

# Combined oral contraception in women after renal transplantation

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## Abstract

**AIM:** To assess safety of combined low-dose oral contraceptives in women after renal transplantation.

**MATERIAL AND METHODS:** Twenty six female renal graft-recipients, aged from 18 to 44 (mean 31 years), who used combined low-dose oral contraceptives after renal transplantation for at least 18 months were enrolled in the study. All patients had stable graft function with mean serum creatinine of 1.3 mg/dl. In 58% of women effective contraception was the mean indication for the therapy, in the remaining group pills were indicated additionally for the development of ovarian cysts and excessive menstrual bleedings. Ethinyl estradiol dose was 20 µg in 73% of cases and 30–35 µg in the remaining group.

**RESULTS:** No case of pregnancy was observed. Contraceptive therapy was discontinued in two cases: for profound vein thrombosis in one and deterioration of liver function in the other case. No side effects of contraceptives were observed in the remaining group of patients within at least 18-month observational period. No case of ovarian cyst was reported. Oral contraceptives were not found to influence body mass index (BMI), mean blood pressure, serum creatinine and biochemical parameters (AST, ALT, total bilirubin, glucose and cholesterol).

**CONCLUSIONS:** Despite the presence of relative contraindications for hormonal drugs (arterial hypertension and deteriorated liver function) in female renal recipients, administration of combined low-dose contraceptive pill should be taken into account as highly effective contraceptive method, that additionally regulates menstrual bleeding patterns, protects from ovarian cysts development and improves life quality of the patient.

**Abbreviations & Units:**

BMI	– Body Mass Index
AST	– aspartate aminotransferase
ALT	– alanine aminotransferase
MAP	– mean arterial blood pressure
PAP smear	– Papanicolau smear
SD	– standard deviation
kg	– kilogram
m	– meter
l	– liter
dl	– deciliter
mg	– milligram
µg	– microgram
IU	– International Units

**Introduction**

End-stage renal failure leads to a number of biochemical disturbances generally described as uraemia. Among systems secondary disturbed by renal failure is hypothalamus-pituitary-ovary axis. Other factors, associated with the regulation of menstrual cycle, like leptin concentration, may also be impaired [7]. In majority of uraemic women menstrual disturbances are observed and consequently highly reduced fertility is reported. Among the variety of disturbances, irregular menstruations, profuse or scant bleeding or amenorrhea are noted in that group of patients. Haemodialysis improves general state of the patients, however is rarely associated with the restoration of regular menstrual patterns, even in women with satisfactory renal parameters.

Nowadays renal transplantation is commonly accepted treatment of end stage renal failure. Successful grafting and stabilization of the graft function result in restoration of ovarian cycles. Most female graft recipients of reproductive age report recurrence of menstruations and fertility within six months after transplantation. Approximately 50% of renal transplanted women with stable graft function are observed to have ovulatory cycles.

First successful renal transplantation in Poland was performed as early as in 1966, but rapid progress in transplant medicine was made in the last decade. Introduction of cyclosporine into the immunosuppressive regimen in the eighties of the 20<sup>th</sup> century and consequently other effective immunosuppressive agents such as tacrolimus, mycophenolan mophetil and rapamycine was associated with significant improvement of graft survivals followed by longer life expectancy of graft recipients.

Over 1000 renal transplantations are performed in Poland yearly, that gives the number of approximately 30 transplantation for 1 million inhabitants. In other European countries such rate varies from 11.7 (Lithuania) to 47.7 (Spain). 1857 female graft recipients, aged 16–48, lived in Poland in 2004 [9]. Social rehabilitation of those patients includes natural need for motherhood. There are a number of reports about successful pregnancies in renal transplanted women in literature. Such pregnancies, however, are considered high risk and associated with increased rate of complications. Moreover deterioration of the graft function may develop in a course of pregnancy in graft recipient. Therefore authors emphasize the

need for careful pregnancy planning. Conception should appear not sooner than one year after transplantation only in patients with stable function of the graft [3]. Family planning accompanied with safe and effective contraceptive methods seem to be of greatest value in that group of women.

Hormonal contraception is known to be the most effective contraceptive method. The use of the most popular and best known combined contraceptive pill, even low-dose pill (containing 20–35 µg of ethinyl estradiol), is associated with the increased risk of thromboembolism. Arterial hypertension and deteriorated liver function, observed in most renal transplanted women, are believed to be relative contraindications for hormonal contraceptives, hence safety of the pill is not clear. In the study we report our experiences with combined contraceptives administration in renal transplanted women.

**Material and methods**

26 renal transplanted women who used low-dose combined oral contraceptive in years 1997–2005 for a period not shorter than 18 months were enrolled in the study. 77% of patients came from cities, one third from big cities with over 200 000 inhabitants, the remaining 23% of women inhabited villages. The most common underlying renal disease were: chronic glomerulonephritis (53%), chronic pyelonephritis (8%) and polycystic kidney degeneration (8%). Contraceptive pills were administered within first 24 months after renal transplantation in 31% of patients, between 24 to 48 months after grafting in 23% of patients, over 48 months after transplantation in 19% of women and in the remaining 15% over 12 years after grafting. The main indications for the therapy in the first two groups (54% of patients) were high contraceptive effectiveness together with the simplicity of the method and the obtained regularity of bleeding patterns. Ovarian cysts were additional indications for oral contraceptives prescribed over 48 months after transplantation. In the group of women who started using hormonal contraceptives over 12 years after grafting the main indications were ovarian cysts and hypermenorrhea resisted for other therapeutic agents. Half of the women were under 30 years of age on therapy onset, the mean age of the group was 31.38 years. 58% of women have never been pregnant, 15% had one and 23% had two children, while the remaining group had the history of spontaneous abortions. Graft function was stable in all cases and mean serum creatinine was 1.31 mg/dl (SD 0.42). Most women (88%) had well controlled arterial hypertension. None of the patients from the group smoke cigarettes.

The dose of ethinyl estradiol in the contraceptive pill was 20 µg in 73% of cases and 30–35 µg in the remaining group. All patients received contraceptives with III<sup>rd</sup> generation progestin. Follow-up visits were performed after one, three and six months of the therapy and every six months thereafter. Body mass, blood pressure, hematocrite, serum levels of creatinine, aspartate aminotrans-

**Table 1.** Changes of BMI (kg/m<sup>2</sup>) in female renal recipients using oral contraceptives (changes not significant).

	0 months	3 months	6 months	12 months	18 months
BMI	20.74 SD 3.61	19.87 SD 3.98	20.16 SD 3.76	21.31 SD 3.89	21.63 SD 4.26

**Table 2.** Biochemical changes observed in female renal recipients using oral contraceptives.

	0 months	3 months	6 months	12 months	18 months
Creatinine (mg/dl)	1.31 SD 0.42	1.4 SD 0.49	1.47 SD 3.76	1.46 SD 0.57	1.58 SD 0.49
Hematocrite (%)	35.8 SD 4.48	37.28 SD 3.31 P<0.01	36.99 SD 2.63 P<0.01	37.44 SD 5.15	37.33 SD 6.3
AST (IU/L)	24.8 SD 11.6	25.3 SD 10.9	25.7 SD 15.8	27.0 SD 11.4	27.5 SD 13.2
ALT (IU/L)	25.2 SD 15.4	28.6 SD 19.9	27.7 SD 20.0	30.0 SD 12.8	35.4 SD 26.8
Total bilirubin (mg/dl)	0.78 SD 0.28	0.74 SD 0.2	0.78 SD 0.3	0.78 SD 0.34	0.7 SD 0.24
Cholesterol (mg/dl)	206.9 SD 33.4	211.3 SD 36.5	208.0 SD 33.6	211.9 SD 39.1	188.8 SD 44.8
Glucose (mg/dl)	80.2 SD 33.4	84.6 SD 14.4	85.56 SD 13.2, p=0,05	85.5 SD 6,7, p=0,05	85.8 SD 10.8

ferase (AST), alanine aminotransferase (ALT), bilirubin, glucose and cholesterol were obtained on every visit. Menstrual patterns on contraceptive pills were noted. Gynaecological examination together with transvaginal sonography was performed. Every six months PAP smears were obtained.

The therapy was administered only in women who expressed their conscious will for hormonal contraception and were aware of the presence of relative contraindications for hormonal contraceptives.

## Results

The period of contraception use was not shorter than 18 months in the study group, the longest period noted was 96 months. In two cases the therapy was discontinued for medical indications. One patient after 18 months of the therapy developed profound vein thrombosis in the left lower leg. Hormonal contraception was discontinued and after anticoagulant therapy administration the prompt regression of symptoms was observed. Another patient ten years after transplantation for chronic glomerulonephritis developed symptoms of the acute graft rejection complicated with intravascular haemolysis. Since the condition was associated with significant deterioration of liver function and serum aminotransferases elevation, hormonal therapy was immediately discontinued. No case of willful discontinuation of contraception was noted.

No case of pregnancy was reported in the study group within the observational period. The bleedings patterns on low-dose contraceptive pills were satisfactory in all cases independent on the patient's immunosuppressive regimen.

Mean body mass index (BMI) of the study group was 20.74 kg/m<sup>2</sup> (SD 3.61), after 18 months of the therapy it increased to 21.63 kg/m<sup>2</sup> (SD 4.26), but the change was not statistically significant (Table 1). Mean initial arterial blood pressure (MAP) in female renal recipients was 99.2 (SD 0.74) and did not differ significantly during the observational period. After 18 months of the therapy it reached 99.8 (SD 0.75).

Mean serum creatinine increased significantly from 1.31 mg/dl (SD 0.42) to 1.40 mg/dl (SD 0.49) after three months and to 1.47 mg/dl after 6 months (SD 0.45) ( $p < 0.01$ ). The creatinine increase observed afterwards was not significant: 1.46 mg/dl (SD 0.57) after 12 months and 1.58 mg/dl (SD 0.49) after 18 months of the therapy. The reported increase of hematocrite was statistically significant. On therapy onset it was 35.80 (SD 4.48) and increased to 36.99 (SD 2.63) after 6 months, to 37.44 (SD 5.15) after 12 months and to 37.33 (SD 6.30) after 18 months. The changes of aminotranferases on hormonal contraception were not significant except the case of the acute graft rejection. Neither total bilirubin concentration nor cholesterol levels differ significantly within 18-month observational period. The mean initial glucose level was 80.2 mg/dl (SD 19.9) and reached 84.6 mg/dl (SD 14.4) after 3 months, 85.56 mg/dl (SD 13.2) after 6 months, 85.5 mg/dl (SD 6.7) after 12 months and 85.8 mg/dl (SD 10.8) after 18 months. The statistical significance of the increase observed after 6 and 12 months was borderline ( $p = 0.05$ ). All changes of biochemical parameters on combined low-dose contraception were gathered in Table 2.

## Discussion

Restoration of both libido and fertility is observed in kidney transplanted women soon after successful grafting. Effective contraceptive methods should be employed in all patients who do not intend to get pregnant. The need for contraception is associated, however, with the presence of a number of contraindications for contraceptive methods in that specific group of patients.

Surgical sterilization (tubal ligation or vasoligation) is highly effective and safe, but illegal by Polish law. The use of intrauterine devices in graft recipients immunocompromised by continuous immunosuppressive therapy is associated with significantly increased risk of pelvic inflammatory diseases [4,5]. In patients with sporadic sexual activity condom use is advised, it should be emphasized however, that the contraceptive effectiveness of the method is relatively low. The use of another barrier method, cervical caps, seem to be contraindicated for the twofold increase rate of urinary tract infections observed in women [6].

Hormonal contraception is known to be the most effective and easily reversible contraceptive method. In 2006 we witness 50<sup>th</sup> anniversary of combined contraceptive pill introduction into family planning methods. A great progress has been made within those years. Ethinyl estradiol dose reduction ( $\leq 35 \mu\text{g}$ ), new ways of administrations (transdermal, subdermal, vaginal) and new progestins introduced have led to decrease in risk of thromboembolism and limitation of contraindications for that comfortable method.

The main well-known complication of combined contraceptive pill is several-fold increase in risk of thromboembolism associated even with low doses of synthetic estrogen and progestin administration. The estimated risk means 20 new cases of vein thrombosis in 100 000 women using combined contraceptive pills yearly [1]. That dangerous complication was observed in one patient from our study group, fortunately it was early diagnosed and successfully treated with anticoagulant agents.

Oral contraceptive users with arterial hypertension are believed to be at the increased risk of myocardial infarction and stroke, but in patients with well controlled hypertension the risk is estimated to be relatively low [2]. The rate of arterial hypertension among renal graft recipients is high (80% of patients from the study group). When the disease is well controlled it does not seem to be absolute contraindication for oral contraceptive administration to transplant woman. There is an increase in aldosterone secretion and renal retention of sodium resulting in increased blood pressure and renal filtration in hormonal contraceptives users. Those changes may be associated with increased microalbuminuria and proteinuria [6]. No case of such complication was observed in the study group on regular nephrologic examinations.

Despite the presence of relative contraindications for oral contraceptives in renal transplanted women, that

family planning method should be taken into account for its high contraceptive effectiveness associated with satisfactory bleeding control and protection from ovarian cysts development. Moreover according to a number of former studies the decreased risk of endometrial and ovarian cancers is observed in oral contraceptive users, that beneficial effect should be suspected in renal transplanted women as well.

## Conclusions

1. Low-dose contraceptive pill used in female renal recipients is observed to be an effective contraceptive method that additionally improves the patients' life quality through regulation of menstrual bleeding patterns and protection from ovarian cysts development.
2. Oral contraceptives administration in renal transplanted women needs frequent follow-up visits and proper cooperation between the patient and the gynaecologist in order to reveal any contraindications or dangerous complications of the medications.

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