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Micro-Environmental Approach of Female Reproductive Diseases: Interactions Between Sex Hormones and Pathogens from Inflammation to Malignancy

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Abstract

Both health and disease are significantly influenced by the female genital tract's distinct microenvironment, which plays a role in the reproductive process. This tract contains a wide variety of components, including, but not limited to, microbes, hormones, metabolites, and components of the immune system. The interactions that take place between these components have the potential to both ascertain the status of one's health as well as the presence or absence of illness. The purpose of this study was to conduct a literature review on the most recent developments in thought and trends regarding the hemostasis and interactions of the microenvironmental factors that are found in the genital tract. This review was to focus on the most recent developments in thought and trends regarding the hemostasis and interactions of the microenvironmental factors. The results of this research offered evidence that confirmed the conclusions of previous studies and highlighted how important it is to keep the immediate surroundings clean.

1. Introduction

The present study explores the interactions between sex hormones and pathogens from inflammation to malignancy. The micro-environment that contains these elements is discussed in detail.

2. The Microenvironment of the Female Reproductive Tract

Microorganisms, metabolites, and immune system components inhabit the female reproductive microenvironment. These three relationships affect female reproductive health and balance. In the reproductive system, out-of-balance bacteria, metabolites, or immunity create diseases, symptoms, and signs. Infectious infections cause infertility, miscarriage, premature birth, and gynecological cancers. In the female reproductive canal, useful and dangerous microbes thrive. This causes metabolites. Dysbiosis, immunity, and environment modify reproductive metabolites. Each produces disease. Microorganisms and metabolites can influence immunity. These occurrences cause repeated genital

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pathogen infections, deteriorating infectious illnesses, poor pregnancy outcomes, and gynecological malignancies. Pathogenic pathways that promote inflammation, unfavorable pregnancy outcomes, and tumor growth can be uncovered by studying bacteria, metabolites, and the immune system in the reproductive tract. It helps diagnose and treat. Microorganisms, metabolites, and the immune system can uncover pathogenic pathways that increase inflammation and poor pregnancy outcomes (Li et al., 2020).

3.The Microbiome of the Female Genital Tract

Menstruation alters the female vaginal microbiome, which is less diverse than the gut. The gut's microbiota is periodically replenished (Chen et al., 2017). Most germs have hosts. 90–95% of bacterial biomass is Lactobacillus. These bacteria keep the vaginal canal acidic and healthy. Competition, antibacterial, and immunomodulatory chemicals reduce infections (Van der Veer et al., 2019). Pathogenic bacteria populating lactobacilli in the female genital tract can cause vaginitis, cervicitis, and pelvic inflammatory disease (PID). These illnesses cause vaginal discharge, pain, and odor. Common vaginitis (Workowski and Bolan, 2015). Dysbiosis-resistant microorganisms vary by subject. Variable microbes. Nutrition, age, lifestyle, immunity, disease susceptibility, or genetic polymorphism may contribute (Serrano et al., 2019). Microflora dominance isn't associated to vulvovaginitis symptoms in non-Lactobacillus-dominant women. Without the host's internal milieu and disease environment, we can't define illness by bacteria or dysbiosis (Scott et al., 2019).

4. Metabolites in the Reproductive Tract

Metabolites in the reproductive tract affect female genital tract inflammation, pregnancy, and reproductive cancers. These metabolites suggest severity, diagnosis, and prognosis (Song et al., 2019).

Metabolites are FRS substrates, intermediates, and byproducts. Diet and microbes trigger these effects (Watson and Reid, 2018). These reactions result from gene expression (McMillan et al., 2015). These metabolites can predict disease phenotype more precisely than the genome, transcriptome, and proteome (2014). Genital infections, pregnancy problems, and malignancies often cause dysbiosis of the female genital system. e.a. They influence amino acid, carbohydrate, and lipid metabolism. These metabolic processes involve living things (Srinivasan et al., 2015). These effects alter host cell function, immunity, disease susceptibility, and reproductive tract health.

5. Host Immune System

Immune systems and microorganisms interact. Interactions are complicated (Delgado-Diaz et al., 2019). Microbial ligands connect to host receptors, creating inflammatory agents, chemokines, and antimicrobials that influence the reproductive tract's immune response (Hooper et al., 2012). Infections and immunological metabolites can harm vaginal epithelium. Clinical Microbiology & Infection (Serrano et al., 2019). Chemical may boost vaginal microbiota metabolism. This boost helps vaginal microbes thrive (Serrano et al., 2019). Local metabolic competition affects immune cell infection response. This influences pathogen proliferation and immune response (Postler and Ghosh, 2017). The reproductive tract's natural equilibrium is maintained by bacteria, metabolites, and immunology (Pruski et al., 2018). Any imbalance can cause phenotypic alterations, illness, and disaster. This page examines reproductive tract microbes, metabolites, and immunology to better understand its microenvironment, illnesses, and bad consequences.

6. Normal Vaginal Microenvironment

Reproductive-age women have five microbiome CSTs (Ravel et al., 2011). CST I strains crispatus, gasseri, jensenii, and iners are most common. Lactose-intolerant CST IV has anaerobic or partially aerobic Lactobacillus spp (Gajer et al., 2012). Nonpregnant women's vaginal microbiota is intermediate or disease-related. STI-free women are affected. High Nugent doesn't create illness or microecological problems. The host's environment stabilizes microbiota. Menstruation affects vaginal microbiota. Sexual activity, hormonal contraception, antimicrobial medicines, lubricants, and douching change vaginal flora. Contraception, antibiotics, lubricants, and douching are variables (Gajer et al., 2012; Mitchell et al., 2012). Menstruation or hormonal contraception don't impact certain women's CST. Scientists must discover if bacterial metabolism is involved.

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Lactobacillus abundance is positively related with lactate, 4-hydroxyphenylacetate, isoleucine, leucine, tryptophan, phenylalanine, aspartate, dimethylamine, sarcosine, and pi-methylhistidine (Srinivasan et al., 2015). Similar metabolic features exist in L. crispatus, L. jensenii, and L. iners (Pruski et al., 2018). L. crispatus' genome is greater than L. iners', a study found (France et al., 2016). Iners ferments less carbon than crispatus (Pruski et al., 2018). Most vaginal amino acids and dipeptides are from L. crispatus or L. jensenii. Ornithine, lysine, glycylproline, phenylalanine increase (Srinivasan et al., 2015). L. iners produces amino acid catabolites. Proline, threonine, aspartate, serine, valinylglutamate (Srinivasan et al., 2015). L. iners and G. vaginalis produce cytolysin (Macklaim et al., 2013). In a healthy vaginal microenvironment, L. crispatus and/or L. jensenii prevail. More research is needed to determine if asymptomatic women's non-Lactobacillus abundance equals L. crispatus and/or L. jensenii dominance.

7. Epithelial Mucous Layer

Pathogens are protected by vaginal epithelial mucus. Mucus lines vaginal epithelium (Aldunate et al., 2015). Epithelial cells produce inflammatory chemicals to fight germs. Germs that bypass defenses. Epithelial PPRs detect pathogens. Henceforth. To avoid infection and preserve immunological balance, lactobacillus must dominate in the vaginal canal (Smith and Ravel, 2017). L. crispatus and L. jensenii decrease vaginal discomfort (Kyongo et al., 2012). Lactic acid increases reproductive immunity (Delgado-Diaz et al., 2019). Low pH reduces proinflammatory cytokines and chemokines with Lactobacillus spp. L-lactic acid. L-lactic acid induces low pH. lactic acid can enhance IL-10 synthesis, limit IL-12 production in DCs, and suppress natural killer cell cytotoxicity (2019). (Ilhan et al., 2019). Microorganisms create anti-inflammatory lactic acid. Vaginal health is vital. Raise IL-1RA synthesis, limit IL-1's proinflammatory signal, and reduce IL-6 and MIP-3 production (Delgado-Diaz et al., 2019). Healthy reproductive tract bacteria, metabolites, and immunology. Any reproductive imbalance affects the whole tract.

8. Normal Developments During Pregnancy

Estrogen and progesterone modify a healthy pregnant woman's vaginal microbiome. Vaginal microflora is low in richness and variety, restricting CST IV hazardous bacteria such as Gardnerella vaginalis, Atopobium vaginae, and Sneathia amnioticum (Serrano et al., 2019). Lactobacillus dominates vaginal flora throughout pregnancy (Serrano et al., 2019). CST I is common in pregnancy. After CSTV,2&4 (MacIntyre et al., 2015). Third trimester vaginal microbiome is nonpregnant. Estrogen and Lactobacillus reduce glycogen after a week. CST IV reduced vaginal flora consistency and conformity while increasing variation. Women experienced postpartum endometritis and puerperal morbidity (MacIntyre et al., 2015). Bacteria are in placentas and amniotic fluid (Nuriel-Ohayon et al., 2016). Several studies suggest placental bacteria may be derived from oral flora, with most being non-pathogenic symbiotic phyla such as Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria. Placental bacteria suggests (Aagaard et al., 2014). Placental microbiota stimulates gut flora migration after birth. Migrating pregnancies (Collado et al., 2016). Healthy placenta and amniotic fluid are germ-free, studies reveal. Using contaminated chemicals or equipment to gather samples can cause this. Both (De Goffau et al., 2019).

Serrano et al2019 found that vaginal microbiota metabolism is strongest in the first trimester. Pregnancy stabilizes and simplifies vaginal microbiota. Hormone-induced. Impaired glucose, cell wall/membrane, protein, and nucleic acid metabolism. Pregnancy balances vaginal microbiota (Serrano et al., 2019). Term-carrying women showed reduced glucose and lipid metabolism in their cervicovaginal secretions in the second and third trimesters. Pregnant women demonstrated (Ghartey et al., 2015). In high-estrogen situations, glycogen deposition and lactic acid metabolization downregulated carbohydrate metabolism (Ghartey et al., 2015). This allows lactobacilli to invade a host's reproductive system and maintain an acidic pH. This reduces pregnancy difficulties and protects the cervix. Term-born women had decreased third-trimester lipid metabolism. Acidity inhibits pathogen development. Second-trimester methyl-4-hydroxybenzoate increases 8.8 times (Ghartey et al., 2015). Amniotic fluid and placental flora metabolize membrane transport, carbohydrates, amino acids, and energy. Placental metabolic circuits (Aagaard et al., 2014; Collado et al., 2016). Healthy pregnancy depends on vaginal flora's metabolic

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activity. Vaginal microbes undertake several activities throughout pregnancy.

"Extended-self" antigens help the mother's immune system absorb paternal fetal antigens. So fetal development can proceed normally (Deshmukh and Way, 2019). Local and systemic regulatory T cell proliferation maintains fetal tolerance during pregnancy (Deshmukh and Way, 2019). Metabolite and immune system connection during pregnancy. L-arginine metabolism reduces pregnancy immune response. Triplets (Kropf et al., 2007). Increased enzyme activity reduces L-arginine, which reduces CD3 and T cell hyporesponsiveness. Full-term placenta arginase increases active arginase (Ismail, 2018). IDO silences T cells to establish immunological tolerance (Kropf et al., 2007). Natural flora increases mother-placental-fetal immunity. This helps fight infections (Mei et al., 2019). Bacteroides and mucosal TCR+ T cells (Ghaemi et al., 2019). Microbiota create regulatory T cells that promote immunological tolerance, endometrial receptivity, and placental implantation (Benner et al., 2018). Dysbiosis causes immune disorders and pregnancy problems (Smith and Ravel, 2017). Examine reproductive system during normal pregnancy to determine pregnancy issues (Wang et al., 2016).

"Extended-self" antigens help the mother's immune system absorb paternal fetal antigens. So fetal development can proceed normally (Deshmukh and Way, 2019). During pregnancy, maternal forkhead regulatory T lymphocytes grow locally and systemically. FET allograft (Deshmukh and Way, 2019; Ghaemi et al., 2019). Metabolite and immune system connection during pregnancy. L-arginine metabolism reduces pregnancy immune response. Triplets (Kropf et al., 2007). Increased enzyme activity reduces L-arginine, which reduces CD3 and T cell hyporesponsiveness. Full-term placenta arginase increases active arginase (Ismail, 2018). IDO silences T cells to establish immunological tolerance (Kropf et al., 2007). Natural flora increases mother-placental-fetal immunity. This helps fight infections (Mei et al., 2019). Bacteroides and mucosal TCR+ T cells (Ghaemi et al., 2019). Microbiota create regulatory T cells that promote immunological tolerance, endometrial receptivity, and placental implantation (Benner et al., 2018). Dysbiosis causes immune disorders and pregnancy problems (Smith and Ravel, 2017). Understanding pregnancy bacteria, metabolism, and immunology can help diagnose problems. Examine pregnancy's reproductive system (Wang et al., 2016).

9. Gynecological Oncology

Dysbiosis causes cancer (Ilhan et al., 2019; Scott et al., 2019). Ilhan et al.; Scott et al. An imbalance in some bacteria can cause host epithelial barrier malfunction, genome integration, genotoxicity, inflammatory activation, immunological abnormalities, and metabolic abnormalities, creating a milieu that promotes tumor formation and contributes to gynecological cancers. Unbalanced microorganism populations cause gynecological cancers (Scott et al., 2019; Laniewski et al., 2020). Inflammation causes cancer (Scott et al., 2019). Microorganism virulence factors can cause chronic inflammation in host tissues, increase cell proliferation, and cause malignancy in non-apoptotic cells. Microbes cause (Scott et al., 2019; Laniewski et al., 2020). Carcinogenesis and phenotypic changes modify cancer's metabolism (Icard et al., 2018). Microorganisms can cause cancer by damaging DNA (Scott et al., 2019). Flora-borne infections can weaken the immune system, increasing cancer growth and spread (Scott et al., 2019; Laniewski et al., 2020). Stability of the reproductive microbiota affects anticancer effects, which affects the reproductive microenvironment.

During HPV infection and cancer progression, host and reproductive microorganisms create a metabolic network. This network influences sickening (Ilhan et al., 2019). Ilhan et al. BV-like amino acid and nucleotide metabolisms in HSILs and CC. BV, CC cause HSILs (Ilhan et al., 2019). ICC patients had a higher vaginal lipid metabolite level (Ilhan et al., 2019). Ilhan et al. This may be due to bacteria-host interactions that enhance carcinogenic pathways in the tumor microenvironment and boost cell proliferation and membrane development, boosting microflora's carcinogenic activity. Changes in cervicovaginal microbial population affect metabolome, immunity, and cancer progression (Ilhan et al., 2019). Ilhan et al. GCDC prevents vaginal flora diseases (Ilhan et al., 2019). Low levels of GCDC and Lactobacillus reduce chronic colitis patients' cancer-fighting abilities.

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10 Immune Cells and Metabolites Produce Tumor-Specific Microenvironment.

Immune cells and metabolites produce tumor-specific microenvironment. IL-8, IL-10, and nitric oxide were higher in CIN patients than controls (Tavares-Murta et al., 2008). Since IL-8 is a proinflammatory Th1-type cytokine while IL-10 is anti-inflammatory, more research is needed. IL-8 causes inflammation, IL-10 reduces it. ICC patients with high IL-1, IL-8, MIP-1, CCL20, RANTES, and TNF had high lipids. It's important. Increased plasmalogens and LCPFA in ICC indicate aberrant cell metabolism, gene expression, and cytokine production. Inflammatory plasmalogens and LCPUFAs. Cytokine precursors plasmalogens and LCPUFA (Ilhan et al., 2019). Metabolites grow cancer. Immunosuppression and Th2 cytokines maintain CMV (Bedoya et al., 2014). In cervical cancer patients, IL-10 and IL-13 cause ASE (CC). L-arginine becomes L-ornithine and polyamines. L-arginine deficiency reduces immunity. Immunosuppression causes cancer (Bedoya et al., 2014). HPV increases CST IV polyamines, promoting tumor growth. HPV vaginal flora. CST IV HPV-positive patients have higher vaginal polyamines (Borgogna et al., 2020). HPV infection, cervical lesions, and bacterial flora, metabolites, and immunity in CC secretions contribute to tumor growth and spread. These impact tumor growth and spread.

11. Infections that are Common in the Genital and Female Reproductive Tracts

Vaginal infections include vaginitis, cervicitis, and PID (Sherrard et al., 2018). Dysbiosis or microbial invasion are likely reasons (Song et al., 2020). Most research on reproductive tract infections focuses on BV, C. trachomatis, and AV. Most U.S. diagnoses are for these three infectious diseases (Ceccarani et al., 2019). Inflammation of the reproductive tract induced by bacterial flora abnormalities is associated to bad pregnancy outcomes and malignancies. BV is another cause (Sherrard et al., 2018). Less study has been done on gonorrhea, vulvovaginal candidiasis, and trichomoniasis. This section discusses bacteria, metabolites, and the host's immune response in AV, BV, and C. trachomatis infections.

12. Candida and Vaginal Infection

Estradiol-based medications cause VUIs. Ovulation removes vaginal neutrophils. Factual (high estradiol) (high estradiol). Neutrophils' vaginal entry is unknown. Neutrophil TEM was studied. Estradiol lowers ectocervix and fornix CD44 and CD47. Estradiol reduces neutrophil-retaining epithelial proteins. Luteal progesterone increases CD44 and CD47 expression, boosting neutrophil migration and killing Candida albicans. Hormones trigger sperm-protecting vaginal neutrophil infiltration. Ovulation reduces immunity. Sex hormones regulate neutrophil TEM, boosting vaginal tolerance and immunity. Sex hormones. lumen vaginal (Salinas-Muoz et al., 2018).

By phagocytosing germs, neutrophils boost mucosal immunity (Nicolas-Avila, 2017). Unregulated metabolite release causes uncontrolled neutrophil migration into tissues. Neutrophils generating hazardous tissue chemicals could cause this harm (Kruger et al., 2015). Neutrophils develop in bone marrow before entering bloodstream (Lahoz-Beneytez et al., 2016). CXCR2-ligand gradients stimulate microcirculation (Nemeth and Mocsai, 2016). Sentinel cells emit proinflammatory mediators and chemoattractants, activating and attracting neutrophils to infection or inflammation sites. Until no sentinel cells remain, this continues (Zec et al., 2017). (Zec et al., 2017). Epithelial cells in the bladder, lung, and stomach release chemoattractants that attract neutrophils to the subepithelium. Urinary, lung, and GI mucosa. Mucosal subepithelial space (Swee et al., 2008). (Swee et al., 2008). Neutrophils cross the epithelial basement membrane, adhere to the epithelium, and migrate through epithelial cells to attack germs. Neutrophils enter the epithelium (Brazil and Parkos, 2016). (Brazil and Parkos, 2016). Neutrophil transepithelial migration (TEM) to the intestinal lumen is known (Parkos, 2016). (Diamantis and Androutsos, 2008).

Vaginal hormones govern commensal and opportunistic bacteria, exogenous spermatozoa, and STDs. Reduces STD risk. Mucus and neutrophils encourage vaginal flora and fight invasive microorganisms. Invasive microorganisms include HPV, C. albicans, T. vaginalis, C. trachomatis, and N. gonorrhea. Cervicovaginal mucus, neutrophils; sperm must survive in the ectocervix for fertilization (Suarez and Pacey, 2006). (Suarez and Pacey, 2006).

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Neutrophils are removed by ovulation (Sasaki et al., 2009). These modifications make ovulating women more infectious. Birth risks rise (Wira et al., 2015). The mechanisms that govern neutrophil influx during the ovarian cycle in humans and rats (Diamantis & Androutsos, 2008) are unknown. Humans and animals' reproductive cycles affect leukocyte counts (Diamantis and Androutsos, 2008). Human and mouse leukocyte counts differ (Diamantis and Androutsos, 2008).

13. Candida and Immune Response

Candida causes vulvovaginal candidiasis (VVC). Unexplained factors boost estrogen. Pregnancy, oral contraceptives, and hormone replacement therapy increase women's VTE risk. This study examines Candida albicans' estrogen response and host-pathogen interactions. Estrogen affects Candida albicans. Estrogen makes C. albicans pathogenic by evading the immune system. Estrogen reduces opsonophagocytosis by increasing fungal Factor H. Fungus is immune-resistant. The immune system can't kill fungus. Gpd2 increases estrogen-induced factor H. This hormone-sensing mechanism may improve women's health and explain fungal infection discrepancies. Walkway opens both doors. Both exploratory routes are shown (Kumwenda et al., 2022).

E2 (17-estradiol) causes yeast infections. Pregnancy or HRT may raise levels. Regardless of source, raises yeast infection risk. Candida albicans' E2 role is unknown. i>C investigations were functional, transcriptomic, and metabolomic. albicans cells were treated to heat, serum, and E2. E2 stimulated cell filamentation. E2 and serum slow filament development. Transcriptomics shows serum and E2 reduce filamentation-related gene expression. Unlike serum or E2. Participate: HWP1/, ECE1/, IHD1/, MEP1/, SOD5/, ALS3. HGT20 and GCV2 are downregulated in serum-supplemented E2 cells. E2 signaling may be crucial in secondary metabolite production. According to metabolomics, treatments released 36 compounds. Key hyphal cell wall carbohydrates and fatty acids. Arabinonic, oleic, octadecanoic, 2-keto-D-gluconic, palmitic, steriacstearic acids. E2 signaling affects C. albicans' morphogenesis and pathogenicity. E2 affects gene expression and metabolite secretion (Bataineh et al., 2022).

14. Candida albicans

Human pathogen Candida albicans is common. Diploid fungi cause mucosal and systemic diseases. Candida causes vaginal candidiasis (VC) (Cassone, 2015). Candida albicans is normal oral, GI, and genital flora. It's three tracts. C. albicans is mammalian-only. It causes numerous diseases. Virulence involves transforming yeast-like cells into elongated ones (pseudohyphal and hyphal filaments). Mutation makes yeast multicellular (Bataineh et al., 2021). Viruses lyse macrophages and neutrophils and overcome endothelial barriers using hyphal filaments. Pregnant, young, and postmenopausal women on hormone replacement treatment are more likely to develop vulvar cancer than non-menopausal women (Cheng et al., 2006). E2 affects the fungus and host's reproductive epithelium to cause and perpetuate VC. Viruses can spread (Ferrer, 2000). Immunosuppressive E2 makes the host susceptible to VC (Wagner and Johnson, 2012). Using E2 to produce and sustain experimental VC in animal models shows synergy (Hirata et al., 2005). Initial E2 studies on Candida albicans focused on germ tube formation and cultured biomass (Gujjar et al., 1997). Later biochemical and molecular study indicated that E2 in the host affects Candida albicans' CDR1 and CDR2 genes and Ebp1p receptor localization (Zhang et al., 2000).

15. Conclusions:

Both health and disease are significantly influenced by the female genital tract's distinct microenvironment, which plays a role in the reproductive process. This tract contains a wide variety of components, including, but not limited to, microbes, hormones, metabolites, and components of the immune system. The interactions that take place between these components have the potential to both ascertain the status of one's health as well as the presence or absence of illness.

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