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Original Research Article

The Value of Danazol in the Conservative Treatment and Long-Term Control of Fibrocystic Disease of the Breast

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ABSTRACT

Background and Objectives: Fibrocystic breast disease is the most common benign breast condition worldwide. Because of the recurrence and bilateral occurrence reported results, surgical excision is being avoided unless histopathological evidence of potential malignancy exists. Multiple medical treatment options had been introduced, and one the most commonly used is Danazol. In our paper, we aim to evaluate the results of Danazol treatment and control of fibrocystic breast disease in the Saudi Arabian females.

Materials and Methods: The treatment outcome of 382 Saudi Arabian female patients who were diagnosed to have a fibrocystic disease of the breast and treated by Danazol between January 2001 and December 2010 was retrospectively analyzed from a computerized database protocol file. The treatment protocol was designed as follows: 3 months cycle of 200 mg oral Danazol once daily in the morning, followed by ultrasound evaluation, and repeating the same protocol until complete disappearance of the cysts.

Results: The patients were classified depending on ultrasound result into four groups: Group 1: Single cyst, unilateral breast. Group 2: Multiple cysts, unilateral breast. Group 3: Single cyst, bilateral breast. Group 4: Multiple cysts, bilateral breast. The success rate of Danazol treatment was 100%, with 0% recurrence rate after five years follow-up.

Conclusion: Danazol is an effective modality in treating the fibrocystic disease of the breast, despite annoying side effects, and could achieve 100% success rate, 0% recurrence rate, and good long term control. The fear of the malignancy risk should not preclude the successful conservative Danazol treatment unless a well-proven potential malignant changes are encountered.

Keywords: Benign Breast Conditions, Danazol, Fibrocystic Breast Disease, Potential Malignant Changes.

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INTRODUCTION

Fibrocystic breast disease (changes), also known as mammary dysplasia, diffuse cystic mastopathy, and chronic cystic mastitis, is the most common benign (non-cancerous) breast condition, with an estimated incidence of more than 70%. More than half of all women could experience fibrocystic breast changes at some point in life. It has a peak incidence between 30 and 50 years of age, rare before 18 years, and rare in postmenopausal women, usually involve the entire breast but may be more severe in the upper, outer area of the breast[1].

It is characterized by a swelling and tenderness, nodularity, palpable lumps, nipple discharge, and inflammation caused by increased engorgement of the glands forming multiple small fluid-filled cysts clustered within the breast. Some clinical studies reported that the fibrocystic changes are a risk factor for breast cancer, and affected females are at a risk of breast cancer 3 to 4 times more than others[2]. The symptoms may manifest during the whole month and often intensify during the menstrual cycle. Fibrocystic breast changes may affect one or both breasts and may vary in severity from month to month. Pain, tenderness, fullness or heaviness, nipple discharge, and multiple round and soft palpable mass are usually severe in the premenstrual phase, and could affect the quality of life of the affected female. The pain is diffuse, and may radiate to the axilla or upper arm[3,4].

The breast tissue in response to the imbalanced sex hormones (estrogen and progesterone) stimulation over time undergoes some morphologic changes of fibrocystic disease which are marked histologically by the overgrowth of fibrous stroma, and epithelial elements (ducts and lobules) that may be considered as aberrations of normal breast involution rather than a part of a disease process. The main morphologic features of the fibrocystic disease are cysts formation, fibrosis, apocrine metaplasia, and calcification fibroadenoma-like picture (fibroadenomatoid mastopathy)[5].

Fibrocystic disease of the breast is classified into proliferative and non-proliferative subtypes. The non-proliferative patterns are associated with cystic changes and fibrosis where the lesions are characterized by an increase in fibrous stroma and dilatation of ducts which lead to the formation of cysts that could be single or multiple, and varying in size from 1 to 5 cm. The composition of the cyst's fluid and the lining of the cyst are important factors determining the chances of malignant transformation[6].

Estrogen predominance and progesterone deficiency are the pathophysiologic hallmarks that result in hyperproliferation of connective tissue (fibrosis), followed by facultative epithelial proliferation. Therefore, the ideal treatment of fibrocystic disease should be directed towards suppression of ovarian estrogen

secretion with a low-estrogen oral contraceptive, or by the administration of a progestogen that modulates the mammary effects of estrogen[7].

Fibrocystic breast disease is diagnosed clinically by symptoms and breast exam. Imaging tests are performed to establish whether the lump is a cyst or not. Ultrasound produces clear images of the breast and can distinguish between fluid-filled breast cysts and solid masses. A cyst is seen as a well-defined, round or oval, anechoic structure with a thin wall. Focal fibrocystic changes may appear as solid masses or thin-walled cysts. Mammography is done for confirmation especially in women over 40 years. A fine-needle aspiration is the histopathological test of choice[8].

Once cancer has been ruled out, some cysts may be aspirated to alleviate pain, treatment of the pain of fibrocystic breast disease could be achieved by conservative methods such as analgesics, properly fitted brassieres, diet (Iodine), the application of local heat, or application of evening primrose oil. A broad range of pharmaceutical products are used, of which is Danazol was reported as the most commonly used by 75% of the surgeons, despite its side effects[9].

Danazol, which is a derivative of the synthetic steroid ethisterone, a modified testosterone, suppresses gonadotropin secretion, prevents luteinizing hormone surge, and inhibits ovarian steroid formation. It was found in controlled clinical trials to relieve breast pain and tenderness in the women treated considerably[10]. Other studies were conducted and showed that treatment with Danazol resulted in 72.1% response rate but was associated with side-effects in one-third of the patients, and were dose related and primarily androgenic, including menstrual irregularity or amenorrhea, acne, hair loss, decrease in voice pitch, weight gain, headache, nausea, rash, anxiety, and depression[11].

In this paper, we aim to evaluate the results of our treatment protocol and outcome of Danazol treatment for fibrocystic breast disease in 382 Saudi Arabian females during ten years.

MATERIALS AND METHODS

The treatment outcome of 382 Saudi Arabian female patients who were diagnosed to have a fibrocystic disease of the breast and treated by danazol between January 2001 and December 2010 was retrospectively analyzed from a computerized database protocol file. The treatment protocol and follow-up were done in Al Ansar general public health hospital in Medina, Saudi Arabia by the same surgeon. All patients were diagnosed, treated, and followed-up in the outpatients clinic. All patients were female. The mean age was 35.5 years (range 27- 43). All patients were married, multiparous, premenopausal, and had a history of contraceptive use. Random selection (age, and clinical history) of all patients was made, and all patients who agreed to try the protocol were consecutively included.

Diagnostic workup was the same for all patients, and consisted of history and breast examination by the same surgeon, initial complete blood count, full chemistry profile, coagulation profile, hormonal profile (prolactin, follicular stimulation hormone, luteinizing hormone, estrogen, and progesterone), chest x-ray, electrocardiogram, ultrasound of the breast, mammogram, and fine needle aspiration. The history data file included symptoms (mass and pain), duration, progression of the disease, menstrual cycle status, any previous medical or surgical treatment, and family history of fibrocystic disease and breast cancer. Depending on ultrasound result, the patients were classified into four groups:

Group 1: Single cyst, unilateral breast.

Group 2: Multiple cysts, unilateral breast.

Group 3: Single cyst, bilateral breast.

Group 4: Multiple cysts, bilateral breast.

The treatment protocol was designed as follows: 3 months cycle of 200 mg oral Danazol once daily in the morning, followed by ultrasound evaluation, and repeating the same protocol until complete disappearance of the cysts. A mammogram was performed to all patients at the end of the treatment as a baseline to check for recurrence. No antibiotics or analgesia were used for any patient at any stage. The treatment protocol, expected outcome, the possibility of treatment length, and possible side effect of Danazol treatment were adequately discussed with all patients.

Follow-up was done at the outpatient clinic by the same surgeon for all patients, and all patients were asked about symptoms, side effects of treatment, and all had a breast examination, and the result of follow-up ultrasound was discussed with the patients. All patients included in the study completed five years follow-up, no drop out was recorded.

RESULTS

382 Saudi Arabian female patients were included, 217 (56.8%) patients were from Medina city, and 165 (43.2%) were from nearby towns and villages. The mean age was 35.5 years (range 27- 43). All patients presented with complaints of breast pain and breast lump (100%).

Disease duration range was 78 – 192 days (median=142, mean= 139.75). 49 (12.8%) patients presented with the first attack, 217 (56.8%) had recurrent attacks treated by herbal medications and creams, 95 (24.9%) had recurrent attacks treated by surgical excision at their local hospital, and 21 (5.5%) had recurrent attacks treated by cyst aspiration. (Figure 1)

369 (96.6%) patients had a negative family history for breast malignancy while 13 (3.4%) had a positive family history of breast cancer (8 maternal, and 5 grand maternal). According to ultrasound results, the patients were classified into 4 groups: Group 1: Single cyst, unilateral breast: 58 (15.2%). Group 2: Multiple cysts, unilateral breast: 47 (12.3). Group 3: Single cyst, bilateral breast: 31 (8.1%). Group 4: Multiple cysts, bilateral breast: 246 (64.4%). The smallest cyst size reported was 2 mm, and the largest was 3.7 cm. Mammograms correlated with ultrasound results; no difference was reported. (Figure 2-4)

Fine needle aspiration showed benign disease in all patients, and cyst fluid cytology analysis was of benign nature in all. Histopathology sections of patients who had previous surgical excision were requested from their local hospitals and reevaluated, and all showed benign disease.

Pain was the first symptom to respond to Danazol treatment. The mean time for pain to completely disappear was as follows: Group 1: 13 days. Group 2: 17 days. Group 3: 15 days. Group 4: 23 days. Cysts disappeared completely in all patients, and each patient had one ultrasound test every 3 months for 5 years follow-up (total of 20 tests) which showed no recurrent cysts. The mean time for cysts complete disappearance was as follows: Group 1: 67 days. Group 2: 79 days. Group 3: 61 days. Group 4: 92 days. (Figure 5)

A decrease in the amount of glandular tissue was observed by mammogram. These changes during treatment were statistically highly significant (p less than 0.001), irrespective of the group of the patient. Side effects due to Danazol treatment were reported by all patients, and the longer the treatment took, the more side effects were reported. In fact, most the major side effects were reported by group 4 patients. 215 (56.3%) had irregular menstrual cycle, 167 (43.7%) had amenorrhea, 27 (7%) developed acne, 74 (19.4%) reported hair loss, 135 (35.4%) reported weight gain, and only 28 (7.3%) complained of an occasional headache. No major systemic or catastrophic side effects were reported by any patient or documented in any data file of the study population. All side effects subsided in all patients within 3-5 months of completing the treatment and stopping Danazol. (Figure 6)

The success rate of Danazol treatment was 100%, with 0% recurrence rate and good control of the disease after five years follow up.

DISCUSSION

Some benign breast disease could be exhibiting a risk factor for a later breast cancer, which could develop in the same or contralateral breast. It represents a variety of histologic entities subdivided into nonproliferative, proliferative without atypia, and atypical hyperplasias, with a reported evidence of increased risk of breast cancer in association with proliferative or atypical lesions.

Retrospective and prospective studies had shown the risk of breast cancer to be about 1.5 to 1.6 for women with benign breast disease compared to other women[12-14]. In our series, all patients had benign disease, with zero (0%) malignant criteria evident by aspiration cytology, histopathology examination of previously excised cysts, and radiological follow-up for five years.

Georgescu et al[15]. classified fibrocystic disease of the II and III degrees as facultative precancerous lesions, and that the occurrence of mammary cancer in fibrocystic disease after sectorectomy was 7.4 times higher than cancer rate in women without the fibrocystic disease.

Adeniji[16] reported that two out of 13 women who were found to have ductal epithelial hyperplasia developed infiltrating ductal carcinoma 10 – 15 months after an initial diagnosis of fibrocystic disease. Petrakis[17] following epidemiological risk factors and cytologic studies of breast secretions obtained by nipple aspiration reported that severe changes in the cytologic characteristics of the fluid were associated with a positive family history of breast cancer and fibrocystic disease. These findings were considered as supporting evidence for the hypothesis that females with a positive family history could have an increased susceptibility to environmental factors that act in concert with atypical epithelial hyperplasia acting as a media for other factors wherever it occurs[18].

With a thorough diagnostic evaluation, appropriate medication, and close follow-up, a high success rate of the treatment of fibrocystic breast disease can be achieved in every patient. Needle aspiration biopsy must be performed in all patients especially with macrocysts and whenever clinical, ultrasonic, and/or mammographic examinations are suspicious for carcinoma. Patients with high risk of breast cancer (positive family history) should have clinical examinations at 3 to 6 months intervals and mammography every 1 to 2 years. Fibrocystic breast disease is a distinct clinical entity which requires treatment to relieve the patient's symptoms, to lower the need of unnecessary breast surgical procedures, and to rule out the risk of breast cancer[7].

Earlier treatment options for fibrocystic breast disease that were dedicated to relief the pain, tenderness and nodularity proved a low success outcome. In 1971, Danazol, a synthetic steroid, was introduced as a potentially useful treatment of benign breast disorders. Many studies had shown that the efficacy and safety of Danazol are promising.

A multicentre study of Danazol in which the drug was administered in dosages of 400 mg/d for two months, followed by 200 mg/d for an additional four months, to 25 female patients diagnosed to have fibrocystic breast disease showed that 18 (79%) of them demonstrated a significant improvement in eliminating their symptoms, and the majority remained asymptomatic for at least one year after treatment, with mild side effects of no clinical significance reported[19]. In our series, a treatment success rate of 100% was achieved in all patients including complete pain and cyst disappearance, though some annoying side effects were reported, no significant or catastrophic clinical occurrences were reported.

In our study, we noticed that all patients had a great sense of fear of breast malignancy, which was a keystone in the patients' compliance with the treatment protocol, and despite the annoying side effects of Danazol, all patients adhered strictly to the protocol until complete healing. We observed that despite that breast pain significantly affects patients' lives due to the discomfort during daytime activity, and even at night rest, the good response to Danazol treatment and disappearance of pain was influenced by the existence of breast lump or cysts in all patients. It was the disappearance of breast lump or cyst that was the major relief to all patients.

We also noticed that the simpler the disease (presentation and pathology), the faster the response to treatment, group 1 was the simplest, and the fastest responding, while group 4 presented with a more complex disease, and hence, responded far longer than the other groups. All groups responded well to Danazol treatment.

We believe that patients reassurance of the fear of malignancy following negative cytology should not negatively influence the management of fibrocystic disease of the breast by Danazol, and it should be explicitly instructed to all patients that strict adherence to the treatment protocol, despite long duration and annoying side effects, is the keystone to achieve complete healing and exclude recurrence.

According to the results of our study, we found Danazol to be very effective in arresting the development of new cysts and thereby, in preventing recurrence for at least five years.

CONCLUSION

We conclude that Danazol is an effective modality in treating the fibrocystic disease of the breast, despite annoying side effects, and could achieve 100% success rate, 0% recurrence rate, and good long term control. The fear of the malignancy risk should not preclude the successful conservative Danazol treatment unless well proven potential malignant changes are encountered.

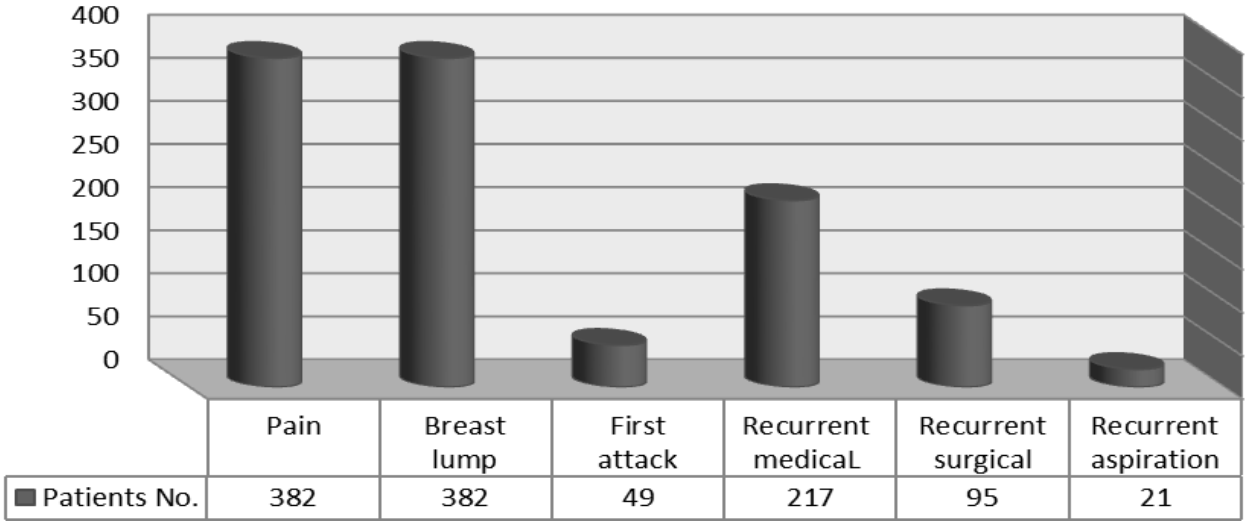

Figure 1: Patients' presentation

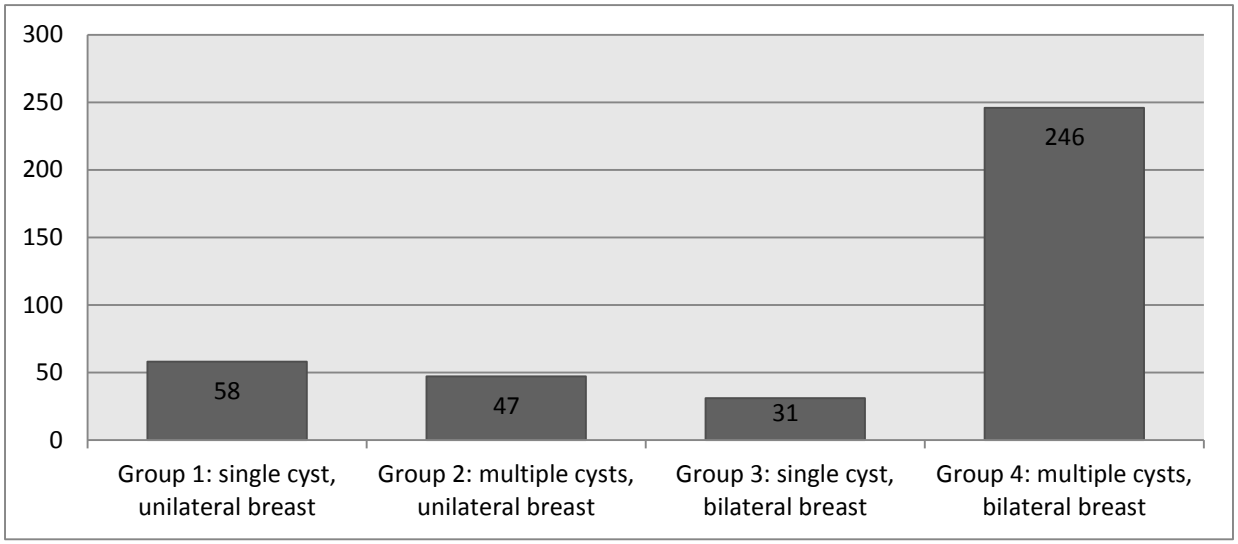

Figure 2: Patients' groups depending on ultrasound results

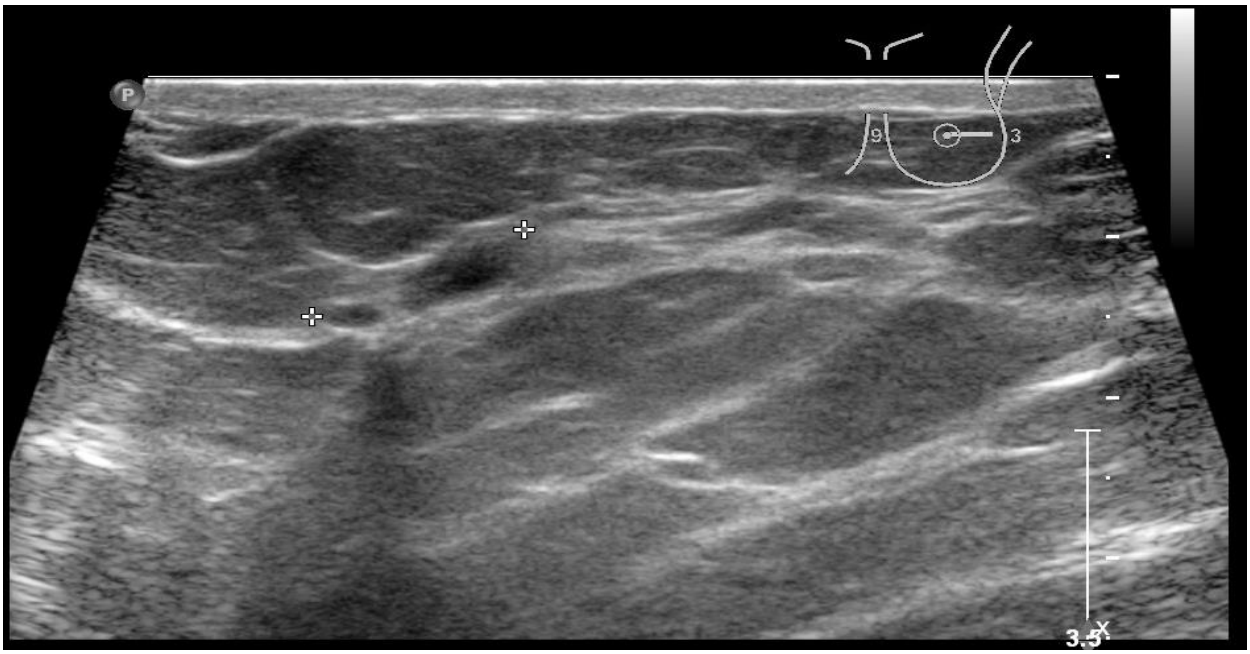

Figure 3: Ultrasound showing fibrocystic changes on the left breast as multiple cysts between 3 and 4 o'clock

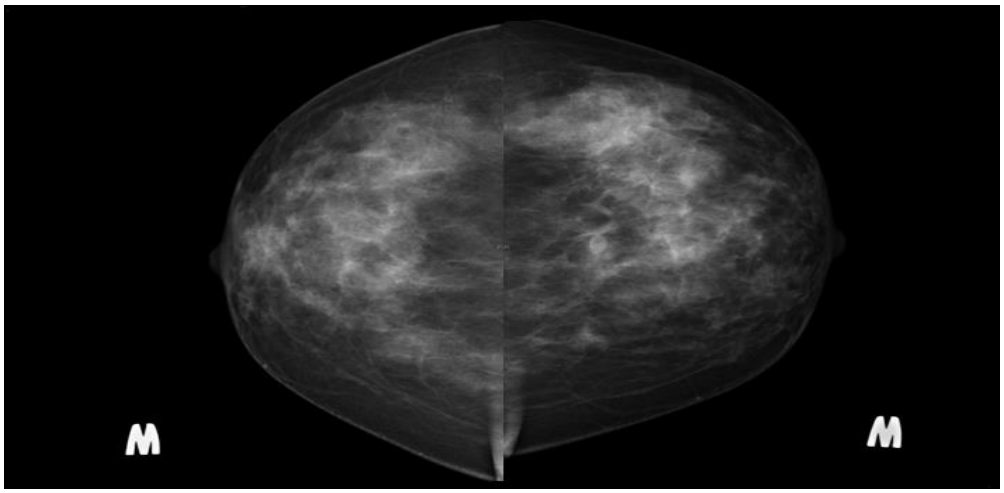

Figure 4: Bilateral mammographic views of both breasts. Overall the breast composition is almost entirely fatty bilaterally (ACR3), focal areas of increased density associated to scattered microcalcification more numerous on the right breast, some of the microcalcifications are grouped together without obvious suspicious spiculated opacities or architectural distortion which correspond to fibrocystic changes

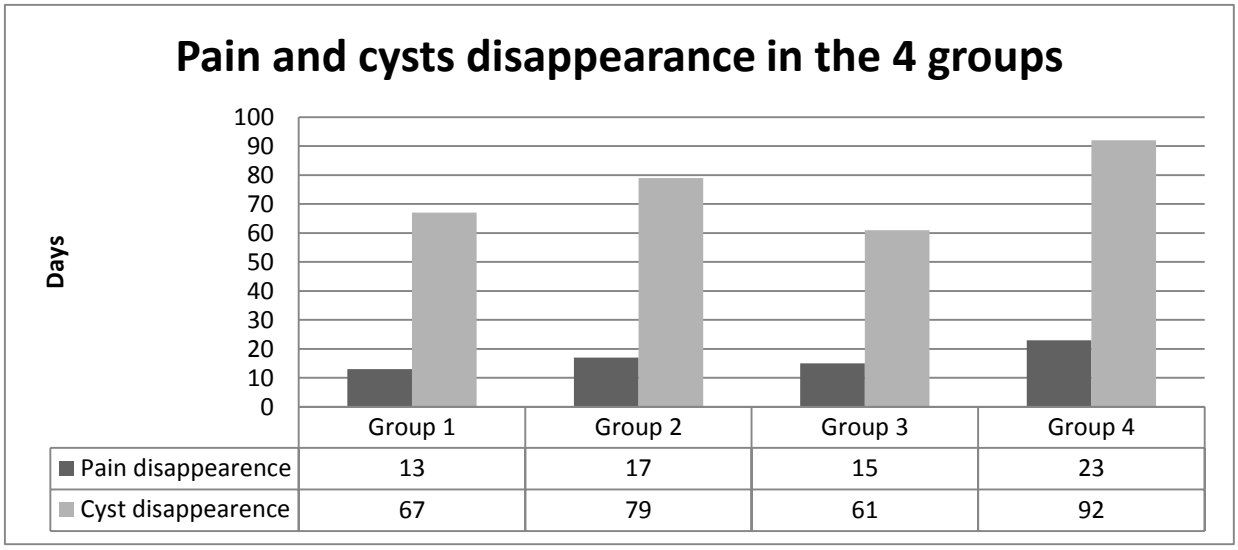

Figure 5: The mean time for pain and cysts disappearance in the four groups

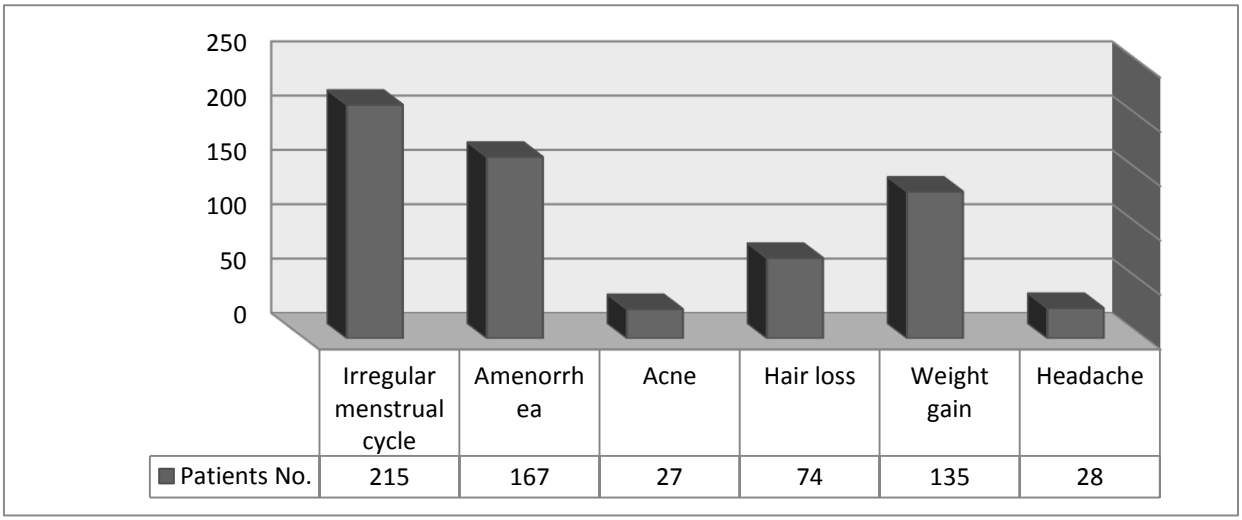

Figure 6: Side effects due to Danazol treatment

AUTHORS' CONTRIBUTIONS

All authors have contributed substantially to the paper. HAS conducted the clinical part of the study. WSA and WNA participated in the pharmacological part of the study. BHS wrote, edited the manuscript, and analyzed the data. All authors read and approved the final manuscript.

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