Postpartum Group A *Streptococcus* Sepsis and Maternal Immunology

Katie L. Mason[1] and **David M. Aronoff**[1,2,3,4,*]

[1]Division of Pulmonary & Critical Care Medicine, University of Michigan Medical School, Ann Arbor, MI

[2]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI

[3]Department of Microbiology & Immunology, University of Michigan Medical School, Ann Arbor, MI

[4]Reproductive Sciences Program, University of Michigan Medical School, Ann Arbor, MI

Abstract

Group A *Streptococcus* (GAS) is an historically important agent of puerperal infections and sepsis. The inception of hand-washing and improved hospital hygiene drastically reduced the incidence of puerperal sepsis, but recently the incidence and severity of postpartum GAS infections has been rising for uncertain reasons. Several epidemiological, host, and microbial factors contribute to the risk for GAS infection and mortality in postpartum women. These include the mode of delivery (vaginal vs. caesarean section), the location where labor and delivery occurred, exposure to GAS carriers, the altered immune status associated with pregnancy, the genetic background of the host, the virulence of the infecting GAS strain, and highly specialized immune responses associated with female reproductive tract tissues and organs. This review will discuss the complicated factors that contribute to the increased susceptibility to GAS after delivery and potential reasons for the recent increase observed in morbidity and mortality.

Keywords

Group A *Streptococcus* (GAS); postpartum sepsis; maternal immunology; female reproductive tract (FRT)

INTRODUCTION

Group A *Streptococcus* (GAS) is an historically important cause of puerperal infections and sepsis. Despite preventive measures, including antibiotic use and hospital sanitation efforts, GAS infections are re-emerging worldwide and remain the most common cause of severe puerperal infections [1-5]. The ability of GAS to establish infection in postpartum patients is influenced by numerous factors, including disrupted mucosal barriers, altered immune status of the mother, antibiotic administration during labor and delivery, delayed diagnosis, environmental exposures of the mother, and specific virulence factors utilized by GAS. The complex interactions of these potential risk determinants complicate our understanding of how and why postpartum GAS sepsis occurs. This review will discuss the complicated

*Corresponding Author David M. Aronoff, M.D. University of Michigan Medical School Internal Medicine – Infectious Diseases 5510-E MSRB I 1150 W. Medical Center Drive Ann Arbor, MI 48109-5680 Phone: 734-615-3604 Fax: 734-763-4168 daronoff@umich.edu.

factors that contribute to the increased susceptibility to postpartum GAS and highlight topics in need of further study.

Methods

Manuscripts cited in this review were identified by searching the available English-language literature using PubMed (U.S. National Library of Medicine, National Institutes of Health, Bethesda MD) for all years available for the following terms or combination of terms: "Group A *Streptococcus*", "GAS", "*Streptococcus*", "*S. pyogenes*", "GAS virulence factors", "STSS", "Bacterial susceptibility", "Maternal immunology", "Maternal innate immunology", "Vagina/Vaginal immunology", "Uterine/Uterus immunology" "Female reproductive tract immunology", "Pregnant/Pregnancy immunology", "Prostaglandin E_2", "PGE_2", "Antimicrobial peptides", "Neutrophils", "Macrophages", "Dendritic cells", "Postpartum sepsis", and "Puerperal sepsis". Additional references were identified within bibliographies provided by PubMed-cited studies.The literature was reviewed through August 31, 2011.

Postpartum Sepsis

An Overview—Globally, puerperal infections cause morbidity in 5-10% of all pregnant women with over 75,000 deaths each year [6, 7]. Despite efforts to meet the United Nations Millennium Development Goal 5 (improve maternal health), the maternal mortality ratio has not improved and infections are an important reason [8]. Several bacterial pathogens can cause postpartum sepsis. While not the scope of this review, Group B *Streptococcus* is more prevalent than GAS, but typically causes less severe maternal disease [9]. Other causal organisms include staphylococci, *Mycoplasma*, *Chlamydia*, *Clostridium sordellii*, coliform bacteria, and bacteria associated with polymicrobial vaginosis [10]. However, GAS postpartum infections remain the most common cause of *severe* maternal postpartum infections and death worldwide [11, 12].

Following efforts by Semmelweis and others to popularize hand hygiene and raise the standards of hospital cleanliness, maternal postpartum infections decreased drastically (reviewed in [13]). Despite the dramatic and sustained decreases in postpartum GAS infections and sepsis experienced in the 20th century, the past two decades have witnessed an unexplained increase in severe postpartum GAS infections, resulting in greater numbers of maternal deaths worldwide [3, 8, 14]. This reemergence has placed a new urgency to better understand the host-microbial determinants of disease that might be targeted for improving preventive and therapeutic measures.

GAS is a ubiquitous human pathogen that causes a wide array of disease including cellulitis, pharyngitis, necrotizing soft tissue infections, scarlet fever and invasive puerperal infections. Puerperal infections present rapidly, within 2 to 48 hours postpartum and can be non-specific, delaying treatment. Primary symptoms include myalgias, fever, confusion, euphoria, dizziness, and abdominal pain [15]. Once GAS is diagnosed, the infection is often advanced. Notably, there does not appear to be an increase in GAS antibiotic resistance [16], so other factors must underlie the re-emergence of GAS postpartum infections.

Routes of maternal infection—GAS can be found in the normal biota of the female reproductive tract, but its colonization is considered to be relatively rare (0.03%) and its presence alone is not sufficient to cause disease [17]. However, GAS is asymptomatically carried on the skin or in the throat by 5-30% of the population and is easily spread by person-to-person contact or aerosolization [18]. The host and microbial factors that influence colonization progressing to infection remain unresolved, but it is apparent that

postpartum and pregnant women are predisposed to bacterial infections in general (reviewed in [19]).

Women can be a source of contamination of their own reproductive tract. Some mothers with a recent history of sore throat succumb to GAS postpartum sepsis [9], suggesting that some women infect themselves after delivery, presumably through contamination of the perineum or through bacterial travel in the bloodstream from distal organ sites. Another frequent source of GAS exposure in the maternal environment is through interaction with children in the house or at work. In a recent report, all investigated patients who died from GAS postpartum sepsis had recent contact with children (frequent GAS carriers) in their home or work environment [9]. Lamagni et al. demonstrated that invasive GAS infections as a whole are on the rise in the general population [20], perhaps contributing to the increase in maternal exposure in the community.

Due to the presence of asymptomatic carriers, nosocomial infections are a significant potential route of maternal infection. The high incidence of healthcare-associated GAS infections in the time of Semmelweis was due to asymptomatic healthcare-worker carriers, resulting in sporadic postpartum GAS outbreaks in hospitals [6, 21]. Cesarean section has been called "the single most important risk factor" for postpartum maternal infection in a hospital and this may be due to several factors, but one obvious factor is the invasive nature of the surgery [21, 22]. Antibiotic administration during or after surgery significantly reduces the risk for postpartum infection [22] but is not 100% effective at preventing infections from progressing and rapidly causing maternal death [9]. It is easy to regard uncomplicated pregnancies with vaginal deliveries as low-risk for sepsis in a hospital setting, but there has been an increase in postpartum sepsis following these seemingly unremarkable deliveries [9]. The non-specific symptoms at the onset of GAS sepsis result in healthy women becoming critically ill and dying within a few hours or days [9, 23]. Regardless of delivery type, postpartum patients have a 20-fold increased incidence of GAS-induced disease compared to non-pregnant women [24]. Interestingly, this increased incidence is higher than that observed in adults over the age of 65 years, the typical age group associated with increased incidence of GAS infections [25]. The high incidence of asymptomatic carriage and multiple routes of inoculation (Figure 1) result in a significant risk for GAS postpartum infections.

Microbiology and immunology of GAS sepsis

GAS virulence factors and Streptococcal toxic shock syndrome (STSS)—GAS
is a versatile human pathogen that utilizes numerous virulence factors to evade immune recognition or clearance. Several recent reviews describe in detail the microbial factors that contribute to GAS pathogenesis [26-30] and will not be discussed in detail. GAS virulence factors aid in evading phagocytosis and facilitate in adherence to host cells, leading to colonization and invasion of the host [26, 31-35]. In addition, GAS has a family of bacterial antigens that are associated with streptococcal toxic shock syndrome (STSS) [36, 37]. This family includes SpeA (Streptococcal pyogenic exotoxin A), SpeC, and others that bind to the MHC class II molecules and T cell receptors, resulting in an excessive release of immunomodulators that activate complement, coagulation, and fibrinolytic cascades, resulting in toxic shock and death. STSS has been reported with invasive GAS soft-tissue infections with a mortality rate of approximately 30% [3]. A recent study of 11 European countries showed a 13% incidence level for STSS from GAS infections with a mortality rate of up to 50% [38]. SpeA is the superantigen most commonly associated with GAS infections that result in STSS in the US [27, 39] and genome sequence comparisons of GAS patient isolates reveal new variants of *speA*, which may be contributing to the increased severity of these clinical strains in postpartum infections [40, 41].

Immune recognition of GAS—Despite diverse evasion strategies, GAS is recognized by the innate immune response. GAS is recognized by an unidentified MyD88-dependent receptor, which is independent of TLR2, TLR4 and TLR9 activation [42] and *in vitro* studies demonstrate GAS activation of p38 MAPK, NF-κB, TNFα, IL-6, and type 1 IFN production [42], indicating host immune activation. GAS was long considered an extracellular pathogen, but recent research has demonstrated GAS survival within multiple host cell types, including epithelial cells, neutrophils and macrophages [43-48]. Biopsies from patients with severe GAS tissue infections contained viable GAS within macrophages, confirming their intracellular survival ability [44]. GAS survival in epithelial cells may contribute to severe GAS postpartum infections by providing a location for systemic invasion or the initiation of STSS. The next few sections detail potential roles for the diverse cellular components of innate immunity in defense against reproductive tract GAS infection.

Epithelial cells and antimicrobial peptides: Epithelial cells (EC) play a pivotal role in maintaining maternal health by forming tight junctions that provide a physical barrier against potentially pathogenic microbes, through antimicrobial molecule release, and TLRs 1-9 expression [49, 50]. Studies of chemokine and cytokine production by EC during pregnancy indicate an overall immune hypo-responsiveness with reduced levels of IL-1β, IL-8 and IL-6 in cervical fluid [51]. The altered antimicrobial peptide production of epithelial cells in the FRT may play a role in the ability of clinical strains of GAS to cause more severe postpartum infections. Numerous endogenous antimicrobials actively protect the pregnant uterus including α- and β- defensins, found in healthy pregnant females (reviewed in [52, 53]). SLPI and elafin are two other antimicrobials present in the pregnant uterus [54] that have anti-protease and anti-inflammatory activities and are thought to regulate inflammation during pregnancy and labor [52]. However, certain pathogens, including GAS can degrade these antimicrobials [55, 56]. GAS might inhibit the innate immune response through molecules like SpeB that can cleave host molecules like LL-37, an antimicrobial peptide [20, 27]. LL-37 is found throughout the FRT and plays an important role in preventing infections, but LL-37 can be inhibited by PGE_2, which is up-regulated at the end of pregnancy, which may contribute to susceptibility to GAS infections in the FRT [52, 57].

Macrophages: Macrophages are an important first line of defense against invading pathogens through phagocytosis, antigen presentation, and cytokine production [58-61]. Previous mouse studies demostrate that when macrophage populations are depleted during a sublethal systemic GAS infection, mice are significantly more susceptible [62]. Macrophages can also promote chemotaxis responses to GAS infections through the activation of transcription factors involved in cytokine signaling and chemokine expression [63, 64]. However, macrophages in the FRT have altered activity compared to macrophages found in other organ/tissue sites (reviewed in [65]).

Macrophages account for approximately 10% of the total leukocytes in the female reproductive tract [66] and display phenotypic changes and up-regulated intracellular reactive oxygen species during pregnancy [67-70]. Estrogen and progesterone levels alter the migration of macrophages in the FRT and there is cyclic variation of macrophage movement due to the hormonal regulation of cytokine and chemokine expression [71, 72]. The mechanism behind these cellular alterations remains unknown and controversial in the field and further work must be done to elucidate the role of hormone alterations, prostaglandins, stage of pregnancy, the indigenous microbiota of the reproductive tract, and other factors that may alter macrophage response to GAS infections in pregnant and postpartum women.

Dendritic cells: Dendritic cells (DC) are present throughout the FRT and within the epithelial layer [73, 74] and are the most potent antigen presenting cells [75]. DC play a vital role in maintaining Th1/Th2 balance [76-78] and secrete soluble immune modulators that alter DC cytokine production [79]. The ability of estradiol and progesterone to alter DC differentiation remains controversial, but GAS can inhibit DC maturation [80] and may be a potential mechanism of GAS colonization and disease in the FRT.

Neutrophils: Neutrophils are an essential part of the innate immune response to invading bacterial pathogens. Neutrophils efficiently phagocytose bacteria, activate the production of reactive oxygen species and neutrophil degranulation, and result in bacterial killing (reviewed in [81]). GAS utilizes several virulence factors to evade ingestion and cellular recruitment by neutrophils in soft tissue infections [26, 82, 83]. Upon neutrophil phagocytosis, GAS up-regulates genes involved in tempering oxidative stress, in cell envelope components and virulence factors [81, 84, 85], suggesting that GAS can effectively respond to different host environments to promote persistence. The rapid response to bacterial infections in soft tissue makes it likely that neutrophils will play a role in susceptibility to GAS postpartum sepsis.

GAS and host genetic susceptibility—Emerging data suggest that host genetics play a significant role in the outcome of GAS infections [86, 87]. Hypervirulent strains of GAS emerged globally in the 1980s and have persisted since, but despite the increase in virulence, there is a wide spectrum of clinical manifestations associated with these strains of GAS [88, 89], suggesting that host genetics are a factor [90-93]. The severity of the response to GAS varies by patient [93-95] and the level of host cytokine production is correlated with the severity of disease [93, 96-100]. Of patients with previous postpartum infections, there were significant changes in allele frequencies compared to control patients for TLR9, hsp70 and IL-1β, suggesting that innate immune response gene polymorphisms are associated with susceptibility to severe GAS puerperal sepsis [101]. These studies have helped to clarify some of the host immune factors that influence infection risk, but further research is needed to clarify genetic predispositions of pregnant and postpartum women to GAS infection (or its complications).

Postpartum physiology and immunology—The gravid female reproductive tract (FRT) environment is unique in its immunology (reviewed in [19]). The maternal immune system must be tolerant to the indigenous bacteria in the reproductive tract, to paternal antigens in sperm and to the immunologically-distinct fetus. Despite this immunological tolerance, the FRT must be able to detect and respond to potentially pathogenic organisms. Pregnancy takes place in a physiologically and immunologically distinct organ with its own mucosal barrier (uterus and decidua) and accommodates an allogeneic fetus [102]. In addition, hormonal products in the FRT alter the immune response, and the fetus progressively challenges the maternal immune system as its size and complexity increases. Prostaglandin (PG)E$_2$, IL-4 and IL-10 are induced by pregnancy and suppress the maternal Th1 immune response (reviewed in [103]) and the systemic down-regulation of the Th1 response results in immune alterations that promote maternal susceptibility to infection [70]. Pregnancy has often been referred to as a Th2-type immune state, but pregnancy is a modulated immune state that is not simply anti-inflammatory, but is continually changing during fetal development [104-106]. Although much is known about immunomodulatory aspects of gestation, these findings have not been studied in the context of invasive GAS infections.

Prostaglandin E$_2$—The lipid mediator PGE$_2$ deserves special mention because it has emerged as an important modulator of host immunity, especially during pregnancy and the

postpartum period [107-112]. PGE_2 is an arachidonic acid-derived mediator that modulates cell behavior via the ligation of four distinct G protein coupled receptors called E prostanoid (EP) receptors, which are numbered EP1-4 (reviewed in [113]). Throughout gestation, PGE_2 dampens maternal immune responses against fetal tissues [107-110, 114] and regulates cervical softening and uterine contractions during labor, where it is found at increased levels [111, 112, 115]. It is also a critical negative regulator of the host immune response, with the ability to down-regulate lymphocyte and neutrophil activity [116], to inhibit production of Th1 cytokines (IL-12 and IFNγ) and to enhance production of Th2 cytokines (IL-5 and IL-10) [117-119]. Elevation in PGE_2 levels has previously been shown to play a role in host susceptibility to infections in many patient populations including pregnant women [114, 120-129].

The capacity for PGE_2 to regulate host-microbial interactions is increasingly evident in the context of streptococcal infections [130-136]. In 1982, Short *et al*. demonstrated increased survival in animals when PGE_2 synthesis was inhibited during Group B *Streptococcus* sepsis [137]. Prostaglandin endoperoxide synthase 2 (COX-2) is the enzyme that converts arachidonic acid into prostaglandin endoperoxide H2 (PGH_2) before PGH_2 is converted into other prostaglandins. In 2010 Goldman et al. demonstrated that COX-2 is up-regulated in human and mouse tissues infected by GAS [130, 138]. Using a mouse model of GAS bacteremia and *in vitro* studies of bone marrow-derived macrophages, they established that PGE_2 signaling via EP2 receptors and cAMP elevation suppressed host defenses against GAS [130]. An unbiased systems genetics approach later identified two PGE_2 synthase enzymes (mPGES-1 and -2) as key participants mediating susceptibility to GAS [86]. However, little is known about PGE_2 and GAS in the FRT [139-141].

FRT mucus, pH, and the indigenous microbiota—Vaginal colonization by GAS appears to be an important preceding event in some cases of puerperal sepsis (following vaginal delivery), yet host-microbial interactions that determine the capacity for GAS to colonize and invade the mucosal surfaces of the FRT need further study. In addition, the innate immune mechanisms that prevent GAS from ascending through the cervical canal into the postpartum uterus remain incompletely understood. Mucus within the FRT protects epithelial cells from bacterial infections through several mechanisms. Mucus can physically trap potential pathogens and inhibit pathogen survival due to the low pH, immunoglobulins, and antimicrobial peptides [142, 143]. The changes in mucus in the postpartum FRT and its effect on GAS colonization and dissemination remain unknown.

The indigenous bacteria in the reproductive tract also provide pathogen resistance through several means, including competitive exclusion of pathogenic microbes and contributing to the acidic vaginal environment through lactic acid production. *Lactobacillus spp.* are the most common bacteria present across all ethnic groups and produce lactic acid in the FRT [142, 144]. Few studies have been done to investigate individual variation between women over time, but these preliminary studies suggest that the bacterial diversity is dynamic even amongst individuals and the vagina is implicated as a significant source of infectious organisms resulting in preterm labor [142, 145-149]. Membranes collected from healthy women following at term cesarean sections demonstrate bacterial DNA in up to 70% of samples indicating a dynamic host control of individual bacterial diversity in healthy pregnancies [150]. The role of the indigenous microbiota in the reproductive tract and its interactions with the host immune response during GAS postpartum infections remain unknown, and whether probiotic approaches would be successful at preventing puerperal GAS infections depends upon more research into how the microbiota creates a colonization and infection resistance against this pathogen.

Conclusions

Pregnancy is a highly immunomodulated state that permits implantation and development of the immunologically distinct fetus. This may result in an immunologically vulnerable FRT that is more easily infected after delivery. The immune changes that progress during pregnancy are complex and remain largely uncharacterized, but recent research suggests GAS infections are re-emerging and postpartum patients are particularly prone to severe GAS infections that result in death [1-4]. The mechanisms behind GAS bacterial virulence, postpartum susceptibility and the immune response to FRT infections remain poorly understood and future work must be done to address the increase in maternal mortality from postpartum GAS infections.

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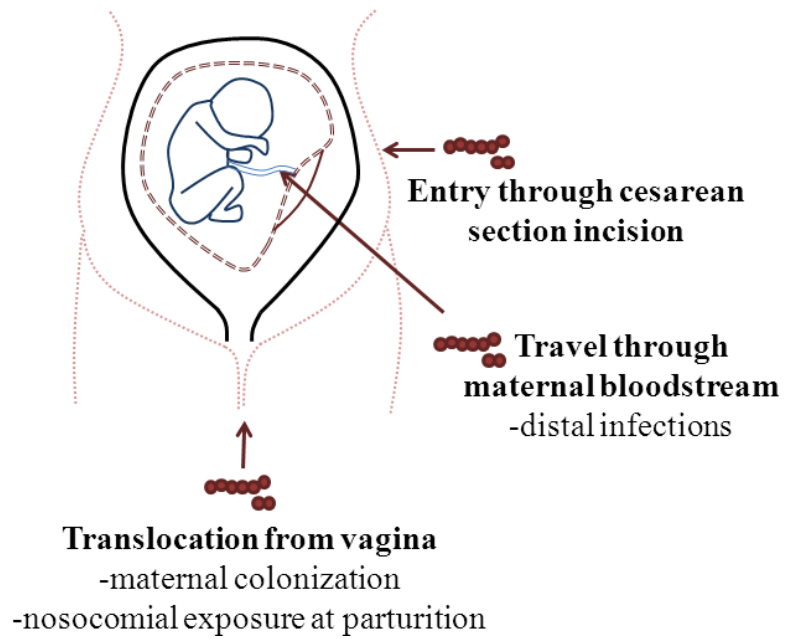
Entry through cesarean section incision

Travel through maternal bloodstream
-distal infections

Translocation from vagina
-maternal colonization
-nosocomial exposure at parturition

Figure 1. Potential routes of GAS infection during pregnancy and postpartum
GAS can enter the incision made during cesarean section, leading to a quickly disseminating infection. GAS infections can also result from distal infections (i.e. pharyngitis) where the bacterium travels through the bloodstream, infecting the reproductive tract and developing fetus. The vagina is another source of GAS infections when maternal colonization is present or when the perineum is contaminated after environmental exposures to GAS.