

## HYPERSENSITIVITY POTENTIAL OF GYNECOLOGICAL DEVICES

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Medical devices encompass an extremely wide range of products used in variety of settings for the diagnosis, prevention, monitoring or treatment of illness or disability. Development of medicine and technology causes constantly increasing number of different medical devices with characteristics corresponding to biomaterials and whose application can lead to development of hypersensitivity reactions. Despite the fact that gynecology is a wide field for biomaterials applications, there are no summarized data about hypersensitivity reactions to gynecological devices. This paper gives an overview of hypersensitivity potential and common clinical manifestations of medical devices that are specifically used in gynecology. Summarizing these data is very important for improvement of current medical practice and also for designing and creating new medical devices.

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### Introduction

Medical devices encompass an extremely wide range of products used in variety of settings for diagnosis, prevention, monitoring or treatment of illness or disability (1). Development of medicine and technology causes constantly increasing number of different medical devices, with characteristics corresponding to biomaterials. They are most commonly used in orthopedics, maxillofacial surgery, dentistry and vascular surgery as artificial joints, bone plates, bone cement, artificial ligaments and tendons, dental implants, dental filings, heart valves, vascular grafts, pacemaker leads, catheters, drug delivery systems etc. (2). Developments in medical devices are enhanced rapidly by technological advances in

diverse fields, such as biomaterials science, bioengineering, electronics, software and IT.

Gynecology and obstetrics are dedicated to women's health and also represent a wide field of biomaterials application. Depending on application, biomaterials used in gynecological practice include: biomaterials used in contraception, biomaterials used for prevention and treatment of infertility, biomaterials that are used during labor and delivery, and biomaterials used in gynecologic surgery (3).

Since biomaterials represent foreign bodies, they can lead to various desirable and undesirable reactions when put in contact with a human organism. One group of adverse and undesired reactions to medical devices represents hypersensitivity reactions.

Despite the fact that gynecology is a wide field for biomaterials applications, there are no summarized data about hypersensitivity potential and hypersensitivity reactions to gynecological devices.

The aim of this paper is to give an overview of hypersensitivity potential and common clinical manifestations of medical devices that are specifically used in gynecology. Summarizing these data is very important for improving current medical practice and also for designing and creating new medical devices.

### Biomaterials and hypersensitivity reactions

According to Second Consensus Conference on Definitions of Biomaterials, biomaterials represent a wide group of natural or artificial "materials that are intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function in the body" (4).

In the preclinical safety biomaterials evaluation, examination of biocompatibility is the first and

the most important step in biomaterials testing. It includes physico-chemical characterization of biomaterials, evaluation of physiological environment effects on materials and effects of materials on the environment through different aspects. Biodegradability, reactions between the tissue and biomaterials, cytotoxicity, genotoxicity, mutagenicity etc. can be predicted through different tests validated *in vitro* and *in vivo* (5, 6, 7, 8), while the problem of hypersensitivity prediction in pre-clinical phase of biomaterials testing still persists.

Hypersensitivity reactions are very common and extensive health problems, to which physicians from almost every field of medicine face in everyday practice. They are considered as excessive and inappropriate immune responses to presence of an antigen (9). A precondition for developing hypersensitivity reaction is previous sensitization of organism to a specific antigen. Manifestation of the hypersensitivity reaction occurs after re-contact of the organism to the antigen to which it is sensitized.

Clinical manifestations of hypersensitivity reactions are very diverse and many of them are mild, while others can be severe and life-threatening. They can be confined to a small area of the body, or may affect the entire body (10).

The first step towards successful treatment of allergic reactions is determining allergen that provoked hypersensitivity reaction. If the allergen remains undetected, the therapy is symptomatic, and this could further lead to recurrence or persistence of symptoms and further impairment of health and quality of life.

Depending on generated effectors, molecules and mechanisms of their action, four types of hypersensitivity reactions have been clearly defined so far (Type I—IgE mediated hypersensitivity, Type II—cytotoxic—IgG/IgM mediated hypersensitivity, Type III—immune complex mediated—IgG/IgM immune complex and Type IV—delayed hypersensitivity or cell mediated hypersensitivity) (11), while the fifth type is still a subject of speculations (12). Type I and Type IV are the only two types of hypersensitivity reactions which are described as an undesirable response to biomaterials.

For confirming a diagnosis of hypersensitivity reactions, several validated *in vitro* and *in vivo* tests are used (skin test prick, *in vitro* measurement of specific IgE antibodies, cutaneous patch testing, lymphocyte transformation tests etc.) (13, 14, 15, 16, 17). However, there are no validated *in vitro* or *in vivo* methods for screening sensitizing potential in the pre-clinical phase of biomaterials testing so far. The problem of immunologically-based hypersensitivity reactions non-predictability is related to lack of appropriate experimental models, because beside biomaterial composition, individual physiological characteristics of the host organism are of primary importance for development of hypersensitivity reactions (18).

Predicting hypersensitive potential in pre-clinical phase of biomaterials testing is currently based on clinical experience and previously published data about confirmed hypersensitivity reactions to specific components of medical devices.

## Gynecological devices

In 2015, 64 percent (%) of married women or common-law wives in reproductive age worldwide were using some kind of contraception (UN 2015) (19). Globally, 22.8% of women using contraception use intrauterine devices (IUDs) (20). Its application includes introducing device into uterus, where it persists several years and where its mechanical and/or chemical action provokes contraceptive effect. Today, two types of IUDs are in use: copper-releasing devices and hormone-releasing devices (21). Both types of IUDs consist of different metallic and polymeric components with different hypersensitivity potential (22).

Nickel, cobalt and chromium are the three most common metals that elicit both cutaneous and extracutaneous allergic reactions from chronic internal exposure (23). In copper releasing devices, approximately 99% of metal components represent copper, while other metal components include nickel, silver and gold (24, 25). Sensitizing capacity of copper sulphate is very low (26), but contact dermatitis and urticaria (27, 28) and endometritis and urticaria-angioedema syndrome in women wearing a copper-containing IUDs have been reported (29). It is interesting that allergy to copper sulphate is usually not monovalent, and is commonly associated with other metal allergies, especially with nickel and cobalt sensitization (22); in these reports, only monosensitization to copper was confirmed. Besides the fact that nickel in IUDs is usually present in very small quantity, and that there are still no reports on hypersensitivity to this component of IUDs, clinical experience suggests that its vast hypersensitivity potential should not be ignored (23).

Hormone releasing IUDs are made of a polymer frame with a central reservoir containing levonorgestrel. Levonorgestrel, a highly potent second generation progestin, thickens cervical mucus and suppresses endometrial proliferation (preventing decidualization of the stroma). This creates a hostile environment for sperm survival, inhibiting motility and capacitation with the net effect combining to prevent fertilization (30). Polymeric components of hormone releasing IUDs often include polydimethylsiloxane, polyethylene, polypropylene and colloid silica, while metal components often include barium sulphate, iron oxide, silver and copper (24, 25). Chen et al. 2014 (31), reported a case of acute urticaria associated with Mirena® implantation, while both Pereira and Coker 2003, (32) and Karry et al. 2006 (33) reported cases of acute dermatitis related to application of Mirena®. No one of the authors analyzed sensitization to specific components of this type of IUDs, but according to the literature data all components of Mirena® possess hypersensitivity potential (34, 35, 36, 37).

Permanent tubal sterilization is a method for irreversible contraception and involves laparoscopic tubal ligation or permanent obstruction of fallopian tubes using tubal devices. For permanent obstruction of fallopian tubes, there are two types of devices with different composition commonly used: inserts composed of polyethylene terephthalate, stainless steel and nickel titanium alloy, and inserts com-

posed of cured silicone (38). Application of both types of intrauterine devices is accompanied with numerous desirable and undesirable, but frequently present, side effects. There are several reports on hypersensitivity reaction to nickel in women after permanent tubal sterilization by Essure® (39, 40). On the other side, there are no publications about adverse effects to inserts composed of cured silicone in terms of hypersensitivity reactions, which suggests lower hypersensitivity potential compared to the previous type of inserts.

Today, one of the options for long lasting reversible contraception is application of subdermal implantable devices. All currently available implantable contraceptive devices are based on the same principle: progestogen hormone is released from one or more biologically inert tubes that are placed in subdermal layer of upper inner aspect of the woman's non-dominant arm. Biocompatible polymers or copolymers of polydimethyl/ polymethyl vinyl-siloxanes or ethylvinylacetate are used for making biologically inert tubes, to hold the steroid crystals and control the rate of progestogen hormone release (41). Up to date, there are several reports of hypersensitivity reactions to Nexplanon® (42, 43, 44) in the form of erythaema, oedema and local itching at the site of insertion. Nexplanon® consists of etonogestrel, ethylene vinyl acetate copolymer and barium sulfate, and authors have associated described hypersensitivity reactions to barium sulfate. Hypersensitivity to barium sulphate is extremely rare (2 per million) (43). It is interesting that in most of these cases, before the use of Nexplanon, women used other contraceptive devices (Implanon, Mirena ...). Some authors confirmed specific hypersensitivity reactions to barium-sulphate, while others did not, and at the same time they did not evaluate possibility of hypersensitivity to other components of this implantable device (45).

Induction of labor is artificial initiation of labor before its spontaneous beginning for the purpose of delivery of the feto-placental unit. The rate of labor induction varies by location and institution, but appears to be increasing. If the cervix is unfavorable, cervical ripening is warranted prior to labor induction. Some of current mechanical methods of cervical ripening include application of hygroscopic dilators (e.g. Laminaria, Dilapan-S®, Lamicel etc.). Laminaria is natural dilator made from dried seaweed, while Dilapan-S® and Lamicel, are produced from synthetic hygroscopic material. So far, there have been several reports about severe anaphylactic reactions to laminaria (45, 46, 47) in patients with at least one previous pregnancy terminated with laminaria. The main hypothesis is that the allergen responsible for IgE reactivity with anaphylactic potential was the carbohydrate component of this plant, called laminarin (47). On the other hand, hypersensitivity reactions to hygroscopic dilators were not described in the literature.

Over past decades, the use of synthetic biocompatible materials has become more common in gynecologic surgery. The most common procedures

involving use of synthetic meshes are the abdominal sacrocolpopexy, suburethral sling, retropubic urethropexy, adhesion prevention and pelvic floor hernias treatment (49). Chemical components of synthetic meshes are commonly polypropylene, polytetrafluoroethylene (PTFE), expanded PTFE, polyethylene terephthalate, polyglycolic acid, polyglactin 910 (49), oxidized regenerated cellulose, chemically modified sodium hyaluronate and carboxymethylcellulose (50). Some components of synthetic meshes possess hypersensitivity potential, and it is not surprising that there have been reported cases of localized allergic reactions to meshes (51), oxidized regenerated cellulose (52) and systemic reaction to midurethral sling (53). It is interesting that carboxymethylcellulose is widely used as an additive in non-pharmaceutical and pharmaceutical industry as a disintegrant for capsules, tablets and granules (54, 55), and also as a component of synthetic meshes used in gynecological surgery. While there are no records of hypersensitivity to carboxymethylcellulose as a component in devices used in gynecological surgery, there are several reported cases of severe hypersensitivity reaction to carboxymethylcellulose as a component of other medical devices, which suggests it has a vast hypersensitivity potential (54, 55).

## Conclusion

Gynecology represents a wide field for medical devices application. Whether or not, in what way and to what extent the host will respond to presence of devices, depends on composition of biomaterials applied, the site of application, and also it greatly depends on the physiological characteristics of the host organism. Since it is proved that great number of medical devices components possess hypersensitivity potential, physicians should always be careful when planning application of new medical devices. It is necessary to counsel patients about their personal history of hypersensitivity reactions and previous use of medical devices. According to this information and composition of available medical devices for specific use, physicians should make plans about further treatment. Also, in case of hypersensitivity reaction where personal anamnesis and/or medical documentation reveals use of any type of medical devices, hypersensitivity to biomaterials should be always considered as potential cause.

## Conflict of interest

The authors report no conflict of interest.

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## HIPERSENZITIVNI POTENCIJAL GINEKOLOŠKIH MEDICINSKIH SREDSTAVA

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Medicinska sredstva obuhvataju izuzetno širok spektar proizvoda koji se koriste u cilju postavljanja dijagnoze, prevencije, praćenja i lečenja bolesti ili invaliditeta. Razvoj medicine i tehnologije uzrokuje konstantno povećanje broja i upotrebe različitih medicinskih sredstava čije karakteristike odgovaraju biomaterijalima i koja istovremeno mogu da dovedu do razvoja hipersenzitivnih reakcija. Uprkos činjenici da je ginekologija široko polje primene biomaterijala, nema sumiranih podataka o hipersenzitivnim reakcijama na ginekološka medicinska sredstva. Ovaj rad daje pregled hipersenzitivnog potencijala i uobičajenih kliničkih manifestacija hipersenzitivnih reakcija na medicinska sredstva koja se specifično koriste u ginekologiji. Sumiranje ovih podataka veoma je važno kako za unapređenje trenutne medicinske prakse, tako i za poboljšanje karakteristika postojećih i dizajniranje novih medicinskih sredstava.

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**Ključne reči:** medicinska sredstva, biomaterijali, ginekologija, hipersenzitivne reakcije