REVIEW PROF-765

MASTALGIA

DR. MUHAMMAD ABID BASHIR, FCPS (PK)
Assistant Professor of Surgery
Independent Medical College, Faisalabad

Correspondence:
Dr. Muhammad Abid Bashir
Assistant Professor of Surgery
Independent Medical College
177-Jinnah Colony, Faisalabad
Tel: 092-41-617122-24
abidbashir@hotmail.com

INTRODUCTION

Mastalgia or mastodynia can be defined as "breast pain of sufficient severity for a women to seek medical advice". Some breast pain or discomfort is experienced by about 2/3rd of women during the premenstrual phase. It may be associated with increased nodularity[1]. This pain is mild, lasts for a short time in the premenstrual phase but more important, it resolves with menstruation. It can be considered with in the spectrum of "normal".

The development of severe pain and nodularity which may last for most, it not all, the menstrual cycle is considered as abnormal and may interfere significantly with patient's everyday activity. More than half of (69%) women reported some discomfort while 36% had consulted health care personnel, and 11% had moderate to severe pain at the time of study. 48% women reported that mastalgia had affected their sexual activity, while effect on physical, social or school/workplace activities was 37%, 12% and 8% respectively[2]. Mastalgia is also a major cause for increased use of mammography (2.2 to 4.7 times) in younger women below the age of 35 years [2,3].

ETIOLOGY & PATHO-PHYSIOLOGY

The underlying cause of severe mastalgia remains unknown. The traditional surgical view, that pain in the breast was largely an expression of psychoneurosis was dismissed in the late 70s by Preece et al[4]. Similarly theory of increased water retention in patients with mastalgia was also disproved[5]. Inflammation as a cause of pain has also been postulated but Ramakrishnan et al. compared expression of three inflammatory mediators (IL-6, TNF-α and IL-1β) in tissue from painful and normal breasts. Even slightly lower levels of IL-6 and TNF-α were found in tissues from painful breasts. Specimens were also examined for evidence of inflammatory infiltrate, but no identifiable histological correlation was found[6]. Recently duct ectasia has been described as a major factor associated with mastalgia. Ultrasonography was used in mastalgia patients to investigate morphological structure and to obtain further insight into pathophysiology of mastalgia. Maximum mean width of milk ducts measured by ultrasound was 1.8 ± 0.84 mm in asymptomatic patients while it was 2.34 ± 1.1 mm in patients with cyclical mastalgia and 3.89 ± 1.26 mm in those with non cyclical mastalgia.

Pain intensity was also positively correlated to the width of milk ducts. In non cyclical mastalgia, location of pain also corresponded to the site of dilated ducts[7].

Hormonal and dietary factors have also been postulated in causation of mastalgia for long time. Recently smoking, caffeine and perceived stress has

been shown to be associated with mastalgia (O.R = 1.52, 1.53 and 1.7 respectively)[2].

Markedly increased levels of gonadotropin hormones throughout the cycle has also been observed in patients with mastalgia[8]. [the use of gonadotropin inhibitors may be trailed in mastalgia patients). These studies showed interesting results but merit further investigations.

CLASSIFICATION

Classification of mastalgia has also been confusing and unsatisfactory. It is usually classified into two groups. Cyclic and non cyclic mastalgia[9]. Cyclic mastalgia account for 67% of cases, usually bilateral, (although may be unilateral) varies during menstrual cycle and is typically worse in the luteal phase. It is relieved on the onset of menopause. Non cyclic pain accounts for the remaining 33%, being further divided into true non cyclic pain and chest wall pain.

The other classification[10] based on etiology is as follows;

1. Cyclic Mastalgia: Cyclic mastalgia is so called since patient has obvious menstrual cycle related pattern i.e. pain increases and decreases with menstrual cycle, maximum being during luteal phase. It is often associated with palpable nodularity. It is bilateral in 50% patients. It is also poorly localized and usually involves upper and outer quadrant, 50% may radiate but usually are confined to breast tissue

2. Trigger Point Pain: There is no cyclic variation. Usually well localized, it may be precipitated or increased by touch. It is rarely bilateral, 50% radiate usually to sub areolar part and inner quadrant. It may have severe burning abscess like exacerbations Trigger point pain has a strong association with clinical, radiological and histopathological features of duct ectasia/periductal mastitis complex of disorders; past or present.

3. Trietze syndrome: It is the painful, swollen, tender costo-chondral junction usually of the 2nd rib. Because of the vicinity of the female breast to the area, pain may be perceived as breast pain.

4. Previous trauma: The breast may have had abscess, biopsy or injury. The scar albeit deep in the breast with no cutaneous component can become a source of pain many years after the initiating injury. Similarly skin incision specially if across langer lines may be a source of pain.

5. Sclerosing adenitis: It is benign condition and usually is histopathology of mammographically diagnosed on defined suspicious lesion (microcalcifications)

6. Carcinoma: Pain does not commonly accompany the onset of cancer in the breast. But despite its infrequency, mastalgia can still be the presenting symptom of operable breast cancer. It has particular potential usefulness for diagnosis of tumors at an early stage even sub clinically with the inherent prognostic advantage of this. Unfortunately no particular such type of pain characterizes these early tumors, to help in distinguishing them from benign disease, except that the pain is usually localized to the tumor.

7. Miscellaneous: occasionally a fibroadenoma or cyst may be painful. Breast discomfort is one of the well recognized earliest symptoms of pregnancy and perhaps by the same mechanism it can follow the start of oral contraceptives. Fat necrosis, thrombo phlebitis of the vessels of the lateral chest wall (Mondor's disease), and tuberculosis are causes of breast pain occasionally. The pathognomonic sign of Mondors's disease is guttering of the superficial veins of the breast. Tuberculosis present either as an abscess or like a malignant tumor, poorly demarcated and with skin attachment. Fat

necrosis may mimic cancer clinically and radiologically.

The pain may be referred from intrathoracic or intra abdominal inflammation to the breast e.g. pain of cholecystitis or pleurisy.

8. Idiopathic: The origin of breast pain remains obscure in some patients, although the majority of patients fall into the one of the categories described above.

CLINICAL EVALUATION & MANAGEMENT

The main stay of evaluation is triple assessment. The aims are to differentiate between cyclic and non cyclic mastalgia, to find out if there is any underlying pathology and to rule out malignancy.

History of pain should include onset, duration, character, severity, site, localization, radiation progression, cyclic changes, relieving and aggravating factors. The systemic enquiry should be performed to rule out causes of referred pain. History of dietary habits, smoking, behavior, stress and tension, occupation and previous surgery should also be sought.

Locally through examination of both breasts should be performed in a systemic order. Tenderness and/or any localized tender spot, nodularity or discreet lump should be sought carefully. Condition of the nipple and any discharge should be noted. Previous scar if any should be properly assessed. Both axillae should be examined. Systemic examination to find out intra-thoracic, intra-abdominal and chest wall pathology should also be performed.

Mammography and/or FNAC should be advised wherever indicated.

Once malignancy is ruled out, patient should be reassured. Carcinoma breast is less likely to be a diagnosis in a woman with breast pain as compared to women who do not complain of breast pain regardless of age and other breast cancer risk factors[11]. It has also been noted that majority of these patients respond to simple reassurance and explanation[1].

Table-1. Cardiff breast pain score (CBS)	
CBS I	An excellent response leaving no residual pain
CBS II	A substantial response leaving some residual pain but considered by patient to be easily bearable
CBS III	A poor response leaving substantial residual pain
CBS IV	No response

If any other obvious pathology is found, it should be treated on its own merit. Simple analgesia, (e.g. Diclofenac sodium or ibuprofen), dietary modifications (avoiding caffeine in tea, coffee and soft drinks and avoiding fatty food) stopping smoking and regular exercise should be advised. Patient is also advised to discontinue contraceptive pills or newly started hormone replacement therapy. Patient is asked to maintain breast pain chart to help assess the pattern of pain (Fig-1).

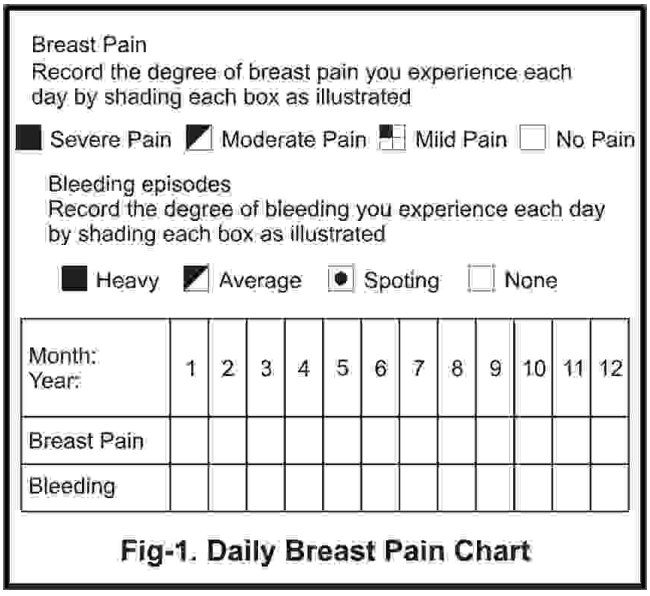

Fig-1. Daily Breast Pain Chart

Use of supportive bra specially at night is also very helpful. Hadi has compared results of wearing sports bra with those of danazol. In danazol group relief of pain was reported in 58% patients but 42% patients had adverse effects, while in patient who were advised to wear sport brassiere for twelve weeks, 100% had some initial discomfort followed by marked relieve in 85% patients with obviously no side effects[12]. Active breast movement on weak suspensory ligaments may contribute considerably to mastalgia. Good external support by sports brassiere can relieve most of patients' symptoms.

The patient should be reviewed after two months. Pattern of pain should be assessed and response should be graded according to Cardiff Breast Pain Score (Table-1). Specific drug treatment should be considered which should be balanced against the chance of response to treatment and risk of side effects. Patient should be reviewed every two to three months. The decision regarding continuation or change of treatment should be made according to patient's response. An algorithm for the treatment of mastalgia is given in Fig-2.

Following is an account of drugs used of mastalgia.

EVENING PRIMROSE OIL

Evening primrose (Oenothera biennis L) is a North American wild flower that has escaped cultivation and is non wildly distributed in fields or along road sides[13]. Named so, because its flowers open in the evening, the evening primrose is in fact not a true primrose. Medicinal use of evening primrose has a long history among native Americans and was transferred to Europe by colonial settlers.

Modern interest has centered on the oil expressed from plant's small dark seeds. This oil is rich in essential fatty acids: approximately 65% Linoleic acid and 8% to 10% gamma linolenic acid[14]. These constituents are precursors in the manufacturing of prostaglandin E_1 one of the anti-inflammatory prostaglandins. Women with mastalgia have abnormal fatty acid profile and decreased levels of linolenic acid metabolites[15]. Treatment with evening primrose oil improves essential fatty acid profile to normal[16]. Although, it may take upto three months to provide relief of symptoms, its effectiveness has been proved in placebo controlled trial with overall response rate of 45% in cyclic mastalgia and 27% in non cyclic mastalgia with fewer side effects (2% for evening primrose oil versus 22% with danazol and 33% with bromocriptin)[17,18].

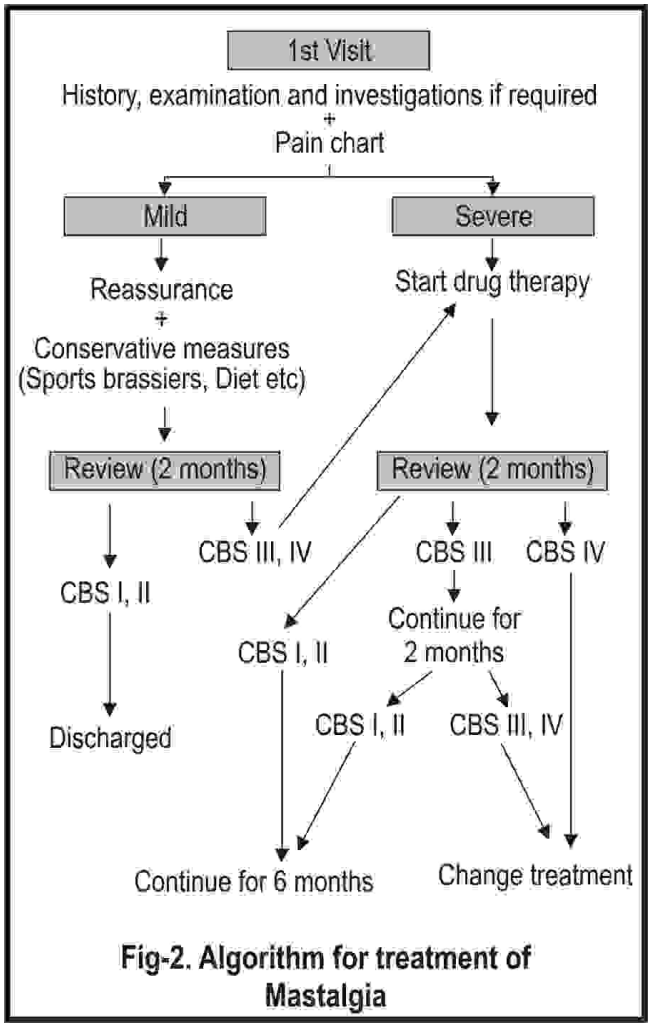

Fig-2. Algorithm for treatment of Mastalgia

Despite mixed results, many clinicians recommend evening primrose oil as a first line treatment for cyclical mastalgia[19,20,21]. In a recent survey 13% to 20% British surgeons recommended evening primrose oil for this use[22]. Patients with severe premenstrual symptoms, in another survey, also rated evening primrose oil as one of the most

effective treatment they had ever used[23]. Evening primrose oil is particularly useful in younger women who may require long term therapy, who wish to avoid anti-hormonal therapy and remain on oral contraceptive. More recently, it has been suggested that addition of an anti oxidant (vitamin E) might improve the efficacy of evening primrose oil treatment by reducing its metabolism via lipid peroxidation. A multicentre controlled trial to test this hypothesis is currently underway in UK[9]. The dose is 2 capsules TDS(2-4gm/day standardizing to 9% gamma linolenic acid) and it should be given for at least 3 months. To obtain full benefit from this regimen it may be necessary to ensure adequate levels of vitamin B1, B6 and Zinc which are cofactors in the proposed metabolic pathway along with vitamin C[10].

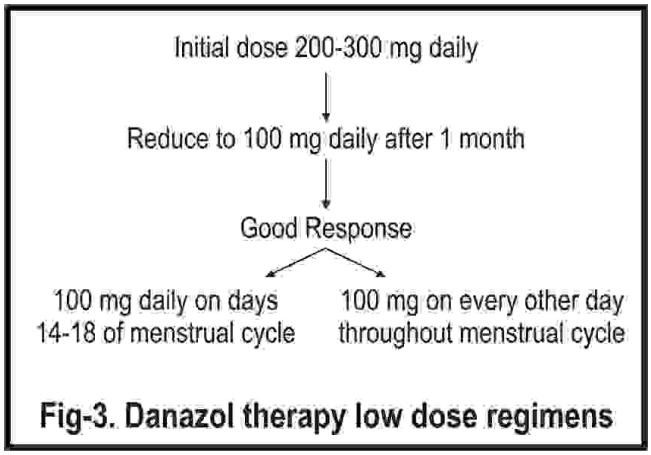

Fig-3. Danazol therapy low dose regimens

Other sources of essential fatty acids may also be considered in future as recently Blommers et al has reported comparable results of fish oil, Corn oil and corn oil with wheat germ oil with those of evening primrose oil for mastalgia [24]. These observations merit further evaluation.

DANAZOL

Danazol is a gonadotropin release inhibitor. It remains the most effective first and second line treatment overall with its effectiveness confirmed in controlled trials[25,26]. A useful response to treatment is observed in 70% of patients with cyclic mastalgia and 31% with non cyclic mastalgia[25].

Unfortunately, it also have high rate of dose related side effects (22%)[17]. Several low dose regimen have been developed to reduce the likely hood of side effect after remission has been induced with a full dose of 200 mg daily[27,28] (Fig-3). These regimens may also be used in patients relapse after stopping treatment.

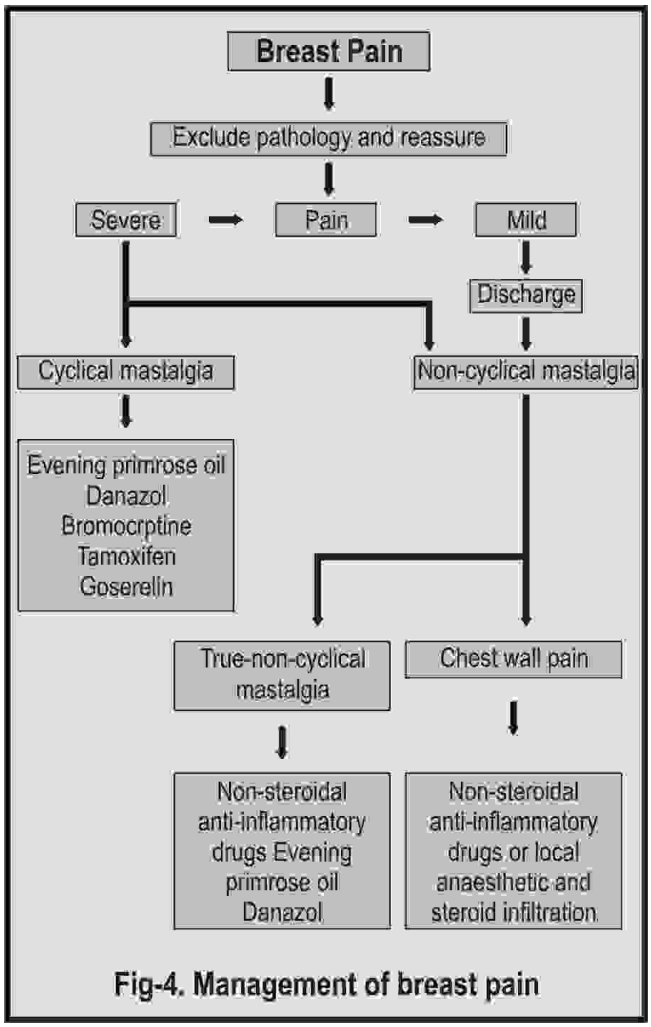

Fig-4. Management of breast pain

The treatment should commence on the first day of the menstrual cycle. It may cause amenorrhea, therefore, adequate contraceptive precautions are required.

BROMOCRIPTINE

Bromocriptine is dopamine agonist which has been successfully used for many years to treat mastalgia. It has been shown to decrease serum prolactin levels in normal and hyperprolactinamic women. Its

effectiveness has been confirmed in several single center controlled trials[29,30] and a large European multicentre study[31].

Clinical improvement is observed in 47% of patients with cyclic mastalgia and 20% with non cyclic mastalgia. As with danazol, the side effect profile is the limiting factor for the more extensive use of this treatment option. Reported side effects include nausea, vomiting, headache, dizziness and fatigue all of which are dose related. To minimize these side effective, an incremental dosing regimen is proposed starting with 1.25 mg at bedtime, increasing by 1.25 mg every three to four days until the full dose of 2.5 mg twice daily is reached. Treatment should be continued for 3-6 months.

TAMOXIFEN

Tamoxifen an anti oestrogen, has many uses in the management of breast disorders. Its effectiveness in the treatment of breast pain has been proven in several clinical trials[32,33]. A lower dose of 10 mg daily has been shown to be as effective in the treatment of mastalgia with a significantly reduced side effects compared with 20 mg daily[34]. The dosage should be tailored to individual patient requirement and symptom control balanced against troublesome side effects. As with other treatment options, a significantly better response is observed in patients with cyclic mastalgia than in those with non cyclic mastalgia. Although yet not licensed for mastalgia treatment in United States, it should be used as 2nd or 3rd line treatment.

GOSERLINE

Goserline, LHRH analogue has shown to be effective in both cyclic and non cyclic mastalgia refractory to first line therapy[35]. It induces reversible ovarian suppression with castrate levels of ovarian hormones being attained within 72 hours[36]. Adverse effects (principally hot flushes) are common and monthly subcutaneous injections does have compliance problem. It should, therefore, be reserved for those patients who fail to respond to other forms of treatment. It may be used to induce a rapid relief of symptoms to be followed by other therapies as maintenance.

MISCELLANEOUS

In a recent study, Lisuride maleate, one tablet of 0.2 mg daily for two months has shown to significantly reduce prolactin level, and significant improvement for cyclic mastalgia with no side effects[37]. It needs further evaluation before being considered as accepted treatment for mastalgia.

As already been stated, any underlying pathology should be treated on its own merits. Simple analgesics may be the only thing required for mild to moderate pain in SOS basis. A persistently localized painful area may respond to local injection infiltration of local anaesthetic and steroid.

A summary of treatment is given in figure-4.

REFERENCES

1. Paddler, DL. **Mastalgia: evaluation and management.** Nurse Pract Form, 2000; 11(4): 213-8.

2. Ader DN & Browne MW. **Prevalence and impact of cyclical mastalgia in a U.S. Clinical based sample.** Am. J. Obstet. Gynecol, 1997; 175(1): 126-52.

3. Ader DN, South-Paul J, Adera, T and Deusta, PA. **Cyclical mastalgia: prevalence and associated health and behavioral factors.** J Psychosom. Obstet. Gynecol June 2001; 22(2): 71-6.

4. Preece PE, Mansel RE, Hughes LE. **Mastalgia: Psychoneurosis or organic disease?** Br. Med. J. 1978 Jan ; 7: 1 (6104): 29-30.

5. Preece PE, Richards AR. Owen GM, Hughes LE. **Mastalgia and total body water** Br. Med. J. 1975 (Nov); 29: 4(5995): 498-500.

6. Ramakrishnan R, Werbeck J, Khurana KK, Khan S A. **Expression of interleukin 6 and tumor necrosis factor alpha and**

histopathologic findings in painful and non painful breast tissue. Breast J. 2003 Mar-Apr; 9(2): 91-7.

7. Barclay, L. **Duct Ectasia linked to mastalgia severity.** Obstet Gynecol 2003; 101: 54-60.

8. Ecochard R, Marret H, Rabilloud M, Boehringer H, Mathieu C and Guerin JF. **Gonadotropin Level abnormalities in women wit cyclic mastalgia.** Eur J Obstet Gynecol Reprod Biol 2001 Jan; 94(1): 92-6.

9. Mansel RE, Fenn NJ, Davies EL. **Benign breast disease and its management; In Recent Advance in Surgery** No. 21. Taylor I, Johnson CD (Ed), Churchill Livingstone Edinburgh, 1988: pp 71-83.

10. Cuschieri A, Giles G.R, Moossa A.R: P.E Preece; **The Breast in Essential Surgical Practice,** Second Edition: P-836-857.

11. Khan SA, Apkarian AV. **Mastalgia and breast cancer: a protective association?** Cancer Detect Prev 2002; 26(3): 192.

12. Hadi MS. Sports Brassiere: **Is it a Solution for Mastalgia?** Breast J 2000 Nov; 6(6): 407-409.

13. Grieve M. A **Modern Herbal. London:** Cresset Press Book 1973.

14. Oil of Evening Primrose. **Monograph. Lawrence Review of Natural Products: Levittown.** Pa: Pharmaceutical Information Associates 1993.

15. Horrobin DF, Manku MS, Brush M et al. **Abnormalities in plasma essential fatty acid levels in women with premenstrual syndrome and with non malignant breast disease.** Nutr Med. 1991; 2: 259-64.

16. Gateley CA, Maddox PR. Pritchard GA et al. **Plasma fatty acid profiles in benign breast disorders.** Br J Surg, 1992; 79: 407-9.

17. Mansel RE, Pye JK, Hughes LE. **Effects of essential a fatty acids on cyclical mastalgia and non cyclical breast disorders. In: Horrobin DF (ed) Omega 6 essential fatty acids. Pathophysiology and roles in clinical medicine.** Wiley-Liss New York, 1990; 557-6

18. Pye JK, Mansel RE, Hughes LE. **Clinical experience of drug treatments for mastalgia** Lancet ii 1985; 373-7.

19. Wetzig NR. Mastalgia. **A 3 year Australian study.** Aust N Z J Surg 1994; 64: 329-31.

20. Genolet PM, Delaloye JF. DeGrandi P. **Diagnosis and treatment of mastodynia (French-English Abstract)** Revue Medical de la Suise Romande 1995; 115: 385-90.

21. Gateley CA, Meirs M, Mansel RE. **Drug treatment for mastalgia: 17 years experience in the Cardiff Mastalgia** Clinic. J Roy Soc Med. 1992; 85:12-5.

22. Pain JA, Cahil VJ. **Management of cyclical mastalgia.** Brit J Clin Pract 1990; 44: 454-6.

23. Cambell EM, Peterkin D, O'Grady K et al. **Premenstrual symptoms in general practice patients. Practice and treatment.** J Reprod Med. 1997; 42: 637-46.

24. Blommers J, de LangeDe Klerk ES. Kuik D J. Bezemer PD, Meijer S. **Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double blind controlled trial.** Am J Obstet Gynecol 2002 Nov; 187(5): 1389-94.

25. Gateley CA, Maddox PR, Mansel RE, Hughes LE. **Mastalgia refractory to drug treatment.** Br J Surg 1990; 77: 1110-2.

26. Hinton CP, Bishop HM, Holiday HW, Doyle PJ, Blamey RW. **A double blind controlled trial of danazol and bromocriptine in the management severe cyclical breast pain.** Br J Clin Pract 1986; 40: 326-30.

27. Harrison DJ, Maddox PR, Mansel RE. **Maintenance therapy of cyclical mastalgia using low dose danazol.** J. R Coll Surg Edinb

1989; 34: 79-81.

28. O'Brien PM, Abukhalil IE. **Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase only danazol.** Am J Obstet Gynecol 1999 Jan; 180(1 Pt 1): 18-23.

29. Mansel RE, Preece PE, Hughes LE. **A double blind trial of the prolactin inhibitor bromocriptine in painful benign breast disease.** Br J Surg 1978; 65: 424-7.

30. During P, Sellwood RA, **Bromocriptin in severe cyclical breast pain.** Br J Surg 1982; 69: 248-9.

31. Mansel RE, Dogliotti LL. **European multicentre trial of bromocriptine in cyclical mastalgia.** Lancet i 1990; 190-3.

32. Fentiman S, Caleffi M, Brame K, Chaudary MA, Hayward JL. **Double blind controlled trial of tamoxifen therapy for mastalgia.** Lancet i 1986; 287-8.

33. Fentiman S, Caleffi M, Hamed H, Chaudary MA, **Dosage and duration of tamoxifen for mastalgia. A controlled trial.** Br J Surg 1988; 75: 845-6.

34. Faiz O, Fentiman IS. **Management of breast pain.** Int J Clin Pract 2000 May; 54(4) : 228-32.

35. Hamid H, Chaudary MA, Caleffi M, Fentiman IS.**LHRH analgue for treatment of recurrent and refractory mastalgia.** Ann R Coll Surg Eng 1990; 72: 221-4.

36. Fraser HM, Sandow J. **Suppression of follicular maturation by infusion of a luteinizing hormone releasing hormone agonist starting during the late luteal phase in the stumptail Macaque monkey.** J Clin Endocrinol Metab 1985; 60: 579-584.

37. Kaleli S, Aydin Y, Erel CT, Colgar U. **Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate. A double blind placebo controlled randomized study.** Fertil Steril 2001 Apr; 75(4): 718-23.