M.L. Travina[1], A.G. Popov[2]
[1] Scientific Center of Children's Health, Moscow, Russian Federation
[2] «MIR SEM'I» Medical Centre, Saint-Petersburg, Russian Federation

Features of the diagnosis of intraductal breast diseases in adolescent girls through the example of clinical cases. The algorithm of examination and treatment of pathologies in adolescence.

Author affiliation:

Marina Travina, MD, Head of the x-ray division of the ray diagnostics department at the clinical and diagnostic center of the Scientific Centre of Children's Health, Moscow, Russian Federation.
Address: 2-1, Lomonosovsky Ave., Moscow, 119991; **tel**.: +7 (495) 967-14-20*2175; **e-mail**: Tvtmarina@mail.ru
Article received: 27.03.2016; **accepted for publication**: 26.04.2016.

Intraductal breast diseases are characterized by a high risk of transformation in breast cancer. Difficulties of diagnosing intraductal lesions are associated with the only symptom — the appearance of pathologic discharge from the breast nipple. In adolescent girls, taking into account the immaturity of the nipple and it flatness, there are difficulties with removing it correctly. On physical examination, as well as with the high density of the surrounding tissue and areola, the control over the presence of pathologic discharge from the mammary ducts is difficult. The intraductal pathology requires ultrasound examination, mammography, and only after a full examination — ductographic research. The article presents its own clinical observations of the intraductal pathology in adolescent girls aged 14 and 15 years. The algorithms of examination and patient surveillance with intraductal pathology are described.
Keywords: *intraductal pathology, ductal papilloma, nipple discharges, adolescent mammology, fibrocystic disease.*
(***For citation***: Travina M.L., Popov A.G. Features of the Diagnosis of Intraductal Breast Diseases in Adolescent Girls Through the Example of Clinical Cases. The Algorithm of Examination And Treatment of Pathologies in Adolescence. *Current pediatrics.* 2016;15(2):183-189. doi: 10.15690/vsp.v15i2.1538.)

Introduction

The prevalence of malignant mammary gland pathology has increased by 30% over the last 10 years, and in the young women cohort (19-39 years) – by 34% [1]. At the same time, the number of primarily detected cases of benign mammary gland pathology is 25 – 30 times higher than the breast cancer (BC) morbidity figures [1]. According to predictions, by 2020 mortality from BC can be 30 cases per 100 000 female population [2]. However, the current data on survival at different stages of BC point at the possibility of reducing female mortality if the mammary pathology is discovered at an early stage through instrumental investigation [3].

Intraductal pathology usually means ductal hyperplasia, hyperplasia with an ill-defined epithelial proliferation, atypical ductal hyperplasia and ductal cancer *in situ* (three stages of differentiation)

[4]. Screening investigations have shown that different intraductal proliferations transform with different frequency into *in situ* cancer and invasive cancer (for simple ductal hyperplasia the conversion to invasive BC is 1.5%, from atypical ductal hyperplasia – 4-5%, while *in situ* cancer develops in 8-10% of cases) [5]. Early detection of this pathology allows to decrease the volume of surgical and medicament treatment in women with intraductal pathology, which allows to improve their quality and length of life [5]. It is important to stress, however, that diagnosing such pathological conditions is difficult to some extent, which is due to the small sizes and non-informativity of the main mammary gland examination methods (x-ray mammography, ultrasound) [6].

Intraductal pathology is expressed through characteristic (bloody, amber, brown) discharges from the nipples of the mammary gland. Their character has to do with the peculiarities of the intraductal pathological process. However, serious difficulties often arise during differential diagnostics. These difficulties can lead to tactical mistakes if the discharges are evaluated only visually, without additional cytological verification [7]. Even during a cytological investigation of swabs and prints it is not always possible to establish the character of intraductal pathology with absolute precision: the absence of pathological elements or the presence of altered erythrocytes in the analyzed portion leads to wrong conclusions [8].

An important and relevant task in diagnosing mammary intraductal pathology is the early detection of tumor elements and concealed blood in the nipple discharges, and after such patients are detected – examining them additionally. These introductal pathology diagnostic peculiarities became the foundation for the following description of the tactics concerning the management of teenage girls with pathological (bloody) discharges from mammary gland nipples.

Clinical case №1

Patient S. Age 15. Complaints about bloody discharges from the right mammary gland nipple. From life anamnesis: menarche at 15 years, regular menstruation, cycle 28 days. According to the patient, nipple discharges first appeared a year ago, was observed by the local pediatrician, was not directed to a specialist. When the character of the discharges changed to bloody and pain appeared in the upper quadrants of the right mammary gland, the patient contacted a child gynecologist (no gynecological pathology detected), redirected to a mammologist.

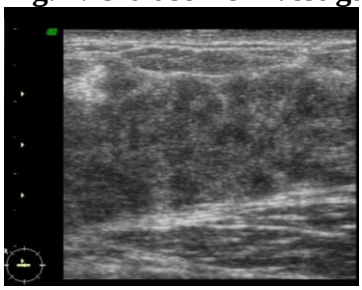
At the time of the mammologist's examination: mammary gland formed, the areola and the nipple are above the mammary gland, moderate areola pigmentation noted. Visually: mammry glands correctly developed, nipples and areolas not altered. At palpation: right mammary gland more dense in the upper quadrants; at examination and pressure applied to this zone, bloody discharges appear from the right nipple ("point symptome"; fig. 1). No discharges when applying pressure to the right nipple and areola. Lymph nodes in axillary zones not enlarged.

Fig. 1. **Bloody nipple discharges**.

A swab-print of the nipple discharges was taken for cytological investigation, as a result of

which elements of blood and an aggregation of cubic epithelium cells in the papillae.

Fig. 2. Ultrasonic investigation of the mammary gland.

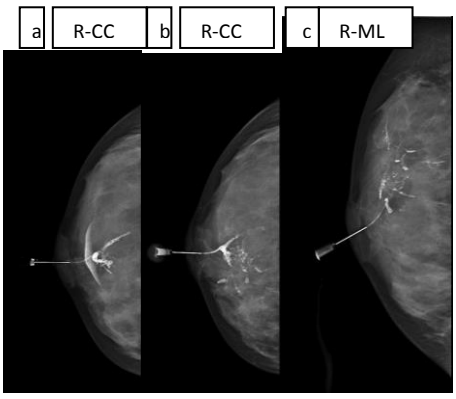


- Skin
- Fascia
- Cooper's ligaments
- Fatty tissue
- Gland tissue
- Adenosis.
- Fascia
- Chest muscle

Ultrasonic investigation (USI) results: the mammary gland tissue is mainly presented by the glandular component with foci of tissue edema and fibrotic changes (fig. 2). No ultrasonic data in favour of architectonic tissue lesions and pathological changes was found. Color flow mapping revealed no increase in local blood flow. Lymph nodes are not visible. In order to exclude oncological pathology, digital mammography was performed prior to contrast mammography. Mammography was performed in two projections. Digital mammography protocol: skin not edematous, the nipple is on contour, the gland body consists of dense glandular tissue. Because after conducting ultrasonic and mammography investigations there was no visible pathology which could explain the presence of pathological bloody nipple discharges and the localization of the pathological process, we conducted a further contrast ductogrphic investigation of the right mammary gland. We introduced the contrast (ultravist) with bringing the contrast substance during the investigation (in order to increase the informativity of the method and to decrease the risk of possible artifacts – air bubbles). The contract was introduced through a cannula into the duct with pathological discharges (fig. 3). During the introduction we controlled the coloring of the contrast with the color of the discharges (criteria of contrast of the duct with integrity lesions due to pathological overgrowth). The x-ray images showed a net of mammary ducts on the borders of the upper quadrants. We discovered many breakages and filling defects in 2-3rd order ducts (fig. 4 a-c). Diagnosis after the investigation: "Intraductal overgrowths in the right mammary gland secondary to diffused fibro-cystic mastopathy".

Fig. 3. Cannula introduction for ductal contrasting.

Fig. 4. Contrast mammography (ductography of the right mammary gland; a-c).



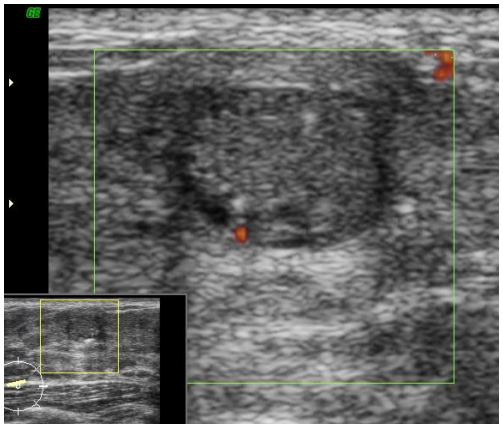
Note. a — contrast (ultravist) is introduced, contrasting defects in the duct and contrasting breakages are visible at 2-3 cm from the nipple; b, c — the remaining contrast is introduced. A ductal net with defects is contrasted in the upper-inner quadrant (closer to the inner quadrant), at 2 cm from the nipple and 2-4 cm in length.

Keeping in mind the high risk of the intraductal pathology malignization [5], the patient was directed for surgical treatment. After surgery and sectoral resection of the mammory gland was completed, we conducted histological and immunohistochemical investigations of the macropreparation. Results of the histological investigation: intraductal papilloma of the mammory gland with typical micropapillae hyperplasia of the papilloma ductal epithelium and the sulcal epithelium of the cystic-expanded ducts. Results of the immunohistochemical investigation of the epithelial lining nuclei of the fibropapilloma cells with estrogen and progesterone expression levels: moderate. Keeping in mind the adolescent age and the high risk of developing reproductive lesions secondary to treatment schemes used for women in their pre- and climax period (buserelin and tamoxifen), the patient was prescribed indole carbinol - a selective modulator of estrogen receptors – at a dosage of 400 mg/day for a period of 6 months. Also, in order to decrease the endocrine profile's influence on the mammary gland tissues, we chose ethinylestradiol – a low-dosage monophasic combined oral contraceptive with antiandrogen properties – for a period of 1 year. Medical examinations every 6 months (discharges control and USI) did not reveal any pathology. The patient is watched for 1.5 years after surgery.

Clinical case № 2

Patient D., age 14. Complaints about bloody discharges from the left mammary gland nipple. From life anamnesis: menarche at 12 years, irregular menstruation, cycle from 25 to 47 days, did not visit the gynecologist. According to the girl, she first noticed the bloody spots on her underwear 2 weeks ago and contacted the mammologist. At the time of the mammologist's examination: mammary glands formed, the areola-nipple complex is above the mammary gland. Expressed areola pigmentation. Visually: the mammary glands correctly developed, nipples and areolas unaltered. At palpation the mammary glands were soft, painless. On the left under the nipple there was an area of increased density, a little painful at palpation, less than 2 cm in size. No discharges from the right nipple were observed. When applying pressure to the left nipple-areola zone – bloody discharges from one of the ducts in significant amounts. Axillary lymph nodes were mobile, up to 0.5 cm, painless at palpation. A swab-print of the left nipple discharges was taken for cytological investigation, which found erythrocytes.

Fig. 5. Ultrasonic investigation of the left mammary gland.



USI results: the mammary gland tissue is presented by glandular and fat components, ducts that were not enlarged from both sides are visible in the central zone. A hypoechogenic neoplasm 1.2 x 0.7 cm in size with a more hypoechogenic border, clear contours, horizontal localization and a strengthened dorsal shadow was visible on the left under the nipple; color flow mapping rendered single color signals (fig. 5). The presence of a neoplasm in the mammary gland is an indication for diagnostic puncture with cytological verification of the neoplasm contents.

Cytological investigation results: aggregations of cubic epithelium cells detected in the papillae, which is characteristic for intraductal pathology. Given the presence of bloody discharges from the nipple together with the cytological conclusion, it was decided to conduct a ductographic investigation in order to ascertain the extent and depth of the ductal system lesions.

Left mammary gland ductographic investigation results: the x-ray images (contrast – ultravist) show a sharply expanded (up to 1.5 cm) main duct unevenly filled with the contrast substance due to pathological parietal overgrowth (fig. 6 a, b). Diagnosis after the conducted investigation: "Intraductal overgrowth in the left mammary gland secondary to fibrotic-cystic mastopathy".

Fig. 6. **Left mammary gland ductography in an oblique projection (a, b)**.

a)

b)

The patients was directed for surgery. Histology investigation results: intraductal papillomatosis of the left mammary gland. Immunohistochemical investigation of the epithelial cell lining nuclei of the fibropapillomae did not show any expression of estrogen and progesterone receptors.

Given the absence of estrogen and progesterone receptors in the fibropapillomae tissue, the patient was not prescribed with any specific therapy.
On examinations once a year (discharges control and USI) no pathology has been detected. The term of observation is 3 years after surgery.

Discussion

According to the International Agency for Research on Cancer (IARC, 2014), the most relevant modern problem is the is the broadening of activities aimed at preventing and early detection of oncological pathology due to the high effectiveness of early treatment of malignant tumors [9]. The number of diagnosed mammary gland diseases is rising in all countries of the world and is coming up to number one [1]. From 2008 to 2012 the number of diagnosed cases of BC in the world rose from 1.38 million to 1.7 million [10, 11]. A tendency towards a more early detection of malignant mammary gland pathology is noted. The proportion of benign and malignant pathology on average is 25-30/1 [1]. Intraductal pathology (based on the results of histological investigation) happens in 10% of all benign changes of the mammary gland [4, 12].

Intraductal pathology can manifest itself at any age, starting from the moment the mammary gland is formed and starts growing. In the presented cases it is important to note the fact that given lengthy pathological discharges from the nipple, the primary care physicians did not pay due attention to the complaints and the patient was not sent to receive specialized help. The absence of epidemiological data on the prevalence of mammary gland pathology in children and

adolescents leads to late discovery of pathologies [13]. According to Order № 572н from 01.11.2012 г. [14], there are set ages of 3, 7, 12, 14, 15, 16 and 17 inclusively, at which the gynecologist should examine mammary glands preventively in order to detect pathology early. Examination includes ascertainment of complaints, genera examination, evaluating the extent of sexual development as well as examining the mammary glands by hand. If additional USI is necessary for detecting nodal changes in mammary gland tissue, which increases the early detection of pathology, a correct physical examination and checking nipple discharges is enough for intraductal overgrowth. The detection of pathological discharges requires these patients to be directed for in-depth investigations in order to diagnose and start treatment, which contributes to the decrease of surgery and detecting pathology at early stages. A late detection of pathological overgrowth in the mammary gland ducts increase the risk of intraductal BC and early relapses [15].

In the given clinical cases, the discharges were due to the presence of overgrowth and integrity lesions in the mammary gland ducts. In the first clinical example, the late detection lead to an increase in the number of damaged ducts and thus to the spreading of the process onto the whole inner-upper quadrant of the gland. Because of this, the whole quadrant had to be removed surgically. After obtaining the results of histological and immunohistochemical analysis it was necessary to stabilize the endocrine profile given the high proliferative activity of the process and the high probability of relapse. For intraductal pathology the tactic of after-surgery dispensary observation includes physical examination of the mammary glands together with controlling the nipple discharges once in 6 months, USI of the mammary glands once in 6 months; it is recommended to conduct contrast MRT of the mammary glands 2 years after the surgery (to control possible relapsing). This group of patients requires dynamic observation 2 times per year for a period of at least 3 years [15].

Over the years the department has been functioning (2009 – 2015) 1233 patients were examined, 521(42,3%) of those – as part of the screening programme, 712 (57,7%) – due to complaints concerning the mammary gland. Nipple discharges were present in 4 (0,8%) of screening patients and in 13 (1,8%) of complaining patients. 17 patients with pathological discharges received further examination. “Intraductal pathology” was diagnosed in 9 girls, which is 53% of all teenaged patients with pathological nipple discharges. Intraductal pathology was detected in 0.2% of screening patients and in the group with complaints – in 1.1% (data not published).

PRACTICAL RECOMMENDATIONS

It is important for neonatologists and pediatricians to evaluate nipple discharges correctly. The patient management tactic depends on the patient’s age. Newborns can have nipple discharges during the early post-natal period, which can be both independent or as a result of applying pressure. Colostric and transparent ones are due to the physiological harshening of the mammary glands (hormonal crisis) and do not require draining or halting breastfeeding. Bloody discharges (like fresh blood) are extremely rare and are due to a sharp edema or a stromal component and trauma of the mammary gland. Discharges do not require a cytological investigation and cease by themselves over the period of 3 months [13]. In teenagers, all mammary gland nipple discharges are pathological and require additional examination. Discharges can be evidence of a forming local pathology in the mammary gland ducts or of dishormonal conditions [16, 17].

A right technique of discharge detection will make it possible not to miss the first symptoms of dishormonal manifestations in the mammary glands. Pressure should be applied to the areola, not to the nipple. The big and pointing finger should be placed onto the areola’s contour, pressed a little bit inwards, then brought together and to the front. If the nipple is not formed, it is possible to use additional instruments to check the nipple discharges. For example, the corrector of the nipple form not only brigs forward a flat or indrawn nipple, but also creates vacuum and thus

helps to check the presence of discharges (fig. 7).

Fig. 7. **Nipple form corrector. Used in the controlling mammary gland discharges**.

The detected discharges require additional investigation. Only colostric discharges during pregnancy and lactation are exceptions. All other discharges need additional investigation: cytological (swab-print), and/or chemical (hematest). Hematest is done in order to exclude the presence of blood in the discharges and serves as a screening method to differentiate between dishormonal processes and intraductal overgrowth. The test utilizes the chemical reaction between the blood concealed in the discharges and an azopiram solution. If there is a purple coloring, the reaction is considered positive, which means there are elements of blood in the discharges, which serves as an indication for an additional investigation: ductography [8].

A cytological investigation requires more time and economic spendings, however it is of principle importance if there are intraductal inflammatory processes or bloody nipple discharges. Inflammatory elements or the presence of tumor cells in the swab-prints are contraindications to introducing contrast into the duct and can significantly change the patient management tactic.
The detected discharges can be grouped according to colour, cytological conclusion, and their identification can help in the diagnosing (tabl.). The characteristics of the discharges are varied – just the processes accompanying them. The discharges can be transparent, white, yellow, cloudy straw colour, green, amber, brown, bloody [18]. At the same time the consistency of the discharged can vary from liquid to thick.

Table. Preliminary diagnosing according to the evaluation of mammary gland nipple discharges and the results of the cytological investigation of the swab-prints

Discharges	**Cytology**	**Diagnosis**
White	Colostric cells	Galactorrhea or lactation period
Cloudy straw colour, green, serous	Unstructured masses , upper epithelium cells	Fibrotic-cystic mastopathy
Light (thick, dense)	Detritus, fat masses	Ductal ectasia
Yellow, green (stretchy)	Neutrophils, macrophages, unstructured masses	galactophoritis, mastitis
Transparent, amber, brown	Unstructured masses	Fibrotic-cystic mastopathy
Transparent, amber, brown, bloody	Neutrophils, macrophages, cubic epithelium cells	Intraductal pathology

The presence of colostric discharges outside the lactation and pregnancy period is called galactorrhea. This can be caused by hormonal malfunction (abortions, emergency contraception), pituitary microadenoma, hypothyroidism, medicine impacts, local prolactin secretion by the mammary gland tissue [19]. Further examinations of patients with such nipple discharges should

include, apart from USI, endocrine profile investigation (prolactin, macroprolactin, TSH, Free T4, TPOAB, TGAB). It is important to control the intake absence of hyperprolactinemia-causing preparations in the anamnesis.

Dark-strawy, green, serous or nearly back discharges from several ducts from two sides do not arouse suspicion of a local pathology and tell us of dishormonal lesions in the body, as well as of fibrotic-cystic mastopathy. A greenish color of discharges has to do with the secretion staying in the ducts for a long time and the cells collapsing to detritus – not with infection. Cytological investigation shows unstructured masses [20]. Serous discharges, including brown ones, can be observed at intraductal papillomae, as well as at proliferation and ectasia of ducts – and require a cytological investigation or an azopiram test [8].

Green and stretchy, sometimes smelly discharges are characteristic for inflammatory processes in the mammary gland. Cytologically they have a lot of neutrophils, fibrin threads, macrophages, during lengthy processes – polykaric cells [18].

Amber and bloody discharges are characteristic for pathological intraductal processes in the mammary gland, usually from a single duct. These discharges can be the first and only symptom of an intraductal or oncological pathology. The swab-print must be studied cytologically. If only erythrocytes or erythrocytes together with macrophages, cubic epithelium cells at various differentiation stages are present, the further tactic for additional examination and treatment is determined [19, 20].

Ductographic investigation should be performed strictly with regard to indications and contraindications. Indications to ductography can be [8]:

1. absolute —
- bloody and amber nipple discharges;
- transparent discharges from one of the ducts;
- discharges from one duct in women after climax;
- cytological investigation shows: erythrocytes, aggregations of cubic epithelium cells in papillae.
2. relative — all cases of pathological secretion outside of pregnancy and lactation.

Contraindication to ductography [8]:
- cases of clinically determined cancer;
- detection of cancer cells in the cytological investigation of the swab (because of the danger of tumor cells migrating in the ductal system);
- inflammatory process;
- allergy to iodine preparations;
- blotchy and necrotic nipple changes;
- possible Paget's disease, подозрение на болезнь Педжета, nipple atheroma;
- pregnancy.

Defects of duct filling, revealed at contrasting, point at the localization of an intraductal pathological process. At the same time, the depth of the pathology focus (relative to the nipple) and its position in the gland's quadrant system is localized [8].

If the contrasting defect of the duct is more than 0.5 cm in size, it is necessary to conduct an additional examination and a morphological verification on a stereotoxic attachement – core-biopsy (thick-needle biopsy with aquiring histological material).

Studies start emerging concerning ductoscopic investigations with the acquisition of morphological material, however the anatomical peculiarities of the ductal system, which is individual in its structure, and different types of branching as well as the variability of the pathology location, do not allow such a method to become routine [21].

Given the high scale of intraductal pathology malignization, sectoral mammory gland resection should be performed as a result of contrast mammography followed by a morphological verification of the histological material and an immunohistochemical analysis. Depending on the results of the latter, different treatment is prescribed (vitamin complexes, selective estrogen receptor modulators, monophase hormonal preparations).

Dispensary observation is necessary for groups with a positive immonohistochemical status. Physical examination, swab control and USI of the mammary glands are necessary 2 times per year.

EXAMINATION ALGORITHM IF PATHOLOGICAL NIPPLE DISCHARGES ARE REVEALED

1. Physical examination of the mammary glands. Control over nipple discharges.
2. Cytological investigation of the discharge.
3. Ultrasonic investigation.
4. Digital mammography.
5. Contrast ductography.

According to the ductography results – surgery and/or conservative theratpy, then – dynamic observation.

Conclusion

No matter what the patients' age is, discharges from the mammary gland nipple are not detected under normal circumstances. The only exceptions are pregnancy and lactation. Pathological nipple discharges in childhood are subject to dynamic observation. In adolescence any nipple discharges require additional investigation. Pathological changes in the ductal system may occur from the moment the mammary gland starts developing, in these cases additional investigations are carried out. According to the results of the ductographic investigation, surgery is performed or not performed. In case of surgery, an immunohistochemical investigation of the resected material makes it possible to evaluate the risk of relapses and to develop the treatment tactic. For this group, dynamic observation is recommended for 3 years.

Funding source

Not stated.

Conflict of interest

The authors declared they have no competing interests to disclose.

REFERENCES

1. Рожкова Н.И. Рентгенорадиологические технологии в маммологическом скрининге. Отчет главного специалиста Минздрава. — М.; 2014. [Rozhkova NI. Rentgenoradiologicheskie tekhnologii v mammologicheskom skrininge. Otchet glavnogo spetsialista Minzdrava. Moscow; 2014. (In Russ).] Доступно по:

http://www.himedtech.ru/articles/?SECTION_ID=128&ELEMENT_ID=1720. Ссылка активна на 13.03.2016.
2. euro.who.int [интернет]. Доклад директора Европейского регионального бюро ВОЗ. Борьба с онкологическими заболеваниями в Европейском регионе ВОЗ. — Женева: ВОЗ; 2010. [Doklad direktora Evropeiskogo regional'nogo byuro VOZ. Bor'ba s onkologicheskimi zabolevaniyami v Evropeiskom regione VOZ. Geneva: WHO; 2010. (In Russ).] Доступно по: http://www.euro.who.int/ru/about-us/regional-director/news/news/2010/07/combatingcancer-in-europe. Ссылка активна на 13.03.2016.
3. *Состояние онкологической помощи населению России в 2012 году* / Под ред. Каприна А. Д., Старинского В. В., Петровой Г. В. — М.: МНИОИ им. П. А. Герцена; 2013. 232 с. [*Sostoyanie onkologicheskoi pomoshchi naseleniyu Rossii v 2012 godu*. Ed by Kaprin A.D., Starinskii V.V., Petrova G.V. Moscow: MNIOI im. P.A. Gertsena; 2013. 232 p. (In Russ).]
4. Мнихович М.В. Внутрипротоковые пролиферативные поражения молочной железы: вопросы морфологической диагностики // *Российский медико-биологический вестник им. акад. И. П. Павлова*. — 2010. — №3 — С. 168–174. [Mnikhovich MV. Vnutriprotokovye proliferativnye porazheniya molochnoi zhelezy: voprosy morfologicheskoi diagnostiki. *Rossiiskii mediko-biologicheskii vestnik im. akad. I.P. Pavlova*. 2010;(3):168–174. (In Russ).]
5. Андреева Е.Н., Леденева Е.В. Основные аспекты этиологии и патогенеза фиброзно-кистозной болезни молочной железы // *Акушерство и гинекология*. — 2002. — №6 — С. 7–9. [Andreeva EN, Ledeneva EV. Osnovnye aspekty etiologii i patogeneza fibrozno-kistoznoi bolezni molochnoi zhelezy. *Akusherstvo i ginekologiya*. 2002;(6):7–9. (In Russ).]
6. Розин Д.Л. *Опухоли молочных протоков*. — Баку; 1989. 332 с. [Rozin DL. *Opukholi molochnykh protokov*. Baku; 1989. 332 p. (In Russ).]
7. Денисов Л.Е., Панина И.Г. Применение ультразвукового исследования для диагностики патологических образований молочных желез // *Вестник рентгенологии и радиологии*. — 1987. — №1 — С. 50–54. [Denisov LE, Panina IG. Primenenie ul'trazvukovogo issledovaniya dlya diagnostiki patologicheskikh obrazovanii molochnykh zhelez. *Vestnik rentgenologii radiologii*. 1987;(1):50–54. (In Russ).]
8. Травина М.Л. *Клиническая оценка патологической секреции в комплексной диагностике внутрипротоковых опухолей молочной железы*: Автореф. дис. … канд. мед. наук. — М.; 2005. 22 с. [Travina ML. *Klinicheskaya otsenka patologicheskoi sekretsii v kompleksnoi diagnostike vnutriprotokovykh opukholei molochnoi zhelezy*. [dissertation abstract] Moscow; 2005. 22 p. (In Russ).]
9. iarc.fr [Internet]. World Cancer Report 2014 [cited 2016 Mar 13]. Available from: http://www.iarc.fr/en/publications/books/wcr/wcrorder.php.
10. Zervoudis S, Iatrakis G, Economides P, et al. Nipple discharge screening. *Womens Health (Lond Engl)*. 2010;6(1):135–151. doi: 10.2217/whe.09.81.
11. Давыдов М.И. *Статистика злокачественных новообразований в России и странах СНГ в 2012 г*. — М.: Издательская группа РОНЦ; 2014. 226 с. [Davydov MI. *Statistika zlokachestvennykh novoobrazovanii v Rossii i stranakh SNG v 2012 g*. Moscow: Izdatel'skaya gruppa RONTs; 2014. 226 p. (In Russ).]

12. Bonnett M, Wallis T, Rossmann M, et al. Histopathologic analysis of atypical lesions in image-guided core breast biopsies. *Modern pathology*. 2003;16(2):154–160. doi: 10.1097/01.mp.0000052375.72841.e2.
13. Травина М.Л., Голов Л.Б. Маммология в педиатрической практике. Проблемы молочной железы у детей и подростков // *Вопросы диагностики в педиатрии*. — 2009. — №2 — С. 73–78. [Golov LB, Travina ML. Mammalogy service in pediatrics. Breast problems in children and adolescents. *Pediatric diagnostics*. 2009;(2):73–78. (In Russ).]
14. Приказ Минздрава России № 572н (ред. от 17.01.2014) от 01.11.2012 «Об утверждении Порядка оказания медицинской помощи по профилю «акушерство и гинекология (за исключением использования вспомогательных репродуктивных технологий)». [Order of the Ministry of Health of the Russian federation № 572n (amend. 17.01.2014) dated November 01, 2012. «Ob utverzhdenii Poryadka okazaniya meditsinskoi pomoshchi po profilyu «akusherstvo i ginekologiya (za isklyucheniem ispol'zovaniya vspomogatel'nykh reproduktivnykh tekhnologii)». (In Russ).]
15. Shiino S, Tsuda H, Yoshida M, et al. Intraductal papillomas on core biopsy can be upgraded to malignancy on subsequent excisional biopsy regardless of the presence of atypical features. *Pathol Int*. 2015;65(6):293–300. doi: 10.1111/pin.12285.
16. Коробкина В.А. Диагностика внутрипротоковых заболеваний молочной железы // *Вестник Российского научного центра рентгенорадиологии*. — 2010. — №10. [Korobkina VA. Diagnostics intraductal mammary gland diseases. *Vestnik Rossiiskogo nauchnogo tsentra rentgenoradiologii*. 2010;(10). (In Russ).] Доступно по: http://vestnik.rncrr.ru/vestnik/v10/papers/korob_v10.htm. Ссылка активна на 13.03.2016.
17. Травина М.Л. Детская и подростковая маммология и лучевая диагностика. Лекция // *Russian electronic journal of radiology*. — 2012. — Т.2. — №3 — С. 7–26. [Travina ML. Children and adolescents mammology and radiology. Lecture. *Russian electronic journal of radiology*. 2012;2(3):7–26. (In Russ).] Доступно по: http://www.rejr.ru/volume/7/l_travina.pdf. Ссылка активна на 13.03.2016.
18. Domanski HA. *Atlas of fine needle aspiration cytology*. Berlin: Springer; 2014. p. 47–86.
19. Голов Л.Б. Синдром патологической секреции - проявление двух патологических процессов // *Маммология*. — 1993. — №1 — С. 10–17. [Golov LB. Sindrom patologicheskoi sekretsii - proyavlenie dvukh patologicheskikh protsessov. *Mammologiya*. 1993;(1):10–17. (In Russ).]
20. Татарчук Т.Ф., Гуньков С.В., Ефименко О.А. Современные подходы к диагностике и лечению гиперпролактинемии // *Репродуктивная эндокринология*. — 2012. — Т.1. — №3 — С. 26–44. [Tatarchuk TF, Gun'kov SV, Efimenko OA. Sovremennye podkhody k diagnostike i lecheniyu giperprolaktinemii. *Reproduktivnaya endokrinologiya*. 2012;1(3):26–44. (In Russ).]
21. Kamali S, Bender O, Kamali GH, et al. Diagnostic and therapeutic value of ductoscopy in nipple discharge and intraductal proliferations compared with standard methods. *Breast Cancer*. 2012;21(2):154–161. doi: 10.1007/s12282-012-0377-7.