Cryotherapy in gynecology in the light of current scientific reports

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Introducion

Cryotherapy (from Greek – *krýos*, meaning *cold* and – *therapeía*, meaning *treatment*) is a form of freezing treatment in medicine employed since time immemorial, which uses temperatures below 0°C. The forms of treatment are as follows: local cryotherapy (also called cryodestruction) and general cryotherapy [1–3].
Local cryotherapy (cryodestruction) involves fitting very low temperature to the skin with the use of special applicator. The temperature is provided to the lesion. Freezing-thawing is repeated multiple times during one cycle. This leads to freezing the cell content, rupturing biological membranes and, ultimately, destruction of tissue. Local cryotherapy is used to treat benign and malignant lesions, changes within mucus membranes as well as benign and malignant lesions within abdominal cavity. Methods used in cryodestruction are: **cryoablation** and **cryocoagulation** [1–4].
Cryoablation is a non-invasive surgical treatment which involves inserting special electrode in the form of catheter into patient's organism. The tip of the catheter is precisely controlled and its movements are monitored by medical staff on special monitor. The tip selectively freezes and destroys small focal points of cells causing lesion, not disturbing the adjacent healthy tissues. Achieving low temperature is similar as in cooling equipment of common use. Through the catheter flows a mix of gases under pressure, which, during expanding, cause lowering of temperature to –70°C at the tip of the catheter.

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The second method (**cryocoagulation**) is a painless and bloodless method of local cryotherapy, which involves shallow destruction of suspicious or dispensable tissue without disturbing its integrity due to freezing. The lesion is subject to low temperature (from –196°C to –21°C as a rule), usually preceded by local anesthetization.

General cryotherapy subjects the whole body (for a short time, up to 3 minutes) to very low temperature (from –160 to –100°C). Contrary to local cryotherapy, correctly applied general cryotherapy leaves tissues intact. The treatment is also called cryostimulation because the aim of it is to administer physiological stress to organism [1–4].

History of cryotherapy

Cryotherapy is a method used in medicine since time immemorial [5,6]. Egyptians used cold in injury and inflammation treatment in 2500 BC. Dominique-Jean Larrey, the eminent surgeon of Napoleon, used cold to facilitate amputation during the historic retreat from Moscow [7]. In 1845 and 1851, James Arnott – from Brighton, England – described the benefits of local cryotherapy used in the treatment of many conditions, including headaches and neuralgia. Arnott applied salt solutions containing crumbled ice (temperature from –24°C to –18°C) to freeze breast, cervix and skin cancers. He observed tumor contraction and severe decrease of pain ailment in his patients. Device for cryotherapy application was designed, which was also shown during the Great Exhibition in London in 1851 [8,9]. However, the device was cumbersome in use, did not have the capacity to freeze and had a limited range of application. Furthermore, Arnott observed the analgesic effect of cold and recommended using local cryotherapy to anesthetise skin before performing surgeries [8,9].

In 1877, Cailletet (France) and Picet (Switzerland) began the development of systems for cooling gases [10,11]. In 1892, James Dewar (United Kingdom) designed the first thermos, which facilitated storing and transshipment of liquefied gases. Von Linde (Germany) was working on commercial method of liquefying air (1895-1896) [12]. For the first time, liquefied air (–190°C) was clinically used in 1889. The first one to accomplish this was Campbell White (USA), who used a swab, spray or brass roller to apply the air. He proved the usefulness of cryotherapy in the treatment of skin conditions, including systemic lupus erythematosus, herpes zoster, chancroid and dermal papillae [13,14]. In 1907 Whitehouse (USA) described fifteen skin cancer cases treated with cryotherapy (with good results). He set out how to use spray, though the technique was difficult and eventually was abandoned in favor of the swab, which was subject to freezing and then applied to the "sick" place [15].

After that, dry ice (–78.5°C) was introduced to clinical use by William Pusey (USA). The solid form of carbon dioxide was commonly used as a cooling agent. Pusey froze dermal papillae, hemangiomae and lesions developed by systemic lupus erythematosus [16]. Referring to these reports, numerous medical practitioners applied these techniques in dermatology. After 1910 liquefied air was seldom used. However, dry ice was the most popular cryogenic agent at the beginning of 1900. Subsequently, liquefied oxygen (–182,9°C) was brought into clinical practice in 1920. Irving and Turnacliff described good results of the cryotherapy of dermal papillae, lichen planus and other skin conditions. Although liquefied oxygen was easily accessible, its use was limited because of its flammability [17]. In 1948 Kile and Welsh published one of the last reports concerning use of liquefied oxygen in more than 1000 patients, with different

benign skin and mucus membrane lesions, including papillae, angioma and leukoplakia [18].

After World War II, liquefied nitrogen (–196°C) became commercially available. In 1950 technique utilizing nitrogen-soaked swabs was introduced to clinical practice in the cryotherapy of benign skin conditions. Afterwards, it became a regularly applied practice in the treatment of dermal papillae and keratosis among others [19].

Modern cryosurgery began from joint work of Irving Cooper and Arnold Lee. They designed a probe which became a prototype of cryotherapy probes used today. The probe consisted of three coaxially arranged pipes. The inner pipe served as a channel for liquefied nitrogen to the tip of the probe, whereas the space between the inner and middle pipe was utilized as a return path for nitrogen from the tip. The space between middle and outer pipe was vacuum-isolated and had a radiation shield. This made liquefied nitrogen to be distributed to the tip without loss in temperature [20].

In the recent years, cryotherapy became a well-established form of treatment of various benign – as well as malignant – skin and mucus membrane lesions. Hence, new freezing ways are utilized, published on a regular basis.

Patomechanism of low temperatures

All morphological, biochemical and physiological phenomena concomitant to freezing are a direct or indirect consequence of ice-crystal formation [1].

The level of tissue lesion depends on the speed of temperature decrease, the time of exposure of cells to temperature below freezing level and the value of the lowest-achieved temperature in the tissue (also depends on the speed of thawing).

Slow cooling of tissues (from –15° to C –5°C) causes formation of great ice-crystals in extracellular environment. The rise in electrolyte concentration in the remaining liquid changes the gradients of concentration between extra – and intracellular environments. This favors dehydration and cell contraction. Hypertonic environment of the cell interior aids in transition of its components outside cell membrane. Cell dehydration also results in the disintegration of lysosomes [1].

During rapid freezing, formation of extra – and intracellular ice-crystals occurs simultaneously. The number of ice-crystals increases with the pace of freezing, while their size decreases. The presence of crystals in the cell interior causes damage to mitochondria and endoplasmic reticulum. Original disorders, hence, involve plasma membranes. Secondary disorders are relative to lesions occurring within proteins and enzymes. The synthesis of DNA is inhibited as a result. The more rapid the freezing, the greater the number of intracellular ice formations and the greater the damage to the cell [1–4].

Thawing exerts a considerable impact on the survival of cell. Rapid thawing gives cells greater chances of survival in comparison to slow thawing. It is associated with the process of recrystallization, which is the aggregation of small crystals into bigger blocks. Recrystallization is significantly increased during slow thawing of cells. The level of damage rises with the increase of the volume of crystals [1].

During cryotreatment, optimal procedure pertains to rapid thawing of cells, the utilization of long enough cryoapplication time, slow and natural thawing (with speed not exceeding 10°C/minute) and possible repetition of the freezing-thawing cycle, which increases the probability of cell death [1–4].

Current methods used in cryotherapy

As has been mentioned, the last three decades brought upon a rapid development of cryotherapy methods and made it one of the most often used treatment of skin and mucus membrane lesions. Cooling agents – also called cryogenic liquids – are utilized in cryosurgical equipment. They are safe in use, inflammable and chemically inactive. The most common in use are as follows:

- liquefied nitrogen (boiling point at 195,8°C);
- nitrous oxide (boiling point at 88,7°C);
- carbon dioxide (boiling point at 78,9°C [2–4].

The so-called snow paste is also utilized in cryotherapy. It is a mix of dry ice (carbon dioxide in solid form) with alcohol, ether or acetone (in ratio 1:15) [21].

The choice of technique depends on the type of lesion, experience and preference of the surgeon. The following are three methods of treatment [2-4]:

1. *Deep steak* – freezing with nitrogen-soaked tampons. This method can be applied only to benign and shallow lesions. Among all the methods, this one has the greatest risk of transferring infection. The HSV, HPV, HBV and HIV viruses may be transferred, if oozing and bleeding wounds are treated. Preventive measure in this method is to use a new nitrogen-soaked swab each time. It is also recommended to fill separate small vessels for each patient and not decant used-up nitrogen to the main container.
2. *Spot freeze* – spray method where liquefied nitrogen or nitrous oxide are utilized as cooling agents. It is used chiefly in the treatment of focal points of maximally 2 cm in diameter. Spraying from 1 cm distance is advised without moving the gas outlet over the centre of lesion. The action allows for better assessment of the freezing area compared with the method where the apparatus nozzle is moved over exanthema according to check or expanding circles pattern. Bigger focal points should therefore be treated step-by-step, dividing them into steps of approximately 2 cm in diameter. Modifications of the spray method used to limit the frozen field of the tissue are as follows: *open spray method* with the use of shields in the shape of cylinder of various diameters and *closed spray method*, in which the shield forms a closed box. Currently in the spray method with employment of nitrous oxide, additional tampon caps are used, which limit rapid gas exhaust, reducing the risk of uncontrolled freezing of bigger regions and explosive tissue stratification.
3. *Contact method*, also known as application method, is performed with the use of contact cryoapplicators; it utilizes nitrous oxide (liquefied nitrogen and carbon dioxide are used rarely) as a cooling agent. Depending on the set of tips, this method allows the treatment of different type of lesions, starting from point to a few centimeters ones in diameter. Great volume exanthema can be treated with overlapping fields method. The contact method is recommended in treatment of lesions localized in places difficult to access. It allows for precise limitation of frozen field to a planned place, thus ensuring lower risk of damaging the adjacent tissues. Treatment time is longer than in the spray method. Attainment of deeper necrosis favors: putting skin-neutral gel in the place of treatment, cooling the tip after pressing it against skin, anemization of the surrounding area through exerting pressure on the applicator or adding norapinephrine to anesthetisation.

Cryotherapy in gynecology

Cryotherapy was implemented in gynecology in the 1960s to treat cervical intraepithalial neoplasia lesions (CIN). Since that time, dozens of thousands of patients have been treated with the use of this technique, which proved to be predictable and reliable. The side effects and complications were occurring very rarely as well [22].

In gynecological practice, cryotherapy is employed in treatment of cervical, vaginal, endometrial and vulvular lesions. However, the treatment is usually utilized in the treatment of lesions localized in the cervix.

Main recommendations for the cryocoagulation of cervix are the following conditions: benign and premalignant (CIN) lesions.

Benign cervical lesions where cryotherapy may be safely applied involve:

- recurrent inflammations;
- glandular erosion (ectropion).

It has to be remembered at all times that correct diagnosis has to be performed and CIN lesions have to be eliminated before cryocoagulation surgery. The aforementioned diagnosis covers: PAP test and colposcopy, possibly histopathological verification in the form of analysis of drawn samples. The PAP

smear itself is not sensitive enough to guarantee absence of premalignant focal points within the cervix.

In the case of abnormal results of PAP smear, colposcopy is a generally accepted diagnostic test verifying the results of PAP smear and allows for drawing selected samples for histopathological assessment. It is performed to establish localization and the extent of CIN lesions (CIN1-CIN3).

The recommended way for advanced diagnosis and CIN treatment is LEEP/LLETZ (loop electrosurgical excision procedure/large loop of the excisione transformation zone). Though this method is recommended in CIN, cryocoagulation is recommended in benign lesions of the CIN1 type (LSIL – low grade squamous intraepithelial lesions) due to its ease of application, minimal complications and low cost [23-26].

The cryotherapy of CIN lesions

IARC (The International Agency for Research on Cancer) issued a recommendation that cryotherapy may be performed in CIN treatment on condition that:

- lesion is localized within ectocervix, not extending onto vaginal mucosa and/or endocervical mucosa;
- lesion is clearly visible and is no bigger than 2-3 mm of the cervical canal;
- there is no evidence (colposcopy, histopathological examination of samples) for malignant cancer or atypia within the endocervical membrane and the cervical mucosa is normal;
- lesion may be completely covered with available tip for freezing, i.e. of 25 mm in diameter [27].

ASCCP (American Society for Colposcopy and Cervical Pathology) on the basis of its own guidelines confirmed in 2006 that ablation therapy is permissible on condition that:

- colposcopy examination is satisfactory – as a result of endocervix biopsy, one does not find CIN and cancer, and the examined lesion is not recurrent [28];
- cryotherapy is employed in the cases of advanced cervical cancer to increase control of bleeding during conventional therapy [29].

Recommendations of the Polish Gynecological Society from 2009 established that cryocoagulation treatments of CIN lesions can be performed under strict conditions which allow this procedure to be carried out in a safe way [30].

Cryotherapy of CIN lesions is not advised by National Health Service Practice Guidelines because of greater percentage of clinical failures [31].

Benedet and his co-workers set criteria which are essential to increase the number of therapeutic successes in CIN treatment [32]:

- minimal dilation of endocervix within the area of lesion;
- clearly visible lesion margins;
- probe and membrane have to fit closely during cryocoagulation;
- satisfactory formation of "iceball" covering the frozen cervix, extending 3-4 mm outside the lesion margins;
- proper gas pressure during cryotherapy.

Therefore, cryotherapy is safe, useful and cheap. This method should be considered when treating patients with CIN1 and CIN2 lesions, especially in young female patients and nulligravidae, and the abnormal region is limited to one or two quarters of the exocervix [22].

Cryotherapy of vagina

Cryotherapy of vaginal lesions is not popular in treatment of VAIN (vaginal intraepithal neoplasia). However, Townsend published results concerning VAIN treatment implementing cryotherapy methods [33]. Due to possible complication after cryocoagulation, the above-mentioned author recommends only one freezing-thawing cycle, with "iceball" extended over 3 mm around the abnormal lesion, assessed in colposcopy.

If the lesion cannot be covered with the probe completely, it has to be segmented and frozen segment-by-segment, putting "iceballs" on one another.

The efficiency and safety of cryotherapy in treatment of VAIN have not been assessed.

Cryotherapy of vulva

Pathological lesions can be treated with the use of cryotherapy. According to Townsend, VIN lesions (vulvar intraepithelial lesion) of less than 2 cm in diameter may be treated with cryotherapy. He recommends use of nitrous oxide, using only one freezing-thawing cycle and creating "iceball" covering at least a 3 mm membrane proper, assessed with prior colposcopy [34].

The biopsy of lesion and colposcopical assessment are crucial in diagnosis. On the other hand, the CO2 laser and ultrasound therapy are currently the most popular in VIN treatment [35].

Cryocoagulation methods can also be used as palliative treatment in the case of recurrent mycosis fungoides of vulva and perineum. In those examples, cryotherapy involves limitation of bleeding from the tumor, odor and patient's discomfort [34].

Cryotherapy also consists of treatment of small papillae on the vulva. Freezing causes local necrosis. Even though treatment is satisfactory and cold has analgetic effect, the application of this method is restricted by the system, the probe and the whole cold application system. Big papillae or warts are more difficult to treat with cryotherapy and in such cases classical surgical methods are more beneficial [36].

Cryotherapy is also utilized in urethral prolapse. This method is extremely efficient – it causes necrosis around urethra and healing of the prolapsed tissue. The procedure may be performed without anesthetization [37].

Cryotherapy of endometrium (cryoablation)

In order to destroy endometrial lesions, cryoablation is used. Together with cryocoagulation (cited above), both methods have been well-described at the outset of this article. The system utilized in cryoablation consists of: probe of 5,5 mm in diameter, which is put into the cervical cavity through the cervical canal. By application of transabdominal ultrasound probe, the practitioner has to confirm the proper localization of probe for cryoablation and monitor the growth of "iceball" created in the process. The system freezing endometrium lowers the temperature inside the uterus from −110°C to −90°C. Endometrial cryoablation is efficient in treating menorrhagia. In these cases, surgical proceedings may be required in 6-20% of women after endometrial cryoablation [38].

Cryoablation is assessed to be highly-efficient and the advantages of this method are easiness of carrying-out the surgery, low costs and high safety [39].

Contraindications concerning cryotherapy in gynecology

In gynecology, cryotherapy is employed chiefly in treating lesions within the cervix.

Therefore, contraindications concerning cryotherapy within cervix involve [25]:

- vulvitis, vaginitis, cervicitis and/or pelvic inflammatory disease (PID);
- cervical cancer;
- intracervical exposure to diethylstilbestrol (DES);
- menstruation;
- insatisfactory colposcopy;
- post-curettage state of the cervical canal;
- persistent CIN lesions after previous cryocoagulation;
- high CIN level;
- lesion bigger than two quadrants of the shield surface of ectocervix;
- lesion extending on more than 5 mm in diameter to cervical canal;
- low CIN level preceded by the HSIL PAP result;
- discrepancy between histopathological, PAP and colposcopy smear results of the drawn sample.

Complications of cryotherapy in gynecology

Cryotherapy is one of the most acceptable ablation techniques utilized in gynecology. Pain and uteral contractions are concomitant during cervical cryocoagulation [40]. In about 20% patients, directly after cervical cryocoagulation, profuse watery vaginal discharge occurs, lasting 2-3 weeks from treatment. Some of the female patients report occurrence of light spotting, which may last for two weeks.

Later complications of these treatments are rare and involve stenosis of the cervical canal. It refers to 1-4% patients [22].

Serious complications associated with cryotherapy treatment are scarce. Vasovagal syncopes, infections and retention of the outflow of mucus from uterus among other can occur, causing strong pain ailments and hemorrhages. However, there is no medical evidence that cryotherapy has any detrimental influence on fertility or later stages of pregnancy [41]. In many patients after cryocoagulation, slight lesion of anatomical relationships occurs within the cervix. In numerous cases, SCJ (squamocellular junction) is not visible. It is caused by improper choice of probe, e.g. with prolonged component which freezes the endocervix [42].

Effects of cryotherapy in gynecology

The acceptance of cryosurgery by patients is very high, though treatments are becoming less and less popular. It is the consequence of numerous publications of results indicating high failure of the therapy. Cryotherapy has a greater clearance rate than other ablation techniques. It is reported that the rate is approximately 95% [32]. However, research shows that the value of the rate is 85% in reality [43].

Similarly as in other ablation techniques, the development of lesion and CIN have influence on treatment efficiency and clearance rate. Those parameters considerably increase the chance of therapy success and completeness of treatment.

Though long-term analysis with 2839 female patients (treated for CIN using local cryotherapy) indicated negligible risk of minimal residue disease connected with leaving abnormal tissues, but there are reports of cervical cancer after cryotherapeutical treatment of CIN lesions [44,45].

Currently, cryoablation methods applied to the cervix are becoming less popular in comparison to electroresection treatment of cervix utilizing LEEP/LLETZ, which may be used in outpatient conditions and assures sampling for histopathological examination [46].

Conclusion

In the past, carcinogenesis within cervix was a recommendation, above all, to perform surgical conization or cervix excision. Surgical methods are associated with significant increase of complication risk related to medical procedure. Considerable reduction of risk after surgical treatment was observed after the introduction of cryotherapy in the treatment of premalignant lesions of the cervix [23].

One also has to remember that up-to-date cryotherapy methods attain capacity and efficiency of surgical treatment, having a lesser risk of collateral actions, greater percentage of recoveries and quality of patient's life [47].

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