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Hyaluronic acid in gynecology and obstetrics

Anna Łopuszyńska (1), Łukasz Ochyra (1), Mateusz Pawlicki (1), Halina Pieciewicz-Szczęśna (2)

(1) Student Scientific Association at Department of Epidemiology and Clinical Research

Methodology Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland

(2) Department of Epidemiology and Clinical Research Methodology of the Medical

University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland

Corresponding author: Anna Łopuszyńska, lopuszynskaania@gmail.com

ORCID ID:

Anna Łopuszyńska <https://orcid.org/0000-0001-5133-4180>, lopuszynskaania@gmail.com

Łukasz Ochyra <https://orcid.org/0000-0002-8586-3619>, lukaszochyra98@gmail.com

Mateusz Pawlicki <https://orcid.org/0000-0001-8318-6573>, pawlak32@gmail.com

Dr n. med. Halina Pieciewicz-Szczęśna <https://orcid.org/0000-0002-0573-7226>, halpiec@gmail.com

Abstract

Introduction: Hyaluronic acid (HA) is a polysaccharide classified in the group of glycosaminoglycans. Naturally it occurs in the dermis and is responsible for the elasticity of the skin. In medicine, it can be found cross-linked, partially cross-linked or non-cross-linked, which is associated with different densities and the ability to bind water molecules. It (HA) is used in many areas, including ophthalmology, rheumatology, and dermatology. There are many studies and reports, that it can be used in gynecology and obstetrics in various diseases.

Material and methods: The PubMed scientific base was reviewed in 2015-2022 using the keywords hyaluronic acid, gynecology, obstetrics.

Results: Intrauterine adhesions are a complication of various procedures performed in the uterine cavity, from curettage to removal of the septum or uterine fibroids. Numerous studies suggest, that hyaluronic acid may be an effective agent in preventing formation of adhesions. This is important, because they cause problems with getting and / or carrying on a pregnancy. For menopausal women, it may relieve symptoms associated with vaginal atrophy. Indocyanine green is used for intraoperative visualization of neoplastic tissues and used in case of cervical cancer. There are reports, that stating hyaluronic acid can increase stability of this substance, which can improve imaging. In the case of hyaluronic acid in the form of vaginal gel, a beneficial effect on hydration and sexual function of women both after childbirth and after menopause was noticed. There are reports of its use in prevention of ovarian failure after chemotherapy and its positive aspects in assisted reproductive techniques.

Conclusions: Hyaluronic acid can be used in many gynecological and obstetric diseases, positively influencing the life of women in both fertility and sexual areas and also in the group of cancer patients. Therefore, further large, randomized, multicentre studies confirming action of this substance, determining its dose, method and schedule of administration are important.

Keywords: hyaluronic acid, gynecology, obstetrics

Introduction

Hyaluronic acid is a linear glycosaminoglycan, that consisting of repeating units of N-acetyl-D-glucosamine and D-glucuronic acid linked by β -1,3 and β -1,4 glycosidic bonds. Under physiological conditions, it takes the form of a negatively charged sodium salt, which is highly hydrophilic. It has unique physicochemical properties, such as biocompatibility and biodegradability, and is also non-toxic and non-immunogenic [1]. Hyaluronic acid is present in many strains of bacterial strains and ubiquitous in vertebrates, abundant in embryonic tissues and extracellular matrix. Its properties make it an excellent pharmacological agent in, among others, ophthalmology (artificial tears), rheumatology (cartilage regeneration) or dermatology (wound healing) [2]. Due to its effectiveness, its application is sought in other fields, therefore there is more and more research on gynecology and obstetrics.

Material and methods

The literature on the PubMed scientific base was reviewed in 2015-2022 with the use of the following keywords: hyaluronic acid, gynecology, obstetrics.

Results

Intrauterine adhesions

Asherman's syndrome is the presence of intrauterine or cervical adhesions. They may be caused by post-delivery curettage of the uterine cavity, after hysteroscopic surgery, or secondary to adhesiolysis [3]. This syndrome is associated with the risk of hypomenorrhea, amenorrhea, infertility, incorrect placenta implantation, and pregnancy loss. These, in turn, can lead to uterine rupture or postpartum hemorrhage, increasing the risk of pregnancy-related morbidity and mortality [4]. Studies on animal models, both in rats and pigs, suggest, that hyaluronic acid may reduce the incidence of postoperative adhesions [5, 6, 7, 8]. Hence, more and more studies are involving patients with gynecological diseases. In a study by S. Tafti et al. the positive effect of hyaluronic

acid was noticed in 65 patients with a septum of the uterus. Thirty four women after septum removal had hyaluronic acid gel administered into the uterine cavity after surgery, and 31 women from the control group received saline. Two months after the intervention, intrauterine adhesions were assessed using hysteroscopy. In the study group, 4 women (11.8%) had mild adhesions, while in the control group, benign adhesions occurred in 12 women (38.7%) [9]. Carried out by CY. Huang et al. a study on 70 women after hysteroscopic myomectomy showed similar results. Twenty four patients were treated with 10 ml of hyaluronic acid anti-adhesive gel containing 40 mg / ml CHA-P gel (PROTAHERE®), another 23 patients - 10 ml containing 30 mg / ml CHA gel (Hyalobarrier® gel), and 23 patients without additional treatment were assigned to control group. In treated women (47), only 6 (12.8%) developed adhesions, of which 5 were mild and one was moderate according to the AFS scale. In women in the control group (23), as many as 9 (39.1%) patients developed adhesions, including 1 mild, 4 moderate and 4 severe [10]. When comparing hyaluronic acid with an IUD (Intra Uterine Device) in the prevention of intrauterine adhesions in infertile patients after hysteroscopic adhesiolysis, positive results were also obtained. After the removal of adhesions was completed, 3 ml of the HA gel was placed in the uterine cavity in group A (30 patients); 3 ml of HA gel and an intrauterine device were placed in group B (24 patients); and only an intrauterine device was inserted in group C (35 patients). After about a month, a hysteroscopic examination was performed to assess the effects of the treatment. In group A, 86.7% did not develop adhesions, in group B - in 70.8%, and in group C - only in 45.7% of respondents [11]. Also meta-analyzes suggest, that hyaluronic acid may be effective in preventing intrauterine adhesions in intrauterine surgery, however, further reports are needed [12, 13, 14].

Menopause

Vaginal atrophy is a common condition after menopause, caused by a drop in estrogen levels. In approximately 45% of women at this stage of life, atrophy may manifest itself clinically as a syndrome of vaginal dryness, itching, irritation and dyspareunia [15]. It may be associated with a decrease in sex drive, which has a negative impact on the quality of life or the mental state of patients [16]. In order to test the effect of hyaluronic acid on this ailment, a study was carried out on 56 menopausal women with vaginal atrophy. Group A (28 subjects) received a 0.625 mg estrogen conjugated cream and group B received hyaluronic acid vaginal cream (containing 5 mg sodium salt) for 8 weeks. The severity of each symptom of atrophy was assessed by VAS and a four-point scale. The degree of cell maturation and pH after cytological examination were also determined. The results of this study showed, that the symptoms of vaginal atrophy were significantly improved compared to the baseline level in both groups. Dryness, itching, dyspareunia, maturation index, PH, and combined vaginal atrophy symptoms were significantly improved in both groups. Urinary incontinence showed improvement only in the hyaluronic acid group ($P < 0.05$). The total symptom scores ($P < 0.001$) in the hyaluronic acid group were better than in the estrogen group [17]. In 20 menopausal patients, multipoint intravaginal injections of Desirial (cross-linked HA) were performed. A statistically significant increase in the expression of the COL1A1 and COL3A1 genes was observed, which suggests the stimulation of collagen formation ($p = 0.0002$ and $p = 0.0010$, respectively). Based on PGI-I, 19 patients (95%) reported varying degrees of improvement, of which 4 (20%) felt slightly better; 7 (35%) better and 8 (40%) much better. A significant reduction in the symptomatology of vaginal and vulvar atrophy was also observed: dyspareunia, vaginal dryness, vulvar itching, vaginal abrasions, as well as a remarkable improvement in all dimensions of the female sexual function index [18]. There are also reports, that hyaluronic acid gel improves sexual function in menopausal endometrial cancer survivors. It is recommended to use 3-5 times a week, more than in the case of menopausal women without an oncological history (1-2 times a week) [19]. The positive effect of hyaluronic acid on patients with gynecologic cancer after radiotherapy was also found in the review by G. Varytè et al.

Other states

A study by Gustavino C. et al. was conducted to evaluate the effect of intravaginal extended-release hyaluronic acid gel on restoring sexual function in the postpartum period. Eighty four patients were randomized either to receive 0.2% Hydeal-D prolonged release vaginal gel ($n = 43$) every three days for 12 consecutive weeks or to 'wait-and-see' treatment ($n = 42$). Women undergoing treatment had an increased elevation in the total score of the female sexual function index (FSFI) ($+15.1 \pm 11.9$ vs $+6.5 \pm 8.9$, $p < 0.001$) and a higher decrease in vaginal pH (-1.2 ± 0.7 vs -0.2 ± 1.1 ; $p < 0.001$). Moreover, the percentage of vaginal swabs with a maturation index (VMI) > 65 was significantly higher (80.6% vs 35.3%; $p = 0.004$) in patients undergoing local vaginal treatment [21].

Indocyanine green (ICG) is a promising agent for the intraoperative visualization of neoplastic tissues and sentinel lymph nodes in early stage cervical cancer. However, it has poor water solubility and a short half-life. ICG and PLGA were coupled with polyethyleneimine (PEI) to increase stability. Hyaluronic acid (HA) was coated with PEI-PLGA-ICG nanoparticles to target CD44 positive cancer cells. The stability of HINP was confirmed at pH 5.0–8.0. It was shown, that compared to free ICG, HINPs had significantly higher internalization by cervical cancer cells than normal cells ($p < 0.001$) and significantly higher accumulation in tumors ($p < 0.001$) [22].

What is more, hyaluronic acid may also prove effective in assisted reproductive techniques. Moderate-quality data indicate, that when added as an adhesive to embryo transfer, it may improve the percentage of clinical pregnancies and live births [23].

However, in a study on rat models, hyaluronic acid administered prophylactically before chemotherapy protected against damage to the ovaries and their premature failure. It was associated with the promotion of granular cell proliferation and expression of PGRMC1 [24].

Conclusions

Hyaluronic acid can be used in many gynecological and obstetric diseases, positively influencing the life of women, both in the area of fertility, sexual and in the case of patients struggling with cancer. Therefore, further large, randomized, multicentre studies confirming the action of this substance, determining its dose, method and schedule of administration are important.

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