Metformin as a New Perspective in the Medical Management of Breast Fibroadenoma; A Randomized Clinical Trial Study

Sadaf Alipour

Breast Disease Research Center, Tehran University of Medical Sciences, Tehran

Mahboubeh Abedi

Department of Radiology, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran

Azin Saberi

Department of Surgery, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran

Arezoo Maleki-Hajiagha

Research Development Center, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran

Firoozeh Faiz

Department of Endocrinology and Metabolism, Arash Women Hospital, Tehran University of Medical Sciences, Tehran

Saeed Shahsavari

Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran

Bitá Eslami (✉ dr.bes.96@gmail.com)

Breast Disease Research Center, Tehran University of Medical Sciences, Tehran

---

Research Article

Keywords: Fibroadenoma, Fibrocystic Breast Disease, Breast Ultrasonography, Metformin, Therapy

Posted Date: February 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-148817/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Endocrine Disorders on August 20th, 2021. See the published version at <https://doi.org/10.1186/s12902-021-00824-4>.

Abstract

Background: Fibroadenoma (FA) is the most common benign solid breast mass in women with no definite method of management. Because fibroadenoma is dependent on female sex hormones, we investigated the effects of metformin, a safe hypoglycemic agent with anti-estrogenic and anti-proliferative properties, in the management of fibroadenoma.

Methods: In this randomized clinical trial study, eligible women with fibroadenomas were assigned randomly to the metformin (1000 mg daily), or the placebo group. Breast physical and ultrasound exam was performed before and after the intervention, and the changes in the size of fibroadenomas were compared in the two groups.

Results: Overall, 83 patients in the treatment, and 92 in the placebo group completed the study. The mean age of participants was 39.65 ± 10.30 years. The amount of reduction in the size of FA was two-fold in the treatment than placebo group. We categorized size changes of FAs into $< 20\%$ enlargement (success) and $\geq 20\%$ enlargement (failure). The odds ratio (OR) for success was 1.48 (95% CI=1.10-1.99) in the treatment group in comparison with the placebo group; and the odds for success was higher in women with multiples fibroadenomas (OR=4.67, 95% CI: 1.34-16.28). Also, the rate of disappearance of fibroadenomas in the treatment group was two-fold higher than the placebo group, although the difference was not statistically significant.

Conclusion: This is the first study that evaluates the effect of MF on the management of fibroadenoma, and the results suggest a favorable effect. Larger studies including only large lesions and using higher doses of metformin are suggested to confirm these results.

Trial Registration: This trial (IRCT20100706004329N7) was retrospectively registered on 2018-10-07.

Background

Fibroadenoma (FA) is the most common benign solid mass of the female breast, with an approximate incidence rate of around 12–25% in young women, albeit the exact incidence is not known. It is most commonly seen in young women between 14 to 35 years old and is much less common in post-menopausal women, but can occur at any age [1, 2]. FA can present as a solitary mass in one breast, or as multiple bilateral lumps, and can sometimes grow to very large sizes. Palpable FA has a typical appearance consisting of a firm, round, very mobile lump; however, in many instances, FA is not palpable and can only be detected by breast imaging. The typical ultrasound (US) picture is a circumscribed, regular, hypoechoic mass that lies parallel to the skin. Both clinical and paraclinical presentations can be atypical and different from the usual image [1, 2].

The main underlying etiology is unknown, but the similarity of the effects of sex hormones on FA and normal breast tissue proposes hormonal pathophysiology [2]. Women with FA are at a slightly increased risk for developing malignancy in comparison with the general population [3]. Diagnosis is based on

histological examination which is available through core needle biopsy of the lesion. Cytological assessment also is helpful but not as accurate. Nonetheless, for a small FA with typical features on physical exam or US scan in a young woman, tissue sampling can be avoided; and the diagnosis can be made clinically with relative accuracy in these cases [1].

Despite the relative benignity of FA, it can impose a significant negative psychological impact on the patient. Stress about misdiagnosis, probable malignant transformation, or even feeling of fear while touching the lump are not uncommon consequences of conservative treatment [2].

Metformin (MF) is an anti-hyperglycemic agent that is being investigated for many conditions. One of the probable properties of MF is its anti-proliferative effects on various cells, including breast cancer cells. Also, anti-estrogenic properties have been reported for MF [4]. Because of the estrogen-dependent features of FA [2], and the anti-proliferative, sex hormone-suppressing characteristics of MF [4], as well as its relatively low frequency of adverse effects, we designed the present study to evaluate the therapeutic effects of MF on FA.

Methods

Study design and participants

This study was conducted according to the principals of the Declaration of Helsinki and the standards of Good Clinical Practice (GCP) and has been approved by the Institutional Research Board (Proposal Code: 97-01-218-37716) and the Ethics Committee (Approval ID: IR.TUMS.VCR.1397.357) of Tehran University of Medical Sciences, Tehran, Iran. This study adheres to CONSORT guidelines. It has been retrospectively registered in the Iranian Registry of Clinical Trials (IRCT), registration number: IRCT20100706004329N7. This is a Primary Registry in the WHO Registry Network set up with the help from the Ministry of Health and Medical Education (MOHME).

This a double-blind, randomized placebo-controlled clinical trial with a parallel group design, that has been held in a single center, Arash Women's Hospital, affiliated to Tehran University of Medical Sciences from October 2018 to March 2020. The study population consisted of women attending the breast clinic of the hospital. All participants read and signed a written informed consent before entering the study.

Study Outcomes

The primary outcomes were overall change in the size of FAs, and less than 20% enlargement of FAs (which by logic encompasses stable size and size reduction) in US scan [5].

Secondary outcomes consisted of occurrence of drug adverse effects and compliance with regular consumption of the medication.

Inclusion criteria

Premenopausal women aged 18–50 years old with one or more, unilateral or bilateral FA(s) less than 3 cm in largest diameter were included in the study. Criteria for the diagnosis of FA were the criteria we usually use in our clinic based on the largest diameter of the lump on US scan.

-In women younger than 40 years of age:

*For lumps less than 2 cm: typical US image of FA, and typical physical exam when palpable

*For lumps 2 cm or larger: a diagnosis of FA in histologic exam of core needle biopsy samples

- In women 40 years of age or above:

*For lumps larger than 1 cm: a diagnosis of FA in histologic exam of core needle biopsy samples

*For lumps less than 1 cm in women with no risk factor for breast cancer and no suspicious finding in mammography: a typical US image

*For lumps less than 1 cm in women with a risk factor for breast cancer or a suspicious image in mammography: FA in histologic exam of core needle biopsy samples

- In all ages:

*For multiple lumps that have been stable for one year or more: a diagnosis of FA in histologic exam of core needle biopsy samples of only the largest one and/or those above 2 cm

Exclusion criteria:

These consisted of pregnancy, breastfeeding, vegetarianism, body mass index (BMI) more than 29.9, history of breast cancer, allergy to biguanides, present diabetes mellitus, hypothyroidism, hyperthyroidism, metabolic syndrome, galactorrhea, hypophysis adenoma, heart disease, epilepsy, renal or hepatic failure, severe iron deficiency anemia, gastroparesis, or severe hyperlipidemia; use of anti-diabetics and hypoglycemic agents, antilipidemics, phytoestrogen containing medications, GnRH agonists and antagonists, clomiphene, tamoxifen, aromatase inhibitors, danazol, oral contraceptives or any medicine containing estrogens or progestins; getting pregnant during the study, showing adverse effects of MF, irregular use of the medication or complete non-compliance.

Random Allocation, Concealment, and Blinding

Random allocation was performed by a methodologist using an online generated randomization list (provided by sealedenvelope.com) based on the block randomization method and 6-piece blocks. The randomization list was concealed from all research staff involved in enrollment and assessment by using sealed envelopes. For blinding, we used MF and identical placebo tablets that were placed in similar bottles with similar labels. Then, bottles were stored in two separate boxes that were coded as A or B by the personnel of the research center who was not involved in drug dispensing, patient visit, and follow-up. Coding of A and B were defined and kept in an envelope, which was disclosed after the analysis of the

results. Participants were allocated to group A or B according to the randomization list, and then the medication dispenser provided the participants with the drug bottle from the corresponding box.

Interventions, measurements, and tests

Eligible women were enrolled in the study by surgeons of the breast clinic based on US findings and/or histology results. All participants underwent a physical examination and breast US. All women aged 40 years and older had undergone mammography in the recent year. US scans were performed by a radiologist experienced in breast US and dedicated to the breast clinic.

Every participant filled in a form containing questions about demographic information, previous breast disease, and personal, menstrual, reproductive, and past medical information. Height, weight, waist and hip circumference of all participants were measured by one trained personnel.

Blood tests including complete blood count, blood sugar, liver and renal function tests were performed for all participants. People with abnormal results were excluded from the study and referred for appropriate management. Then, participants were allocated into treatment and placebo groups. The treatment group received 500 milligrams MF tablets (Osveh Pharmaceutical Company, Iran) twice daily for six months. The placebo group received placebo tablets that were quite similar to MF tablets (Osveh Pharmaceutical Company, Iran) twice daily. Women in both groups were asked not to change their routine dietary habits. They were also requested to update us on any changes in their diet and medications, or newly diagnosed diseases.

We provided a drug-reminder table for each participating woman to check, record, and trigger their compliance with the assigned intervention and asked them to checkmark the corresponding box each time they consumed the tablet. They were also given only one drug bottle containing tablets for three months of use and were asked to attend three months later for the second box. Also, short messages were sent every two weeks as a reminder to use the drugs regularly, and they were asked to come for the second drug bottle by phone call. The second US scan and the last examination were scheduled by phone calls. At the end of the sixth month of intervention, the breast US scan, anthropometric measurements, and renal function test were repeated for all participants who had complied to the end, and the size of FA(s) and results of measurements were recorded.

Sample size calculation

Since this study for the first time evaluates the effect of metformin on fibroadenoma, considering the results of other studies, we estimated that 106 patients would be required in each group to detect 25% and 10% reduction size of fibroadenoma in MF and Placebo group, respectively; with a power of 80% and $\alpha = 0.05$ by using Epi Info Site.

Statistical Analysis Methods

The statistical analyses were performed using IBM SPSS 24 (IBM Corp. Released in 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Data are presented as mean $\pm$ standard

deviation for continuous variables and number with percentages for categorical variables. Comparison between the two groups was conducted by Student t-test and Chi-square test.

The total number of breast masses and average mass size before and after the intervention were calculated in each woman. The percentage of change of the size of the breast masses was calculated as the ratio of mass size before minus after intervention over before intervention, or $(\text{Size after} - \text{Size before}) / \text{Size before} \times 100$.

Since there was more than one mass in the majority of women and since our quantitative response data are correlated, marginal model and generalized estimate equation (GEE) model with exchangeable correlation matrix was performed for comparison of changes. GEE is a quasi-likelihood approach for correlated data which does not fully specify the distribution of response in each patient as a cluster [6]. The comparison between study groups was performed in the GEE model in which more than one measurement of each patient was treated as correlated, baseline measurements as covariates and the study group as the independent effect factor. In addition, we used logistic regression when our response was binary. A p-value of less than 0.05 was considered significant. Moreover, all of the dropped-out cases occurred before the first follow-up visits. Therefore, we had no intention-to-treat analysis.

Results

Flow of Patients

First, 217 patients were enrolled into the study, consisting of 111 women in the placebo group and 106 patients in the treatment group. Four women (one in the treatment and three in the placebo group) were excluded during the intervention due to incompetency with drug adherence, and one in the placebo group underwent cosmetic reduction mammoplasty and was withdrawn. Also, COVID-19 restrictive conditions supervened throughout the study, thus 22 and 15 patients were lost to follow-up in the treatment and placebo group, respectively. Ultimately, 175 patients completed the study; 83 in the treatment and 92 in the placebo group. These are demonstrated in Fig. 1. No serious adverse effect leading to withdrawal from the study occurred. Only one patient in the treatment group left the study for irregular use of MF, described as non-compliance.

Characteristics of Patients and Fibroadenomas at Enrollment

The mean age of all the participants was 39.65 ± 10.30 years. The two groups were similar regarding age (0.76), BMI ($p = 0.35$) and waist to hip ratio ($p = 0.75$). Demographic, anthropometric, and reproductive characteristics of patients in the two groups at the time of entering the study are demonstrated in Table 1.

Table 1
Demographic, anthropometric, and reproductive features in the two groups at the time of entering the study.

Variables	Group A (n = 92)	Group B (n = 83)	p-value
Age	39.42 ± 10.14	39.90 ± 10.54	0.76 ^a
Body mass Index (BMI)	26.36 ± 6.95	25.51 ± 4.72	0.35 ^a
Waist/hip ratio	0.86 ± 0.13	0.86 ± 0.07	0.75 ^a
Age of menarche	13.32 ± 1.39	13.13 ± 1.33	0.37 ^a
Parity	1.51 ± 1.10	1.53 ± 1.13	0.91 ^a
Age at first delivery	18.35 ± 10.73	16.99 ± 11.12	0.41 ^a
History of twin pregnancy	4 (4.3)	2 (2.4)	0.48 ^b
History of abortion	0.25 ± 0.59	0.45 ± 0.80	0.07 ^a
History of breastfeeding	70 (76.1)	60 (72.3)	0.57 ^b
History of Infertility	7 (7.7)	7 (8.4)	1 ^b
History of PCO	2 (2.2)	4 (4.8)	0.34 ^b
History of OCP use	26 (28.3)	25 (30.1)	0.79 ^b
History of HRT use	5 (5.4)	6 (7.2)	0.52 ^b
^a Independent t-test. ^b Chi-square test. PCO = polycystic Ovarian Disease, OCP = oral contraceptive, HRT = hormone replacement therapy.			

Multiple FAs were seen in 83 patients (47.4%), and 92 women (52.6%) had a single FA. Overall, women in the placebo group had 172 FAs, and patients in the treatment group had 190 FAs at the point of entry in the study.

Metformin and Fibroadenoma Enlargement

Considering that one of the main clinical concerns about FA is size stability, and since a 20% enlargement is contemplated as significant [5], we categorized size changes as < 20% enlargement (including also size reduction and size stability), and ≥ 20% enlargement; the former was considered as a success, and the latter as a failure. The marginal logistic regression model an odds ratio (OR) of 1.48 [95% confidence interval (CI): 1.10–1.99] for success in the treatment group in comparison with the placebo group (p = 0.01).

Since medical management of FA cannot target every single mass of patients with multiple FAs, we examined patients with multiple FAs by considering success as $< 20\%$ FA enlargement –encompassing size stability or regression- in all the masses of a patient, and failure as $\geq 20\%$ FA enlargement in even one mass of a patient. Logistic regression model showed that the odds for success was more than four-fold in the treatment than the placebo group (OR = 4.67, 95% CI: 1.34–16.28, $p = 0.02$). However, this difference did not apply in patients with single FAs ($p = 0.938$).

Metformin and Overall Size Changes in Fibroadenomas

The result of marginal model analysis when considering overall mass size as the response variable showed that the amount of size regression was more than two-fold in the treatment than the placebo group after the intervention (30.57% size reduction in the former vs. 14.1% size reduction in the latter group); this difference was statistically significant ($p = 0.03$).

When analyzing the subject in individual participants by independent paired t-test, the mean size reduction for each patient in the treatment group was around 2-fold that of the placebo group ($22.42 \pm 39.89\%$ vs. $11.65 \pm 60.67\%$); however this difference was not statistically significant ($p = 0.17$).

Metformin and Complete Fibroadenoma Shrinkage

Overall women had 198 and 173 FAs at the time of entry in the study, and 163 and 161 FAs after the intervention in the treatment and placebo groups, respectively. This yields a rate of disappearance of around 18% in the former, and 7% in the latter.

In order to compare the rate of vanishing of FAs in the two groups, we used the mean number of FAs in each individual before and after the intervention. The rate of disappearance of FAs was two-fold in the treatment group ($14.22 \pm 39.87\%$ vs. $7.73 \pm 41.45\%$). However, the difference was not statistically significant in the independent T-test analysis ($p = 0.30$).

Discussion

In this study, use of MF as a treatment for breast FA has been assessed for the first time, and a superior effect has been detected for MF compared to placebo.

Many treatments have been proposed for FA. These consist of a spectrum from pure observation to surgical excision. Surgical excision of FA is certainly the most effective treatment of FA. However, this is an invasive modality, and the objective of studies is to find the best non-invasive substitute. The high recurrence rate of vacuum-assisted excision of FA [7], the frequent conversion of endoscopic to open excision [8], and the invasive nature of these techniques exclude them from first-choice options. Non-surgical ablation techniques have a rate of complete shrinkage of around 70–80% in different methods [9–12]. These rates are notable and exceed the disappearance rate caused by MF in our study. However, the effects appear very gradually during around one year, while MF was prescribed for only six months in our study. Also, the dose of MF was low, while doses around 1500 to 2000 mg are used for other

purposes. Therefore, longer usage or a higher dose could lead to similar or superior results. In addition, ablation methods are minimally invasive and rely on access to advanced equipment; this shifts the advantages toward MF, which can be easily available and used everywhere.

Several clinical studies and reviews had proposed a conservative approach to FA as soon as the 1980s and 1990s; in favor of only observing and following up the size of cytologically- or histologically-proved small FAs in women who opt for it, are younger than 35 years of age, and have no family history or other risk factor for breast cancer [13, 14]. This approach is acceptable, but when FA size or symptoms dictates treatment, or the patients are unwilling to undergo the “watch and wait” mode, an effective medical treatment could be the best conservative management.

Various medications have been explored in this regard. Evening primrose oil is rich in gamma-linolenic acid, which is known to affect the metabolism of prostaglandins and has thus been investigated for treatment of benign breast conditions [15]. Kollias et al [16] assessed its effects on FA smaller than 3 cm, and half of their 21 cases got smaller, with no significant difference with the control group. This is in contrast with MF, which showed significantly better effects in FA treatment than the placebo.

Considering the estrogenic-dependent features of FA, anti-estrogenic compounds have been brought to trials that dealt with FA. Tamoxifen is a selective estrogen receptor modulator (SERM) widely used in breast cancer treatment and prevention that has seldom been studied for treatment of benign diseases of the breast, but a decrease in risk of developing FA [17], and a size reduction of existing FA [18] have been shown to be induced by tamoxifen, but the rate of shrinkage has not been explored. Centchroman is another SERM that has been prescribed for a period of 3 or 6 months for treatment of FA; the masses completely disappeared in 28–44% and showed size reduction in around 30% [19–22]. Although this rate of disappearance of FA is higher than the rates in our study (28–44% vs. 18%), the rate of FA size reduction is comparable with our results. On the other hand, SERMs have several bothering side effects, including hot flushes, menstrual irregularity, headache, depression, thromboembolic events, ocular disturbances, leg cramps, endometrial hyperplasia, uterine polyps, and endometrial cancer [23, 24]; these side effects prohibit their widespread consumption for management of benign disorders. Contrarily, MF is a medicine with an approved safety profile and tolerability [25]. The most common adverse effects of MF consist of gastrointestinal disturbances such as mild anorexia, diarrhea, nausea and vomiting, or abdominal discomfort. Other adverse effects are more serious but very rare and include lactic acidosis, hepatotoxicity, acute pancreatitis, pernicious anemia, or hypoglycemia with high doses of MF (e.g. 850 mg × 3 daily) [26]. In our study, no serious adverse effect was recorded, and the medicine was well-tolerated by all users. Also, the compliance of women in consuming the medicines was excellent in the treatment group. However, the dosage of MF that was prescribed in this study was only 1000 mg daily, while many studies prescribe 1500–2000 mg of MF daily. Therefore, the much lower rate of serious adverse effects of MF, and the high rate of compliance in comparison with SERMs [27, 28] make use of MF probably more applicable.

Other than the present study, MF has not yet been investigated as a medical treatment of FA; but as far as we know, the effect of MF on benign breast lesions has been reported in one published study. Talaei et al have compared the effects of MF, a placebo, and no treatment in women with fibrocystic breast changes. They detected a significant improvement in cysts number and size as well as breast tenderness and nipple discharge in the MF group in comparison with the two other groups [29].

To our knowledge, this is the first study investigating the benefit of MF in the management of FA. Our rationale for anticipating a positive role for FA in this regard was related to the mechanisms described for MF in breast cancer cells, and the pathophysiology of FA formation: MF has been shown to decrease cell proliferation [30], thus growth of FA could be expected to be suppressed. Also, MF has anti-estrogenic features which have made it an effective adjunct in management of some ovarian function and reproductive disorders, such as polycystic ovarian disease and estrogen-dependent infertility [31, 32]. This also is a suggestion for use of MF in other sex-hormone-related disorders, like FA.

According to this expectation, MF showed a favorable effect on FA in our study. The most important positive findings were: 1. Significant enlargement was nearly 50% less probable for FAs under MF treatment. 2. In women with multiple FAs, MF increased more than four-fold the probability of a safe course of all the masses of a patient by decreasing the chance for significant enlargement. 3. FAs under MF treatment had a two-fold size decrement compared with those under placebo. 4 & 5. Women receiving MF had experienced a two-fold regression of FA size in comparison with the placebo group, and the rate of complete shrinkage of FAs was two-fold under treatment; although the differences were not statistically significant. These probably could show significance in a larger sample size.

This study had some limitations. The medium size of FAs was small in our study because we did not define any minimum size limit as inclusion criteria. Also, we could not follow around 17% of cases due to COVID-19 limitations, which restricted hospital access for non-emergent and non-malignant cases. Also, we entered women with both single and multiple FAs, which might behave differently clinically. We suggest further study including only large FAs, and by defining sample sizes separately for cases of single or multiple FAs.

Conclusion

In conclusion, this is the first study which evaluates the effect of MF as a management option in breast FA. The results suggest a favorable effect, especially in women with multiple FAs. Larger studies including only large FAs, and using higher doses of MF, are suggested in order to confirm this effect.

Abbreviations

FA: Fibroadenoma; OR: Odds ratio; US: Ultrasound; MF: Metformin; IRCT: Iranian Registry of Clinical Trials; BMI: Body mass index; GEE: Generalized estimate equation; CI: Confidence interval; SERM: Selective estrogen receptor modulator.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran approved the study (Approval ID: IR.TUMS.VCR.1397.357). All participants read and signed a written informed consent before entering the study.

Consent for publication

Not applicable.

Availability of data and material

All data analyzed during this study are included in this published article and raw-data are available from the corresponding author on reasonable request.

Competing Interest

The authors have no conflict of interest to declare.

Funding

The study was funded by an academic research grant from the Deputy of Research of Tehran University of Medical Sciences, Tehran, Iran (Proposal Code: 97-01-218-37716).

Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by M.A., A.S., F.F., and A.MH. Data analysis was performed by S.Sh. and B.E. The first draft of the manuscript was written by S.A. and all authors commented on previous versions of the manuscript. All authors reviewed the final manuscript.

Acknowledgements

The study was funded by an academic research grant from the Deputy of Research of Tehran University of Medical Sciences, Tehran, Iran (Proposal Code: 97-01-218-37716). We would like to thank Dr. Mannan Hajimahmoodi for her great support in providing MF and placebo tablets, Dr. Akram Seifollahi for

interpreting histologic results of biopsies, Dr. Kamran Yazdani for providing assistance in the analysis, Mrs. Maryam Azari, Mrs. Marzieh Orouji, and Mrs. Farzaneh Ahari for their kind and active help in data gathering.

References

1. Smith G, Burrows P. Ultrasound diagnosis of fibroadenoma—is biopsy always necessary? *Clin Radiol*. 2008;63(5):511-5.
2. Coriaty Nelson Z, Ray RM, Gao DL, Thomas DB. Risk factors for fibroadenoma in a cohort of female textile workers in Shanghai, China. *Am J Epidemiol*. 2002;156(7):599-605.
3. Levi F, Randimrison L, Te VC, la Vecchia C. Incidence of breast cancer in women with fibroadenoma. *Int J Cancer*. 1994;57(5):681-3.
4. Chae YK, Arya A, Malecek MK, Shin DS, Carneiro B, Chandra S, et al. Repurposing metformin for cancer treatment: current clinical studies. *Oncotarget*. 2016;7(26):40767-80.
5. Dialani V, Chansakul T, Lai KC, Gilmore H, Sayegh NY, Slanetz PJ. Enlarging biopsy-proven fibroadenoma: Is surgical excision necessary? *Clin Imaging*. 2019;57:35-9.
6. Hanley JA, Negassa A, Edwardes MDd, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol*. 2003;157(4):364-75.
7. Grady I, Gorsuch H, Wilburn-Bailey S. Long-term outcome of benign fibroadenomas treated by ultrasound-guided percutaneous excision. *Breast J*. 2008;14(3):275-8.
8. Waleed Y, Mohamed AS, Ahmed AD, Magdy M. Endoscopic Resection of Breast Fibroadenoma. *Med J Cairo Univ*. 2018;86:2861-9.
9. Dowlatshahi K, Wadhwani S, Alvarado R, Valadez C, Dieschbourg J. Interstitial Laser Therapy of Breast Fibroadenomas With 6 and 8 Year Follow-Up. *Breast J*. 2010;16(1):73-6.
10. Yang BR, Kim HJ, Shin KM, Cho SH, Jang Y-J, Lee HJ, et al. Serial Ultrasound Findings After Laser Ablation for Benign Breast Lesions on Long-Term Follow-Up: Implications for Evaluation of Procedural Success. *Photomed Laser Surg*. 2015;33(8):404-8.
11. Li P, Xiao-Yin T, Cui D, Chi J-c, Wang Z, Wang T, et al. Evaluation of the safety and efficacy of percutaneous radiofrequency ablation for treating multiple breast fibroadenoma. *J Cancer Res The*. 2016;12(7):138.
12. Brenin DR, Patrie J, Nguyen J, Rochman CM. Treatment of breast fibroadenoma with ultrasound-guided high-intensity focused ultrasound ablation: a feasibility study. *J Breast Imaging*. 2019;1(4):316-23.
13. Dixon J, Dobie V, Lamb J, Walsh J, Chetty U. Assessment of the acceptability of conservative management of fibroadenoma of the breast. *Br J Surg*. 1996;83(2):264-5.
14. Wilkinson S, Anderson T, Rifkind E, Chetty U, Forrest A. Fibroadenoma of the breast: a follow-up of conservative management. *Br J Surg*. 1989;76(4):390-1.
15. Bayles B, Usatine R. Evening primrose oil. *Am Fam Physician*. 2009;80(12):1405-8.

16. Kollias J, Macmillan R, Sibbering D, Burrell H, Robertson J. Effect of evening primrose oil on clinically diagnosed fibroadenomas. *Breast*. 2000;9(1):35-6.
17. Tan-Chiu E, Wang J, Costantino JP, Paik S, Butch C, Wickerham DL, et al. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. *J Natl Cancer Inst*. 2003;95(4):302-7.
18. Viviani R, Gebrim L, Baracat E, De GL. Evaluation of the ultrasonographic volume of breast fibroadenomas in women treated with tamoxifen. *Minerva Ginecologica*. 2002;54(6):531-5.
19. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. *World J Surg*. 2007;31(6):1180-6.
20. Tejwani PL, Nerkar H, Dhar A, Kataria K, Hari S, Thulkar S, et al. Regression of fibroadenomas with centchroman: a randomized controlled trial. *Indian J Surg*. 2015;77(2):484-9.
21. Gupta N. A Prospective Study to study the Efficacy and Side Effects of Ormeloxifene in Regression of Mastalgia and Fibroadenoma: Is It the Ideal Drug? *SAFGO*. 2016;8(1):48-56.
22. Roy SB, Hembram R. A comparative study of efficacy of centchroman and evening primrose oil in treatment of benign breast disease. *J Evol Med Dent Sci*. 2018;7(31):3518-25.
23. Buckley MM-T, Goa KL. Tamoxifen. *Drugs*. 1989;37(4):451-90.
24. Ellis AJ, Hendrick VM, Williams R, Komm BS. Selective estrogen receptor modulators in clinical practice: a safety overview. *Expert Opin Drug Saf*. 2015;14(6):921-34.
25. Heckman-Stoddard BM, Gandini S, Puntoni M, Dunn BK, DeCensi A, Szabo E, editors. Repurposing old drugs to chemoprevention: the case of metformin. *Semin Oncol*. 2016: 43(1):123-33.
26. Shurrab NT, Arafa E-SA. Metformin: A review of its therapeutic efficacy and adverse effects. *Obes Med*. 2020;17:100186.
27. Huiart L, Dell'Aniello S, Suissa S. Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. *Br J Cancer*. 2011;104(10):1558-63.
28. Zeidan B, Anderson K, Peiris L, Rainsbury D, Laws S. The impact of tamoxifen brand switch on side effects and patient compliance in hormone receptor positive breast cancer patients. *Breast*. 2016;29:62-7.
29. Talaei A, Moradi A, Rafiei F. The evaluation of the effect of metformin on breast fibrocystic disease. *Breast Dis*. 2017;37(2):49-53.
30. Cheng G, Zielonka J, Hardy M, Ouari O, Chitambar CR, Dwinell MB, et al. Synergistic inhibition of tumor cell proliferation by metformin and mito-metformin in the presence of iron chelators. *Oncotarget*. 2019;10(37):3518-32.
31. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod*. 2002;17(11):2858-64.
32. Løvvik TS, Carlsen SM, Salvesen Ø, Steffensen B, Bixo M, Gómez-Real F, et al. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(4):256-66.

Figures

Figure 1

Summary of CONSORT flowchart.