Review Article

Putative Effects of Sex Hormones on Urinary Tract Infection

(kidney disease / bacteriuria / bladder / oestrogen / testosterone / progesterone)

T. BRACHTLOVÁ, R. GARDLÍK, L. TÓTHOVÁ

Institute of Molecular Biomedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia

Abstract. Urinary tract infections affect mostly females. The infection and possible consequent ascent of bacteria is enhanced by various risk factors. Sex hormones regulate gene transcription implicated in immune cell development and maturation, in regulation of immune responses and immune signalling pathways. Limited knowledge is available; however, recent findings underline the importance of understanding the interactions between sex hormones and urinary tract infection to diminish the occurrence of complications related to this infection. This review summarizes and discusses the current knowledge on the correlation and impact of sex hormones on urinary tract infections.

Introduction

Urinary tract infections (UTI) are one of the most prevalent and familiar types of bacterial infections responsible for a range of complications. UTI are among the most common healthcare-associated infections in catheterized patients, patients and residents in long-term facilities and also the most common infectious complication after kidney transplantation (Castañeda et al., 2013; Abbo and Hooton, 2014). Uropathogenic *E. coli* (UPEC) is generally responsible for over 80 % of UTI, followed by *S. saphrophyticus* (5–15%). The remaining percentage is mostly comprised of *Klebsiella* species and *Proteus mirabilis* (Ragnarsdóttir and Svanborg, 2012; Enderle et al., 2014). The clinical picture of UTI ranges from asymptomatic and symptomatic bacteriuria, through acute and persistent UTI, to more complicated cystitis and pyelonephritis (Lüthje et al., 2014). Generally, the risk factors include frequent sexual intercourse (Schmiemann et al., 2010; Hooton, 2012), contraceptive methods using spermicides (Schmiemann et al., 2010; Hooton, 2012), vaginal diaphragm, depot medroxyprogesterone acetate (DMPA) (Schmiemann et al., 2010), or catheterization (Abbo and Hooton, 2014). History of previous UTI or UTI in a first female relative (Hooton, 2012), uncommon anatomical features or deformations (Fihn, 2003; Schmiemann et al., 2010), or pregnancy (Fihn, 2003) are considered risk factors for the development of UTI as well.

It is estimated that 175 million people suffer from UTI, the majority being women (Cegelski et al., 2008). The relationship between age and increasing incidence of UTI is unclear, ranging between 4 % and 15 %, depending on the geographic region (Foxman, 1999). Clinical presentations between pre- and postmenopausal women differ. Postmenopausal women are less likely to experience symptoms of lower UTI and more likely to suffer from ascending infection affecting kidneys (Foxman, 1999). Urinary incontinence, anatomical changes, menopause-associated oestrogen deficiency or other underlying morbidities, such as diabetes, are considered risk factors for elderly women (Brown et al., 2001; Lüthje et al., 2014). Among male population, the incidence of UTI is highest in infants with urological anomalies, older males with prostatic hypertrophies and patients who were subjected to invasive surgeries of urogenital tract or catheterization (Hoepelman et al., 1992; Cegelski et al., 2008). Male sex was reported to be a risk factor for acquiring UTI in elderly patients, and association with other morbidities at the age of 60–69 years was suggested to be in favour of increased prevalence (Omoregie et al., 2010).

Different incidence of UTI in males and females, along with different manifestation in pre- and postmenopausal women, points toward the possible role of sex

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Corresponding author: Tereza Brachtlová, Institute of Molecular Biomedicine, Comenius University, Sasinkova 4, 811 08 Bratislava, Slovakia. Phone: (+421) 904 404 174; e-mail: tereza.brachtl@gmail.com

Abbreviations: A-ICs – α-intercalated cells, DMPA – depot medroxyprogesterone acetate, E2 – 17β-oestradiol, ER – oestrogen receptor(s), GAG layer – glycosaminoglycan layer, HBD 1, 2 – human β-defensin 1, 2, ICAM-1 – intracellular adhesion molecule 1, IL-4, 6, 8, 10 – interleukin 4, 6, 8, 10, LL-37 – human cathelicidin LL-37, LPS – lipopolysaccharide, NFκB – nuclear factor κB, NK cells – natural killer cells, OVX – ovariectomized, P4 – progesterone, PAMP – pathogen-associated molecular pattern, QIR – quiescent intracellular reservoirs, TGF-β – transforming growth factor β, TLR4/MyD-88 – toll-like receptor 4/myeloid differentiation primary response protein 88, TNF-α – tumour necrosis factor α, TST – testosterone, UPEC – uropathogenic *Escherichia coli,* UTI – urinary tract infection(s), VEGF – vascular endothelial growth factor.

hormones in modulating the course of UTI. The possible mechanism of action includes several contributing factors, including influence on the immune system, barrier functions, and elimination of the pathogens. Thus, sex hormones can act on several levels simultaneously.

Sex hormones and the urogenital tract

Oestrogens, mostly 17β-oestradiol (E2), have their primary role in reproductive tissues. E2 is secreted by ovaries and mainly promotes cell proliferation and growth of mammary glands and uterus (Wend et al., 2012; Wall et al., 2014). Oestrogen receptors (ER) are expressed throughout the lower urogenital tract. ERα prevails in the uterus epithelium, stroma and myometrium (Matthews and Gustafsson, 2003). ERβ is mostly present in the ovarian granulosa cells as well as in the epithelium and detrusor of urinary bladder (Matthews and Gustafsson, 2003). Females exhibit glomerular enlargement or diminished kidney function, once ERα is not present (Lane, 2008). Transcription of genes encoding ERα and ERβ is present in the female bladder epithelium; however, only ERβ is expressed as a protein (Tincello et al., 2009).

Progesterone (P4) is produced in corpus luteum after ovulation and by placenta during pregnancy, as well as in adrenal glands and in the nervous system (Schumacher et al., 2012). Both oestrogen and progesterone receptors are present in the vaginal epithelium (Koskela et al., 2009; Han et al., 2010; Spark and Willis, 2012; Stanczyk et al., 2013). Progesterone receptor expression is present in urethral squamous epithelium, receptor A being the primary isoform (Tincello et al., 2009). The expression is diminished during the onset of menopause, probably due to gradually decreasing oestrogen secretion. Recently, it was found that oestradiol induces expression of progesterone receptor isoforms differentially, through alternative promoter regulation (Vázquez-Martínez et al., 2016). Application of oestrogen therapy as a therapeutic drug may serve as protection of endometrium due to simultaneous progesterone rise in postmenopausal women. However, the definitive clinical effects are yet to be confirmed.

Testosterone (TST) is crucial for differentiation and preservation of the male phenotype. Production of TST is dependent on the gonadotropin-releasing hormone, which triggers release of the luteinizing hormone that in turn stimulates release of testosterone, which interacts with a single androgen receptor, directly influencing gene expression (McEwan, 2004; Basaria, 2014). Conversion of testosterone to oestrogen can also be responsible for influencing the hormone levels and hence has an impact on UTI progression as one of the factors. Figure 1 summarizes the known impact of sex hormones on urogenital tract and the risk factors influencing contraction of UTI.

Sex hormones and genes determining susceptibility to UTI

Genetic predisposition is suggested to influence susceptibility to UTI. Candidate genes have been suggested for increased risk of UTI due to their involvement in antibacterial defence of epithelia (Zaffanello et al., 2010). The physical barrier is the first line of protection against bacterial attachment and invasion. Alteration of genes encoding proteins associated with the epithelium increases the risk of contracting UTI, as the composition of the epithelium is changed and the susceptibility to bacterial entry is increased.

Bates et al. (2004) suggest Tamm-Horsfall protein to act as a soluble receptor, inducing elimination of bacteria from the urinary tract. Vascular endothelial growth factor (*VEGF*) and *TGFb1* gene polymorphisms have been previously linked to predisposition and development of renal disease due to the corresponding protein overproduction (Zaffanello et al., 2010). Blush et al. (2004) demonstrated E2 to dismantle pro-fibrotic effects of TGF-β *in vitro* as well as *in vivo* using cultured murine mesanglial cells, transgenic mice overexpressing TGF-β1 and C57BL/6JxCBA mice, respectively. Yu et al. (2009) showed interactions of sex hormones with VEGF-A expression in the female rat bladder tissue. VEGF-A protein expression was significantly lower in ovariectomized rats compared to sham-operated controls. Progesterone alone did not distinctly influence VEGF-A protein expression, but in combination with oestrogen resulted in improvement of VEGF-A levels in comparison with ovariectomized mice. Testosterone increased VEGF-A expression most prominently; however, the expression still did not reach the values of sham-operated rats (Yu et al. 2009). It is evident that sex hormones, both independently and in cooperation, influence expression and action of numerous genes implicated in the susceptibility to UTI. The effect of sex hormones on gene expression can be an interesting subject for further research, as their effect can be modulated.

Interactions between sex hormones and components of the immune system

The immune system generally responds to UTI infection by innate immune defence, inflammatory mediators, cytokines and antimicrobial peptides. The barriers and tight junctions in the urothelium are also important during the immune response. Females generally present with greater number and activity of immune cells and inflammatory responses than males. Cytotoxic T-cell activity and up-regulation of antiviral and pro-inflammatory genes are substantially modulated by oestrogen. Even though macrophages and T cells both express androgen, oestrogens and progesterone receptors, males present with lower numbers of $CD4^+$ and $CD3^+$ cells, regulatory T cells, and lower activity of cytotoxic T cells than females (Snider et al., 2009; Kaushic et al., 2011; van Lunzen and Altfeld, 2014). Testosterone and pro-

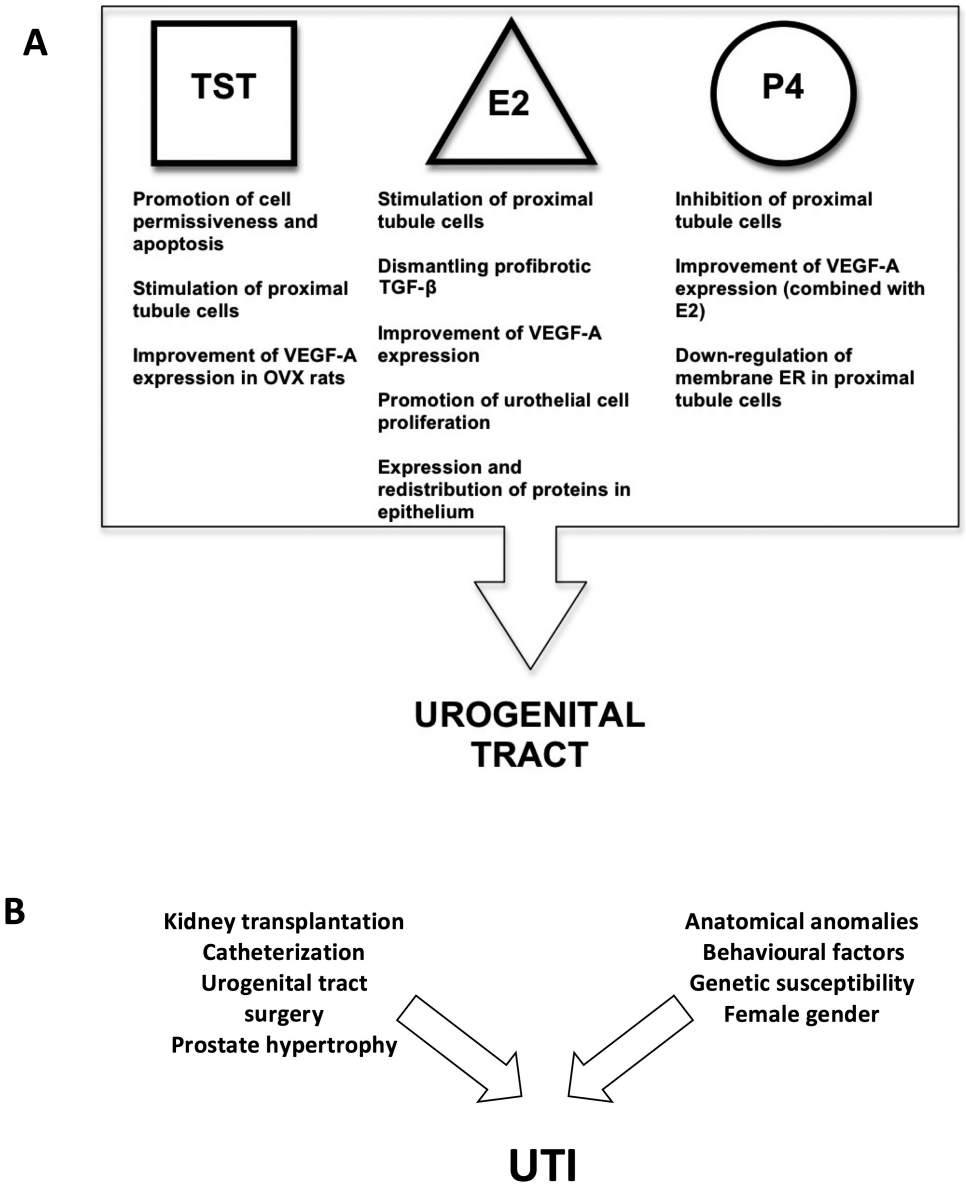

Fig. 1. (**A)** General summary of the known influence of sex hormones on urogenital tract *in vitro* and *in vivo*. (**B)** The correlation between sex hormones and UTI is not established as strongly; however, several risk factors are known.

gesterone might act as immunosuppressants, decrease NK cell activity, impair production of TNF and nuclear factor κB (NFκB) signal transduction. Both hormones are involved in Th2-mediated response and production of anti-inflammatory cytokines including IL-10 and IL-4 (Snider et al., 2009; Klein et al., 2010; Klein, 2012; van Lunzen and Altfeld, 2014). Oestrogen enhances TNF production, Th1-mediated immune responses and antigen-specific $CD4^+$ T-cell responses. On the other hand, high levels of oestrogens may present with diminished migration of T cells and macrophages, down-regulation of ICAM-1 and E-selectins, and increased levels of IgG and IgA (Snider et al. 2009; Klein et al., 2010; Kaushic et al., 2011; Klein 2012; van Lunzen and Altfeld, 2014). Anand et al. (2013) observed oestrogen modulating composition of the glycosaminoglycan (GAG) layer, rather than its thickness at the initial level. On the other hand, increased oestrogen levels influenced the time response of GAG layer thickness to UPEC infection, resulting in earlier increment of the layer thickness (Anand et al., 2013). Taken together, the direct impact of sex hormones on the activity of immune system cells represents one of the avenues on which the relationship between the two is built.

Besides the cellular components of the immune system, the molecular part is influenced by sex hormones as well, although on a different level. Toll-like receptors (TLRs) are capable of recognizing pathogen-associated molecular patterns (PAMPs) and consequently induce production of pro-inflammatory cytokines, chemokines, antimicrobial peptides and interferons (Song and Abraham, 2008; Spencer et al., 2014a). TLR5 is mainly present on bladder cells, TLR11 on renal cells and TLR4 can be detected on both types of cells in both locations (Song and Abraham, 2008, Spencer et al., 2014a). Although not fully investigated, recent research sug-

gests fluctuating levels of oestrogen to have an impact on the difference in TLR expression. All TLR expression levels, apart from TLR 11, vary depending on the oestrous cycle (the highest levels were seen during the dioestrus phase), as was shown by Yao et al. (2007) in murine vaginal epithelial cells.

Ovariectomized (OVX) mice were shown to have significantly higher inflammatory response and increased production of IL-6 upon UPEC infection compared to sham-operated mice (Wang et al., 2013). Sex differences in LPS- and IFN-γ-stimulated production of TNF-α in neutrophils isolated from peripheral blood were studied by Aomatsu et al. (2013). Male neutrophils had distinctly higher production of TNF-α after stimulation with LPS and IFN-γ compared to females (Aomatsu et al., 2013). Flores-Espinoza et al. (2014) demonstrated progesterone to reduce LPS-induced TLR4/MyD88 expression, as well as to diminish LPS-induced IL-6, IL-8, and TNF-α levels in human amniotic epithelium. IL-10 expression was not affected (Flores-Espinosa et al. 2014). Other studies showed that TST replacement therapy in elderly or hypogonadal males decreased TNF-α, IL-6 and increased IL-10 production (Khosla et al., 2002; Malkin et al., 2004).

Described endogenous antimicrobial peptides (AMPs) present in the urinary tract include, e.g., defensins, cathelicidin (LL-37), hepcidin and ribonuclease 7 (RNAse 7) (Zasloff, 2007; Linde et al., 2013; Spencer et al., 2014a, b). Other proteins with antimicrobial properties include lactoferrin, lipocalin and secretory leukocyte proteinase inhibitor (Ragnarsdóttir and Svanborg, 2012; Spencer et al., 2014a). Han et al. (2010) showed modulation of human β-defensin 2 (HBD-2) by oestrogen and progesterone. The results of their study showed that lack of oestrogen or use of progesterone-based contraception may detrimentally influence HBD-2 production and increase the risk of contracting recurrent UTI or bacterial vaginitis (Han et al., 2010). Lüthje et al. (2013) also reported increased expression of HBD-1 and HBD-2 when oestradiol is present. LL-37, the only cathelicidin present in humans, is capable of inducing damage by binding to the outer bacterial membrane. Lüthje et al. (2013) demonstrated positive effects of oestradiol on LL-37 expression. Ribonuclease 7 is the most potent antimicrobial peptide in humans, also present in the urothelium of the lower urinary tract. Lüthje et al. (2013) showed oestradiol to increase the expression of RNAse7. α-Intercalated cells (A-ICs) are essential for maintaining acid-base homeostasis within the collecting ducts of the kidneys. Paragas et al. (2014) have reported that A-ICs act as a very important element in the host response to pathogens by producing and secreting bacteriostatic lipocalin 2 (LCN2) upon binding UPEC. Guo et al. (2012) showed the lack of LCN2 to significantly reduce the levels of serum E2 and to down-regulate ERα expression in multiple metabolic tissues in *Lcn2*$^{-/-}$ mice.

According to the recent research results presented above, it can be concluded that sex hormones significantly influence the performance of innate immunity, including in the urogenital tract. The presence of progesterone has a down-regulative effect on the innate immune system. The absence of oestrogen increases the inflammatory response; the presence of testosterone promotes anti-inflammatory cytokine IL-10. Their misbalance may explain the increased severity of infection in postmenopausal women. The general overview of interactions between sex hormones, UTI and immune system is summarized in Fig. 2.

The effects of sex hormones *in vitro*

Several studies investigated the relationship between sex hormones and the urogenital tract using cell cultures *in vitro*. Oestrogen promotes expression and redistribution of the proteins associated with cell-cell contact and epithelial integrity, as demonstrated by Lüthje et al. (2013). Koskela et al. (2009) investigated the effect of oestradiol on culturing human urothelial cells, showing a positive effect of the hormone on cell proliferation. Interestingly, proliferation was not influenced by the concentration of oestradiol. According to these authors, a high plasma level of oestradiol in the clinical setting may be linked with detrimental side effects of hormone replacement therapy (Koskela et al., 2009). Han et al. (1999) observed stimulatory effects of E2, testosterone and tamoxifen in primary rabbit kidney proximal tubule cells. An inhibitory effect was seen with progesterone.

Sex hormones in the animal model of UTI

Several papers examined the impact of oestrogens on the growth of UPEC, as shown on the course and severity of UTI. Wang et al. (2013) showed a significant increase of quiescent intracellular bacterial reservoirs in OVX mice with UPEC infection by immunostaining the bladder tissue. Supplementation of oestrogen reversed the ovariectomy-induced conditions of UTI in these mice. On the other hand, experiments conducted by Curran et al. (2007) indicated detrimental effects of high-dose oestrogen treatment on mice. The high-dose treatment resulted in increased bacterial infection, independent of lipopolysaccharide (LPS) signalling. The results of Lüthje et al. (2013) offer an explanation for a positive correlation between oestrogen levels and susceptibility to UPEC. The authors show that the presence of high levels of oestrogen increased expression of infection-promoting receptors (uroplakin Ia and β-1 integrin). On the other hand, low levels of oestrogen down-regulated production of antimicrobial peptides (Lüthje et al., 2013). Contradictory results suggest that the direct influence of oestrogens on UTI might be dose-dependent. Likewise, the effects of testosterone on UTI remain unknown. One of the most recent papers revealed that although males suffer from symptomatic uropathogenic colonization in the bladder less frequently, the severity of upper-tract UTI is more severe, with extensive intrarenal abscess formation, subsequent renal scarring and diminished renal function (Olson et al.,

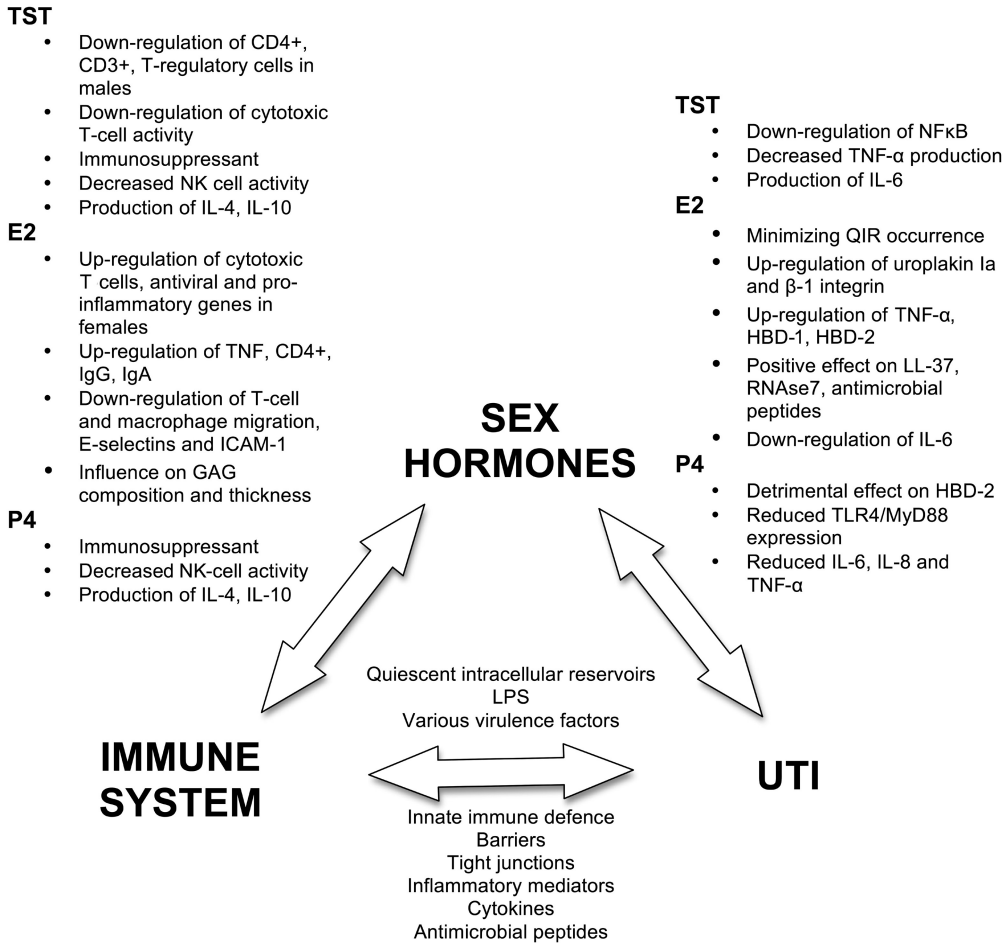

Fig. 2. General summary of known associations and influences of sex hormones affecting the immune system *in vitro* and *in vivo* compared to associations between sex hormones and UTI. Interactions between the immune system and UTI are mentioned as well.

2016). Apart from pointing out testosterone as most important in the UTI course, a new model of UTI was developed and verified. A murine male UTI model, through a mini-invasive approach, allows further investigation of the host and the microbial mechanism underlying UTI in both genders, which was not possible until recently, thus providing more complex answers in the near future.

Future outlook

Antibiotics are the first choice treatment of UTI. The treatment, however, is becoming less effective and problematic due to the increasing emergence of antibiotic-resistant strains, prolonged use of antibiotics, and disruption of the symbiotic relationship between the host and the microbiome (Cegelski et al., 2008).

Considering the most recent findings, sex hormones are important modulators of the UTI course, at least in animal models. The influence of sex hormones on the immune system is undisputable; therefore, their administration could be one of the options for minimizing the occurrence of recurrent UTI. Yet, due to the side effects, indication for hormonal replacement therapy needs to be carefully considered and is currently not recommended for management of UTI. Until recently, the experiments on both genders were difficult to perform, but with the development of a new male model, further research unmasking the exact pathophysiological role of sex steroids should bring more light into this field.

Conclusion

The interaction between sex hormones and the incidence, progression and morbidity of UTI is not fully understood. Controversial results were published, showing both positive and negative consequences of this interaction. Oestrogens are the most studied hormones in this sense, since the incidence and prevalence of infection is significantly higher in women. The ability of sex hormones to increase production of antimicrobial peptides, combined with the effect on epithelial integrity or distribution of proteins associated with cell-cell contact, to mention a few, place them as possible candidates for supportive treatment of UTI. Clinical data, however, are not conclusive, and the supplementation can have potentially serious side effects that need to be evaluated before administration. Further investigation needs to be performed in both animal models and humans.

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