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Manifestation of migraine in adolescents: Does it change in puberty?

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ABSTRACT

Purpose: To analyze the association between pubertal stage, menstrual cycle and migraine attacks in girls with migraine. In addition, headache frequency, accompanying symptoms, duration and onset in relation to the specific phase of the cycle were investigated.
Methods: Girls between 7 and 18 years old, diagnosed with headaches that met "International Classification of Headache Disorders II" diagnostic criteria for migraine without aura, kept a daily headache and menstrual cycle diary over 8 weeks. Ovulatory cycles were identified by weekly progesterone saliva tests.
Results: 47 girls participated in the study and were divided into three groups according to Tanner stage and onset of regular menstruation: pre- (n = 16), peri- (n = 19) and post-pubertal (n = 12). A significant difference in migraine frequency was found between pre- and post-pubertal girls (p = 0.005). No significant differences with regard to headache characteristics were detected. Interestingly, a higher frequency of attacks in follicular phase occurred compared to luteal phase in peri- and post-pubertal girls (p = 0.030).
Conclusion: During puberty, migraine patterns in girls change to a typical adult pattern of migraine in a stepwise manner not clearly related to menarche. The first sign of this transition phase could be the higher frequency of migraine attacks in post-pubertal girls.

1. Introduction

Migraine is the most common disabling disorder in children of all age groups [1,2]. The prevalence of migraine rises with increasing age and particularly during adolescence [3]. Until puberty, migraine occurs in males and females with the same frequency. After the onset of puberty, headaches are markedly more prevalent in females [3]. Women of reproductive age are up to three times more likely to suffer from migraines than men [3]. Half of women describe a relation between headache attacks and their menstrual cycle.

In a large Austrian study in adolescents 82.1% of the girls and 67.6% of the boys experience regular headaches [4]. Girls report a higher frequency of headache attacks and higher intensity of pain compared to boys of the same age [5].

A decline in estrogen concentration after exposure to high levels of estrogen for several days, like at the beginning of the menstrual cycle (2–3 days prior to menstruation), has been found to be a potential trigger factor for migraine attacks [6]. Data on hormonal changes occurring during puberty leading to the typical hormonal pattern in women with ovulatory cycles are sparse.

Migraine in children is more often characterized by features like bilateral pain, frontal location and shorter attacks compared to adults [7,8]. The age at which classical migraine occurs is not clearly defined yet.

Two different types of menstrual migraine have been proposed by the "International Classification of Headache Disorders" (ICHD) of the International Headache Society [8]: „Pure menstrual migraine" refers to migraine attacks that occur exclusively in close temporal

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relationship to menses, within a time frame from two days before onset until the third day of menstrual bleeding. „Menstrual related migraine" describes migraine associated with the menses in women who also describe migraine attacks at other occasions during their menstrual cycle [8]. It occurs in about 35–50% of premenopausal women and adolescent girls [6,9]. Compared to non-menstrual attacks, menstrual migraines tend to be more severe, last longer and are less responsive to acute medication [10–12]. Menstrual migraines are usually not associated with aura.

This prospective study investigated the occurrence of migraine headaches in adolescent female patients in relation to menstrual cycle and pubertal status. Furthermore, the study aimed to describe headache characteristics in prepubertal, peri-pubertal and post-pubertal girls with migraine and the development of headache attacks through puberty taking into account Tanner stage, onset of regular menstruation and progesterone levels.

2. Material and methods

2.1. Study population

Girls aged between 7 and 18 years suffering from headaches that met "International Classification of Headache Disorders" (ICHD-II) diagnostic criteria for migraine without aura were recruited from the Department of Pediatric Neurology, Children's Hospital Datteln, Witten/Herdecke University and the Department of Pediatrics and Adolescent Medicine, Medical University of Innsbruck between 01/2016 and 12/2018. These criteria include at least five attacks with the following characteristics: duration between 4 and 72 h, either with or without unsuccessful treatment, headache with at least two of the following criteria: unilaterally located headache, pulsatile character, causing moderate or severe pain and deteriorating during routine activities like walking and either nausea and/or vomiting or photo- or phonophobia.

In all patients a clinical neurological examination was performed. Routinely blood pressure was measured and most of the patients had an ophthalmological examination. In patients with suspected intracranial lesion imaging methods were performed.

Patients were divided into three groups: prepubertal, peri- and post-pubertal according to their Tanner stage and to progesterone levels in their saliva. Exclusion criteria included headaches explainable by other conditions and intake of hormonal contraceptives. Patients and their parents gave written informed consent.

2.2. Methods

At the beginning of the study a detailed headache and menstruation history was taken and Tanner Stage was assessed during a clinical examination, including weight, height and body mass index (BMI). Each participant was asked to complete a daily headache and menstrual diary for eight weeks or two menstrual cycles. This included the duration of the attacks as well as the occurrence of accompanying symptoms including nausea, vomiting, photophobia, phonophobia, pain worsening with physical activity or aura. Any additional medication was documented.

Using menstrual diaries and elevated saliva progesterone levels, luteal phase was differentiated from follicular phase as follows: Starting at the first day of the study, weekly saliva samples were collected in the morning and stored in the participants cooler. Progesterone levels in saliva were quantitatively measured by an enzyme immunoassay (IBL, Hamburg, Germany) in order to detect the rise of progesterone in luteal phase. Before collecting the sample patients were advised not to eat, drink, brush their teeth or chewing gum for 30 min. According to validated test results the following cut-off values were defined: Follicular phase was assumed when progesterone levels were between 28-82 pg/mL whereas luteal phase was assumed within a range of 127–446 pg/mL. A progesterone rise above 127 pg/mL was defined as post-ovulatory and indicated the presence of a corpus luteum.

The sensitivity of the test was 3.13 pg/mL; inter- and intra assay coefficients of variation were below 9.6% for the entire range of saliva progesterone concentrations.

2.3. Statistical analysis

Standard methods of descriptive statistics (mean, median, range, standard deviation) were used. Patients were divided into three groups according to Tanner stage: pre-, peri- and post-pubertal. Tanner stages 1 and 2 were considered prepubertal, Tanner 3 and 4 peri-pubertal and Tanner stage 5 and/or the presence of menstrual bleedings was classified as post-pubertal.

Differences in number of migraine attacks, accompanying symptoms and duration of pain between the three groups (pre-, peri- and post-pubertal) were analysed using Mann-Whitney-U-test. Wilcoxon test was performed when analyzing differences in follicular and luteal phase in peri- and post-pubertal girls. Statistical analysis was performed with IBM SPSS (version 22, IBM Corporation, Armonk, NY). P-values <0.05 were considered significant.

2.4. Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Medical University of Innsbruck (reference number (AN2013-0027)).

3. Results

In total, 47 girls participated in this prospective study. 34% ($n = 16$) were classified as prepubertal, 40% ($n = 19$) as peri- and 26% ($n = 12$) as post-pubertal according to Tanner stage and/or menstrual bleeding.

The mean age of the children was 12.5 ($SD = 2.8$) years (Table 1). In the prepubertal group mean age was 9.8 years ($SD = 1.9$), peri-pubertal 12.6 years ($SD = 1.5$) and post-pubertal 16 years ($SD = 1.0$). The mean BMI differed significantly between all groups (pre-pubertal vs peri-pubertal: $p = 0.0147$; peri-pubertal vs post-pubertal: $p = 0.001$; pre-pubertal/post-pubertal: $p = 0.0001$).

Patients reported the following numbers of headache episodes during eight weeks: prepubertal 8.88 ± 9.3 attacks (mean, ±SD), peri-pubertal 10 (±9.8) attacks and post-pubertal 28 (±20.9) attacksTable 1. In post-pubertal girls significantly more migraine attacks were reported than in pre- and peri-pubertal girls ($p = 0.005$ and $p = 0.012$, respectively). Comparing the three groups no significant differences were found with regards to accompanying symptoms or duration of pain (Table 2). There was a tendency that prepubertal girls suffer more frequently from unilateral headache compared to post-pubertal girls but these results were not significant ($p = 0.578$).

With regard to the number of migraine attacks during follicular and luteal phase, significantly more episodes were reported in follicular phase in peri- and post-pubertal girls than in luteal phase ($p = 0.030$). Accompanying symptoms ($p = 0.414$), duration of pain ($p = 1.0$) and aura did not differ significantly between follicular and luteal phase.

4. Discussion

This prospective study examined the relationship of migraine attacks and the menstrual cycle in adolescent girls, taking into

Table 1
Characteristics of participating girls and distribution over the three groups pre-, peri- and post-pubertal girls (mean ± standard deviation).

	Total	Prepubertal girls	Peri-pubertal girls	Post-pubertal girls
Age in years	12.5 ± 2.8	9.8 ± 1.9	12.6 ± 1.5	16.0 ± 1.0
Weight in kg	50.3 ± 17.4	34.7 ± 8.9	51.4 ± 9.5	69.7 ± 16.9
Height in cm	156.5 ± 13.7	141.7 ± 11.9	162.6 ± 7.1	166.2 ± 6.3
BMI kg/m ^{2}	20.0 ± 4.6	17.1 ± 2.4	19.5 ± 2.9	25.0 ± 5.5

Table 2
Comparison of episodes and migraine characteristics in pre-, peri- and post-pubertal girls (mean ± standard deviation).

	prepubertal	peripubertal	postpubertal	p- value (pre- vs. post-pubertal)
Number of episodes	8.88 ± 9.3	10 ± 9.8	28 ± 20.9	0.005
Accompanying symptoms	2.1 ± 1.5	2.20 ± 1.2	3.10 ± 1.4	0.103
Duration in h	9.50 ± 10.9	9.60 ± 9.6	11.70 ± 7.6	0.167

account clinical pubertal status and ovulatory cycles assessed by progesterone concentrations in saliva.

4.1. Frequency

The most important result of the present study is a significant increase of migraine attacks after puberty. This is in accordance to numerous previous studies demonstrating a higher prevalence of migraine in adolescent girls compared to boys of the same age and in women of reproductive age [3,5,13]. Compared to a large study including 359 paediatric patients [7] the frequency of attacks in the present study is similar with an average of 9–11 attacks per month. In contrast, in an Italian study frequency of attacks was reported to be as high in only 25% of the girls [5]. However, this study was performed as a questionnaire study in schools and not in girls explicitly presenting with headaches as in our cohort.

4.2. Puberty

Puberty was shown to be a predictor for headache [14] whereas pubertal status is assumed to be a better predictor than age [15]. Nevertheless, menarche itself was not a predictor in a large longitudinal questionnaire study [16] as some patterns already changed before. However, the determination of Tanner stages and hormone levels was not performed and parents were asked about the precise timing of menarche. Therefore, neither a specific cycle phase nor regular cycles with ovulation could be determined in this previous study.

We believe that the higher frequency of migraine in post-pubertal girls might be the first step towards an adult pattern of migraine. Although we also found a higher frequency of post-pubertal migraine headaches, we did not detect a change in migraine characteristics in post-pubertal girls when compared to prepubertal girls. Migraine features in children differ from adults, but the transition phase or age of change towards classical characteristics of migraine is not clear [7]. According to our results this might occur rather after than during puberty.

4.3. Accompanying symptoms

One study, based on a standardized questionnaire, showed an association between migraine attacks and menstruation beginning with menarche and associated with more accompanying symptoms [9]. These characteristics like photophobia, phonophobia or nausea however are not typical for adult menstrual migraine [17]. In our study we found an increase of accompanying symptoms during the course of puberty but this effect was not statistically significant, possibly due to the small sample size. A higher percentage of photophobia for example has been reported in adolescents compared to children [7]. In another large retrospective cohort study age- and sex-related differences in children were found. These included a higher frequency of headache attacks, less nausea and vomiting and a higher incidence of co-morbid anxiety in adolescents [7].

4.4. Duration of the attacks

The mean duration of a headache attack in the presented study was around 10 hours. Compared to other studies which report a mean duration of less than half an hour in one third of the patients but up to several hours in 20% [5] of the patients the duration is rather short. Presumably, girls in our cohort used efficient medication to relieve the pain as all included girls were already under treatment.

4.5. Menstrual migraine

Generally, menstrual migraine is associated with adult characteristics of migraine [9]. In contrast to our results, a large retrospective analysis on nearly 900 girls identified the change to an adult pattern of migraine including menstrual migraine already during adolescence. In line with our results, authors concluded that the incidence of menstrual migraine increases with increasing age of the girls as a stepwise development. They found an onset of menstrual migraine patterns already with menarche and even before. Further, they speculated that hormonal fluctuations preceding menarche are the cause for menstrual migraine patterns[9]. One should keep in mind the retrospective design of this study. Our prospective study design allowed to exactly define the specific phase of the menstrual cycle and to verify this by progesterone levels.

Typically, menstrual and non-menstrual attacks differ with regard to duration and to treatment response but not in other characteristics like associated or prodromal phenomena [12]. In a prospective diary study in women with menstrual migraine, attacks during menstruation were characterized by a longer duration and severe nausea compared to non-menstrual attacks [18]. As we did not detect an increased frequency of attacks around menses, these features do not apply to our cohort.

4.6. Body mass index

Interestingly, obesity has been shown to be a risk factor for migraine frequency and progression of the disease in adults and

children [19,20]. This aspect contributes to the higher frequency of migraine attacks in adults as the distribution of adipose tissue changes in adulthood [21]. In adolescents, weight loss programmes led to an improvement of migraine symptoms whereas patients with insulin resistance were prone not to benefit and to suffer from persisting migraine attacks [20,22]. In our study we could confirm significant differences in BMI between the groups, correlating with an increase of migraine attacks. This is in accordance with the described association of obesity and migraine. A multifactorial pathophysiological mechanism is assumed as central and peripheral pathways of feeding and migraine pathophysiology seem to overlap [21]. An involvement of serotonin, orexin, pro-inflammatory cytokines and adipocytokines like leptin are currently investigated [21].

Unfortunately, we did not test for insulin resistance in this study but we will include this parameter in future studies as well as the recommendation of weight loss programmes in order to improve migraine.

4.7. Cycle phase

The observation that migraine attacks occur less often during luteal phase compared to follicular phase is in line with previous reports [23]. Former studies found that high progesterone levels are accompanied by an increased number of days with headache in older girls and by a decreased number of days with headache in younger girls. These results underline the influence of age and pubertal development on the effect of ovarian hormones and on days of headache onset [23]. In adult women, a decreased frequency of headache attacks in mid-luteal phase as well as under gestagen-only contraceptives have been described before [24–26]. MacGregor et al. [26] confirmed these results and explained the lower incidence of migraine in the late luteal phase due to falling estrogen levels. No threshold level of estrogen could be identified to date, supporting the assumption of an individual predisposition [26].

4.8. Pathophysiological hypotheses

The exact pathophysiological mechanisms of the induction of migraine attacks by hormones still have to be elucidated. Direct and indirect effects of estrogens on neuronal excitability have been demonstrated [27]. Furthermore, close interactions between estrogens and neurotransmitters in the brain certainly play a key role as it has been illustrated for serotonin, dopamine, endorphins within the opiatergic, GABAergic and noradrenergic systems [6]:

Migraine attacks have been linked to low serotonin plasma levels [21]. Estrogens may increase the serotonergic tone and influence serotonin synthesis, reuptake and degradation [6]. This association might further contribute to the frequency of headache attacks when estrogen levels fall and consecutively serotonin plasma levels decrease as well. Other mechanisms of action are a modulation of gene expression and/or binding potentials of serotonin receptors by estrogens.

Estrogen also has an effect on the glutaminergic system which in turn has an impact on neural excitability within the trigeminal nucleus caudalis [28].

In contrast, progesterone suppresses neuronal transmission and neuronal activity supposedly via GABAergic mechanisms [6].

These interactions have been shown to be cycle-dependent which could possibly explain a cycle-dependence of menstrual migraine. In mid-cycle with high estrogen and low progesterone levels an up-regulation of serotonergic and glutamatergic mechanisms is assumed. In the mid-luteal phase with high progesterone levels an up-regulation of GABAergic mechanisms and a down-regulation of serotonergic systems might occur. They play a role in the pathogenesis of migraine with an interaction with neurotransmitters in the trigeminal nucleus caudalis [6,28].

Another mechanism of interaction might be the opioid system. It is known to be profoundly influenced by sex steroids [17,29]. Pathways involving opioids are also known to participate in the regulation of trigeminal pain pathways leading to migraine attacks [17,29]. Low levels of β-endorphin and cortisol in response to naloxone and corticotropin-releasing hormone applications have been shown to lead to an opioid hyposensitivity in patients with migraine in the premenstrual phase in contrast to patients without migraine. This opioid hyposensitivity may contribute to the development of menstrual migraine by an alteration of pain sensitivity [27].

Furthermore, sex hormones may directly influence pain-processing networks in the brain and lead to an altered pain perception [30]. Magnesium deficiency and prostaglandin release may also be involved in the interaction of estrogens and neurotransmitter systems finally leading to migraine attacks [6].

4.9. Strengths and limitations

One strength of our study is that the established IHS criteria for migraine were applied. The importance of a distinct diagnosis of migraine by physicians was postulated by former studies to enable comparisons between different studies [27]. Furthermore, this was a questionnaire study with a prospective design. Diary studies are considered as the best approach to analyze the relation between days of headache onset and menstrual cycle [31]. We decided to combine two different tools to determine the specific cycle phase and to detect anovulatory cycles: menstrual diary and progesterone saliva measurements. If irregular cycles occur, which is common during puberty, one cannot clearly identify follicular and luteal phase by the use of diaries only. Nevertheless, we are aware that progesterone assays in saliva are not the gold standard for hormone measurements during menstrual cycle as this method is prone to false negative results. An alternative would have been repeated blood sampling at least five times during a menstrual cycle to detect progesterone and estradiol levels. For ethical and practical reasons we did not consider this as an option for our study population. However, our aim was the determination of the post-ovulatory status by measuring a progesterone rise over a defined cut-off value.

In addition, the study comprises a well characterized group of girls, although a larger sample size would provide a better statistical power.

5. Conclusions

Puberty seems to modulate frequency and onset of migraine in girls but not the headache characteristics as a first step towards an adult pattern of migraine. The mechanisms especially with regard to hormonal dependence and changes are still under debate. In order to improve treatment strategies and quality of life, further prospective studies in adolescent girls suffering from migraine are needed.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Medical University Innsbruck (reference number (AN2013-0027)).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on request.

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Declaration of competing interest

The authors declare that they have no competing interests.

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References

[1] M.J. Mortimer, J. Kay, A. Jaron, Epidemiology of headache and childhood migraine in an urban general practice using Ad Hoc, Vahlquist and IHS criteria, Dev. Med. Child Neurol. 34 (12) (1992) 1095–1101.
[2] J.M. Elser, R.C. Woody, Migraine headache in the infant and young child, Headache 30 (6) (1990) 366–368.
[3] T.W. Victor, X. Hu, J.C. Campbell, D.C. Buse, R.B. Lipton, Migraine prevalence by age and sex in the United States: a life-span study, Cephalalgia 30 (9) (2010) 1065–1072, https://doi.org/10.1177/0333102409355601.
[4] J. Philipp, M. Zeiler, C. Wöber, G. Wagner, A.F.K. Karwautz, T.J. Steiner, et al., Prevalence and burden of headache in children and adolescents in Austria - a nationwide study in a representative sample of pupils aged 10-18 years, J. Headache Pain 20 (1) (2019) 101–112, https://doi.org/10.1186/s10194-019-1050-8.
[5] T. Foiadelli, A. Piccorossi, L. Sacchi, M. De Amici, M. Tucci, I. Brambilla, et al., Clinical characteristics of headache in Italian adolescents aged 11-16 years: a cross-sectional questionnaire school-based study, Ital. J. Pediatr. 44 (1) (2018), https://doi.org/10.1186/s13052-018-0486-9, 44–11.
[6] V.T. Martin, M. Behbehani, Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis–part I, Headache 46 (1) (2006) 3–23, https://doi.org/10.1111/j.1526-4610.2006.00309.x.
[7] S.L. Wilcox, A.M. Ludwick, A. Lebel, D. Borsook, Age- and sex-related differences in the presentation of paediatric migraine: a retrospective cohort study, Cephalalgia 38 (6) (2018) 1107–1118, https://doi.org/10.1177/0333102417722570.
[8] Headache classification committee of the international headache society (IHS) the international classification of headache disorders, Cephalalgia 38 (1) (2018) 1–211, https://doi.org/10.1177/0333102417738202, third ed.
[9] M.J. Crawford, L. Lehman, S. Slater, M.A. Kabbouche, S.L. LeCates, A. Segers, et al., Menstrual migraine in adolescents, Headache 49 (3) (2009) 341–347, https://doi.org/10.1111/j.1526-4610.2009.01347.x.
[10] F. Granella, G. Sances, C. Zanferrari, A. Costa, E. Martignoni, G.C. Manzoni, Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women, Headache 33 (7) (1993) 385–389.
[11] E.G.M. Couturier, M.A.M. Bomhof, A.K. Neven, N.P. van Duijn, Menstrual migraine in a representative Dutch population sample: prevalence, disability and treatment, Cephalalgia 23 (4) (2003) 302–308, https://doi.org/10.1046/j.1468-2982.2003.00516.x.
[12] F. Granella, G. Sances, G. Allais, R.E. Nappi, A. Tirelli, C. Benedetto, et al., Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres, Cephalalgia 24 (9) (2004) 707–716, https://doi.org/10.1111/j.1468-2982.2004.00741.x.
[13] B. Kröner-Herwig, M. Heinrich, L. Morris, Headache in German children and adolescents: a population-based epidemiological study, Cephalalgia 27 (6) (2007) 519–527, https://doi.org/10.1111/j.1468-2982.2007.01319.x.
[14] L. LeResche, L.A. Mancl, M.T. Drangsholt, K. Saunders, M. Korff Von, Relationship of pain and symptoms to pubertal development in adolescents, Pain 118 (1–2) (2005) 201–209, https://doi.org/10.1016/j.pain.2005.08.011.
[15] H. Rhee, Relationships between physical symptoms and pubertal development, J. Pediatr. Health Care 19 (2) (2005) 95–103, https://doi.org/10.1016/j.pedhc.2004.10.004.
[16] B. Kröner-Herwig, N. Vath, Menarche in girls and headache–a longitudinal analysis, Headache 49 (6) (2009) 860–867.
[17] S. Sacco, S. Ricci, D. Degan, A. Carolei, Migraine in women: the role of hormones and their impact on vascular diseases, J. Headache Pain 13 (3) (2012) 177–189, https://doi.org/10.1007/s10194-012-0424-y.
[18] K.G. Vetvik, J.Š. Benth, E.A. MacGregor, C. Lundqvist, M.B. Russell, Menstrual versus non-menstrual attacks of migraine without aura in women with and without menstrual migraine, Cephalalgia 35 (14) (2015) 1261–1268, https://doi.org/10.1177/0333102415575723.
[19] A.D. Hershey, S.W. Powers, T.D. Nelson, M.A. Kabbouche, P. Winner, M. Yonker, et al., Obesity in the pediatric headache population: a multicenter study, Headache 49 (2) (2009) 170–177, https://doi.org/10.1111/j.1526-4610.2008.01232.x.
[20] A. Verrotti, A. Di Fonzo, L. Penta, S. Agostinelli, P. Parisi, Obesity and headache/migraine: the importance of weight reduction through lifestyle modifications, BioMed Res. Int. 2014 (4) (2014), https://doi.org/10.1155/2014/420858, 420858–7.
[21] B.L. Peterlin, A.M. Rapoport, T. Kurth, Migraine and obesity: epidemiology, mechanisms, and implications, Headache 50 (4) (2010) 631–648, https://doi.org/10.1111/j.1526-4610.2009.01554.x.
[22] A. Verrotti, S. Agostinelli, C. D'Egidio, A. Di Fonzo, M. Carotenuto, P. Parisi, et al., Impact of a weight loss program on migraine in obese adolescents, Eur. J. Neurol. 20 (2) (2013) 394–397, https://doi.org/10.1111/j.1468-1331.2012.03771.x.
[23] V.T. Martin, J.R. Allen, T.T. Houle, S.W. Powers, M.A. Kabbouche, H.L. O'Brien, et al., Ovarian hormones, age and pubertal development and their association with days of headache onset in girls with migraine: an observational cohort study, Cephalalgia 38 (4) (2018) 707–717, https://doi.org/10.1177/0333102417706980.
[24] R.E. Nappi, G. Sances, G. Allais, E. Terreno, C. Benedetto, V. Vaccaro, et al., Effects of an estrogen-free, desogestrel-containing oral contraceptive in women with migraine with aura: a prospective diary-based pilot study, Contraception 83 (3) (2011) 223–228, https://doi.org/10.1016/j.contraception.2010.07.024.
[25] G.S. Merki-Feld, B. Imthurn, R. Langner, P.S. Sándor, A.R. Gantenbein, Headache frequency and intensity in female migraineurs using desogestrel-only contraception: a retrospective pilot diary study, Cephalalgia 33 (5) (2013) 340–346, https://doi.org/10.1177/0333102412473373.
[26] E.A. MacGregor, A. Frith, J. Ellis, L. Aspinall, A. Hackshaw, Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen, Neurology 67 (12) (2006) 2154–2158, https://doi.org/10.1212/01.wnl.0000233888.18228.19.
[27] L.C. Newman, Understanding the causes and prevention of menstrual migraine: the role of estrogen, Headache 47 (Suppl 2) (2007) S86–S94, https://doi.org/10.1111/j.1526-4610.2007.00819.x, s2.
[28] V.T. Martin, J. Lee, M.M. Behbehani, Sensitization of the trigeminal sensory system during different stages of the rat estrous cycle: implications for menstrual migraine, Headache 47 (4) (2007) 552–563, https://doi.org/10.1111/j.1526-4610.2007.00714.x.
[29] B. Böttcher, B. Seeber, G. Leyendecker, L. Wildt, Impact of the opioid system on the reproductive axis, Fertil. Steril. 108 (2) (2017) 207–213, https://doi.org/10.1016/j.fertnstert.2017.06.009.
[30] F. Facchinetti, E. Martignoni, L. Fioroni, G. Sances, Genazzani AR Opioid control of the hypothalamus-pituitary-adrenal axis cyclically fails in menstrual migraine, Cephalalgia 10 (1) (1990) 51–56, https://doi.org/10.1046/j.1468-2982.1990.1001051.x.
[31] K.G. Vetvik, M.B. Russell, Are menstrual and nonmenstrual migraine attacks different? Curr. Pain Headache Rep. 15 (5) (2011) 339–342, https://doi.org/10.1007/s11916-011-0212-4.