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POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

**ISSN:** 0017-0011

**e-ISSN:** 2543-6767

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**DOI:** 10.5603/gpl.102573

**Article type:** Review paper

**Submitted:** 2024-09-13

**Accepted:** 2024-10-24

**Published online:** 2025-01-15

REVIEW PAPER / GYNECOLOGY

# Gynecological complications and treatment strategies in patients after hematopoietic stem cell transplantation

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## ABSTRACT

In women after hematopoietic stem cell transplantation (HSCT), complications associated with the original disease and therapies used both before and after transplantation often occur, which significantly affects their quality of life. The most common gynaecological complications include secondary cancers, premature ovarian insufficiency (POI), infertility and chronic graft-versus-host disease (cGVHD). Cervical cancer is the most common secondary genital cancer in patients after HSCT. Regular screening and vaccination against HPV (Human Papillomavirus) can significantly reduce the risk for its occurrence. The specific complication after allogeneic hematopoietic stem cell transplantation is graft-versus-host disease (GVHD), the genital form of which can lead to labial and vaginal adhesions, significantly reducing the women's quality of life. The basis of treatment is local steroid therapy and immunosuppression. A consequence of chemotherapy and radiation therapy may be damage to the gonads leading to premature ovarian insufficiency and the onset of menopause symptoms. The basis of treatment is systemic hormone therapy used until middle age when natural menopause is reached. Women after HSCT who are of reproductive age also suffer from infertility. An important role of the doctor is to educate patients about the risk for infertility and to suggest appropriate methods of preserving fertility before starting treatment. The recommended procedure for fertility preservation is cryopreservation of embryos or oocytes. The

freezing and retransplantation of ovarian tissue is becoming an increasingly popular method of fertility protection.
Preventive examinations and early detection and treatment of gynaecological complications significantly improve the comfort of life and health of women after HSCT.

**Keywords:** hematopoietic stem cell transplantation; graft vs host disease; primary ovarian insufficiency; hormone replacement therapy

## INTRODUCTION

Hematopoietic stem cell transplantation involves the removal of abnormal hematopoietic stem cells through radio- and chemotherapy in the conditioning process, followed by transplantation of autologous stem cells or from a donor to renew the hematopoietic and immune systems. The material for transplantation is obtained from bone marrow, peripheral blood or cord blood. The first successful bone marrow transplantation in Poland was performed in 1984 by Prof. Wiesław Jedrzejczak [1], and over the next 40 years the number has been constantly growing [1, 2]. According to Poltransplant data, in 2022 19 transplantation centres in Poland performed 1135 autotransplantations of hematopoietic cells and 798 allogeneic transplants [2]. The most common indications for autologous transplantation are multiple myeloma (59%), non-Hodgkin's lymphoma (21%) and Hodgkin's lymphoma (13%). Most allogeneic transplants were performed due to acute myeloid leukaemia [2]. The ever-increasing number of transplants and the increase in survival after HSCT result in an increasing number of patients, of whom approximately 45% are women. It is observed that in this group of patients' complications often occur, resulting from both the previous disease, as well as the treatments used before transplantation or after its completion. These complications are particularly pronounced among women of reproductive age, affecting their quality of life. Aggressive cytostatic treatment and chronic immunosuppression can lead to graft-versus-host disease, HPV-related dysplasia or cervical cancer, along with premature menopause and infertility [3, 11]. Preventive gynaecological care, early detection and treatment of complications are key elements in improving quality of life as well as reducing morbidity and mortality among women after HSCT [11].

## SECONDARY CANCERS

Patients with hematopoietic cell transplantation are at increased risk for secondary cancers, including cervical cancer (4). The main risk factors for the development of these cancers are the occurrence of chronic GVHD disease and long-term immunosuppression [6, 7].

A 2009 study by Rizzo et al. [5], which included more than 28000 people following allogeneic bone marrow transplantation, found that patients with chronic GVHD had a 5-fold higher risk for squamous cell carcinoma, including cervical cancer, compared to the general population. Human Papillomavirus is thought to be responsible for the development of more than 90% of cervical cancers and about 70% of vulvar and vaginal cancers. Immunocompromised individuals, including those following bone marrow transplantation, are at a higher risk for activation of latent forms of the virus resulting in the development of dysplasia and cervical cancers [8].

In a study published in 2008, Savani et al. [9] showed an increased incidence of cervical dysplasia among women after bone marrow transplantation compared to the period before transplantation. Of the 35 women who underwent allogeneic bone marrow transplantation, more than 40% developed cervical dysplasia. Among abnormal cytologies, more than a third were associated with HPV infection [20% were high-grade squamous intraepithelial lesion (HSIL), and 14% low-grade squamous intraepithelial lesion (LSIL)].

The authors also showed that use of immunosuppressive therapy to treat chronic GVHD for longer than 3 years is associated with a 4.6-fold higher risk for HPV-related cervical dysplasia [9]. In an Italian 2014 study of 54 women following allogeneic bone marrow transplantation, the rate of abnormal cytology results was 24.1% [7.4% atypical squamous cells of undetermined significance (ASCUS), 11.1% LSIL and 5.6% atypical squamous cells, in which a high-grade squamous intraepithelial lesion (ASC-H)] could not be excluded. Of the three patients diagnosed with ASC-H, two were subject to further histological diagnostics (cervical biopsy and conisation), which showed no dysplastic changes in the cervix. The third patient underwent a co-test, which was negative. It was reported that in all three patients with ASC-H, busulfan compounds were used in the conditioning process. The authors emphasized that cellular atypia occurring after treatment with busulfan may lead to false positive cytology results, and thus unnecessary colposcopy and cervical biopsy [10]. In recent years, HPV vaccination has been proven to reduce the risk for gonorrhoea and cervical cancer in the healthy female population and is now recommended among adolescents and young adults [11, 13, 14, 16]. In 2018, the Food and Drug Administration (FDA) approved the extension of the use of 9-valent Gardasil vaccine to the age of 45 [17]. A 2020 study that included 64 women of reproductive age vaccinated against HPV after bone marrow transplantation showed a strong immune response against the virus, similar to the population of healthy women. The recommended time to start HPV vaccination is 6-12 months after transplantation. It is recommended to vaccinate all patients after allogeneic hematopoietic cell transplantation (allo-HCT), including those who have been vaccinated before transplantation. Three doses of the vaccine should be given in a 0-, 2-, 6-month schedule [11, 13, 14, 16]. HPV vaccines are well tolerated by

hematopoietic cell transplant recipients and do not exacerbate the symptoms of GVHD. The side effects of vaccination are usually mild and limited in time [15].

Annual screening for dysplasia and cervical cancer is recommended in patients with cGVHD or chronic immunosuppression. In case of abnormal cytology results, the patient should be referred for colposcopy with possible cervical disc and cervical canal biopsy [18].

## GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease is one of the most common complications occurring after allogeneic hematopoietic cell transplantation. It is usually associated with a significant reduction in patients' quality of life and is the main cause of late mortality not associated with the recurrence of the underlying disease [19, 20]. The pathophysiology of chronic GVHD results from an immune response in which transplanted immune cells, mainly T lymphocytes, recognize recipient tissues as foreign and attack them [21]. The most common symptoms of genital GVHD include dyspareunia, dysuria, itching, burning, dryness, abnormal vaginal discharge [23–25]. The incidence of this complication in the anogenital area according to various authors varies between 6 and 88% [20, 23–25]. The diagnosis and treatment of chronic GVHD of the genital organs faces difficulties due to insufficient reporting of symptoms, incorrect treatment directed at infectious or menopause aetiology, and the presence of a serious disease interfering with referral to a gynaecologist [20].

A higher frequency and severity of cGVHD was observed among patients after transplantation of peripheral blood stem cells compared to bone marrow [22]. A risk factor for the development of genital cGVHD is its occurrence in other organs, with the most common location in the mouth, skin, eyes, lungs and liver [23, 24]. The diagnosis of GVHD of genital organs is based on the evaluation of clinical symptoms and the results of a physical examination. In differential diagnosis, oestrogen deficiency and infections should be considered [25]. Although the symptoms of this disease may be misdiagnosed as genital atrophy during premature ovarian failure after HSCT, the differences in physical examination are significant. In the gynaecological examination of patients with genital organ cGVHD, redness, ulcers, erosion, fissures and labial adhesions, loss of the architecture of the labia and clitoris, vaginal occlusion are often observed [23–25]. A diagnostic problem may also be pain and redness of the vestibule of the vagina, which are characteristic of both vulvodynia and the mild form of cGVHD. The presence of vulvodynia before transplantation may be helpful to distinguish these two disease entities [26]. The frequent asymptomatic course of genital cGVHD may cause a delay in diagnosis [27] leading to severe complications in the form of vaginal stenoses that prevent gynaecological examination and cytology and in menstrual women to the formation of hematometra or hematocolpos [27–29]. In 2014, the National Institute of Health proposed a 4-degree division of genital cGVHD according to the severity of symptoms [30].

Spiryda et al. [31] showed that the severity of symptoms in the genital area does not correlate with the severity of GVHD in other organs. Histopathological diagnosis is not necessary in the case of symptoms typical of the genital form of cGVHD, i.e. changes similar to lichen planus or sclerosus, and vaginal adhesions or stenosis. A biopsy can be helpful when there are non-characteristic symptoms of the disease in the form of ulcers, fissures, erosion [30, 33]. The conclusion drawn in the work of da Silva Lara et al. [32] indicates the usefulness of biopsies in distinguishing GVHD from secondary hypoestrogenism.

Early diagnosis of GVHD and the implementation of appropriate treatment allows severe complications in the form of narrowing and occlusion of the vagina to be avoided [23, 29]. Gynaecological examination is recommended for all female patients after bone marrow transplantation, even those without symptoms, especially if signs of chronic GVHD occur in the mouth [30]. In post-menopausal women or those experiencing symptoms of hypoestrogenism as a result of premature ovarian failure, local or systemic oestrogen therapy is recommended. This is to avoid delay in the diagnosis of GVHD of the genital organs [25, 29, 34]. To prevent skin irritation of the vulva, it is advisable to rinse with warm water, as well as avoid perfumed washing agents and synthetic and tight underwear [34, 35]. Moisturising creams and lubricants can help relieve symptoms [35]. Topical steroid therapy (clobetasol, betamethasone) and immunosuppression (cyclosporine, tacrolimus) is the basis for GVHD treatment [25, 29, 31, 34, 35]. Frey et al. [36] propose the use of clobetasol propionate ointment once daily at night for 4 weeks in the case of newly diagnosed genital cGVHD or its exacerbation. In the case of progressive disease that does not respond to topical treatment, the inclusion of systemic immunosuppression should be considered [25, 34]. Severe complications in the form of partial or complete vaginal occlusion require surgical treatment. To avoid them, patients should be encouraged to have regular intercourse and use vaginal dilators [34, 35].

## PRIMARY OVARIAN INSUFFICIENCY AND INFERTILITY

Women of reproductive age who undergo chemo- or radiotherapy before HSCT are at increased risk for gonadal damage and infertility [36–38]. Primary ovarian insufficiency is a name for hypogonadotropic hypogonadism, occurring in women before the age of 40. According to the recommendations of the European Society of Human Reproduction and Embryology (ESHRE), POI is characterized by amenorrhea for at least 4 months and elevated follicle stimulating hormone (FSH) levels above 25 mIU/L on two occasions a month apart [39]. Risk factors for ovarian function loss in hematopoietic cell recipients are older age at the time of transplantation, higher doses of alkylating drugs and whole-body radiotherapy during conditioning [37, 40, 41]. Of the chemotherapy drugs, busulfan was found to be the most gonadotoxic, leading to ovarian failure in

45–89% of patients [37, 40, 41]. A study by Pascale Jadoul et al. [37] showed that the best-preserved ovarian function is achieved when transplantation occurs before the age of 10 and treatment does not include whole-body irradiation. Patients who have undergone hematopoietic cell transplantation during the pre-pubertal period are at high risk for uterine damage due to irradiation of the pelvic area during conditioning. It has been shown that radiation doses between 14 and 30 Gy can cause a reduction in uterine growth and abnormal blood flow through the muscle [42, 43]. Women with premature ovarian insufficiency experience amenorrhea and severe menopausal symptoms such as hot flashes, night sweats, mood swings, sleep disorders, vaginal dryness or dyspareunia [39, 44]. Oestrogen deficiency in young girls may prevent the development of secondary sex characteristics, increase the risk for cardiovascular disease and osteoporosis, and impair cognitive function [34, 39]. The basis for the treatment of women diagnosed with POI is systemic hormone therapy, which should be applied until the average age of natural menopause, i.e. around 51 years of age, regardless of the occurrence of symptoms [34, 38, 45]. A study by P. Piccioni et al. [45] showed that despite the recommendations for each HSCT patient to be given hormone therapy, only half received treatment. The main reason hormones may not be offered are contraindications to the use of oestrogens resulting from complications of the original treatment — liver failure, severe cholestasis in the course of chronic GVHD or recurrence of the underlying disease. However, nearly 30% of women refuse hormone therapy due to fear of secondary cancers [45]. Oestrogen supplementation is highly effective in relieving vasomotor symptoms, and helps maintain normal bone mass levels, protecting against later fractures [45]. The transdermal supply of the hormone reduces the risk for thromboembolic events in women with risk factors, compared to oral therapy. In women with a preserved uterus, gestagens should be additionally administered in a continuous or sequential regimen to protect the endometrium against hyperplasia and cancer [45–47]. Selective serotonin reuptake inhibitors may be an alternative for women with POF who have contraindications to the use of oestrogens, eliminating vasomotor symptoms and improving sleep quality [48]. Selective oestrogen receptor modulators such as tamoxifen or raloxifene may be used to protect women with oestrogen deficiency from bone loss. At the same time, these drugs may increase urogenital atrophy and vasomotor symptoms [49]. There are no studies on the efficacy of phytoestrogens in addressing menopausal symptoms and therefore these preparations should not be routinely recommended for women after HSCT.

The preservation of fertility is a very important issue for women after hematopoietic cell transplantation. It is important to educate girls and young women who require transplantation about the significant risk for infertility associated with therapy and to propose appropriate methods of fertility preservation. Results regarding the incidence of pregnancy after HSCT in many studies are mixed but remain relatively low [37, 38, 50]. In a multi-centre analysis from 2001 [38], 19 412

post-allo-HCT and 17 950 post-auto-HCT retrospective assessments were performed, and 312 pregnancies were reported among 232 (0,6%) of patients or partners of patients after stem cell transplantation. Sanders et al. [50] reported 72 pregnancies in 41 patients among 790 women undergoing bone marrow transplantation (5%). Pregnancy complications were significantly more common among allogeneic transplant patients than autologous ones and were mainly associated with pre-term delivery and low birth weight of children [38, 50]. The cause of these complications is considered incorrect implantation caused by whole-body irradiation and the occurrence of graft-versus-host disease in the uterus [38].

Discussion with patients about the possibility of preserving fertility should take place as early as possible, preferably before starting gonadotoxic therapy. Women who express a wish to have children in the future should be directed to assisted infertility treatment centres. The recommended method of fertility preservation is cryopreservation of embryos or oocytes [51]. These procedures require prior ovarian stimulation, which may cause a delay in the initiation of oncological treatment. A lack of a partner or the woman's philosophical or religious objections may be further contraindications to embryo freezing [51]. Freezing and retransplantation of ovarian tissue is becoming an increasingly popular method of preserving fertility [52, 53]. Due to the increasing amount of evidence for its effectiveness, this method is no longer considered a medical experiment [53]. This procedure does not require prior ovarian stimulation, thereby avoiding delay in the treatment of the underlying disease. In addition, this method does not require sexual maturity and may be the only option to preserve fertility for girls in the pre-pubertal period. A limitation of this method in patients with haematologic cancers is the theoretical risk for retransplantation of cancer cells in the collected fragment of the ovary. No such case has been reported in studies conducted so far [54]. According to the recommendations of the Working Group on the Preservation of Fertility in Oncology Patients (GROF) of the Polish Society of Oncology, ovarian tissue should be collected in this group of women only after induction chemotherapy and complete remission of the cancer in the blood [52].

**SUMMARY**

As the number of young women undergoing hematopoietic cell transplantation increases, the extent of gynaecological complications faced by this group of patients is becoming increasingly apparent. To improve the quality of care, it is necessary to disseminate knowledge about these problems among doctors and to regularly perform specialist gynaecological examinations. Early detection of pathological changes and the implementation of appropriate treatment significantly improves the quality of life of patients. Effective care of a patient after a hematopoietic cell transplant requires close cooperation of doctors of various specialisations, including primarily haematologists,

oncologists, gynaecologists and transplantologists. This integrated medical practice enables comprehensive monitoring of the patient's health and an individual approach to their health needs.

## Article information and declarations

### *Author contributions*

KW conceptualized and drafted the manuscript. MR conducted the literature search and data collection. KW and MRJ analyzed the findings and wrote the manuscript. BP and MW critically reviewed and revised the manuscript for intellectual content. All authors reviewed and approved the final version of the manuscript.


### *Funding*

The authors received no financial support for the research.


### *Conflict of interest*

All authors declare that they have no conflicts of interest.

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