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The Bidirectional Link: Hormonal Modulation of Urinary Tract Infection Susceptibility and the Indirect Association with Menstrual Irregularity: A Systematic Review

Sonya Kamegni Mombo Nkonda[1], Saeeda Wasim[2], Subuhi Anwar[3]

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ABSTRACT

UTIs are one of the most common bacteriological infections among women that recur repeatedly and significantly deteriorate quality of life. UTIs in contact with hormonal milieu, especially concerning the menstrual cycle is a field of growing scientific interest. Despite the lack of real evidence to support the existence of a direct, causal relationship between an active UTI and menstrual irregularity, indirect relationships have become increasingly identified as mediated by changing sex-steroid hormones, modifications in the urogenital microbiome, the presence of systemic inflammation, and the use of hygiene practices. This systematic review will identify the current world and Indian studies to elucidate the complicated reciprocal association among UTIs and hormonal factors and investigate the identified association with the presence of a menstrual cycle abnormalities, a comprehensive literature search was conducted to identify the studies that determine the role of estrogen and progesterone in uroepithelial integrity, the relationships between the menstrual cycle phases and the UTI vulnerability, and effects of UTIs on the hypothalamic pituitary ovarian (HPO) axis, including menstrual cycle changes induced by stress and inflammation processes. This review highlights that low estrogen levels during the premenstrual period increase the risk of UTI due to microbiome disruptions in the vagina and urine. On the contrary, extreme infection or the related systemic stress may temporarily impair HPO axis, which may also lead to menstrual delay or irregularity. Moreover, the Indian studies reveal that poor management of menstrual hygiene is a crucial and alterable risk factor that relates menstruation to reproductive and urinary tract infections. These complex physiological and behavioural interrelationships need a better comprehension to enable the formulation of specific preventive and curative measures in female health.

KEYWORDS: *Escherichia coli, HPO axis, Microbiome, UTI, Psychosocial stress.*

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INTRODUCTION

UTI is a significant burden on the global population, especially among women and it is estimated that around 50% and 60% of women have at least one episode of this infection in their lives.[1,2] Most of them are caused by uropathogenic *Escherichia coli* (UPEC).[3] The reproductive years of females can be described as cycling menstrual period, which is regulated by the highly sensitive hormonal communication of hypothalamic-pituitary-ovarian (HPO) axis.[4] One of the common gynecological complaints and an important indicator of health in a spectrum of conditions, such as metabolic syndrome and psychological stress, is menstrual irregularity, which is defined as a cycle length shorter than 21 days or longer than 35 days.[5]

The close location of female genitourinary organs as well as their embryological origin, makes the lower urinary tract and vagina extremely susceptible to sex steroid hormones, especially estrogen and progesterone.[6] The menstrual cycle is based on the hormonal changes, which become more involved in the predisposition to UTIs. It questions the possibility of an active UTI or even the hormonal and immunological changes occur before it, which can have adequate systemic effects to alter the normal functioning of the HPO axis and be presented as menstrual irregularity.

This systematic review of the current literature assesses the multifaceted and indirect relationship of UTIs and hormonal health with respect to the observed but poorly understood relation to menstrual abnormality. The synthesis is arranged to offer not only global knowledge on the background pathophysiology but also a local approach to the situation in India where sociocultural and hygienic factors are central.[7]

[1]American University of Barbados School of Medicine, Wildey, Bridgetwon, Saint Michael, BB-11100, Barbados,

[2]Department of Gynaecology, Nova IVF Infertility, Hazratganj, Lucknow, U.P. India-226003.

[3]Department of Pathology, Era's Lucknow Medical College & Hospital, Era University, Lucknow, Uttar Pradesh, India- 226003.

Corresponding Author: Sonya Kamegni Mombo Nkonda

Email: sonyakameni@gmail.com

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Pathophysiology of UTI: The Hormones and the Menstrual Cycle

The vulnerability of women to UTIs is inherently connected to the brevity of sex hormone-induced cycles caused by the nature of the urethra anatomy and its location relative to the anal region yet it is also fundamentally important to the cyclic nature of the sexual hormones.[6]

Protective Effect of Estrogen and Susceptibility of UTI: It is well known that estrogen has a trophic and protective effect on the urogenital tract. Vagina, urethra, bladder, and pelvic floor muscles express estrogen and progesterone receptors (ERα, ER 2, and PGR).[6]

Vaginal and Urinary Microbiome Modulation: The preservation of the vaginal microbiome is one of the mechanisms. Vaginal epithelial cells proliferate with the help of estrogen that contains a lot of glycogen.[8] The glycogen is metabolised by Lactobacilli to lactic acid to maintain a protective acidic vaginal pH of 3.5-4.5.6[8] This acidic environment is unfavorable to uropathogens like *E. coli*. In its turn the decreased levels of estrogen, which is a natural consequence of the peri-menopausal period and processes in the late luteal/menstrual phase results in the loss of glycogen increased vaginal PH and consequently, reduced protective lactobacilli.[6,9] This condition promotes colonisation of the peri-urethral region by the pathogenic bacteria and hence predisposes the development of ascending infection.[9]

Direct Urothelial and Immune Effects: In addition to microbial modulation estrogen is a direct effector of the innate urothelium immunity.[10] Have proven the existence of positive estrogen effects on the generation of antimicrobial peptides, including human 2 defenses (HBD 2), and on the tight-knit of the epithelial membrane, which reduces bacterial sticking and invasion.[11] Observed that the same pathways such as NF- κB (nuclear factor κ-light-chain activation -BD cells) could regulate the production of pro-inflammatory cytokines by estrogen which inhibits their synthesis.

Influence of progesterone on Urodynamic: The action of progesterone mainly affects smooth muscle of urinary tract.[6] Emphasized that high levels of progesterone (observed in a luteal phase or pregnancy) inhibit some estrogenic activities. In particular, progesterone causes the ureteral smooth muscle tone to relax, decreasing the force and speed of urine voiding, which may increase the likelihood of increasing the urinary stasis.[6] Urinary stasis, or retained urine is also known to be a risk factor of the overgrowth of bacteria and consequent infection.[2]

UTI Incidence and Menstrual Cycle Phase: A number of studies have explored how menstrual cycle is related to the time of occurrence of urinary tract infection (UTI).[9] Performed a significant prospective cohort study with the risk factors of symptomatic UTI, and presented a possible increase in the UTI incidence in the pre-menstrual and mid-cycle periods, even though the most significant correlations were with sexual intercourse and the use of a diaphragm. It is possible that reduced estrogen, decreased Lactobacillus populations and the alkaline environment created by menstrual effluent, which offers a favorable medium in which the pathogen can thrive, are the reasons behind the perimenstrual augmentation.[7,9,14]

The Interrelationship: UTI, Inflammation and Menstrual Irregularity

It is evident that due to the variability of hormones during the menstrual cycle, UTI susceptibility is moderated, but the reverse effect that menstrual irregularity is caused by UTI is often incorrectly interpreted. There is a growing amount of evidence which indicates that there is no likelihood of a direct causal relationship but indirect pathways such as systemic illness and psychosocial stress can be involved.[5]

Systemic Stress and Disruption of HPO Axis: The hypothalamic-pituitary-ovarian axis controls the regularity of the menstrual cycle. Great systemic stressors have the ability to disrupt the hypothalamic gonadotropin-releasing hormone (GnRH) release and therefore interfere with the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary.[5]

A severe infectious disease with symptoms, i.e. an acute UTI or pyelonephritis is a severe physiological stressor. This is followed by the liberation of pro-inflammatory cytokines (e.g., IL-1B, TNF-A) by the resulting immune reaction.[6,15] Research on infectious disease indicates that these cytokines are capable of disrupting GnRH signaling leading to temporary HPO axis inhibition and an ovulatory cycles or delayed ovulation.[6,15] Found that a severe infection mimics systemic inflammation conditions and women with such disorders usually have temporary delays in their menstrual cycles. Thus UTI, which is presented as a debilitating systemic disease, can trigger a temporary menstrual pause in a stress- and cytokine-mediated process and not in a direct genitourinary relationship.

Pharmacological Interference: The pharmacotherapeutic regimen should be considered in the background of an active UTI. Most of the antibiotics used in the treatment of uncomplicated UTIs, (e.g., nitrofurantoin, trimethoprim-sulfamethoxazole) do not disrupt menstrual cycle hormonal control.[9] But on the other hand, hepatic cytochrome P450 enzymes are highly induced by rifampin which could be used in complicated cases or in certain prophylaxis. This induction may quicken the metabolism of steroid hormone such as contraceptive hormone and theoretically change the metabolism of endogenous sex hormone although this is not a commonly reported cause of menstrual irregularity in patients of UTI.[2]

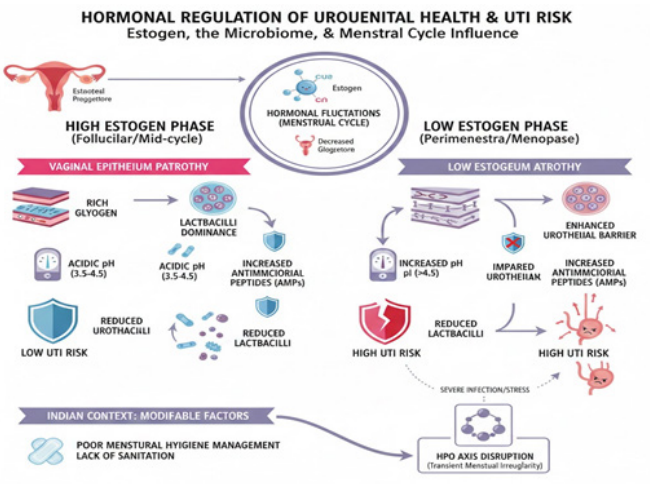

Figure 1: Hormonal Regulation of Urogenital Health and UTI Risk: The Bidirectional Influence of Estrogen, the Microbiome, and Menstrual Cycle.

The figure shows the effect of menstrual cycle-timed oscillating estrogen levels on the risk of UTI. The high-estrogen phase (follicular/mid-cycle) is an environment dominated by estrogen maintaining a glycogen-rich acidic Lactobacillus-dominated environment, which lowers the risk of UTI. On the contrary, elevated UTI risk is observed in the condition of epithelial atrophy, high PH and low levels of Lactobacillus in the case of low-estrogen (premenstrual/menopause). An alternative indirect pathway is also illustrated in which severe infection or stress alters the HPO axis and this leads to transient menstrual irregularity. Lastly, are region-specific variables, including ineffective menstrual hygiene management (MHM), as increases the risk of UTI.

Global and Indian Environment: Hygiene and Exposure to Risk

Although the above physiological processes are universally applicable, local socioeconomic and behavioural factors have a significant impact on the prevalence of UTIs and their relationships with menstrual health.

Importance of Public Toilet Use in the Incidence of UTI and Menstrual Functionality

Regular interactions with communal toilets more precisely, the fear of touching them and reluctance to use them is an important under-acknowledged risk factor of UTIs around the globe, especially in the areas where hygiene levels are uneven.[14] The threat does not depend on personal contact but is mainly caused by the three processes: fomite or splash-back contamination, urinary retention, and psychosocial stress.[2,12]

Reasons of Transmission and Physiological Harms

In poorly-sanitized places, there are high levels of fecal bacteria, e.g., uropathogenic Escherichia, uropathogenic *E. coli* (UPEC) on surfaces, e.g., toilets, floors and taps.[3] Splash-back contamination. However, can transmit UPEC to the periurethral region, but the threat of this is mostly caused by the behavioral adjustment of women who intentionally delay or suppress the urge to urinate (urine-holding) to avoid using the perceived unsanitary community facilities.[12] Such a long-term urine-retention habit causes:

- Urinary stasis: Lasting urine retention results in the existing bladder bacteria growing into infectious levels, which is a vital phase in the pathogenesis of UTI.[9]
- Weakened bladder lining: In case of chronic urine-retention, the urothelium may be distended and micro-traumatized, which may increase the adhesion and invasion of bacteria.[11]

Stress and Effects on Menstrual Function Indirectly

The main effect of poor sanitation in common lavatories is an increased rate of urinary tract infection (UTIs). Stress pathways are the overriding mediating factors in the association between the acquisition of UTI and exposure to poor quality public toilets and the development of menstrual irregularity.

Physiological Stress resulting of Infection: Severe symptomatic UTI or resultant pyelonephritis is as a major systemic stressor as was discussed above. The production of pro-inflammatory cytokine disrupts the production of gonadotropin-releasing hormone (GnRH) pulse in the hypothalamus temporarily suppressing the hypothalamic-pituitary-ovarian (HPO) axis, leading to an anovulatory cycle or delayed ovulation and thus appearing as menstrual irregularity or missed period.[5]

Psychological Stress due to avoidance: The high levels of anxiety, pre-occupation and behavioral change, e.g., limiting fluid intake to reduce the number of public toilets visits, accompanying the navigation in poor public sanitation, can be a major chronic psychological stress factor.[5,15] emphasize, chronic psychological stress increases the level of cortisol and other stress hormones, which are already known to inhibit the HPO axis and cause the normal variability of the menstrual cycle either through functional hypothalamic amenorrhoea or through the menstrual cycle subtle variability.

Thus the causal pathway is as follows: **Poor Public Sanitation → Behavioural Stress/UTI Risk Public → Systemic Stress/inflammation → HPO Axis Disruption → Menstrual Irregularity**

Prevention Measures in regard to Public Toilets.

- *Improving Sanitation*: Franco Johny and V.T. Krishnadas Menon (2024) suggest improving the access to the state of public toilets, the presence of clean water and soap, especially in cities and schools.
- *Behavioral Modification*: Women should be educated

on issues of the danger of urine retention[2] and other specialists advise that the bladder should be voided after every 45 hours (5).

Women are often advised to sit over public seats or use disposable toilet seat covers or wipes, but the main consideration should be made on the aspect of post-voiding hygiene (front-to-back wiping) and avoiding urine retention.[12]

The Forthcoming of Menstrual Hygiene Management (MHM)

The menstrual hygiene management (MHM) tends to mediate the critical connection between UTIs and menstrual cycle in the Indian context. In different parts of India, studies have always indicated that there is a correlation between unhygienic practices and increased prevalence of urogenital infections.

A microbial load in the periurethral area is caused by practices like infrequent changing of absorbent material, use of reusable cloth material that has been dried and stored without hygiene, and inadequate perineal washing.[12,13] Practices that are identified as a contributing factor to a large microbial load in the periurethral area

In the study by Muthulakshmi and Gopalakrishnan, (2017), the authors found that women of reproductive age in Tamil Nadu had a high prevalence of UTI that was strongly correlated with the socioeconomic status, education level, and the presence of poor hygiene practices, which consistently offer a source of bacteria to rise to the urethra.[7]

Ghanshamnani *et al.* (2021) have established that urogenital infections which include UTI, have a significantly lower prevalence in women who transitioned to menstrual cups, an intra-vaginal device that minimizes the risk of contact with the surface compared to external pads, thus indicating the kind of menstrual product and its management to be an important modifiable factor in the Indian population.

Other Contextual Factors

- Water and Sanitation: These factors are two risk factors independent of each other in UTI: lack of clean and accessible toilet and washing facilities, a common occurrence in most of the areas of India, forces women either to use urine retention or insufficient hygiene.[12,13]
- Sexual Activity: Sexual intercourse is one of the strong risk factors of UTIs globally and in India, especially during the immediate post-coital phase, women might be afraid of pregnancy, which is usually associated with altered sexual behaviour, which increases the risk of UTI, thus confounding the symptomology.[1,13]

Diagnostic and Management in Menstrual Health

The symptomatic feature of a urinary tract infection (UTI) may often be confused with normal pain experienced during the menstrual cycle causing diagnostic confusion.[2] Characteristic of dysmenorrhea (painful periods) are common symptoms of uncomplicated cystitis (pain in suprapubic or pelvic area, cramping, and low-back pain).[5]

Diagnostic Problems and Differentiations: Clinical history and microbiological confirmation should be done to achieve proper diagnosis.[13] Highlight the importance of having a clean-catch midstream urine sample as a culture and sensitivity test sample. In UTI, haematuria is a frequent condition that has to be distinguished from menstrual blood contamination, particularly when the patient is in premenstrual period. A positive leukocyte esterase (indicating white blood cells) and nitrite (indicating Gram-negative bacteria such as *E. coli*) result on a urine dipstick is a strong indicator of UTI, but a positive result in isolated pain in the pelvis with negative nitrite and leukocyte esterase indicates the possibility of primary dysmenorrhotic.[1]

Young children with recurrent UTI (rUTI) Management Strategies: Hormonal changes are often found to be a major trigger in women who suffer frequent urinary tract infections.[1] As a result the treatment regimes go beyond the routine of antibiotic prophylaxis.

v Hormonal Interventions: Local vaginal estrogen therapy has been very effective in preventing rUTI in perimenopausal or reproductive-aged women with deficient endogenous estrogen production, including those on specific contraceptives or with polycystic ovary syndrome (PCOS) that disrupts the process of estrogen cycling.[6] The mechanism behind this is that the vaginal epithelial glycogen is repleted, thus re-establishing an acidic and Lactobacilli dominant microbiome as depicted by Reid (2008).

v Antibiotic Counseling and Use: Although antibiotics continue to provide the basis of the disease treatment of acute UTI, the possible existence of systemic physiological stress, even it is mild, must be taken into consideration in patients who complain of subsequent menstrual disorders.[15] Besides patient counselling, including focused on low probabilities of antibiotic impact on menstrual cycling, prohibition of the use of rare hepatic enzyme inducers etc., is crucial to relieving anxiety, which is in turn capable of triggering menstrual delay.[5]

Hygiene Education as a Preventive Tool

The significance of the Menstrual Hygiene Management (MHM) campaigns within the framework of preventing rUTI is supported by solid epidemiological evidence in India.[7,12] where the situation with access to hygiene products and high-quality sanitation is limited. The main actions that should be recommended to MHM are:

- Changing of sanitary pads or cloths (at least every 4 to 6 hours).
- Proper wiping after voiding and defecation.
- Menstrual cups and other modern menstrual products

are safe to use and clean, as already mentioned by Ghanshamnani *et al.* (2021).

Future Directions and Research Gaps

Although a considerable body of knowledge has been established to define hormonal control of susceptibility to UTI, there still exist a number of gaps in the literature, including the issue of temporary disruption of the HPO axis.

Precision Timing of Hormonal Shifts: Current literature generally classifies the risk of UTI by more general menstrual periods such as follicular, luteal, pre-menstrual and does not resolve the temporal differences.[1] To identify the exact correlation between the pace of hormonal loss (e.g., during luteolysis) and the development of UTI in the future, daily hormonal measurements (estradiol and progesterone) should also be included in high-risk women which would help to find out potentially more complex instigators.[6]

Microbiome and Immunological Interplay: The hypothesis of urogenital microbiome shift requires additional explanation. The next-generation sequencing studies are needed to monitor the alterations in the urinary microbiome, vaginal microbiome and the local urothelial immune markers (e.g., defensins) throughout the entire menstrual cycle and correlate the changes with the reported UTI episodes.[10,11] Point out that the research on the effects of different estrogen concentrations on the expression of cytokines in the bladder in the presence of active infection is still in the process of clarification.

Standardized Evaluation of Menstrual Irregularity: Studies that connect UTI/systemic inflammation with menstrual irregularity are often based on self-report or retrospective data of patients.[15] The exposure of standardized definitions of menstrual irregularity and verified inflammatory markers (e.g., CRP, TNF -a) in a prospective cohort study over the span of a recorded UTI is necessary to identify the actual prevalence and persistence of HPO axis dysfunction.[5]

CONCLUSION

UTIs and hormonal health are closely connected with each other as they have a complex bidirectional interrelation. Vaginal microbiome and innate urothelial immunity are both directly affected by the levels of estrogen and progesterone, which coordinate a menstrual cycle and make the urogenital tract a more susceptible environment. Women are at risk of increased UTI due to low estrogen status, especially during the pre-menstrual period.

On the other hand, although no conclusive mechanism that links straightforward UTI to menstrual dysfunction has been established, the incidence of a serious infection triggers a systemic response to stress marked by a rise in inflammatory cytokines. This stress has a temporary ability to impair the pulse generator of the Hypothalamic-Pituitary-Ovarian (HPO) axis leading to random delay in menstruation or ovulation.

More so, context-specific phenomena, particularly in the Indian subcontinent, highlight the importance of insufficient Menstrual Hygiene Management (MHM) as a risk factor, which is critical and modifiable, connecting menstruation-infection vulnerability. The clinical practice should then take the methodological approach of integrating both the acute infection and underlying hormonal and behavioural factors that may be the cause of recurrent UTIs including offering comprehensive counselling to differentiate infection-related symptoms as opposed to the primary dysmenorrhea and stress-related menstrual abnormality. Further studies should use accuracy techniques to comprehensively chart the time dynamics of hormones, microbes, and immune system to formulate the creation of specific preventive methods that do not require antibiotics.

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Orcid ID:

Sonya Kamegni Mombo Nkonda - https://orcid.org/0009-0005-0651-6037

Saeeda Wasim - https://orcid.org/0000-0003-0084-1021

Subuhi Anwar - https://orcid.org/0000-0002-0505-1494