

Correlation between correction of Menstrual Irregularity and Diminution of Cyclic Mastalgia

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Article Info

doi:10.30699/jogcr.4.4.135

Received: 2020/04/15;

Accepted: 2020/05/19;

Published Online: 19 May 2020;

Use your device to scan and read the article online



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ABSTRACT

Background & Objective: Cyclic mastalgia is clinically related to alterations in sex hormone levels during the menstrual cycle. A derangement in normal menstrual cycle leads to exacerbated mastalgia; which can also cause menstrual irregularities and abnormal uterine bleeding (AUB). A decrease in severity of mastalgia is observed in patients with simultaneous cyclic mastalgia and menstrual irregularities/AUB, following correction of menstrual irregularity. This study was designed and conducted to investigate the possibility of whether correction of menstrual irregularities can diminish cyclic mastalgia.

Materials & Methods: This case-control study was carried out on women suffering from simultaneous mastalgia and menstrual irregularity. One-hundred and fifty patients were randomly distributed between case and control groups, each including 75 patients. Patients in both groups took 100 mg vitamin E oral tablet daily for 3 months. Patients in case group also received low-dose oral contraceptive pills (OCP-LD) to correct menstrual irregularity. Patients recorded the severity of mastalgia in Cardiff breast pain chart using Visual Analogue Scale (VAS).

Results: At the beginning of study, there was no significant difference in the number of days suffering from mild and severe mastalgia between two groups. However, at the end of the study, mild and severe mastalgia reduced significantly in the case group compared to the control group ($P=0.003$ and $P=0.045$, respectively).

Conclusion: In women with cyclic mastalgia, correction of menstrual irregularity leads to significant pain relief. Correcting menstrual irregularity is suggested as a first-line treatment in women with mastalgia.

Keywords: Abnormal Uterine Bleeding, Breast Pain, Mastalgia, Menstrual Irregularity, Oral Contraceptive, Vitamin E



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Introduction

Cyclic mastalgia is mild breast pain that occurs before menstrual cycle and lasts for less than 5 days. If the pain is severe, it lasts for more than 5 days, interfering with daily activities, and/or forcing the patient to seek medical care, which is considered abnormal. Mastalgia is among the most common causes of concern, and leads to repeated medical visits by women (1-3). Near two-thirds of women with mastalgia experience a disruption in their daily activities and about 10% of them require treatment. Cyclic mastalgia is the most common type of breast pain and accounts for 60-70% of mastalgia cases (4).

Most patients with mastalgia are concerned about the probability of breast cancer (5). In breast cancer, pain occurs in advanced stages, is unilateral, localized, and noncyclic. Mastalgia is rarely a sign of cancer (6). Cyclic mastalgia is very common (6) and closely associated with alternations in sex hormone levels during the menstrual cycle. Mastalgia usually begins in the luteal phase and ends with the onset of menstruation. Due to correlation between cyclic mastalgia and sex hormone alterations in menstrual cycle, it seems that derangements in this cycle exacerbates mastalgia. Measuring serum levels of sex

hormones in these patients rarely indicates irregularity and is not usually performed. Taking drugs containing female sex hormones, e.g. to treat ovarian dysfunction, usually brings about mastalgia. Breast tissue becomes tender and painful after taking estrogen and progesterone. Hormone replacement therapy (HRT) in postmenopausal women can also cause mastalgia (7).

The major manifestation of menstrual irregularity is abnormal uterine bleeding (hereinafter referred to as AUB). AUB is a prevalent complaint; 10-15% of women experience AUB sometime during childbearing age. AUB is the cause of 30% of women's outpatient visits (6). Any aberration from normal menstruation is called a menstrual irregularity. The characteristics of a normal menstrual cycle are as follows: frequency every 24 to 38 days, bleeding period up to 8 days, and bleeding volume up to 80 mL. Any alternation in these indicators is considered a menstrual irregularity. After ruling out other causes of uterine bleeding, such as inflammation, infection, malignancy, miscarriage, etc., it can be stated that AUB has occurred as the result of a derangement in normal cycle of sex hormones and is considered a menstrual irregularity.

In patients whose mastalgia is associated with menstrual irregularity, it is observed that severity of mastalgia diminishes after correcting the menstrual irregularity. Given the prevalence of mastalgia, it is important to consider the correlation between correction of menstrual irregularity and diminution in severity of mastalgia. The question is whether correction of menstrual irregularity leads to a statistically significant reduction in severity of mastalgia? If this is proven, a new treatment will be proposed for patients with mastalgia who suffer from menstrual irregularity. This study aimed to evaluate the response of cyclic mastalgia to the correction of menstrual irregularity. Examining the scientific databases on Internet revealed no study conducted to assess this correlation.

Materials and Methods

Eligible patients were selected from women visiting the breast disease clinic of Imam Khomeini Hospital affiliated with Tehran University of Medical Sciences, Tehran, Iran, from September 2018 to February 2019. The inclusion criteria were age ≥ 18 years, simultaneous cyclic mastalgia and menstrual irregularity, and consent to enter the study. The exclusion criteria were age < 18 years, breast pain from causes other than cyclic mastalgia, severe menstrual irregularity that required urgent treatment, and no consent to take part in study. The main objectives and conditions were explained to the patients, and those who signed the informed consent entered the study.

This was a case-control study. The calculated sample size was at least 75 patients for each group and duration of study was 3 months. The participants were assigned to the case and the control groups using computer-assisted randomization. Patients in both groups took

100 mg vitamin E oral tablet every day for 3 months. Patients in the case group also took low-dose oral contraceptive pills (OCP-LD) to correct menstrual irregularity. The Cardiff breast pain chart (8), Figure 1, was given to the patients to record their mastalgia. They were asked to complete the chart every day throughout the study period. Instead of using geometric shapes applied in this chart, patients were taught to write numbers indicating the severity of pain, according to Visual Analogue Scale (VAS). Patients were asked not to take analgesic as far as possible. If obliged to, they should record the severity of pain before taking analgesic. They should also record that they took analgesic. Patients were contacted via regular telephone calls during the study period to ensure precise recording of data. Also, a cellphone number was provided to the patients for calling or texting in case of any questions. After 3 months, the charts were collected and patients were re-evaluated for their menstrual status and complaints of mastalgia. This study was designed and implemented following the principles of the Helsinki Declaration (2008) and the rules of medical ethics. Its ethical code, IR.TUMS.IKHC.REC.1396.4537, was issued by the Research Ethics Committee of Tehran University of Medical Sciences.

The data analysis was performed using SPSS 21 (SPSS Inc., Chicago, IL., USA). First, the normality of quantitative variables was evaluated descriptively using skewness and kurtosis. After assessing the normality of the skewness and kurtosis of the data distribution, the Shapiro-Wilk test was used to confirm the normality of the data, which had a normal distribution ($P < 0.05$). To describe the patients' characteristics, descriptive statistical methods, including frequencies, percentages, means, and standard deviations, were applied. The Pearson correlation coefficient was employed to determine the association of smoking and marital status with mastalgia severity. Moreover, the independent T-test and one-way analysis of covariance (ANCOVA) were used to assess the association of the quantitative characteristics, like age, with the severity of mastalgia. Furthermore, the first error level of smaller than 0.5 was considered significant.

DAILY BREAST PAIN CHARTING

Name : _____ **Age:** _____ **Date:** _____

Record the amount of breast pain you experience each day by shading in each box as shown
 प्रतिदिन स्तन में होने वाले दर्द के अनुसार दिखाये गये तरीके में प्रत्येक खाने को रंगिए

Severe Pain अत्याधिक दर्द
 Mild Pain मामूली दर्द
 No Pain कोई दर्द नहीं

For example: If you get severe breast pain on the fifth day of the month then shade in completely the square under 5
 उदाहरण: यदि माह की पाँचवीं तारीख को आपको स्तनों में अत्याधिक दर्द होता है तो 5 के नीचे वाला खाना पूरा रंगे

Please note the day your period starts each month with the letter "P"
 इस माह जिस तारीख को मासिक शुरू हो उस दिन के कोष्ठ में "म" लिखें

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31					
माह	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31					

Note : Please bring this card with you on each visit.
 नोट: कृपया हर बार यह कार्ड अपने साथ लायें।

Figure 1. The Cardiff breast pain chart (8)

Results

A total of 180 candidates were selected to enter the study; eventually, 150 patients were chosen, and using an online software, Randomizer.org, were randomly assigned to two groups of case and control groups with 75 patients in each group. Mean age, weight, height, BMI, and number of menstruation days in two groups were not statistically different ($P < 0.05$) (Table 1).

One-hundred and twenty-two participants (81.3%) were married and the rest (18.7%) were single. One-hundred and twenty-eight participants (85.3%) complained of bilateral mastalgia and the rest (14.6%) complained of unilateral mastalgia. The two groups did not differ significantly in terms of marital status and bilateral/unilateral involvement. Eighteen participants (12%) had a history of smoking. Smoking was higher in the control group than in the case group ($P = 0.020$) (Table 2).

The mean score of mastalgia severity was 5.4 ± 3.4 ranging from 0.95 to 16.8. The mean number of days suffering from severe mastalgia was 4.95 ± 2.29 ranging from 1 to 15 days, and the mean number of days suffering from mild mastalgia was 9.44 ± 4.04 ranging from 3 to 21 days. Mastalgia was divided into mild and severe based on the need to take analgesic. Mild mastalgia did not require analgesic, and severe mastalgia forced the patient to take analgesic. Results of statistical analysis showed that, groups did not have significant difference in number of days suffering from mild and severe mastalgia at the beginning of study. At the end of the study, menstrual irregularity was corrected in all of the patients in the case group. Mild and severe mastalgia, both, diminished significantly in the case group compared to the control group ($P = 0.003$ and $P = 0.045$, respectively) (Table 3). Data obtained from 3 patients in control group was not reliable, and not considered in statistical analysis.

Table 1. A comparison of the quantitative variables (age, weight, height, and BMI and the number of menstruation days) in the two groups

Variables	Group Name	Number	Mean	Std. Deviation	P-value
Age	Treatment	75	32.19	5.952	0.178
	Control	75	33.53	6.239	
Weight	Treatment	75	72.40	7.548	0.951
	Control	75	72.48	8.209	
Height	Treatment	75	1.6501	.04351	0.667
	Control	75	1.6535	.05079	
BMI	Treatment	75	26.29	2.985	0.509
	Control	75	26.64	3.412	
Menstruation days	Treatment	75	5.00	.944	0.177
	Control	75	5.23	1.098	

Table 2. A comparison of the qualitative variables (smoking, marital status, and the side involved in mastalgia) in the two groups

Variables	Status	Treatment	Control	Total	P-value
Marital Status	Single	11	17	28	0.295
	Married	64	58	122	
Smoking	Yes	6	12	18	0.020
	No	69	63	132	
Side of mastalgia	1-sided	13	9	22	0.125
	2-sided	62	66	128	

Table 3. A comparison of the number of days suffering from mild and severe mastalgia in the two groups before and after the treatment

Variables	Group Name	N	Mean	Std. Deviation	P-value
Days with severe mastalgia before the treatment	Treatment	75	4.93	2.617	0.120
	Control	72	4.96	1.931	
Days with severe mastalgia after the treatment	Treatment	75	3.47	2.683	0.045
	Control	70	2.83	2.559	
Days with mild mastalgia before the treatment	Treatment	75	8.75	3.821	0.096
	Control	72	10.17	4.176	
Days with mild mastalgia after the treatment	Treatment	75	5.04	3.818	0.003
	Control	72	5.82	4.495	

Discussion

Various treatments are offered for cyclic mastalgia, including a variety of anti-inflammatory drugs, diuretics, androgenic drugs, anti-estrogen, anti-prolactin, and fatty acid metabolism modifiers. In recent years, new herbal medicines have also been studied (9). The reason for this wide range of treatments is that none of them succeeds on its own. It seems that the mechanism which leads to mastalgia has not yet been well understood. A hypothesis is that cyclic mastalgia occurs due to hormonal stimulation of breast tissues in late luteal phase (10). Accordingly, menstrual cycle disorder and resulting menstrual irregularity can change the pattern of cyclic mastalgia. Menstrual irregularity caused by hypothalamic-ovarian axis imbalance may be associated with ovulation disorder and abnormal change in the serum levels of female sex hormones. Alterations in serum sex hormone levels are almost always within the normal range, and laboratory tests often do not show abnormal findings. Wypych K *et al.* examined 119 women with cyclic mastalgia aged 16 to 55 years (mean 35.4 years). Ovulation-free cycles occurred in 63% of them. Vaginal smears showed an increase in estrogen function by 24.1% and a decrease in progesterone effects by 20.3%. Serum estradiol levels increased by 10.6% and progesterone levels decreased by 39.1% in these

patients. The mean endothelial progesterone-estrogen index was reduced to 0.99 (11). Irregular bleeding occurred in 16.8% of these women, aged 41 to 48 years.

One hypothesis about cyclic mastalgia is the relative deficiency of progesterone production. Oral, parenteral, and topical progesterone taken in luteal phase significantly improves mastalgia in 66-80% of women (12-13). Also, relative increase in serum estrogen level is an important causative factor for cyclic mastalgia; and estrogen inhibitors, such as tamoxifen, are the drugs of choice for first-line treatment of resistant-mastalgia (14). Thus, relative alterations of serum estrogen and progesterone levels play an important role in cyclic mastalgia, which if corrected, by reducing estrogen level and increasing progesterone level in luteal phase, can help inhibit mastalgia. Clinical observation in patients who suffer simultaneous cyclic mastalgia and menstrual irregularity showed that with correction of menstrual irregularity, mastalgia diminishes significantly. Menstrual irregularity is a manifestation of sex hormone disorder which also leads to mastalgia, hence correction of menstrual irregularity by correcting hormonal disorder will also control mastalgia. Therefore, mastalgia can be controlled by correcting menstrual

irregularity. This study was designed and implemented to test this hypothesis, and the results are in favor of its validity. Based on the results of statistical analysis, the groups did not have significant difference in number of days suffering from mastalgia at the beginning of the study. However, at the end of study, two groups differed significantly in number of days suffering from mild and severe mastalgia ($P=0.003$ for mild mastalgia and $P=0.045$ for severe mastalgia) (Table 3).

Patients in both groups took 100 mg vitamin E oral tablet/day during the study period. Vitamin E is a well-known first-line drug in treatment of cyclic mastalgia that does not affect the sex hormone cycle. In patients with mastalgia, the level of saturated fatty acid esters is high and the level of unsaturated fatty acid esters are low; this results in an increased binding tendency of hormonal receptors. Vitamin E can prevent the oxidation of unsaturated fatty acids, due to its antioxidant effect. This leads to an increase in the level of unsaturated fatty acid esters which reduces binding tendency of hormonal receptors, thus reducing the severity of mastalgia. Vitamin E was chosen as the baseline treatment and was taken by patients in both groups so they were matched in this regard.

Therefore, significant decrease in mastalgia in the case group can only be the result of correction of menstrual irregularity.

The limitations of this study were the relatively small number of patients and the short duration of study. We used a software to randomly distribute the patients between the case and the control groups. However, this study was not registered at any official clinical trial site; therefore, we named it a case-control study. The authors are designing a randomized clinical trial with larger number of patients and longer follow-up to be implemented in near future.

Conclusion

In women with cyclic mastalgia, correction of menstrual irregularity leads to significant pain relief. Correcting menstrual irregularity is suggested as a first-line treatment in women who complain from mastalgia and suffer menstrual irregularity.

Acknowledgments

The authors would like to thank all those who helped them writing this paper.

Conflict of Interest

Authors declared no conflict of interests.

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How to Cite This Article:

Karimian F, Akhavan S, Marzoughi A, Keramati M R, Ashouri M. Correlation of Menstrual Irregularity and Diminution of Cyclic Mastalgia. J Obstet Gynecol Cancer Res. 2019; 4 (4) :135-140

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