



THE ASSOCIATION BETWEEN GUT MICROBIOME AND SEX HORMONES

Obstetrics & Gynaecology

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ABSTRACT

The gut microbiome, a complex ecosystem of microorganisms in the digestive tract, can significantly influence the body's endocrine system, impacting hormone production. A balanced gut microbiome is essential for maintaining a healthy immune system. When the gut microbiota is imbalanced, it can trigger chronic low-grade inflammation throughout the body, including the reproductive organs. Inflammation can disrupt hormone production and signalling, potentially leading to irregular menstrual cycles, ovulation problems, and decreased sperm quality. Imbalances in the gut microbiota can alter this process, leading to imbalances in estrogen levels. Excessive levels of estrogen or the accumulation of certain estrogen metabolites can disrupt the delicate hormonal balance necessary for conception and successful pregnancy. Gut hormones, gastric inhibitory peptide (GIP), play an important role in fertility, particularly PCOS. GLP-1, (Glucagon-like Peptide-1) An incretin hormone that can influence fertility and may have direct effects on the ovaries and reproductive axis. Adiponectin, a hormone, has anti-inflammatory and antidiabetic effects and is also implicated in fertility and reproductive processes. Prolactin plays a crucial role in reproductive health, including fertility, menstrual cycles, and embryo implantation. Other Gut hormones, ghrelin, leptin, and peptide YY (PYY), indirectly affect reproductive health. The gut microbes can alter the levels of estradiol, progesterone, and corticosterone and produce neurosteroids like allopregnanolone. These are important for reproductive function. They can modify steroid hormones through enzymatic processes, impacting the menstrual cycle and other reproductive events. The production of allopregnanolone by specific bacteria has been linked to increased levels in pregnant women, suggesting a role in postpartum mood regulation.

KEYWORDS

GLP-1 (Glucagon-like Peptide-1), Gastric inhibitory peptide (GIP), Serotonin, Dopamine, Ghrelin, Leptin, Peptide YY (PYY), Estradiol, Progesterone, Corticosterone, Allopregnanolone, Adiponectin

INTRODUCTION

An increasing body of research highlights the importance of gender differences in the epidemiology, pathophysiology, and treatment of various diseases, especially non-communicable diseases (1).

Furthermore, females are at a greater risk of suffering from osteoarthritis, heart disease, urinary tract problems, stroke, depression, and anxiety (2).

However, although females comprise almost half of the human population, there is a reported discrepancy in the presentation of the genders in health studies (3).

In humans, it has been shown that the gut microbiota is influenced by changes in estrogen and androgen levels due to factors such as pregnancy, puberty, menopause, or PCOS. In this regard, women with PCOS (hyperandrogenic) show a markedly altered microbiota (4,5)

It changes from the first to third trimester of pregnancy, with an overall increase in Proteobacteria and Actinobacteria and reduced richness (6,7)

A bidirectional relationship is established between host hormones and the host's gut microbiome. Moreover, sex hormones can affect bacterial growth and virulence. Namely, the sex hormones estradiol and estradiol inhibit bacterial virulence through hindering quorum sensing, while progesterone was shown to enhance the development of oral Bacteroides species and Prevotella intermedia (8).

Sex differences in gut microbiota composition increase at puberty, with girls' gut microbiota becoming more similar to that of adults with pubertal progression. These results might also suggest that gut microbiota may affect the timing of puberty, possibly by regulating host sex hormone levels (9,10)

In men and postmenopausal women, urinary estrogen levels have shown a strong association with gut microbiota richness and alpha-diversity, whereas premenopausal female estrogen levels, highly variable when collected during menstrual cycles, did not show this association (11,12)

Regarding hormonal changes associated with puberty, no differences in microbial alpha-diversity have been observed in prepubertal mice, while the microbiota of post-pubertal mice shows a sex bias (13).

In another study, after reducing androgen levels by castration, the microbiota of castrated males showed more similarities with the microbiota of females than with the microbiota of gonadal-intact males. Gonadectomy has demonstrated the influence of sex hormones on the observed sexual bias in gut microbiota composition (14)

It has recently been suggested that part of the sex bias of the gut microbiota may depend on bile acids, as the bile acid pool is larger in males than in females (15,16)

After being synthesized in the liver from cholesterol, they are metabolized by the gut microbiota into secondary bile acids, which in turn can modify the structure of the microbiota and lead to various pathologies (17,18)

Recently, it has been reported that the gut microbiota of postmenopausal women is more similar to that of men than that of premenopausal women, with no significant differences actually observed between postmenopausal women and men of equivalent age (19,20)

SEX HORMONES ARE BRAIN HORMONES

The gut microbiota performs several essential protective, structural, and metabolic functions for host health, including food processing, digestion of complex host-indigestible polysaccharides, pathogen displacement, and synthesis of vitamins (21–22).

As well as a direct action on the gut mucosa and the enteric nervous system (ENS), the metabolic output of the gut microbiota gives it a reach well beyond the local GI compartment. Thus, considering the ability to influence the function of distal organs and systems, in many respects, the gut microbiota resembles an endocrine organ (23,24).

The gut microbes release their hormonal products into interstitial tissue to be picked up by blood and lymph capillaries, and these secretions are usually effective in low concentrations on target organs

or tissues remote from the enteric microbiota. As well as providing an important direct source of humoral agents, both active compounds and precursors, which act at distal sites, the microbiota also plays an indirect role in regulating complex endocrine networks. Moreover, specific members of the overall microbial community can respond to hormones secreted by the host (25,26).

The gut microbiota and, despite the obvious physical dissimilarity, its ability to function as a collective to influence other organs within the host and, in turn, to be responsive to the secretions of other host organs satisfies the most important conditions of any conceptual definition of an organ (27).

SEROTONIN-THE MOOD STABILIZER.

Lactococcus lactis subsp. *cremoris* (MG 1363) 201, *L. lactis* subsp. *Lactis* (IL1403) 201, *Lactobacillus plantarum* (F18595) 201, *Streptococcus thermophilus* (NCFB2392) 201, *Escherichia coli* K-12 156, *Morganella morganii* (NCIMB, 10466) 202, *Klebsiella pneumoniae* (NCIMB, 673) 202, bacteria release Serotonin. Serotonin helps regulate mood, sleep, appetite, and digestion. It is closely linked to feelings of happiness and emotional balance. Low levels often lead to depression.

DOPAMINE ---THE REWARD HORMONE

Bacillus cereus 33, *B. mycoides* 33, *B. subtilis* 33, *Proteus vulgaris* 33, *Serratia marcescens* 33, *S. aureus* 33, *E. coli* 33, *E. coli* K-12 156, *M. morganii* (NCIMB, 10466) 202, *K. pneumoniae* (NCIMB, 673) Dopamine is responsible for the feelings of pleasure, motivation, and reward. It helps to reinforce positive behaviours by a sense of satisfaction when achieving something.

GABA

L. brevis DPC6108 10, *B. adolescentis* DPC6044 10, *B. dentium* DPC6333 10, *B. dentium* NFB2243 10, *B. infantis* UCC35624 10, and *L. rhamnosus* YS9 71

In the gut, trillions of microbes form a complex community, commonly known as the gut microbiota. (28)

Gut microbiota produces thousands of unique small molecules or metabolites that can potentially affect host health (29)

Commonly identified metabolites include short-chain fatty acids (SCFAs), bile acids, choline metabolites, vitamins, amino acids, and neurotransmitters. (30,31)

The bidirectional communication pathway between the gut microbiota and the gut and their interaction with the central nervous system is termed the brain-gut-microbiome axis (32)

The gut microbiota and its metabolites affect host health through the brain and peripheral systems (33)

Metabolites travel by sending signals to the brain via the vagus nerve or blood-brain barrier (BBB) after crossing the intestinal barrier (34).

These metabolites are considered postbiotics because they can improve disease phenotypes and regulate the gut microbiota and metabolic pathways (35). In contrast, the gut microbiota and postbiotics leads to a variety of diseases in the host, such as metabolic, cardiovascular, and neurological diseases (36,37)

ACETYLCHOLINE

L. plantarum 122 Histamine *L. lactis* subsp. *cremoris* (MG 1363) 201 *L. lactis* subsp. *Lactis* (IL1403) 201 *L. plantarum* (F18595) 201 *S. thermophilus* (NCFB2392) 201 *M. morganii* (NCIMB, 10466) 202 *K. pneumoniae* (NCIMB, 673) 202 *H. alvei* (NCIMB, 11999)

The Gut Microbiome: "virtual organ"

The gut microbiota performs several functions and is described as a "virtual organ." (38)

The microbiota can produce diverse compounds that play a major role in regulating the activity of distal organs, including the brain. The influence of the microbiota in regulating metabolic activity is now recognized, with increasing evidence suggesting involvement in

glucose and weight regulation. Microbial signatures that increase the risk of diabetes mellitus and obesity have been put forward. Likewise, a role for the microbiota in regulating the HPA axis has been established, as well as the serotonergic system via modulating tryptophan availability. Unlike other endocrine organs, the microbiota has intense plasticity and can alter dramatically and rapidly in response to diet. (39)

Unlike other endocrine systems or organs, which secrete a single or at most a small number of humoral agents, the gut microbiota has the potential to produce hundreds of products. From a morphological and biochemical perspective, it is far larger and more biochemically heterogeneous than any other endocrine organ in man. The biochemical complexity of the gut microbiota even exceeds that of the brain, and many of the hormones produced by the microbiota are also neurotransmitters within the central nervous system (CNS). For example, aminobutyric acid (GABA), the most important inhibitory transmitter in the brain, is produced by several lactobacilli. Monoamines such as noradrenaline, dopamine, and serotonin are also produced by certain strains of bacteria

The Association Between Gut and Fecundity: Recent Discoveries

The bacteria residing in your gut, collectively known as the gut microbiome, can affect reproductive health. They influence hormone production and nutrient absorption, both of which are essential for fertility. A healthy gut is essential for maintaining hormonal balance, which is vital for the success of conception and pregnancy. The connection between the gut microbiota and your body's endocrine system helps to regulate the production and metabolism of hormones like oestrogen and progesterone. Imbalance of these hormones can disrupt the menstrual cycle and affect conception. Without proper nutrient absorption, your body may lack the vitamins and minerals necessary for fertility. To support your gut health and improve fertility, it's improved fertility, it is important to focus on nurturing the gut microbiome through a diet rich in specific nutrients and beneficial bacteria. (40)

The gut microbiota evolves from childhood to old age and can be altered due to exogenous pressures, including poor nutrition, smoking, stress, drug exposure, and antibiotic exposure (41,42)

Trillions of good bacteria reside in gut. The bacteria are responsible for converting bound oestrogen to active oestrogen. With a healthy microbiome, oestrogen breakdown and function can become impaired and may lead to health issues, including endometriosis, PCOS, and fertility.

The gastrointestinal (GI) tract contains the largest endocrine organ in the body. A large number of endocrine cells are dispersed among the epithelial cells of the gut mucosa and react to changes in gut contents by releasing hormones that are, in general, targeted to other parts of the digestive system (47)

There are at least 14 different populations of enteric endocrine cells scattered throughout GI epithelia (48)

Enteric endocrine cells release various biologically active compounds such as gastrin, secretin, somatostatin, cholecystokinin, chromogranins (Cgs), and serotonin (5-hydroxytryptamine: 5-HT) (49)

The hormones released from the enteric endocrine cells are important enteric mucosal signalling molecules influencing gut physiology. Alteration of endocrine cell function, particularly in the context of 5-HT, is associated in several GI diseases, including inflammatory bowel disease (IBD), coeliac disease, enteric infections, colon carcinoma, and functional disorders such as irritable bowel syndrome (IBS) (50)

"Gut-Reproductive Hormones Axis"

Female infertility is a multifactorial condition influenced by various genetic, environmental, and lifestyle factors. Recent research has investigated the significant impact of gut microbiome dysbiosis on systemic inflammation, metabolic dysfunction, and hormonal imbalances, which can potentially impair fertility. The gut-brain axis, a bidirectional communication system between the gut and the brain, also plays a significant role in regulating reproductive functions. Emerging evidence suggests that the gut microbiome can influence brain functions and behaviour, further emphasizing the importance of the microbiota-gut-brain axis in reproduction (51)

The gut hormone connection

The gut-hormone axis significantly influences women's health impacting menstrual cycles, mood, and conditions like PMS and PCOS. Gut dysbiosis disrupts estrogen metabolism. Bacteria produce β -glucuronidase, an enzyme that determines whether oestrogen is recycled within the body or properly eliminated. The imbalance of gut hormones produces premenstrual syndrome, endometriosis, and uterine fibroids. Leaky gut syndrome can trigger systemic inflammation and elevate cortisol level. (52)

CONCLUSION

Recent studies on immunoendocrine interaction have generated new interest in elucidating the role of gut hormones in the inflammatory process and immune function. In addition to enhancing our understanding of the pathogenesis of inflammatory changes, these studies give new information on 5-HT in the context of immunoendocrine interactions in the gut and intestinal homeostasis. Steroids and metabolic hormones play vital roles in intestinal homeostasis, and dysbiotic microbiota may trigger intestinal barrier dysfunction and affect other organs, leading to chronic low-grade inflammation, metabolic disorders, and immune dysfunction. Together, estrogens, androgens, progestogens, insulin, and other hormones regulate women's health.

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