ENDOMETRIAL CANCER AND THE MICROBIOME- Review

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Abstract

Incidence rates for endometrial cancer (EC) are rising, particularly in postmenopausal and obese women. Low levels of gonadal circulating estrogen observed in post-menopausal women can adversely impact a diverse range of physiological factors, with clinical implications for brain cognition, gut health, the female reproductive tract and other aspects of women's health. Endometrial microbiota interplay in the uterus.

Several studies demonstrated that asymptomatic women harbour commensal microbial communities in their uterus, and that the uterine microbiome seems to be altered in women who suffer gynaecological pathologies such EC.

We need larger studies to further confirm an association of certain microorganisms in women with EC compared to our healthy women in our office. However, there are large gaps in knowledge regarding the association between the gut microbiome and gynecologic cancers, and research characterizing the reproductive tract microbiome is insufficient.

This review aims to shed light on the role of the gut microbiota in estrogen-modulated disease, the bi-directional relationship between the metabolic profile (including estrogen levels) and gut microbiota in estrogen-driven disease will also be discussed.

Keywords:

microbiome, endometrial microbiota, endometrial cancer, vagino-uterine microbiome

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The incidence and prevalence of **endometrial cancer (EC)** is increasing globally. Endometrial cancer can present with different symptoms depending on how much the cancer has progressed.

Early symptoms of endometrial cancer, such as abnormal vaginal bleeding, can also be signs of other conditions, so it's important to have any new symptoms checked out right away.

Like other cancers, early detection of endometrial cancer is key to treating and beating it. Endometrial cancer is diagnosed most often in postmenopausal women at an average age of 60 years.

Risk factors include smoking, being overweight, and not getting enough exercise.

Obesity and insulin resistance are associated with higher risk and worse outcomes for endometrial cancer.

The link between estrogens and obesity stems from adipose tissue's ability to synthesize estrogen.

Polycystic ovary syndrome (a disorder of the hormones made by the ovaries), and Cowden syndrome are inherited conditions that are linked to an increased risk of EC. Women with a family history of endometrial cancer in a first-degree relative (mother, sister, or daughter) are also at increased risk of endometrial cancer.

Estrogens play a mitogenic role in the normal endometrium, driving tissue growth as part of pregnancy anticipation during the menstrual cycle.

Progesterone inhibits estrogen-induced endometrial growth during the luteal phase. This balance between pro-growth estrogens and anti-growth progestogens is often dominated by estrogens during cancer formation (1,2,5).

The endometrium possesses a functional microbiome in physiological conditions. Like the normal vaginal microbiota, the endometrium of healthy and asymptomatic women is often dominated by Lactobacilli. Microbes in the vaginal environment of women suffering from EC differed from the microbes in women who did not have the illness (Fig,1).

Endometrial cancer is a multifactorial disease, but one of the strongest risk factors is exposure to excess estrogen and/or a relative lack of progesterone. This is because estrogen stimulates rapid growth of endometrial cells, whereas progesterone counters this action.

The two major female sex hormones, estrogen and progesterone, control the menstrual cycle, and a balance between these two hormones is crucial for maintenance of a healthy endometrium.

Estrogen promotes endometrial epithelial cell growth, while progesterone inhibits estrogen-mediated epithelial cell growth in the endometrium.

Physical inactivity and obesity are well-documented risk factors associated with the development of EC. This can be attributed to significant increases in exposure of the endometrium to estrogen generated by fatty tissue deposits.

Endometrial cancer pathogenesis is unknown.

It is becoming increasingly evident that microorganisms play an important role in our health and well-being through the producti-

on of bioactive molecules shaping a healthy microbiota, which in turn, interacts with our own cells to regulate and influence our metabolism, physiology, and immune functions that ultimately shape our health and resistance to a disease.

Endometrium seems to be an immunologically suited niche for microbiota with its possible function in modulating inflammatory and immune responses (6-12).

Estimations of uterine bacteria load are estimated between 100 and 10,000 times less bacteria than the vaginal microbiome (13,14)

The uterine and vaginal microbiome distinguishes patients with EC from those without.

The gut microbiota regulates estrogens through secretion of β-glucuronidase, an enzyme that deconjugates estrogens into their active forms. When this process is impaired through dysbiosis of gut microbiota, characterized by lower microbial diversity, the decrease in deconjugation results in a reduction of circulating estrogens.

The alteration in circulating estrogens may contribute to the development of conditions discussed herein: obesity, metabolic syndrome, cancer, endometrial hyperplasia, endometriosis, polycystic ovary syndrome, fertility, cardiovascular disease and cognitive function (15), (Fig,2).

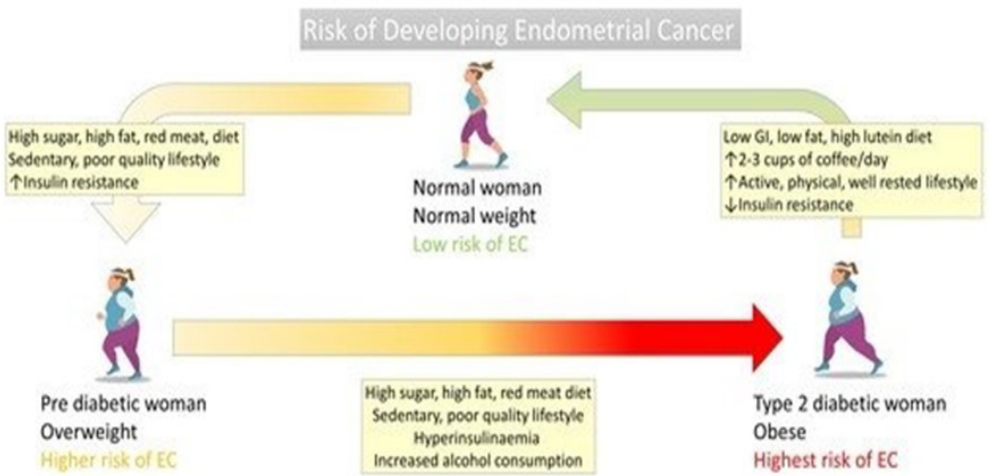

Fig. 1 Risk of developing endometrial cancer (5)

Endometrial cancer is the most common type of uterine cancer and is subdivided into two types by histopathology.

Postmenopausal women with a high body mass index are at an increased risk for Type I EC because of higher plasma estrogen.

High levels of estrogen stimulate glycogen-dependent metabolism within the vaginal mucosa, leading to increased colonization by lactobacilli (16).

Type II EC develops in a background of endometrial atrophy, but hormonal risk factors are unknown, making early identification and treatment important to improved patient prognosis (17,18).

Lactobacilli also metabolize glycogen to produce lactic acid, contributing to a low vaginal pH that is thought to reduce the risk of infection (19).

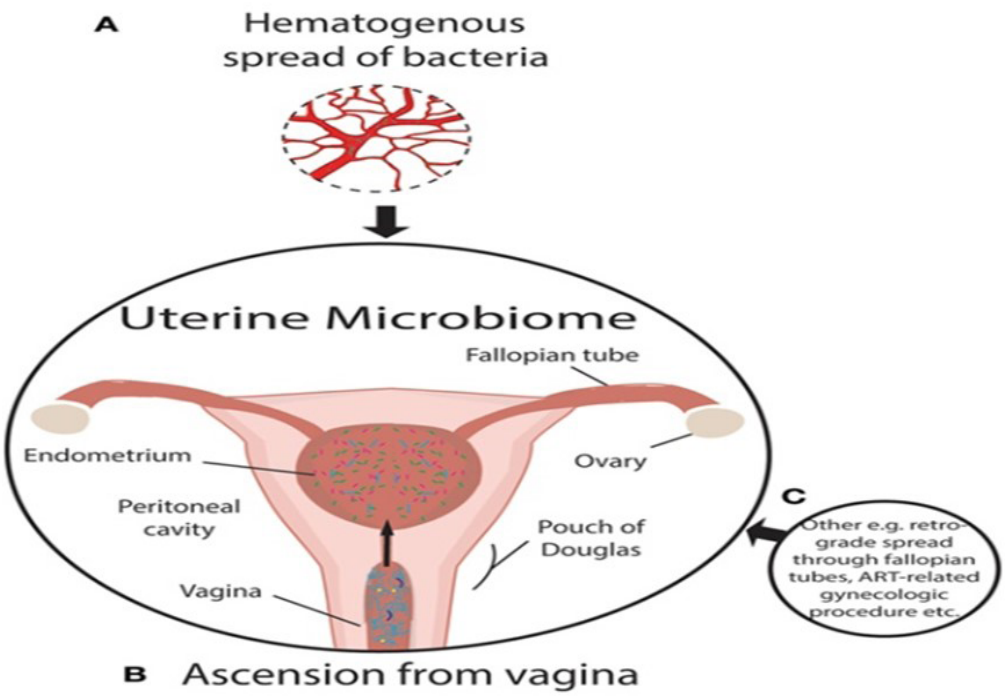

Fig. 2 Established and putative bacterial transmission routes between uterine microbiome and distal sites

A. Putative hematogenous spread of bacteria emanating from the gut and oral microbiome or other means of circulation of bacteria through the blood. **B**. Ascension of bacteria through the cervix has been well established and is a likely source of bacterial transmission. **C.** Transmission of bacteria through routes, other than those illustrated, include assisted reproductive technology-related gynecologic procedures whereby bacteria from the vaginal microbiome are introduced to the uterus, such as oocyte retrieval (6).

In postmenopausal women, ovarian estrogen production has ceased, leading to lower glycogen levels, a propensity for lower lactobacilli colonization, and more basic vaginal pH levels, which may help explain the significant difference in pre- and postmenopausal reproductive tract microbiota (20,21).

Molecular mechanisms underlying the interaction between microbiome and pathogenesis of endometrial cancer still need elucidation.

The gut microbiome is influenced by multiple factors including diet and lifestyle (22).

If the microbiome does play a role in endometrial cancer, beyond being a marker for it, this could have important implications for endometrial cancer prevention.

Probiotic bacteria have the ability to both increase and decrease the production of anti-inflammatory cytokines which play an important role in prevention of carcinogenesis (23-25).

A variety of factors related to diet and lifestyle can increase the chances of developing endometrial cancer; chief among them is the consumption of foods high in animal fats and sugars whereas diets high in vegetables and fruits (especially those high in lutein) have lower risk (5).

Further investigation is needed to better understand the role of the microbiome in the manifestation, cause or progression of EC.

Because of the modifiable nature of the microbiome, our findings may hold promise in the development of strategies for EC prevention.

Endometrial cancer - is the most common type of cancer that affects the female reproductive system. Cancer treatment, especially hormone therapy and pelvic therapy (radiation therapy), can often affect sexual function.

In addition, depression and anxiety, which are common in cancer patients, can contribute to sexual problems.

Thus, sexual dysfunction is common to survivors and can cause exacerbation of suffering and have a negative impact on quality of life. However, sexual function is not often discussed with cancer patients.

Reasons for this include a lack of training of specialist doctors, the discomfort of doctors on this topic and insufficient time for discussion during visits.

However, there are effective strategies for treating female sexual dysfunction, making these discussions a critical part of caring for cancer patients.

Female sexual problems refer to issues such as sexual desire and arousal, orgasm and pain.

Sexual dysfunction after cancer treatment is common in cancer patients.

At regular intervals, cancer survivors should be asked about their sexual function, including sexual function prior to cancer treatment, their current sexual activity, and how cancer treatment affected their sexual function and privacy.

Patients with concerns about their sexual function should be further evaluated, including screening for possible symptoms and psychosocial problems (eg, anxiety, depression, relationship issues, body image concerns, drug or alcohol use), which can contribute to sexual dysfunction.

Traditional risk factors for sexual dysfunction, such as cardiovascular disease, diabetes, obesity, smoking and alcohol abuse, should also be assessed, as should the oncology patient's history and treatment history.

If anticancer treatments have led to menopause, menopausal symptoms and effects on sexual function should be evaluated.

A physical examination should be performed or a recommendation for gynecological examination should be made to note the points of sensitivity, vaginal atrophy and anatomical changes associated with cancer and cancer treatment.

Female sexual dysfunction is often multifactorial. Therefore, the treatment of sexual dysfunction often requires a multidimensional treatment plan that addresses the underlying problems, which can be physiological (e.g., menopause, illness), disease-induced, medication-induced, psychological (e.g., anxiety, depression) and interpersonal.

Psychotherapy can be helpful for women with sexual dysfunction, although there is limited evidence of its effectiveness.

Options include cognitive behavioral therapy, for which there is some evidence of efficacy in survivors of breast, endometrial, and cervical cancer survivors.Recommendations for psychotherapy, sexual counseling or gynecological care should be given accordingly.

A multidisciplinary treatment plan can be very helpful in situations where psychosocial dysfunction contributes to sexual dysfunction.

For some women, hysterectomy can affect sexual intimacy.

Regarding the risk of recurrence, experts recommend careful monitoring after completion of treatment for endometrial cancer, especially in the first three years after diagnosis, when the risk of recurrence is highest.

Sexual problems: Changes due to vaginal scarring, dryness of the vagina or the feeling of pressure can affect sexual appetite or can make sexual intercourse unpleasant, painful.

These can be caused by hysterectomy, radiation therapy, chemotherapy or hormone therapy. Some effects may resolve over time. Your doctor and nurse can give you suggestions for treating these effects on your sexual health.

The implications of hysterectomy on sexuality are somatic in nature, but they also have a psychic component.

For many women, the lack of a uterus means a loss of femininity. Hysterectomy performed for oncological pathology has a definite negative effect on sexual function.

Conclusions

A part from hormonal influences and genetic predisposition, obesity and metabolic syndrome are increasingly recognised as major factors in endometrial cancer risk, due to changes in lifestyle and diet, whereby high glycaemic index and lipid deposition are prevalent.

All these studies support the evidence that the uterine microbial composition is clinically relevant and requires further investigation.

If the microbiome does play a role in EC, beyond being a marker for it, this could have important implications for endometrial cancer prevention

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