Evaluation Of Female Sexual Function Among Renal Transplant Recipients

Thesis
Submitted for partial fulfillment of Master degree in
Dermatology & Andrology
By
Nermin Yassin Mohamed
Faculty of Medicine, Juba University (Sudan)

Supervised by
Prof. Dr. Mohamed Abbas
Assistant Professor of Andrology, Sexual Medicine and S.T.Ds
Faculty of Medicine, Cairo University

DR. Ashraf Selim Zeidan
Lecturer of Andrology, Sexual Medicine and S.T.Ds
Faculty of Medicine, Cairo University

DR. Saheer Al Kashab
Lecturer of Internal Medicine
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
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LIST OF ABBREVIATIONS

ACE: Angiotensin-converting enzyme
AFUD: American Foundation of Urologic Disease
AQPs: Aquaporins
ASEX: Arizona Sexual Experiences Scale
ATP: Adenosine triphosphate
CKD: Chronic kidney disease
CNTF: Ciliary neurotrophic factor
DHEA: Dehydroepiandrosterone
DM: Diabetes mellitus
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
E2,: Estradiol
ED: Erectile dysfunction
ESRD: End stage renal disease
FSD: Female sexual dysfunction
FSF: Female sexual function
FSFI: Female Sexual Function Index
GFR: Glomerular filtration rate
GnRH: Gonadotrophin releasing hormone
HD:  Heamodialysis
HLA:  Human leukocyte antigen
HPG:  Hypothalamic-pituitary-gonadal
HPV:  Human papilloma virus
HTN:  Hypertension
KDOQI:  Kidney Disease Outcomes Quality Initiative
KTx:  kidney transplantation
MMF:  Mycophenolate mofetil
NO:  Nitric oxide
PDE:  Phosphodiesterase
PDS:  Personal Distress Scale
PFSF:  Profile of Female Sexual Function
PRL:  Prolactin level
QOL:  Quality of life
RRT:  Renal replacement therapy
SD:  Sexual dysfunction
SNRIs:  Serotonin–norepinephrine re-uptake inhibitors
SSRIs:  Selective serotonin re-uptake inhibitors, VIP: vasoactive intestinal peptide
**ABSTRACT**

*Introduction:* To date, there is little information in the literature about changing menstrual patterns, sexuality, and fertility after kidney transplantation.

*Aim:* To prospectively determine the effect of renal transplantation for end stage renal disease (ESRD) on female sexual function and relationship to sociodemographic and clinical variables.

*Methods:* We enrolled 100 women, 50 as control group and 50 patients that received kidney transplantation. Patients included were 18–45 years old, on hemodialysis for 12.71±5.62 months following fully functioning kidney transplantation, and on stable corticosteroids immunosuppressive regimen. Demographic data was obtaining from all patients and asked to fill out the Female Sexual Function Index (FSFI).

*Main Outcome Measures:* We evaluated the prevalence of Female Sexual Dysfunction according to the FSFI cutoff points, pregnancy, and menstrual status after kidney transplantation.

*Result:* The result of current study summarized as following: there was a significant decrease in score of total female sexual function score and all domain that include desire, arousal, orgasm and vaginal lubrication except pain (P=0.49) in comparison between renal transplant (Tx) and control women. There was a decrease in full FSFI score as the duration of dialysis increased.

*Conclusion:* We found that restrictions in the lives of women with transplanted kidneys included ceasing sexual activity and leaving active working life and these were due to fear of possible organ damage, although Tx is the most effective way and best choice of renal replacement therapy (RRT) to retain good sexual function in women. Women with transplanted kidneys must be informed about posttransplant sex life and the requirement for regular examinations by a gynecologist. Hence, close collaborations should be formed between patients, andrologists and gynecologists.

*Key words:* Female sexual dysfunction. Renal failure. Renal transplant. Dialysis
INTRODUCTION

Based on the National Health and Social Life Survey scores of 1,749 women, aged between 18 and 59 years, the prevalence of Female Sexual Dysfunction (FSD) was reported to be 43% in the United States (Berman JR 2004).

Sexual dysfunction is more prevalent for women (43%) than men (31%) in US (Laumann et al. 1994).

Sexual dysfunction (SD) refers to a problem during any phase of sexual response cycle that prevents the individual or couple from experiencing satisfaction from sexual activity.

Difficulties with sexuality and sexual functioning are most likely a result of both psychological and physiological factors. For example chronic illness as liver, cardiovascular or kidney disease, side effects of required medications, such as weight gain, hirsutism, and acne can significantly affect one's feelings of being sexually attractive (Matas AJ 2002). So it can have a major impact on quality of life and is a highly prevalent health problem, affecting 22 to 93% of women, with variations according to age groups. Impaired sexual function can have damaging effects on the confidence, sense of wholeness, social relation and marital status of women.

According to National Health Survey, it was estimated that 6.2 million people older than 12 years had chronic renal failure. Chronic renal failure (CRF) and dialysis have a negative effect on sexual function. Sexual dysfunction is common in female patients with CRF and incidence estimates run from 9% before starting dialysis to 60–70% in women on chronic dialysis. More than 50% of women on chronic dialysis complain of decrease of libido and reduced ability to reach orgasm, with the consequence of marked decline in the frequency of intercourse.

Furthermore, posttransplant complications and/or comorbid conditions such as hypertension and depression can require medications that may cause erectile dysfunction (ED), decreased desire, arousal, ability to orgasm, overall sexual satisfaction, and delayed ejaculation in
men (Kennedy SH 2006) and reduce the capacity for orgasm and lubrication in women (Croft H 1999).

Almost all transplantrecipients have or will eventually develop one or more comorbid conditions (eg, diabetes) (Lindau S 2007), or experience side effects from treatments (Kettas E 2008)) as medications that can have a negative effect on their sexuality or sexual functioning.

One of the more recent and largest studies was conducted by Diemont et al in 2000, who compared sexual problems among 3 groups on renal replacement therapy (RRT): HD (n = 208), peritoneal dialysis (n = 192), or renal transplant (RTx; n = 300) and a control group (n = 591) without known kidney disease. The prevalence of sexual problems in the RTx group was 48% in men and 44% in women. For women with an RTx, the most frequently reported sexual problems were reduced libido, lubrication, and problems reaching orgasm. The authors concluded that the prevalence of sexual problems among persons receiving Renal Replacement Therapy (RRT), including Renal transplant (RTx), is substantial and needs further exploration.

In another study Turkish researcher have examined the prevalence of sexual dysfunction, using the Arizona Sexua Expe riences scale (ASEX), in 98 men and women who had received a kTx. The authors reported 94% of women and 57% of men were classified as having a sexual dysfunction. The most commonly reported sexual dysfunctions in women were problems with arousal, reaching orgasm, and low satisfaction with orgasm. (Ozdemir C 2007)
AIM OF THE WORK

The aim of this study is to prospectively determine the effect of renal transplantation for ESRD on female sexual function among premenopausal (Tx) women, as compared to general female population.
Female Pelvic Anatomy

An understanding of female pelvic anatomy and physiology is essential to evaluate and treat female sexual dysfunction. Although the female pelvis is comprised of a continuum of organs interrelated in structure and function, it is helpful to group the pelvic organs into two categories: external and internal genitalia.

The organs of the external genitalia are collectively known as the vulva, which is bound interiorly by the symphysis pubis, posteriorly by the anal sphincter, and laterally by the ischial tuberosities. The vulva consists of the labia, interlabial space, clitoris, and vestibular bulbs. The internal genitalia consist of the vagina, uterus, fallopian tubes and ovaries.

The vagina is an internal genital organ and the vaginal opening (introitus) is usually a median fissure, under the urethral meatus. The hymen is circumferential and is sentinel for vaginal tube. The anterior vaginal wall is separated from the posterior urethral wall by the urethrovaginal septum and there are no secretary glands in the vagina (Williams PL 1995).

Vestibule

The vaginal vestibule is triangular in shape. It corresponds to the dorsal wall of the male cavernosa urethra. Here the external orifice of the urethra with the paraurethral (Skene’s) ducts opening on both sides are localized (Testus L 1990). Their length is 0.5–3 cm and they are found, in women, with the intraurethral (Skene’s) gland which has been named the female prostate (Zavizic M 2000).
This structure can be affected by the same diseases as the male counterpart, including carcinoma and prostatitis; the secretion of these glands, expelled during the female orgasm (female ejaculation) into the vaginal vestibule through the urethral meatus or through the orifices of the paraurethral ducts, contains prostate-specific antigen (Zavizeic M. 2000).

From a physiological point of view the term ‘‘female emission’’ is more accurate than female ejaculation (in a few women there is a powerful expulsion of this fluid); in the male it corresponds to the phase of emission of seminal liquid which is ejected out in the prostatic urethra (Giulinano F 2005).

The lack of the ejaculation phase in the female could explain why women do not have a refractory period and are able to have multiple orgasms. In the mid-line of the vestibule is located a longitudinal formation 4–5 mm wide, with defined margins and more pale than the nearby tissue, thin and well wedged in the dermis of the vestibule, which goes up from the urethral orifice to the sulcus of the inferior surface of the corpora cavernosa of the clitoris up to the glans, described first by Pozzi in 1984 and named “‘masculine bride” (habenulæ uretrales). It corresponds to the dorsal part of the male corpus spongiosum of urethra: it is the female corpus.

**Vagina**

The vagina is a cylindrical organ that connects uterus with external genitalia, usually measuring 7 to 15 cm in length depend on position of uterus. The wall of the vagina consists of three layers: an inner a glandular mucous membrane epithelium, an intermediary, richly supplied, vascular
muscularis layer, and an outer adventitial supportive mesh. Vaginal mucosa is a mucous type, stratified, non-keratinized, squamous cell epithelium that undergoes hormone-related cyclical changes during the menstrual cycle. The middle muscularis layer is highly infiltrated with smooth muscle and an extensive tree of blood vessels, which engorges during sexual arousal. The surrounding outer fibrosa layer provides structural support to the vagina. The vestibule of the vagina, consisting of the fourchette and the inner surfaces of the labia minora up to and immediately adjacent to the urethra, has a portion of mucous membrane that is of endodermal embryological origin. The epithelial appendages differ from those of the surrounding ectodermal skin and consist of tiny mucous-secreting acini with ducts lined by transitional cell epithelium (minor vestibular glands) (Woodruff J 1983).

The major appendages are Bartholin glands, which are the site of well-defined clinical disease which end upon the sides of the vaginal opening. Perglandular inflammation of this area can become a source of pain and is associated with vulvar vestibulitis (Prayson R 1995). Bartholin’s glands secrete a sticky liquid similar to the mucus preceding orgasm and, as in the male, this pre-orgasmic secretion is light and more frequent after prolonged sexual stimulation (Master WH; Johnson VE 1966). Endocrine cells producing serotonin, calcitonin, bombesin, katacalcin and alpha-hCG have been found in Bartholin glands (Fetissof F 1989).

The vagina has much reggae, which are necessary for the distensibility of the organ and are more prominent in the lower third of the vagina. Smaller ridges increase frictional tension during intercourse (Weber et al 1995; Levin M 1981). Immunohistochemical studies have revealed an abundance of nerve fibers in the anterior distal vagina, as
compared to the most proximal part (*Hiliges M* 1995). When performing bladder suspension procedures and vaginal hysterectomies, it is important to recognize this area of increased innervations for potential damage, because it plays an important role in sexual function.

*Perry JC and Wipple BL in 1981* have identified Grafenberg or G-spot as site can lead to orgasm when stimulated. They describe G-spot as sensitive area that can be felt through anterior vaginal wall, half way between the back of pubic bone and the cervix, along the course of urethra.

**Labia minora and majora**

The labia minora, or nymphs, are two small cutaneous folds (inner lips), 3– 4 cm long. They are normally approximated together. They correspond to the ventral wall of both the cavernosa urethra and the corpus spongiosum of the urethra in the male (*Williams PL* 1995). They vary in size. They may be almost unrecognizable or may protrude from the labia majora (outer lips), ‘‘hypertrophic’’ labia minora should not be considered a malformation. In addition they can be asymmetrical or double on one or both sides (*Sakamato H* 2004). In some races the labia minora can be very large because of the practice of stretching them: in some African populations they can be as large as 20 cm and are known as ‘‘Hottentot apron’’ (*Testut L* 1972); today this is classified in the type IV female genital mutilations (*Catania L. 2007*). Upper points converge to form the prepuce and frenulum of the clitoris; posteriorly they form the frenulum of the labia minora but they can be also separated (*Willim PL. 1995*). The labia minora contain erectile tissue constituted by a thick connective tissue rich in small blood vessels. With sexual arousal the labia minora, because of engorgement with blood, become turgid,
doubling or tripling in thickness. They have a great sensitivity, due to the considerable number of nerve endings and sensory receptors. Among these, as in the male, the most important for erogenous sensitivity are the genital corpuscles (typical receptors of the external genitals); the Krause–Finger corpuscles (corpuscles of voluptuousness) are predominant. Pacini and Meissner corpuscles (cutaneous mechanoreceptors distributed on various areas of the skin, but concentrated in areas especially sensitive to light touch are also present (Yang CC; Cold CJ 2006).

**Fig 1.** Anatomy of the female genital system: External view (Seely R.R. et al., 1998).
Clitoris

In 1974 Kaplan described the clitoris as "knob of tissue located below symphysis pubis" (Master EH; Johnson VE 1966).

The clitoris is an erectile organ similar to the penis, and arises from same embryological structure, genital tubercle. It is composed of three parts: the outermost glans or head, the middle corpus or body, and the innermost crura. The glans and body of the clitoris are 2–4 cm long and the crura are 9–11 cm (Tarcan T 1999). The clitoris consists of fused midline erectile bodies (corpora cavernosa) that give rise to bilateral crura. The glans clitoris is visible as it emerges from the labia minora. The labia minora bifurcate to form the upper prepuce anteriorly and the lower frenulum posteriorly. Each corpus cavernosum is comprised of lacunar sinusoids, which are surrounded by a trabecula of vascular smooth muscle and collagen fibers.

The tunica albuginea in the clitoris is unilaminar, unlike the bilaminar structure found in the penis. Thus, no mechanism for venous trapping exists within the clitoris and, consequently, sexual stimulation results in clitoral engorgement but not erection. In the male, the bilaminar tunica albuginea possesses a rich venous plexus that, during sexual excitement, expands, reducing venous outflow and making the penis rigid. The absence of the venous plexus in the clitoris allows this organ to achieve tumescence, but not rigidity during sexual arousal. The two separate crura of the clitoris, formed from the separation of the most proximal parts of the corpora in the perineum, attach bilaterally to the undersurface of the pubis along the ischiopubic rami (Jennifer R; Berman et al. 2003). Duplex ultrasounds of the clitoris reveal that, during sexual simulation, the clitoris increases in length and diameter and
blood flow almost double. Prospective measurement of clitoral dimensions in 200 normal women at routine gynecologic examination in an office setting, suggested that the clitoris is not influenced by age, height, weight, or current use of oral contraceptives, but in pregnant women it was significantly larger (Medina CA 2002).

**Vestibular bulbs**

The vestibular bulbs are two erectile organs and correspond to the urethral bulb in the male, lie along the sides of vaginal orifices. The bulbs are situated in the anterior region of the perineum, the bulboclitoral region, which is homologous to penile region in the male. Their dimensions in the flaccid state are 3–4 cm in length and they become engorged or “erected” during arousal, when in the lower third of the vagina the “orgasmic platform” of Masters and Johnson is reached (Yang CC; Cold CJ 2006).

The two bulbs are joined together, under the vestibule of the vagina, by the commissure of the bulbs and, through the corpus spongiosum or “pars intermedia”, they extend to the base of the glans. The corpus spongiosum is constituted by cavernous tissue which thin towards the glans and is situated underneath the vestibular epithelium (Van Turnhut AA 1995).

Recent cadaver dissections reveal that in young premenopausal women, the bulbs lie on the superficial aspect of the vaginal wall and do not form the core of the labia minora. Furthermore, there are considerable age-related variations in the dimensions of the erectile tissue between young premenopausal specimens and older, postmenopausal specimens. (European J 2010)
In the angle of the clitoris, in the space between the corpora cavernosa and the female corpus spongiosum, there is the venous plexus of Kobelt, responsible for communication between the venous circulation of the bulbs and of the corpora cavernosa of the clitoris; it corresponds to the inferior veins of the male corpora cavernosa, which open in the inferior median sulcus between corpora cavernosa and the male urethra, and receives the veins coming from the upper part of the male corpus spongiosum (William PL 1995).

The bulbs are covered by the bulbocavernosus muscles, which are implicated in inferior vaginismus, while the pubovaginal muscle is responsible for superior vaginismus. Some studies have suggested that the components of the levator ani muscle are the puborectal, iliococcygeal, pubovisceral muscles, further subdivided into pubovaginal, puboperineal and puboanal. This terminology was accepted in 1998 by the Federative Committee on Anatomical Terminology (Kerney R 2004). The rhythmic contractions of lower third of the vagina during orgasm are mainly due to the contractions of the bulbocavernosus muscle (Master WH; Johnson VE 1966).

**Corpus spongiosum of the female urethra**

The corpus spongiosum of the urethra is present in all women, as in the male. It is a cavernous tissue rich in veins, situated at submucosal level and among the muscular bundles of the smooth muscular tunica of the urethral wall. It becomes engorged, or “erect”, with sexual arousal and Grafenberg in 1950 wrote “In the course of sexual stimulation the female urethra begins to enlarge” (Grafenberg E. 2010). Female urethral sensibility has been little investigated until now, though Dickinson, wrote in 1949 “Indeed, the meatus is largely endowed with special sensibility”