Gynecological issues after organ transplantation

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Abstract

Organ transplantation has become universally accepted treatment of end-stage organ failure. The main problem focuses on prevention the graft from rejection with the use of immunosuppressive agents. High incidence of infections is the most frequent adverse effect of immunosuppressive therapy. Symptoms of inflammation are often reduced in immunosuppressed patients. All invasive diagnostic and therapeutic procedures should be associated with the increase in dose of steroids and prophylactic antibiotics. Ovarian and menstrual function is usually restored in transplanted women. Function of the hypothalamus-pituitary-ovary axis in transplant women is believed to be normal. Most common abnormal uterine bleedings in graft recipients are: prolonged or profuse menstruations and intermenstrual bleeding or spotting. Among the underlying diseases there are lesions of the uterus (fibroids, endometrial or cervical polyps), infections of sex organs or hormonal disturbances. Higher rate of endometrial hyperplasia (without atypia) is reported in renal graft recipients. Organ transplantation results in the restored fertility thus effective family planning method is necessary in women of reproductive age who do not want to conceive. Vaginal diaphragms are not advised and intrauterine device are contraindicated. Observational studies indicate for safety and high rate of acceptance of oral or transdermal hormonal contraception in transplanted women. Over ten-year experiences of HRT administration in graft recipients have proved the benefits of the therapy. Patients after organ transplantation have three to four-fold increased incidence of malignancy compared with general population. All transplant women must undergo regular gynecological screening for premalignant and malignant lesions of sex organs and breast.

INTRODUCTION

Organ transplantation has become universally accepted treatment of end-stage organ failure. Dynamic progress in clinical transplant medicine made in the last decades of twentieth century enabled to save many lives and improved life quality of patients with end-stage organ failure. Grafts that are most frequently transplanted are: kidney, liver, heart, pancreas-kidney and recently lungs, lungs-heart and intestine. Continuous progress in operative techniques, tissue storage and post-operative management is accompanied with the improved results of transplant medicine worldwide.

The main problem focuses on prevention the graft from rejection with the use of immunosuppressive agents. Common practice is to use a combination of immunosuppressive drugs with

Abbreviations & Units:

PAP smear – Pappanicolau smear
BSR   – blood sedimentation rate
IUD   – intrauterine device
WBC   – White Blood Count
CsA   – Cyclosporine A
Aza   – Azathioprine
Tac   – Tacrolimus
MMF   – mycophenolan mophetil
GS   – glicocoticosteriods
Rapa   – Rapamycine
HRT   – hormonal replacement therapy

different action mechanisms what improves immuno-suppressive efficacy and throughout the decrease in doses, diminishes the adverse effects of the treatment. The immunosuppressive regimens most often used nowadays are:

1. Cyclosporine A (CaA) or tacrolimus (Tac) + azathiophrine (Aza) or mycophenolate mofetil (MMF) +/- glicocorticosteroids (GS)
2. CsA or Tac + rapamycine (Rapa) +/- GS
3. Rapa + MMF +/- GS
4. CsA lub Tac + Rapa +/-MMF

Highest level of immunosuppression is necessary in early postoperative period, after three to six months low maintenance levels are administered or the number of immunosuppressive agents is reduced. Except preventing from graft rejection immunosuppressive therapy is always associated with the increased risk of infections, malignancy and potential toxicity for the recipient's tissues (Penn 1979, Penn 1996, Tolkoff-Rubin & Rubin 1994).

The therapeutic blood concentration of the drug necessary to maintain the graft function without the toxic symptoms or infectious complications is known as "therapeutic_window". The therapeutic window of immunosuppressive agents, however, is usually narrow and overlap the toxic effects. Among the most common side effects of immunosuppression are: neutotoxicity, arterial hypertension, hyperlipidemia, disturbed glucose tolerance, myelosuppresion and liver toxicity (EBPG Expert Group 2002).

MOST COMMON GYNECOLOGICAL PROBLEMS IN TRANSPLANT WOMEN

1. Infections

High incidence of infections is the most frequent adverse effect of immunosuppressive therapy (Tolkoff-Rubin and Rubin 1994). The environment, the graft, the endogenous flora or latent viruses may become the source of infection. Symptoms of inflammation are often reduced in immunosuppressed patients and in some cases cryptogenic course of the disease can lead to life-threatening states. Only mild stomach aches with-out rebound tenderness may associate the diffuse peritonitis. Sometimes the only symptom of sepsis is slight temperature increase while the laboratory tests (white blood count – WBC, C-reactive protein and blood sedimentation rate – BSR) remain in normal limits. Different tissues and vital organ affection and generalization of the inflammatory process can appear rapidly. After the acute phase of the disease, chronic or recurrent states are often observed. The prognosis depends on early diagnosis followed by early onset of accurate treatment. Most infections can be detected with regular microbiologic screening in asymptomatic patients and with further examinations performed dependent on the clinical state. Different kinds of pharmacological prophylaxis as well as active and passive immunization are employed to prevent infections in graft recipients. All invasive diagnostic and therapeutic procedures must strictly follow sanitary regulations. The increase in dose of steroids before the procedure as well as prophylactic antibiotics are mandatory. In case of surgical procedures antibiotics, mainly II generation cephalosporin, sometimes combined with metronidazole, should be taken for at least seven days. In post-operative period immunosuppressive agents can be administered orally or, in particular cases intravenously, as most of them have intravenous counterparts (EBPG Expert Group 2002).

2. Hormonal disturbances

Successful organ transplantation performed after long-term organ failure results in the restoration of endocrine function of the organism. Ovarian and menstrual function is usually restored in renal transplanted women within an average of six months (Lessan-Pezeshki *et al.* 2004, Phocas *et al.* 1992) and in liver recipients within nine-ten months (Cundy *et al.* 1990, Mass *et al.* 1996, Parolin *et al.* 2004). Serum levels of gonadotropins and prolactine after kidney transplantation are similar to those observed in general population, hence function of the hypothalamus-pituitary-ovary axis in transplant women is believed to be normal. The rate of ovulatory cycles in regularly menstruated renal recipients is similar to the rate in healthy women, however, a significant part (40%) of the patients develop the defect of lutheal function (Lessan-Pezeshki *et al.* 2004, Mattix Kramer *et al.* 2003). There are reports of the decreased levels of testosterone due to its disturbed production in the suprarenal glands associated with the use of steroids in immunosuppressive regimen. Besides higher levels of estradiol are reported in renal graft recipients compared to healthy women (Phocas *et al.* 1992). Notably, hirsutism observed in some transplant women is not associated with androgen defect but with the direct influence of cyclosporine A on the hair follicles.

Abnormal uterine bleedings in graft recipients are relatively common. These are prolonged or profuse menstruations and intermenstrual bleeding or spotting. Among the underlying diseases there are lesions of the uterus (fibroids, endometrial or cervical polyps),

infections of sex organs or hormonal disturbances associated with the dysfunction of the hypothalamus-piruitary-ovary axix or failure of organs involved in sex hormones metabolism (Jabiry-Zieniewicz *et al.* 2006, Mass *et al.* 1996, Mattix Kramer *et al.* 2003). Sometimes abnormal uterine bleeding may be the symptom of endometrial hyperplasia or cancer (Bobrowska *et al.* 2005, Bobrowska *et al.* 2007, Penn 1986). In all cases perceptive diagnostic process is mandatory. Imaging, laboratory and sometimes hormonal examinations should be employed and the diagnosis confirmed with endometrial sampling.

3. Endometrial hyperplasia

Women after renal transplantation, as mentioned above, often develop abnormal uterine bleedings. In reflect of the increased risk of malignancy in immunosuppressed patients, in order to exclude cancer development, dilatation and curettage (D&C) and histopathological evaluation of the removed tissues is recommended in diagnostic process. Higher rate of endometrial hyperplasia (without atypia) is reported in renal graft recipients with abnormal uterine bleedings compared to general population (Bobrowska *et al.* 2006, Bobrowska *et al.* 2007). Similar tendency is observed in liver graft recipients (unpublished data). Hyperplasia is believed to be associated with the increased estrogen stimulation and is usually successfully treated with progestogens. Left untreated carries the risk of endometrial cancer development. Early detection and proper treatment may contribute to diminish the rate of endometrial pathologies and invasive diagnostic procedures, and consequently protect the patients from malignancy.

4. Contraception

Organ transplantation results in the restored fertility of graft recipients thus effective family planning method is necessary in women who do not want to conceive. The problem seems to be complex and difficult since there are a number of contraindications for particular contraceptive methods in graft recipients. Intermittent sexual intercourse is universally practiced, not only in that group of patients, but its efficacy is so low that many authors do not even consider intermittent intercourse as a contraceptive methods. Vaginal diaphragms are not advised because of the two-fold increased frequency of urinary tract infections and low efficacy of the method (Fihn *et al.* 1985). Surgical procedures (tubal ligation or vasoligation) are believed to be highly effective and safe, however are prohibited in some countries, including Poland.

The use of intrauterine device (IUD) in graft recipients should be limited because immunosuppressive therapy may increase the risk of inflammatory complications, and moreover, decrease the IUD-related endometrial "pseudo inflammatory" effect, consequently leading to its disturbed contraceptive efficacy (Lessan-Pezeshki *et al.* 2004, Neyhart 1998). There are reports, however, of successful use of the levonorgestrel-releasing intrauterine system in renal transplant patients, with the additional inhibitory effect on uterine myomas growth and associated menorrhagia (Yoke-Fai & Kuldip 1999).

Condoms with spermicides prevent from sexually transmitted diseases and can be the excellent choice for women who do not lead regular sexual life or have many partners, the patients must be informed, however, about their relatively low efficacy (Neyhart 1998). The failure rate for condoms is estimated to reach 12%, noteworthy, it may decrease to 2% for condoms with spermicides when used consistently (Speroff & Darney 1996).

Hormonal contraception is known to be the most effective contraceptive method, that should be employed particularly in women with regular intercourses (Speroff & Darney 1996). There are, however, relative contraindications for hormonal contraception in graft recipients, mainly frequently coexisting arterial hypertension and disturbed liver function, especially in patients under Cyclosporine A (Riely 2001). High doses of progestogen alone, used as implants or intramuscular injections, may lead to gross menstrual disturbances, weigh gain and impaired liver function and therefore are difficult to accept. The most popular and best known hormonal contraceptive method is combined contraceptive pill. It additionally regulates the rhythm and intensification of the bleeding as well as protects from ovarian cysts development. The progress that has been made since the invention of the pill 50 years ago, seen in the diminished dose of 17-B ethinyl estradiol (not more than 35 mcg) and invention of new progestogens, led to the decrease in risk of thromboembolic complications and limitation of contraindication for that effective and comfortable contraceptive method (Speroff & Darney 1996). The main side effect of combined hormonal contraceptives, even low-dose pills, is several-fold increase of vein thrombosis. Women with arterial hypertension are observed to have increased risk of stroke and myocardial infarction, however, the increase seems to be only slight in patients with good hypertension control (Neyhart 1998). On the other hand, according to a number of case-control and cohort studies, contraceptive pills intake has been associated with significantly lower rate of endometrial and ovarian cancers (Speroff & Darney 1996). It is worth to remember that oral contraception may affect renal sodium resorption leading to increased filtration and blood pressure, followed by increased proteinuria and microalbuminuria.

Regular surveillance of all women under hormonal contraception for any adverse affects or appearing contraindications is mandatory. The new transdermal way of hormone administration has enabled to employ that method in patients with impaired liver function. Observational studies indicate for safety and high rate of acceptance of oral or transdermal hormonal contracep-

tion in transplanted women (Jabiry-Zieniewicz *et al.* 2007, Pietrzak *et al.* 2007, Pietrzak *et al.* 2006).

5. Hormonal replacement therapy

The number of women after organ transplantation, who may benefit from hormonal replacement therapy (HRT), is observed to increase gradually (Burger *et al.* 2004). In a subgroup of graft recipients with a long history of organ failure premature menopause may occur, older patients more often experience menstrual irregularities and earlier cessation of menses (Appelberg *et al.* 1998). Long-term immunosuppressive treatment with corticosteroids in graft recipients is associated with an increased risk of osteoporosis. Besides, the population of menopausal transplanted women increases due to constant growth of mean age of patients. Over ten-year experiences of HRT administration in graft recipients have proved the benefits of the therapy, especially significant improvement of life quality throughout the reduction of menopausal symptoms and decreased risk of osteoporosis development (Appelberg *et al.* 1998, Pietrzak *et al.* 2006, Pietrzak *et al.* 2006a). The main side effect of HRT, irrespective of the way of administration, is the disturbed liver function, in some cases resulting in the need to discontinue therapy (Hung *et al.* 1996, Pietrzak *et al.* 2006). Therefore regular attentive follow up with biochemical screening is essential for safe continuation of HRT.

Hormonal replacement therapy has been believed to decrease the risk of cardiovascular diseases. Data from recent studies however (Grodstein *et al.* 2006, Halley *et al.* 1998, Hodis *et al.* 2003, Hsia *et al.* 2006, Naftalin *et al.* 2004) failed to prove that potential advantage, moreover indicated for the increased risk of cardiovascular events in menopausal women treated with standard dosages. According to WHI study the use of combined HRT is associated with the reduced risk of colorectal cancer, endometrial cancer and fractures (Cauley *et al.* 2003, Writing *et al.* 2002). On the other hand in particular groups of patients it may increase the risk of coronary heart disease, cardiovascular events and breast cancer (Beryl *et al.* 2003, Cauley *et al.* 2003, Speroff 2003). In reflect of these data careful inclusion criteria as well as frequent clinical surveillance is of the greatest value in users of HRT.

Its worth to emphasize that regression or significant reduction of climacteric symptoms together with osteoporosis prevention and treatment remain the main indications for HRT administration both in general population and in transplant recipient (Pietrzak *et al.* 2006a, The North American Menopause Society 2003).

6. Prophylaxis and treatment of gynecological malignancies

Patients after organ transplantation have three to fourfold increased incidence of malignancy compared with general population (Penn 1979, Penn 1996). According to many authors, it is the chronic use of immunosuppressive agents, what promotes carcinogenesis through the disturbed mechanisms of detection and elimination of cells with possibly dangerous mutations. Moreover immunosuppressive agents may intensify the influence of some environmental carcinogenic factors and increase the risk of infections with viruses of oncogenic potential (Bobrowska *et al.* 2005). The malignancies most often seen in transplant patient are: skin cancer (usually basal cell carcinoma), cervical cancer, malignancies related to Epstein-Barr Virus infection and Kaposi sarcoma. Besides some rare types of kidney and liver tumors have been relatively often reported among graft recipients (Penn 1979, Penn 1980, Penn 1986, Penn 1996, Saadat *et al.* 2007).

In reflect of the above data, all transplant women must undergo regular gynecological screening for premalignant and malignant lesions of sex organs and breast. At least one time a year cervical colposcopy and transvaginal sonography should be performed and PAP smear should be obtained. Besides sonographic examination of the br east, and in older women mammography should be carried out yearly. Any detected abnormalities need to be verified with sampling followed by histopathological evaluation and in case of malignancy radical surgical treatment should be performed.

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