RESEARCH

Positive association between progestins and the evolution of multiple fibroadenomas in 72 women

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Abstract

Objective: Multiple fibroadenomas (MFA) of the breast is a rare benign disease, thus its natural history is poorly understood. The aim of our study was to describe the radiological evolution of MFA and to evaluate the influence of different factors on this evolution.
Methods: This was a longitudinal cohort study. All patients included had two clinical and radiological assessments (breast ultrasound (US) and/or MRI) at least 5 years apart.
Results: Seventy-two women were followed for 7.6 ± 2.1 years. The radiological evolution showed a decrease or stability in the number of fibroadenomas (FA) in 26/44 cases on the MRI and in 38/64 cases on the US. There was a decrease of size in 35/44 cases on the MRI and in 53/64 cases on the US. An increase in the number of FAs was found in 18/44 cases in the MRI and 26/64 cases in the US with, for the majority, a decrease of size (19/26 by MRI and 16/18 by MRI). Older age at the first FA ($P < 0.0001$) and at the diagnosis of MFA ($P < 0.0001$), pregnancy ($P = 0.003$) and progestin use ($P < 0.001$), particularly lynestrenol ($P < 0.0001$), had a beneficial effect on the evolution of MFA.
Conclusion: This is the first longitudinal study describing women with MFA. The radiological evolution of MFA seamed favorable and similar to that expected for a single FA. We identified factors influencing the evolution of the disease, including progestin treatments such as lynestrenol, which could have a beneficial effect. Our cohort should be followed further in order to expand our knowledge of MFA, especially concerning the risk of breast cancer.

Key Words
- fibroadenomas
- progestins
- contraception
- pregnancy
- breastfeeding

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Introduction

Multiple fibroadenomas (MFA) of the breast, defined by the unilateral or bilateral existence of at least three fibroadenomas (FA) in one breast, is a rare benign disease, and thus its natural history is poorly understood (1). The incidence of MFA has been estimated at between 15 and 20% in a population of women with FA (2). The benefits of the mammography, which is one current breast imaging technique, may be limited in cases of MFA for different reasons (breast density, the young age of patients), and so, the preferred breast imaging techniques are US or MRI depending on the number of lumps (3). MFA lesions seem to have the same radiological

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characteristics as a simple FA (4). The etiology of MFA still remains unknown, but previous studies have suggested a possible role of certain hormones in the pathogenesis of FA (5, 6). The concentrations of estrone and estradiol have been found to be higher in FAs compared with those in the rest of mammary gland (7). Moreover, estradiol and progesterone receptor levels were also higher in FAs recently detected (8). The possible role of prolactin has also been suspected (9). However, no established systemic hormonal imbalance has been demonstrated as of yet (9, 10).

Although MFA seems to have the same clinical, radiological and histological characteristics as a simple FA, it is not clear yet whether MFA is a natural continuum resulting from a simple FA or a *de novo* phenomenon corresponding to a well-defined disease entity. Furthermore, its evolution is unknown and there is no consensus regarding its treatment, which has been sparsely studied and evaluated. Follow-up of MFA patients seems to be fundamental to improve our knowledge of this disease and avoid radical treatments such as surgery wherever possible. We, therefore, designed a prospective study to determine the radiological evolution of MFA and to identify factors that might be positively associated with its evolution, such as the role of hormonal treatment in particular.

Patients and methods

Patients

A cohort of MFA patients has been set up since 2003 in the Endocrinology and Reproductive Medicine department of La Pitié Salpêtrière Hospital.

The first assessment of this cohort was published in 2009 (10). Briefly, patients prospectively underwent breast ultrasonography and/or MRI and it was reported that MFA had the same radiological characteristics as a single FA. The mean numbers of FAs per breast found on the ultrasound and MRI were 4.4 ± 4.0 and 3.9 ± 3.2, respectively, with a mean size of 12.6 ± 6.8 and 12.9 ± 5.6 mm. The evaluation of gonadal and lactotroph function revealed no hormonal imbalance. All tumors removed surgically underwent pathology and immunochemistry examination, which showed that fibroadenomas were common and that 6.3% of the tumors were of the benign phyllodes type. Estrogen and progesterone receptors were detected in 85 and 98% of samples, respectively. The median percentage of Ki-67 staining was less than 5%. We identified two constitutively active prolactin receptor (hPRLR) variants in exon 5 (I76V: ten patients, eight controls) and exon 10 (one patient, no control). No phenotypic difference was observed between carriers and non-carriers of either hPRLR variant.

The second evaluation took place from January 2013 to April 2014 after a longitudinal follow-up period with regular consultations. Women were included if they had MFA followed in our department for at least 5 years, with an initial radiological evaluation by breast US and/or MRI. Patients who were pregnant or breastfeeding, living abroad or who refused to complete the questionnaire or to undergo radiological evaluation were excluded. The study was approved by CPP Ile-de-France VI, Groupe Hospitalier Pitié-Salpêtrière, the local ethical committee, and all patients provided written informed consent.

Assessment of MFA

The second evaluation took place during a 1-day hospitalization and consisted of a personal interview, the collection of personal and family mammary/gynecological history from the medical file, and careful recording of the hormonal treatments used since the first assessment. Finally, participants underwent a radiological evaluation with bilateral breast US and/or breast MRI if possible. The number, size and accurate localization of various FAs were recorded to allow for a precise comparison of the images with those from the initial assessment. FAs removed surgically were recorded accurately to avoid a bias in the comparative analysis. Their size and localization were identified based on the surgical reports. For each patient, we evaluated the number of FAs in a first time, and then for each group ('increase', 'stability' and 'decrease of FAs number') the average size of FAs was evaluated (excluding FA surgically removed).

Breast ultrasonography

Breast ultrasonography was performed with an Aplio^{MC} 500 CV (Toshiba) by one single-skilled radiologist working in our hospital. Patients were in dorsal decubitus and the mammary glands were scanned with a 7–14 MHz high-frequency transducer.

Breast MRI

Breast MRI was performed with a 1.5 Tesla (Philips) until 2013 and then with a 3 Tesla (Siemens, SKYRA 3T). Transverse planes in T2-weighted, short-tau inversion-recovery (STIR) sequences were used. Then transverse planes with section thickness of 4 mm were performed in T1-weighted (Gradient Recalled Echo) sequences with

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one pre-contrast and four post-contrast acquisitions. Subtraction of the pre-contrast from the post-contrast images was done to better visualize the enhancing foci. We ended with sagittal planes with section thickness of 0.8 mm in late 3D T1-weighted sequences. The T1-shortening contrast agent used was 0.1 mmol/kg of IV gadolinium chelate.

Statistical analysis

Descriptive statistics were used, with numbers compared to total number of patients as qualitative variables and means ± S.D. or medians (Q1–Q3) as quantitative ones. Four criteria were defined for the determination of the factors impacting the evolution of MFA: the standardized difference in the number of nodules and the mean nodule size, observed by US and MRI. Standardization of the differences observed was necessary because the time between the two evaluations varied: the observed criteria differences were divided by the time to calculate the standardized differences. The results are presented over a period of 10 years. Mean standardized differences were compared by Student *t*-tests for binary variables and by ANOVAs for qualitative variables with more than two possible values. Relationships between criteria and quantitative factors were assessed by linear regression. All tests were two-tailed, with a *P*-value less than 0.05 considered as significant. The statistical calculations were performed using the SAS V9.3 statistical analysis software (SAS Institute Inc., Cary, NC, USA).

Results

Selection of the population

Among the 233 patients in our cohort, 126 met the inclusion criteria (Figure 1). Patients lost to follow-up accounted for 33/126 and refusals were 14/126. The main reasons for refusal were the wish to stop thinking about their MFA and a lack of availability for professional reasons.

Description of the population

The mean age was 28.9 ± 9.9 years (range: 13–58 years) at the initial evaluation and 36.8 ± 10.6 years (range: 21–66 years) at the second one. The mean follow-up period was 7.6 ± 2.1 years. The clinical characteristics of the patients are presented in Table 1. Only one of our patients was

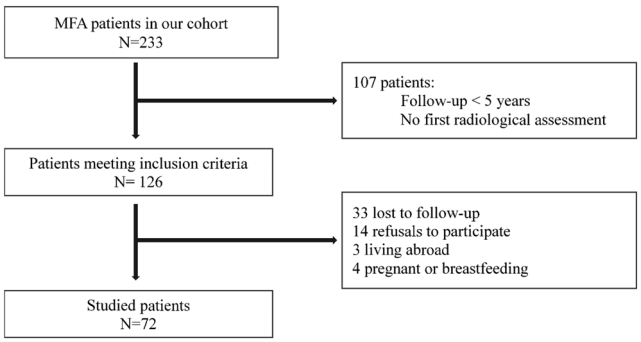

Figure 1
Population selection.

menopausal. The group of patients lost to follow-up was similar to the one that underwent the second assessment in the age at first FA (21.8 ± 7.3 vs 21.8 ± 8.2 years; $P = 0.981$), age at diagnosis of MFA (26.1 ± 9.1 vs 25.1 ± 9.7 years; $P = 0.557$) and age at first assessment (28.8 ± 8.9 vs 28.9 ± 9.9 years; $P = 0.957$).

During the follow-up period, there were 52 pregnancies in 26 women: 37 childbirths, 8 miscarriages, and 7 abortions. Eighteen patients breastfed for 11.1 ± 10.5 months (median = 6 months, range 1.5–32.0). Between the two assessments, 65/72 patients took a hormonal treatment for their MFA or hormonal contraception (Table 2). Each patient could have received several treatments. Thirty-one patients among the 72 patients of this study underwent surgical removal of their lumps during the follow-up period. Thirty-nine surgeries, mainly motivated by atypical radiological images, were done and 60 lesions were removed, for a mean number of 1.9 lesions per woman. The size of these lesions could be evaluated for 28 women and was 22.1 ± 1.9 mm. Histopathology of 53 of the 60 removed lumps concluded that they

Table 1 General characteristics of the 72 MFA patients.

Age at 1st FA (years)	21.9 ± 8.2
Age at MFA diagnosis (years)	25.2 ± 9.6
Family history of breast cancer (*n*)	
1st degree	12
2nd degree	20
1st and 2nd degree	4
Family history of FA (*n*)	
1st degree	20
2nd degree	11
1st and 2nd degree	7
Smoking (*n*)	9
BMI (kg/m^2)	
1st eval.	22.8 ± 3.1
2nd eval.	24.4 ± 3.9[a]

eval: evaluation; *n*: number of patients.
[a]$P < 0.05$.

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Table 2 Hormonal treatment and contraception used by MFA patients between the two assessments.

	n	Duration of use (months ± s.d.)
Progestins	64	56.3 ± 4.8
Chlormadinone acetate	31	34.1 ± 4.9
Nomegestrol acetate	20	42.5 ± 8.3
Lynestrenol	35	40.7 ± 7.4
Promegestone	5	27.2 ± 12.4
Cyproterone acetate	6	34.0 ± 11.5
75 µg desogestrel-only contraception	11	31.4 ± 18.6
Combined contraceptives	12	14.2 ± 4.7

n: number of patients.

were FAs. Five among all removed lumps were phyllodes tumors (PT), with four benign tumors and one borderline tumor. Two breast cancers were diagnosed. One was an invasive lobular carcinoma in a 46-year-old woman and the other was an invasive ductal carcinoma in a 36-year-old woman. Both had a family history of breast cancer, had respectively three and two pregnancies and breastfed.

Radiological evolution

For the second radiological assessment, 64/72 women underwent breast US. The mean number of FAs was 7.5 ± 5.1 vs 6.9 ± 4.1 at the first assessment (P = 0.25). The mean FA size decreased significantly at the second assessment (respectively, 5.6 ± 4.4 mm vs 10.3 ± 5.5 mm, $P < 0.0001$). A breast MRI was done for 44/72 women. We found 10.2 ± 11.1 FAs per patient vs 6.8 ± 4.9 FAs at the first assessment (P = 0.02). They were significantly smaller (6.6 ± 6.9 mm vs 11.2 ± 9.4 mm, $P < 0.0001$). There was no statistical difference between the two imaging techniques concerning the mean number and mean size of FAs, during the first and the second assessment. In other words, in the hands of an experienced radiologist, US have the same relevance as MRI for evaluation of MFA.

When the radiological evaluation of MFA of each patients was analyzed in greater detail, there have been found a decreased/stable number of FAs by US and MRI for majority of our patients (respectively, 38/64 patients and 26/44 patients) and also a decreased size of FAs for majority of our cohort (respectively, 53/64patients and 35/44 patients) (Figure 2).

Factors positively associated with the evolution of MFA

As the assessment of MFA by US and MRI was similar and as US remains the first-line radiological exam, we only present factors impacting the evolution by US (Table 3), given that the results were nearly superimposable by MRI.

Age at first FA and age at the diagnosis of MFA

An older age at the first FA was positively associated with the evolution of MFA (decrease of FA size per year of life in addition at diagnosis of the FA, and at the diagnosis of MFA: −0.2 ± 0.04 mm, $P < 0.0001$ over a 10-year period of evolution).

Family history of breast cancer

Having a family history of breast cancer seemed negatively associated with the evolution of MFA with an increase in the number of lesions (over a 10-year period of evolution: increase of 2.1 ± 1.0 FAs per additional relative with breast cancer, P = 0.04). Surprisingly, the size of the lesion decreased gradually per additional family case of breast cancer (−3.4 ± 2.0 mm, P = 0.04 over a 10-year period of evolution).

Hormonal treatment

Progestins were positively associated with a reassuring evolution of MFA. There was actually a decrease in the size of the lesions evaluated by US with progestins (−0.1 ± 0.02 mm per month of progestin use, over a 10-year period of evolution, $P < 0.001$), although there was no significant decrease in the number of FAs. Regarding the different progestins, chlormadinone acetate and lynestrenol had a positive association on the evolution of MFA. The mean size of the FAs by US decreased by 0.1 ± 0.04 mm per month of chlormadinone acetate use over 10 years of follow-up (P = 0.02). Regarding lynestrenol, the users had significantly smaller lesions than non-users (−4.5 ± 7.4 mm by US, P = 0.006). Moreover, we have demonstrated that lesion size decreased especially if lynestrenol use was prolonged (over a 10-year period of evolution, decrease of −0.2 ± 0.03 mm per month of use, $P < 0.0001$).

Regarding oral contraceptives, there was no association on the evolution of MFA, regardless of whether combined oral contraceptives (COC) or only progestin (75µg of desogestrel) were used.

Pregnancy and breastfeeding

The evolution of FA seemed to be associated with pregnancy and breastfeeding. The size of the lesions decreased by −2.4 ± 1.0 mm per pregnancy over a period of 10 years of follow-up (P = 0.014). In the case of breastfeeding, the number of FAs also decreased (−1.1 ± 6.5 FA; P = 0.03).

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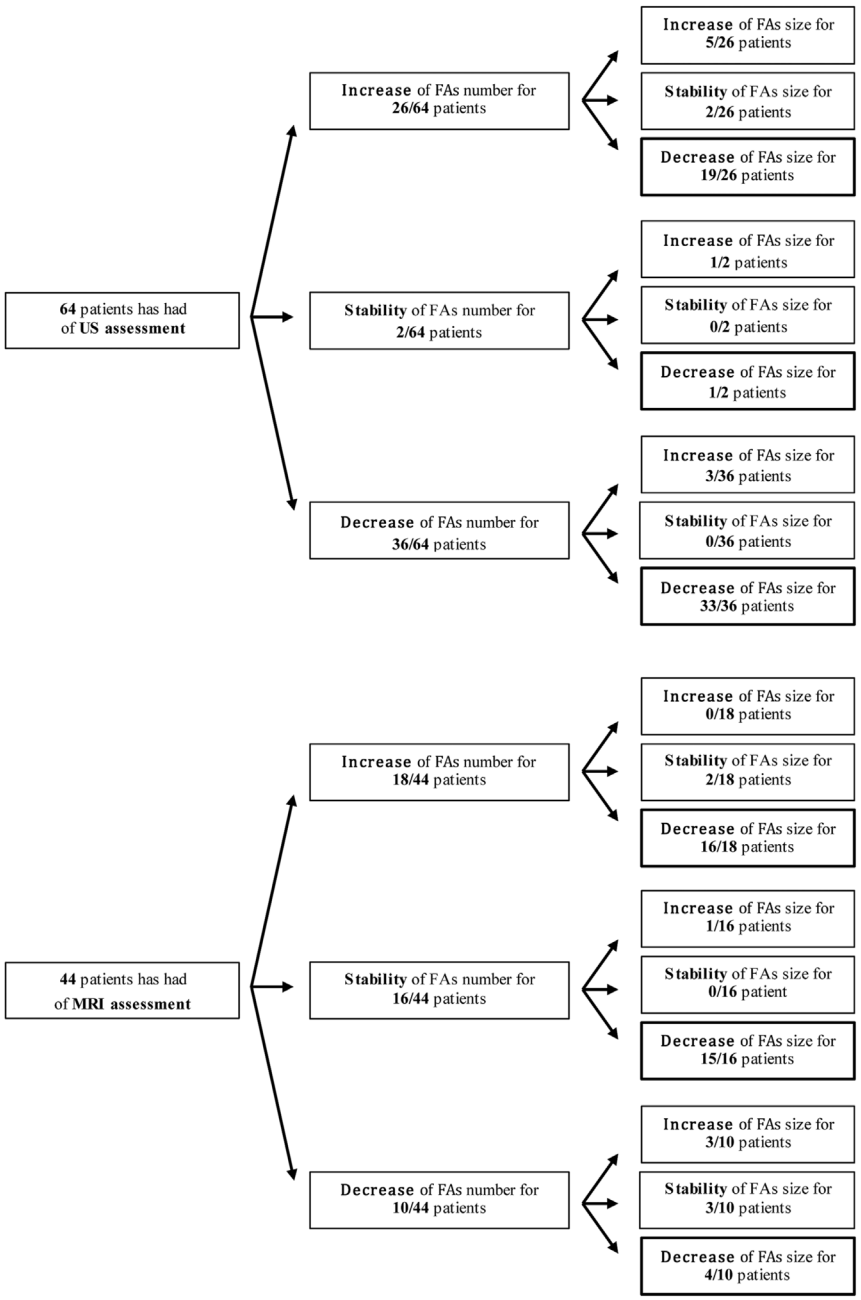

Figure 2
US and MRI evolution of the number of lumps in MFA patients, then evolution of the size of the lumps in each group (increase, stability and decrease of the number of FA).

As for its influence on the evolution of FA size, breastfeeding also had a positive effect on the evolution of MFA that increased with the period of breastfeeding (−0.4 ± 0.2 mm per month of breastfeeding, $P = 0.09$).

Discussion

MFA is a rare disease whose natural history still remains poorly understood. Our study found that the evolution MFA was close to that of single FAs. MFA evolved favorably, with a decrease or stability of the number of lesions by US and MRI in more than half of the women, as well as a decrease in size in the vast majority of cases. Similarly, the evolution of single FAs showed either a decrease or stability in 70% of cases (11,12). Cant *et al.* found the same regression rate between single FAs and MFA in their cohort, with an average resolution period of 61 months (13). Furthermore, we report that US and MRI are equally relevant for assessment. Therefore, US scans done by an experimented radiologist must remain the first-line radiological exam and MRI, which is more

Table 3 Overview of factors associated with number and size by US assessment of MFA in 72 women.

	Number	Size
Beneficial association	Breastfeeding	Older age at 1st FA Older age at MFA diagnosis Family history of breast cancer Obesity Pregnancy and gravidity Breastfeeding Progestins Chlormadinone acetate Lynestrenol
Negative association	Family history of breast cancer	None

expensive and could be reserved for difficult situations like the monitoring of very numerous FAs per breast.

Among our patients, the majority of the lumps removed surgically were actually FAs (88.3%), which is consistent with the data in the literature (12,13). Recently, an American study reported a rate of 94% of FAs after histological analysis of breast lumps initially diagnosed as FAs (14). This corroborates the good concordance between radiological and histological diagnoses of FA and argues for avoiding surgery and only proposing radiological monitoring. However, we did find a higher rate of PT (9% of the lumps removed) than rates reported in the literature (0.8 to 3.0%) (14,15). Those rates were diagnosed based on histology after surgery to remove a suspicious lump with atypical radiological and clinical FA characteristics. The differential diagnosis between PT and FA is still difficult, but the invasive capacity of PT necessitates close examination and most importantly requires prompt histological control of atypical lumps (16,17). Clinical and radiological monitoring of MFA is therefore recommended, but all lumps should not be systematically biopsied (damaging and complicated). If some atypical criteria appear, microbiopsies must be organized so as not to disregard a PT.

One of the major questions regarding the evolution of MFA is obviously its link with breast cancer. We found two breast cancers in women with a family history of breast cancer (BRCA1/2 genetic status not known). Clearly, we cannot draw conclusions about a possible higher risk of breast cancer in this MFA population described in an observational study, because our patients are still too young to develop breast cancer, the sample is too small, and there is no control group. However, and first, breast cancer arising within a FA is rare (0.02 to 0.1%) (18) and the most predictive factor remains aging (14). Secondly, is MFA a risk factor for developing breast cancer? The relative risk of breast cancer in patients with a non-proliferative pathology like typical FAs was not increased (RR: 0.89; IC95% (0.62–1.3)) (19). Even if Dupont and Page have shown an excess risk for proliferative benign breast disease without atypia in patients with a family history of breast cancer (20), the same has not been proven for typical FAs (20,21). However, like for PT and to avoid missing a cancer diagnosis, histological confirmation of atypical FAs is essential and monitoring with US should be longer in MFA than for simple FAs, because clinical examination is not relevant.

Our study is the first to highlight factors positively associated with the evolution of MFA.

One of our major outcomes is the favorable evolution of MFA with progestins. A state of relative hyperestrogenism locally in breast tissue or globally has been suggested to play a role in the genesis of breast diseases. Therefore progestins would naturally seem to be beneficial in terms of restoring a hormonal balance. To our knowledge, there is no literature supporting our finding regarding progestins, but two studies confirm their safety, with a decreased risk of breast cancer in the population with benign breast disease (22) or with no negative effects on the evolution of FA (26). Another comforting finding of our work is the absence of negative effects of COC on the evolution of MFA. This neutral effect (regardless of the estrogen dose) or even a protective trend as the duration of COC use increases has been found in numerous studies (23, 24, 25, 26, 27). To date, it is therefore legitimate to be reassuring about the prescription of COCs in women with FA, and therefore by extrapolation, with MFA.

Pregnancy and breastfeeding were positively associated with the evolution of MFA. Previous studies have shown that multiparity seems to be protective in the development of FAs (24,28). As for breastfeeding, this relationship is still up for discussion (24,29). It is conventionally assumed that FAs grow during pregnancy under the influence of hormones and then regress during the postpartum period. First of all, the drop in estradiol and progesterone levels immediately after birth as well as the fall of PRL levels after the end of breastfeeding could induce a regression of hormone-dependent lesions like FA. Second, as with the natural involution of the mammary glands at the end of breastfeeding, MFA lesions could also evolve favorably.

Our work is the first longitudinal description of the evolution of MFA which is still a poorly understood disease. Despite the rarity of this breast pathology, we have been

able to regularly follow a significant number of patients included in the largest MFA cohort described to date. Our work probably lacks the necessary power to demonstrate the influence of certain parameters, which remained at the border of significance, like breastfeeding or some treatments. Even though we are a referral center, MFA is a rare benign and mostly asymptomatic disease and it is therefore difficult to include and maintain follow-up. Moreover, our recruitment in only one referral center may not be representative of the general MFA population as a whole.

To conclude, this description of the evolution of MFA reinforces our idea that MFA is a well-defined breast disease with multiple lumps similar to simple FAs and following the same natural evolution. Its evolution seems rather slow, like for FAs, which is consistent with the reassuring results of histological analyses. It may be asked if the rest of the breast tissue is healthy or if there are factors driving the development of FAs. Today, to our knowledge, this matter still remains poorly understood because there are no data. We show the interest of progestins, but confirmation of the causal relationship of their efficacy would require further studies. Moreover, as for simple FAs, pregnancy and breastfeeding appear to be protective in the evolution of MFA. Because lumps are numerous and benign, surgery should only be considered in rare cases, except when they are big or grow rapidly, which could suggest the presence of a phyllodes tumor. For this reason, US supervision seems required, because clinical examination is not relevant considering the numerous lumps. MRI must be used as a second-line assessment procedure. Finally, the risk of breast cancer seems low but remains difficult to evaluate, and long-term follow-up of our young cohort compared to a control group would be necessary in order to increase our knowledge on this subject.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Zeina CHAKHTOURA performed conception and design of the work, interpretation of data, and wrote the manuscript. Virginie GROUTHIER performed design of the work, acquisition, analysis, interpretation of data for the work, and wrote the manuscript. Isabelle TEJEDOR built the patient cohort database. Yasmina BADACHI was the radiologist who performed breast US and MRI assessments. Vincent GOFFIN performed interpretation of data. Philippe TOURAINE performed conception of the work, interpretation of data and is Head of the Center for Rare Gynecological Disorders

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