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

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

Over the past decade, the development of more conservative techniques for the diagnosis and treatment of the early stages of cervical cancer has progressed reducing mortality and improving the chance of women to conceive following treatment. These have included new cytologic sampling instruments, new methods for processing the cytological samples, and methods for review of cytologic interpretation. Many of these methods, have been designed specifically to reduce the rate of false-negative results [6].

Cancer of the cervix uteri or cervical area, is the 9th most common cancer among women (especially between 50–55 years) in Ireland, and is caused by a sexually transmitted virus HPV. It is usually preceded by precancerous changes in the cells on the surface of the cervix, it may present with abnormal vaginal bleeding, bleeding after intercourse, or discharge. As stated previously cervical cancer is usually preceded by changes in the cells on the surface of the cervix, which may be detected on a smear test. The Pap smear is an effective screening test, but confirmation of the diagnosis of cervical cancer or pre-cancer requires a biopsy of the cervix. There are many different types of cancer which affect the cervix, including: squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and small cell carcinoma. Features of squamous cell carcinoma – dyskaryotic cells with marked nuclear changes, variation in size and shape of nuclei beyond that usually associated with CIN III, coarse chromatin clumping, aggregation of nuclear chromatin so marked that translucent "holes" or "windows" appear, large irregular macronucleoli. The type of treatment used for cervical cancer depends on the stage of disease. The FIGO staging system is listed below.

International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical carcinoma [1]:

Stage 0 or *in situ* ("in place") – cancer has only been found in the layer of cells lining the cervix, and has not invaded the deeper tissues of the cervix. *Treatment options:* cauterization, cone biopsy, cryosurgery, laser.

Stage I. Cancer has spread from the lining of the cervix into the deeper connective tissue of the cervix(still confined to the uterus)

IA – the earliest form of stage I cancer, only a small amount of cancer is visible upon microscopic

examination. *Treatment option*: trachelectomy, hysterectomy, radical hysterectomy, sometimes radiation therapy and chemotherapy are needed.
IA1 – the area of invasion-less than 3 mm deep and less than 7 mm wide.
IA2 – invasion between 3 mm and 5 mm deep and less than 7 mm wide.
IB **–** cancer can be seen without a microscope**.** This stage also includes cancers seen only with a microscope and have spread deeper than 5 mm into connective tissue or are wider than 7 mm. *Treatment options*: radical hysterectomy with radical bilateral pelvic lymph node removal, radiation therapy, and sometimes high dose internal and external radiation therapy with chemotherapy.
IB1 – cancer is no larger than 4 cm.
IB2 – cancer larger than 4 cm.

Stage II. In this stage cancer is spread beyond the cervix to nearby area but is still inside the pelvic area.
IIA – cancer has spread beyond the cervix to the upper part of the vagina, but does not involve the lower third of the vagina. *Treatment option***:** high-dose internal and external radiation therapy
IIB – cancer has spread to the tissue next to the cervix (the parametrial tissue). *Treatment option*: internal and external radiation therapy and chemotherapy.

Stage III. This stage cancer has spread to the lower part of the vagina or the pelvic wall. The cancer may be blocking the uterus. *Treatment options*: radiation therapy and chemotherapy (Platinol or other drugs).
IIIA – cancer has spread to the lower third of the vagina but has not spread to the wall.
IIIB – cancer has spread to the pelvic wall and/or block urine flow to the bladder.

Stage IV. Cancer has spread to other parts of the body.
IVA – this stage includes cancer that has spread to the bladder or rectum (organs close to the cervix). *Treatment options*: radiation therapy and chemotherapy with cisplatin or other drugs.
IVB – cancer has spread to distant organs beyond the pelvic area, such as the lungs.

Treatment options focus on relieving cancer symptoms and extending survival time. Before taking a decision about the choice of surgery, the patient should carefully consider the risks involved such as the morbidity of surgical procedures, the impact on quality of life, sexual function and cosmetic appearance. More recently, a lot of emphasis is being placed on how to preserve fertility potential [3]. Fertility preservation has become a major issue in the management of cervical cancer in younger and this is why we chose to study this case.

INVESTIGATIONS AND DIAGNOSIS

This study will focus on a 33-year-old woman who presented with postcoital bleeding. Her cytology smear results revealed CIN III and she was immediately referred for colposcopy and biopsy to confirm. Histology examination of the biopsy showed high grades quamous intraepithelial lesion (CIN III, severe dysplasia) focally extended to involve the endocervical margin (FIGO stage 1A2). No invasive carcinoma was seen. In order to preserve fertility in this woman, it was decided that the best form of treatment was to perform a trachelectomy. This study will examine the above-mentioned technique in detail.

The patient in this study had a radical trachelectomy for treatment of stage 1A2 cervical cancer. At the time of this diagnosis she had not yet conceived any children. When this patient first presented

with her symptoms of post coital bleeding a cervical smear was taken which revealed severe dyskaryosis consistent with CIN III. Figures 1–4 show dyskaryotic cervical cells from the patients 1st smear. This smear was quite scanty but there were enough cells present to make a definite diagnosis.

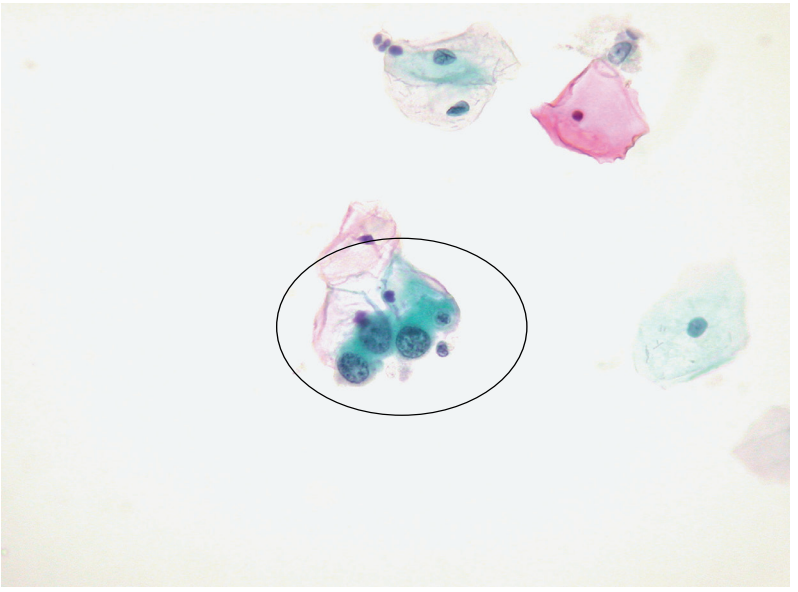

Fig. 1. Nuclear enlargement and hyperchromatism

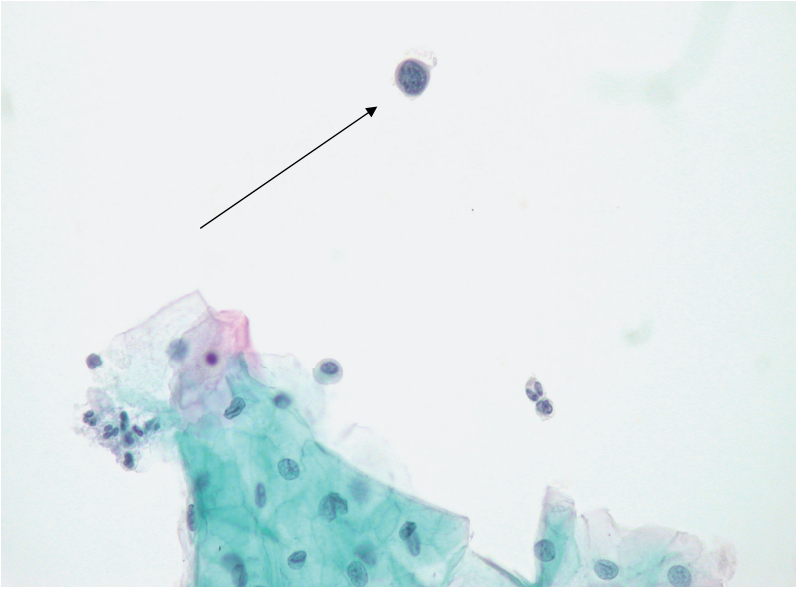

Fig. 2. The nucleus is hyperchromatic and has enlarged to occupy over two thirds of the cell

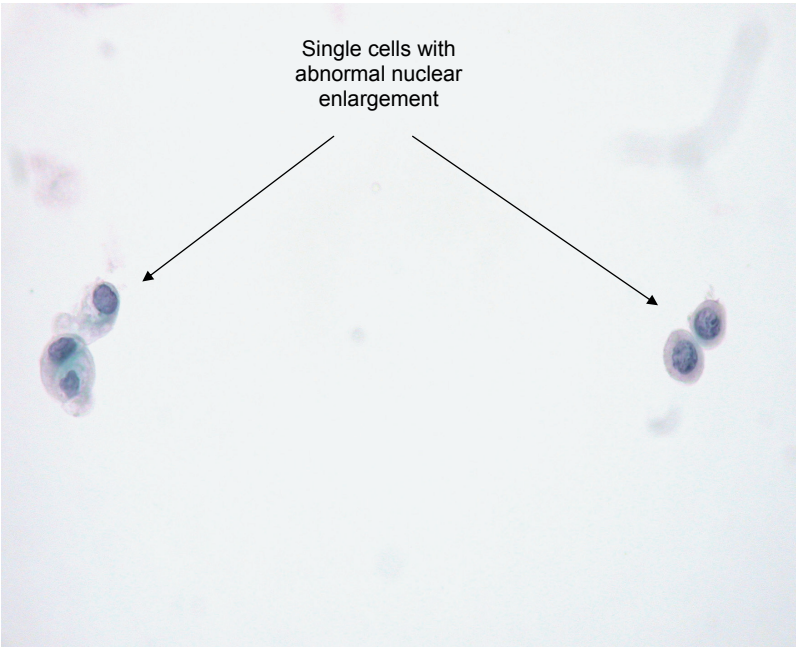

Fig. 3. Single cells

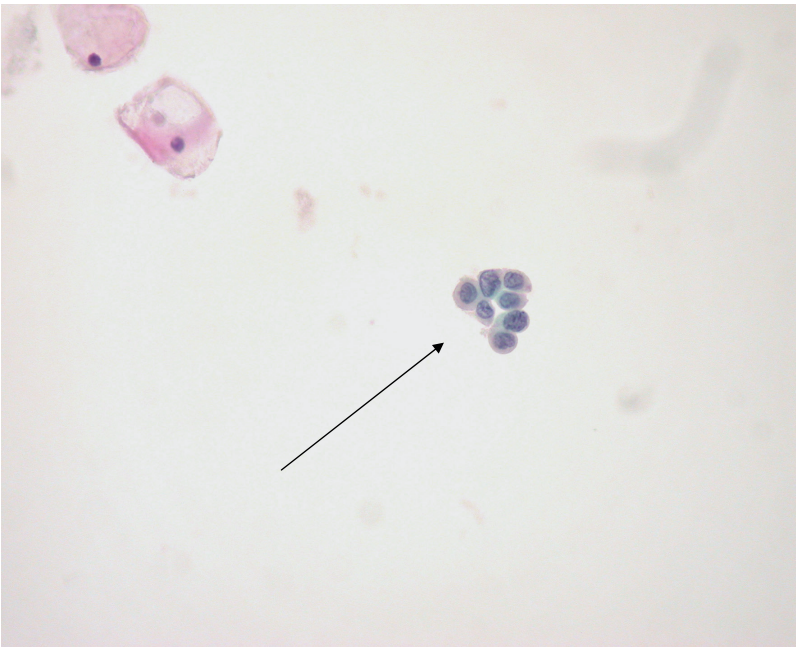

Fig. 4. A group of cells showing features of CIN III

COLPOSCOPY

Colposcopy is an examination of the cervix using a specially designed microscope (colposcope). The colposcope was first invented by Dr. Hans Hinselmann in 1925. It is a large electric microscope designed to allow examination of the cervix with magnifications ranging between x6 and x40. After examination of the cervix a cervical smear may be taken, but it is not advisable to do smear at colposcopy. The main reason for performing **colposcopy** is to detect pre-cancerous changes of the cervix although other conditions can also be diagnosed during a colposcopic examination. The most common indications for colposcopy are: an abnormal smear, bleeding after intercourse, an identified abnormality on the cervix, persistent vaginal discharge, bleeding between periods. Colposcopy can be done safely during pregnancy, although treatment is usually left until after delivery. Special dyes are often applied to the cervix during the examination. It may also be necessary to take a small sample of tissue (a biopsy) from the surface of the cervix. The colposcopy shows the type and extent of an abnormal area on the cervix. During the colposcopy, the gynecologist focuses on the areas of the cervix where light does not pass through. Abnormal cervical changes are seen as white areas, the whiter the area, the worse the cervical dysplasia (Fig. 5). Abnormal blood vessel changes are also apparent through the colposcope. Abnormal vascular changes can occur in dysplasia. Typically, the worse the vascular changes are the worse the dysplasia.

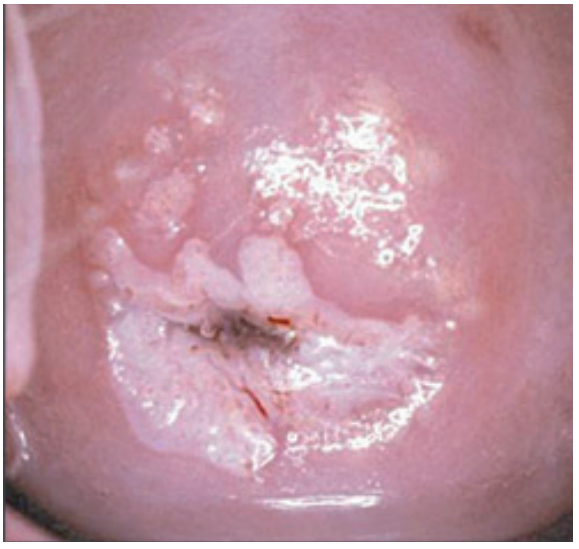

Fig. 5. Abnormal areas of the cervix are shown in white

If a physician is able to view the entire abnormal area through the colposcope, a tissue sample or biopsy is taken from the whitest abnormal areas and sent to the lab for further evaluation. Cryosurgery or a freezing of the abnormal cells may be performed next and, in some cases, can make this a diagnostic/treatment procedure in one. If a physician is unable to view the entire abnormal area, as when the abnormal area extends inside the cervix, another procedure such as a cone biopsy or LLETZ procedure is performed. Following any biopsies, an endocervical curettage (ECC) may also be done. As stated previously, treatment for cervical cancer depends on two factors: the stage of the disease

and the extent of its spread. There are three standard modes of treatment: surgery, radiation therapy and chemotherapy. At colposcopy, the patient in my case study had the smear diagnosis of CIN III confirmed and a biopsy was taken. The results of the biopsy revealed extensive CIN III with micro-invasion measuring 1mm in width and 3.2 mm in depth. A FIGO staging of 1A2 was confirmed. In order to preserve fertility in this 33 years old woman, it was decided that the best form of treatment for her was a trachelectomy.

TRACHELECTOMY

Trachelectomy, also called cervicectomy, is a surgery to remove the cervix (the end of the uterus that forms a canal between the uterus and the vagina). The upper part of the vagina and certain pelvic lymph nodes may also be removed. It is a viable option for those in stage I cervical cancer, which has not spread. Daniel Dargent and his colleagues first developed radical trachelectomy in France in 1987 (Trachelectomy comes from *trachelos*, a Greek word meaning the neck or a neck-like structure; the cervix is essentially the neck of the uterus). Radical trachelectomy and pelvic lymph node dissection for early Stage I carcinoma of the cervix, is a safe and effective surgery. A radical trachelectomy can be performed abdominally or vaginally; it is a conservative but locally radical procedure, preserving the corpus uteri and therefore fertility potential. The surgeon removes the cervix parametrium (tissue immediately next the cervix) and the upper two centimeters of the vagina, but does not remove the uterus. See Fig. 6.

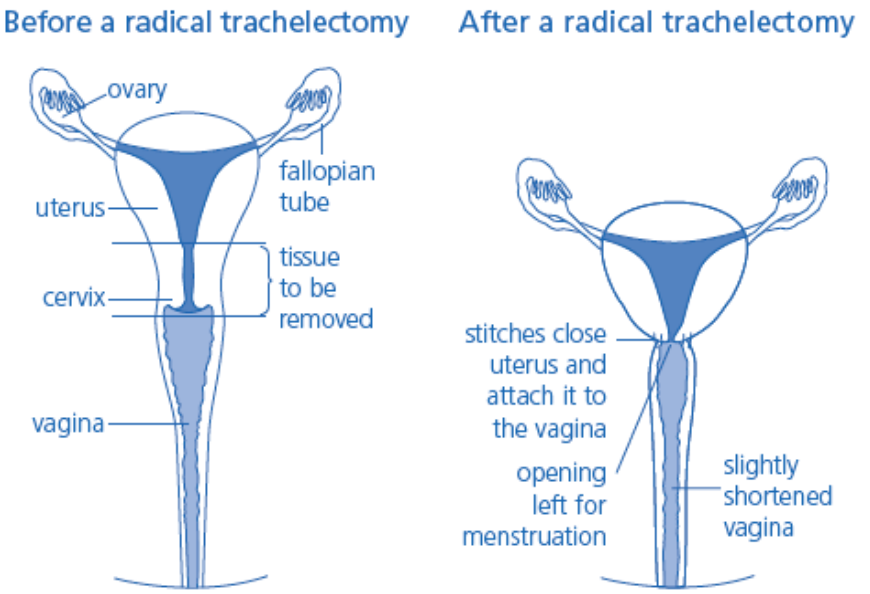

Fig. 6. Radical trachelectomy

There is no specific age restriction to this surgery. All patients interested in future fertility can be candidates for this procedure. About 40% of cervical cancer is diagnosed in women of childbearing age [3]. Women who would be considered as good candidates for this treatment have: either

squamous carcinoma or adenocarcinoma, a tumor less than 2 cm in diameter, no tumor in the upper cervical canal, no evidence the cancer has spread, interested in future fertility, no extensive history of infertility Following this patient's surgery, examination of the tissue samples revealed widespread CINIII extending through the full thickness of the squamous epithelium. See Fig. 7.

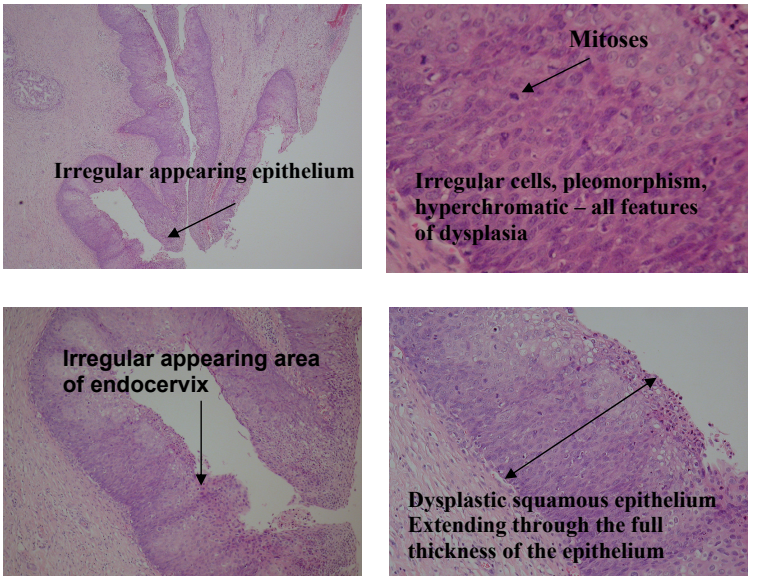

Fig. 7. Images from the patient's trachelectomy specimen showing areas of abnormalities

Radical trachelectomy is a smaller operation than radical hysterectomy and offers women hope that they might be able to have children after treatment. In this operation, the surgeon tries to remove the tumor, but leaves the internal opening of the cervix behind. This is then stitched closed, leaving a small opening to allow the woman to menstruate as normal. The stitch is designed to support a growing pregnancy until the baby can be delivered by Caesarean section. The surgeon may not know how successful the operation will be as it may not be possible to determine how far up the cervix the cancer has grown. The part of the cervix that is removed is examined under a microscope while the woman is still in the operating theatre. If there are no cancer cells around the edge of the tissue that has been removed and the surgeon is confident that all the cancer has been removed, there is no need to have any more tissue removed. If the lab results show that some cancer remains, more tissue will have to be removed and hysterectomy may have to be performed. This can be done during the same operation if a woman has given her consent beforehand.

After the checks have been done, if all is well, the surgeon will put in the stitch that will hold the cervix closed. Because there is a small risk of cancer spread to the lymph nodes in stage 1B cancers and some stage 1A cancers, the surgeon may also need to remove some lymph nodes from around the womb. This is usually done with a laparoscope. There may be up to 5 small incisions around a woman's abdomen when she wakes up. These are the openings the surgeon used to remove the lymph nodes. The lymph nodes will be checked under a microscope to see if they contain any cancer cells. If they do not, then there is no need for any further treatment. If there are cancer cells in any lymph nodes, then this is proof that some cancer cells have escaped from the cervix and a cancer could

begin to grow again. The doctor is likely to suggest that the patient has some radiotherapy to kill off any other cancer cells that may have been left behind. If a patient has radiotherapy, unfortunately, it destroys their chance to have a baby afterwards.

After radical trachelectomy cancer reoccurs in about 4% cases and 2.5% ends with death. This is similar to statistics for radical hysterectomy. The most frequent complications are: bladder problems, vulvar swelling, mass of lymph fluid (lymphocyst), infertility, cessation of menstruation, IMB (intermenstrual bleeding).

BIRTH AFTER TRACHELECTOMY

In a recent study by Plante et al. [4], which examined the obstetrical results in 72 patients following vaginal radical trachelectomy a total of 50 pregnancies occurred in 31 women. The majority (66%) had only one pregnancy, 19% had 2 pregnancies and 16% had 3 pregnancies or more. 16% of these patients had a first trimester miscarriage, 4% had a second trimester miscarriage and 2 women (4%) chose to have pregnancy termination. A total of 36 pregnancies (72%) reached the third trimester. Of those, 3 (8%) ended prematurely at <32 weeks gestation, 5 (14%) delivered between 32 and 36 weeks and 28 (78%) delivered at term (>37 weeks). Seven patients (10%) had fertility problems, of which 2 successfully conceived with IVF. This study concluded that the obstetric outlook is encouraging. It has been shown there is a higher risk of cancer reoccurrence or need for postoperative radiation therapy in women who do not meet the specific criteria [5].

CONCLUSIONS

This case study focused on a 33-year-old patient who first presented to her Doctor with symptoms of post coital bleeding. The first course of action was to take a cervical smear, which revealed severe dyskaryosis consistent with CIN III. She was immediately referred for colposcopy and biopsy to confirm this diagnosis. The results of the biopsy revealed extensive CIN III with micro-invasion measuring 1mm in width and 3.2 mm in depth. A FIGO staging of 1A2 was confirmed. As stated above, treatment for cervical cancer depends on two factors: the stage of the disease and the extent of its spread. Most treatments are radical and invasive and may involve radiation and chemotherapy. As this patient had been diagnosed with an early stage of disease and was of childbearing age, it was decided that the best form of treatment for her was a trachelectomy. Prognosis is dependent on surgical findings, patient recovery and any subsequent treatments. It is estimated that 40% of cervical cancers are diagnosed in women of reproductive age [2]. The trachelectomy procedure for early Stage I carcinoma of the cervix, is a safe and effective surgery. In a recent paper reviewing the outcome of 72 consecutive cases of trachelectomies, the median age of the patients was 31, most of whom did not have any children. A review of pre and postoperative complications revealed that five patients (6%) suffered minor difficulties during the operation and thirteen (16%) suffered short-term bladder complications after surgery. At 60 months the patients were followed up. Only three of the 72 women had a recurrence of cancer, and two had died[3]. Trachelectomies have been routinely performed for over 15 years now and have proven to be oncologically safe and effective in patients with early stages of disease.

The patient in this study had a radical trachelectomy for treatment of stage 1A2 cervical cancer. She is attending the colposcopy clinic for regular follow up and the disease has not recurred. At the time of this study she had not yet conceived any children.

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SUMMARY

The development of more conservative techniques for the diagnosis and treatment of the early stages of cervical cancer has progressed, reducing mortality and improving the chance of women to conceive following treatment. This study focuses on a 33-year-old woman who presented with postcoital bleeding. The patient in this study had a radical trachelectomy for treatment of stage 1A2 cervical cancer.

STRESZCZENIE

Nowe konserwatywne techniki w diagnozie oraz leczeniu raka szyjki macicy w jego przedinwazyjnej fazie pozwalają zmniejszyć umieralność oraz zwiększają szansę kobiet na posiadanie potomstwa po leczeniu. W pracy opisano te techniki na przykładzie 33-letniej pacjentki z nowotworem w stadium 1A2 wg klasyfikacji FIGO.