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**Case Report / Приказ болесника**

Aleksandra Beleslin[1,*], Olga Mihaljević[1], Branislav Milošević[1,2], Igor Pilić[1,2], Katarina Stefanović[1,2]

# Insulin resistance as a risk factor for endometrial cancer – a case report of fertility-sparing treatment of early-stage endometrial cancer

Инсулинска резистенција као фактор ризика за карцином ендометријума – приказ случаја конзервативног лечења раног стадијума карцинома ендометријума

[1]University Clinical Centre of Serbia, Clinic for Gynaecology and Obstetrics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia



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***Correspondence to:**
Aleksandra BELESLIN
Clinic for Gynaecology and Obstetrics, University Clinical Centre of Serbia**,** Koste Todorovića 26, Belgrade 11000, Serbia
E-mail: **aleksandrabeleslin@gmail.com**

# Insulin resistance as a risk factor for endometrial cancer – a case report of fertility-sparing treatment of early-stage endometrial cancer

## Инсулинска резистенција као фактор ризика за карцином ендометријума – приказ случаја конзервативног лечења раног стадијума карцинома ендометријума

**SUMMARY**

**Introduction** Endometrial cancer is the most common gynecological malignancy and up to a quarter of cases are diagnosed in patients under the age of 45. Important risk factors that create a hyperestrogenic environment are obesity, polycystic ovary syndrome, insulin resistance and type 2 diabetes mellitus. The standard treatment is a classic hysterectomy with bilateral salpingo-oophorectomy, but this treatment leads to the fertility loss, which poses an issue for younger patients who have not completed reproduction. Therefore, in certain cases, hormonal therapy could be used as a treatment for early-stage endometrial adenocarcinoma to preserve fertility.

**Case outline** A 32-year-old female patient with insulin resistance presents with ultrasonographic finding of endometrial polyp and after hysteroscopy and thorough evaluation well-differentiated adenocarcinoma of the endometrium (G1) stage IA was verified. A conservative treatment was carried out with levonorgestrel intrauterine device and GnRH analogue for 6 months. After six months of therapy there were no signs of malignant cells and she conceived naturally. Eventually, the patient delivered a healthy baby.

**Conclusion** Insulin resistance is potentially modifiable risk factor and thus important in cases of fertility preservation treatment. Management could reduce cancer risk and improves reproductive outcomes. Further studies are needed to better understand the impact of insulin resistance treatment on the success of fertility sparing management and rate of recurrence.

**Keywords:** endometrial cancer; oncofertility; fertility-sparing treatment of endometrial cancer; insulin resistance

**САЖЕТАК**

**Увод** Карцином ендометријума је најчешћи гинеколошки малигнитет и скоро четвртина случајева се дијагностикује код пацијенткиња млађих од 45 година. Важни фактори ризика који стварају хиперестрогену средину су гојазност, синдром поликистичних јајника, инсулинска резистенција и дијабетес мелитус типа 2. Стандардни вид лечења је класична хистеректомија са билатералном аднексектомијом, али овај третман доводи до губитка фертилитета, што представља проблем за млађе пацијенткиње које још нису завршиле репродукцију. У одређеним случајевима, могуће је спровести хормонску терапију као вид конзервативног лечења у циљу очувања фертилитета.

**Приказ болесника** Болесници старој 32 године са инсулинском резистенцијом као фактором ризика је урађена хистероскопска полипектомија због ултразвучног налаза ендометријалног полипа. Након хистопатолошке верификације и евалуације дијагностикован је добро диферентован аденокарцином ендометријума стадијум IA. Споведен је конзервативни третман применом интраутериног улошка са левоноргестрелом и *GnRH* аналозима током 6 месеци. С обзиром да је након шест месеци терапије урађена контролна хистероскопија и да хистопатолошки налаз није указао на присуство малигнитета, саветована је трудноћа. Болесница је спонтано затруднела и успешно изнела терминску трудноћу и родила здраво мушко дете.

**Закључак** Инсулинска резистенција је фактор ризика на који можемо да утичемо и тако смањимо ризик за настанак малигнитета, али и побољшамо репродуктивни исход. Његова улога је посебно важна у конзервативном лечењу карцинома ендометријума и зато су потребна додатна истраживања како би се боље разумео утицај лечења инсулинске резистенције на успех конзервативног лечења, али и на појаву рецидива.

**Кључне речи:** карцином ендометријума; онкофертилитет; поштедно лечење ендометријалног карцинома; инсулинска резистенција

## INTRODUCTION

Endometrial cancer (EC) has an incidence of 4.3% and is the most common malignancy of genital tract among Caucasians [1]. Available data suggests that up to a quarter of cases are diagnosed in patients under the age of 45 who have not yet completed reproduction [2]. In these



 

cases, the diagnosis is often made incidentally after hysteroscopy or curettage of the uterine cavity, typically performed as part of an infertility evaluation, due to ultrasound findings of an endometrial polyp or irregular bleeding. Although most histopathological types of EC are considered hormone-sensitive, lifestyle and environmental factors have a significant impact on the development of cancer [3]. Known risk factors for EC include age, race, early menarche, late menopause, nulliparity, and conditions that create a hyperestrogenic environment – such as obesity, polycystic ovary syndrome, insulin resistance (IR), type 2 diabetes mellitus and metabolic syndrome [4]. Metabolic disorders characterized by hyperinsulinemia can impact carcinogenesis through various molecular mechanisms [3]. IR is a fundamental of metabolic syndrome and many studies have linked IR with cancer [5]. Genetic predisposition, such as Lynch syndrome and *BRCA* mutation, is also significant nonmodifiable risk factor [6, 7].

The importance of discussing treatment options for EC among premenopausal women is significant. The standard treatment is a classic hysterectomy with bilateral salpingo-oophorectomy [8]. However, this treatment results in the loss of reproductive function, which poses an issue for younger patients who have not completed reproduction and wish to become pregnant. Thus, in certain cases, hormonal therapy could be used as a treatment of choice for early-stage adenocarcinoma of the endometrium to preserve fertility [9]. This treatment option is also important in terms of quality of life because five-year survival rate of stage 1 EC is 85% [10].

According to the guidelines of the leading European societies for gynecological oncology (European Society of Gynecological Oncology - ESGO), radiotherapy and oncology (European Society for Radiotherapy & Oncology - ESTRO) and pathology (European Society of Pathology - ESP), a conservative treatment approach could be taken for patients under 45 years old with well-differentiated early-stage endometrial adenocarcinoma [9]. Hormonal therapy may include oral progestins, GnRH analogues and an intrauterine device with levonorgestrel. In case of complete response, pregnancy is recommended. After successful pregnancy and completing childbearing, a definitive surgery - standard hysterectomy is advised, as the recurrence rate can be high as 25% [11].

Since EC is strongly associated with modifiable risk factors such as insulin resistance, timely recognition and adequate treatment is important. It could be substantial for EC prevention, success of fertility sparing treatment and lowering recurrence risk. Therefore, the aim of this case is to emphasize the significance of modifiable risk factors in a cancer patient.



 

## CASE REPORT

A 32-year-old female patient, G0P0, presented with ultrasonographic finding of endometrial polyp during regular check-up with regular menstrual cycles and no irregular intermenstrual bleeding. Apart from insulin resistance calculated by HOMA index *(Homeostatic Model Assessment for Insulin Resistance Calculator)*, there was no other comorbidity. The patient was taking only metformin. Body mass index was normal (BMI 20kg/m$^3$). Family history was insignificant for heredity. As a gold standard for endometrial polyp evaluation, hysteroscopy was done. Well-differentiated adenocarcinoma of the endometrium (G1) was verified after hysteroscopy, polypectomy and uterine curettage. Next step was to determine clinical stage according to FIGO classification [12]. An MRI of abdomen and pelvis was performed to rule out myometrial invasion, adnexa involvement and concomitant ovarian tumor. According to pelvic MR, endometrial lining was non-homogeneous with hypovascular lesion of 3 mm within the endometrium without myometrial invasion, the endometrial-myometrial junction was intact. In order to start conservative treatment, it is required to have assessment of two expert pathologists to confirm the diagnosis, which was also done, confirming the diagnosis of endometrioid adenocarcinoma (G1) of endometrium. Standard evaluation for patients preparing for fertility sparing treatment includes a lung X-ray, hormonal and thyroid status check, Pap smear for cervical cancer screening and breast ultrasound. After complete evaluation, an early stage of well-differentiated adenocarcinoma (FIGO stage IA) was diagnosed. Considering type and stage of EC, young age, no children and strong desire to preserve fertility, the Clinical Board approved conservative treatment that involves insertion of levonorgestrel intrauterine device (LNG-IUD) along with GnRH analogue for 6 months. The ultrasound examination after 3 months of therapy was insignificant and no side effects were reported. Menstrual bleeding ceased after 3 months of therapy. Intrauterine device extraction and control hysteroscopy with curettage of uterine cavity was performed after 6 months. The histopathological finding showed no atypia or malignant cells. After two negative biopsies six months apart and three months after last hysteroscopy, the patient became spontaneously pregnant. She had uncomplicated pregnancy and delivered a healthy male child weighing 4500 grams via elective caesarean section. Post-delivery hysteroscopy and curettage revealed no signs of malignancy.

According to the journal's position on issues involving ethical publication, the written consent for publication of this article has been obtained from the patient.



 

## DISCUSSION

The case of a young patient with insulin resistance as a risk factor for endometrial cancer, who was successfully treated conservatively with hormone therapy, is presented.

There are two types of endometrial cancer that differ in their pathogenesis, aggressiveness and prognosis. The far more common type is type I, which is found in almost 90% of cases [8]. It is considered an estrogen-dependent, well-differentiated cancer and is associated with insulin resistance, obesity and type 2 diabetes mellitus [8, 10]. Type 1 occurs more frequently before menopause and during early menopause and has a favourable prognosis [8]. In contrast, type II is estrogen independent, less differentiated, occurs in older patients and carries a higher risk of rapid progression and an unfavourable outcome [3, 13].

The case presented is a type I, well-differentiated carcinoma that occurred in a young patient with no symptoms. The incidence of this malignancy is increasing in women younger than 50 years old [14]. This trend could be linked to today's sedentary lifestyle and the higher incidence of risk factors among the younger population such as obesity, insulin resistance and type 2 diabetes mellitus [15].

The only risk factor noted in this patient was insulin resistance. The influence of insulin resistance on the development of malignancy can be explained by metabolic dysregulation involving inflammatory cytokines, growth factors, various enzymes and free fatty acids [16]. Elevated insulin levels, chronic inflammation and hyperactivation of growth pathways are associated with the development and progression of cancer [17]. An important metabolic pathway activated by insulin and insulin-like growth factor 1 (IGF-1) is the PI3K/AKT/mTOR pathway leading to cell proliferation, invasion, and metastasis [16]. This pathway is also crucial for understanding the effect of treatment with metformin, which is the drug of choice [18]. Metformin leads to the suppression of the mTOR signaling pathway, reducing the concentration of insulin and IGF-1, thus suppressing protein translation and cell proliferation [19]. Although previous studies' results are controversial regarding the reduction of cancer incidence in patients with diabetes treated with metformin, it is still important to recognize risk factors [16, 20]. Timely recognition of risk factors such as insulin resistance, diabetes and obesity and their treatment as part of conservative treatment for early-stage endometrial cancer is valuable because it reduces the effect of insulin and IGF-1 on the endometrium [21]. Insulin is thought to influence estrogen receptor expression thus affecting endometrial proliferation and potential carcinogenesis [22]. This influence may contribute to the better endometrial response to local action of the levonorgestrel intrauterine device. An intrauterine device with levonorgestrel alone or in



 

combination with oral progestins or GnRH analogues are the recommended form for conservative treatment of endometrial adenocarcinoma [9]. The latest guideline from European Society for gynaecological oncology advises levonorgestrel intrauterine device and/or oral progestins as first line treatment [9]. GnRH analogues is an alternative therapy with protective effects on ovarian reserve contributing to improved pregnancy rates and many studies reported satisfactory results with GnRH analogues [9]. Standard protocol in our Institution for conservative treatment of early-stage endometrial cancer consisted of levonorgestrel intrauterine device with GnRH analogues during six months and was introduced over a decade ago [23].

Although no statistical significance was observed in studies examining the effect of insulin resistance on mortality after hysterectomy in endometrial cancer, the effect of insulin resistance on the outcome of conservative treatment could be more significant because the uterus remains and endometrium could still alter malignantly [20]. This is supported by the results of the study by Li et al., who showed that the time to relapse in patients with endometrial cancer treated conservatively is significantly shorter in those with insulin resistance compared to those without [21]. Also, considering the normal values of the body mass index in our patient, the influence of obesity and peripheral conversion of estrogen on the endometrium and tumor formation is ruled out.

Furthermore, recognizing risk factors is important because they affect fertility, fertilization and could complicate pregnancy and the aim of conservative treatment of endometrial cancer is to achieve a successful pregnancy [9]. Insulin resistance is linked to recurrent miscarriages, gestational diabetes and gestational hypertension [19, 24, 25]. This impacts the fetus leading to macrosomia and the need for operative delivery, which carries its own risks [25]. The best way to prevent these complications is to establish proper glycoregulation before conception [19]. Despite our patient's normal OGTT during pregnancy, the newborn weighted 4500 grams, exceeding the 90th percentile for that gestational age [26].

Nevertheless, in terms of generally high survival rate for early-stage of endometrial cancer the aforementioned risk factors are associated with lifelong cardiovascular morbidity and mortality [10]. This should be noted especially in cases of definitive radical treatment where protective estrogen effect is lost.



 

## CONCLUSION

Insulin resistance is recognized as significant and potentially modifiable risk factor for endometrial cancer. Its role could be particularly important in cases of fertility preservation treatment. Early identification and management of metabolic abnormalities could reduce cancer risk, but also improves reproductive outcomes. Multidisciplinary approach including endocrinologist is essential to optimize cancer treatment and reproductive potential. Further studies are needed to better understand the impact of insulin resistance treatment on success of fertility sparing management and rate of recurrence.

**Conflict of interest:** None declared.



 

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