

## Comorbid pathology of the mammary glands and endometriosis: risk factors and prognosis

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### ABSTRACT

**Aim:** based on a retrospective analysis, the relationship between external genital endometriosis and comorbid breast pathology was established and risk factors were identified, their comparison and the formation of a prognostic risk criterion were determined.

**Materials and Methods:** to address the objectives of the study, a retrospective analysis of 470 cases of patients treated for external genital endometriosis after surgical treatment and comorbid breast pathology was conducted. The control group included 30 healthy non-pregnant women. Statistical processing was performed on a personal computer using the statistical software package Statistica 10.

**Results:** As a result of the analysis, the age of the patients ranged from 23 to 40 years. The average age of patients in the study group was  $(32.2 \pm 1.18)$  years, and in the control group  $(31.1 \pm 1.35)$  ( $p > 0.05$ ). The groups were homogeneous in terms of age ( $p > 0.05$ ), marital status ( $p > 0.05$ ) and level of education ( $p > 0.05$ ). Close relatives in 208  $(44.25 \pm 2.18)$  % ( $OR = 8.86$ ; 95 % CI:  $(0.68-10.53)$ ;  $p < 0.002$ ) cases suffered from benign (hormone-dependent) tumours and tumour-like diseases of the uterus and appendages in isolation or in various combinations (fibroids, adenomyosis, endometrial hyperplasia). It was also found that 102  $(21.70 \pm 1.67)$  % of patients had endometriosis, which may indicate a genetic predisposition to this disease. In the closest relatives of EM patients: in 118  $(25.10 \pm 2.01)$  % of the examined parents, breast problems were noted, in 66  $(14.04 \pm 1.12)$  % – diabetes mellitus, and in 98  $(20.85 \pm 1.22)$  % thyroid diseases were detected, which in total amounted to  $(60.00 \pm 2.23)$  % ( $OR = 9.12$ ; 95 % CI:  $(0.58-11.54)$ ;  $p < 0.002$ ). Early menarche almost tripled the risk of EM ( $OR = 2.72$ ; 95 % CI:  $(1.02-5.11)$ ;  $p < 0.002$ ), and menstrual irregularities doubled it ( $OR = 2.04$ ; 95 % CI:  $(1.09-3.14)$ ;  $p < 0.05$ ), higher education, urban residents – 2.2 times higher ( $OR = 2.27$ ; 95 % CI:  $(1.11-3.63)$ ;  $p < 0.05$ ), diseases of the gastrointestinal tract and hepatobiliary complex – 5.2 times higher ( $OR = 5.27$ ; 95 % CI:  $(1.89-12.03)$ ;  $p < 0.05$ ), frequently recurrent inflammatory diseases of the appendages – 3 times higher ( $OR = 3.14$ ; 95 % CI:  $(0.91-5.14)$ ;  $p < 0.05$ ), dysmetabolic manifestations (thyroid dysfunction) – 5 times higher ( $OR = 5.11$ ; 95 % CI:  $(1.61-9.503)$ ;  $p < 0.002$ ).

**Conclusions:** Thus, in endometriosis and dyshormonal diseases of the mammary glands, menstrual and generative function disorders, along with clinical symptoms of pelvic pain, dysmenorrhoea, autonomic nervous system disorders and sexual dysfunction, are significant components of this problem, initiating comorbidity processes in target organs in the setting of hormonal maladaptation. Therefore, these comorbidities become a trigger for the activation of systemic hormonal imbalance and become an urgent interdisciplinary problem that requires further study.

**KEY WORDS:** endometriosis, mammary glands, risk factors, hormonal imbalance, inflammation

Wiad Lek. 2024;77(2):247-253. doi: 10.36740/WLek202402109 DOI

## INTRODUCTION

The problem of combined damage to hormone-dependent target organs in the structure of gynaecological pathology is a leading one [1, 2]. The peculiarities are changes in their condition in accordance with the hormonal background of a woman as a result of physiological processes (menstrual cycle dynamics, different age periods of a woman) and in pathology of the reproductive system [3, 4]. According to scientific publications, the frequency of dyshormonal diseases of the reproductive system has been increasing in recent years [5]. A patient with dyshormonal disorders is examined by various narrow-profile specialists, such as

obstetrician-gynaecologist, mammologist, endocrinologist. However, there is a lack of a holistic view of the patient, prescription of complex medications, when one pathology is defined as the main one and the other as concomitant, although the cause and effect relationship is not always clearly traced. According to recent scientific studies, in this cohort of patients, endometriosis is diagnosed in 10–15 % of women of reproductive age, 70 % of women with chronic pelvic pain, and 40–60 % of women with algodysmenorrhoea [6, 7].

To date, the causes and triggering mechanisms for the development of benign and malignant breast tumours have not been fully elucidated. However, the results

of multi-purpose epidemiological and experimental studies have identified a number of factors that increase the risk of breast tumours [6].

Modern types of surgical and medical treatment of this disease are not effective in all cases and are accompanied by a high frequency of relapses. Recent scientific developments indicate that women with endometriosis have a significantly lower pregnancy rate than healthy women [8, 9]. It has been established that in the population, 10–15 % of fertile women are diagnosed with endometriosis during laparoscopy, while in patients with infertility, 15–80 % are diagnosed with endometriosis [10]. According to WHO statistics, more than a million new cases of breast cancer are diagnosed worldwide every year.

Mortality from this pathology exceeds 50 % of all patients. The reduction of this figure is hampered by the lack of organised, high-quality preventive screening of the population for the early detection of malignant breast tumours. An analysis of breast cancer screening methods shows that mortality among high-risk women who participated in a preventive treatment programme for diffuse breast disease is 30–50% lower than in groups where breast cancer prevention was not carried out. The search for the causes and ways of developing this disease is ongoing to develop optimal treatment methods. The issues of early diagnosis, search for new methods of treating dysgynadonal breast diseases and improving the effectiveness of therapy, especially in combination with infertility, require further study [11, 12]. The relationship between benign breast pathology and endometriosis and infertility is well known, but the mechanisms of fertility disorders in this pathology have not been fully studied [13].

That is, the condition of the mammary glands depends on the function of the hypothalamic-pituitary-ovarian system both in different periods of a woman's life and in various pathological conditions [14]. It should be noted that much attention is paid in the literature to the interaction of the target organs of the reproductive system, but there is virtually no data on the possibility of development and the relationship between endometriosis and benign breast dysplasia in women with various types of infertility [15, 16].

Recently, scientists and doctors have been paying attention to the potential of mesenchymal stem cells as a new approach to treating endometriosis. Mesenchymal stem cells are a special type of cell that have the ability to self-renew and differentiate into different types of tissues in the body [17, 18].

## AIM

To conduct a retrospective analysis of the relationship between comorbid breast pathology and external

genital endometriosis in order to identify risk factors and form a prognostic risk criterion.

## MATERIALS AND METHODS

At the first stage, we studied the correlation between benign diseases and breast cancer over 5 years in the Ternopil region.

To address the study objectives, a retrospective analysis of 470 medical records of patients treated for comorbid breast disease and external genital endometriosis after surgical treatment and in the gynaecological department of 'Municipal non-commercial enterprise ternopil municipal city hospital №2', Ternopil, Ukraine was conducted. The main source of information for the clinical and anamnestic analysis was the «patient's medical record» (f. 003/o). A questionnaire was developed for the patients included in the study, which included (age of menarche, characteristics of the menstrual cycle, previous pregnancies and their outcomes, use of hormonal therapy, surgical history, family history, family history regarding endometriosis and dysgynadonal breast and thyroid diseases), gynaecological examination (bimanual or rectovaginal) and imaging studies such as transvaginal ultrasound, MRI or cystoscopy if necessary.

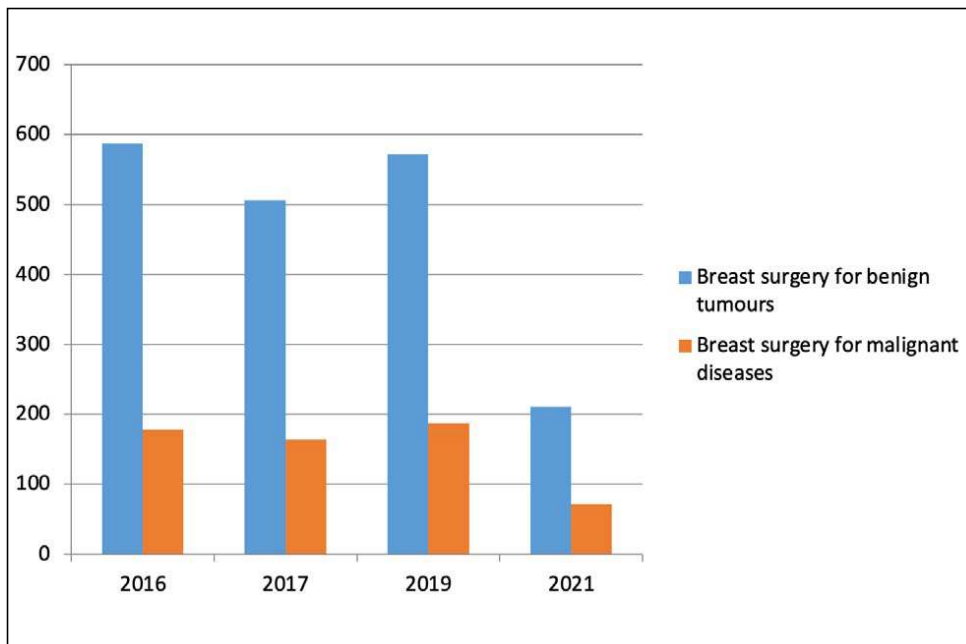
Statistical processing was carried out on a personal computer using the Statistica 10 statistical software package, namely, using the Student's t test. The difference between comparative means was considered significant at  $t > 3.85$  and  $p < 0.001$ .

Prior to the study, ethical approval was obtained from the Clinical Trials Ethics Committee of the I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (Protocol No. 72 of 6 January 2023) in accordance with the Declaration of Helsinki. The study was conducted retrospectively, and signed informed consent was obtained from all subjects.

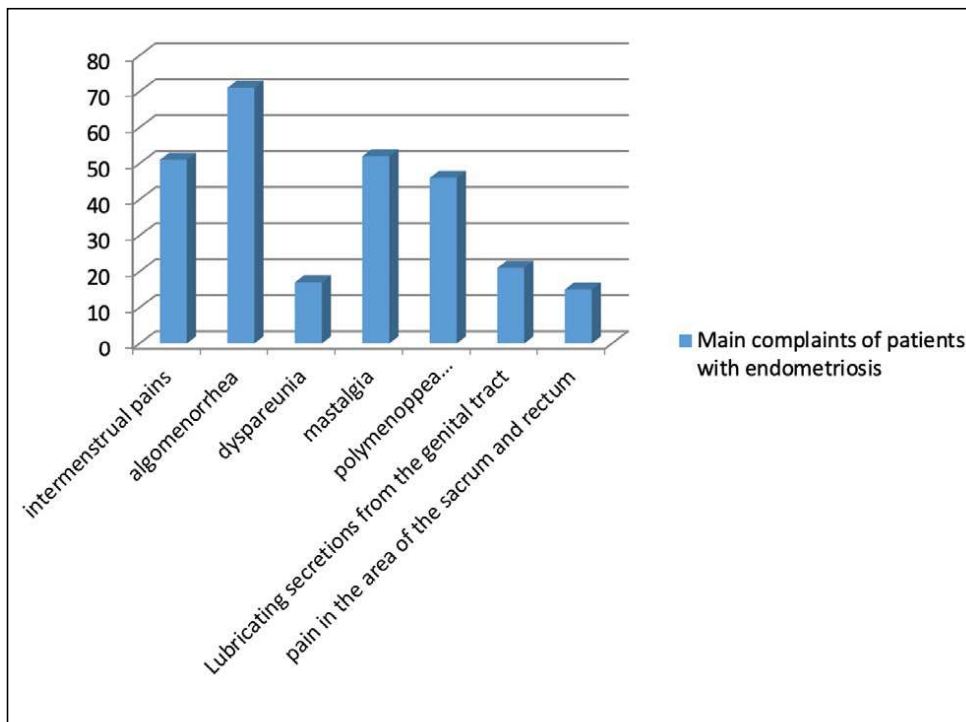
## RESULTS

At the first stage of the study, a comparative assessment of the ratio of breast surgery for benign breast disease and cancer was carried out. The analysis revealed that since 2016, there has been a stable ratio between surgical interventions for benign breast disease and cancer (Fig. 1). Our results indicate that breast cancer accounted for (23.2) % in 2016, (24.2) % in 2017, (24.6) % in 2019, and (25.5) % in 2021. Thus, the ratio of surgical interventions for benign and malignant tumours remained stable.

As a result of the retrospective analysis at the second stage, the patients' ages ranged from 23 to 40 years. The control group included 30 healthy non-pregnant women.



**Fig. 1.** Comparative data of breast surgery.



**Fig. 2.** Main complaints of patients with endometriosis.

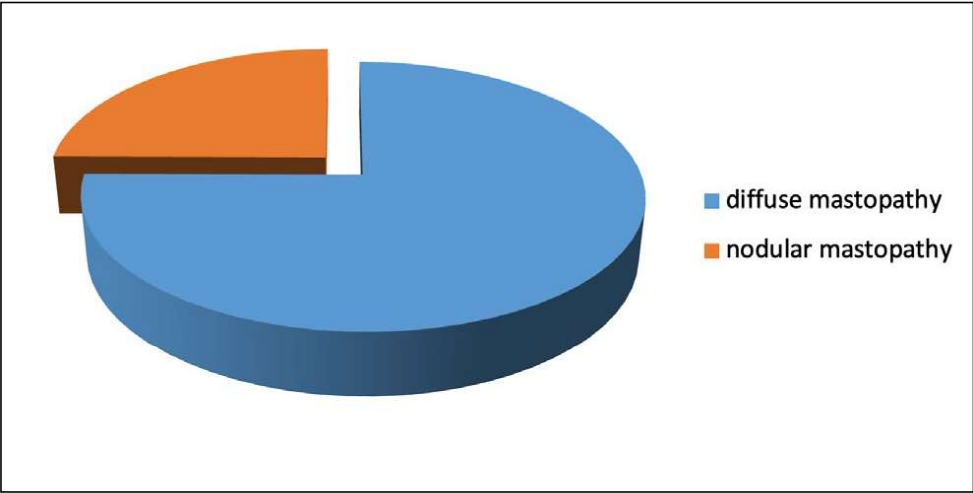
The average age of patients in the study group was ( $32.2 \pm 1.18$ ) years, and in the control group ( $31.1 \pm 1.35$ ) ( $p > 0.05$ ). The groups were homogeneous in terms of age ( $p > 0.05$ ), marital status ( $p > 0.05$ ) and level of education ( $p > 0.05$ ). When studying the family history of the examined patients, it was found that close relatives in 208 ( $44.25 \pm 2.18$ ) % ( $OR=8.86$ ; 95 % CI: (0.68-10.53);  $p < 0.002$ ) cases suffered from benign (hormone-dependent) tumours and tumour-like diseases of the uterus and appendages in isolation or in various combinations (fibroids, adenomyosis, endometrial hyperplasia). It was also found that 102 patients ( $21.70 \pm 1.67$ ) % had endometriosis, which may indicate a genetic predisposition to this disease. Gynaecological surgeries in relatives.

The high frequency of endocrine disorders in the closest relatives of patients with endometriosis is noteworthy: 118 ( $25.10 \pm 2.01$ ) % of the examined parents had breast problems, 66 ( $14.04 \pm 1.12$ ) % had diabetes mellitus, and 98 ( $20.85 \pm 1.22$ ) % had thyroid diseases, which totalled ( $60.00 \pm 2.23$ ) % ( $OR=9.12$ ; 95 % CI: (0.58-11.54);  $p < 0.002$ ).

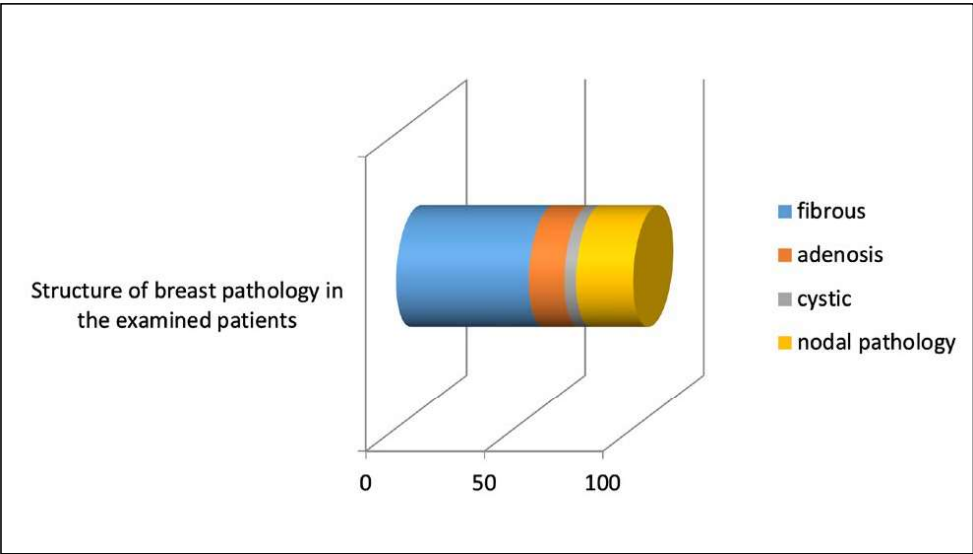
Thus, among the factors that have prognostic significance in the development of endometriosis, we can name the factor of burdened heredity, more often on the maternal side (first-degree relatives), mainly benign and malignant tumours of the genital organs and tumours of extragenital localisation of various etiologies.

**Table 1.** Structure of breast pathology in the examined patients

Group	Distribution of patients by type of mastopathy							
	Diffuse pathology						Nodal pathology	
	fibrous		adenosis		cystic			
	n	%	n	%	n	%	n	%
418	234	6	9	4,6	19	4,5	104	4,9



**Fig. 3.** Distribution of patients by type of mastopathy.



**Fig. 4.** Structure of breast pathology.

In addition, a high percentage of endocrine tumours was found – (60.00 ± 2.23) %.

An analytical assessment of the significance of risk factors for endometriosis suggested that early menarche almost tripled the chances of developing endometriosis (OR=2.72; 95 % CI: (1.02-5.11); p < 0.002), menstrual irregularities – twice (OR=2.04; 95% CI: (1.09-3.14); p < 0.05), chronic inflammatory diseases of the appendages (OR=3.14; 95% CI: (0.91-5.14); p < 0.05).

The analysis of childhood infections (measles, rubella, chickenpox, scarlet fever, mumps in various combinations), diseases of the ENT organs (chronic tonsillitis, deviated nasal septum, sinusitis, etc.), as well as influenza and acute respiratory virus infections in patients,

revealed a high proportion (90.11 ± 1.48) % of infectious diseases in childhood and adolescence.

When analysing the history of chronic extragenital diseases in the study group, it was found that more than half of the patients had a combination of two or more extragenital diseases.

Diseases of the gastrointestinal tract and organs of the hepatobiliary complex (chronic gastritis, enterocolitis, cholecystitis, hepatitis) were detected in (OR=5.27; 95 % CI: (1.89-12.03); p < 0.05), cardiovascular diseases (hypertension, hypotension) – in 66 (14.0 %), mastalgia – in 400 (85.1 %), chronic inflammatory diseases of the upper respiratory tract – in (30.1 %), chronic pyelonephritis – in 16.0 %.

The main symptoms of endometriosis were pain, dyspareunia, dysfunction of adjacent organs (dysuria), psycho-neurological disorders, reproductive disorders (infertility and miscarriage), accompanied by mastalgia of varying severity (Fig. 2).

All the examined women complained of meno- and metrorrhagia. The occurrence of cyclic pain syndrome, which increased from the moment of menarche, was detected in 405 ( $86.17 \pm 1.23$ ) % of patients. The duration of menstruation ranged from 7 to 10–12 days, with the duration of the menstrual cycle ranging from 21 to 26 days (Fig. 3).

In 78 ( $16.59 \pm 1.98$ ) % of EM patients, there was a history of 1 delivery, in 36 ( $7.65 \pm 1.21$ ) % – 1–2 spontaneous miscarriages and frozen pregnancies of different gestational ages, in 8 ( $3.82 \pm 0.62$ ) % – postpartum complications (lochiometra, uterine subinvolution, metoendometritis).

Infertility was detected in 236 ( $50.20 \pm 2.51$ ) % of women, of which 191 ( $80.93 \pm 1.27$ ) % were primary and 45 ( $19.07 \pm 0.46$ ) % were secondary. The duration of infertility was ( $5.7 \pm 2.2$ ) years.

The structure of breast pathology revealed during mammological ultrasound screening revealed mastopathy in 418 ( $88.93 \pm 1.98$ ) %, of which: in 314 (75.1 %) women diffuse forms of breast mastopathy were detected during the examination and in 104 (24.5 %) % nodular forms.

Benign breast changes are more common in women of childbearing age. Of the diffuse forms of mastopathy in patients with endometriosis, fibrous 234 (55.9 %) prevailed, which is associated with the unity of pathogenetic proliferative processes in the target organs (endometrium, mammary gland) of the reproductive system (Table 1, Fig. 4).

Therefore, women with these factors should be considered to be at high risk of developing complicated endometriosis. Early menarche almost tripled the odds of developing endometriosis (OR=2.72; 95 % CI: (1.02–5.11);  $p < 0.002$ ), menstrual irregularities doubled the odds (OR=2.04; 95 % CI: (1.09–3.14);  $p < 0.05$ ), higher education and urban residence increased the odds 2.2 times (OR=2.27; 95 % CI: (1.11–3.63);  $p < 0.05$ ), diseases of the gastrointestinal tract and organs of the hepatobiliary complex – 5.2 times higher (OR=5.27; 95 % CI: (1.89–12.03);  $p < 0.05$ ), frequently recurrent inflammatory diseases of the appendages – 3 times higher (OR=3.14; 95 % CI: (0.91–5.14);  $p < 0.05$ ), dysmetabolic manifestations (thyroid dysfunction) – 5 times higher (OR=5.11; 95 % CI: (1.61–9.503);  $p < 0.002$ ).

## DISCUSSION

Adenous mastopathy and cystic mastopathy were detected less frequently. Adenous mastopathy was more commonly detected in women who were pregnant but

did not give birth (history of pregnancies that did not develop or ended in early termination).

In cystic mastopathy, depending on the size of the cyst, a puncture biopsy was additionally performed under ultrasound guidance.

Mortality from this pathology exceeds 50 % of all patients. The reduction of this figure is hampered by the lack of organised, high-quality preventive screening of the population for the early detection of malignant breast tumours. An analysis of breast cancer screening methods shows that mortality among high-risk women who participated in a preventive treatment programme for diffuse breast disease is 30–50% lower than in groups where breast cancer prevention was not carried out. The search for the causes and ways of developing this disease is ongoing to develop optimal treatment methods. The issues of early diagnosis, search for new methods of treating dyshormonal breast diseases and improving the effectiveness of therapy, especially in combination with infertility, require further study [11, 12]. The relationship between benign breast pathology and endometriosis and infertility is well known, but the mechanisms of fertility disorders in this pathology have not been fully studied [13].

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## CONCLUSIONS

Thus, given the significant percentage of surgical treatment of breast pathology, it is advisable to expand the search for predictors of dyshormonal breast diseases.

Dyshormonal diseases of the mammary glands and endometriosis accompanied by menstrual and generative function disorders, pelvic pain clinic, dysmenorrhoea, autonomic nervous system disorders and sexual dysfunction are significant components of this problem, initiating comorbidity processes in target organs in case of hormonal maladaptation. Therefore, these comorbidities become a trigger for the activation of systemic hormonal imbalance and become an urgent interdisciplinary problem that requires further study.

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## CONFLICT OF INTEREST

The Authors declare no conflict of interest

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**RECEIVED:** 17.10.2023

**ACCEPTED:** 02.02.2024

