

Sexual and Reproductive Function in Chronic Kidney Disease and Effect of Kidney Transplantation

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1. Introduction

Chronic renal failure has been known to be associated with impotence and loss of libido in men and for many women, infertility and menstrual irregularities. There have been ongoing improvements in survival and quality of life after renal transplantation. These have been accompanied by an improvement in reproductive function and reversal of the relative infertility that occurs despite maintenance hemodialysis. One of the most impressive aspects of successful renal transplantation in the young person is the ability of the male patient to father a child and the female patient to give birth to a healthy baby.

Pregnancy does not appear to have any adverse effect on the long-term survival of renal allografts. Because the outcome of pregnancy in transplantation are so different than those in chronic dialysis, it is advisable to treat end-stage renal disease patients with transplantation and wait until renal function has been stable before undertaking a planned pregnancy. Women are usually advised to wait at least 1 year after living-related kidney Transplantation, and 2 years after cadaveric kidney transplantation; however, waits of 5 years or more have been associated with impaired renal function post-partum.

All women of child-bearing age should be counseled about the possibility and risks of pregnancy after kidney transplantation. Types of immunosuppressive regimens and assessment of graft function should be considered during preconception counseling. Contraceptive counseling should be provided before transplantation surgery, because ovulatory cycles may begin within 1 to 2 months after transplantation in women with grafts that are functioning well. It is strongly advised that every sexually active transplant recipient attend a family-planning counseling session, ideally before transplantation is performed. Breastfeeding is discouraged for patients taking any immunosuppressive drugs. In this chapter we will first have a short review on reproductive physiology in male and female and irregularities caused by end stage renal disease and then we will review the experience of women undergoing child birth after transplantation, with a focus on outcomes and suggested management strategies including contraception counseling.

2. Male reproduction

2.1 Physiology of reproduction in men

The male reproductive tract consists of the testis, epididymis, vas deferens, prostate, seminal vesicles, ejaculatory duct, bulbourethral glands, and urethra. The testes contain two cell types: the Sertoli cells, which line the seminiferous tubules (the site of spermatogenesis), and the Leydig cells (the site of androgen synthesis). In the male, the pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which act on the testes. LH stimulates the synthesis and secretion of testosterone by the Leydig cells, and FSH stimulates the Sertoli cells to secrete inhibin. FSH and testosterone act on the seminiferous tubules to stimulate spermatogenesis. In human it takes about 75 days for spermatogonia to develop into mature sperm cells (Berek 2002).

During ejaculation, mature spermatozoa are released from the vas deferens along with fluid from the prostate, seminal vesicle, and the bulbourethral glands. The semen released is a gelatinous mixture of spermatozoa and seminal plasma; however it thins out 20 -30 minutes after ejaculation by a process called liquefaction (Berek 2002).

Both LH and FSH play roles in normal spermatogenesis. Thus, spermatogenesis does not occur spontaneously in men who have hypogonadotropic hypogonadism of prepubertal onset. Spermatogenesis can be initiated in these men by the administration of human chorionic gonadotropin (hCG), which has potent LH effects, and an FSH preparation, such as human menopausal gonadotropin (hMG) (Finkel 1985).

2.2 Male reproduction in end stage renal disease

For many male patients with renal failure, impotence and loss of libido have been seen frequently; these problems may improve but rarely normalize with the institution of maintenance dialysis, commonly resulting in a decreased quality of life (Holdsworth 1978; Diemont 2000; Rosas 2003). By comparison, a well-functioning renal transplant is much more likely to restore sexual activity; however, some features of reproductive function may remain impaired.

The uremic milieu plays an important role in the genesis of sexual dysfunction in end stage renal disease. Psychologic and physical stresses that may contribute to disturbances in sexual function are also commonly present in patients with chronic renal failure (Holdsworth 1978; Steele 1996; Toorians, Janssen et al. 1997).

2.2.1 Gonadal function

Advanced chronic kidney disease is associated with impaired spermatogenesis and testicular damage (Holdsworth 1977; Holdsworth 1978). Semen analysis typically shows a decreased volume of ejaculate, oligo- or complete azoospermia, and a low percentage of motile sperm. Testicular histology shows reduced spermatogenic activity varying from decreased numbers of mature spermatocytes to complete aplasia of germinal elements. Other findings include damage to the seminiferous tubules, atrophy of Sertoli cells, and interstitial fibrosis and calcifications.

The factors responsible for testicular damage in uremia are not well understood. It is possible that plasticizers in dialysis tubing, such as phthalate, may play a role in patients undergoing maintenance hemodialysis.

Uremia also impairs gonadal steroidogenesis. The serum total and free testosterone concentrations are typically reduced, although the binding capacity and concentration of sex

hormone-binding globulin are normal (Lim 1976; Levitan 1984; de Vries 1984). Another manifestation of diminished testosterone secretory capacity is the subnormal and delayed testosterone response to the administration of human chorionic gonadotropin (HCG), a compound with luteinizing hormone-like actions (Stewart-Bentley 1974). By comparison, although the total plasma estrogen concentration is frequently elevated, the serum estradiol concentration is typically normal (Lim 1978).

2.2.2 Pituitary function

The serum concentration of luteinizing hormone (LH) is elevated in uremic men (Lim 1978); this is due to diminished testosterone feedback.

Follicle stimulating hormone (FSH) secretion is also elevated, although to a more variable degree (Holdsworth 1978; de Vries 1984). Elevated FSH levels are probably the result of decreased testosterone and inhibin, a Sertoli cell product. The plasma FSH concentration tends to be highest in those uremic patients with the most severe damage to seminiferous tubules and presumably the lowest levels of inhibin. It has been suggested that increased FSH levels may portend a poor prognosis for recovery of spermatogenic function after renal transplantation. The gonadotropin reserve is generally intact, since the plasma level of both gonadotropins increased appropriately following administration of gonadotropin-releasing hormone (GnRH) (LeRoith 1980). The appropriate increase in FSH and LH in response to the administration of clomiphene (a nonsteroidal antiestrogen that stimulates gonadotropin secretion by blockade of estrogen mediated negative feedback on the hypothalamus) (Lim 1978), also indicates a normal gonadotropin reserve.

2.2.3 Hyperprolactinemia

The basal levels of serum prolactin are elevated in the majority of uremic patients, and the response to thyrotropin-releasing hormone (TRH) is reduced and delayed (Hagen C 1976). The mechanisms for the hyperprolactinemia in chronic renal failure are not well defined. Increased autonomous production rate of prolactin is a major mechanism for the hyperprolactinemia but decreased metabolic clearance rate may also play a role (Cowden 1981). The demonstration of resistance to stimulation or suppression of prolactin in CRF is consistent with increased autonomous production (Pece 1979). The state of secondary hyperparathyroidism of CRF may contribute to the increased production rate of prolactin, because PTH stimulates prolactin secretion (Issac 1978). The treatment of CRF patients with erythropoietin was associated with a decreased in serum prolactin levels and improvement in sexual dysfunction (Schaefer, Stanhope et al. 1989), but did not normalize rate of the response to TRH (Ramirez 1976). These observations suggest that either anemia and/or deficiency of erythropoietin per se participate in the genesis of the hyperprolactinemia of CRF.

2.2.4 Gynecomastia

Variable degrees of gynecomastia are often encountered in the male uremic patient treated with maintenance hemodialysis (Lim 1978). Gynecomastia usually develops during initial months of dialysis and regresses as dialysis continues. It may be transient or may last for periods of several months. The etiology may be related to the improvement in the nutritional status of uremic patient with dialysis therapy and, as such, is similar to the mechanism of refeeding gynecomastia. It must be emphasized that in almost all cases of

Gynecomastia, there is an alteration either in the ratio between the serum level of androgen and estrogen, in favor of the latter, or in the ratio between the action of androgen and estrogen at the tissue level (Sawin 1973). Indeed, in patients with advanced CRF and those treated with hemodialysis, the ratio between the serum levels of free testosterone and estradiol is reduced because of a decreased in testosterone levels.

2.3 Erectile dysfunction in end stage renal disease:

Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse. It may result from psychologic, neurologic, hormonal, arterial or cavernosal impairment or from a combination of these factors. Most of the studies in sexual dysfunctions in CRF patients have focused on impotence. Erectile dysfunction is common in patients with CRF and is observed in excess of 50% of these patients (Procci 1981). These data are based on results obtained from interviews with or by the completion of questionnaires by the patients and/or their spouses. Several factors appear to participate in the genesis of impotence in CRF patients. These include abnormalities in the neurohormonal control system of erection hormones of the hypothalamic-pituitary-gonadal axis, secondary hyperparathyroidism and, dysfunction of the corporal smooth muscle of the penis or in their response to relaxing stimuli and/or derangements in the arterial supply or the venous drainage of the penis (Schrier RW 2001). Patients with a history of abnormal erectile function prior to the onset of renal disease may have a secondary cause, such as a neuropathy or peripheral vascular disease.

The presence of a neurogenic bladder suggests an underlying neuropathy, while findings of peripheral vascular disease point toward inadequate penile blood flow. The lack of secondary sexual characteristics combined with small soft testicles suggests hypogonadism. The ingestion of a number of medications, such as beta blockers and tricyclic antidepressants, may be a cause of erectile dysfunction.

Among those without an obvious cause of impotence after an initial evaluation, consideration should be given to a psychologic difficulty, such as stress or depression. The values of Nocturnal Penile Tumescence (NPT) among a large population of uremic patients are significantly lower than normal. The administration of a nocturnal penile tumescence test may help distinguish between an organic and a psychologic disorder; the absence of an erection during sleep suggests underlying organic dysfunction. A positive test, however, does not exclude a physical cause.

2.3.1 Management

The first step in the treatment of uremic men with sexual dysfunction is increasing the delivered dose of dialysis, discontinuing medications with side effects of impotence and correcting the anemia of chronic renal disease. As an example, the administration of recombinant human erythropoietin to raise the hematocrit to 33 to 36 percent may enhance sexual function (Delano 1989).

Sildenafil has been effectively used in the treatment of erectile dysfunction in both hemodialysis and peritoneal dialysis patients and is often used for psychologic, vascular, or neurogenic causes (Ifudu 1998; Palmer 1999; Turk 2001; Seibel 2002; Rosas 2003; Grossman 2004). Concurrent use of sildenafil and nitrates in any form, regularly or intermittently, is contraindicated.

Since the elevation of serum levels of prolactin plays a role in the impotence of male uremic patient, correction of hyperprolactinemia by bromocriptin is also associated with improvement of sexual dysfunction.

Cabergoline, which causes nausea much less often than does bromocriptine and is at least as effective in treating hyperprolactinemia, should be tried first (Biller BM; Molitch ME; Vance ML; Cannistraro KB; Davis KR; Simons JA; Schoenfelder JR; Klibanski A 1996). The administration of testosterone to uremic men usually fails to restore libido or potency, despite normalized serum testosterone.

A vacuum tumescence device may be effective in restoring potency in uremic impotent males unresponsive to medical therapy. Administration of zinc is also a reasonable therapeutic option in uremic men.

2.4 Renal transplantation

Kidney transplantation is the best and most effective option that can be offered to patients with severe renal damage to restore their health and the possibility of recovering their sexual and reproductive functions.

After successful transplantation, about two thirds of male patients observe improved libido and a return of sexual function to predialysis levels. Fertility as assessed by sperm counts, improves in half patients. The sex hormone profile tends to normalize; plasma testosterone and follicle stimulating hormone levels increase; and luteinizing hormone levels which may be high in dialysis patients, decrease to normal or low levels (Danovitch GM 2005).

The factors that might cause certain difficulties for the recovery of sexual and reproductive functions in this type of patients include prolonged use of peritoneal dialysis, high follicle stimulating hormone (FSH) serum levels before the transplant, and a deficient function of the graft (De Celis and Pedron-Nuevo 1999).

A certain improvement has been reported as to semen quality in the three main parameters (number, morphology, and motility of the spermatozoa) in patients after kidney transplantation (De Celis and Pedron-Nuevo 1999).

Several studies conducted to evaluate the effects of immunosuppressive regimens suggest that some of these agents are potentially gonadotoxic since they affect testicular function and decrease fertility. This is mainly due to an indirect effect on the hypothalamus-pituitary-gonadal axis, or directly suppressant on the germinal epithelium of the testis, where the spermatogenetic process is primarily affected because of an interruption of the cycle needed for the development of an adequate amount of normal spermatozoa.

This would result in oligo/asthenozoospermia, teratozoospermia, or azoospermia. Cyclosporine (CSA) is an important therapeutic agent and a common component in multiple immunosuppressive regimens used in recipients of kidney transplants and for a growing number of autoimmune disorders. Some studies imply that CSA is a potentially gonadotoxic drug, producing adverse effects on the reproductive capability in experimental models as well as in humans. In certain animal species, such as the Sprague-Dawley strain rats, Seethalakshmi et al. showed that the administration of CSA induces a deficient intratesticular synthesis of androgens and a reduction in spermatogenesis, although this reduction was reversible after exogenous gonadotrophins were administered (Seethalakshmi 1990). On the other hand, it has also been possible to observe the adverse effect of CSA by means of testicular biopsies performed in dogs (Seethalakshmi 1988) and rats (Seethalakshmi 1990) treated with CSA for short periods, where marked abnormalities

in spermatogenesis were seen. Cyclosporine (CSA) may impair testosterone biosynthesis through direct damage to leydig cells and germinal cells, an indirect impairment of the hypothalamic-pituitary-gonadal axis has also been suggested.

Computer-aided sperm analysis (CASA) in infertile renal transplant recipients showed that both sperm concentration and straight line velocity (VSL) were inversely correlated to the cyclosporine whole blood trough levels. Stabilization of the cyclosporine whole blood trough level within the target therapeutic level could improve the fertility potential in kidney transplant recipients. Duration of hemodialysis before transplantation is also important in this regard. The time spent on hemodialysis is inversely correlated with the percentage of motile spermatozoa and the amplitude of lateral head displacement (ALH) (Eid, Abdel-Hamid et al. 1996).

Azathioprine (AZA), another drug that is frequently combined with CSA, is considered to be genotoxic (Olshan 1994). However, very few studies have analyzed the effects of AZA on the reproductive function of humans. Several studies suggest that prednisone might not be involved in sperm cell damage.

Kaczmarek and coworkers found that heart transplant recipients treated with sirolimus had significantly lower free testosterone levels and significant higher levels of gonadotropic hormones luteinizing hormone and follicle-stimulating hormone compared with calcineurin inhibitor-based immunosuppression group (Kaczmarek 2004). Patients treated with sirolimus throughout the post-transplant period have a significantly reduced total sperm count compared to patients who did not receive sirolimus and a decreased proportion of motile spermatozoa. Moreover, the fathered pregnancy rate was lower in patients receiving sirolimus-based regimens (Zuber, Anglicheau et al. 2008).

There is also concern about infertility associated with Ganciclovir which is used for treatment of cytomegalovirus (CMV) infection in transplant patients (Nevins and Dunn 1992). There is no increased incidence of neonatal malformations in pregnancies fathered by transplant recipients (Danovitch GM 2005).

2.4.1 Sexual functions in renal transplant patients

Renal transplant recipients have all suffered from uremia. They have frequently spent a significant amount of time on dialysis and often have other comorbidities including hypertension and diabetes. Although a successful transplant may improve erectile function and return of libido, in many cases some degree of sexual dysfunction may persist. On the contrary a recent study showed that, erectile function worsens after RT in patients <45 yr (Mirone, Longo et al. 2009).

Hypertension is common among transplant patients; CSA can exacerbate preexisting high blood pressure and also induce hypertension in patients, who had normal blood pressure prior to the kidney transplant.

Antihypertensive medications have negative effects on male sexual functions, such as libido and erection (Matthew RW 2005). Those medications which are implicated in erectile dysfunction include beta blockers (propranolol, labetalol), Alpha blockers (prazosin), sympatholytics (clonidine), vasodilators (hydralazine), and diuretics (thiazides, spironolactone).

Other drugs which may also play a role in erectile dysfunction in transplant patients are: HMG- CoA reductase inhibitors (lovastatin, simvastatin), antidepressant (serotonin reuptake inhibitors, tricyclics, monoamine oxidase inhibitors) and H2 antagonists (cimetidine, ranitidine, famotidine).

Ketoconazole which is used in some transplant centers in order to increase cyclosporine level and reducing the cost of calcineurin inhibitors can cause erectile dysfunction because of its antiandrogenic action.

Additional factors such as smoking and alcohol intake may account for failure of male sexual function to improve after transplantation.

Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle (Juenemann 1987). Alcohol in small amounts improves erection and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts can cause central sedation, decreased libido, and transient erectile dysfunction. Chronic alcoholism may cause hypogonadism and polyneuropathy, which may affect penile nerve function (Miller 1988).

Autonomic neuropathy may impair erectile function, and interruption of both hypogastric arteries may occasionally impair vascular supply.

2.4.2 Management of erectile dysfunction in transplant patients

Male patients should be asked about their sexual function and referred for urologic evaluation when necessary. Historically, androgens were touted as enhancing male sexual function. Today, more effective treatments are available, and testosterone therapy should be discouraged in men in whom erectile dysfunction is not associated with hypogonadism (Lue T F 2000). Sildenafil is a selective inhibitor of phosphodiesterase type 5, which inactivates cyclic GMP. Since its release in March 1998, it has become the drug of choice for most men with erectile dysfunction. When sexual stimulation releases nitric oxide into the penile smooth muscle, inhibition of phosphodiesterase type 5 by sildenafil causes a marked elevation of cyclic GMP concentrations in the glans penis, corpus cavernosum, and corpus spongiosum, resulting in increased smooth-muscle relaxation and better erection. Sildenafil has no effect on the penis in the absence of sexual stimulation, when the concentrations of nitric oxide and cyclic GMP are low (Lue T F 2000). Sildenafil has little effect on libido. Among more than 3700 men with 1631 patient years of exposure to sildenafil, most adverse events were mild to moderate and self-limited in duration (Esteban de la Rosa, Bravo Soto et al. 2003). Among men taking 25 to 100 mg of sildenafil, 16 percent reported headache, 10 percent flushing, 7 percent dyspepsia, 4 percent nasal congestion, and 3 percent abnormal vision (described as a mild and transient color tinge or increased sensitivity to light). These rates were twice as high among men taking 100 mg of sildenafil as among men who were taking lower doses. The visual effect is probably related to inhibition of phosphodiesterase type 6 in the retina. No chronic visual impairment has been reported, and the incidence of visual side effects was similar in diabetic and nondiabetic men (Price 1998). Nevertheless, because of the short duration of the clinical trials and the difficulty in detecting subtle retinal changes, the long-term safety of sildenafil treatment is still unknown. In men with retinal diseases, an ophthalmologic consultation may be warranted before sildenafil treatment is initiated. Adverse cardiovascular events (nasal congestion, headache, and flushing) were mild and transient in the majority of men. The rate of serious cardiovascular events (angina and coronary-artery disorder) is low. Sexual activity was thought to be a likely contributor to myocardial infarction in only 0.9 percent of 858 men in one study (Muller, Munder et al. 2009). Thus, the absolute increase in risk caused by sexual activity is low (one chance in a million for a healthy man). According to data from the National Center for Health Statistics and the Framingham Heart Study, the rate of death from myocardial infarction or stroke for

men in the age range in which erectile dysfunction is common is approximately 170 per million men per week. Therefore, it appears that sildenafil therapy is safe for most men. Nevertheless, given that most of the men who died had underlying cardiovascular disease; cardiovascular status should be carefully assessed before treatment. The combination of nitrates and sildenafil has resulted in severe hypotension and 16 deaths in the United States. Therefore, nitrate therapy is an absolute contraindication to sildenafil therapy (Lue T F 2000).

Sildenafil is absorbed well during fasting, and the plasma concentrations are maximal within 30 to 120 minutes (mean, 60). It is eliminated predominantly by hepatic metabolism, and the terminal half-life is about four hours. The recommended starting dose is 50 mg taken one hour before sexual activity. The maximal recommended frequency is once per day. On the basis of effectiveness and side effects, the dose may be increased to 100 mg or decreased to 25 mg (Lue T F 2000). There is no specific contraindication to use of sildenafil (Viagra) in transplant patients so long as standard precautions are taken regarding concomitant coronary artery disease.

Oral vardenafil (Phosphodiesterase-5 Enzyme Inhibitor) therapy has a high efficacy and a low incidence of adverse events for kidney transplant recipients with ED (Yang, Ju et al. 2008). Vardenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum; when sexual stimulation causes local release of NO, inhibition of PDE-5 by vardenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. so it can prolong erectile duration of ED patients (Wang and Huang 2009); at recommended doses, it has no effect in the absence of sexual stimulation.

Transurethral administration of alprostadil (synthetic form of prostaglandin E₁) or intracavernous injection resulting in an erection sufficient for intercourse has been used successfully. The most effective intracavernous therapy used is a three-drug mixture containing papaverine, phentolamine, and alprostadil (trimix). The usual dose of trimix solution ranges from 0.1 to 0.5 ml. The rate of response to this solution is as high as 90 percent (Bennett 1991). In case of drug treatment failure, penile prosthesis can be considered even in transplanted patients (Lasaponara, Pasquale et al. 2009; Phe, Roupret et al. 2009).

3. Female reproduction

3.1 Menstrual cycle

The menstrual cycle is a hormonally controlled process of events occurring through the hypothalamic-pituitary-ovarian axis and reflected by the histological changes in the endometrium.

The normal menstrual cycle is a tightly coordinated cycle of stimulatory and inhibitory effects that results in the release of a single mature oocyte from a pool of hundreds of thousands of primordial oocytes.

The menstrual cycle lasts 25 to 30 days in most women. It is divided into two successive phases: the follicular phase and the luteal phase. By convention, the day of menstruation is designated as day 1 of the menstrual cycle. The luteal phase is remarkably constant in length and lasts 13 to 15 days, but length of the follicular phase is variable. The average duration of flow is 4 to 6 days but can be as few as 2 days and as many as 7 days. A flow of longer than 7 days deserves evaluation (Higham 1990). The average blood loss during one menses is about 30 mL. A flow of 80 mL or more can lead to anemia and should be evaluated (Cohen

and Galbraith 2001). However, it is not necessary to measure menstrual flow; a patient's perception of abnormal menses deserves evaluation and treatment.

By definition menorrhagia is excessive and prolonged uterine bleeding at regular intervals; metrorrhagia is irregular, intermenstrual bleeding. Menometrorrhagia is heavy, prolonged, irregular bleeding at frequent, irregular intervals. Polymenorrhea is frequent, regular episodes of uterine bleeding at intervals of less than 21 days. Oligomenorrhea is irregular bleeding occurring at prolonged intervals of more than 35 days. Amenorrhea is absence of uterine bleeding (Sciarra J 2001).

There is relatively little cycle variability among women between the ages of 20 and 40 years. In comparison, there is significantly more cycle variability for the first 5 to 7 years after menarche and for the last 10 years before cessation of menses (Treloar 1967).

3.2 Menstrual cycle irregularities in end stage renal disease

Menstrual problem is common among women with renal insufficiency. It is partly because of abnormal bleeding time due to platelet dysfunction and also because of failure to ovulate or sustain adequate corpus luteum function.

Amenorrhea is common by the time the patient reaches end-stage renal disease. The menstrual cycle typically remains irregular with scanty flow after the initiation of maintenance dialysis, although normal menses are restored in some women (Holley 1997). In others, menorrhagia develops, sometimes leading to significant blood loss and increased transfusion requirements.

Oligo/ anovulation is the major factor for these menstrual cycle abnormalities in uremic women. Uremia is associated with hypothalamic-pituitary-gonadal dysfunction.

Leptin is one of the responsible factors involving in this cycle abnormality. In general, serum leptin levels are significantly elevated in patients with renal failure, particularly when compared to age and body mass index (BMI)-matched controls (Wolf 2002). Leptin appears to be one of several factors that influence the maturation of the gonadotropin-releasing hormone (GnRH) pulse generator.

Hyperprolactinemia is common in women with chronic renal failure due to increased secretion and decreased metabolic clearance of this hormone (Sievertsen 1980). The elevated prolactin levels may impair hypothalamic-pituitary function and contribute to sexual dysfunction and galactorrhea in these patients. Although kidney transplantation greatly improves menstrual pattern, but irregular bleeding is still a major problem among women with a transplanted kidney. In a study on 114 women with a transplanted kidney we found normal menstruation in 49%, oligo/ hypomenorrhea or amenorrhea in 31.3% and hypermenorrhea in 19.8% (Lessan-Pezeshki, Ghazizadeh et al. 2004).

In order to reduce the chance of endometrial hyperplasia that results from chronic stimulation of the endometrium with estradiol, medroxyprogesterone acetate (Provera), 10 mg/day orally for 5 days is prescribed. Patients with adequate endogenous estrogens will bleed within 3 to 5 days after medication, indicating adequate endogenous estrogen stimulation of the endometrium. Patients with relatively low levels of endogenous estrogens may have a limited response to the progesterone challenge.

3.3 Sexual dysfunction in uremic women

Sexual desire or drive is defined as the frequency or intensity with which a person desires to participate in sexual activity. Both organic and psychological variables contribute to this

interest. Hormones can act on sexual behavior indirectly by influencing general mood. They can influence sexual interest levels by their peripheral action, such as by increasing genital vasocongestion and sexual sensation or by enhancing the sexual attractiveness of the female by means of smell. Women receiving chronic dialysis tend to experience decreased libido and reduced ability to reach orgasm.

Uremic patient's sexual difficulties are often worsened by hemodialysis, with a lowered frequency of intercourse, reduced sexual desire, and an increased incidence of sexual failure (Thurm JA 1976). Initial treatment goals for uremic women with sexual dysfunction include increasing the adequacy of dialysis, and correcting the anemia of chronic renal failure.

Amenorrheic dialysis patients may have low estradiol levels; this may lead to vaginal atrophy and dryness, thereby resulting in discomfort during intercourse. Such patients may benefit from local estrogen therapy or vaginal lubricants. Successful transplantation is clearly the most effective means to restore normal sexual desire in women with chronic renal failure (Diemont 2000). Sexual desire increases significantly after successful transplantation in most patients, however improvement in frequency of sexual activity and overall sexual satisfaction is not as high as sexual desire.

Low dose testosterone may be effective but, due to potential toxicity, is rarely used. The administration of bromocriptine may help restore sexual function in those with hyperprolactinemia.

3.4 Pregnancy in end stage renal disease

Fertility is reduced in the presence of end-stage renal disease. Conception is rare for women on dialysis, and occurs at a rate of one in every 200 patients (Rizzoni, Ehrich et al. 1992). Pregnancy is often diagnosed late because of menstrual irregularities; thus, early spontaneous abortion may be overlooked. The diagnosis of pregnancy may be difficult in women with end-stage renal disease; particularly because serum levels of beta-human chorionic gonadotropin (beta-hCG) may be increased in the absence of pregnancy. The main risks for a fetus include death, prematurity, and growth retardation. A review by Hou of 37 pregnancies associated with chronic renal dialysis found that 75% to 80% resulted in spontaneous abortion, stillbirth, or neonatal death. (Hou S 1987) Placental abnormalities included abruption, infarction, and microscopic areas of necrosis. No developmental abnormalities were reported, and the incidence of congenital abnormalities appeared to be no greater than for normal pregnancies.

Hypertension is a major problem and may prove very difficult to control. Forty-nine percent of the patients reviewed by Hou became hypertensive during pregnancy. The infants of hepatitis carriers should receive hepatitis B immune globulin and vaccine in the first 72 hours to avoid becoming carriers.

Since 1976, chronic ambulatory peritoneal dialysis (CAPD) has been increasingly used to manage end-stage renal failure. It has several theoretical advantages over hemodialysis for the management of pregnant patients (Mahanty, Cherikh et al. 2001). A more constant intrauterine environment without rapid shifts in fluid, solutes, and electrolytes may benefit a fetus, Redrow compared eight pregnancies managed with peritoneal dialysis with seven managed with hemodialysis (Redrow 1988). Hypotensive episodes appear to be less frequent, hematocrits higher, and control of insulin and glucose levels more exact in the group on peritoneal dialysis. Further experience is needed to determine if this is the preferred mode of dialysis in pregnancy. If peritoneal dialysis is used, the exchange volumes should be decreased (eg, to 1.5 liters) and the frequency should be increased (Jungers and Chauveau 1997).

3.4.1 Management

An increased dose of dialysis appears to be beneficial, with reports of Kt/V values of 6 to 8, on hemodialysis 5-6 days per week (Henrich WL 2004), with the BUN being maintained at under 50 mg/dL or even under 45 mg/dL. Ameliorating the uremic milieu can avoid polyhydramnios, help control hypertension, and improve maternal nutrition. Increased doses of erythropoietin are required to maintain hemoglobin levels in an acceptable range (10 to 11 g/dl) and transfusions are sometimes required (Chao 2002). Protein intake should be 1 g/kg per day plus an additional 20 g/day for fetal growth. Diet should be supplemented with water soluble vitamins and zinc. Metabolic acidosis and hypocalcemia should be corrected. Careful uterine and fetal monitoring during hemodialysis, such as assessment of the fetal heart rate (particularly during the last portion of a session), combined with measures aimed at preventing dialysis-induced hypotension should be performed. In many cases, patients are hospitalized around week 20 of gestation for management of blood pressure, dialysis fluid balance, nutrition and anemia.

If peritoneal dialysis is used, the exchange volumes should be decreased (eg, to 1.5 liters) and the frequency should be increased.

3.5 Pregnancy in renal transplantation

Fertility is usually restored in women with renal transplants and pregnancy is common, occurring in 12% of women at childbearing age in one series (Sturgiss and Davison 1995). Pregnancy success rate exceeds 90% after the first trimester. The recovery of fertility is less common in women who undergo transplantation close to the end of their childbearing years (Hou S 1987). The first reported successful pregnancy occurred in a recipient of a kidney transplant from an identical twin sister performed in 1958 (Murray 1963). Since then, there have been hundreds of successful pregnancies reported in renal transplant recipients (Davison JM 1987). During the last decade there has been a steady increase in the number of pregnancies following renal transplantation (Sgro, Barozzino et al. 2002).

Pregnancy in transplant recipients provides an opportunity to investigate biological processes that may have an impact on graft outcome as well as pregnancy outcome. For example, immunologic adjustments are believed to be involved in implantation as well as a successful acceptance of the allogenic fetus by their mother (Matthew RW 2005).

3.5.1 Effect of pregnancy on graft function

Although pregnancy can cause an increase in the glomerular filtration rate, which could theoretically lead to hyperfiltration and resultant glomerulosclerosis, the hyperfiltration of pregnancy is flow related, with no concomitant increase in intraglomerular pressure (Denton and Baylis 2007).

In cyclosporine treated patients, graft dysfunction after pregnancy was seen in patients with higher mean serum creatinine levels and lower mean cyclosporine doses prior to conception (ArmentiVT, Radomski JS et al. 2000). Overall, in the majority of recipients studied, pregnancy does not appear to cause excessive or irreversible problems with graft function if the function of transplant organ is stable prior to pregnancy (Armenti, Constantinescu et al. 2008).

The long-term effect of pregnancy on renal function is less clear. Two small studies in which matched nonpregnant controls were used found conflicting results: no deleterious effect in one with 15 year follow-up; and an increase in the plasma creatinine concentration of 0.5 to

0.7 mg/dL at 3 to 12 months in the other (Salmela, Kyllonen et al. 1993; Sturgiss and Davison 1995). The latter report also suggested that a second pregnancy might carry a greater risk, as renal function deteriorated in three of seven women (Salmela, Kyllonen et al. 1993).

The incidence of acute rejection is not greater than expected for non-pregnant transplant patients. The incidence of acute rejection during pregnancy and three months after delivery varies between 9 and 14.5% in the published series. Rejection is sometimes difficult to diagnose and an ultrasound-guided biopsy may be helpful to diagnose acute pyelonephritis, recurrent glomerulonephritis, and severe pre-eclampsia. Renal biopsy should be performed before starting anti-rejection therapy, and high steroid doses are the first line of treatment. It has been suggested that acute rejection during the puerperium may be due to a return to a normal immune status or to a rebound effect from the altered gestational immune responsiveness. Therefore, immunosuppression should be re-adjusted immediately after delivery.

3.6 Immunosuppressive drugs in pregnancy

Immunosuppression in pregnancy is a concern from the perspective of both maternal and fetal safety issues. Blood volume and volume of distribution increase during pregnancy thus blood levels of immunosuppressive drugs are often lower, though there is no evidence that effective immunosuppression is inadequate if pre-pregnancy doses are used. We currently have limited information regarding the toxicities and teratogenic potentials of these agents, although our knowledge has recently increased as more women maintained on immunosuppressive therapy for solid organ transplants have opted to become pregnant.

3.6.1 Glucocorticoids

The most commonly used glucocorticoids are the short acting agents; prednisone, prednisolone and methyl prednisolone. Radiolabeled prednisone and prednisolone can cross the placenta, but maternal / cord blood ratios are approximately 10:1 (Beitins 1972). In utero exposure to high-dose steroid and immunosuppressive agents does not seem to be associated with an increased incidence of congenital anomalies in the offspring of pregnant women with a renal transplant. Adrenal insufficiency and thymic hypoplasia have occasionally been described in the infants of transplant recipients, but these problems are unlikely if the dose of prednisone has been decreased to 15 mg. Cases of cleft palate, mental retardation, have also been described in humans after in utero corticosteroid exposure. Glucocorticoid therapy during pregnancy can result in premature rupture of the membranes (PROM) and intrauterine growth restriction. The increased risk of PROM with prednisone therapy likely reflects the inhibitory effects of glucocorticoids on fetal membrane extracellular matrix synthesis. Alternatively, PROM may be the result of prednisone's stimulatory effects on fetal membrane, placental, and decidual corticotropin releasing hormone. Furthermore, pregnancy-induced hypertension, gestational diabetes, and osteoporosis can be exacerbated.

Doses of prednisone greater than 20 mg/d have been associated with serious maternal infection, however treatment of rejection with steroids, if necessary, should not be avoided during pregnancy (Lessan-Pezeshki M 2002).

Current data suggest that steroids and immunosuppressive agents in the doses used to prevent graft rejection in transplant recipients are well tolerated by the fetus. Long-term

studies are required to determine whether there may be other effects, particularly an increase in the incidence of malignancies or abnormalities in the subsequent generation. FDA rates the risk of prednisone use in pregnancy as C which implies that "Risks can not be ruled out".

3.6.2 Azathioprine

Azathioprine is an antimetabolite, an imidazole derivative of 6- mercaptopurine . It is commonly used during pregnancy in transplant recipients. Radioactive labeling studies in humans have shown that 64 - 93 percent of azathioprine administered to mothers appears in fetal blood as inactive metabolites (Sarikoski 1973). Azathioprine can cause transient gaps or breaks in lymphocyte chromosomes. Germ cells and other tissues have not been studied. In the adult, azathioprine is metabolized to 6- mercaptopurine. The immature fetal liver lacks the enzyme inosinate pyrophosphorylase, needed for conversion, and the fetus is relatively protected from the effects of the drug (Lessan-Pezeshki M 2002). The desired drug dose of azathioprin is 2 mg/kg/day or less. In high doses (6 mg/kg), azathioprine is teratogenic in animals. In human studies low birth weights, prematurity, jaundice, respiratory distress syndrome and aspiration have been reported in kidney transplant recipients. Azathioprine has been associated with a dose related myelosuppression in the fetus, but leukopenia is not usually a problem in the neonate if the maternal white blood count is maintained at greater than 7500 /mm³ (Armenti, Constantinescu et al. 2008).

FDA rated azathioprine use during pregnancy as D which implies that "positive evidence of risk exists but potential benefit may outweigh the risk"

3.6.3 Cyclosporine

Cyclosporine is a small cyclic polypeptide of fungal origin that inhibits calcineurin. There is little or no transplacental passage of cyclosporine in rodents (Safwenberg, Backman-Bave et al. 1977). In comparison, there are conflicting reports on the transfer of cyclosporine across the human placenta. Studies in pregnant rats have generally shown no effect of cyclosporine on organogenesis, although some renal proximal tubular cell damage can occur (Bailie, Elder et al. 2007). Human data showed that administration of cyclosporine was associated with low birth weights and a higher incidence of maternal diabetes, hypertension and renal allograft dysfunction. Cyclosporine metabolism appears to be increased during pregnancy and higher doses may be required to maintain plasma levels in the therapeutic range (Murirhead 1992). In women several years post-transplant with stable renal function, the pre-pregnancy dose can be continued. Some of the pregnancies in cyclosporine- treated women were complicated by preeclampsia. Cyclosporine increases production of thromboxane and endothelin, which have both been implicated in the pathogenesis of preeclampsia. Because of this, some physicians have suggested that the dose be limited to 2 to 4 mg/kg per day (Lindheimer Md and 1992).

Although the safety of cyclosporine is not well established in pregnancy, but it does not appear to be a major teratogen, as suggested by the results of a meta-analysis of 15 studies (Bar Oz 2001).

FDA rates the risk of cyclosporine use in pregnancy as C.

3.6.4 Tacrolimus

Tacrolimus is another calcineurin inhibitor. Experience with tacrolimus in pregnancy is limited. Among 100 pregnancies in 84 women treated with tacrolimus, of whom 27 percent

were renal transplant recipients, 68 progressed to a live birth, with 60 percent of deliveries being premature (Kaniz and 2000). It has been associated with neonatal hyperkalemia. As with cyclosporine, patients taking tacrolimus require frequent monitoring of renal function and drug levels. During pregnancy, the hepatic cytochrome p450 enzymes may be inhibited, which can lead to increased serum level of tacrolimus. The dose may therefore have to be significantly reduced to prevent toxicity (sometimes as much as 60 %) (Lessan-Pezeshki M 2002).

FDA rates the risk of tacrolimus use in pregnancy as C.

3.6.5 Mycophenolate Mofetil (MMF)

MMF is a selective antimetabolite which impairs lymphocyte function by blocking purine biosynthesis via inhibition of the enzyme inosine monophosphate dehydrogenase. Mycophenolate was developed as a replacement for azathioprine for maintenance immunosuppression. It is not nephrotoxic, and has less bone marrow toxicity than azathioprine.

MMF has been reported to cause head and eye malformations in the offspring of rat. Reported experience in human pregnancy with MMF is limited. There have been birth defects in few cases, but current data are insufficient to determine incidence of specific malformation. Among the 14 MMF-exposed offspring that has been reported, the underlying maternal conditions were kidney transplantation (N=7), lupus nephritis (N=4), liver transplantation, heart transplantation, and recurrent erythema multiforme. All were exposed in early pregnancy. The most distinctive malformation was moderate-to-severe microtia or anotia in 12, with external auditory canal atresia in 9. Other common craniofacial malformations and minor anomalies included orofacial clefts, hypertelorism, coloboma, and micrognathia. Six had cardiovascular malformations, of which three were either conotruncal or aortic arch defects (Anderka, Lin et al. 2009).

The manufacturer of MMF recommends that women of child-bearing age should have a negative pregnancy test prior to the initiation of therapy. We currently recommend that allograft recipients who wish to conceive should change from MMF to azathioprine, if there are no contraindications to the switch. MMF should be stopped 6 weeks prior to conception. FDA rates the risk of MMF use in pregnancy as D.

3.6.6 Sirolimus

Sirolimus is a macrolide antibiotic compound that is structurally related to tacrolimus. Following entry into the cytoplasm, sirolimus binds to the FK binding protein and presumably modulates the activity of the mammalian target of rapamycin (mTOR). The mTOR inhibits interleukin-2 mediated signal transduction, resulting in cell cycle arrest in the G1-S phase (Danovitch GM 2005). It causes delayed ossification in animal reproductive studies, and its use is contraindicated in human until more data are available. Its use should also be discontinued at least 6 weeks prior to attempted conception.

In general, we recommend that women post-transplant who wish to conceive be switched prior to conception from sirolimus to cyclosporine. Upon delivery, it is recommended to switch the mother back to her basal immunosuppression in view of the potential benefits of the newer agents to prevent late acute rejection and chronic allograft nephropathy.

FDA rates the risk of sirolimus use in pregnancy as C.

3.6.7 OKT3 and polyclonal antibodies

OKT3 is a mouse antibody licensed for antirejection therapy, being directed against the CD3 antigen that is closely associated with the T cell receptor. It crosses the placenta. The National Transplantation Pregnancy Registry (NTPR) has reported the treatment of five women with OKT3 during pregnancy, with four surviving infants (Eisenberg 1997). The effect of polyclonal antibodies on the developing fetus is not known, but the IgG component would be expected to cross the placenta.

3.6.8 Intravenous Immune Globulins (IVIG)

Pooled human gamma-globulin preparations which were initially developed for the treatment of humoral immune deficiency disorders, proving to be invaluable in certain defined situations in clinical transplantation when used alone or in combination with plasmapheresis, such as antibody mediated rejection (Danovitch GM 2005). IgG is selectively transported across the placenta and the amount transferred increases with gestational age and dose. No cases of human deficiency virus (HIV) transmission have been reported with the use of IVIG, but adverse effects include thrombosis, alopecia, liver function disturbances, transient neutropenia, chills, nausea, flushing, tightness of chest and anaphylactic reaction in those with IgA antibodies.

There is little information regarding the teratogenicity of IVIG in animals. One report showed that IVIG was well tolerated in pregnant mice with induced antiphospholipid antibody syndrome (Bakimer 1993). In humans, IVIG appears to cross the placenta after 32 weeks of gestation, even after modification that alters the Fc binding sites (Hockel 1986). There have been no reports of fetal malformations in humans. However, IVIG is not completely benign, since hemolytic disease of the newborn and transmission of hepatitis C has been reported in selected cases.

3.6.9 Leflunomide

Leflunomide is an antimetabolite with both immunosuppressive and antiviral activities. It has been used successfully in the treatment of polyoma virus nephropathy (Danovitch GM 2005). It has marked teratogenic properties.

FDA rates its use during pregnancy as X. This medication should not be used during pregnancy or breast feeding.

3.7 Management of pregnancy in kidney transplant patient's guidelines:

All women of childbearing age should be counseled concerning the possibility and risks of pregnancy after kidney transplantation. Women who are not rubella immune should receive the rubella vaccine before transplantation, because live virus vaccines are contraindicated post transplantation (Hou S and 1999). Women are usually advised to wait at least one year after living related donor transplantation and two years after cadaveric renal transplantation (Lessan-Pezeshki M 2002). However, waiting 5 or more years may result in impaired renal function post partum that fails to recover, because of gradually deteriorating renal function secondary to chronic allograft nephropathy.

Criteria that should be ideally met before conception are shown in table 1.

At least 1 year post transplantation
 Stable renal function with creatinine < 1.5 mg/dl
 No recent episodes of acute rejection
 BP \leq 140/90 mmHg on medications
 Proteinuria < 500 mg/ day
 Prednisone \leq 15 mg/day
 Azathioprine \leq 2 mg /kg/day
 Cyclosporine 2- 4 mg/ kg/ day
 Normal allograft ultrasound

Table 1. Criteria for transplant recipients contemplating pregnancy

3.7.1 Management of preeclampsia and chronic hypertension

Preeclampsia is the most common complication, affecting 30% of pregnancies in renal transplant recipients, especially those with pre-transplant hypertension. Women with mild to moderate hypertension should be watched closely, warned about signs of early superimposed preeclampsia.

In transplant recipients, changes in urinary protein excretion, plasma uric acid, platelet count, or liver function tests seem to be less useful as markers of preeclampsia than in the normal population. Blood pressure, renal function, proteinuria and weight should be monitored every 2-4 weeks, with more attention during the third trimester. Anti-hypertensive agents should be changed to those tolerated during pregnancy.

3.7.2 Antihypertensive drugs used in pregnancy

Safety and efficacy of Alpha Methyl dopa are supported in several randomized trials and in 7.5 years follow up study of children born to treated mothers.

Beta Blockers; especially Atenolol and Metoprolol, appear to be safe and efficacious in late pregnancy; but fetal growth retardation has been noted when treatment was started in early or midgestation (Lindheimer MD. Davison JM 2001).

Hydralazine is safe and used frequently as adjunctive therapy with α methyl dopa and β blockers.

Calcium Channel Blockers such as Nifedipine, Nicardipine and Verapamil have been used in severe hypertension. They do not appear to be associated with any increase in congenital anomalies when used in the first trimester.

Calcium channel blockers may potentiate the hypotensive effects and neuromuscular blockade of magnesium and the interaction should be kept in mind when the drugs are used in women with a possibility of developing preeclampsia (Dynder 1988).

Labetalol appears to be as effective as methyl dopa, but there is little follow up information on children born to mothers treated with this drug.

The second and third trimester exposure to ACE inhibitors and AT1 antagonists may be associated with serious adverse fetal effects. Most of these problems have been disturbances of fetal and neonatal renal function, such as oligohydramnios, neonatal anuria, renal failure and death (Pryde 1993). The fetal outcome is generally good in women who present in early pregnancy while taking an ACE inhibitor if the drug is stopped.

Continued administration of an ACE inhibitor during pregnancy is contraindicated (Shotan 1994).

The use of thiazide diuretics has been approved in women with chronic hypertension if prescribed before gestation; however, the recommendation is against their use in preeclamptic women, who often manifest decreased intravascular volumes and poor placental perfusion.

3.7.3 Management of infection

Pregnancy is associated with suppression of the adaptive immune system. There is evidence that pregnant women in general are more susceptible to infection. Infection also is an important consideration in any patient receiving immunosuppressive drugs, including transplant patients.

3.7.3.1 Bacterial

Urinary tract infections are the most common bacterial infections and occur in up to 40% of pregnant transplant recipients, and are particularly common in patients who develop end-stage renal disease due to pyelonephritis. These women should have monthly screening urine cultures (Armenti, Constantinescu et al. 2008), if asymptomatic bacteriuria is present; the patient should be treated for 2 weeks and may be treated with suppressive doses of antibiotics for the rest of the pregnancy (Lessan-Pezeshki M 2002). If there is a need for invasive procedures such as fetal monitoring with scalp electrodes or intrauterine pressure monitoring, prophylactic antibiotics are recommended. Aseptic technique should be used for even minor surgery and steroid therapy augmented.

3.7.3.2 Viral

Cytomegalovirus (CMV) remains the most frequent cause of viral infection post transplantation, however if the patient waits the recommended time after transplantation to become pregnant, she has passed the peak time of risk for CMV infection.

Infection in the fetus can be diagnosed by culturing the amniotic fluid. Titers of anti-CMV IgG and IgM during pregnancy are recommended, Ganciclovir has caused birth defects in animals when administered at twice human dose (Hou S and 1999). Herpes Simplex Virus (HSV) infection before 20 weeks gestation is associated with an increased rate of abortion. A positive HSV cervical culture at term is an indication for cesarean section. This can minimize the risk for neonatal herpes. Acyclovir can be safely used in pregnancy (Andrew 1992).

Continuous exposure to CsA in utero seems to impair T-, B- and NK-cell development and function in neonates. This effect is prolonged throughout the first year of life. In addition, low levels of serum immunoglobulins occur at the same time. This leads to suggest a delayed administration of classical vaccinations (after the first 6 months of life) in view of the potential risks of both sub-optimal immunologic responses, and adverse events after the administration of live, attenuated vaccines in infants born from young female organ transplant recipients (Schen 2002).

An infant born to an HBSAg - positive mother should be given hepatitis B immunoglobulin within 12 hours of birth and HBV vaccine at another site within 48 hours followed by a booster injection at 1 and 6 month.

The combination of immunoglobulin and vaccine offers protection for more than 90% of infants.

Vertical transmission is believed to be low (<7%) with hepatitis C unless the patient is also infected with the human immunodeficiency virus (Lessan-Pezeshki M 2002).

3.7.4 Labor and delivery

The incidence of pre-term delivery is 50%, because of presence of preeclampsia, renal function deterioration, fetal distress, premature rupture of membrane and premature labor. Intrauterine growth retardation showing small-for-age babies is present in 20% of pregnancies. In general, successful fetal outcome is related to better renal function at conception. Despite immunosuppressive therapy there is no increase of fetal abnormalities. A transplanted kidney rarely obstructs labor, vaginal delivery is recommended in most transplant recipient women. Cesarean section should be performed only for standard obstetric reasons. Delivery should occur in a specialized centre. Care must be taken to avoid fluid overload and infection. At the time of delivery, instrumentation should be minimized. Patients with renal insufficiency may be particularly at risk for water retention secondary to oxytocin (Lessan-Pezeshki M 2002).

In the perinatal period, the steroid dose should be augmented to cover the stress of labor and to prevent postpartum rejection. Hydrocortisone, 100 mg every 6 hours, should be given during labor and delivery. In the puerperium, renal function, proteinuria, blood pressure, cyclosporine/tacrolimus blood levels and fluid balance should be closely monitored.

3.7.5 Breastfeeding

Breastfeeding is discouraged for patients taking any immunosuppressive drugs. Cyclosporine measurement in maternal blood and breast milk revealed a mean breast milk/maternal blood level ratio of 84% (Munoz-Flores- thiagarajan and 2001).

Azathioprine is also appears in breast milk, these levels can be toxic to a newborn, and nursing is not recommended. Similar recommendations exist for tacrolimus or any other immunosuppressive agents.

In summary, Because the outcome of pregnancy in transplantation are so different than those in chronic dialysis, it is advisable to treat end-stage renal disease patients with transplantation and wait until renal function has been stable for 1 to 2 years before undertaking a planned pregnancy. Such planned pregnancies offer the mother and fetus the best chance of favorable outcome. Before any woman with a renal transplant embarks on a pregnancy, she should be counseled by an obstetrician and transplant physician. Pregnancy appears to have no significant effect on graft function or survival; however, an important concern is that a mother may not survive to bring up the child that she bears. (Davison JM 1987)

3.8 Contraception for transplant patients:

Most female transplant recipients are unaware that transplantation has reversed the relative infertility associated with end-stage renal disease. The incidence of unwanted pregnancy among female kidney transplant recipients is significantly higher than general population. An unplanned pregnancy puts this special group at higher risk; either an induced abortion or continuing the pregnancy without a preconceptional evaluation could be harmful (Lessan-Pezeshki and 2004). Outcomes for unwanted pregnancies are inferior to outcomes for planned pregnancies, so it is strongly advised that every sexually active transplant recipient attend a family-planning counseling session. Contraceptive counseling should be provided before transplantation surgery, because ovulatory cycles may begin within 1 to 2 months after transplantation in women with grafts that are functioning well. Women who

do not desire pregnancy should be protected by an effective method of contraception. Surgical contraception (sterilization) should be considered for those who have completed their family. Tubal ligation can be performed at the time of transplantation surgery. Vasectomy is also an effective form of permanent contraception with little morbidity. The risk for infection may be increased with the use of an intrauterine device in immunocompromised patients, and their efficacy decrease because of anti-inflammatory effects of immunosuppressive agents (Zerner J, Doil KL et al. 1981). New devices containing levonorgestrel are more effective than previous copper containing devices, with fewer side effects (Fong and Singh 1999).

Depot medroxyprogesterone acetate injection at three months interval is another effective method of contraception for these patients but return of fertility after discontinuation is not fast and loss of bone mineral density is a concern with its long-term use.

Although low dose estrogen progesterone oral contraceptive preparations are not contraindicated for transplant patients, but they should be used with caution because they may cause or aggravate hypertension or precipitate thromboembolism, especially in the context of cyclosporine immunosuppression. Calcineurin inhibitors levels should also be monitored soon after the contraceptive is started. Because of unfounded fear of using contraceptive pills, a significant number of kidney transplant recipients use less effective methods such as coitus interruptus. In our study on unwanted pregnancy we found that 92% of women with unwanted pregnancies were using coitus interruptus as the only method of contraception (Ghazizadeh 2005). Progestin-only pill is an option for women who have contraindication to use estrogen but their failure rate is higher than combined oral contraceptive pills. Barrier contraceptives such as male condom are the safest modality but depend on user compliance for efficacy. It provides some protection against sexually transmitted diseases. Patients should know about emergency contraception in case of a broken condom. Two tablets of 0.75 mg of Levonorgestrel pills are administered within 72 hours of unprotected intercourse. Considering the above mentioned issues, unplanned pregnancy should be avoided by proper use of effective contraception.

4. Conclusion

Chronic kidney disease affects reproductive and sexual functions in both sexes. Although adequate dialysis will improve this dysfunction to some extent, but successful kidney transplantation has a better impact on fertility and reproductive functions.

Reproductive success is a common, expected outcome for male and female recipients of kidney transplant. One of the most impressive aspects of successful renal transplantation in the young person is the ability of the male patient to father a child and the female patient to give birth to a healthy baby. There are, however, important maternal and fetal complications that need to be considered to provide optimal care to the mother and her infant.

5. References

- Delano, B. (1989). "Improvements in quality of life following treatment with r-HuEPO in anemic hemodialysis patients." *Am J Kidney Dis*(14): 14.
- Diemont, W., Vrugink, PA, Meuleman, EJ, et al. (2000). "Sexual dysfunction after renal replacement therapy." *Am J Kidney Dis* 35: 845.

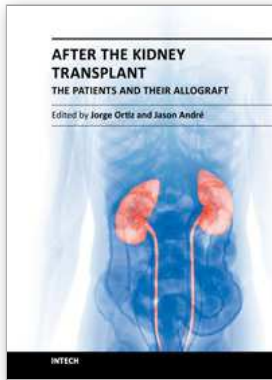
- Finkel, D., Phillips, JL, Snyder, PJ. (1985). "Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism." *N Engl J Med*(313): 651.
- Grossman, E., Swan, SK, Muirhead, GJ, et al. (2004). "The pharmacokinetics and hemodynamics of sildenafil citrate in male hemodialysis patients." *Kidney Int*(66): 367.
- Hockel, M., Kaufmann, R, (1986). "Placental transfer of class G immunoglobulins treated with B-propiolactone (P-PL) for intravenous application a case report." *J Perinat Med* 14: 205.
- Holdsworth, S., Atkins, RC, de Kretser, DM. (1977). "The pituitary-testicular axis in men with chronic renal failure." *N Engl J Med* (296): 1245.
- Holdsworth, S., de Kretser, DM, Atkins, RC (1978). " A comparison of hemodialysis and transplantation in reversing the uremic disturbance of male reproductive function." *Clin Nephrol*(10): 146.
- Holley, J., Schmidt, RJ, Bender, FH, et al. (1997). "Gynecologic and reproductive issues in women on dialysis." *Am J Kidney Dis* 29: 685.
- Ifudu, O. (1998). "Care of patients undergoing hemodialysis." *N Engl J Med*(339): 1054.
- Levitan, D., Moser, SA, Goldstein, DA, et al. . . (1984). "Disturbances in the hypothalamic-pituitary-gonadal axis in male patients with acute renal failure." *Am J Nephrol* (4): 99.
- Lim, V., Fang, VS. (1976). "Restoration of plasma testosterone levels in uremic men with clomiphene citrate." *J Clin Endocrinol Metab*(43): 1370.
- Rosas, S., Joffe, M, Franklin, E, et al. (2003). "Association of decreased quality of life and erectile dysfunction in hemodialysis patients." *Kidney Int*(64): 232.
- Sawin, C., Longcope, C, Schmitt, GW, Ryan, RJ. (1973). "Blood levels of gonadotropins and gonadal hormones in gynecomastia associated with chronic hemodialysis. ." *J Clin Endocrinol Metab* 36: 988.
- Sievertsen, G., Lim, VS, Nakawatase, C, Frohman, LA, (1980). "Metabolic clearance and secretion rates of human prolactin in normal subjects and patients with chronic renal failure. ." *J Clin Endocrinol Metab* 50: 846.
- Turk, S., Karalezli, G, Tonbul, HZ, et al. (2001). "Erectile dysfunction and the effects of sildenafil treatment in patients on haemodialysis and continuous ambulatory peritoneal dialysis." *Nephrol Dial Transplant*(16): 1818.
- Wolf, G., Chen, S, Han, DC, Ziyadeh, FN, (2002). "Leptin and renal disease." *Am J Kidney Dis* 39: 1.
- Anderka, M. T., A. E. Lin, et al. (2009). "Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature." *Am J Med Genet A* 149A(6): 1241-8.
- Andrew, E., Yankaskas, BC, Cordero, JF, Schoeffler, K, Hampp, S: (1992). "Acylovir in pregnancy registry: six years experience." *Obstet Gynecol*(79): 7-13.
- Armenti, V. T., S. Constantinescu, et al. (2008). "Pregnancy after transplantation." *Transplant Rev (Orlando)* 22(4): 223-40.
- ArmentiVT, Radomski JS, et al. (2000). "Report from the National Transplantation Pregnancy Registry(NTPR) outcome of pregnancy after transplantation." *Clin Transpl* 123-34.
- Bailie, G. R., S. J. Elder, et al. (2007). "Sexual dysfunction in dialysis patients treated with antihypertensive or antidepressive medications: results from the DOPPS." *Nephrol Dial Transplant* 22(4): 1163-70.

- Bakimer, R., Guilburd, B, Zurgil, N, Schoenfeld, Y, (1993). "The effect of intravenous gamma globulin on the induction of experimental antiphospholipid syndrome. ." *Clin Immunol Immunopathol* 69: 97.
- Bar Oz, B., Hackman, R, Einaron, T, Koren, G, (2001). " Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis." *Transplantation* 71(8): 1051-5.
- Beitins, I., Bayard, F, Ances, IG, et al. (1972). "The transplacental passage of prednisone and prednisolone in pregnancy near term." *J Pediatr* (81): 936.
- Bennett, A., Carpenter, AJ, Barada, JH, (1991). "An improved vasoactive drug combination for a pharmacological erection program. ." *J Urol* 146 1564-5.
- Berek, J. S. (2002). *Novak's Gynecology*, Lippincott Williams & Wilkins.
- Billir BM; Molitch ME; Vance ML; Cannistraro KB; Davis KR; Simons JA; Schoenfelder JR; Klibanski A (1996). "Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline." *J Clin Endocrinol Metab* 81(6): 2338-43.
- Chao, A., et al (2002). "Pregnancy in women who undergo longterm dialysis." *Am J Obstet Gynecol* 187: 152-156.
- Cohen, D. and C. Galbraith (2001). "General health management and long-term care of the renal transplant recipient." *Am J Kidney Dis* 38(6 Suppl 6): S10-24.
- Cowden, E., Ratcliff, WA, Ratcliff, JG, et al (1981). "Hypothalamic-Pituitary function in uremia." *Acta Endocrinol* 98: 488.
- Danovitch GM (2005). *Handbook of Kidney Transplantation*, Lippincott Williams&Wilkins.
- Davison JM (1987). "Renal transplantation and pregnancy. ." *Am J Kidney Dis* 9: 374.
- De Celis, R. and N. Pedron-Nuevo (1999). "Male fertility of kidney transplant patients with one to ten years of evolution using a conventional immunosuppressive regimen." *Arch Androl* 42(1): 9-20.
- de Vries, C., Gooren, LJG, Oe, PL. (1984). "Hemodialysis and testicular function." *Int J Androl*(7): 97.
- Denton, K. and C. Baylis (2007). "Physiological and molecular mechanisms governing sexual dimorphism of kidney, cardiac, and vascular function." *Am J Physiol Regul Integr Comp Physiol* 292(2): R697-9.
- Diemont, W., Vrugink, PA, Meuleman, EJ, et al. (2000). "Sexual dysfunction after renal replacement therapy." *Am J Kidney Dis* (35): 845.
- Dynder, S., Cardwell, MS, (1988). "Neuromuscular blockade with magnesium sulfate and nifedipine." *Am J Obstet Gynecol*(161): 35-36.
- Eid, M. M., I. A. Abdel-Hamid, et al. (1996). "Assessment of sperm motion characteristics in infertile renal transplant recipients using computerized analysis." *Int J Androl* 19(6): 338-44.
- Eisenberg, J., Armenti, VT ,Mc Grovy, CH, et al (1997). "National transplantation pregnancy registry(NTPR) : Use of muromonab-CD3(OKT3) during pregnancy in female transplant recipients." *Am Soc Transplant phys*(20): 108.
- Esteban de la Rosa, R. J., J. A. Bravo Soto, et al. (2003). "Influence of age, sex, and hepatitis C virus infection on peripheral blood lymphocyte subsets in stable kidney transplantation." *Transplant Proc* 35(8): 2905-7.
- Fong, Y. F. and K. Singh (1999). "Effect of the levonorgestrel-releasing intrauterine system on uterine myomas in a renal transplant patient." *Contraception* 60(1): 51-3.

- Ghazizadeh, S., Lessan-Pezeshki, M, Khatami, MR, Mahdavi, M, (2005). "Unwanted Pregnancy in Kidney Transplant Recipients in Iran." *Transplantation Proceedings* 37(7): 3085-3086.
- Hagen C, O. K., McNeilly AS (1976). "Prolactin and the pituitary gonadal axis in male uremic patients on regular dialysis. ." *Acta Endocrinol (Copenh)*(82): 29.
- Henrich WL (2004). *Principles and Practice of Dialysis*, Lippincott Williams&Wilkins.
- Higham, J., O'Brien, PMS, Shaw, RM, (1990). "Assessment of menstrual blood loss using pictorial chart." *Br J Obstet Gynaecol* 97: 734.
- Hou S (1987). "Pregnancy in women requiring dialysis for renal failure." *Am J Kidney Dis* 9 368.
- Hou S and (1999). "Pregnancy in chronic renal insufficiency and end stage renal disease. ." *Am J Kidney Dis* (33): 235.
- Issac, R., et al (1978). "Effect of parathyroid hormone on plasma prolactin men." (47): 18.
- Juenemann, K.-P., Lue, TF, Luo, JA, Benowitz, NL, Abozeid, M, Tanagho, EA. (1987). "The effect of cigarette smoking on penile erection." *J Urol* 138 438-41.
- Jungers, P. and D. Chauveau (1997). "Pregnancy in renal disease" *Kidney Int* 52: 871-885.
- Kaczmarek, I., Groetzner, J, Adamidis, I, Landwehr, P, (2004). "Sirolimus impairs gonadal function in heart transplant recipients. ." *Am J of Transplantation* 4: 1084.
- Kaniz, A., Harabacz, I, Cowirick, IS, et al. and (2000). "Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. ." *Transplantation proceeding*(70): 1718.
- Lasaponara, F., G. Pasquale, et al. (2009). "[Penile prosthesis implantation in kidney-transplanted patients.]." *Urologia* 76(2): 95-97.
- LeRoith, D., Danovitz, G, Trestian, S, Spitz, IM. (1980). "Dissociation of pituitary glycoprotein response to releasing hormones in chronic renal failure." *Acta Endocrinol (Copenh)*(93): 277.
- Lessan-Pezeshki M (2002). "Pregnancy After Renal Transplantation, Points to Consider " *Nephrol Dial Transplant* 17: 703-707.
- Lessan-Pezeshki, M., S. Ghazizadeh, et al. (2004). "Fertility and contraceptive issues after kidney transplantation in women." *Transplant Proc* 36(5): 1405-6.
- Lessan-Pezeshki, M., Ghazizadeh, S, Khatami, M, R, Mahdavi, M, Razeghi, E, Seifi, S,Ahmadi, F, Maziar,S, and (2004). "Fertility and contraceptive issues after kidney transplantation in women " *Transplantation proceeding* (36): 1405-1406.
- Lim, V., Kathpalia, SC, Henriques, C. (1978). "Endocrine abnormalities associated with chronic renal failure." *Med Clin North Am* 62: 1341.
- Lindheimer Md, K. A. and (1992). "Pregnancy in the renal transplant patients." *Am J Kidney Dis* (19): 173.
- Lindheimer MD.Davison JM, K. A. (2001). "The kidney and hypertension in pregnancy: twenty exciting years." *Semin Nephrol* 21 (2): 173-189.
- Lue T F (2000). "Erectile dysfunction." *The New England Journal of Medicine* 342(24): 1802, 12.
- Mahanty, H. D., W. S. Cherikh, et al. (2001). "Influence of pretransplant pregnancy on survival of renal allografts from living donors." *Transplantation* 72(2): 228-32.
- Matthew RW (2005). *Medical Management of Kidney transplantation*, Lippincott Williams & Wilkins.
- Miller, N., Gold, MS. (1988). "The human sexual response and alcohol and drugs." *J Subst Abuse Treat* 5: 171-7.

- Mirone, V., N. Longo, et al. (2009). "Renal transplantation does not improve erectile function in hemodialysed patients." *Eur Urol* 56(6): 1047-53.
- Muller, I., M. Munder, et al. (2009). "Polymorphonuclear neutrophils and T lymphocytes: strange bedfellows or brothers in arms?" *Trends Immunol* 30(11): 522-30.
- Munoz-Flores- thiagarajan, K., Easterling, T, Davis, C, Bond, EF. and (2001). " Breast-feeding by a cyclosporine- treated mother." *Obstet Gynecol*(97): 816 -8.
- Murirhead, N., Sabharwal, AR, reider, MJ, et al (1992). "The outcome of pregnancy following renal transplantation- the experience of a single center." *Transplantation* proceeding(54): 429.
- Murray, J., Reid, DE, Harrison, JH, et al (1963). "Successful pregnancies after human renal transplantation." *N Engl J Med*: 269:346.
- Nevins, T. E. and D. L. Dunn (1992). "Use of ganciclovir for cytomegalovirus infection." *J Am Soc Nephrol* 2(12 Suppl): S270-3.
- Olshan, A., Mattison, DR, Zwanenburg, TS, (1994). "International Commission for Protection against Environmental Mutagens and Carcinogens. Cyclosporine A: review of genotoxicity and potential for adverse human reproductive and developmental effects. Report of a working group on the genotoxicity of cyclosporine A,." *Mutat Res* 317: 163-173.
- Palmer, B. (1999). "Sexual dysfunction in uremia." *J Am Soc Nephrol* (10): 1381.
- Pece, S., et al , (1979). "Prolactin in chronic renal failure, hemodialysis and transplant patients " *Proc Eur Dial Transplant Assoc* (16): 700.
- Phe, V., M. Roupret, et al. (2009). "[Erectile dysfunction and renal chronic insufficiency: etiology and management]." *Prog Urol* 19(1): 1-7.
- Price, D., Gingell, JC, Gepi-Attee, S, Wareham, K, (1998). "Sildenafil: Study of a novel oral treatment for erectile dysfunction in diabetic men." *Diabet Med* 15: 821-5.
- Procci, W., Goldstein, DA, Adelstein, J, (1981). "Sexual dysfunction in the male patient with uremia; a reappraisal." *Kidney Int* 19: 317.
- Pryde, P., Sedman, AB, Nugent, CE, Barr, M Jr. (1993). "Angiotensin converting enzyme inhibitor fetopathy." *J Am Soc Nephrol* (3): 1575.
- Ramirez, G., O'Neil, W, Jubiz, W, et al (1976). "Thyroid dysfunction in uremia: evidence for thyroid and hypophyseal abnormalities." *Am Intern Med* 84: 627.
- Redrow, M., Cherem, L, Elliott, J, Mangalat, J, (1988). "Dialysis in the management of pregnant patients with renal insufficiency." *Medicine* 67(4): 199-208.
- Rizzoni, G., J. H. Ehrich, et al. (1992). "Successful pregnancies in women on renal replacement therapy: report from the EDTA Registry." *Nephrol Dial Transplant* 7(4): 279-87.
- Safwenberg, J., U. Backman-Bave, et al. (1977). "The effect of blood transfusions on cadaver kidney transplants--an analysis of patients transplanted in Uppsala." *Scand J Urol Nephrol Suppl*(42): 59-61.
- Salmela, K. T., L. E. Kyllonen, et al. (1993). "Impaired renal function after pregnancy in renal transplant recipients." *Transplantation* 56(6): 1372-5.
- Sarikoski, S., Seppala, M. (1973). " Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus." *Am J Obstet Gynecol*(115): 1100.
- Schaefer, F., R. Stanhope, et al. (1989). "Pulsatile gonadotropin secretion in pubertal children with chronic renal failure." *Acta Endocrinol (Copenh)* 120(1): 14-9.

- Schen, F., Stallone, G, Schena, A, Manfredi, G, Derosa, C, Procino, A, Di Paolo, S. (2002). "Pregnancy in renal transplantation: immunologic evaluation of neonates from mothers with transplanted kidney." *Transpl Immunol* 9(2-4): 161-4.
- Schrier RW (2001). *Diseases of the kidney and urinary tract*, Lippincott Williams&Wilkins.
- Sciarra J (2001). *Gynecology &Obstetrics*, Lippincot Williams & Wilkins.
- Seethalakshmi, L., Diamond, DA, Malhotra, RK, Mazanitis, SG, Kumar, S, Menon, M, (1988). "Cyclosporine induced testicular dysfunction: a separation of the nephrotoxic component and an assessment of a 60-day recovery period. ." *Transplant Proc* 20 (Suppl 3): 1005-1010.
- Seethalakshmi, L., Flores, C, Carboni, AA, Bala, R, Diamond, DA, Menon, M, (1990). "Cyclosporine: its effect on testicular function and fertility in the prepubertal rat. ." *J Androl* 11: 17-24.
- Seethalakshmi, L., Flores, C, Diamond, DA, Menon, M, (1990). "Reversal of the toxic effects of cyclosporineA (CsA) on male reproduction and kidney function of rats by simultaneous administration of hCG and FSH." *J Urol* 144: 1489-149.
- Seibel, I., Poli De, Figueiredo CE, Teloken, C, Moraes, JF. (2002). "Efficacy of oral sildenafil in hemodialysis patients with erectile dysfunction." *J Am Soc Nephrol* (13): 2770.
- Sgro, M. D., T. Barozzino, et al. (2002). "Pregnancy outcome post renal transplantation." *Teratology* 65(1): 5-9.
- Shotan, A., Widerhorn, J, Hurst, A, Elkayam, U, (1994). "Risks of angiotensin converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms and recommendations for use." *Am J Med*(96): 451.
- Steele, T., Wuerth, D, Finkelstein, S, et al. (1996). "Sexual experience of the chronic peritoneal dialysis patient." *J Am Soc Nephrol*(7): 1165.
- Stewart-Bentley, M., Gans, D, Horton, R. (1974). "Regulation of gonadal function in uremia." *Metabolism* (23): 1065.
- Sturgiss, S. N. and J. M. Davison (1995). "Effect of pregnancy on the long-term function of renal allografts: an update." *Am J Kidney Dis* 26(1): 54-6.
- Thurm JA (1976). " Effect of chronic renal disease on sexual functioning." *Med Asp Human Sex* 10: 81.
- Toorians, A. W., E. Janssen, et al. (1997). "Chronic renal failure and sexual functioning: clinical status versus objectively assessed sexual response." *Nephrol Dial Transplant* 12(12): 2654-63.
- Treloar, A., Boynton, RE, Behn, BG, Brown, BW, Brown BW, (1967). "Variation of the human menstrual cycle through reproductive life." *Int J Fertil* 12: 77.
- Wang, H. Y. and Y. F. Huang (2009). "Vardenafil for refractory erectile dysfunction: the latest advances." *Zhonghua Nan Ke Xue* 15(11): 1035-8.
- Yang, J., W. Ju, et al. (2008). "Efficacy and safety of vardenafil for kidney transplant recipients with erectile dysfunction." *Zhonghua Nan Ke Xue* 14(10): 911-3.
- Zerner J, Doil KL, et al. (1981). "Intrauterine contraceptive device failures in renal transplant patients." *J Reprod Med.* 26(2): 99-102.
- Zuber, J., D. Anglicheau, et al. (2008). "Sirolimus may reduce fertility in male renal transplant recipients." *Am J Transplant* 8(7): 1471-9.



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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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