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# Staphylococcal Infection and Infertility

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## Abstract

*Staphylococcus* sp. is not only a commensal bacterium but also a major human pathogen that causes a wide range of clinical infections, such as skin and soft tissue infection, pleuropulmonary and osteoarticular infection, and endocarditis as well as life-threatening systemic infections. More evidence is currently emerging to show that *Staphylococcus*, particularly *Staphylococcus aureus*, can colonize the reproductive systems and affect their structure and function. Staphylococcal infection has become one of the most common causes of infertility in both males and females. This chapter focuses on the epidemiology, pathophysiology, clinical manifestations, and treatment of staphylococcal infection and infertility.

**Keywords:** *Staphylococcus*, infection, infertility

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## 1. Introduction

Bacterial infection in reproductive organs is one of the most common causes of infertility in both male and female patients. It is also associated with sexually transmitted infections and adverse pregnancy outcomes. Infection with different microorganisms, such as chlamydia, mycoplasma, and certain bacteria, may lead to various clinical manifestations of human reproductive function. *Staphylococcus* sp., although a commensal bacterium, is a leading cause of skin and soft tissue infections and life-threatening systemic infections. More evidence is currently emerging to support the vaginal colonization of *Staphylococcus* sp. and its involvement in heterosexual transmission and infertility, but the knowledge is relatively scarce. In this chapter, genital staphylococcal infection and its relationship with infertility are discussed in detail.

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## 2. Overview of staphylococcal infection

### 2.1. The staphylococci

Bacteria in the genus *Staphylococcus* are referred to Gram-positive spherical bacteria that widely affect man and other mammals. The bacteria are about 0.5–1.0  $\mu\text{m}$  in diameter and grow in clusters, pairs, and occasionally in short chains. Staphylococci are divided into two groups based on their ability to clot blood plasma. The coagulase-positive staphylococci constitute the most pathogenic species *Staphylococcus aureus*. The coagulase-negative staphylococci (CNS) comprise over 30 other species, most of which are commensals of skin without causing infections. However, the incidence of infections of *Staphylococcus epidermidis* and other CNS has currently been rising. Among the known staphylococci, *S. aureus* is the most important human pathogen and causes a wide range of clinical infections [1]. It colonizes mainly the nasal passages, but also the other anatomical locales, such as skin, oral cavity, and gastrointestinal tract. Critically, *S. aureus* has been proved to be one of the most prevalent organisms in male and female genital tract, and its implication in the pathogenesis of reproductive diseases and infertility has attracted increasing attention [2]. In addition, the CNS strains such as *S. epidermidis* and *Staphylococcus haemolyticus* are also listed as the bacteria that can occupy and associated with male infertility.

### 2.2. The pathogenesis of *Staphylococcus aureus*

*S. aureus* is the leading cause of bacterial infections affecting an enormous population worldwide. By invading the bloodstream, lower respiratory tract, and skin and soft tissue, *S. aureus* can potentially cause some of the most severe hospital-associated and community-acquired illnesses. *S. aureus* produces a myriad of virulence factors that allow the organism to gain entry into tissues, attach to host cells, and secrete exoproteins and toxins. The known virulence factors include lipoteichoic acid (LTA), toxic shock syndrome toxin-1 (TSST-1), staphylococcal enterotoxin A (SEA), and staphylococcal enterotoxin B. In addition, *S. aureus* expresses a cohort of special factors that indirectly exert pathogenic effects through interfering with host defense mechanisms. This category involves capsular polysaccharide, protein A, and leukocidin. The classical Pantan and Valentine (PV) leukocidin is considered as a contributing factor for necrotizing skin infections due to its leukotoxic activity [3]. Recently, a novel strategy was invented whereby *S. aureus* successfully escapes neutrophil-mediated defensive machinery and establishes its invasion and infection. In this case, *S. aureus* secretes the nuclease and adenosine synthase to convert neutrophil extracellular traps (NETs) to deoxyadenosine, which triggers the caspase-3-triggered death of immune cells [4].

### 2.3. The host defense against staphylococcal infection

Neutrophils represent the host's first line of defense against invasion by *S. aureus* and a critical determinant in the outcome of staphylococcal infections. Following the uptake of bacteria, neutrophils typically undergo accelerated apoptosis and are cleared by macrophages through efferocytosis. This process results in eradication of the microbe and recovery of inflammation.

The pathogen recognition pattern receptor, toll-like receptor (TLR2), is proved to be the dominant receptor for *S. aureus*. TLR2 on the surface of innate immune cells recognizes the components of the bacterial cell wall such as teichoic acid, LTA, and PGN-embedded lipopeptides [5]. TLR2 then dimerizes with either TLR1 or TLR6 and recruits the adaptor proteins, such as TIRAP and MyD88, and the serine/threonine kinases IRAK-1 and IRAK-4 to initiate the subsequent signaling. The signaling cascade ultimately leads to the activation of the transcription factor nuclear factor-kappa B (NF- $\kappa$ B) and mitogen-activated protein kinases (MAPKs), which promotes the production of proinflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-12p70 and chemokines such as (C-C motif) ligand (CCL)2, CCL3, and CCL4. Besides TLR2, C-type lectin receptors (CLRs) can also bind to surface sugars of *S. aureus* and enhance the phagocytic ability of antigen-presenting cells (APCs) [6]. The cytokines and chemokines released by the innate immune cells and/or the infected tissue cells have important roles in combating infection of *S. aureus*. They can recruit the innate immune cells to site of infection and activate the immune cells to phagocytose and kill the microbes. However, the extensive infiltration of inflammatory cells and the copious secretion of proinflammatory mediators may also cause tissue damage and immunopathology if the inflammation is unresolved.

When innate immune mechanisms are not sufficient to clear the bacterial infection, an adaptive immunity against *S. aureus*, such as T helper (Th)1 and Th17, and humoral antibody responses, might be required [7]. The production of IL-1 and IL-17A, upon activation of Th1 or Th17 cells, is presumably conducive to the abscess formation at site of infection. Abscessification is regarded as a hallmark of *S. aureus* infections and is essential for the clearance of bacteria through phagocytosis and oxidative burst. On the other hand, Th1 response during *S. aureus* infections is frequently associated with the activity of staphylococcal superantigens (SAGs). For example, TSS has been found to activate roughly 20% of T cells and trigger massive proliferation of T cells and production of cytokines [8]. A strong proinflammatory/Th1 response was also ascribed to the effect of SEA, which is another staphylococcal SAG.

#### 2.4. Clinical manifestations of staphylococcal infection

Manifestations of staphylococcal infections usually depend on the type of infection, the site, the route, and the microbial dose. Common types of infections include skin infections (e.g. folliculitis, furuncles, impetigo, wound infections, and scalded skin syndrome), soft-tissue infections (e.g. pyomyositis, septic bursitis, and septic arthritis), toxic shock syndrome, purpura fulminans, endocarditis, osteomyelitis, pneumonia, food poisoning, and urinary tract infection [1, 9]. Despite associated with such a wide spectrum of clinical manifestations, *S. aureus* is still a commensal bacterium. Approximately 30% of the human population is colonized with this microbe [10]. However, with a growing number of health care-associated and antibiotic-resistant strain-driven infections, the pathogenic staphylococcal infection has significantly increased during the past two decades. In particular, the dramatic rising of antibiotic-resistant strains has become a serious threat to public health. The term MRSA refers to methicillin-resistant *S. aureus* with the potential to resist all  $\beta$ -lactam antibiotics such as penicillins and cephalosporins. Resistance is usually conferred by the acquisition of a non-

native gene encoding a penicillin-binding protein (PBP2a) that has significantly lower affinity for  $\beta$ -lactams [11]. In addition to MRSA, the vancomycin-intermediate/resistant *S. aureus* (VISA/VRSA) strain has also been reported in staphylococcal infection, particularly in some cases of enterococcal infection.

### 3. Epidemiology of genitourinary staphylococcal infection

Barring the role of a few bacteria such as *Chlamydia* whose impact on fertility has been well established, the significance of other bacteria in infertility is controversial. An epidemiological research revealed that the prevalence of bacterial vaginosis (BV) as 70.34% among infertile women. Previously, the categories of organisms with the potential to cause bacterial infection in female reproductive system have involved *Gardnerella vaginalis*, *Mobiluncus* sp., *Bacteroides* sp., *Prevotella* sp., and *Mycoplasma* sp. [12]. In general, Gram-positive bacteria were significantly higher in number than the Gram-negative bacteria. Series of epidemiological studies have revealed that *Staphylococcus* is among the top bacterium detected from reproductive organs and is closely related with infertility. For example, Momoh et al. [13] reported a prevalence rate of 38.7% *S. aureus* from high vaginal swab and endocervical swabs and a prevalence of 75% from semen cultures of infertile couples. Another investigation identified *S. aureus* as the most prevalent vaginal pathogen (57.33%) among local infertile women, followed by *Escherichia coli* (25.33%) [14].

Parallel to the situation in females, abnormal presence of *Staphylococcus* sp. has been increasingly evidenced in the genitourinary system of male patients with fertile problem. In a study of a total of 140 sperm samples collected from the University of Benin Teaching Hospital, *S. aureus* (28.3%) and *S. saprophyticus* (13.0%) were the most common pathogens found and have negative effects on sperm motility and morphology [15]. The commonest bacteria isolated from 160 men attending infertility clinics in South-eastern Nigeria were *Proteus* sp., *S. aureus*, and *E. coli*, and most of the detected strains were resistant to antibiotics assessed [16]. Besides the *S. aureus*, other staphylococci are also commonly found in infertile male patients. *S. epidermidis* was found to be one of the most common bacteria in 295 infertile males at the Hospital Juárez de México, and the bacteria profoundly affected the sperm motility, pH, morphology, and viscosity [17].

In healthy women of child-bearing age, the protective mucosa in the vagina is populated with microflora typically dominated by lactobacilli, and their dominance over pathogenic anaerobes is positively associated with vaginal health. Thanks to the biological antagonism provided by a healthy vaginal microbiota, opportunistic microorganisms are in very low numbers in normal vagina. It is proven that lactobacilli provide a constant acidic pH value and maintain the appropriate concentration of hydrogen peroxide in the genital environment. While under the condition of BV, the concentration of lactobacilli reduces but of some pathogenic bacteria, especially anaerobes or microaerophiles, increase [18]. BV represents the most common vaginal syndrome that affects fertile, premenopausal, and pregnant women, with an incidence rate ranging from 20% to 50% [19, 20]. BV is not caused by one specific



pathogenic microorganism but rather by an imbalance of vaginal microbiota. *Staphylococcus* sp., as a kind of amphimicrobial, has been established as one of the specific pathogenic bacteria related to BV. BV is frequently disregarded because the symptoms are often absent or insignificant. However, this vaginal disorder has already become the most common lower genital tract disorder among women of reproductive age and the most prevalent cause of vaginal discharge and malodour.

Genitourinary MRSA carriage and infection are not rare. A retrospective study was previously conducted on 57 pregnant women positive for MRSA over a 4.5-year period. The data showed that skin and soft tissue infection accounted for 96% of cases and recurrent infection occurred in 58% of the women [21]. Vaginal colonization with *S. aureus* and MRSA was further valued by Chen *et al.*, who reported that 507 *S. aureus* isolates (17.1%) were obtained from vaginal cultures of 2963 pregnant women, of which 14 (2.8%) were MRSA [22]. In addition, MRSA has become the predominant pathogen that causes the surgically managed infections in the genitourinary area. *S. aureus*, along with *E. coli*, *Streptococci*, and *Trichomonas vaginalis*, forms the abnormal vaginal flora that contributes to the onset of aerobic vaginitis. These pathogenic bacteria substantially alter the vaginal lactate concentration and increase the levels of inflammatory cytokines such as IL-6, IL-1 $\beta$  and leukemia inhibitory factor (LIF) in the vaginal fluid. Two methicillin-sensitive strains of *S. aureus* (MNPE and CDC587) have been documented to induce the expression of IL-8 in human vaginal epithelial cells [23]. Alterations in vaginal microbiology have been associated with many pathological conditions such as endometritis, miscarriage, premature labor, and infertility [24]. Moreover, the flora and cytokines imbalance has implicated in the pathogenesis of pelvic inflammatory disease (PID) and cervicitis and is also a risk factor for urinary tract infection and sexually transmitted disease (STD) [25].

#### 4. Staphylococcal infection and male infertility

Urogenital tract infections in males are one of the significant etiological factors in infertility. The infection of bacteria such as *Staphylococcus* sp. has been detected at the male reproductive tract. Staphylococcal infection in male reproductive organs and accessory glands may exert detrimental effect on sperm activity. Previous studies indicated that staphylococci not only affect the sperm activity but also impact the secretory capacity of the epididymis, seminal vesicles, and prostate [26]. In fact, staphylococci have been identified as one of the most common strains that can be detected in the male reproductive system. However, the percentages of males that get infected with staphylococci vary with the different isolation methods and procedures used in different studies. It has been demonstrated that *S. aureus* infection significantly interferes with semen quality and activity. It deteriorates the volume of semen and the concentration of sperm as well as the motility, morphology, and vitality of sperm. Therefore, a causative relationship may exist between staphylococcal infection and male infertility. A previous study reported a 20.6% infection of *S. aureus* in the semen samples from males with fertility problems. More importantly, *S. aureus* infection was found to be closely related to poor semen quality and reduced sperm motility [27]. Also, an investigation by a

Poland group associated *S. aureus* infection with abnormal semen parameters or other surogenital tract infection [28].

Besides these prospective studies, several *in vitro* studies also support the effect of *Staphylococcus* on sperm activity and its relation with infertility. It was revealed that infection of the normal human ejaculated spermatozoa with *S. haemolyticus* profoundly impacted the architecture and integrity of the sperm plasma membrane. Bacterial infection serves as a contributing factor for severe injury of sperm membrane stability and mitochondrial activity with potential consequences of male fertility [29]. In addition, exposure of ejaculated spermatozoa to *S. haemolyticus* was found to trigger a simultaneous decrease in the percentage of sperm with normal  $\Delta\Psi_m$  and an increase in the proportion of sperm with Annexin V staining, indicative of apoptotic cells. The data suggested a determinant role of staphylococcal infection in sperm fate [30]. Despite the above findings, the role for staphylococci in male infertility has remained somewhat controversial. A previous study showed that, although *Staphylococcus* sp. was the most common bacteria isolated in 299 asymptomatic men undergoing fertility evaluation, the bacterial counts were not correlated with semen parameters [31].

In an effort to understand the mechanism whereby staphylococci modulate sperm activity, investigators currently identified some of the key molecules that have profound effect on sperm activity. Kaur and Prabha *et al.* firstly identified sperm agglutinating factor (SAF). Based on the observation that *S. aureus* can adhere to the sperm head as well as sperm tail and agglutinate mouse spermatozoa, the group finally isolated a protein with a molecular weight of approximately 57 kDa from *S. aureus* and implicated the protein in control of sperm motility and survival. Moreover, SAF potentially affects various sperm parameters such as  $Mg^{2+}$ -dependent ATPase activity, acrosome status, and apoptosis. In support of this, a profound morphological alteration occurs in the spermatozoa upon binding with SAF, as detected with scanning electron microscopy. Also, SAF has a spermicidal effect at high concentrations and may have the potential to function as active ingredient of a vaginal contraceptive. Further studies indicate that the interaction of SAF with spermatozoa is receptor mediated, and the receptor has been isolated and purified from human spermatozoa. This sperm surface receptor component showed homology to glutamate decarboxylase and major histocompatibility complex (MHC) class I molecule [32]. Intriguingly, the receptor was shown to be able to counteract the detrimental effects of SAF on sperm parameters and alleviate SAF-induced infertility in mice [33]. In addition, Prabha *et al.* isolated the SAF from an *E. coli* strain. This kind of SAF also leads to sperm agglutination, the compromised  $Mg^{2+}$ -dependent ATPase activity, and spermatozoa apoptosis.

In 2009, another protein with sperm regulatory effect, named sperm immobilization factor (SIF), was identified from *S. aureus*. SIF is a protein with the molecular weight of approximately 20 kDa. Similar to SAF, SIF causes multiple defects in the head, midpiece, neck, and tail region of human spermatozoa [34]. It can completely inhibit  $Mg^{2+}$  ATPase activity of spermatozoa at the concentration of 100  $\mu\text{g/ml}$  and reduce calcium ionophore-induced acrosome reaction. The interaction between SIF and spermatozoa is also ligand-receptor dependent. The analysis by matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) showed that the receptor shares sequence similarity with MHC class II antigen. Interestingly, SIF has been

found to impede motile bacteria, in addition to sperm, such as *E. coli*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. The molecular mimicry of SIF receptor has been confirmed between spermatozoa and bacteria [35].

In addition to the effector molecules mentioned above, some novel mechanisms responsible for the staphylococcal regulation of sperm have now been discovered. A recent study on the semen of 589 infertile males indicated that other virulence genes in *S. aureus*, such as *hlg* (33.3%), *scn* (23.3%), *cna* (20%), *hly* (20%), and *clfA* (18.3%), were possibly responsible for spermatozoal immobilization [36]. Berktaş et al. raised another point of view that, rather than the direct interaction between bacteria and sperm, the alteration in genital microenvironment or over-consumption of energy by high dose of bacterium led to the loss of sperm motility [37].

## 5. Staphylococcal infection and female infertility

Bacterial infection in female reproductive system, such as staphylococcal infection, can profoundly affect all the phases of a woman's life in relation to the period of pre-pregnancy, fertilization, pregnancy, and reproduction. It has been demonstrated that BV is the most common lower genital tract disorder among women of reproductive age. In particular, staphylococcal infection is presumed to be a contributing factor for the adverse pregnancy outcomes and female infertility. Staphylococcal infection causes malodorous vaginal discharge and is causally associated with sexually transmitted infections. Also, it has been implicated in the development of endometritis (endometriosis), another crucial factor to female infertility.

### 5.1. Inflammatory response and hypothalamic endocrine

An immune/inflammatory challenge is considered as an important factor that impinges the reproduction process in animals and humans [38]. It can affect reproduction at the level of the hypothalamus, pituitary gland, or gonads. Nonetheless, the major impact is thought to occur within the brain or the pituitary gland [39]. Bacterial endotoxins can trigger the release of cytokines and other immune mediators in the hypothalamus, where the luteinizing hormone (LH)-releasing hormone and gonadotropin-releasing hormone (GnRH) neurons are located [40]. Numerous *in vitro* and *in vivo* studies showed that the immune stress and the subsequent action of proinflammatory cytokines have a profound impact on the secretory activity of GnRH and LH neurons in the hypothalamus [41]. These interconnections between the immune and the neuroendocrine systems are suggested to be based on the mutual sharing of receptors and mediators.

As described above, staphylococcal infection either in peripheral or directly in vagina can arouse strong immune/inflammatory reaction systematically or locally. The released cytokines and chemokines then act on the pituitary gland and reproductive organs, which may finally lead to menoxenia, irregular ovulation, and infertility. Evidences have shown that staphylococcal infection generates a large quantity of cytokines in female reproductive system. These mediators have an important role in the control of reproductive neuroendocrine, ovarian physiology, fetal implantation and development, and placenta function. Previous study



revealed a correlation between BV, elevated IL-1 $\beta$  and IL-8, and idiopathic infertility, suggesting that abnormal vaginal flora and the vaginal inflammatory response may be responsible for the idiopathic infertility in women undergoing *in vitro* fertilization [42].

## 5.2. Premature ovarian failure

Female mammals are born with a finite number of oocytes that gradually decreases during prepubertal development and adult life [43]. Each oocyte is encircled by somatic granulosa cells (GCs) to form the basic functioning unit of the ovary — the follicle. The size of the oocytes at birth and the rate of endowment depletion dominate the ovarian functional lifespan. On the other hand, programmed cell death (apoptosis) has been considered one of the most prevalent mechanisms that contribute to the age-related exhaustion of oocytes. Therefore, a precise balance has to be achieved between prosurvival and proapoptotic molecules to maintain the final destiny of the follicle [44, 45].

It is well recognized that immune/inflammatory response participates in many aspects of reproductive physiology, such as ovulation, menstruation, and implantation. Recent studies suggest that the inflammatory stress caused by staphylococcal infection may also affect ovarian reserve and cyclicity in women. Proinflammatory reaction, such as its correspondent neurotransmitter secretion, inflammatory gene transcription, and signaling pathway activation, was thought to play essential roles in the process. Moreover, the production of neurotransmitter, such as sphingolipid ceramide, further acts as a second messenger to promote age-related apoptosis of oocytes. Evidence showed that lower ceramide levels observed in acid sphingomyelinase-deficient mice resulted in a larger postnatal pool of oocytes compared with their wild-type counterparts. Conversely, Bax-null female mice exhibited to extend the ovarian lifespan [46]. These data may provide novel perspectives on the regulation of oocyte dynamics by bacterial infection and link the critical biological processes such as infection, inflammation, cell survival, and female fertility.

## 5.3. Bacterial vaginosis and endometritis

BV is a polymicrobial syndrome mainly due to an imbalance of vaginal microbiota. Colonization and proliferation of staphylococci is supposed to be one of the reasons for the increase in pathogenic bacteria, anaerobic bacteria, or microaerophiles. During the pathogenesis of BV, the overgrowth of anaerobes promotes the production of noxious substances, such as polyamines and other compounds. These metabolic products may further trigger the release of proinflammatory cytokines IL-1 $\beta$  and IL-8 and thus cause tissue damage and physiological imbalance [47]. BV can directly affect congenital formation and female fertility as an ascending dissemination of the related bacteria species proved to cause tubal factor infertility.

Another complication accompanied by vaginal staphylococcal infection is chronic endometritis (CE), a local inflammatory disease characterized by unusual plasmacytic infiltration in the endometrial stromal areas [48]. CE frequently happens in the later stage of the infection or under repeated infection. It tends to be neglected in gynecologic practice because of its less apparent symptom and the requirement of time-consuming histopathologic examinations. In most cases, the diagnosis is made based on gynecological indications, such as abnormal uterine bleeding (AUB) and infertility [49]. In a study on 64 CE patients and 28 healthy women, the

biochemical analysis revealed that IL-6, IL-1 $\beta$ , and TNF- $\alpha$  levels were markedly higher in menstrual effluents of women with CE when compared with control subjects [50]. It is suggested that the infection and inflammation alter the endometrial cytokine profiles, which may further impair endometrial function and lead to menstrual abnormalities and reduced embryo receptivity [51]. Moreover, the proteomic analysis identified the key signaling pathways involved in inflammation and oxidative stress are closely related with carcinogenic processes. These studies associate the onset of CE with female infertility, obstetric and neonatal abnormality, and complications. The altered endometrial gene expression may explain the impaired endometrial receptivity and endometrial hyperplastic lesions observed in women affected by CE [52].

#### 5.4. Abnormal fetal implantation

In rodents and humans, implantation is the first coordinated encounter between mother and baby. The abnormal implantation and placentation may lead to various dysfunctions throughout the pregnancy. Pre-eclampsia (PE) is a pregnancy-induced disorder characterized by hypertension and proteinuria. It is estimated to affect about 8% of pregnancies and is thought to be unique to humans [53]. The etiology of PE still remains poorly understood, but abnormal placentation is proved to be a major reason for this disease. In addition, local infection and immune responses are critically involved in the process of implantation [54]. Increased placental secretion of proinflammatory cytokines as well as the angiogenic regulators has been implicated in the widespread maternal endothelial dysfunction and the development of PE. It has been shown that cytokines produced within the uterine microenvironment can alter trophoblast action [55], impair implantation, and placenta vascularization, which may account for the recurrent miscarriage in women [56]. Elevated circulating IL-15 levels, proportional to severity of diseases, have been detected in the serum of PE mothers when compared with healthy controls [57]. Also, IL-11 is also proved to be a contributing factor for the impaired trophoblast invasion, spiral artery remodeling, and altered placental labyrinth morphology. These functional abnormalities further lead to the development of PE-like features, such as elevated systolic blood pressure (SBP), proteinuria, and kidney glomerular pathology. Another proinflammatory cytokine, interferon (IFN)- $\gamma$ , was also elevated in plasma, circulating leukocytes, and decidua of patients with PE [58]. Besides this, decidual natural killer (dNK) cells, the predominant immune cell, coincide with the decidualization at the maternal-fetal interface in human and mice. All of these studies point to a critical role of immune/inflammatory response during the implanting and placental development. More importantly, vaginal *Staphylococcus* infection, an infectious agent frequently observed in the uterus, may participate in the development of implantation disorder presumably by the induction of local immune reaction.

## 6. Therapy

Antibiotic strategy is considered the most potential therapeutic methods against staphylococcal infection and the resultant infertility. However, the emergence of antibiotic resistance has dramatically increased in the past two decades and becomes a serious threat to the worldwide

public health. According to the National Healthcare Safety Network (NHSN) and Centers for Disease Control and Prevention, *S. aureus* and *Enterococcus* are the two most commonly reported pathogens, accounting for 15.6% and 13.9% of health care–associated infections, respectively. In particular, *S. aureus* is notorious for its ability to acquire the resistance to any antibiotic during the treatment of infection-associated infertility.

### 6.1. Methicillin

The introduction of penicillin in the early 1940s significantly reduced fatal invasive staphylococcal infection. However, the resistant strains, mostly *S. aureus* strains, emerged rapidly. These strains possess a plasmid-encoding enzyme, penicillinase, which can irreversibly hydrolyze the  $\beta$ -lactam, thus acquiring the drug resistance. Methicillin is a narrow-spectrum  $\beta$ -lactam antibiotic of the penicillin class. It can effectively block the synthesis of bacterial cell walls by inhibiting the peptidic cross-linkage between the linear peptidoglycan polymer chains. Therefore, the antibiotic destroys the integrity of the cell wall and selectively kills Gram-positive bacteria. Compared with penicillin, methicillin harbors an orthodimethoxyphenyl group attached to the side chain of the  $\beta$ -lactam, which, in turn, forms a steric effect to prevent penicillinase from hydrolyzing the  $\beta$ -lactam. Even though, the first strain of MRSA, with an altered PBP2a to reduced affinity for the  $\beta$ -lactam, was reported two years later [59]. Now, MRSA refers to any strain of *S. aureus* that has developed resistance to  $\beta$ -lactam antibiotics such as the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins. Resistance is generally conferred by the acquisition of the *mecA* gene, which encodes a PBP2a. Due to the significantly decreased affinity for  $\beta$ -lactams, MRSA strains restore the ability of cell wall biosynthesis to continue even in the presence of typically inhibitory concentrations of antibiotic [11].

### 6.2. Vancomycin

Vancomycin belongs to the glycopeptide antibiotic class and is effective in treatment of serious infections caused by *Staphylococcus*. It is one of the main resources for combating infections caused by MRSA but is not recommended to treat the disease caused by methicillin-sensitive *S. aureus* (MSSA). Vancomycin is a complex compound consisting of a branched tricyclic glycosylated peptide and is a rare example of a halo-organic natural compound containing two covalently bonded chlorine atoms. The bactericidal activity of vancomycin is associated with its ability to bind at the D-Ala-D-Ala dipeptide terminus of the nascent peptidoglycan in Gram-positive bacteria and thereby to inhibit the peptidoglycan synthesis [60]. Common side effects associated with this antibiotic involve pain in the area of injection and allergic reactions, and problems with hearing, low blood pressure, or bone marrow suppression occasionally occur. The strain with the reduced susceptibility to vancomycin (VISA) was first described in 1996, and the alteration of the D-Ala-D-Ala dipeptide was supposed to be the main reason underlying this resistance.

### 6.3. Linezolid

Linezolid has been used for treatment of serious infections caused by Gram-positive bacteria that are resistant to other antibiotics such as MRSA. Its spectrum of activity is similar to that

of vancomycin, a well-established antibiotic for MRSA infections. Either linezolid or vancomycin has been recommended by the US guidelines as the first-line treatment for hospital-acquired (nosocomial) MRSA pneumonia [61]. Mechanistically, linezolid binds to the 50S subunit of the bacterial ribosome through interaction with the central loop of the 23S rRNA and thus impedes the growth of bacteria by disrupting their production of proteins. Point mutation of 23S rRNA is the most common mechanism of linezolid resistance [62]. The common side effects of linezolid include diarrhea, headache, nausea, vomiting, rash, constipation, altered taste perception, and discoloration of the tongue, although they happen relatively rarely.

#### 6.4. Daptomycin

Daptomycin is the first cyclic lipopeptide approved for clinical use in 2003. It is a calcium-dependent antibiotic comprising a lipid molecule conjugated with anionic peptide. Daptomycin interacts with the cytoplasmic membrane in a calcium-dependent, leading to the cell membrane depolarization, ion loss, and cell death [63]. Many antibiotic-resistant strains, such as MRSA and VRSA, were found to be effectively inhibited by daptomycin. Till 2008, the first case of daptomycin resistance was reported, and the underlying mechanism is currently still not very clear [64]. However, the mutation of the *mprF* gene, which encodes lysyl-phosphatidyl glycerol (LPG) synthetase, might be related to the occurrence of resistant strains. LPG can catalyze the coupling of lysine to PG and transfer the lysyl-PG to the outer leaflet of the membrane. In this way, LPG increases the positive charge and thus reduces the binding of  $\text{Ca}^{2+}$ -bound daptomycin to bacterial membranes [65].

Besides the routinely used antibiotics mentioned above, numerous new antibiotics are developed to serve as the alternatives in treating staphylococcal infection and the associated infertility. For example, teicoplanin or quinupristin/dalfopristin has been widely used with daptomycin to treat Gram-positive bacterial infection. Some of the potential antibiotics, such as oritavancin and iclaprim, are currently in the early stages of clinical development, and other promising candidates, such as ceftobiprole, dalbavancin, and telavancin, are still being developed [66].

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