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Short Communication



# Infertility Does Not Increase the Rate of Breast Fibroadenoma

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## Abstract

**Background:** Fibroadenoma (FA) and infertility can share common risk factors and probably common underlying pathophysiology, but yet there is no study evaluating the prevalence of FA in infertile women. Therefore, the aim of in the present study, the purpose was evaluating the association of FA and infertility for the first time.

**Methods:** This short communication is a secondary analysis of a primary study that was performed in Arash Women's Hospital, Tehran, Iran. Participants were selected among reproductive-aged women with a history of infertility as the case and women without infertility as the control group. The criteria for diagnosis of FA were histopathologic assessment for lumps 1 *cm* in size or larger, and a typical ultrasound image for smaller lumps. Assisted reproductive technology (ART) was defined as any previous history of undergoing ovulation stimulation, intrauterine insemination, intracytoplasmic sperm injection, or in vitro fertilization.

**Results:** Overall, 155 cases with a mean age of 39.2±6.9, and 167 controls with a mean age of 43.08±8.3 were included (p=0.0001). Interestingly, the incidence of FA was lower in the case group (18.7% *vs*. 25.7%), however, the difference was not statistically significant (p=0.13). Also, logistic regression analysis showed that the chance for an infertile woman who undergoes ART to get FA is 1.7 times higher in comparison to non-ART group, although the difference was not significant (p=0.21).

**Conclusion:** Infertility and ART were not associated with increased risk of FA; however, larger prospective studies should be conducted in the future in order to achieve conclusive results.

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## Introduction

Fibroadenoma (FA) is the most common neoplastic mass of the breast in premenopausal women and accounts for about 12% of breast masses in menopausal women (1). Formerly, FAs were originally classified as non-proliferative lesions, but today they are considered proliferative lesions (2). The simple form of FA cannot increase the risk of malignancy in the future, but in case of proliferative changes or significant family history of breast cancer, the risk of subsequent cancer is slightly elevated (2, 3). Although its main etiology is unknown, the hormone-depend-

ent behavior of this tumor suggests that unknown endocrine pathways can be the most probable cause of these benign lesions; since FA usually develops in adolescence and young age at the same time of breast development, it grows with pregnancy and regresses after menopause (4). Also, it has been shown that hyperestrogenic status can increase the incidence or size of FA (5).

On the other hand, it is known that most infertility-related etiologies are related to important medical conditions that are significantly associated with hormonal disorders such as un-ovulatory infertility. Also, most infertility treatments require extensive hormonal manipulations (6). This fact is the base of many studies investigating the association of breast cancer and infertility, or assisted reproductive technology (ART).

It was observed that the number of infertile women who attended consultation because of a breast FA before planning for pregnancy was much more than women without infertility. This could be because of the higher rate of pre-conception breast assessment in infertility, but it also could be that the tumor was more frequent in these women due to its dependency on steroid hormones. Therefore, this study was conducted to assess the association between FA and infertility.

## Methods

The study was performed in Arash Women's Hospital. Participants were selected among premenopausal women attending the gynecology and infertility clinics in an interval of six months. Patients with a history of infertility were considered as the case, and women without infertility were considered as the control group.

Exclusion criteria consisted of a history of breast cancer or recent breast surgery. All participants underwent breast examination and breast ultrasound and the presence of FA was recorded. The criteria for diagnosis of FA were histopathologic assessment for tumors 1 *cm* in size or larger, and a typical ultrasound image for smaller lumps. The age of menarche, parity, and use of oral contraceptives were recorded. Women in the case group were also asked about previous ART which was defined as any previous history of undergoing ovulation induction, intrauterine insemination, intracytoplasmic sperm injection, or in vitro fertilization.

## Results

Overall, 155 infertile and 167 non-infertile were entered in the study as the case and control groups, respectively. The mean age of the participants was 39.2±6.9 and 43.08±8.3 years in cases and controls, respectively; the difference was statistically significant (p=0.0001). Other basic characteristics of the two groups are shown in table 1. FA was detected in 29 women in the case group (18.7%) and 43 women in the control group (25.7%). Interestingly, the incidence of FA was lower in the case group than the controls, however, the difference was not statistically significant

**Table 1.** Demographic and reproductive features in two groups

| Variables | Infertile women (n=155) | Non-infertile women (n=167) | p-value |
|---|---|---|---|
| **Age (year)*** | 39.32±6.9 | 43.08±8.3 | 0.0001 ‡ |
| **Menarche *** | 13.25±1.62 | 13.22±1.55 | 0.88 ‡ |
| **Parity *** | 0.73±0.86 | 1.68±1.30 | 0.0001 ‡ |
| **Mensuration †** | | | |
| Regular | 98 (64.1) | 86 (51.5) | |
| Irregular | 45 (29.4) | 59 (35.3) | 0.037 § |
| Menopause | 10 (6.5) | 22 (13.2) | |
| **Types of infertility †** | | | |
| Primary | 112 (72.7) | | |
| Secondary | 38 (24.7) | - | - |
| Both | 4 (2.6) | | |
| **History of OCP use †** | 60 (38.7) | 92 (55.4) | 0.002 § |
| **History of HRT use †** | 5 (3.2) | 6 (3.6) | 0.55 § |

* Data presented as mean ± SD, * Data presented as number (percentage), ‡ Independent t-test, § $Chi^2$.
OCP = Oral Contraceptive Pills, HRT = Hormone Replacement Therapy

(p=0.13); this did not change after adjustment for age. The logistic regression analysis showed no effect for age (p=0.11), age of menarche (p=0.66), parity (p=0.69), and use of oral contraceptives (p= 0.83) on this association.

Moreover, the association of ART with FA was analyzed in the case group. Ninety-one (58.7%) of infertile women underwent ART; the prevalence of fibroadenoma was slightly higher in ART compared to the non-ART group (19.8% versus 15.4%); however, this difference was not statistically significant (p=0.52). Logistic regression analysis showed that the chance for an infertile woman who undergoes ART to get FA is 1.7 times higher in comparison to infertile women who do not undergo ART, although the test did not show any significant difference in this regard (p=0.21).

## Discussion

In the present study, it was interestingly found that the incidence of FA was lower in infertile women compared to fertile group; however, the difference was not statistically significant. Contrary to the growing evidence existing about the association of breast cancer and infertility, to the best of our knowledge, this is the first study to investigate the association of FA, as a benign breast lesion with infertility. Therefore, the objective was to compare our findings with those studies that had focused on the risk of developing breast cancer following infertility or ART. The findings of population-based studies investigating the effect of infertility on the incidence of breast cancer are very controversial; some showed that infertility can be an important risk factor for breast cancer (7), while others confirm that there is no relationship between infertility and breast cancer risk (8).

One of the hypotheses that tries to rationalize the link between breast cancer and infertility is the administration of various hormonal compounds during ART (9); this hypothesis arose from the fact that most breast cancer cells are sensitive to estrogen, so hormonal stimulation can increase endogenous estrogen levels and consequently, the risk of breast cancer (10). This point of view can also be applied to FAs since the same pathophysiological pathway is suggested for FA development under the hyperstrogenic microenvironment. It has been reported that a higher in-situ concentration of estrone and estradiol (11) and higher estradiol and progesterone receptor expression level (12) is observed in FA compared to the rest of breast tissue.

According to a recently published population-based cohort study with 61579 participants, it has been shown that the risk of breast cancer is slightly increased in infertile women after ART treatment in comparison to age-matched, untreated women (13). Given all these facts, it is hypothesized that the use of ovarian stimulation drugs can be associated with increased risk of FAs. In the present study, despite the slightly elevated incidence of FA in the ART group, our findings were not statistically significant and probably a history of ART cannot predict the probability of getting FA. However, considering our small sample size, the clinical significance of our results is not still conclusive and this finding must be interpreted with caution.

One of the other factors that can explain the association of breast cancer and ART is age-related vulnerability to hormone exposure during ART (13) and prolonged nulliparity (14). Most infertile women start their infertility treatments at older ages due to different reasons and initiate ART treatment when they are aged above 40 years; higher hormone doses during ART treatment may explain this elevated risk. In the present study, despite the significant difference between the two groups regarding age and parity, the logistic regression analysis showed no effect for age and parity on the prevalence of FA between the two groups.

On the other hand, several researchers believed that infertility and its treatment methods alone are not generally associated with increased risk for breast cancer, but some agents that are used for ovulation induction like clomiphene citrate can elevate the risk of breast cancer (15-17). Unfortunately, in the present study, no data were found in this regard. Since both causes and consequences of infertility might affect cancer risk, explanation of this relationship is complex and previous studies also could not provide a precise conclusion in this regard; some found that all causes of infertility slightly elevate breast cancer risk (13) while others found no relationship (18, 19).

One of the limitations of the present study is that the data presented in this manuscript was a secondary analysis of another study, so case and control groups were not as well-matched as they should be. So, our findings might be confounded by the differences existing between the two

groups of the study, including age, parity, menstruation pattern, and history of OCP use. Also, the etiology of infertility was not recorded in the case group.

## Conclusion

Despite the surprisingly and slightly declined incidence of FA in the infertile group, no significant relationship was found between infertility and FA. Also, the chance for an infertile woman who undergoes ART to get FA was higher in comparison to infertile women who do not undergo ART, but it was not statistically significant. Our results are interesting because they contradict the association between infertility or ART and FA and can be the cornerstone of later studies in the future. In fact, larger prospective studies should be conducted to determine the actual role of different causes of infertility, different types of ART and hormonal intervention used for infertility treatment, and even risk factors that make infertile women more vulnerable to breast neoplastic lesions following infertility treatments.

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## Conflict of Interest

There is no conflict of interest to declare.

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