Review

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Possible Effects of Immunosuppressive Therapy on Male Fertility and Pregnancy Outcomes After Paternal Exposure in Kidney Transplant Patients

Renal Transplant Hastalarında İmmünosupresif Tedavinin Erkek Fertilitesi ve Paternal Maruziyet Sonrası Gebelik Sonuçlarına Olası Etkileri

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ABSTRACT

Kidney transplantation is a crucial treatment for improving the quality of life of patients with renal failure. Immunosuppressive drugs are necessary to prevent organ rejection and are vital for the success of the transplantation. However, there is limited information on the potential adverse effects of these drugs on male fertility. Observational studies suggest that paternal drug exposure, as well as maternal drug exposure, may contribute to the risk of teratogenicity. This presents challenges in managing the treatment of men on chronic medication who are planning to conceive. The purpose of this article was to raise awareness among clinicians of this issue by examining the impact of immunosuppressive drugs used in renal transplant patients on paternal fertility and teratogenicity. Although further studies are required to understand the long-term effects of these drugs, it is recommended that options such as sperm banking should be considered in patients who are planning to have children and are considering immunosuppressive therapy.

Keywords: Kidney transplantation, male, fertility, paternal exposure, teratogens, pregnancy

ÖZ

Renal transplantasyon, renal yetmezlikli hastalar için yaşam kalitesini belirgin şekilde artıran önemli bir tedavi seçeneğidir. Transplantasyon sonrası hastalara verilen immünosupresif ilaçlar, organ rejeksiyonunu önlemek için vazgeçilmezdir ve transplantasyon başarısında önemli role sahiptirler. Ancak, bu ilaçların paternal maruziyetinin erkek fertilitesi üzerinde olası olumsuz etkileri hakkında bilgiler sınırlıdır. Bunun yanında yapılan gözlemsel çalışmalar, teratojenite riskinde sadece maternal ilaç maruziyetinin değil, aynı zamanda paternal ilaç maruziyetinin de rol oynayabileceğini desteklemektedir. Bu durum, bebek sahibi olmayı planlayan kronik ilaç kullanan erkeklerde tedavi yönetiminde güçlüklere yol açmaktadır. Makale, renal transplant hastalarında kullanılan immünosupresif ilaçların paternal teratojenite ve fertilite üzerine etkilerini değerlendirerek, klinisyenlerin bu konudaki farkındalığını artırmayı hedeflemektedir. Bu ilaçların uzun dönem etkilerini anlamak için daha kapsamlı çalışmalara ihtiyaç duyulmakla birlikte çocuk sahibi olmayı planlayan ve immünosupresif tedavi alması planlanan hastalarda, sperm bankacılığı gibi seçeneklerin de göz önünde bulundurulması önerilmektedir.

Anahtar Sözcükler: Renal transplantasyon, erkek, fertilite, paternal maruziyet, teratojenler, gebelik

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Introduction

Today, kidney transplantation has become an important treatment option that significantly improves the quality of life of patients with renal failure. Immunosuppressive drugs given to post-transplant patients are essential to prevent organ rejection and are one of the most important factors in improving transplant success (1). The etiology of two-thirds of congenital anomalies in newborns is not yet known. However, unknowingly being exposed to or forced to use drugs during pregnancy is one of the important factors blamed. With the increasing awareness of drug use during this period, the effects of maternal drug exposure on the infant have been investigated in detail by observational studies. Recent studies support that not only maternal drug exposure but also paternal drug exposure may play a role in the risk of teratogenicity (2). Scientific data on the effects of paternal exposure on the infant are still limited (3). However, paternal exposure to drugs is known to be harmful to the baby during pregnancy, and the intense anxiety about this may complicate the treatment management of men who are chronic drug users and planning to have a baby (4). Another more important concern for men regarding medication is the issue of fertility. The possible adverse effects of immunosuppressive drugs given to male renal transplant recipients on male fertility may cause anxiety and compliance problems in long-term drug use. However, there are various clinical studies on the adverse effects of some immunosuppressive drugs on sperm morphology, motility and sperm count (5); more comprehensive and long-term studies are still needed for many drugs.

Currently, there is limited information on the potential of these pharmacological agents to cause male infertility and possible fetal anomalies after paternal exposure following kidney transplantation. This lack of information is causing confusion and anxiety among clinicians and patients.

Clinical and Research Consequences

Calcineurin Inhibitors

Cyclosporin-A: Cyclosporins are fungal metabolites that function as immunosuppressants. One of these compounds, cyclosporine A, is clinically used after tissue and organ transplantation, in treating lupus, and in ocular inflammation associated with keratoconjunctivitis sicca. There have been no extensive human reports of possible adverse effects of cyclosporine exposure on male reproduction. However, in prepubertal male rats, chronic administration of low doses of cyclosporine caused impaired testosterone production, spermatogenesis and fertility. In mature male rats treated with cyclosporine A at 30 mg/kg orally for 28 days, decreased testicular weight and damage to germ cells were observed (6). In a study evaluating sex hormone levels in male patients receiving cyclosporine (n=21) and tacrolimus (n=16) after kidney transplantation, hormone levels were found to be normal (7).

Partners of three out of four male renal transplant patients on cyclosporine could conceive (8). Potential effects on fertility are thought to be associated with higher doses. Therefore, if low serum drug levels can be achieved while maintaining allograft function, pregnancy may be attempted (9). A study of male renal transplant recipients found that erectile dysfunction was more common with cyclosporine than with other immunosuppressants (10).

In a study in which paternal cyclosporine use was analysed, therapeutic abortion and congenital malformation rates of 152 pregnancies were evaluated. Of 152 pregnancies, two resulted in therapeutic abortion, and four resulted in congenital malformations (11). Although information on the paternal use of cyclosporine is limited, it has not been shown to increase the risk of adverse teratogenic pregnancy outcomes (12).

Tacrolimus: Tacrolimus is a macrolide derived from Streptomyces and used as an immunosuppressant in transplant patients. It is also used topically for the short-term treatment of atopic dermatitis (6). No decrease in basal or human chorionic gonadotropin- stimulated testosterone was observed in male rats treated with tacrolimus at a daily dose of 2 mg/kg. Daily administration at 1 mg/kg dose did not affect testicular weight and histology. Culturing Leydig cells with tacrolimus up to 1 mg/L did not result in impaired viability or decreased basal or stimulated testosterone production (13). There are not enough studies on the effect of tacrolimus on human fertility. However, studies are reporting an increase in sperm quality after switching to tacrolimus in patients with impaired sperm quality during sirolimus use (5). Normal sex hormone levels have been reported in male patients using cyclosporine and tacrolimus after kidney transplantation.

Six different studies, including case series and case reports, analysed the effects of paternal use of cyclosporine, tacrolimus or sirolimus on pregnancy outcomes. No association between tacrolimus and adverse pregnancy outcomes was reported (5). In another study evaluating the rates of therapeutic abortion and congenital malformations in 255 pregnancies with paternal tacrolimus use, 8 of 255 pregnancies resulted in therapeutic abortion, and 10 resulted in congenital malformations (11).

Clinical data on the paternal use of tacrolimus and its effect on teratogenic pregnancy outcomes are limited. Based on the limited data, tacrolimus is compatible with paternal exposure in pregnancy (14).

Anti-proliferative (Anti-metabolite) Agents

Mycophenolate: Mycophenolate mofetil is an immunosuppressant used in organ transplantation, rheumatoid arthritis and lupus. Following oral administration, mycophenolate mofetil is converted to the active metabolite mycophenolic acid (6). Mycophenolate sodium is frequently used in renal transplant patients. According to the product label, mycophenolate in male rats causes no adverse effects on fertility at oral doses lower than the recommended dose for renal and heart transplant patients based on body surface area (15).

Information on the effects of mycophenolate on male fertility or pregnancy outcomes following paternal exposure is limited;

however, available data do not indicate safety concerns (4,12). In a study in which paternal mycophenolate mofetil use was analysed, therapeutic abortion and congenital malformation rates of 313 pregnancies were evaluated. Of these pregnancies, eight resulted in therapeutic abortion, and nine resulted in congenital malformations (11). The manufacturer recommends that sexually active male patients and their partners use effective contraception for 90 days following the last dose of the patient's treatment. The recommendation, also based on animal data, is that semen should not be donated for 90 days after the last dose of mycophenolate treatment. Nevertheless, based on limited human data, mycophenolate may be considered for men with musculoskeletal and rheumatic diseases who plan to have children (16,17).

Azathioprine: Azathioprine is an antimetabolite agent used in immunosuppression, metabolised to mercaptopurine and 6-thioguanine. Azathioprine and its metabolites are cytotoxic purine analogues. Numerous clinical data are available. In 23 men with inflammatory bowel disease, semen quality did not decline after 1-4 years of treatment with azathioprine, and six of the patients had seven healthy children while on this drug regimen (18). Among 164 male renal transplant patients receiving long-term immunosuppressive therapy with azathioprine and other drugs, no adverse effects on fertility were observed (19). A prescription registry study of the infants of 54 men who were prescribed azathioprine or mercaptopurine before their wives became pregnant identified four infants with congenital anomalies (20).

A teratology information service study followed up 115 pregnancies fathered by men treated with azathioprine or 6-mercaptopurine. In 101 of these pregnancies, the father had drug exposure at the time of conception (21). There were 9 spontaneous abortions and 11 children with congenital anomalies. Three of the children had major anomalies (ventricular septal defect, horseshoe kidney and motor defect), and eight had minor anomalies (umbilical hernia, small haemangioma, hip dysplasia, xanthoma and persistent foramen ovale). This series of results was consistent with the general population experience. In 37 pregnancies fathered by men treated with azathioprine for inflammatory bowel disease, there was no increase in adverse pregnancy outcomes (22). No adverse effects on cancer, autism spectrum disorders, psychoses (including schizophrenia) or attention deficit hyperactivity disorder were found in 735 children whose fathers used azathioprine/6-mercaptopurine three months before conception (23). In another study, therapeutic abortion and congenital malformation rates were evaluated in 59 pregnancies with paternal azathioprine use. Of these, two resulted in therapeutic abortion, and four resulted in congenital malformations (11).

Available data have not shown that azathioprine adversely affects male reproductivity or increases the risk of adverse teratogenic pregnancy outcomes when used within three months prior to conception (4,11,24).

mTOR Inhibitors

Sirolimus: It is an mTOR kinase inhibitor macrolide antibiotic used as an immunosuppressant. Like tacrolimus, sirolimus interacts with interleukin-2 (IL-2), but the interaction mechanism is different for the two drugs. According to the product label, male rats exposed to a dose level 10 times the human dose relative to body surface area showed a decrease in sperm count. Male monkeys were given sirolimus for four weeks at therapeutic human dose levels and developed testicular tubule degeneration (25). Rats exposed to these levels for eight weeks showed impaired spermatogenesis (26). In another rat study, the adverse effects of sirolimus on the testis appeared to be reversible by discontinuation of the drug (27).

There are also human studies suggesting that sirolimus treatment is associated with decreased testosterone production, sperm count and fertility in renal transplant patients (6). Fifteen studies involving 492 patients (263 cases and 229 controls) were analysed in a systematic review conducted in 2020, all of whom received sirolimus or cyclosporine for organ transplantation (mostly kidney transplantation). In 11 of these studies, sperm quality abnormalities and reproductive-related hormonal changes (low testosterone and high FSH/LH levels) were reported after exposure to sirolimus. Some of these studies reported that infertility due to sirolimus treatment was reversible (5).

In one study, seven pregnancies with paternal sirolimus use were evaluated for therapeutic abortion and congenital malformations. Therapeutic abortion and congenital anomalies were not observed (11). There are insufficient studies to assess the risk of paternal use of sirolimus and its teratogenic effect on pregnancy outcomes.

Everolimus: It is a mammalian mTOR inhibitor that inhibits T and B cell activation. It is used for the prevention of transplant rejection, treatment of some cancers and seizure control in patients with tuberous sclerosis complex. Male rats treated with everolimus at a dose of 5 mg/kg/day developed infertility due to decreased sex organ weights and seminiferous epithelial abnormalities. Complete recovery was not observed after 13 weeks of treatment interruption (6).

Male transplant patients given everolimus at two doses (1.5 or 3 mg/day) showed increases in mean testosterone, FSH and LH values compared to baseline. Since there was no control group in this study, it was impossible to conclude whether the changes were clinically significant (28). A 30-year-old male patient who received everolimus after kidney transplantation presented with infertility, and sperm concentration was found to be less than 0.5 million/mL. Semen analysis was not performed before treatment. Three months after the treatment was stopped, the sperm concentration increased to 130 million/mL, and the patient's wife became pregnant one month later (29).

In a study, five pregnancies with paternal everolimus use were evaluated in terms of therapeutic abortion and congenital malformations. No congenital anomaly was observed in these

five pregnancies, and therapeutic abortion was observed in 1 of them (11). There are insufficient studies to assess the risk of paternal use of everolimus and its effect on teratogenic pregnancy outcomes. However, patients whose partners may become pregnant should be advised to use effective contraception during treatment and for four weeks after the last everolimus dose (30).

Prednisolone, Methylprednisolone: Prednisolone, the active metabolite of prednisone, is a glucocorticoid. It is used in treating autoimmune connective tissue-vascular diseases and as an immunosuppressant. Although short-term treatment with corticosteroids has been reported to be used to treat immunological infertility in men, some researchers have not found this treatment effective. It has been reported that long-term, high-dose glucocorticoid use may impair spermatogenesis, and recovery may require as long as six months. However, it does not affect chromosome number or sperm morphology (6). Although asthenospermia and oligospermia are adverse effects of the drug, the frequency of these adverse effects has not been reported (30).

In a study in which paternal glucocorticoid use was analysed, therapeutic abortion and congenital malformation rates of 298 pregnancies were evaluated. Of these pregnancies, ten resulted in therapeutic abortion, and nine resulted in congenital malformations (11). There are insufficient studies to evaluate the teratogenic effect on pregnancy outcomes in fathers who use prednisolone and methylprednisolone.

Basiliximab: Basiliximab, an IL-2 receptor antagonist, is used to prevent acute organ rejection in patients with kidney transplantation. There are no studies on the effect of basiliximab on fertility, paternal use and its effect on teratogenic pregnancy outcomes (6).

Dacliximab: Dacliximab (Daclizumab) is a monoclonal antibody that binds to the IL-2 receptor. Dacliximab was used in the treatment of multiple sclerosis and as an immunosuppressive agent after transplantation. However, it was withdrawn from the market due to its association with inflammatory brain disorders (6). No adverse effects on sperm count, motility, morphology, serum testosterone, organ weights or testicular histopathology were found at dose levels of dacliximab up to 200 mg/kg every two weeks for 60 days in monkeys (31). The effect on fertility has not been evaluated. There are no studies on the paternal use of dacliximab and its effect on teratogenic pregnancy outcomes.

Muromonab-CD3 (OKT3):

The monoclonal antibody OKT3 (Orthoclone, Muromonab CD3) is a mouse-derived antibody used to treat allograft rejection. However, it was withdrawn from the market in 2010 due to numerous side effects, better-tolerated alternatives and declining utilisation (32). There are no studies on the paternal use of Muromonab CD3 and its effect on teratogenic pregnancy outcomes.

Antithymocyte Globulin, Antilymphocyte Serum: Antithymocyte globulin (anti-lymphocyte serum) is a purified immunoglobulin G used to prevent and treat acute organ rejection after transplantation. The product label indicates that it does not alter hormone concentrations or mating behaviour when administered to male monkeys at doses up to 40 mg/kg/day. Fertility impairment occurred in five female and one male patient immunoablated with cyclophosphamide and antithymocyte globulin prior to stem cell transplantation. A relationship between cumulative cyclophosphamide dose and infertility has been established, but the effect of antithymocyte globulin is unclear (6). There are no studies on the paternal use of antithymocyte globulin and its effect on teratogenic pregnancy outcomes.

Alemtuzumab: It is a human IgG monoclonal antibody against the cell surface CD52 glycoprotein. CD52 is present in human and rodent reproductive tissues. Treatment of mice carrying the humanised CD52 gene with alemtuzumab at a dose seven times higher than the human dose based on plasma concentration (area under the curve) resulted in a less than 10% decrease in sperm count and up to 3% abnormal sperm forms. However, there was no effect on reproductive capacity (6).

A sub-study of 13 male patients receiving alemtuzumab treatment found no evidence of aspermia, azoospermia, increased motility or morphological abnormalities (33). However, there is still insufficient clinical safety data on the effect of alemtuzumab on fertility. Similarly, there are no studies on paternal exposure and its teratogenic effect on pregnancy outcomes.

Belatacept: Belatacept is a fusion protein consisting of the Fc fragment of human IgG1 immunoglobulin. The drug blocks T-cell activation and is used to prevent graft rejection. Fertility was not affected in male or female rats at exposures up to 25 times the human dose (6). Serum testosterone, FSH, LH and inhibin were measured before and after transplantation in 53 male patients with chronic renal failure. Four of these patients were reported to be taking belatacept (34). However, this study did not establish a relationship between belatacept and male fertility because the results of patients using belatacept were not discussed separately. In a study, six pregnancies with paternal belatacept use were evaluated in terms of therapeutic abortion and congenital malformations. Therapeutic abortion and congenital anomalies were not observed in these six pregnancies (11). There are insufficient studies to assess the risk of paternal use of belatacept and its effect on pregnancy outcomes.

Conclusion

In conclusion, scientific data on the effects of many immunosuppressant agents on paternal teratogenicity and fertility are still limited. Since there are not enough human studies on most drugs, data from animal studies have been utilised to give an idea. It should be kept in mind that the results obtained in animal studies cannot be directly adapted to humans but may be guiding.

This study aimed to raise awareness about the effects of immunosuppressive agents used in renal transplant patients on male fertility and pregnancy outcomes after paternal drug

exposure. Based on this, sperm banking may be considered as an option in patients who are planning to have a child and in whom immunosuppressive treatment is planned to be initiated.

Ethics

Authorship Contributions

Concept: E.H., İ.Y., Design: E.H., İ.Y., Y.Ö.İ, Data Collection or Processing:E.H., İ.Y., Analysis or Interpretation: İ.Y., Y.Ö.İ, Literature Search:E.H., İ.Y., Writing: E.H., İ.Y., Y.Ö.İ.

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