenorrhoea. Similarly, the odds of experiencing dysmenorrhoea were found to decrease by 0.18 with age; therefore, women are less likely to experience this condition as they get older [20]. This research showed that a good lifestyle can reduce the severity of dysmenorrhoea, with appropriate dietary behaviours, regular physical activity, self-care, good social relationships and reduced stress levels. Similarly, given the negative impact of dysmenorrhoea on quality of life, it is recommended that measures should be taken to increase awareness of dysmenorrhoea and appropriate lifestyles among the female population in order to reduce its occurrence and impact [20].

In terms of specific professions, Chiu et al. [12] developed a study to investigate the impact of dysmenorrhoea on nurses, based on three main objectives. Firstly, to describe the demographic and menstrual characteristics of dysmenorrhoea; secondly, to establish the knowledge of the disorder and menstrual attitudes of nurses in the hospital habitus; and thirdly, to identify significant differences between groups and to investigate factors affecting the disorder. As a result, they found that out of a total of 420 participating nurses, 297 (70.7%) had experienced dysmenorrhoea in the previous 6 months, and significant differences were found in: age (P<0.001), marital status (P<0.001), fertility status (P<0.001), age at menarche (P<0.05), and the ratio of three rotating shifts (P<0.05) between the group with and without dysmenorrhoea. Specifically, compared to the group without dysmenorrhoea, participants with dysmenorrhoea were significantly younger (t = -3.78, P <0.001), more often single (77.78%, χ^2 = 20.03, P <0.001), had no history of childbirth (83.16%, χ^2 = 19.38, P <0. 001), and more frequently had an age at menarche <12 years (15.49%, χ^2 = 4.70, P = 0.03), as well as a higher percentage of participants with dysmenorrhoea, working a three-shift rotation (91.25%, χ^2 = 6.06, P = 0.014) [12].

The MAS (Menstrual Attitude Scale) outcome analysis revealed significant differences between the groups with respect to the consideration of menstruation as a debilitating (P <0.001) or annoying event (P <0.05), anticipation and prediction of the onset of menstruation (P <0.01) and denial of any effect of menstruation. (P <0.001). Regarding attitudes toward menstruation, after standardizing, the

highest scoring dimension among the dysmenorrhea group was "considering menstruation as a debilitating event" and "considering menstruation as a natural event," in the non-dysmenorrhea group. The lowest scoring dimension in both groups was "denial of any effect of menstruation" [12]. In conclusion, the authors focus their results on supporting nursing managers to provide adequate assistance to high-risk groups, build a caring and friendly work environment, ensuring self-care at work, improving their comfort level, increasing their job satisfaction and performance [12].

In contrast, the study by Hirata et al. [65] considered that traits related to primary and secondary sexual characteristics have a significant impact on the daily lives of women in adolescence and adulthood, including dysmenorrhoea. To this end, they performed a GWAS analysis on 11,348 Japanese female subjects, assessing a total of 22 phenotypic variables related to gynaecology, as well as significant associations for breast size, pain severity (dysmenorrhoea) and menstrual fever. Analysis of breast size identified significant association signals in CCDC170-ESR1 (rs6557160; $P = 1.7 \times 10^{-16}$) and KCNU1-ZNF703 (rs146992477; $P = 6.2 \times 10^{-9}$), and found that one third of the known associations for European ancestry were also present in the sample analysed for Japan. The eQTL data found pointed to CCDC170 and ZNF703 as functional targets of these signals, and for menstrual cramps, a then-new association was identified in OPRM1 (rs17181171; $P = 2.0 \times 10^{-8}$), with large variants in multiple tissues. Similarly, a known dysmenorrhoea signal near the NGF gene replicated in their data (rs12030576; $P = 1.1 \times 10^{-19}$) and was associated with expression of RP4-663N10. 1, a putative lncRNA enhancer of the NGF gene, while a novel dysmenorrhoea signal at the IL1 locus (rs80111889; $P=1.9\times10^{-16}$) contained SNPs previously associated with endometriosis and was most significantly associated with IL1A expression [65].

The authors analysed dysmenorrhea pain severity using linear regression analysis and identified two strongly associated loci at chr1: 115.81-115.83 Mb (top SNP: rs12030576; $P = 1.13 \times 10^{-19}$) and chr^2: 113.48-113.58 Mb (top SNP: rs80111889; $P = 1.90 \times 10^{-16}$), which were also observed for secondary dysmenorrhea phenotypes [65]. For menorrhagia (impact on QoL), a nominally significant association signal was observed at chr6: 154.33-154.46 Mb (top SNP: rs17181171; $P = 1.98 \times 10^{-8}$), which overlaps more than half of the 5' end of opioid receptor mu 1 (OPRM1) and contains 65 high LOD SNPs [65]. Three of these variants are in highly conserved intronic regions (rs3778146, rs3778150, rs9479759), but only two SNPs overlap with any epigenomic mark, and both were DNAase hypersensitivity sites (DHS) with no evidence of promoter or enhancer activity [65]. This study supports the benefits of analysing diverse phenotypes in different samples from ethnic populations, and demonstrates the advantages of using eQTL datasets composed of different tissue types. Using GWAS/eQTL colocalisation analysis, it was possible to demonstrate that the top GWAS SNPs at each of the loci identified in this study were also associated with the expression of a protein-coding gene and/or lncRNA, and that further research is needed to elucidate how these eQTLs influence human phenotypic variation [65].

A contrasting, multifactorial cut-off study is addressed by Lee et al. [14]. These authors suggest that dysmenorrhoea in later life often coexists with many chronic functional pain disorders, and these show a large-scale association with changes in the distribution of brain regions, so it is unknown whether female with primary dysmenorrhoea (PDM) show such changes. Using resting-state functional magnetic resonance imaging (fMRI) and graph-theoretic network analysis, we investigated the global, regional and modular network metrics of functional brain networks in female with PDM. No significant differences were obtained between groups with respect to age (PDM: 23.1 ± 2.27 years of age, control: 23.7 ± 2.40 years of age, $P = 0.147$), age at menarche (PDM: 12.2 ± 1.19 years of age, control : 12.2 ± 1.11 years of age, $P = 0.811$), years of menstruation (PDM: 10.9 ± 2.53 years, control: 11.5 ± 2.69 years, $P = 0.194$) or mean duration of a menstrual cycle (PDM: 29.3 ± 1.41 days, control: 29.5 ± 1.19 days, $P = 0.525$). Although women with PDM reported significantly higher scores regarding: anxiety status, anxious traits, Beck Anxiety Inventory, Menstrual Phase Pain Catastrophizing Scale (MENS) and periovulatory phase (POV), in contrast to serum gonadal hormone measurements; no significant differences were found between groups for estradiol, progesterone and testosterone concentrations during both phases [14].

In this study, we also found no significant differences between groups for metrics of global and local network efficiency of information transfer between nodes, indicating that the population examined may retain the integrity of the connectivity properties of functional brain networks, despite the presence of

maladaptive neuroplasticity. This implies that it is plausible that the absence of significant changes in the intrinsic functional architecture of the brain allows female with PDM, to maintain normal psychosocial interactions, during the pain-free follicular phase [14].

Next, and to conclude this section, the results of the systematic reviews analysed are described. In the study conducted by Latthe & Champaneira [14], they sought to identify evidence on the effectiveness of pharmacological interventions for the treatment of primary dysmenorrhoea. They found that non-steroidal anti-inflammatory drugs (NSAIDs) reduced moderate to severe pain compared to placebo, but no significant differences were found between the NSAIDs evaluated, so it is unknown whether one has a superior effect to the others [14]. For simple analgesics, aspirin was found to reduce pain in women with primary dysmenorrhoea in the short term compared with placebo, although few trials were of good quality and it is not known whether paracetamol is more effective than placebo in reducing pain [14]. However, it was possible to determine that combined oral contraceptives may be more effective than placebo in reducing pain; however, few trials were of good quality and no significant differences were found in whether or not intrauterine progestins reduced dysmenorrhoea [14].

In the systematic review by Petraglia et al. [31] on the same topic, it was reported that heavy menstrual bleeding and duration of menstrual bleeding were often associated with dysmenorrhea. Childbearing was also identified as a highly influential factor for less dysmenorrhoea, and increasing age was also associated with less severe dysmenorrhoea. Early onset of pain was associated with more severe pain, and a family history of dysmenorrhoea was associated with a significantly higher prevalence. The authors also suggest that dysmenorrhoea may be part of a somatoform syndrome, as anxiety and depression are often associated [26]. In terms of treatment, it was noted that NSAIDs are usually the first-line treatment, and if they are not sufficient alone, they can be combined with oral contraceptives (OCs) (ACOG, 2005). The authors conclude that, given the wide availability of NSAIDs, the management of dysmenorrhoea is mainly a matter of self-care [7,81, 82].

Susceptibility-associated genes

From the search and systematic analysis of studies that have identified susceptibility genes for dysmenorrhoea, its severity and its correlation with lifestyle, a total of 11 effective studies are reported, from 2007 to the present, as follows 2 in 2007, 2016 and 2017, and 1 in 2013, 2014, 2018, 2020 and 2021. The findings in relation to the identified genes, SNPs and pro-inflammatory factors are listed below, based on the aim and scope of the study, from its results and perspectives.

CYP1A1 gene (CYP1A1MspI and CYP1A1HincII polymorphisms)

In 2007, Li et al. [83] investigated how the association between passive smoking exposure and primary dysmenorrhoea is modified by the expression of two susceptibility genes, CYP1A1MspI and CYP1A1HincII. They recruited 1645 female textile workers in Anqing, China, from 1997 to 2000. To conduct the study, they collected information on their (passive) smoking exposure and primary dysmenorrhoea status, and blood samples were collected for association analysis (multiple logistic regression) between the above-mentioned polymorphisms of the CYP1A1 gene and passive smoking exposure [83].

The theoretical-physiological basis of this association lies in the ability of an individual to convert the toxic metabolites of cigarette smoke into less harmful fractions to minimize adverse health effects. Specifically, the researchers address the detoxification of PAHs (polycyclic aromatic hydrocarbons), which in humans involves two phases: Phase I, in which inhaled hydrophobic PAHs are converted mainly through arylhydrocarbon hydroxylase activity into hydrophilic ones, and Phase II, in which reactive hydrophilic intermediates, such as epoxides, are covalently bound to macromolecules, especially DNA, and may be more toxic than the original form [84]. Aryl hydrocarbon hydroxylase is encoded by the cytochrome P450 1A1 (CYP1A1) gene, a well-studied phase I enzyme and is particularly relevant to the metabolism of chemicals in cigarette smoke. This gene is highly polymorphic in the population [47,85] and its polymorphisms have been associated with its encoded enzymatic activities [86]. Its variants also play an important role in estrogen metabolism and have been linked to women's health conditions, including breast cancer and the onset of menarche [87-89].

The study by Li et al. [89] found some interesting

results; it significantly associated passive smoking with dysmenorrhoea when the population was stratified by HincIIa or MspI genotypes. When passive smoking and CYP1A1 genotypes were considered together, the strongest association was found in passive smoking women with the Ile/Ile462 polymorphism in CYP1A1HincII and C/C6235 in CYP1A1MspI. In the unexposed group, CYP1A1 genetic susceptibility alone did not contribute to a significant adverse effect, suggesting that CYP1A1 genotypes would modify the effect of passive smoking on primary dysmenorrhoea [89]. The increased risk of primary dysmenorrhoea compared to reference groups in the presence of passive smoking may be due to a reduced ability to convert toxic metabolites of cigarette smoke into less harmful hydrophilic compounds, therefore these authors demonstrated that passive smoking is associated with primary dysmenorrhoea under modification of CYP1A1 gene polymorphisms, providing evidence of the combined effects of the genetic environment and supporting the importance of assessing the role of genetic susceptibility in the evaluation of reproductive toxins because of its important implications for women's health [89].

In this context, authors such as Wu et al. [90] found that CYP2D6 and GSTM1 variant genotypes were associated with an increased risk of recurrent dysmenorrhoea [90]. And when the genotypes were considered together, an increased risk of the disease was found in women with variant genotypes in both CYP2D6 and GSTM1. Crofts et al. [91] found that variant genotypes at the HincII site were significantly associated with increased CYP1A1 gene inducibility and also observed a significant interaction between HincII polymorphism and smoking at the mRNA level [89].

In the same year, Liu et al. [92] investigated the same association, but in this case, they included a population of 1645 newly married women workers (1124 without dysmenorrhoea, 521 with dysmenorrhoea) who did not smoke or drink in the same place in China, but in the period between June 1997 and 2000. In this case, we analysed using multiple logistic regression models. It was found that passive smoking was significantly associated with dysmenorrhoea and, in addition, both the Ile/Ile462 variants in CYP1A1HincII and C/C6235 in CYP1A1MspIm were significantly associated with the disorder. When passive smoking and CYP1A1 genotypes were considered together, the statistical behaviour was very similar to that reported by Li et al. [89], where a stronger association was found in passive smoking women with Ile/Ile462 in CYP1A1HincII and C/C6235 in CYP1A1MspI than in the unexposed group, where CYP1A1 genetic susceptibility alone did not contribute to a significant adverse effect, suggesting that CYP1A1 genotypes would modify the effect of passive smoking on dysmenorrhoea [92].

CYP1A1 MspI and HincII genotypes were found to modify the association between passive smoking and dysmenorrhoea based on the investigators' research hypothesis that women passively exposed to tobacco smoke have a number of genetic susceptibility factors, including metabolic enzyme activities, which influence the levels of toxic substrates entering the blood and would further influence dysmenorrhoea [92]. Directionally, the study found that female passive smokers who had the CYP1A1 MspI variant of the C/C6235 genotype or the CYP1A1 HincII wild-type Ile/Ile462 genotype, which results in a reduction in the individual's ability to convert toxic metabolites of cigarette smoke into a less harmful hydrophilic compound, had significantly the highest risk of dysmenorrhoea compared to the reference groups. They also found that the more women were exposed to secondhand smoke, the greater the risk in the CYP1A1 MspI group C/C6235 and CYP1A1 HincII group Ile/Ile462, suggesting a dose-response relationship between secondhand smoke and dysmenorrhea [92]. Like Lu [93], the researchers showed that passive smoking is associated with dysmenorrhoea. However, this association is modified by an individual's genotype [92].

Altered expression of genes encoding cytokines

Primary dysmenorrhea may be associated with dysregulation of normal menstruation, which in response to progesterone withdrawal, depends on complex interactions between ovarian hormones and the immune system [94]. A variety of immune factors in the endometrium contribute to decidualization, menstruation and subsequent tissue repair [95]. In this context, many cytokines have been identified that could potentiate or inhibit decidualization, including IL-1, TNFa, LEFTY, bone morphogenetic proteins (BMPs), and GSF2 [94, 96]. Therefore, dysmenorrhea is considered to be caused by an exaggerated response to physiological processes at the time of menstruation and there is evidence that women with primary dysmenorrhea experience uterine hypercontractility in

the perimenstrual phase [96-98].

During contractions, uterine blood flow is compromised, resulting in relative tissue ischemia and pain. Peripheral blood analysis of dysmenorrheic women has revealed excessive synthesis and concentrations of oxytocin (OT), PGF2a, vasopressin (VAP) and IL-6 [96, 99-101]. Particularly, on the first day of menstruation, plasma vasopressin levels and PGF2a metabolites were found to be significantly higher in women with severe primary dysmenorrhea [102]. Plasma concentrations of oxytocin and IL-6 were also markedly higher in dysmenorrheic patients than in healthy volunteers during menstruation [96, 101]. According to Ma et al. [96] these mediators could increase uterine contractility [94] and play an important role in the pathophysiology of primary dysmenorrhea.

In 2013, Ma et al. [96] compared 84 gene expression profiles of common peripheral blood mononuclear cell (PBMC) cytokines in six female with primary dysmenorrhea and three unaffected controls on the seventh day before menstruation (secretory phase), the first (menstrual phase) and the fifth day (regenerative phase) of the menstrual period; using a real-time PCR array assay combined with pattern recognition and gene function annotation methods. Comparisons between women with dysmenorrhoea and normal controls identified 11 (nine up-regulated and two down-regulated), 14 (five up-regulated and nine down-regulated) and 15 (seven up-regulated and eight down-regulated) genes with a ≥2-fold difference in expression (P=0.05) in the three phases of menstruation, respectively. In the menstrual phase, genes encoding pro-inflammatory cytokines (IL1B, TNF, IL6 and IL8) were positively regulated and genes encoding members of the TGF-b superfamily (BMP4, BMP6, GDF5, GDF11, LEFTY2, NODAL and MSTN) were negatively regulated [96].

Functional annotation of the genes further revealed an excessive inflammatory response and insufficient signalling of TGF-b superfamily members with anti-inflammatory consequences, which may directly contribute to menorrhagia. In the secretory and regenerative phases, increased expression of pro-inflammatory cytokines and decreased expression of growth factors were also observed. These factors may be involved in regulating decidualisation, endometrial degradation and repair, and indirectly exacerbate primary dysmenorrhoea [96]. In this type of dysmenorrhoea, gene expression levels of proinflammatory cytokines (IL1B, TNF, IL6 and IL8) were significantly increased on the first day of menstruation, while those of anti-inflammatory cytokines (ILF5 and IL11) were significantly reduced compared to unaffected controls. Similarly, the expression of TGF-b family genes (BMP4, BMP6, GDF5, GDF11, LEFTY2, NODAL and MSTN) was down-regulated on the first day of menses [96].

Significant differences in peripheral blood mononuclear cell (PBMC) gene expression were also observed between healthy and dysmenorrhoeic women during the repair phase of the menstrual cycle. Gene annotations from the Database for Annotation, Visualisation and Integrated Discovery (DAVID) showed upregulation of inflammatory response (IL6, IL8, IL1B) and downregulation of cell proliferation (BMP4, TNFSF4, PDGFA, IL9, IL21) and wound response (IFNA2, TNFSF4, PDGFA, IL9, IL1F6). These changes suggest that prolonged acute inflammation, impaired T-cell immunity and delayed endometrial repair occur after the experience of menstrual pain [96]. In conclusion, the gene expression pattern observed in female with primary dysmenorrhoea revealed dysregulated inflammatory responses with extensive down-regulation of TGF-b family genes associated with anti-inflammatory responses and up-regulation of genes encoding inflammatory pro-cytokines. Changes in gene expression occurred not only on the first day of menstruation but throughout the cycle, and may be involved in the regulation of menstrual events (e.g. decidualisation, endometrial degradation and repair) and indirectly act to exacerbate primary dysmenorrhoea [96].

Other proinflammatory factors

Pickles et al. [103] and Lundström & Green [57] suggested that one of the factors contributing to dysmenorrhoea may be an increase in the premenstrual concentration of prostaglandins, and demonstrated that these are produced in excess in patients suffering from dysmenorrhoea [57]; this in the context of the symptoms associated with the disorder during the menstrual period [104]. Prostaglandins cause narrowing of the blood vessels supplying the uterus, resulting in abnormal contractile activity, ischaemia, hypoxia and increased sensitivity of nerve endings [59,104]. In addition to hormonal changes in the body, other factors such as diet, early age at menarche, stress, duration and severity of menstruation, and the presence of premenstrual

syndrome (PMS) may contribute to its pathological mechanism [56].

In addition, authors such as Finn [105] have suggested that menstruation could be considered an inflammatory event, as leukocyte invasion and subsequent production of inflammatory mediators are observed [56]. In response to these questions, Barcikowska et al. [56] sought to establish a complete understanding of the pathomechanism of dysmenorrhoea through a systematic review. They reported that previous research indicates the complexity of biochemical reactions between the endocrine, vascular and immune systems in the disorder, and noted that prostaglandins play an important role in its pathomechanism, while cytokines and other proinflammatory factors (in primary dysmenorrhea) are less well studied. They also noted that more and more studies are showing the efficacy of non-pharmacological methods over pharmacological ones for its treatment [56].

Specifically, progesterone has an anti-inflammatory effect and inhibits the release and activation of metalloproteinases during the secretory phase. It also affects the regulation and synthesis of prostaglandins and leukocytes [106]. After ovulation, fatty acids accumulate in the phospholipids of the cell membrane; omega-6 fatty acids and arachidonic acid are only released when progesterone levels begin to fall. The secretion of prostaglandins and leukotrienes then begins, causing uterine contractions, but also symptoms such as vomiting, tympanitis, nausea and headaches. Arachidonic acid is metabolised by two pathways, the cyclooxygenase pathway and the 5-lipoxygenase pathway. The former produces prostaglandins (PGF2α and PGE2), prostacyclins and thromboxanes. Leukotrienes are formed in the 5-lipoxygenase pathway. Arachidonic acid metabolites, such as prostaglandin PGF2α and cyclooxygenase, cause vasoconstriction, contraction of uterine smooth muscle leading to ischaemia and lowering of the pain threshold, resulting in pain [56, 107, 108].

Prostaglandins have also been shown to be associated with inflammation and are produced during menstruation. Prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) have specific roles in the inflammatory process. PGF2α mediates the constriction of the arcuate vessels, leading to local hypoxia of the endometrial tissue, and stimulates smooth muscle contraction, which in turn promotes menstrual bleeding. The effects of PGE2 depend on the type of receptor, but may include relaxation of endometrial blood vessels, increased swelling and recruitment of leukotrienes [108]. In addition, prostaglandins may be involved in the formation of other chemokines and growth factors involved in the inflammatory response or repair process after menstruation [56, 108].

Regarding vasopressin, Barcikowska et al. [56] point out that vasopressin concentration is lower in the follicular phase and then increases during ovulation; this may contribute to an increase in uterine contractile activity and reduce uterine blood flow, which in turn may lead to ischaemia and dysmenorrhoea [99,102]. Several authors highlight the role of vasopressin in the pathomechanism of the disorder [99,102], in particular Liedman et al. [99], showed that vasopressin levels during ovulation were lower in women with dysmenorrhoea than in healthy women, whereas no significant changes were observed during menstruation. According to Strömberg et al. [102], women with premenstrual syndrome or dysmenorrhoea had higher vasopressin concentrations than women without similar symptoms, but other studies do not confirm the role of vasopressin in dysmenorrhoea [56,109]. In these cases, the authors compared vasopressin levels in women with dysmenorrhoea and healthy women and found that there was no significant difference in levels between the two groups [56,109].

Val66Met polymorphism of the BDNF gene

According to Lee et al. [110], brain-derived neurotrophic factor (BDNF) is considered a modulator of pain due to its involvement in activity-dependent synaptic plasticity within pain circuits. With a pro-nociceptive role, BDNF generates the hyperalgesic responses in inflammatory models of pain [111] and also plays a key role in the production of central sensitisation, contributing to chronic pain conditions [111,112]. It may also be involved in stress-related mood disorders [63], such as major depression [110].

Conditions such as stress [63] or chronic pain [113] reduce BDNF expression in brain structures that control mood and have been shown to mediate the effects of sex hormones in the hippocampus. Therefore, the interaction between estrogen and BDNF in this brain region may underlie menstrual cycle-related problems [114,115]. In this regard, Lee et al. [110] reported that the Val66Met (rs6265) BDNF polymorphism results in the substitution of

methionine (Met) for valine (Val) at codon 66 of the proBDNF protein, and the Met allele leads to reduced activity-dependent BDNF secretion from neurons and impaired BDNF signalling [116]. It may therefore be involved in both chronic pain conditions and mood disorders [110].

In this regard, Lee et al. [110] investigated and genotyped the Val66Met (rs6265) BDNF polymorphism in 99 Taiwanese women with primary dysmenorrhea (PDM, aged 20-30 years) and 101 age-matched healthy female controls. We investigated whether the polymorphism might be associated with an increased risk of PDM in Asian individuals and concluded that PDM homozygotes Met/Met might have a higher perception of menstrual pain and more negative emotions compared to PDM individuals carrying the Val polymorphism. Similarly, the relationships between the Val66Met BDNF polymorphism genotypes and pain-related clinical manifestations, emotions in PDM and psychophysical assessments (pain sensitivity to experimentally induced thermal cutaneous pain) were investigated. We found that the frequency of the Met allele of the polymorphism was significantly higher in the PDM group. In addition, BDNF Met/Met homozygosity had a significantly stronger association with dysmenorrhoea of primary origin compared to Val carrier status. These results also suggest the Val66Met BDNF polymorphism as a possible regulator of menstrual pain and pain-related emotions in PDM [110].

In 2016, Wei et al. [64] reported structural and functional connectivity (FC) changes in the periaqueductal grey (PAG) of individuals with primary dysmenorrhea. Since brain-derived neurotrophic factor (BDNF) acts as a pain modulator within the PAG and the Val66Met BDNF polymorphism contributes to PDM susceptibility, an imaging genetics study was proposed to investigate the influence of the single nucleotide Val66Met BDNF polymorphism and whether this genotype is involved in downstream pain modulatory systems in the context of the PAG-embedded FC pattern. The study involved 56 women with PDM and 60 controls, who underwent resting-state functional magnetic resonance imaging (fMRI) during the menstrual and periovulatory phases, with parallel blood sampling for genotyping [64].

The results of these authors suggest that the Val66Met BDNF polymorphism is associated with different functional expressions of downstream pain modulatory systems. Furthermore, PAG FC patterns in pain-free controls were observed to be altered in a genotype-specific manner in women with PDM. Such resilient brain dynamics may underpin individual differences and shed light on vulnerability to chronic pain disorders in PDM subjects [117]. Similarly, they note that the Val66Met BDNF polymorphism is associated with the differential functional expression of downstream pain modulatory systems in the context of PAG-seeded PK. Val/Val PDM subjects show more adaptive neuroplasticity, whereas Met/Met PDM subjects show more maladaptive neuroplasticity. Such resilient brain dynamics may underpin individual differences and shed light on the vulnerability of PDM-affected subjects to chronic pain disorders [117].

Similarly, in 2018, Low et al. [118] genotyped the Val66Met BDNF SNP Val66Met in 80 women with primary dysmenorrhoea (20 Val/Val, 31 Val/Met, 29 Met/Met) and 76 healthy female controls (25 Val/Val, 36 Val/Met, 15 Met/Met). Multiscale entropy analysis (MSE) was applied to neural source activity estimated from resting-state magnetoencephalography (MEG) signals during the pain-free state. Changes in brain complexity were found to be associated with interactions between the Val66Met BDNF polymorphism and the experience of menstrual pain; in healthy female controls, Met carriers (Val/Met and Met/Met) showed lower brain complexity than Val/Val homozygotes in large brain regions, suggesting a possible protective role of Val/Val homozygosity in such complexity. However, after experiencing long-term menstrual pain, complexity differences between different genotypes in healthy controls were significantly reduced in PDM women, particularly in the limbic system, including the hippocampus and amygdala [118].

These authors also found that, first, the Val66Met BDNF polymorphism (Met / Met homozygosity) is a potential genetic risk factor associated with primary dysmenorrhea, which is consistent with previous studies [64,110]. Second, their findings suggest that long-term experience of menstrual pain alters the effects of the Val66Met BDNF polymorphism on brain complexity. When comparing brain complexity in women of different genotypes with or without menstrual pain, a characteristic trend with considerable genotype-specific complexity differences was identified in CON (control) women, where Met (Val/Met and Met/Met) carriers showed much lower

brain complexity compared to Val/Val CONs. However, complexity differences were significantly reduced in PDMs, suggesting the role of chronic recurrent pain attacks on brain complexity. Third, they observed pain-associated changes in brain complexity in limbic regions, particularly the hippocampus and amygdala, in women with the same Val66Met BDNF genotype. Overall, their findings suggest that pain experience overwhelmingly influences the effect of the Val66Met BDNF polymorphism on brain complexity, and also highlight the potential use of resting-state brain complexity for the development of new therapeutic strategies in patients with chronic pain [118].

In the same vein, a study by Li et al. [15] investigated the associations between Val66Met BDNF polymorphisms, menstrual pain severity and hippocampal volume in young subjects with PDM. We recruited 115 subjects with PDM, including severe cases (n = 66), moderate cases (n = 44), and 117 female (aged 20-30 years) as a control group (CON), for both polymorphism genotyping and MRI examination. Evaluation at the hippocampal volume level included analysis at different anatomical resolutions, i.e. total hippocampal volume, hippocampal subfields and volumetric analysis using voxel-based morphometry (VBM). These authors investigated the means by which Val66Met BDNF polymorphisms contribute to structural plasticity of the hippocampus and its subfields, and how these effects are modulated by pain severity in PDM subjects. The aim is to elucidate genotype-specific morphometric dynamics that may shed light on individual differences in long-term stress-induced hippocampal plasticity [15].

This study postulated that interactions between the Val66Met BNDF polymorphism, PDM severity and its effects on hippocampal volume could be used as a basis for investigating the mechanisms that predispose individuals to chronic pain disorders. This was achieved by adopting a strategy that included hippocampal volumetry at different levels of structural resolution, i.e. total volume, subfields and voxel-based morphometry (VBM) volumetric analysis. No main effects of group, genotype or group-genotype interactions on bilateral total hippocampal volumes were observed. Significant interactions between PDM severity and Val66Met BDNF genotype were observed in the right whole hippocampus, subiculum and molecular layer. Post-hoc analysis showed that the mean hippocampal volume of subjects with moderate PDM and Val/Val homozygotes was larger than that of subjects with severe PDM. Similarly, the right hippocampal volume was larger in the Val/Val group than in the Met/Met group, particularly in the right posterior hippocampal region [15].

Dose-response analysis revealed a positive dose-dependent relationship between the Val allele and volume of the right whole hippocampus, subiculum, molecular layer and right posterior hippocampal region as defined by VBM only in the moderate PDM subgroup. These findings suggest that PDM subjects with Val/Val homozygosity are resistant to moderate intermittent pain-related stress, whereas PDM subjects carrying Met are susceptible, and provide evidence for a dose-dependent protective effect of the Val allele on hippocampal structure. However, in Val variant cases, these effects were modulated according to the severity of menstrual pain. In addition, these results suggest that the BDNF Met/Met polymorphism may render an individual susceptible to deleterious effects (e.g. hippocampal volume) resulting from adverse early life events (PDM in the current study), whereas the BDNF Val/Val polymorphism appears to confer protective effects at the hippocampal level [15].

The A118G polymorphism of the mu-opioid receptor (OPRM1)

According to Wei et al. [119] the experience of pain and clinical response to opioid analgesics varies between individuals, and the analgesic effects of opioids are mediated largely by the mu-opioid receptor (OPRM1) in the central nervous system [120]. The single nucleotide polymorphism A118G causes a substitution of adenine (A) for guanine (G) at codon 118 in the human OPRM1 gene and is associated with reduced expression of the gene. It is also associated with hypersensitivity to pain [121] and increased use of analgesics for clinical purposes [122]. Despite its importance, it was only in 2017 that the question of how the A118G OPRM1 polymorphism interferes with the descending pain modulatory system (DPMS) to relate to individual pain experience was addressed. As a proposal, Wei et al. [119] conducted an imaging genetics study (using neuroimaging as an endophenotypic test to assess genetic associations, with pain as an environmental stress); investigating the neural network mechanisms of the polymorphism for central pain modulation in women - otherwise healthy - but diagnosed with primary dysmenorrhea (PDM) [119].
The aim of this study was to investigate whether

differences in functional connectivity (FC) of the DPMS between A118G OPRM1 polymorphisms could provide a possible explanation for differences in pain experience in patients. The study involved 61 people with PDM and 65 controls who underwent functional magnetic resonance imaging (fMRI) at rest, during menstruation and ovulation. Blood samples were also taken for genotyping, and three aspects of pain experience were examined: mnemonic pain (remembered general menstrual pain), present pain (spontaneous menstrual pain) and experienced pain intensity (thermal pain) [119].

As a result, G allele carriers were found to have functional hypo-connectivity between the anterior cingulate cortex (ACC) and in the periaqueductal grey (PAG) compared to AA homozygotes. Furthermore, G allele carriers lost correlation with spontaneous pain experience and exhibited dysfunctional DPMS via PAG-seeded FC dynamics. Thus, the OPRM1 A118G-DPMS interaction was considered a plausible neurological mechanism underlying individual differences in pain experience. The authors believe that such differences may be due to different pain processing mechanisms and neuromodulators loaded by genotypes in the brain, particularly the DPMS system [119].

Taken together, the data obtained suggest active cortical modulation of current (momentary) menstrual pain and may explain why AA homozygotes rated their current pain experience sub-significantly lower than G allele carriers [119]. In contrast to some previous genetic studies of the A118G OPRM1 polymorphism, no differences in pain-heat thresholds were observed. There are several explanations for these inconsistencies, including sex ratio differences (sex by genotype interaction appears for heat pain, [123]), pain modalities (neither electrical stimulation [121] or pressure [123], ethnicity (Asians differ from Caucasians in G allele variability [124] and in the phenotype of the A118G OPRM1 polymorphism [119,125].

To the authors' knowledge, this is the first study to provide new insights into the previously unexplored neurodynamic influences of the A118G OPRM1 polymorphism in PAG-based DPMS PKs. Such genetic variations shape the functional organisation of DPMS and may predict or underpin differential analgesic efficacy (responsive or non-responsive) [126] and may ultimately contribute to susceptibility to the development of chronic pain late in life in PDM subjects [64,119].

The SNP rs7523086 colocalized in the NGF (nerve growth factor) gene

To better understand variation in dysmenorrhea pain severity and identify genetic predisposing factors, Jones et al. [68] conducted a genome-wide association study (GWAS) of dysmenorrhea pain (self-reported) in participants from the 23andMe cohort [127]. This study investigated an association at the nerve growth factor gene locus in a cohort of women of European ancestry (n = 11.891) aged 18-45 years who rated their dysmenorrhoea pain as moderate. Their findings suggest that pain severity is partly determined by the genetic component, as the NGF gene is known to play an established role in chronic pain disorders, suggesting that the gene may be an important mediator of gynaecological and/or pelvic visceral pain [68].

The presence of the risk allele corresponded to a predicted 0.1-point increase in pain intensity on a 4-point ordinal pain scale (1q13.2, neutrophin colocalised with NGF).Although the putative effects on NGF function and/or expression remain unknown, the genetic variation correlated and colocalised with active epigenetic marks in adipose, ovarian and aortic tissue expression levels of non-coding RNA flanking the NGF gene, explaining 0.48% of the observed variance [68]. Similarly, two previously reported modulators of dysmenorrhoea severity were identified: age [128,129] and body mass index (BMI) [130]. Increased pain was correlated with younger age (P 5 1.2 3 10217) and lower BMI (P 5 3.8 3 10225). The effect estimates for age and BMI were only slightly stronger than the main genetic variant, explaining 0.62% and 0.52% of the observed variance in the endpoint, respectively [68]. Similarly, participants who reported extreme pain from dysmenorrhoea were more likely to report having endometriosis, polycystic ovarian syndrome, depression and other psychiatric disorders [68].

The authors concluded that the common genetic pleiotropy between dysmenorrhoea, painful gynaecological conditions, depression and other related disorders is an important area of research to better understand these conditions. The current GWAS data for these conditions have not identified a signal at the NGF locus [70,131], which may be because these studies were designed to identify genetic factors that specifically influence disease risk

rather than disease-associated pain severity [68]. Similarly, the authors recommend that further experimental validation exploring and defining the biological mechanisms of the role of the NGF gene in dysmenorrhoea pain severity is key to repurposing analgesics targeting the NGF pathway for this disorder and related conditions [68].

Conclusion

Despite the important findings on the incidence and causality of dysmenorrhoea (generally primary or PDM) that have been identified in recent years, it is clear that the heterogeneity of the studies, the shortcomings in the establishment of protocols and baselines in their development, as well as the lack of systematicity to ensure their reproducibility over time and in different populations, affect the potential of their results and reduce their impact in terms of global applicability. The implementation of new-generation sequencing techniques, genetic imaging studies and the preservation of blood tests as a discriminatory factor could, in the short term, make it possible to establish causality and therefore treatment options for different ethnic groups, taking into account their lifestyles and habits, which, in the opinion of this researcher, are often underestimated and, given the findings in the literature, appear to play an important role in the incidence and severity of pain associated with dysmenorrhoea. Cultural recognition that the pain and disability caused by menstruation is not part of a natural or normal symptomatology will allow us to provide treatment and improve the quality of life of women affected by this painful and debilitating disorder.

Consent for publication

The authors read and approved the final manuscript.

Competing interest

The authors declare no conflict of interest. This document only reflects their point of views and not that of the institution to which they belong.

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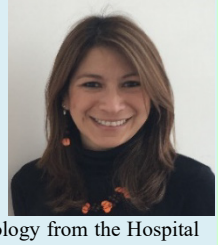

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