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Effectiveness of progesterone in management of cyclic mastalgia among adolescents: A clinical trial

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Abstract

Background: Mastalgia can be defined as "breast pain sufficient for medical consultation. Although mastalgia remains an under-reported and poorly recognized illness, it is the most frequent reason for breast consultations in family practice. Breast pain is recently classified into: cyclic mastalgia, non-cyclic mastalgia, and non-breast chest pain. Despite of wide varieties of regimens for management of cyclic mastalgia, there is no standard one.

General objective of the study: was promotion of adolescent health and the specific one was evaluation of the effectiveness of progesterone pills versus placebo on reducing the pain of cyclic mastalgia and minimizing its impact on education, daily activities, sleep and quality of life.

Methods: Two hundred and twenty three adolescent females (aged 14-18 years) with cyclic mastalgia 6 months before conduction of the study were recruited to a randomized, double-blind, placebo-controlled, clinical trial. Eligible patients were randomly assigned after their consent into two groups. Patients in the intervention group received progesterone pills for 6 menstrual cycles. Patients in the placebo group took placebo in a similar way. Breast pain, tenderness, nodularity and impact of pain on lifestyle parameters were assessed before, during and after the intervention based on patients' daily self-assessment using the Visual Analogue Scale.

Results: Severity of mastalgia and its impact on education, daily activities, sleep and quality of life pre and post trail in each individual group and in-between the groups were statistically insignificant ($P>0.05$). Development of adverse reaction were significantly much higher among progesterone versus placebo group ($P<0.001$) such as headache (19.1% vs.5.6%), appetite changes (16.2% vs.2.8%), acne (17.6% vs.10.8%), and mood swings (14.7% vs.2.1%).

Conclusion: Progesterone have no superiority over placebo in reducing the cyclic mastalgia rather than it induce a variety of adverse reactions

Keywords: Cyclic Mastalgia, Visual Analogue Scale, Progesterone

1. Introduction

Mastalgia can be defined as "breast pain of sufficient severity for females to seek medical advice" [1]. Although mastalgia remains an under-reported and poorly recognized condition specialy among adolescent with recent menstruation, it is the most frequent reason for breast consultations among adolescents in family practice [2]. WHO identifies adolescence as the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to19 years. Some breast pain or discomfort is experienced by about two thirds of females during the premenstrual phase [3]. Mastalgia may be associated with breast nodularity [4]. A recent classification of breast pain consists of three types: cyclic mastalgia, non-cyclic mastalgia, and non-breast chest pain [5]. Cyclic mastalgia occurs in the second half of the menstrual cycle and resolves with the onset of menstruation. It is typically reported as fullness or heaviness in the breasts and usually affects the upper outer quadrant [6]. Non-cyclic mastalgia may occur at any stage of menstrual cycle and usually not affected by it. It may be has a progressive or interrupted course, and is often unilateral or localized to one part of the breast [7]. Non-breast chest pain can originate from any other chest structures such as lung, heart, chest wall and even the abdomen (typically from gall bladder) [8]. Diagnostic strategies for adolescent females with mastalgia varies from ECG, chest x ray, breast ultrasound, breast mammography, hormonal assay to fine needle biopsy [9]. Most of females (85%) with mastalgia just need reassurance only that, the pain is not due to cancer [10]. Although the prevalence and causes of mastalgia has not been well established, some authors have concerned elevated estrogen and low progesterone levels, or an abnormal estrogen/progesterone ratio. They also reported that, progestogen supplementation can correct this 'relative hyper oestrogenism' so it can improve the mastalgia [11, 12]. Hence, there is a currently much controversy regarding the role of progestogen supplementation in the treatment of cyclic mastalgia, so the main objective of this study was adolescent health promotion and the specific objective was evaluation of the effectiveness of progesterone pills compared with placebo

on reducing the pain of mastalgia and its impact on education, daily activities, sleep and quality of life of adolescent females.

2. Subjects & Methods

Type of the study: The study was a randomized double blind placebo-controlled clinical trial.

Sample size: The maximum number of patients required for this design was 135 to have 80% power of the study, 95% confidence interval at 5% level of significance. It was increased to 223 to overcome any dropping out during the study procedure.

Population of the study: Adolescent Females (14-18 year-old) attending the family health center-Alshoadaa, Mnoufia, Egypt with mastalgia and fulfill both inclusion and exclusion criteria.

Inclusion criteria: Adolescent females having moderate to sever mastalgia for more than 6 cycles.

Exclusion criteria: Adolescent females who: 1) have irregular cycles, 2) Using drugs as, progesterone, danazol, vitamin B, evening primrose oil, non-steroidal anti-inflammatory drugs. 4) have breast abnormalities, uncompensated cardiac insufficiency, angina, hepatic failure, history of cancer or thrombo-embolic disorders (all can be exaggerated by progesterone supplementation).

Tools of the study: 1) Linear Visual Analogue Scale (VAS) which simply indicates the intensity of pain on a graduated line from 0 to 10 (0 equals no pain; 10 equals the most worst imaginable pain). It is more beneficial than a descriptive version (as "I feel terrible") because we not having to verbalize and describe the pain, we can get a truer understanding of what the level of pain actually is and we can judge how well any treatment options or preventive strategies are working. ''The overall severity of pain'' and ''the effect of pain on quality of life and the lifestyle parameters '' (education, daily activities and sleep) were subjectively measured and marked by the patients themselves. Literate patients or a family member in the case of sub-literate were taught to maintain a pain diary during the follow up period [13].

2) Measurement of health related quality of life (HRQL): A VAS ranging from 0 to 10 was presented to the respondents who were told that, zero signifies HRQL associated with death, and 10 HRQL associated with perfect health). The respondents were asked to report verbally the number on the scale, which represents their general HRQL during the previous month [14, 15].

Procedure of the study: 1) All patients having mastalgia (No 223) were enrolled in a none medicated baseline cycle where they were subjected to: A) Full history taking. B) Thorough clinical examination. C) Breast pain score (BPS) estimation .Patients were trained on daily recording of their breast pain on a linear VAS from the first day of menstruation and the mean of the daily scores within a menstrual cycle was calculated. Patients with a score of ≥ 4 verifying moderate to severe mastalgia were assigned as qualified patients. 2) Qualified patients (No 182) entered a single-blind run-in phase designated the placebo lead-in cycle where they received placebo for one menstrual cycle. Only those having BPS reduction <25% after the placebo lead-in cycle (No 168) were entered the subsequent randomized double-blind placebo-controlled clinical trial. 3) Patients were randomly assigned into two groups. Patients in the progesterone group (No 84[16 withdrawn]) received progesterone once per day from day 10 to 26 of the menstrual cycle and patients in the placebo group (No 84[13 withdrawn]) took placebo in a similar manner. The active ingredient of a progesterone tablet was Levonorgestrel 0.03 mg, and the inactive ingredients of the placebo tablets were maize starch. The patients were recommended not to use any other medications during the study. Breast tenderness and nodularity were subjectively assessed by patients on one day of the luteal phase of the cycle using the VAS. At pre and post trail visits, 10 ml of blood was taken and centrifuged within 2 hour of vein-puncture. Serum samples were stored at – 20 °C until, where they were assayed at the end of the study for sex steroid hormones using the radioimmunoassay technique. The treatment code was held by a pharmacist and broken only when the patient completed the study or withdrawn for ethical issue.

3. Evaluation of Intervention

After initial evaluation, patients were seen monthly for 6 months. Specific enquiry into side-effects was made at each clinic visit; also weight and menstrual regularity were recorded .Each patient was examined late in each menstrual cycle and breast tenderness and nodularity were recorded. The patient's subjective assessment of pain impact on HRQL and life style parameters as education, daily activities and sleep was assessed using a 10 cm linear VAS.

4. Statistical Analysis

The results were collected, tabulated and statistically analyzed using a personal computer with SPSS (Statistical Program for Social Sciences) software program, version 14 under windows XP. Quantitative data were expressed as mean and standard deviation ($\chi \pm SD$) and analyzed by Student's t test .Qualitative data were expressed as number and percentage (No. and %) and analyzed by Chi- Square test (χ^2). The level of significance was set at a P value < 0.05.

5. Results and Discussion

Mastalgia is the commonest reason for adolescent females with breast related symptoms to consult her family physician. Mastalgia may be severe enough to interfere with education, daily activities, sleep and HRQL which are the indicators for active management. Causes and optimal treatment of mastalgia are still inadequately defined [16]. Because of increasing awareness about breast cancer and the fear that, breast pain may be a sign of it, more and more females are seeking for treatment of mastalgia. As breast cancer seldom presents with pain, patients are often misdiagnosed by ill trained physicians with no formal evaluation, no reassuring explanations and often with a prescribing of drugs which have no established therapeutic values or drugs with some or even potentially dangerous side-effects [17].

Many of lifestyle and medical interventions have been recognized to relieve mastalgia with varying responses. In this study, analysis of the past treatment revealed that, none of the patients had been reassured about the nature of the pain and the absence of serious breast pathology. As reassurance is the main management of mastalgia, it is not surprising that, these adolescent females continued to seek further advice and management, for what they perceived as a serious illness. 45% of them had received analgesics which are considered non-standard drugs as the literatures supporting their use are conflicting and currently inconclusive. Only a minority of the patients had been treated with danazol, bromocriptine and

evening primrose. Many articles showed that, both danazol and bromocriptine had adverse reactions (22% vs. 45%) and therefore their prescription must be carefully balanced versus the severity of mastalgia [9]. Only few medications have been studied in controlled trials and showed more effectiveness than placebo such as danazol, bromocriptine, evening primrose oil, topical or systemic non-steroidal anti-inflammatory drugs, and tamoxifen. However, the potentially serious adverse effects and the costs of these medications limit their use [18]. There is a controversy on the role of progestogens in the treatment of mastalgia. Mauvais-Jarvis et al., study showed a low luteal progesterone levels among adolescent females with mastalgia. So they recommended progestogen to ameliorate the illness [11]. To the best of our knowledge; there are lake of reports that evaluates the effect of oral progesterone in the management of mastalgia among adolescents [18]. We conducted a randomized, double blind, placebo-controlled study to investigate the effects of systemic use of progesterone in management of cyclical mastalgia. The study showed that, there is no significant improvement of the breast pain scores as well as its effect on the lifestyle in both groups during the treatment period. Mastalgia was slightly improved in both groups with no significant deference in-between. Similar to the findings of the current study, a placebo response rate around 14% has been reported previously in patients with mastalgia [10]. This result may be related to the potential impact of psychological factors on the initial response to treatment. Many mastalgia patients are extremely anxious that they may have breast cancer; however reassuring effects by their family physician are likely to alleviate this feeling and contribute to the response of most patients participating in the trial, regardless of received treatment. The conflicting findings between the present study and those of Mauvais-Jarvis et al. [11] are difficult to explain. They gave a sequential administration of an oral progestogen (lynestrenol, 10 mg/day for 15 days/cycle). They reported a spectacular improvement in mastodynia (96%) and nodularity (85%) along with the correction of the systemic hormonal insufficiency which lends biological plausibility to the hypothesis. Their findings were also echoed by Colin *et al*. [19] who reported a useful improvement in mastodynia using the same dosage of lynestrenol in a double-blind trial. He also reported lowered lutealogesterone levels relative to the control group. Evidence of this inadequate corpus luteum function in mastalgia has not been found in a number of other studies examining adolescent females with cyclic mastalgia [20]. According to the results of our study, progesterone has insignificant effect on the patient's lifestyle as a measure for quality of life and this effect was similar to placebo. Pretrial luteal serum progesterone levels were found to lie within the normal range (3-95nmol/l), and did not significantly rise after supplementation with progesterone or on placebo. The mean levels of estradiol were similarly within the normal range (180-1100 pg/mL) for patients before entry and did not significantly change during treatment; also there was no significant change in the estrogen/progesterone ratio either on or off therapy, in addition to development of adverse reaction were significantly much higher among progesterone than placebo group (P<0.001) as headache (19.1% vs. 5.6%), appetite changes (16.2% vs. 2.8%), acne (17.6% vs. 10.8%), skin changes (13.2% vs.3.8%) and mood swings (14.7% vs.2.1%).

6. Tables and Figures

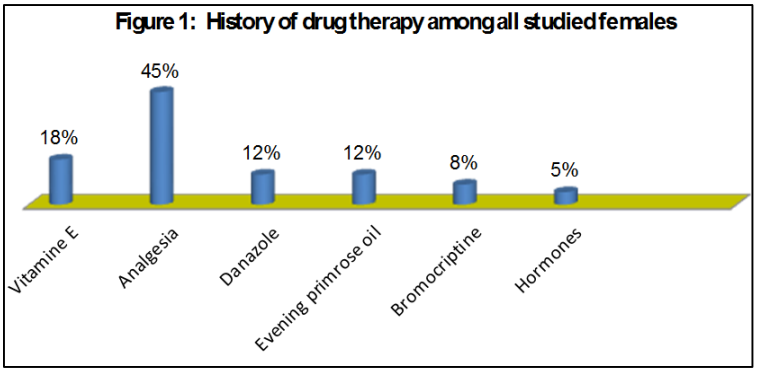

Fig 1: History of drug therapy among all studied females

Table 1: Socio-demographic characteristics of studied groups

Socio-demographic criteria	Females with mastalgia who completed the trail				Test of significance	P value
	Drug group (No. 68)		Placebo-group (No. 71)			
Residence	No.	%	No.	%	χ^2	
Urban	30	44.1	30	42.25		
Rural	38	55.9	41	57.74	0.05	>0.05
Education Level						
Read and write	16	23.5	17	30.0		
Primary	12	17.7	14	19.7		
Preparatory	17	25.0	16	22.5	0.17	>0.05
Secondary	23	33.8	24	33.8		
Socioeconomic level						
High	28	41.17	27	38.0		
Middle	18	26.47	20	28.2	0.15	>0.05
Low	22	32.35	24	33.8		

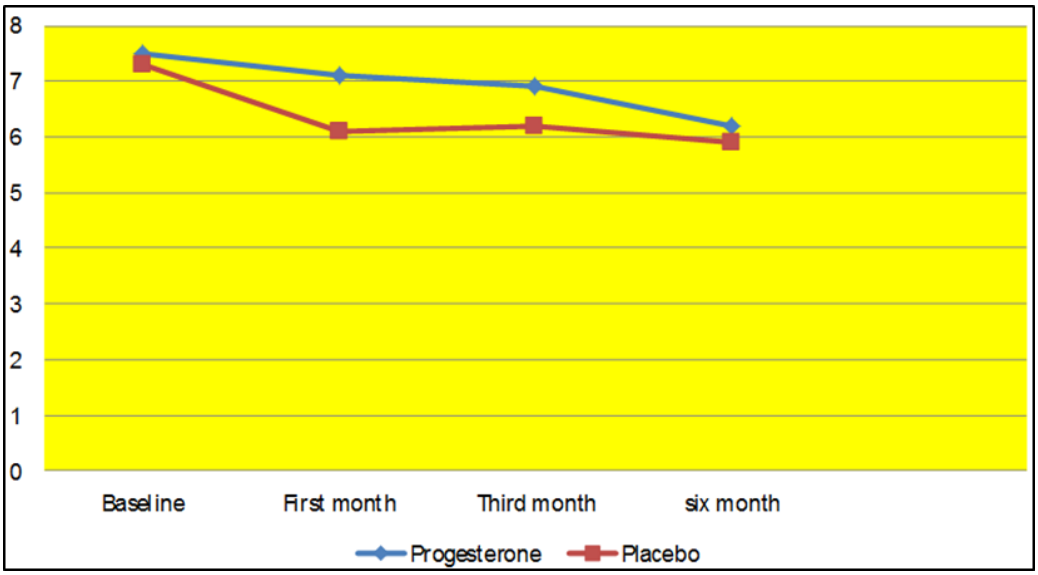

Fig 2: Mean of breast pain scores at the base line and monthly follow up visits of both group

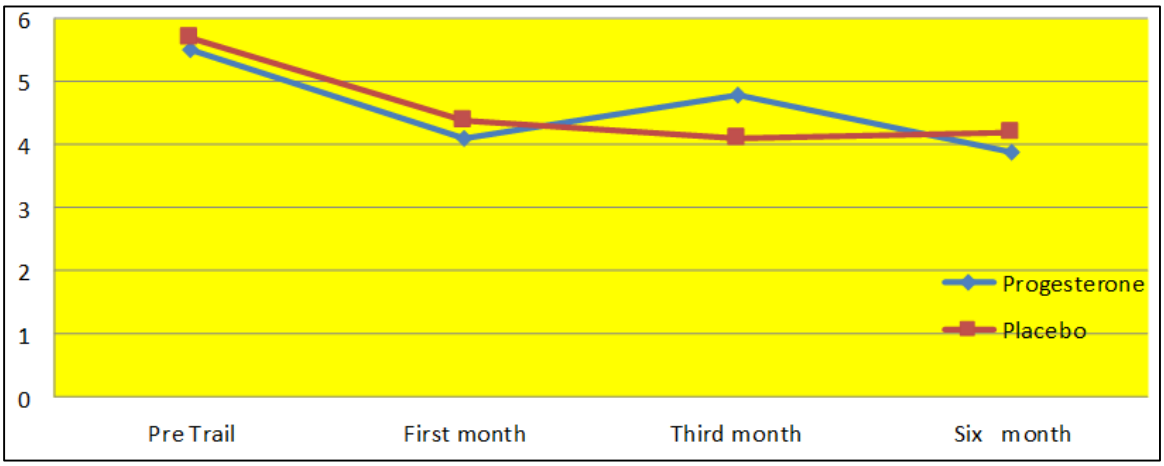

Fig 3: Scores of subjective assessment of impact of progesterone and placebo on quality of life at the baseline and monthly follow up visits

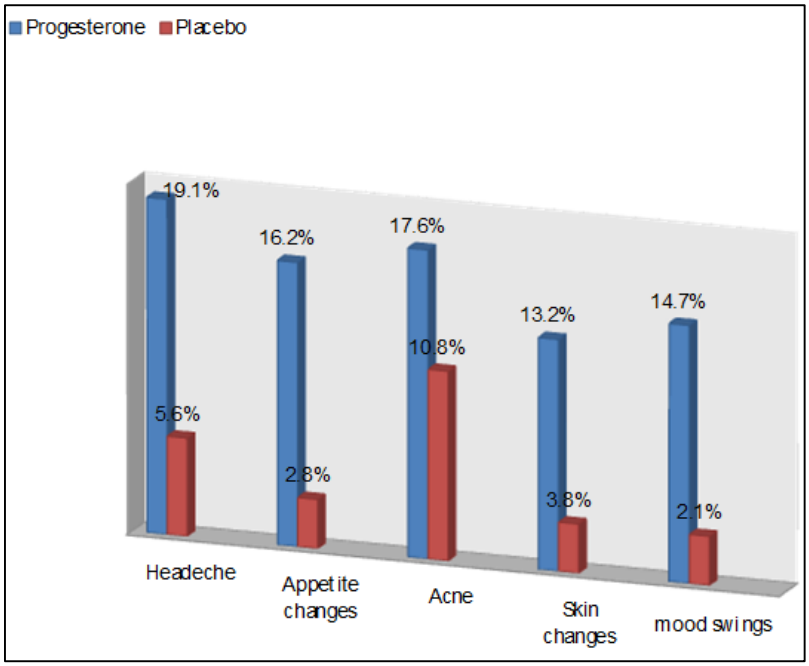

Fig 4: Comparison between progesterone and placebo groups regarding to the development of side effects

Table 2: Comparison between progesterone and placebo groups regarding to the Impact of pain on the lifestyle parameters (education, sleep and daily activities) at pre and post trail assessment

Studied groups	Mean scores (± SD)of subjective assessment of impact of mastalgia on education, sleep and daily activities on VAS			
	Pretrial	Post trail	t test	P value*
Drug group (N0 = 68)				
Impact of mastalgia on education	7.5 ± 0.4	7.6 ± 2.7	0.30	>0.05
Impact of mastalgia on daily activities	5.9 ± 0.8	5.7 ± 2.7	0.59	>0.05
Impact of mastalgia on sleep	7.1 ± 1.2	7.3 ± 3.1	0.50	>0.05
Placebo group (N0 = 71)				
Impact of mastalgia on education	7.1 ± 1.9	6.8 ± 2.8	0.75	>0.05
Impact of mastalgia on daily activities	6.2 ± 1.4	6.1 ± 2.1	0.33	>0.05
Impact of mastalgia on sleep	6.9 ± 1.8	6.6 ± 2.9	0.74	>0.05

*Also comparing both groups either at pretrial or post trail for different items was insignificant (P> 0.05)

Table 3: Comparison between drug and placebo groups regarding to mean of subjective assessment scores of breast tenderness and nodularity at the pre and post trail assessment

Studied groups	Mean scores (± SD)of subjective assessment of breast tenderness and nodularity on VAS			
	Pre-trial	Post-trail	t test*	P value*
Drug group (N0 = 68)				
Breast tenderness	2.8 ± 0.1	2.7 ± 0.8	1.02	>0.05
Breast nodularity	2.6 ± 0.3	2.5 ± 0.4	1.66	>0.05
Placebo group (N0 = 71)				
Breast tenderness	2.8 ± 0.5	2.7 ± 0.1	1.65	>0.05
Breast nodularity	2.2 ± 0.5	2.1 ± 0.6	1.08	>0.05

* Also comparing both groups either at pretrial or post trail for different items was insignificant (P> 0.05)

Table 4: Comparison between drug and placebo groups regarding to the luteal serum hormone levels at the pre and post trail assessment

Studied groups	luteal hormone levels (mean ± SD)			
	Pre-trial	Post-trail	t test*	P value*
Drug group (N0 = 68)				
Estradiol (pg/mL)	229±29	221±32	1.53	>0.05
Progesterone (nmol/l)	21±17	22±19	0.32	>0.05
Placebo group (N0 = 71)				
Estradiol (pg/mL)	222±26	218±22	0.99	>0.05
Progesterone (nmol/l)	21±14	23±19	0.71	>0.05

* Also comparing both groups either at pretrial or post trail for different items was insignificant

7. Conclusions

On the basis of our data, progesterone seems to be ineffective for cyclic mastalgia, as its therapeutic response is no better than placebo in addition to its undesirable side effects.

8. Limitations of the Study

Mastalgia as a subjective variable was hard to quantify and measure its severity. Limited published articles on this topic. Potential impact of psychological factors on treatment response as well as Patient adherence declined with longer duration of intervention.

9. References

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