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Others Section

Menstrual Disorders and its Association with Migraine

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ABSTRACT

Introduction: Migraine is a common disorder which can be seen in approximately 18% of women. The highest prevalence of this disorder has been reported vastly in the women of age between 18 and 49, when they are in the menstrual period and this is supposed to be associated with the same.

Aim: To study the menstrual disorders in women with and without migraine.

Materials and Methods: A case-control study was conducted with total population of 175 women (Jan 2018-Feb 2019), diagnosed with migraine, using International Headache Society criteria. Age and sex-matched control group was included in the present study. A semi-structured questionnaire about migraine and migraine-related disabilities, menstrual and headache history was conducted. All results were evaluated by SPSS version 22.0 statistical software; Independent t-test and to investigate the relationship between quantitative variables, Spearman's correlation coefficient was used.

Results: In case group, 25.6% of women had menstrual cycle <24 days, and their population was significantly more than control group (10.1%). Also, in case group, 12.8% of women had menstrual cycle >38 days, which was significantly more than control group. The proportion of women with period lasting <4 days in case group (17.4%) was significantly more than that in control group (6.7%). In addition, the percentage of women with last period more than 8 days in case group was 12.8% and in control groups it was (6.7%) which was significantly high.

Conclusion: There is significant relation between period duration, oligomenorrhea, polymenorrhea and prevalence of migraine; however, there is no significant relation between other menstrual disorders such as dysmenorrhea and menstrual regularity with migraine. This study demonstrates no relation between severity and duration of headache and menstrual disorders.

Keywords: Female, Headache, Menstrual migraine

INTRODUCTION

Menstruation is a vivid sign of a healthy body. After puberty, in order to keep hormonal balance, the body starts ovulation. However, sometimes imbalances of hormonal levels lead to menstrual abnormalities [1]. Menstrual disorders, an abnormal cycle length, such as amenorrhea, menorrhagia, dysmenorrhea, polymenorrhea, oligomenorrhea are the common issues in adolescents and young adult females which sometimes cause serious problems. Among these, dysmenorrhea is the most common form, reported in 60% to 90% of women [2-4]. Oligomenorrhea is defined as less than six to eight periods during a year. Dysmenorrhea is classified into two categories such as primary and secondary dysmenorrhea [5]. Menorrhagia is a heavy yet regular menstrual bleeding (loss of 80 mL blood per cycle) in a woman which is thought to be caused by disordered prostaglandin production and abnormal uterine [6]. Polymenorrhea is another type of abnormal uterine bleeding and defined as a menstrual length cycle which lasts less than 21 days [7].

Migraine is known as a common disorder, and according to the international headache society's criteria, there are at least 5 episodes of headaches with the duration of 4-72 hours. Except for other secondary causes, minimum two of four causes should be involved in the headache's quality; unilateral headache, from moderate to severe mood, interference with the daily physical activity. Moreover, one of these symptoms such as nausea, photophobia, phonophobia, vomiting should be present in migraine. Migraine is categorised by moderate to severe headaches and includes 18% of women over 18-49 ages as they are in the menstrual ages [8].

In clinical practices, the association between migraine and menstruation has been reported in 50% of women [9]. It has also been indicated that many women with menstrual disorders might show severe, longer, and fewer responses to the drugs against migraines compared to others in menstrual ages [10,11].

As per the International Headache Society (IHS) "The endogenous menstrual cycle results from complex hormonal changes in the hypothalamic, pituitary, ovarian axis resulting in ovulation suppressed using of combined oral contraceptives. Therefore researcher should separately work on the women using the hormonal treatment and those who not use hormonal treatment. Several diary card studies have assessed the clinical association between migraine and menstruation [12-14] whilst there has not been much research reported on the menstrual disorders in those who have suffered from migraine. This, therefore, motivated the present clinicians to conduct a study relation between menstrual disorders in women with migraine and without migraine.

MATERIALS AND METHODS

This was a case-control study, conducted in one year (Jan 2018-Feb 2019) among women referring to neurological clinic at one of the academic hospitals in Iran. The study was based on a convenience sample of 175 female patients, aged 18-49 years old. This study received the Ethical Committee approval (IR.SBMU.MSP.REC.1395.55) and all the patients were enrolled after obtaining their consent.

According to International Headache Society (IHS) by a same neurologist, the subjects were separated in two groups; case and control groups and 86 women were put in case group that suffered from migraine, and 89 were put in control group without any signs of migraine. Women with a history of hysterectomy and HRT and the patients with history or suspicion for Polycystic Ovary Syndrome (PCOS), endometriosis, hyper/hypothyroidism were excluded from study.

A written questionnaire was filled by participants according to their vernacular language (Persian). The questionnaire was validated and reliability checked by mean alpha score 0.7 designed by Zandifar A et al., and consisted of two major sections: menstruations-related and headache-related questions [15]. The menstruation-related questions were involved in both quantitative and qualitative responses. Quantitative questions included the duration of periods; interval between periods, number of pad/tampons required on heavy flow day of menstruations, and the number of days that they feel intensity of menstrual blood flow is increased. In order to evaluate the menstrual blood loss, the Pictorial Blood Loss Assessment Chart (PBLAC) was used. PBLAC is a semi-quantitative method for evaluation of menstrual blood loss (score >100) defined by Higham JM and validated by Janssen CA et al., [16,17].

Qualitative questions addressed the woman's perception of the length of periods (4-8 days, <4, >8), the length of the interval between the periods (24-38 days, <24, >38), and the regularity. The intensity of flow and abdominal pain was indicated as mild, moderate, severe, defined by WALIDD score [18]. The participants were also asked about the onset, current intensity, frequency, and duration, as well as about the following headache features and associated symptoms: vomiting, nausea, photophobia, phonophobia, laterality, aura, throbbing, worsening by routine physical activity.

STATISTICAL ANALYSIS

Descriptive statistics were utilised to characterise the study population. All results were expressed using the lowest, median, highest data, frequency and percentage. To control the effect of defaceable variables, statistical tests such as independent t test, was used. Logistic regression was used for effectiveness of migraine. The present authors also used Spearman coefficient of correlation for finding quantitative variables and chi-square test for comparison variables. All analysis was expressed as the mean±SEM at the level of 0.05 and all results were evaluated by SPSS version 22.00 statistical software.

RESULTS

In the control group, 55 people (61.8%) were married while in the case group 62 (72.1%) women were married. There was no considerable difference in the level of education, and both groups had pre-university degrees (p=0.164) [Table/Fig-1].

Variable		Control (n=89)	Case (n=86)	p-value
Age*		31.07±7.63; (18,49)	32.41±8.39; (18,49)	0.271
BMI*		24.05±4.03; (17.19,39.04)	25.28±5.42; (16.42,45.84)	0.091
Marital status‡	Single	34 (38.2)	24 (27.9)	0.148
	Married	55 (61.8)	62 (72.1)	
Medical problem‡	Heart problem	1 (1.1)	6 (7)	0.061
	Aspiration	2 (2.2)	5 (5.8)	0.272
	Digestion	7 (7.9)	17 (19.8)	0.022
	Endocrine	6 (6.7)	3 (3.5)	0.497
	Haematology	11 (12.4)	3 (3.5)	0.031
	Psychiatry	6 (6.7)	8 (9.3)	0.532
	Allergy	5 (5.6)	6 (7.1)	0.696
	Urology	4 (4.5)	2 (2.3)	0.682
Education‡	Primary school/illiterate	13 (14.6)	24 (27.9)	0.164
	Diploma	28 (31.5)	29 (33.7)	
	Technician	10 (11.2)	6 (7)	
	B.S	20 (22.5)	12 (14)	
	MS/MD/PhD	18 (20.2)	15 (17.4)	

[Table/Fig-1]: Comparison of demographic characteristics between cases and controls.
*data are shown as mean±SD; median(min, max); ‡data are shown as N (%)
Independent T-test; SPSS

The proportion of women with menstrual cycle <24 was 25.6% and 10.1% in case and control group in order (p=0.020). Also, the proportion of women with menstrual cycle >38 days' in case group 12.8% vs 11.2% in control group which showed a significant relation, while the proportion of women with a duration of 24-38 days was 61.6% in case group vs 78.7% in control group [Table/Fig-2]. As in [Table/Fig-3], by controlling factors such as age, BMI and other variables, pictorial score was found to affect migraine in a way that the risk of getting migraine would increase to 1% just by increasing 1 unit of the scale (OR=1.01: p=0.031). The characteristics of headache in case group are illustrated in [Table/Fig-4].

Variable		Control n=89	Case n=86	p-value
Pictorial score		90 (82.5); (7,400)	99 (141.5); (5,310)	0.166
Cycle duration	Less than 24 days	9 (10.1)	22 (25.6)	**0.020**
	24-38 days	70 (78.7)	53 (61.6)	
	More than 38 days	10 (11.2)	11 (12.8)	
Period regularity	Irregular	19 (21.3)	18 (20.9)	0.445
	Regular, more than 5 days	21 (23.6)	51 (59.3)	
	Regular, less than 5 days	49 (55.1)	17 (19.8)	
Menstrual duration	Less than 4 days	6 (6.7)	15 (17.4)	0.025
	4-8 days	77 (86.5)	60 (69.8)	
	More than 8 days	6 (6.7)	11 (12.8)	
Dysmenorrhea		48 (53.9)	35 (40.7)	0.080
Any consumption of drugs related to menstruation		0 (0)	0 (0)	
Delivery type	None	48 (53.9)	36 (41.9)	0.405
	César	17 (19.1)	19 (22.1)	
	NVD	18 (20.2)	25 (29.1)	
	Both NVD and César	6 (6.7)	6 (7)	
Contraceptive	None	37 (41.6)	23 (26.7)	0.139
	Pill	8 (9)	16 (18.6)	
	Surgery	5 (5.6)	2 (2.3)	
	Withdrawal	18 (20.2)	19 (22.1)	
	Barrier	14 (15.7)	20 (23.3)	
	IUD	7 (7.9)	6 (7)	
Amenorrhea		0 (0)	0 (0)	
Parity number	None	48 (53.9)	34 (39.5)	0.047
	One	11 (12.4)	12 (14)	
	Two	16 (18)	19 (22.1)	
	Three and more	14 (15.7)	21 (24.4)	
Child number	None	49 (55.1)	36 (41.9)	0.078
	One	14 (15.7)	17 (19.8)	
	Two	20 (22.5)	22 (25.6)	
	Three and more	6 (6.7)	11 (12.8)	
Abortion	None	75 (84.3)	65 (75.6)	0.326
	One	12 (13.5)	19 (22.1)	
	Two or more	2 (2.2)	2 (2.3)	

[Table/Fig-2]: Comparison of menstruation related history between cases and controls.
Independent T-test; SPSS

Moreover, there was no significant linear relationship among cycle duration, period regularity, and menstrual duration, dysmenorrhea, on severity and duration of headache [Table/Fig-5]. No significant

Variable	B	SE	p-value	OR	95% CI for OR	
					Lower	Upper
Age	-0.02	0.03	0.503	0.98	0.93	1.04
BMI	0.05	0.04	0.209	1.05	0.97	1.14
Pictorial score	0.01	0.002	0.031	1.01	1.00	1.01
Parity number	0.21	0.18	0.237	1.23	0.87	1.75
Cycle duration (ref: More than 38 days)						
Less than 24 days)	1.41	0.80	0.075	4.09	0.87	19.34
24-38 days	0.22	0.59	0.704	1.33	0.40	3.95
Menstrual duration (baseline: less than 4 days)						
4-8 days	-1.71	0.62	**0.006**	0.18	0.05	0.61
More than 8 days	-1.94	0.95	**0.041**	0.14	0.02	0.92

[Table/Fig-3]: Logistic regression of migraine risk factors.
logistic regression; SPSS V22

Variable	Mean±SD	Med (IQR); min-max
Age at onset	23.6±5.37	24 (9.5); 12-32
Headache timing	15.47±17.73	8(17) 4-72
Pain severity	7.42±1.58	8 (3) 1-10
Categorical variable	**Levels**	**N (%)**
Pain relief number	0	6 (7)
	1	53 (61)
	2	25 (29.1)
	3	2 (2.3)
Pain duration	For months	12 (14)
	For years	74 (86)
Pain frequency	once a month	19 (22.1)
	once a week	20 (23.3)
	two times or more in a week	42 (48.8)
	daily	5 (5.8)
Pain location	alternative	63 (73.3)
	one sided	10 (11.6)
	bilateral	13 (15.1)
Quality	Pulsatile	74 (86)
	Tensional	12 (14)
Aura	none	65 (75.6)
	Visual	14 (16.3)
	Sensory	4 (4.6)
	olfactory	2 (2.3)
	visual and olfactory	1 (1.2)
Pain provoker	light	4 (4.7)
	noise	5 (5.8)
	smell	2 (2.3)
	Daily activity 0	2 (2.3)
	stress	1 (1.2)
	light and noise	20 (23.3)
	light and noise and daily activity	41 (47.7)
	light and noise and smell	11 (12.8)
Associated symptoms	none	10 (11.6)
	Nausea	54 (62.8)
	Nausea and vomiting	21 (24.4)
	others	1 (1.2)
Precipitating factor	none	51 (59.3)
	menstruation	35 (40.7)
Family history of migraine		64 (74.4)

[Table/Fig-4]: Charectristics of headache in case group.

Variable		Headache severity (mean±SD; med (min, max))	p-value	Timing of headache (hour) (mean±SD; med (min, max))	p-value
Cycle Duration	less than 24 days	7.71±1.65; 8 (4,10)		16.27±19.61; 8 (2,72)	
	24-38 days	7.26±1.61; 7 (1,10)	0.429	16.17±18.41; 8 (4,72)	0.800
	more than 38 days	7.64±1.29; 8 (6,9)		9.27±6.53; 6 (5,24)	
Period regularity	Irregular	7.41±1.5; 6 (6,10)		17.72±21.15; 9.5 (2,72)	
	regular/more than 5 days	7.07±1.59; 7 (4,9)	0.582	21.64±24.48; 8.5 (4,72)	0.735
	regular/less than 5 days	7.52±1.61;8 (1,10)		12.87±13.87; 7.5 (4,72)	
Precipitating factor	None	7.65±1.27; 8 (5,10)	0.149	18.53±21.36; 8(4,72)	0.210
	Menstruation	7.11±1.90; 7 (1,10)		11.31±9.89; 6 (4,48)	
Menstrual duration	less than 4 days	6.71±2.02; 7 (1,9)		12.80±17.38; 7 (2,72)	
	4-8 days	7.57±1.40; 8 (5,10)	0.344	15.52±17.64; 7.5 (4,72)	0.860
	more than 8 days	7.55±1.81; 8 (4,9)		17.64±19.59; 10 (4,72)	
Dysmenorrhea	No	7.63±1.36; 8 (5,10)	0.305	15.51±18.09; 8 (4,72)	0.717
	Yes	7.12±1.84; 7 (1,9)		15.03±17.33; 7 (2,72)	
Contraceptive	None	6.87±1.87; 7 (1,9)		9.74±7.54; 6 (4,24)	
	Pill	7.813±1.22; 8 (5,9)		14.25±8.13; 12.5 (4,24)	
	Surgery	8±1.41; 8 (7,9)	0.350	39±46.67; 39 (6,72)	0.476
	Withdrawal	7.16±1.74; 7 (4,10)		14.84±17.71; 8 (4,72)	
	Barrier	7.95±1.31; 8 (6,10)		18.55±23.96; 6 (2,72)	
	IUD	7.5±1.05; 7.5 (6,9)		22.33±25.48; 14 (5,72)	
Abortion	No	7.44±1.59; 8 (1,10)	0.814	15.15±16.55; 8 (2,72)	0.427
	Yes	7.38±1.57; 8 (4,10)		15.81±21.26; 6 (4,72)	

[Table/Fig-5]: Patients' comparison of (headache) severity and headache timing according to the period history.
chi-square test

		Parity num	Child num	Pictorial score	Age	Age at onset	BMI
Headache severity	rho	0.15	0.18	0.04	0.02	0.01	-0.07
	p-value	0.159	0.103	0.714	0.870	0.903	0.543
Timing headache	rho	0.18	0.245	0.02	0.07	0.08	0.06
	p-value	0.095	0.023	0.850	0.521	0.481	0.605

[Table/Fig-6]: Correlation of (headache) severity and headache timing and patients characteristics.
Spearman correlation coefficient

relationships between any of variables such as, the number of births (r=0.15), number of children (r=0.18), pictorial score (0.04), age (r=0.02), age of onset of headache (r=0.01), BMI (r=-0.07) [Table/Fig-6].

DISCUSSION

Following study considered the prevalence of migraine which is significantly higher among women with oligomenorrhea, polymenorrhea, also in women with abnormal menstrual duration

(<24 or >38) [19]. This study was designed to compare women in reproductive age, as prior studies reported the prevalence of migraine among women in reproductive age is more than twice of men in the same age, there is a significant decline in rate of migraine after 65 years of age in both sexes [20,21]. Since menarche, hormonal changes affect the intensity and timing of migraine attacks in women. However, the present authors achieved no significant influence on the intensity or time duration of headache in the present study. Migraine in women in adolescent and reproductive age is more prolong and more resistant to treatment in comparison to women in non-productive ages.

In a case-control study by Tietjen GE et al., the frequency of menorrhagia was evaluated and it was defined by at least 3 severe consecutive menses and Endometriosis in migraine sufferers which finally resulted in no signs of episodes of migraine [10]. They enrolled 50 women who suffered from migraine at the age of 22-50. They were also diagnosed to have migraine, and based on the international headache society's criteria; they all were compared with 52 healthy women. It has been revealed that the women with migraine are more susceptive to menorrhagia and endometriosis, as the amount of menorrhagia in women with migraine was measured (63% vs 37%) (p=0.009). The results of menorrhagia are similar to present study. In 2015, Spiering ELH and Padamse A, published a research during which the menstrual cycle abnormalities in acute and chronic migraine were investigated, and 96 women ageing 18-45 years were examined via questionnaire and they were separated into two different groups [22]; including episodic and chronic migraine. Data recorded menstrual cycle disorders consisted of oligomenorrhea, polymenorrhea, irregular cycles of dysmenorrhea, menorrhagia, and finally the prevalence of menstrual cycle disorders. It has been illustrated that the percentage of such features in group with chronic migraine was 2.41% vs 2.22% in other groups. Furthermore, the prevalence of dysmenorrhea was 51% vs 9.28% in women with chronic migraine showing the higher proportion rather than that in episodic ones (p≤0.05). The result of this study is in line with prior studies, which showed the higher number of chronic migraine between migrainous populations suffering from menstrual disorders.

Neurogenic inflammation is another hypothesis to explain migraine pain [23]. According to this theory, inflammation agents play a main role of sensitisation nociceptors and induce migraine headache. A common origin of pain signals is trigemino-vascular structure in the meninges which carry out pain to the cortex [24]. Trigemino-vascular activation causes the release of nociceptors neuropeptides such as Calcitonin Gene-Relatedpeptide (CGRP), prostaglandins, Vasoactive Intestinal Peptide (VIP), Somatostatin (SST), Substance p (SP). Release of these inflammatory agents induce a cascade mechanism which consist of dilation of cerebral arteries, increase cerebral blood flow, increase sensitisation of nociceptors and increase pressure and pain of migraine [23,25,26]. As a consequence of this theory, elevated CGPR and other nociceptors neuoropeptides which seems to be increasing in migraineous women during migraine attack [27-29] induced peripheral and central sensitisation, perceive as headache, photophobia, and phonophobia [30]. Menstrual migraine is a special type of migraine influenced by neuroendocrine fluctuation due to menstrual cycle. Reduction of oestrogen levels prior to luteal phase may induce menstrual migraine attacks more feasible in premenstrual period that triggered by oestrogen withdrawal after high oestrogen level [31]. MacGregor EA et al., investigated migraine prevalence among 38 migraineous women, comparison revealed that the incidence of period is raised with falling in oestrogen level during the late luteal or early follicular phase, in comparison to elevated oestrogen phase [32]. Further migraine occurring during menstruation bleeding is more severe than other times [33]. In a study by Granella F et al., assessed menstrual related migraine among 64 women, reported that, migraine attacks which occurred between 2 days prior to menstruation time to day 7 of menstruation cycle [34], last long and less responsive to drugs, also they have high recurrency rate as compared to other episodes of migraine [35]. Moreover, endometrial prostaglandins level increase from follicular phase to luteal phase and become much higher during timeframe. Releasing of the Prostaglandins as an inflammatory agent into blood circulation inducing neurogenic inflammation [36]. Prostaglandin indicated to be a related biochemical factor for menstrual disorders, but there are other correlated conditions such as oestrogen withdrawal may inevitably coordinate in migraine accuracy in subjects with menstrual disorders. Therefore migraine pain may impute to inflammation and similar biochemical changes [33].

Limitation(s)

Due to lack of resources, the present authors did not examine the mechanism of menstrual disorders and its effectiveness on migraine. However, this study could not found out any relation between severity and duration of headache with menstrual disorders.

CONCLUSION(S)

According to the finding of the present study, Migraine is more common among women with menstrual disorders. Further research is needed to find the exact mechanisms behind that.

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