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Role of microbial flora in female genital tract: A comprehensive review

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ABSTRACT

The female genital tract is a complex of microbial colonization, which shows a prominent role in the development of either a healthy or diseased condition. The aim of the present review is to describe the diverse components of both the protective and defective mechanisms induced by microbial species present in the female genital tract. The protective mechanism was induced by indigenous microbial flora colonized in the female genital tract, which includes innate immunity, secretions containing cytokines, antimicrobial peptides and inhibitory substances like organic acids, H_2O_2, bacteriosin and toll-like receptors. On the other hand, abnormal microorganisms produce virulence factors and enzymes, which cause life-threatening infectious diseases including cancer. The review summarizes that depending upon the presence and/or absence of normal and abnormal microorganisms, the female genital tract shows either a healthy and/or infectious condition.

1. Introduction

A diverse group of microorganisms is associated with different parts of the human body from birth to death. The human body routinely harbours about 1 014 bacteria which are collectively called normal or indigenous microbial species. They are widely distributed in various parts of the body, including eyes, skin, nails, oropharynx, gastrointestinal and genital tracts. These microbial florae are stable during normal conditions and do not cause any harmful effects to the human body[1]. Anatomically, the female genital tract is a very favourable atmosphere for the occurrence of a number of microorganisms. Most of these normal microorganisms play a significant role in the defense mechanism for maintaining the healthy environment to that particular part or organ especially in female genital tract[2].

In 1892, Albert Doderlein first reported that the vaginal microbial flora was colonized with Gram-positive rods, popularly known as "Doderlein's bacilli". These bacteria are popularly known as *Lactobacillus* species and are predominant species of the genital microflora along with some aerobic and anaerobic bacterial species[3]. It is well established that lactobacilli are one of the defense mechanism against pathogenic organisms. Although several means of protection have been suggested, their mechanism of interaction is not fully understood. The improvement in the number and metabolic activity of lactobacilli plays an essential role in the prevention and treatment of different infectious diseases along with already available therapeutic interventions[4].

Historical data indicate that the majority (70%) of genital tract infections (GTIs) are caused by the abnormal microbial population[5]. Furthermore, abnormal microbial flora of the vagina and cervix causes various infectious diseases, such as bacterial vaginosis (BV) and sexually transmitted viral infections (human simplex virus and human papilloma virus), which can lead from moderate to severe infectious conditions, and sometimes they may also cause death[6]. The major cause of GTIs in females is bacterial infections, formerly known as nonspecific vaginitis which is defined

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as an infection of the female genital tract, characterized by the presence of an amine (putrescine and cadaverine) and clue cells with increased pH[7,8].

The complex mixture of both normal and abnormal microbial flora of the female genital tract shows their activity in either a protective or defective manner, respectively, as shown in Figure 1. Therefore, the present review was focused on how these normal and abnormal microbial florae and their products act as a boon and curse to female reproductive health management.

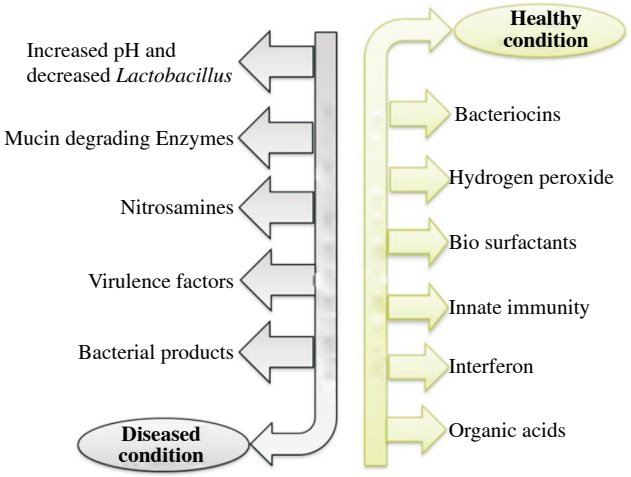

Figure 1. Protective and defective roles of normal and abnormal microbial flora of the female genital tract.

2. Normal flora of the female reproductive system

The female reproductive system (ovaries, fallopian tubes, uterus, cervix, vagina and vulva and cervix of the uterus) is normally colonised by a complex mixture of indigenous microbial flora. Some well-established experimental and clinical studies have been devoted to elucidating the microbiota of the vagina and to a lesser extent, the cervix and vulva[9].

Several weeks after birth, the vagina of a new-born girl remains under the influence of predominantly normal flora of *lactobacillus*. Due to the influence of maternal hormones, the pH of the infant vagina increases to neutrality and remains neutral until puberty. In childhood, the normal flora of the genital tract consists of a variety of cocci and rod-shaped bacteria and is highly susceptible to a variety of bacterial pathogens [*Streptococcus pyogenes* and *Neisseria gonorrhoeae* (*N. gonorrhoeae*)]. During puberty, lactobacilli again become prominent, although a smaller number of yeasts and other bacterial species are also present and are more resistant to infection. After menopause, the vaginal tract returns to a neutral pH and consists of mixed flora, again susceptible to infection[10].

2.1. Indigenous microbial flora of female genital tract – Lactobacillus

The prevalence of indigenous microbiota of the female genital tract consists of *Lactobacillus* spp., especially *Lactobacillus crispatus*, *Lactobacillus jensenii* and *Lactobacillus iners*[11,12]. The symbiotic association between vaginal lactobacilli and its host is regulated by the circulating hormones in a woman's body, which stimulates the vaginal epithelial cell to produce glycogen[13]. The secreted glycogen is converted to lactic acid by *Lactobacillus* resulting in an enhanced acidic pH (< 4.5) that inhibits the growth of many potential pathogens. The acidic environment of a healthy vagina does not generally permit the growth of many potential pathogens[14,15]. Thus, the occurrence of normal flora (*Lactobacillus*) is resistant to the female genital tract infection that is often associated with a women's health status. The common species found in the vagina of healthy females are *Lactobacillus iners*, *Lactobacillus crispatus*, *Lactobacillus gasseri* and *Lactobacillus jensenii*[16], and approximately 10^8 lactobacilli cells can be found per milliliter of vaginal fluid[17].

In addition to lactobacilli, some yeast cells, *Mycoplasma* and *Ureaplasma* species are colonized up to 20%[18,19]. The bacterial flora in the vagina is regulated by the normal flora, and is referred to as bacterial interference, the condition when the indigenous microbial flora competes exogenous flora. Bacterial interference is accomplished through various mechanisms, such as synthesis of antimicrobial substances, hydrogen peroxide and bacteriocin-like substances, which compete for both nutrition and binding sites rather than the exogenous microorganisms[14,20].

2.2 Protective role of Lactobacillus

In addition to the impact of the indigenous microbiota, some mechanisms are assumed to compete the growth of pathogenic microbes, but their interaction was not well established[21]. A large body of evidence stated that the *Lactobacillus* is one of the primary protective mechanism to maintain the indigenous microbiota[22]. The indigenous microbiota of *Lactobacillus* forms a massive growth of biofilm, which tightly attaches to the surface of the vaginal epithelia, creating the first line of defence against potential pathogens as shown in Figure 2 under the normal microbial flora[13], whereas abnormal microbial flora produces mucin degrading enzymes which facilitates the entry of pathogens and finally cause infections including cancers. Stratified squamous epithelium of the vaginal wall has moisture due to vaginal fluid secreted by cervical and vestibular glands through the vaginal wall[23]. The vaginal fluid contains significant concentrations of organic acids, peroxides and polypeptides which are sufficient to be considered as antibacterial activity against pathogenic microbes[4]. Figure 3 shows that the protective role of *Lactobacillus* through the production of inhibitory substances block the adhesion sites and degradation of toxin receptors[24].

2.2.1. Production of inhibitory substances

Lactobacilli produce a variety of substances that inhibit the growth of both Gram-positive and Gram-negative bacteria. The inhibitory substances include bacteriocins, hydrogen peroxide and organic acids[25]. These compounds may reduce not only the number of viable bacterial cells, but may also affect the bacterial metabolism and its toxin production. *Lactobacillus* spp. produced