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Current knowledge of cervical cancer: classification, diagnosis, prevention and treatment. Part II

Rak szyjki macicy: klasyfikacja, diagnoza, zapobieganie i leczenie. Część II

Cervical cancer kills more than 288,000 women each year. Prevention of cervical cancer means: regular cervical screening test, HPV vaccination, life style (early onset of sexual activity, early age of first pregnancy, multiple sexual partners and "high risk partners"), treatment of pre-cancer changes and early stages of cervical cancer. Screening of cervical cancer is effective because it is minimally invasive, easy to perform and efficacious in diagnosing the disease process in its pre-invasive stage.

EXFOLIATIVE CYTOPATHOLOGY

The microscopic study of cells obtained from the surface of the cervix is one of the best means of screening for malignancy in its early stages. The exfoliated cells are collected, mounted, stained and then examined under a microscope. Regular Pap tests, follow up smears and pelvic exams gives us an opportunity to find and treat changing cells before they turn into invasive cancer. The mortality from cervical cancer has decreased by 70–80% since the introduction of the conventional Papanicolaou smear [19], but data for the past 5 years indicate that only about 5% of women in developing countries are screened. Data on the natural history of HPV infection and the incidence of high-grade lesions and cervical cancer suggest that screening can safely be delayed until 3 years after the onset of sexual activity or until age 21 [18]. HPV-related cancers are more treatable when diagnosed and treated early. HPV testing and screening procedure may reduce the number of false-negative screening reports. Testing for the presence of HPV-DNA in the cervical cells is a potentially useful screening method which could be incorporated in a cervical cancer screening programme [18]. HPV DNA is detected in the majority of the tumors [3]. The specimen for HPV-DNA testing can be obtained by using a cell suspension from LBC samples or by using the endocervical cytobrush. A negative HPV test result would indicate a very low risk of progression to cancer. HPV positive women need more intensive follow-up screening [3].

SCREENING PROGRAMMES

Screening programmes for cervical cancer have been instituted in developed countries for decades and over a period of time have been shown to be effective in reducing the mortality and incidence of this disease [1]. The aim of National Cervical Screening Programme is to carry out a national cervical cancer screening service for the early diagnosis and treatment. The National Cervical Screening Programme encourages all women in the target population to have regular Pap smears. The Programme screens all women aged 25-60 years (in Ireland).The risk of developing invasive cervical cancer is three to ten times greater in women who have not been screened [2, 4, 8, 13].

The best protection of women against developing of cervical cancer is having regular cervical smear test. The majority of cervical cancers (USA statistics) occur in women who have never been screened or who have not been screened within the past 5 years; additional cases occur in women who do not receive appropriate follow-up after an abnormal Pap smear [9,11]. A Pap test is a quick and simple test to check the cervix. If every woman had a Pap smear every 2 years, 90% of cervical cancers could be prevented [10,14]. The Pap smear, while not perfect, is the best test available to detect early changes that can then be monitored to prevent cervical cancer. One of the factors determining the prevention is the quality of the smear for microscopic examination. The best results in the detection of pre-cancerous changes in the cervix depend on adequate sampling of the transformation zone (the area of cervix originally lined by columnar epithelium in which squamous metaplasia occurs transforming the columnar to squamous epithelium) [7]. This is performed with a broom (see Fig. 1). The cells are either spread on the glass slide and sprayed with a fixative solution in conventional method or rinsed into preservative solution in LBC method.

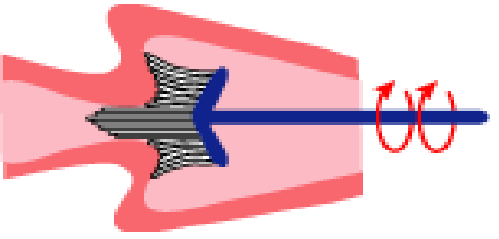

Fig. 1. Sample taking: Speculum inserted to the vagina.
Cervix should be visualized and any features noted.
Sample taken using sampling device (rotate through 360x5 with brush or spatula)

THE TRADITIONAL SMEAR METHOD

This was the only method used for many years, The Papanicolaou smear for cervical cancer screening was introduced in 1949 as a test to detect cervical cancer [17] and it has become an integrated part of most heath care systems, and so the cervical screening test was known as the “cervical smear test”. The conventional cervical smear (see Fig. 2) is cheaper than liquid based cytology (LBC) but only a selected proportion of the cells are placed on glass slide. Cell distribution on the slide is uneven, it is not a truly representative sample, the slide cannot be reproduced and the smear is more likely to be unsatisfactory.

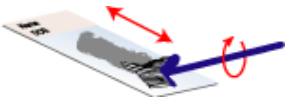

Fig. 2. Cells are spread on the glass slide

LIQUID BASED CYTOLOGY

LBC is a newer method that is gradually replacing the conventional smear. In this method, a disposable brush is used to collect the cells from the os of the cervix (Fig.1). The cells are rinsed into preservative solution in a vial known as "preservcyt transport medium" (Figures 3, 4 and 5). The vial is sent to the laboratory for processing using a LBC technique (ThinPrep or SurePath system). The liquid-based preparation (LBP) has become the primary method for cervicovaginal screening because of the improved specimen quality and detection of squamous intraepithelial lesions [16]. The cells are then placed on a slide and looked at under a microscope to see if there are any abnormal cells present.

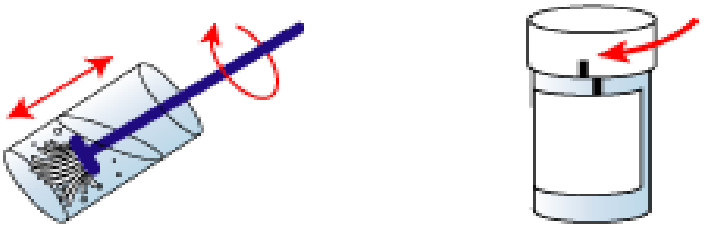

Fig. 3 and 4. Rinse the brush in the preservative solution than close the vial; small black mark and the corresponding line on the vial should passes, full patients name and date of birth should be recorded on the label. and sent to the laboratory as a homogeneous cell suspension

Fig. 5. A Thinprep vial containing transport medium and disposable brush

LBC advantages: gives a representative sample, more even distribution of cells, reduction in cellular debris (blood, mucus) and red blood cells, multiple slide preparations can be made, there is a greatly reduced inadequate or unsatisfactory cases [6,15], also detection rates of low and high grade CIN improves; increasing of productivity and sensitivity. The most consistent improvements shown with LBC are the detection of low-grade abnormalities, up to 12% better with LBC compared to conventional smears [15].

SCREENING

Cervical smears are stained by the Papanicolaou staining method – type of trichrome stain in which different dyes stain different cell components; Harris's haematoxylin stains nucleus of the cell and chromatin details, blueing converts nuclear colour from red/brown to blue, O.G.6 stains intermediate filaments such as keratin orange, EA 50 stains cytoplasm pink in superficial squamous cells and blue/green in intermediate squamous cells.

The aim of cervical screening is to identify the precursor lesion of cancer, screener checks details on slide and form, smears with abnormalities go to consultant cytopathologist for reporting, smears over which the primary screener has some doubts go for checking. The primary screener reports negative and inadequate smears, a patient history is checked on the computer to ensure that the correct management is given. Smear reporting uses either The Bethesda System of Classification (TBS) or the BSCC (British Society for Clinical Cytology).TBS is used in most other countries outside of the UK. BSCC or CIN terminology is commonly used in the UK and Ireland. BSCC terminology was originally published in 1986 and although highly successful, required revision. Through a process of professional consensus and literature review this has been undertaken by the BSCC. The revision takes account of recent developments and improvements in understanding of morphology and disease process and is compatible with other terminologies in use elsewhere, whilst still maintaining a focus on practice in the UK (also Ireland) cervical screening Programme [5]. Classification of cervical cytology by the BSCC system: Neg, Inadequate, BNA (Borderline Nuclear Abnormalities), CIN I – mild dyskaryosis, CIN II – moderate dyskaryosis, CIN III – severe dyskaryosis, CIN III – invasive carcinoma, CGIN. Cytological criteria: nuclear and cytoplasmic features: total cell size, cell shape; size, shape, and density of nucleus; type of nucleus, nuclear/cytoplasmic ratio. The pattern of the cells is very important and should be consistent with the clinical details.

There are multiple factors that can contribute to an unsatisfactory or inadequate smear: too few cells in preparation, cells obscured by polymorphs, cytolysis, severe inflammatory changes, yeast contamination, too bloody, severe atrophy or a human error in sampling. Inadequate samples can range from 8% [12, 20]. The most common reasons for conventional smear being reported as unsatisfactory are obscuring by purulent exudates, cytolysis, scanty cellular material or air-drying artifact. See Fig. 6 and 7.

Normal (benign) cervical smear can contain superficial, intermediate, parabasal and basal squamous cells (basal squamous cells, which lie on the basement membrane, do not normally exfoliate, they are only occasionally seen in smears from post menopausal women), metaplastic epithelial cells, endocervical glandular cells, endometrial glandular cells, mucus, commensal organisms, leucocytes, lymphocytes, red blood cells and histiocytes (see Fig. 8)

Borderline abnormalities: cells changes are not dysplastic but cannot be recognized as inflammatory, reactive or metaplastic: nuclear enlargement and size variation, mild chromatin irregularity, nuclear membrane wrinkling, abnormal keratinisation, koilocytosis (well defined clearing around nucleus, condensed peripheral cytoplasm, enlarged nucleus, wrinkled, loss of nuclear details, becomes hyperchromatic, pyknotic, binucleation). See Fig. 9.

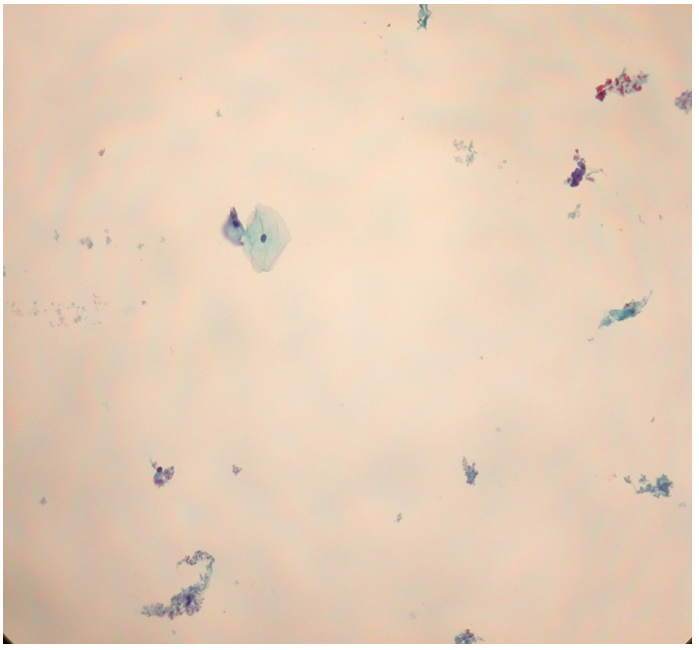

Fig. 6. Unsatisfactory smear

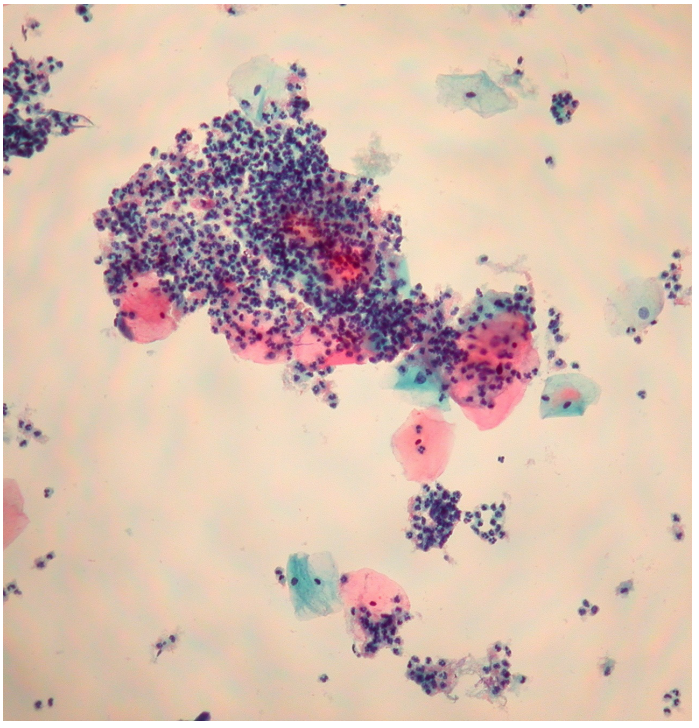

Fig. 7. Unsatisfactory smear

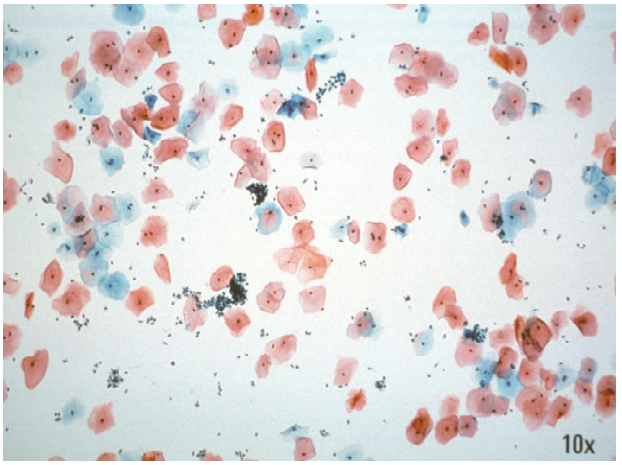

Fig. 8. Normal (Neg) smear

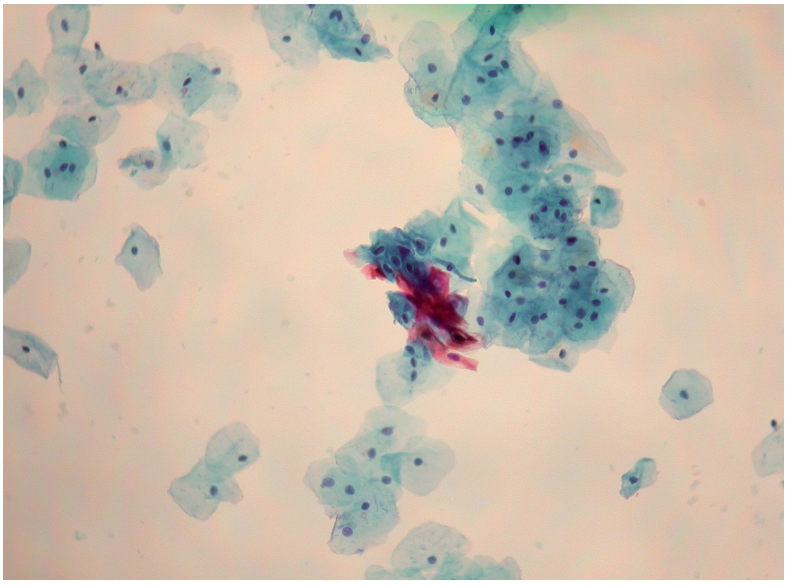

Fig. 9. BNA

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

CIN or cervical intraepithelial neoplasia describes pre-cancerous changes of the cervix. The cytological hallmark of this in the cervical smear is the dyskaryotic cell. Papanicolaou first coined the term dyskaryosis, which means abnormal nucleus. Nuclear abnormalities in dyskaryotic cells include disproportionate nuclear enlargement, irregularity in the form and outline of nucleus, hyperchromatic irregular chromatin distribution, multinucleation, abnormal multiple nucleoli. There are three histological grades of cervical intraepithelial neoplasia which are defined by the proportion

of the mucosa replaced by immature crowded cells with abnormal nuclei: CIN I, CIN II, CIN III. The equivalent cytological terms for CIN are: mild dyskaryosis (CIN I), moderate dyskaryosis (CIN II) and severe dyskaryosis (CIN III).

Mild dyskaryosis (CIN I): enlarged nucleus does not occupy more than one half of the cell, hyperchromasia and stippled chromatin pattern, irregular nuclear membrane, there may be multinucleation. Intermediate and superficial cells are involved. Distinguish from: Reactive and inflammatory changes (see Fig. 10).

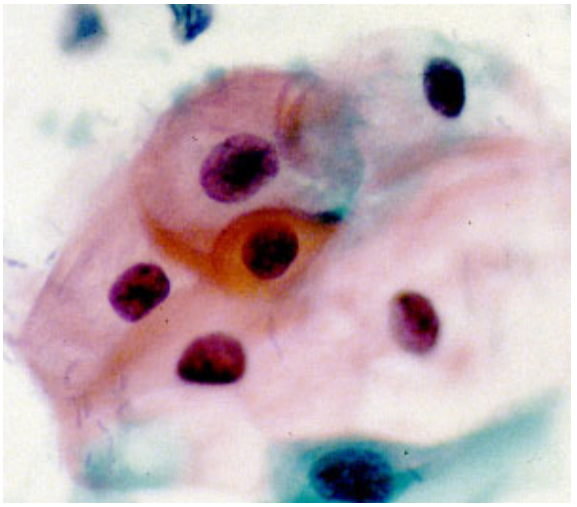

Fig. 10. CIN I

Moderate dyskaryosis (CIN II): nuclear/cytoplasmic ratio: nucleus occupying not more than two thirds of the cytoplasmic area, nuclear hyperchromasia, stippled chromatin pattern, irregular nuclear membrane. Intermediate and parabasal cells. Distinguish from: Immature squalors metaplasia.

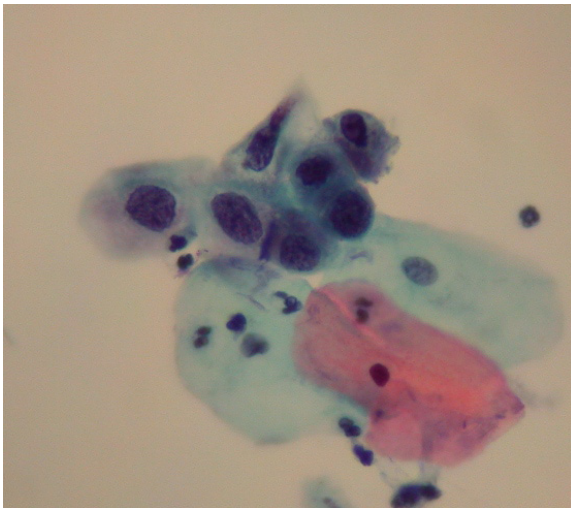

Fig. 11. CIN II

Severe dyskaryosis (CIN III): abnormal nucleus only surrounded by a narrow band of cytoplasm, abnormal chromatin pattern, nuclear hyperchromasia, irregularity of the nuclear membrane, multiple abnormal nuclei, abnormal maturation of cytoplasm including keratinization, cell borders smooth or irregular, bizarrely shaped cells, sometimes including fibre cells (see Fig. 12).

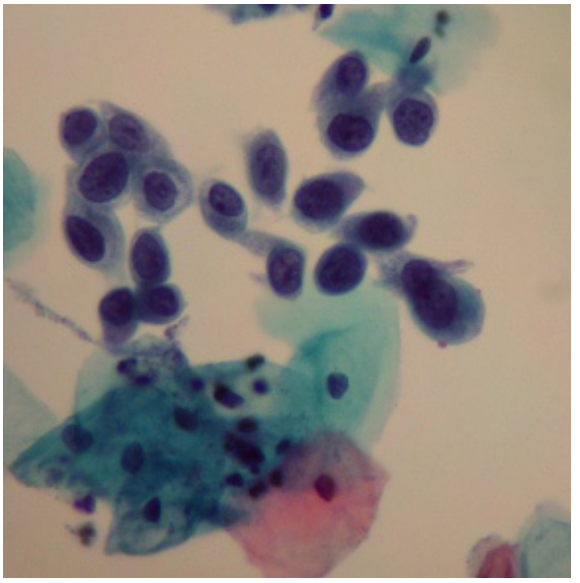

Fig. 12. CIN III

CERVICAL GLANDULAR INTRAEPITHELIAL NEOPLASIA (CGIN)

Glandular abnormalities may also be identified but cervical smear is not a screening method for such abnormalities. These patients are usually symptomatic and the smears are taken in association with other diagnostic tests. On primary screening identification is often made on the architectural features of cell groups. Cells are arranged in rosettes and pseudostratified strips, we can see clusters

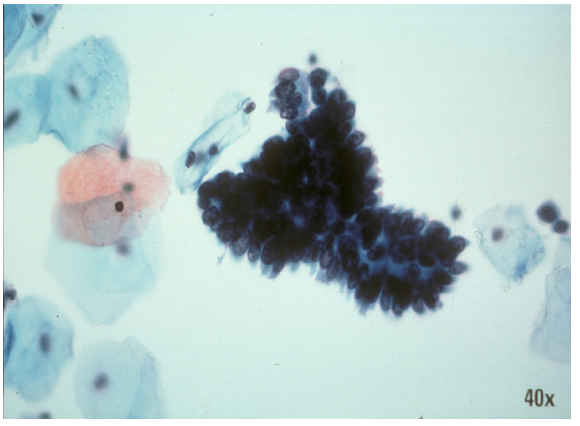

Fig. 13. CGIN (endocervical abnormal cells)

of cells with some nuclear overlapping and crowding. There could be poor cohesion of cells at the edges of the groups, this appearance is known as "feathering". The nuclear features of CGIN are similar to those of CIN dyskaryosis; irregularity of nuclear membrane, coarse and stippled chromatin with granules, variation in size and shape, enlarged nuclei. CGIN can be subclassified into low grade CGIN ("glandular dysplasia" and high grade CGIN ("adenocarcinoma-in-situ"). See Fig. 13.

CONCLUSIONS

Regular cervical screening test is the most common method of prevention of cervical cancer. National Cervical Screening Programme carries out a national cervical cancer screening service for the early diagnosis and treatment. As cervical cancer is usually preceded by precancerous changes in the cells on the surface of the cervix exfoliative cytopathology is one of the best means of detecting malignancy in its early stages and prevent women from developing this disease. Women are asked to have regular cervical screening tests (Pap. tests) in order to prevent cervical cancer. HPV vaccination gives very good effect and can give almost 100% of protection. Patient management depends on the classification of the smear test. Women with negative test results are invited for re-screening in intervals of 3–5 years, those with BNA or mild dyskaryosis at a reduced screening intervals, patient with moderate or severe dyskaryosis or persistent inadequate and BNA should be refer to colposcopy (and biopsy) for confirmation.

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SUMMARY

Cervical cancer kills more than 288,000 women each year. The best protection of woman against developing cervical cancer is having regular cervical smear test. The majority of cervical cancers occur in women who have never been screened. The mortality from cervical cancer has decreased since the introduction of the conventional Papanicolaou smear. LBC is a newer method that is gradually replacing the conventional smear. The liquid-based preparation (LBP) has become the primary method for cervicovaginal screening because of the improved specimen quality and detection of squamous intraepithelial lesions The aim of cervical screening is to identify the precursor lesion of cancer. BSCC or CIN terminology is commonly used in UK and Ireland.

STRESZCZENIE

Rak szyjki macicy każdego roku zabija 288 tysięcy kobiet. Najlepszą formą ochrony przed tym typem nowotworu jest regularne badanie cytologiczne. Większość przypadków nowotworu szyjki macicy zdiagnozowano u kobiet, które nigdy nie zgłaszały się na badanie cytologiczne. Umieralność na raka szyjki macicy znacznie spadła od momentu wprowadzenia Pap testu. Płynna cytologia jednowarstwowa jest nowszą metodą, stopniowo wypierając konwencjonalny rozmaz, stając się główną metodą screeningu, którego zadaniem jest wykrycie stanów przednowotworowych szyjki macicy. Laboratoria w Irlandii i Wielkiej Brytanii do oceny rozmazów cytologicznych używają klasyfikacji BSCC.