

Risk Factors for Acute Uncomplicated Urinary Tract Infection in Premenopausal Women: Implications for Reproductive Health Programming

VM Lema^{1*} and A-P V Lema²

¹Professor of Obstetrics and Gynaecology, Honorary Faculty, The Aga Khan University, Nairobi, Kenya

²Medical Officer, The Nairobi Hospital, Nairobi, Kenya

*Corresponding Author: VM Lema, Professor of Obstetrics and Gynaecology, Honorary Faculty, The Aga Khan University, Nairobi, Kenya.

Received: November 03, 2017; Published: December 18, 2017

Abstract

Acute uncomplicated urinary tract infections (UTIs) occur in otherwise healthy individuals with no structural or functional urinary tract abnormalities. Young sexually active women are at highest risk thereof.

Its pathogenesis is complex, influenced by the host's biological and behavioural factors and virulence properties of the infecting micro-organisms. The main source of the micro-organisms is the individual's faecal flora. *E. coli* is the commonest bacteria accounting for 75 - 90% of the isolates. The major risk factors include frequency of and recent sexual intercourse, use of contraceptive diaphragm, male condoms and spermicides, previous history of UTI and use of antimicrobials.

Young women are not only highly sexually active, but also with a potential of variety of partners, and sexual activities such as heterosexual anal intercourse, which increase the risk of UTI. Sexual and reproductive health programmes stress the importance of safer sex including use of barrier contraceptive methods to prevent unwanted pregnancy, HIV infection and STIs. This has resulted in significant uptake of spermicide-coated condoms amongst young people globally.

The association of acute uncomplicated UTI with sexual activities including vaginal and heterosexual anal intercourse (HAI), and use of spermicide-coated condoms may persuade some to stop using condoms, thus negatively impacting on the gains made in reproductive health programmes. There is need for a paradigm shift in international and national reproductive health programming, as well as public education on sexual and reproductive health. There is also need for locally relevant operations research to better understand the risk factors, among other issues so as to inform health service programming and delivery, including preventive strategies.

Keywords: Urinary Tract Infection (UTI); Premenopausal Women; Reproductive Health Programming

Introduction

Urinary tract infection (UTI) is defined as the invasion of non-resident pathogenic microorganisms into the urinary tract and its multiplication, resulting in an inflammatory response in the urothelium, which progresses to overt disease. Urinary tract infections (UTIs) are considered one of the most common bacterial infections, and by some authorities the most common globally, accounting for a significant proportion of medical consultations in primary as well as secondary outpatient settings [1,2].

The actual magnitude of UTI is unknown and is difficult to establish because it is not a notifiable health condition, some patients opt to self-diagnose and self-medicate, and quite often in outpatient settings uncomplicated UTI is treated symptomatically without microbiological evidence. The differences in reported incidences/prevalence rates are influenced by the criteria used for its diagnosis and the specimen-collection technique among other factors. Hooton, *et al.* (1996), in their study on young people in the USA, estimated the

Citation: VM Lema and A-P V Lema. "Risk Factors for Acute Uncomplicated Urinary Tract Infection in Premenopausal Women: Implications for Reproductive Health Programming". *EC Gynaecology* 6.5 (2017): 173-182.

incidence of UTI at 0.5 to 0.7 per person per year [3]. Other estimates indicate that UTI accounts for ≥ 8.6 million physician visits and ≥ 1.0 million hospital admissions each year in the USA [4]. In a population-based study in Canada, Nicolle, *et al.* (1996), reported that the overall rate of hospitalisation for pyelonephritis in women was about 1:1000 population [5], which was considered an underestimate cognisant of the fact that not all patients with acute pyelonephritis get admitted or require hospitalisation [6]. This did not include acute cystitis, which is more common than pyelonephritis.

According to the new classification of urinary tract infection, acute uncomplicated urinary tract infection (UTI) includes sporadic and recurrent community-acquired episodes of acute cystitis and acute pyelonephritis, in otherwise healthy individuals with no known risk factors, with risk of recurrences but no risk of more severe outcome, and partly extra-urogenital risk factors, based on the ORENUC system [7,8]. Young sexually active healthy women are particularly at risk of acute uncomplicated (or community-acquired) urinary tract infections. Community-acquired UTI is infrequent before puberty and sexual debut. Its incidence increases significantly thereafter, with about a third of women having UTI requiring antimicrobial therapy by age 24 [9,10]. It is also estimated that 40 - 50% of women will experience at least one episode in their adult lifetime [11,12] with a quarter or more having a second episode and 20 - 50% of them having recurrent UTI, defined as ≥ 3 laboratory confirmed episodes of UTI over a twelve months period [13].

Although acute uncomplicated urinary tract infection is not accompanied by long term sequelae, it is associated with significant morbidity and health costs, because of its magnitude, the symptomatology and recurrences thereof.

This paper discusses the pathogenesis of uncomplicated UTI in premenopausal women, with specific reference to the major risk factors, i.e. vaginal intercourse and other sexual behaviours/activities, the use of barrier contraceptives and implications thereof to sexual and reproductive health programming and service delivery, especially in a developing country context.

Pathogenesis

Pathogenesis of acute uncomplicated UTI is reportedly complex, influenced by many biological (i.e. structural and functional characteristics of the genitourinary and alimentary systems) and behavioural factors of the host, (i.e. the individual woman); and virulence properties of the infecting microorganisms [14,15]. For an infection to occur in any part of the human body, the pathogenic microorganisms must gain entry into the body, organ or tissue in question, survive therein by either avoiding or overcoming the local immune mechanisms, multiply and invade the respective tissues, cause an inflammatory response which then presents with related clinical symptoms. Most body tissues, such as the urinary tract, the vulval and vagina, have innate and adaptive immune mechanisms which protect them against invasion by, survival and multiplication of non-resident microorganisms. As opposed to complicated UTI, acute uncomplicated UTI is not associated with any underlying structural or functional abnormalities in the urinary tract. It is infrequent in young girls and early adolescence, its incidence increasing dramatically following sexual debut, often in late adolescence and early 20s, remaining high throughout the woman's adult life [16], when she is sexually active.

The primary route in the acquisition of uncomplicated UTI in women is by ascendance of the microorganisms [17]. Haematogenous and lymphatic spread of uropathogens to the urinary tract is either rare or unknown [18]. Most of the uropathogens in community-acquired UTI in young sexually active women originate from the rectal flora [14,18]. The possibility of sexual transmission of UPEC from a partner has been suggested [19], but is perhaps very rare. Vaginal colonisation by the uropathogens is a pre-requisite to and an initial step in the pathogenesis of community-acquired UTI in young women, which is accompanied by colonisation of the peri-urethral area and lower third of the urethra from where the uropathogens is massaged into the bladder during sexual intercourse or urethral manipulation [14].

The uropathogens: Uropathogenic *Escherichia coli* (UPEC) is the commonest microbial agent in acute uncomplicated UTI, responsible for 75 - 90% of infections [20-22], followed by *Staphylococcus saprophyticus* which accounts for 5 - 15% of infections [3,23]. Other bacteria include *Proteus* spp, *Klebsiella*, *Pseudomonas* spp, *Citrobacter*, *Enterobacter*, *Enterococcus faecalis* which are an infrequent cause of

community-acquired UTI in young sexually active women [11,24]. Certain virulence determinants of uropathogens are said to confer a selective advantage to the strains possessing them which enable the microorganisms to colonise and infect the urinary tract [20,25]. Uropathogens' virulence determinants or properties are considered more important in the normal host than those with urinary tract abnormalities [14].

E. coli being the commonest bacteria causing UTI has been studied most with regards to its pathogenicity and virulence than the others. *E. coli* is a commensal of the large intestine where it is considered beneficial. However some of its strains deviate from their commensal status and assume a pathogenic course capable of infecting tissues and causing diseases in the same body, such as UTI [26,27]. There is also evidence to suggest that UPEC originates from eating poultry contaminated with avian *E. coli* (APEC) [28]. UPEC possess an enhanced ability to cause infection outside the intestinal tract such as UTI by changing from its harmless nature in the nutrient-rich intestine to a virulent pathogen in a nutrition-depleted environment such as the urinary tract [27,29,30].

It is able to utilise diverse carbon sources for its energy [30,31]. It is capable of evading or surviving the effects of neutrophils during UTI. Its specific virulence factors i.e. adhesive organelles, called fimbriae or pilli, allow it to bind and invade host cells and tissues in the urinary tract [13]. Some *E. coli* strains express an increase K-antigen production which confers protection to the microorganism from leucocyte phagocytosis, thereof enabling UPEC to survive and multiply in the urinary tract [14]. Expression of iron-chelating factors which enable it to pilfer iron stores, depleting available iron from urothelium, deployment of array of toxins such as haemolysin and cytotoxic necrotising factor 1 which not only facilitate invasion of tissues, but also release of host nutrients and disable the immune effector cells [20,32,33], have been suggested. *Staphylococcus saprophyticus*, the second most common bacteria causing community-acquired UTI has also being shown to possess several virulence properties such as haemagglutination, adherence to human uroepithelial cells, production of extracellular enzymes such as urease, which inhibit growth of bacteria [34].

Host Factors: These include anatomical (structural), biological (functional) features of the female genito-urinary and alimentary systems and behavioural characteristics of the individual woman.

Anatomical: The anatomical arrangement of the female external genitalia and the anus (Figure 1) are important in the pathogenesis of community-acquired urinary tract infection in young women This explains why they are at greater risk thereof than men. The female urethral meatus is within the vestibule, enclosed by the labia majora and minora, an environment which is most of the time wet or moist. It is in close proximity to the vaginal introitus which expose it to a risk of trauma as well as bacterial contamination during sexual intercourse. The vaginal introitus and urethral meatus are in close proximity to the anus making it easy for enteric bacteria to gain access into the vagina and urethra. The female urethra is quite short, measuring approximately 4 cm long, straight and lies adjacent to the vagina a factor which enhances the massaging effect of the urethra during sexual intercourse, pushing uropathogens into the bladder. The distance between the urethra and anus was shown to be more important as the shorter the distance the higher was the risk of UTI in one study [35].

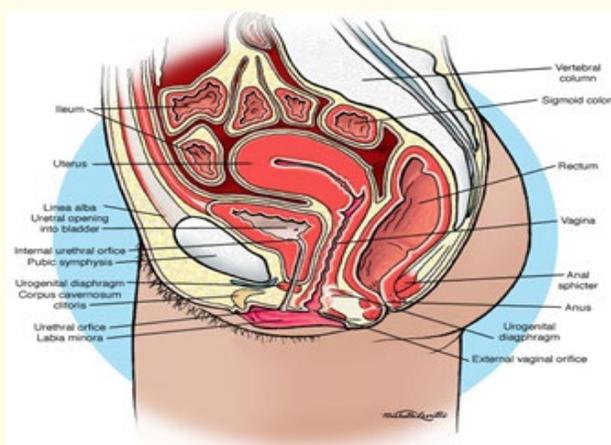


Figure 1: Diagram showing anatomical arrangement of the urinary system, female genitalia and anus.

Biological properties: Studies have provided evidence showing that alterations of normal vaginal flora is critical in facilitating vaginal colonisation by pathogenic organisms such as coliforms, setting the stage for development of UTI. Loss of the hydrogen peroxide-producing *lactobacilli* which is protective may predispose a woman to vaginal colonisation by uropathogens [22].

The urinary system has its protective mechanisms against infection. These include the high urine flow rate, voiding frequency, urine osmolality, pH and organic acids; bladder mucopolysaccharides, secretory IgA and other proteins secreted by the uro-epithelial cells.

Factors that interfere with or interrupt these protective mechanisms facilitate bacterial colonisation of the vagina, entry into the urethra and bladder, its multiplication and survival therein leading to infection and symptoms related thereto.

Behavioural factors

Sexual intercourse: UTI is infrequent in girls and young adolescents, but increases dramatically following sexual debut [9,37,38]. Some of the earliest studies on the association between sexual intercourse and community-acquired UTI showed that it was preceded by sexual intercourse in young women and the female on-top position was the most frequently used position by those with infection [39]. Foxman, *et al.* (1995) reported that UTI increased from 12.5% in age group 14 - 17 to 37.8% in those aged 18-24 [37].

Penile-vaginal intercourse has been shown to be a major risk factor for community-acquired UTI in premenopausal women, in particular frequency and recent activity [14,15,37,40]. The relative odds of acute cystitis during the first 48 hours after sexual intercourse increase by a factor as great as 60 [41]. Nicolle, *et al.* (1982) showed that about 80% of UTI in young college girls occurred within 24 hours after sexual intercourse [42]. Hooton, *et al.* (1996) reported that sexual intercourse on a frequency of three days a week increased the risk of UTI by 2.6 times when compared to those who never had sexual intercourse, and if one had sexual intercourse daily the risk increased nine-fold [3]. Studies have not shown an association between the number of partners and risk of sporadic acute uncomplicated UTI. A study comparing women with two or fewer sexual partners (n = 793) to those who had three or more partners (n = 204), in the preceding year did not show significant difference ($\chi^2 = 0.036$; $p > 0.05$). However significant bacteriuria occurred most often (11.2%) in women who had had sexual intercourse within the preceding 24 hours [43].

Vaginal sexual intercourse is thought to increase the risk of UTI through bacterial contamination of the vaginal introitus and peri-urethral area and introducing uropathogens into the urethra and bladder by massaging the urethra and possibly trauma to the urethral meatus [3,14,15].

Vaginal acquisition of uropathogens from a woman's infected male partner/spouse has been reported, but is considered a rare cause of uncomplicated UTI [14]. Al-Walli, *et al.* (1989) reported a case of recurrent UTI in a young woman whose husband had chronic prostatitis [44].

Other sexual activities are also associated with an increased risk of UTI. In their study, Foxman, *et al.* (1995) noted that all types of sexual behaviour/activities were associated with increased risk of UTI, i.e. vaginal intercourse alone, or in combination with digital stimulation and or receptive oral sex [37]. Heterosexual receptive anal intercourse (HAI) has been reported to confer an increased risk of uncomplicated UTI in premenopausal women [24,45,46]. Lema (2015) published case-reports of young women with severe uncomplicated UTI in Nairobi Kenya. They had vaginal intercourse following anal intercourse within the preceding seven days and the men did not wash their penises in between anal and vaginal intercourse [46]. Following these reported cases the author has attended to a few more young sexually active women with similar stories in his private clinic. Handley, *et al.* (2002) opined that anal intercourse may facilitate transfer of uropathogens from the female anus into the vaginal vestibule and urethra leading to UTI [24], after which vaginal intercourse may facilitate their entry into the urethra and bladder.

Contraceptives: Use of diaphragm with or without spermicides, male condoms with or without spermicides and spermicides themselves, has been shown to significantly increase the risk of UTI in young women [14,15,37]. In their study on the association of diaphragm and first UTI Foxman and Frerichs (1985) showed that sexually active women with primary UTI who had intercourse three or more times per week and used the diaphragm had at least a 63 per cent chance that their primary UTI was attributable to use of diaphragm [47]. The diaphragm is thought to cause urinary stasis because of its positioning in the vagina among other mechanisms.

Foxman., *et al.* (1997) in their study on first time UTI among university female students noted that use of lubricated condoms increased the odds ratio of UTI by 29% (95% CI = 3.1 - 1,335), and that spermicide cream/gel with unlubricated condoms was associated with a 2 to 8 fold increased risk of first time UTI [48]. In an earlier study Foxman., *et al.* (1995) had shown that vaginal intercourse with condoms increased the risk of UTI by 43% (OR =1.43, 95% CI = 1.09 - 1.89) [37]. Handley., *et al.* (2002) showed that use of male condoms was associated with an increased UTI risk and that the largest risk was associated with exclusive condom use and use of Nonoxynol-9 coated condoms [40]. The male condom increases the risk of acquiring UTI in the woman through an allergic reaction to the latex rubber or the lubricant, and mechanical trauma of sexual intercourse [49].

Spermicides on their own have been shown to increase the odds of uncomplicated UTI by *E. coli* or by *S. saprophyticus* by a factor of 2 to 3, irrespective of whether a diaphragm or spermicide-coated condoms were used concurrently [3,49]. The risk increased with frequency of its use [49]. Spermicides are thought alter the vaginal microflora, i.e. depletion of *lactobacilli*, and by increasing vaginal colonisation by other micro-organisms [49,50]. A study by Rosenstein., *et al.* (1998) showed that there was an increase in vaginal coliforms and a decrease in vaginal *lactobacilli* after Nonoxynol-9 instillation into the vagina in the absence of sexual intercourse or diaphragm use [50]. Nonoxynol-9 suppresses growth of *lactobacilli* in the vagina as well as enhance bacteria adherence to the vaginal epithelial cells [50,51]. However not all studies have shown significant effects of Nonoxynol-9 on hydrogen-producing *lactobacilli*.

Antimicrobials: The use of certain antimicrobial agents has been shown to increase the risk of uncomplicated UTI in young women by adversely affecting vaginal microflora [52,53]. Smith., *et al.* (1997) in their prospective study on premenopausal college women showed an increased risk of UTI among those who had used antimicrobial agents in the previous 15 - 28 days (i.e. three to four weeks) but not in the previous \leq 14 days. The explanation was that in the first two weeks possibly the antimicrobial effects were still in effect but would have worn off by the end of that period [53].

Recurrent Uncomplicated Urinary Tract Infections

It is defined as more than two separate episodes of uncomplicated UTI in the preceding six months or at least three episodes in the preceding twelve months, confirmed by bacteriological culture [54-56]. They are symptomatic UTIs that occur after resolution of an earlier episode usually following appropriate treatment, and include relapses (i.e. recurrent UTIs caused by previously isolated bacteria after treatment and with a negative urine culture in the intervening period) or a recurrent UTI caused by a different bacteria from the one isolated in the previous episode [57]. They are quite common and a cause of significant morbidities to the individual woman as well as impacting on her social and sexual well-being. Of the women who get one episode of acute uncomplicated UTI, 25-50% will experience recurrent UTI [9,13,56].

Most recurrent UTIs are thought to represent infection with the same microorganism [57,58], *E. coli* accounting for the highest proportion (70 - 95%), followed by *S. saprophyticus* (10 - 15%) [23,59]. It's been suggested that following resolution of a UTI, small numbers of the original strains of uropathogens may persist in the hosts urinary system e.g. as infection stones (i.e. *P. mirabilis*), from which a new infection may arise. Infections may also arise from a reservoir of bacteria in the vagina and/or alimentary system of a susceptible individual [59].

The risk factors or recurrent UTI are essentially the same as those responsible for sporadic episodes of UTI, suggesting possible individual susceptibility to UTI. They include behavioural factors such as frequency of sexual intercourse, new partnership and use of

diaphragm with spermicides [54,58]. In a case-control study, Scholes, *et al.* (2000) reported that women with recurrent UTIs were ten times more likely to have had sexual intercourse more than nine times in the preceding twelve months and twice more likely to have used spermicides in the same period. They also had a higher number of sexual partners than those without recurrent UTI [41]. These factors are said to increase the risk of vaginal and urethral colonisation by uropathogens [58] just like in the sporadic UTIs. A maternal history of UTI and history of UTI before age 15 was also shown to be associated with a increased risk of recurrent UTI [54], as well as family relatives harbouring the uropathogens thus suggesting a possible genetic predisposition to rUTI [60,61].

Among biological/genetic factors known to increase the risk of recurrent UTI, are anatomical factors, i.e. short distance between the urethra and anus [35], the location of the urethral meatus relative to vaginal introitus and anus; and biochemical i.e. lower levels of 25-hydroxyvitamin D [62]. Non-secretors of histo-blood group antigens are said to be more susceptible to recurrent UTI, though some studies have not shown such an association [61]. Interleukin-8 receptor (IL-8R) or CXCR1, which has been shown to be expressed to a significant lower extent in pyelonephritis-prone children and their relatives [63], is also thought to play a part in the pathogenesis of recurrent UTI.

Discussion

Acute uncomplicated urinary tract infections (UTIs) are very common among sexually active premenopausal women [3,8]. Reportedly about half of women globally will have at least one episode in their life time and up to about half of that will have at least three episodes in a year. Going by these estimates, which some consider underestimates, it is safe to aver that the magnitude of UTI in premenopausal women is significant. It has significant social, health effects and negatively impacts the individual's quality of life and sexual functioning. It is associated with high health costs due to its prevalence, need for investigative procedures and repeated treatment for the recurrences [64].

Penile-vaginal intercourse, with or without barrier methods of contraception, namely diaphragm, and male condoms with or without spermicides and spermicides themselves are the major behavioural and avoidable risk factors [15,37,41]. Vaginal introital and urethral meatal trauma during sexual intercourse is considered possible mechanisms through which sexual intercourse facilitates vaginal colonisation and introduction of the uropathogens into the urinary bladder. Foxman, *et al.* (1995), opined that any sexual activity/behaviour may increase the risk of UTI [37]. Young people are not only creative but also explorative and adventurous in all manners of life including sexual activities. It is not surprising therefore that HAI, which is reportedly quite common amongst them globally [45,46], has been reported to be a risk factor for community-acquired UTI as well [40,45,46]. Quite often these same individuals engage in other forms of sexual activities such as digital stimulation, receptive oral sex which may be annilingus or felatio or combination thereof, which may also increase the risk of UTI in the female partners. There is also an increase, though undocumented, in the use of sex toys such as vibrators and dildos by young women either in lesbian relationships or solo. Whether and to what extent these may increase or contribute to the increased risk of community-acquired UTI has not been determined. It is however worthy of mention and research.

Other common sexual practice which have not been investigated to elucidate their extent and/or impact on the individual's health, are dry and wet sex. These are widely practiced in some parts of sub-Saharan Africa, and the Carribeans [65,66]. The process of drying the vagina following arousal or during sexual intercourse include insertion of dry leaves, powder, dry cloths, douching which on their own may bruise the vaginal walls. The dry sex is known to cause trauma to the vaginal walls [65,67,68]. These practices may increase the risk of infection i.e. colonisation of the vagina which may then be pushed into the urethra and bladder leading to UTI.

The international health community and related agencies have expended significant resources on advocating for safer sex, including delaying sexual debut, having few sexual partners and one at a time, use of barrier contraceptive methods such as male or female condoms to prevent unwanted pregnancy, STIs, HIV and HPV responsible for cancer of cervix. These efforts have led to an increase in the uptake of condoms and in particular spermicide-coated ones, by young people. The gains made thus far may be eroded as these individuals may opt not to use the barrier methods to avert UTI. The alternative sexual practices may not increase risk of UTI, but also HIV/AIDS, cervical, oropharyngeal and anal cancers.

There is therefore need for a paradigm shift in the sexual and reproductive programming at the international as well as national levels; including re-packaging of health messages appropriate and relevant for certain groups of individuals. There must be novel approaches in health care service delivery, emphasising the importance detailed sexual history in cases of genitourinary complaints. There is also need for appropriate and locally/nationally relevant operations researches to better understand the magnitude of acute uncomplicated UTI and their determinants among other factors. These will inform appropriate reproductive health programming as well as health care delivery and messaging.

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Volume 6 Issue 5 December 2017

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