Nipple discharge in nulliparous women: an update on causes and diagnosis

Alice Balaceanu[1,2], Camelia Diaconu[1,3], Gheorghita Aron[1,2]

1. University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
2. Internal Medicine Clinic, "Sf. Ioan" Clinical Emergency Hospital, Bucharest, Romania
3. Internal Medicine Clinic, Clinical Emergency Hospital, Bucharest, Romania

Correspondence: Alice Balaceanu, MD, PhD, e-mail: alicebalaceanu@yahoo.com

Abstract

Nipple discharge is a common problem in nulliparous women, requiring appropiate investigation. Nipple discharge could be physiological and pathological. It is caused by benign disorders in most of the cases. Bloody or clear niple discharge could hide solitary intraductal papilloma or even ductal carcinoma in situ. The diagnostic approach comprises different modalities, depending on the patient's history, age and clinical examination. Sometimes, multiple diagnostic methods are needed for early detection of breast cancer. If mammography, ultrasonography, magnetic resonance imaging are already stated, other methods are under evaluation.
Keywords: *nipple discharge, breast, ultrasonography*

Introduction

Galactorrhea or physiologic nipple discharge is defined as nipple discharge unrelated to pregnancy or breastfeeding[1,2]. It could occur in nulliparous women. Pathological nipple discharge is reffered to a specific lesion of the breast.

Causes

In most cases galactorrhea is caused by hyperprolactinemia, especially in women with amenorrhea[1,3]. Multiple disorders are responsible for hyperprolactinemia[1,2,3]:

- pituitary lesions (adenomas/prolactinomas);
- hypothalamic or infundibular disorders (tumors like craniopharyngioma and meningioma, infiltrative disorders like histiocytosis and sarcoidosis);
- hypothyroidism;
- hyperestrogenemia (ovarian hyperstimulation syndrome);
- renal insufficiency;
- drugs (metoclopramide, cimetidine, methyldopa, verapamil, reserpine, estrogen, oral contraceptives, antipsychotics, tricyclic antidepressants, neuroleptics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors opioids and cocaine);
- chest wall lesions (herpes zoster, burns or trauma, spinal cord injury, mammoplasty), or excessive nipple manipulation (sex or suckling) causing neurogenic stimulation; and
- stress.

In some cases, prolactin levels are normal and the patient has galactorrhea and normal menses[3,4]. This phenomenon appears after correction of elevated prolactin from drug-induced hyperprolactinemia[4] or in acromegaly due to lactogenic effect of the growth hormone[3].

In most cases (52 to 57%) papilloma is responsible for pathological nipple discharge, with or without atypia or ductal carcinoma *in situ*[1]. In 14 to 32% of cases there are other benign causes like ductal ectasia[1]. Purulent nipple discharge could appear in infections[1]. The malignancy is found in 5 to 15% of cases[1]. In teenager patients the nipple discharge has the same causes as in adults. The bloody nipple discharge is rare and it is commonly associated with duct ectasia and intraductal papilloma[5].

Clinical particularities

The clinical features in physiologic nipple discharge are commonly bilateral nipple discharge from multiple ducts full of white or clear fluid. Sometimes the nipple discharge could be unilateral and has other colours, as yellow, brown, gray or green[1]. Usually the characteristics of the pathological nipple discharge are: unilateral, single ductal ectasia, persistent and spontaneous secretion, with serous, sero-sanguineous or bloody aspect[1].

Diagnosis

The diagnosis workup include: patient history, clinical breast examination for breast lump, ultrasonography, mammography (recommended for patients older than 30 years), pregnancy test, prolactin and thyroid-stimulating hormone levels, renal function tests, guaiac test of bilateral nipple discharge[1,2].

Patient history relates to drug administration, endocrine disorders, trauma, gynecomastia, amenorrhea or oligomenorrhea[3]. The physical examination is done

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gently, massaging from the areola to the nipple in the four quadrants[3]. The prolactin level should be checked before the breast massage, the maneuver increasing the secretion of prolactin[3].

Bloody or clear nipple discharge could hide solitary intraductal papilloma or even ductal carcinoma *in situ* (DCIS). In the United States in 2011 from 230,480 estimated new cases of invasive breast cancer, 11,330 were in women under 40 years old[6]. In the same statistic report, from 57,650 estimated cases of *in situ* breast cancer, 1,780 were expected in women under 40 years old[6]. Nullipara women or with late parity (after the age of 30) have a relative risk for breast cancer of 1.2-1.7[7]. Atypical ductal lesion rises the relative score to 4.0[7]. Because of the faster growth rate of the tumor in younger women and poorer detectability on mammogaphy, screening methods must be better defined in this group[7].

Few risk factors for early onset breast cancer (under age 40) were detectable in a small percentage of cases[8]. The incidence of breast cancer in younger women remains stable over time, despite changing the country of residence, making local exposures unlikely[8]. Genetic factors are responsible for 10% of cases[8]. Lean body mass, oral contraceptives, family history of breast cancer, not breastfeeding, therapeutic radiation are considered risk factors for breast cancer in women under 40 years[8]. Early age at diagnosis is one of the strongest predictive factors for a short period of time from diagnosis to local recurrence, for contralateral breast cancer and high mortality after recurrence[8].

For the early detection of breast cancer in asymptomatic women 20-39 years old, with average-risk, the American Cancer Society Guidelines recommend clinical breast examination at least every 1 to 3 years and optionally breast self-examination[6]. For women aged over 40 annual clinical breast examination, annual mamography and optional breast self examination are recommended[6].

The NCCN guidelines recommend stopping compression of the breast and reporting any spontaneous discharge to women under 40 years with non-spontaneous nipple discharge and without palpable mass observation[9]. For women over 40 years the guidelines add mammography[9]. Spontaneous, persistent and reproducible nipple discharge, unilateral or from a single duct, clear, serous, serosanguineous or sanguineous needs mammography with or without ultrasonography[9]. For the Breast Imaging Reporting and Data System (BI-RADS) cathegories 1-3 the next recommanded diagnostic method is ductogram[9]. If the lesion appears benign or indeterminate on mammography, BI-RADS categories 4-5 benefit of the same recommendation[9].

Regular breast examination after menstruation and imaging evaluation by experienced professionals are recommended to young women[1]. Until now, mammography is the best imaging method for detecting early breast cancer[10]. But its sensitivity depends on the breast density, reaching 90% in women over the age of 50[10]. Because of the dense breast tissue in young women, clinical examination is followed by ultrasonography[10]. Ultrasound exam should be performed at any time of menstrual cycle[10]. Core biopsy and/or fine needle aspirate cytology would be the next step in diagnosis of suspected lession[10]. For adding further information or detecting the extent of the tumor, mammography is recommended in negative or inconclusive cases[10]. Magnetic resonance imaging (MRI) recommendations are: newly diagnosed invasive lobular cancer, high-risk for breast cancer, a size discrepancy of more than 1 cm between mammography and ultrasound and an expected impact on the treatment decision[10]. MRI should be performed in the second week of menstrual cycle and mamography in the first 2 weeks of the menstrual cycle[10]. The hormonal contraception doesn't influence any imaging method[10].

Ultrasonography is the first imaging method recommended in women under 30.

Breast ultrasonography is the best imaging method to identify ductal ectasia (Figure 1), the number and location of ducts (Figure 2), the lesions within the duct and guided biopsy, other coexistent unpalpable breast mass, and lymph nodes involvement (Figure 3). In ultrasonography, the dilated ducts are filled with fluid[11]. Sometimes, intraductal echoes in the fluid appear, representing concentrated secretions and debris[11]. The differential diagnosis of intraductal lesion is made by the movement of echogenic materials in the real-time

Figure 1. *Ultrasound aspect of a dilated duct with irregular caliber, located in the central quadrant (personal collection)*

Figure 2. *Ultrasound aspect of multiple dilated ducts, one of them with higher caliber (personal collection)*

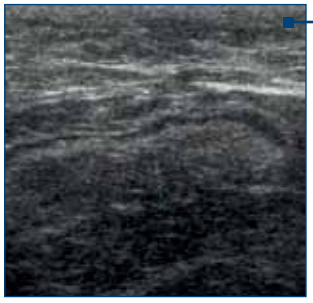

Figure 3. *Ultrasound aspect of the benign axillary lymph node in a 34-years old patient with nipple discharge: oval shape, thin peripheric hypoechoic cortex and echogenic hilum (personal collection)*

examination[11]. Nipple discharge could hide solitary intraductal papilloma. It is usually located centrally or in the retroareolar region. Ultrasonographic aspect is of a well-defined solid nodule or a mural-based nodule in a dilated duct[12]. A flow arising from a vascular feeding pedicle is visible on Doppler colour ultrasonography[12]. Ductal extension of DCIS has a sonographic appearance of a projection from a hypoechoic and irregular shaped mass to a visible duct[13]. Ultrasonographic calcifications are usually malignant[13]. The ultrasonographic overlap between DCIS, intraductal papiloma and ductal epithelial hyperplasia require biopsy for diagnosis[13].

Ultrasonography is suitable for percutaneous biopsy, does not use ionizing radiation, but it is an operator-dependent examination and needs a trained sonologist for performance[14]. Ultrasonogaphy has a special value in mammographic dense breasts[12]. In women with dense breast, screening ultrasonography rises the detection of breast cancer[7]. Small papilloma, located in retroareolar region, is rarely seen on mammography[11]. The dense breast and the relative low compression of the retroareolar region are responsible for this fact[11]. In younger women with dense breast, the harm effects of mammography could exceed the favorable benefits[15].

In the screening of women with average risk of breast cancer, who don't have dense breasts, one review didn't detect any controlled studies that provided evidence for or against the use of adjunct ultrasonography to mammography[16].

Mammography and ultrasonography are complementary methods in detecting breast cancer[9]. Multiple societies use both methods in the guidelines for breast cancer screening, while breast self-examination is optional or not stated[7]. DCIS meanly detected by imaging methods reaches almost 25% of breast cancers[7].

Mammography is the only screening method proved to reduce mortality of breast cancer[7]. Digital mammography raises the contrast between the tumor and the surrounding parenchyma, being more sensitive in women with dense breasts[7]. In some cases, clinical breast examination can detect mammographically-missed tumors[7].

Calcifications and breast masses are commonly investigated by mammography[6,9]. Clustered pleomorphic microcalcifications on mammography are highly suggestive for DCIS[13], but 6-23% of DCIS can't be detected on mammography[17].

MRI has a moderate specificity in nipple discharge evaluation[1]. On MRI, the intraductal papillomas can be seen as enhancing nodules with intraductal component, when being larger[12]. Ultrasonography and MRI are very useful in case of ductal dilatation, when vascularized tumors could be identified[17]. MRI is not recommended for screening in general population because of the higher costs and the higher rate of false positive results[7].

Commonly, multiple imaging methods and ductoscopy are necessary to evaluate the patients with nipple discharge[18,19]. If the duct is cannulated, ductography or ductoscopy will be performed[1]. Citology has no definite benefits in positive diagnosis of the nipple discharge[1,2]. Needle and excisional biopsies are the gold standard methods in differential diagnosis between benign and malign lesions in specific cases[1,19].

Sometimes, multiple diagnostic modalities are needed for early detection of breast cancer. If mammography, ultrasonography, MRI are already stated, other methods will be under evaluation[20]. For instance: contrast-enhanced mammography or contrast-enhanced ultrasonography, tomosynthesis, nuclear imaging and elastography, which have been proved their potential benefits in detecting breast neoplasia[20].

Conclusions

Nipple discharge in nulliparous women underlies multiple causes and the diagnostic approach comprises different modalities, depending on the patient's history, age and clinical examination. ■

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