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SYSTEMATIC REVIEW

Outcomes and management of pregnancy and puerperal group A streptococcal infections: A systematic review

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Abstract

Introduction: Group A streptococcus (*Streptococcus pyogenes*) is one of the most lethal bacterial pathogens of humans, with increased risk of progression to septic shock and multiorgan failure in the pregnant population. The objective of this study is to systematically review the outcomes and management strategies for pregnancy and puerperal group A streptococcus infections in an effort to provide further guidance for prevention and treatment of a rare but lethal infection worldwide.

Material and methods: A comprehensive search using *puerperium* and *streptococcus pyogenes* terms was completed across several registered databases. A total of 902 articles investigating pregnancy and puerperal group A streptococcus infection were identified, with 40 studies fulfilling inclusion criteria of original research articles in humans published from 1990 onwards reporting four or more unique cases of group A streptococcus in pregnancy or postpartum. This study was registered in PROSPERO: CRD42020198983.

Results: A total of 1160 patients with pregnancy and puerperal group A streptococcus infection were identified. Most infections occurred postpartum (91.9%), with 4.7% reported antepartum and 0.6% intrapartum. Bacteremia was present in 49.0% of patients and endometritis in 45.9%. Puerperal sepsis was described in 28.2% of cases and progressed to streptococcal toxic shock syndrome in one-third of such cases. Overall, the case fatality ratio was 2.0%, with one-third of the deaths from antenatal cases including 3/22 (13.6%) cases of septic abortion and 10/46 (21.7%) antenatal cases of group A streptococcus infection.

Conclusions: Group A streptococcus infection remains an important contributor to pregnancy and puerperal morbidity and mortality. Early recognition, diagnosis and aggressive management are important for favorable outcomes given the serious risk of sepsis and streptococcal toxic shock syndrome.

KEYWORDS
group A streptococcus, pregnancy, puerperium, *Streptococcus pyogenes*

Abbreviations: GAS, group A streptococcus; IVIG, intravenous immunoglobulin; RR, relative risk; sTSS, streptococcal toxic shock syndrome.

1 | INTRODUCTION

Infection is the third most common cause of pregnancy-related mortality worldwide, representing approximately 10.7% of pregnancy-related deaths in low- and middle-income countries and 4.7% of deaths in high-income countries.[1] Further, it is estimated that for every death, there are 50 pregnant people with life-threatening morbidity from sepsis.[2] The incidence of puerperal sepsis has risen over the last decade, in some cases doubling,[3] with increasing rates of severe sepsis contributing to mortality.[3,4] Underlying this trend is increasing virulence of group A streptococcal infection, which contributed to 50% of direct sepsis deaths in two European studies.[2,5,6] This is suspected to be due to the predominance of *emm*1 and *emm*28 genotypes, which have higher associations with mortality, as well as increasing maternal risk factors for infection such as obesity and rates of cesarean section.[2]

Group A streptococcus (*Streptococcus pyogenes*) (GAS) is one of the most lethal bacterial pathogens of humans.[7] It is a facultative, gram-positive coccus which has reservoirs in human skin and mucous membranes.[7] Outside of pregnancy, the case fatality rate of invasive GAS infection is 15%–20% which increases to 40%–60% with progression to septic shock.[8–10] Pregnancy is a highly immunomodulated state which increases the risk of invasive GAS infection by 20-fold in comparison to the non-pregnant population.[11] Most people develop invasive GAS from ascending infection of the genital tract and endometrium, which can quickly progress to septic shock and multiorgan failure within 48–96 hours as evidenced by multiple case reports in the literature.[12]

The objective of this study was to systematically review the pregnancy and puerperal outcomes and management strategies in cases of GAS infection in an effort to provide further guidance for prevention and treatment of a rare but lethal infection worldwide.

Key message

Group A streptococcal infection remains an important contributor to puerperal morbidity and mortality despite advances in infection control protocols. Early recognition, diagnosis and aggressive management are important for favorable outcomes given the serious risk of sepsis and toxic shock syndrome.

2 | MATERIAL AND METHODS

This protocol was registered with PROSPERO (CRD42020198983). With the assistance of an information specialist, a comprehensive search of the Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Latin American and Caribbean Health Sciences Literature (LILACS) and PubMed (in-process and non-MEDLINE) databases was conducted. In addition, Clinicaltrials.gov, WHO International Clinical Trials Registry and the International Standard Randomized Controlled Trial Number Registry were reviewed along with the first 200 results from Google Scholar. Reference lists from relevant trials, reviews and commentaries were manually searched. Prior to manuscript submission, the search was updated on January 15, 2022. Subject headings and keywords were used to search for *puerperium* and *streptococcus pyogenes* terms. A detailed search strategy along with results is attached in Table S1.

Two authors independently reviewed non-duplicate titles and abstracts and retrieved full texts of eligible studies for further evaluation. Disagreements were resolved by consensus and adjudication by a third author. All studies meeting inclusion criteria of original research articles in humans published from 1990 onwards reporting four or more unique cases of GAS in pregnancy or postpartum were evaluated. Articles recording carrier or screening status for GAS were excluded. Conference abstracts were excluded. There were no language restrictions. Study characteristics, patient demographics, infection characteristics, management strategies, and patient outcomes were extracted. Statistics were grouped according to outcomes and reported in terms of frequency of outcome with percentages calculated according to the summed number of people meeting inclusion criteria within each study. Studies with missing information were not included in the calculations for that particular outcome.

Two authors evaluated the research quality of included studies using the Newcastle–Ottawa Scale for cohort and case control studies which was converted to meet the Agency for Healthcare and Research and Quality standards with thresholds supplied by the National Center for Biotechnology Information,[13] and the National Institutes of Health assessment tool for case series (Table S2).[14]

3 | RESULTS

A total of 982 articles investigating puerperal GAS infection were identified, with 40 studies fulfilling inclusion criteria (Figure 1). Study design and patient population characteristics of the included studies are described in Table 1. Sixteen prospective studies including 498 patients across three cohort, three case–control and 10 case series were included in the review. Most of the studies were retrospective in nature, totaling 662 patients, with 20 case series, two cohort and two case–control studies meeting inclusion criteria.[2,8,10,11,15–50] Descriptive analysis was performed, as meta-analysis was not possible given the heterogeneity of the patient populations, dominant study design, and study outcome definitions.[2,8,10,11,15–50]

Figure 2 summarizes the reported patient outcomes by study (which are further detailed in Table S3). A total of 1160 patients with puerperal GAS infection were identified. Most infections occurred in the postpartum period (893/972; 91.9%), with 4.7% reported antepartum (46/972) and only 0.6% noted intrapartum (6/972)

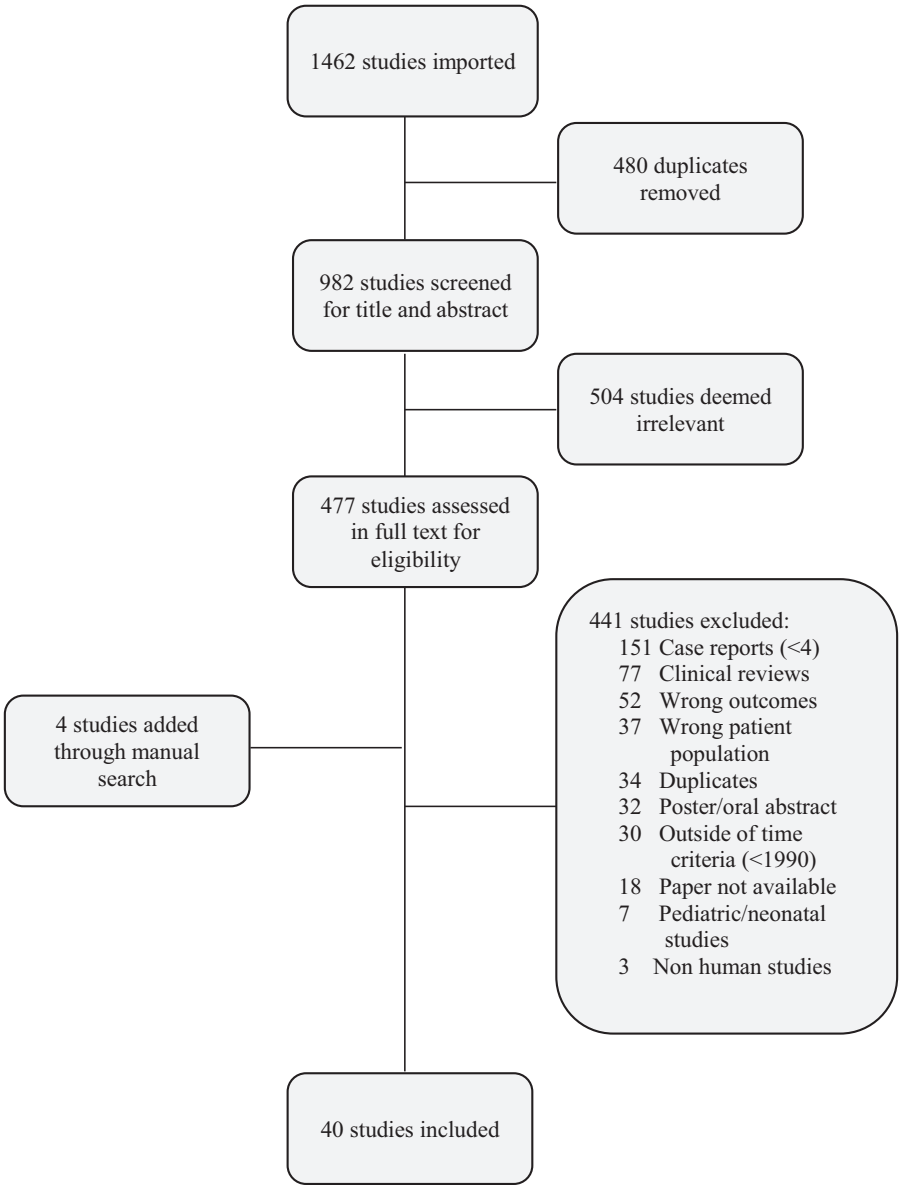

FIGURE 1 PRISMA flow chart for included studies

(Figure 3). Septic abortion (pregnancy loss secondary to infection <20 weeks gestational age) and complications from elective therapeutic abortion were both uncommon (22/972 [2.3%] and 5/972 [0.5%], respectively).

When reported, the timing of antepartum infections was distributed across trimesters, with one infection in the first trimester, six in the second and six in the third. However, timing was not reported for more than two-thirds of the antepartum infections (33/46; 71.2%). When details were provided, the majority of patients were described as healthy without pregnancy complications prior to infection. Streptococcal toxic shock syndrome (sTSS) was specifically described in three patients; however, a study by Tanaka et al.[41] reported an additional seven patients who died within 24 hours of presentation, suggesting advanced infection. Intrauterine fetal demise was diagnosed in 39.5% of pregnancies (17/44; 38.6%) and when combined with septic abortions, 57.4% of all cases resulted in not achieving a live birth (39/68). Stillbirth was most often diagnosed at time of admission to hospital.

Twenty-one septic abortions and one septic ectopic pregnancy were described across six studies. All septic abortions underwent dilation and curettage as part of management of the infection. Three cases of sTSS were reported (3/22; 13.6%) with two progressing to death (2/22; 9%) despite surgical management of septic abortion.

Of the studies reporting patient characteristics in postpartum GAS infections, 74.5% (213/286) were multiparous, with the majority delivering vaginally (402/499; 80.6%) at term (238/273; 87.1%). Premorbid or delivery risk factors reported in studies were variable without a specific trend. However, the majority (81%) of patients in these studies had no reported risk factors for GAS infection. Approximately half (53%) of the studies reporting postpartum infections detailed time from delivery to presenting signs, with 49.9%

TABLE 1 Characteristics of included studies

Study, year	Collection dates	Study design	Study setting	Primary objective(s)	Secondary objective(s)
Acosta, 2014	June 1, 2011–May 31, 2012	Prospective Case–Control	Obstetrician-led maternity units, UK	Estimate the incidence, describe the causative organisms and sources of infection, and identify the risk factors for severe maternal sepsis in the UK	None
Alberts, 2018	2010–2014	Retrospective case series	Swedish insurance company reports of injury in connection with care database	Study reported obstetric care injuries related to bacterial pathogenesis	None
Alexander, 2018	February 2015–March 2016	Retrospective case series	Large academic medical center, US	Rule out potential transmission by a health care worker of GAS following a series of cases identified in postpartum women	None
Anteby, 1999	June 1987–December 1994	Retrospective case–control	University hospital, Jerusalem	Identify factors characteristic of non-epidemic puerperal group A streptococcal infection.	None
Aronoff, 2008	August 1996–August 2000	Retrospective case series retrospective cohort	Hospitalizations, across the state of Florida	Report the detailed clinical and epidemiologic features of women hospitalized for postpartum invasive GAS disease in Florida during the 4-year period of 1996–2000	Secondary comparative analysis of a large Florida hospital discharge dataset obtained from the Florida Agency for Health Care Administration for women carrying the diagnosis of postpartum invasive GAS disease who were residents of Florida
Barnham, 2001	1980–1999	Retrospective case series	Harrogate, York and Northallerton districts of North Yorkshire	To describe the features of invasive per-partum *Streptococcus pyogenes* infection as it occurs in current day practice in North Yorkshire	None
Bauer, 2015	1999–2006	Retrospective case series from cohort of maternal deaths	Various hospitals, Michigan	Identify maternal deaths due to sepsis in the state of Michigan from 1999 to 2006, review the events leading to diagnosis, and evaluate treatment to identify areas for improvement	None
Bengner, 2019	2018	Retrospective case series	Various hospitals, Sweden	Describe two minor outbreaks of cot fever in various hospitals in Sweden, where investigation was able to detect infection from staff to patients.	None
Busowski, 2013	Not reported	Retrospective case series	Single hospital, Orlando, Florida	Present recent, single institution experience with four GAS peripartum cases occurring over a 5-year period	None
CDC, 1999	July 1996–August 1997	Retrospective case series	Single hospital, Maryland	Describe nosocomial outbreaks of GAS infection in Maryland during 1996–1997	None
Chuang, 2002	1995–2002	Retrospective cohort study	Various hospitals, USA	Quantify the burden of invasive postpartum GAS disease in a multistate population	None

(Continues)

TABLE 1 (Continued)

Study, year	Collection dates	Study design	Study setting	Primary objective(s)	Secondary objective(s)
Dan, 1990	1979–1986	Retrospective case series	Two urban hospitals, Tel Aviv	Review our experience with the clinical spectrum produced by group A streptococcal bloodstream invasion and propose a practical classification of its various presentations	None
Daneman, 2005	January 1, 1992–December 31, 2000	Prospective, population-based surveillance (Cohort)	All microbiology laboratories serving Ontario hospitals	Describe the epidemiology of hospital-associated invasive GAS infections in Ontario and evaluate the risk of cross-transmission in hospitals	None
Davis, 2010	1991–2009	Prospective case–control	Two tertiary care centers in Salt Lake City, Utah	Investigate the association of innate immune response gene polymorphisms and puerperal group A streptococcal sepsis.	None
Denoude, 2005	August 2, 2001–December 31, 2003	Retrospective case series	Institute for Public Health Surveillance reporting across 18 establishments, France	Describe reported cases of nosocomial infections of invasive GAS	None
Deutscher, 2011	2007–2009	Retrospective case–control	Population-based multistate surveillance	Describe the burden and characteristics of infection in pregnant and postpartum women	To determine whether pregnant and postpartum women are at higher risk of pneumococcus, GAS and GBS infections and of complications from these infections, compared with nonpregnant women.
Dietz, 2003	May–June 2002	Retrospective case series	University Hospital, Belgium	Describe the course, diagnostics and treatment of a pseudo epidemic of puerperal GAS	Discuss measures to prevent epidemic and prevent further spread of infection
Eriksson, 2003	November 1, 1996–October 31, 1997	Prospective case–control	Laboratory-based prospective surveillance of all public bacteriological laboratories in Sweden	Survey epidemiological and clinical characteristics of invasive GAS infections in Sweden during 1996–1997	Study the spread of GAS clones among invasive and non-invasive infections
Gordon, 1994	Not reported	Retrospective case series	Maternity ward, UK	Report an outbreak of eight cases of GAS puerperal sepsis in which communal use of bidets during the postnatal period appears to have been responsible for the spread of infection.	None
Gustafson, 2017		Retrospective case series	Denmark	To present the clinical differences in group A streptococcal infection	None

TABLE 1 (Continued)

Study, year	Collection dates	Study design	Study setting	Primary objective(s)	Secondary objective(s)
Kaiser, 2018	January 1991–September 2017	Prospective case series	Registry from voluntary reporting by physician or microbial case log, Salt Lake City Region	Identify admission clinical and demographic characteristics associated with adverse outcomes including death, hysterectomy, ICU admission, mechanical ventilation and blood transfusion	Facilitate patient counseling, prognostication, and resource allocation
Knowles, 2015	January 1, 2005–December 31, 2012	Prospective cohort	Two tertiary referral maternity hospitals in Dublin, Ireland	Incidence, bacterial etiology, gestation/ stage at delivery, mode of delivery, antibiotic resistance, admission to augmented care, maternal, fetal and neonatal outcome	None
Lamagni, 2008	January 1, 2003–December 31, 2004	Prospective cohort	Strep-EURO project: 11 participating European countries	Compare the epidemiological patterns of invasive *S. pyogenes* among the 11 participating countries in the Strep-Euro project	None
LeBail, 2007	January 1, 1997–December 31, 2005	Prospective cohort	University hospitals, France	Incidence of postpartum infections with GAS in maternity hospitals	None
Leonard, 2019	January 1, 2010–December 31, 2016	Retrospective cross-sectional	London and the South East of England	Describe postpartum invasive GAS infection including management of mothers and their neonates to determine whether public health guidelines have been followed	None
Lepoutre, 2011	November 2006–November 2007	Prospective cross-sectional	Acute care hospitals (voluntary) across 22 administrative regions, France	Estimate the burden of invasive GAS infections with or without a positive blood culture, characterize the clinical presentations, assess predisposing factors and outcomes, describe the molecular characteristics and antibiotic susceptibility of GAS strains isolated from invasive infections and assess the level of implementation of the recommendations on antibiotic prophylaxis among household contacts.	None
Lev-Sagie 2017	February 2008–August 2010	Prospective cohort	Tertiary care hospitals, Hadassah University, Israel	Evaluate the incidence of long-term vaginal carriage of GAS among women with a prior infection	None
Luca-Harari, 2008	2003–2004	Prospective population-based surveillance	Microbiology departments, Denmark	Understand the epidemiology of invasive GAS disease in Denmark	None
O'Loughlin, 2007	January 1, 2000–December 31, 2004	Population-based surveillance	Centers for Disease Control and Preventions' Active Bacterial Cord surveillance, 10 US sites	Report the current epidemiologic characteristics of invasive GAS infections and estimate potential impact of a multivalent vaccine	None
Rottenstreich, 2019	2005–2017	Retrospective cohort	University hospitals (2), Israel	Determine incidence, associated risk factors, clinical course and outcome of pregnancy-related GAS infections	None
Safar, 2011	January 1, 2005–December 31, 2006	Prospective cohort	Auckland public hospital (metropolitan) surveillance data	Study the effects of invasive GAS on the Auckland population	Establish the direction of further investigations and focus interventions in New Zealand

TABLE 1 (Continued)

Study, year	Collection dates	Study design	Study setting	Primary objective(s)	Secondary objective(s)
Schuitemaker, 1998	1983–1992	Retrospective case series	Maternal Mortality Committee, Central Bureau of Statistics and Dutch Perinatal Database systems	The effect of the changed epidemiology of GAS on maternal mortality was investigated	None
Shinar, 2016	January 2008–May 2015	Retrospective case series	Tertiary care center, Israel	Describe the epidemiologic and clinical characteristics of peripartum GAS infections in an attempt to develop better preventive strategies	None
Strobaek, 1991	January 1, 1987 to December 31, 1989	Retrospective cohort	58 general hospitals in Denmark (of 99) and one hospital in Greenland	Determine whether the epidemic of GAS was reflected within the hospitals by nosocomial cases among hospitalized patients	None
Strus, 2010	October 16–23, 2007	Retrospective case series	Hospital of the Ministry of Internal Affairs and Administration in Krakow, Poland	To analyze the characteristics of the *S. pyogenes* strains involved in the outbreak in Krakow Poland, including the *emm* gene as well as genes coding for superantigens	Pulse field gel electrophoresis (PFGE) was used to determine the genetic relatedness among the isolates. The source of infection and probable routes of transmission of the outbreak strain were investigated using fluorescent in situ hybridization (FISH) as a rapid method for detecting *S. pyogenes* carriage
Tanaka, 2019	January 2010–December 2016	Retrospective case series	Japanese healthcare institutions	Provide an in-depth analysis of the maternal death cases related to sepsis reported in Japan	None
Thewessen, 1999	NR	Prospective case series	University hospital, Netherlands	Describe a cluster of patients with puerperal infection and report the epidemiological and microbiological investigation	None
Trell, 2020	August–December, 2018	Retrospective case series	Single hospital in Lund, Region Skaane, Sweden	Describe the use of whole genome sequencing to investigate an outbreak of postpartum *S. pyogenes emm*75 infections related to an asymptomatic carrier working in a maternity ward	None
Viglionese, 1991	May 1987–April 1990	Retrospective case series	Single center, Boston, Massachusetts	Report characteristics and typing of two clusters of group A streptococcal postpartum infections	None
Wahl, 2007	1996–2002	Retrospective cohort	National Reference Center, Germany	Identify the predominant *emm* types among a large collection of *S. pyogenes* isolates from invasive infections	Define the incidence and demographical risk-factors for acquisition of invasive *S. pyogenes* infection in Germany

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Acosta, 2014	All peripartum women diagnosed with severe sepsis (including septic shock)	Incomplete data	Severe sepsis without septic shock	All women giving birth in the UK (no specific number)	365	32	32	757
Alberts, 2018	Suspicion of obstetric infection or inter injury between 2010–2014	None	None	50	50	6	6	0
Alexander, 2018	Postpartum GAS	None	None	5	5	5	5	NA
Anteby, 1999	Patients from OBGYN department diagnosed with intrapartum or puerperal group A streptococcal infection	None	General population of women giving birth during that time, extracted from computerized medical records	25 822	3403	47	47	
Aronoff, 2008	-Hospitalized with invasive GAS disease and reported to the Florida Department of Health -Isolation of GAS from a normally sterile site and clinically compatible presentation -Endometritis/postpartum sepsis noted on epidemiology surveillance form and/or pregnancy/peripartum checked in risk factor portion of the form and infection within 42 days of delivery -Women carrying the diagnosis of postpartum invasive GAS disease who were residents of Florida	None	None	257 + 2643	257 + 2643	257 + 2643	7	0
Barnham, 2001	Mother and/or baby with detected *S. pyogenes* bacteremia	None	None	11 000	9	9	5	0

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Bauer, 2015	Maternal sepsis	None	None	1 047 857 live births; 558 pregnancy-associated deaths; 151 pregnancy-related deaths	22	4	4	0
Bengner, 2019	Invasive GAS infection in puerperium	None	None	823	5	5	5	0
Busowski, 2013	Puerperal sepsis	None	None	4	4	4	4	0
CDC, 1999	GAS isolated from nonpharyngeal site in patient whose symptoms began more than 12 hours after admission	None	Randomly selected patients on obstetric ward during study period	12	12	12	9	5
Chuang, 2002	Isolation of GAS from a normally sterile site (eg blood or CSF) or from a wound tissue culture when accompanied by necrotizing fasciitis or TSS in a resident of a surveillance area who was pregnant or in the postpartum period (ie </=30 days after delivery) or who had clinician-defined puerperal fever, chorioamnionitis, or septic abortion.	Cases in which GAS was isolated from the amniotic fluid or the placenta alone.	None	3957	87	87	87	0
Dan, 1990	Patients with GAS bacteremia	None	None	36	33	33	5	0
Daneman, 2005	GAS isolated from sterile-site specimen. Cases were identified as hospital-acquired if disease was neither present nor incubating at the time of hospital admission. Specific definitions were given for surgical site and peripartum infections.	None	None	2351	291	291	86	0

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Davis, 2010	Cases demonstrated clinical evidence of endometritis and/or had febrile illness during the postpartum period. They also had at least one positive culture for group A streptococcus from a normally sterile body site.	Unable to contact or declined participation	Racially matched healthy women with a history of term, uncomplicated deliveries and no history of puerperal infection	48	28	28	28	54
Denoude, 2005	Invasive infection of GAS in postoperative or postpartum patients	Community infections or infections outside of specific patient population	None	32	29	29	18	0
Deutscher, 2011	Illness in a woman aged 15–44 years with streptococcus isolated from a normally sterile body site during 2007–2009.	None	Non-pregnant women with GAS infection	1848	1848	439	90	349
Dietz, 2003	Invasive infection of GAS in the puerperium	None	None	5	5	5	5	0
Eriksson, 2003	Women with GAS isolated from a normally sterile site or from a superficial site in a patient who developed a necrotizing infection or STSS. Also included were women with clinical signs of endometritis postpartum and for whom GAS was isolated from the cervix.	None	The first five GAS isolates from throat and superficial skin infections from 3 laboratories during the first 7 months of surveillance	255	255	255	20	144
Gordon, 1994	Mothers and infants with positive swabs for GAS whom were admitted or recently admitted to the maternity ward following the first identified case	None	None	11	11	11	8	0
Gustafson, 2017	Postpartum GAS infection	None	None	4	4	4	4	0

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Kaiser, 2018	All patients with at least one positive culture for group A streptococci from a normally sterile body site (ie blood, urine, or endometrium) or non-sterile body site (ie genital tract, wound) in addition to clinical suspicion for endometritis, defined as postpartum fever with no other alternative source identified	None	Women within the cohort were characterized into adverse and no adverse outcome groups*	71	71	71	71	0
Knowles, 2015	All pregnant and postpartum women with sepsis	None	Patients without a diagnosis of sepsis	136897	276	12	12	136625
Lamagni, 2008	Patients with *S. pyogenes* isolated from a normally sterile site or a nonsterile site in combination with clinical signs of STSS	None	None	5522	3894	3894	107	0
LeBail, 2007	Women presenting with signs of clinical infection and GAS positive culture in the puerperium	None	None	31	17	17	17	0
Leonard, 2019	All mothers or newborns with confirmed invasive GAS with onset within 28 days of birth, defined as either (1) isolated from a sterile site or (2) isolated from a normally nonsterile site but accompanied by a severe clinical presentation	None	None	3216238 (1598069 live maternities)	155	155	134	0

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Lepoutre, 2011	Isolation of bacterium from a usually sterile site or from samples obtained from deep-body-site aspirates, intraoperative specimens, or a nonsterile site in association with one of the following clinical conditions: necrotizing fasciitis, clinically ascertained pneumonia, endometritis, salpingitis. or TSS not attributable to any other cause and defined according to the US Working Group on Severe Streptococcal Infections definitions.	None	None	664	664	664	32	0
Lev-Sagie 2017	Woman with prior vaginal GAS infection	None	Women admitted for labor without previous GAS infection, participating in a cross-sectional study for the detection of vaginal group B streptococcus and GAS	45	25	25	11	436
Luca-Harari, 2008	All GAS isolation from blood or another normally sterile site of from non-sterile sites with evidence of sepsis or sTSS recovered from hospitalized patients	None	None	278	253	253	12	0
O'Loughlin, 2007	Isolation of GAS from a normally sterile site or from a wound specimen obtained from a surveillance area resident with necrotizing fasciitis or sTSS	None	Non	5400	5400	5400	57	0

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Rottenstreich, 2019	All symptomatic cases of culture-proven pregnancy-related GAS infection	Asymptomatic patients or those with GAS positive cultures from the throat only	All other deliveries	140429	124	124	124	140314
Safar, 2011	Patients with invasive GAS (isolate cultured from a previously sterile body cavity) residing in metropolitan Auckland	Women from whom GAS was isolated from amniotic fluid or placenta alone were excluded. Isolation of GAS from nonsterile site. Residence outside of metropolitan Auckland at the time of diagnosis.	None	343	225	225	7	0
Schuitemaker, 1998	All cases of maternal death between 1983 and 1992 attributed to genital tract sepsis	None	None	10	10	7	7	0
Shinar, 2016	All women with peripartum fever or marked abdominal tenderness and positive GAS cultures	None	None	37	37	37	37	0
Strobaek, 1991	Patients with GAS bacteremia	No information from hospitals or when samples could not be traced back to patients.	None	240	240	240	5	0
Strus, 2010	Patients with symptoms of suspected invasive GAS infection	None	Surgical procedures performed in same operating room period	6	6	6	4	48 (10 CS, 38 other procedures)
Tanaka, 2019	All cases of maternal death related to sepsis reported to the Japan Association of Obstetricians and Gynecologists	None	Maternal deaths related to infection from organisms other than GAS	317	24	13	13	11

TABLE 1 (Continued)

Study, year	Inclusion criteria	Exclusion criteria	Comparison group	Total eligible patients	Total patients enrolled	Total GAS infection	Total patients included	Total controls (if applicable)
Thewessen, 1999	Women presenting with signs of clinical infection and GAS positive culture in the puerperium	None	None	6	6	6	6	0
Trell, 2020	Women with signs and symptoms of postpartum infection in same maternity ward in southern Sweden	None	None	6	6	6	6	0
Viglionese, 1991	Postpartum fever with positive GAS culture	None	Vaginal deliveries by physician at hospital	9792	14	14	14	776
Wahl, 2007	Invasive GAS: isolation of *S. pyogenes* from either a normally sterile sample or from samples obtained from deep body site aspirates or intraoperatively.	Clinical data not available	None	475	165	165	9	0

within the first 48 hours (212/425), 36.5% within 3–7 days (155/425) and only 13.6% more than 7 days post-delivery (58/425) (Figure 3).

Fever was the most common symptom associated with puerperal infection (297/333; 89.1%), with abdominal pain (106/333; 31.8%) and vaginal discharge (27/333; 8.1%) less frequently reported. Few details were given regarding presenting signs, but in a study by Kaiser et al.,[30] comparing 71 patients with puerperal infection in terms of outcomes, they found that people presenting with tachycardia (relative risk [RR] 1.08, 95% CI 1.01–1.15, $p = 0.02$), hypotension (RR 0.93, 95% CI 0.89–0.97, $p = 0.002$), and tachypnea (RR 1.03, 95% CI 1.01–1.05, $p \leq 0.001$) were more likely to experience adverse outcomes. In the two studies that detailed laboratory findings, leukocytosis and elevated C-reactive protein (per laboratory criteria) were common, with leukocytosis reported in 81%–94% of patients[36] and elevated C-reactive protein in 96%–100%.[38]

Culture site was available for 682 patients (682/1160; 58.6%), with positive blood cultures in approximately half (338/682, 49.6%), genital tract (vaginal or cervical swab) in 43.7% (298/682) and positive cultures in more than one site in 15.4% (105/682). Positive urine (71/682; 10.4%) wound (21/682; 3.1%), intrabdominal (12/682; 1.8%), throat (10/682; 1.5%), endometrial (8/682; 1.2%) and anal cultures (2/682; 0.3%) were rare.

Of the studies reporting puerperal outcomes (Figure 2, Table S3), bacteremia was present in 49% of patients (382/780) and endometritis in 45.9% (283/617). Puerperal sepsis was described in 28.2% of cases (276/979) and progressed to streptococcal toxic shock syndrome (sTSS) in one-third of such cases (92/942; 9.8%). Multiorgan complications included necrotizing fasciitis ($n = 13$), acute respiratory distress syndrome (ARDS) (9), acute liver failure (10), acute kidney injury (8), disseminated intravascular coagulopathy (10), pneumonia (3), septic embolization (1) and endocarditis (1).

Almost all studies (37/40) reported carrier death rate, with a case fatality rate of 2% (22 deaths among 1081 cases). Three case series only reported maternal deaths and therefore were not included in the case fatality ratio, given an unknown denominator of GAS infections.[19,41,49] However, they detailed another 24 deaths (including two septic abortions, nine antepartum, six postpartum infections, and seven timing unknown), which highlights the sinister nature of invasive GAS.[19,41,49] Details surrounding these additional cases are presented in Table S4. A third of the deaths were reported in cases presenting in the antenatal period, including 3/46 (6.5%) cases of septic abortion and 10/46 (21.7%) antenatal cases of GAS infection (Figure 4). Rapid deterioration occurred in 72.7% (8/11) of the antenatal cases, with death occurring within 36 hours of presentation. There were 18 deaths of the 866 postpartum cases reported (2.1%). Timing was not reported in 15 (15/46; 32.6%) cases of maternal death (Figure 4). There were strong themes of sepsis, sTSS and death within 48 hours when cases were analyzed qualitatively (Table S4). Very few studies described neonatal infections, with only 29 cases among 10 studies (29/427; 6.8%) and there were three reported neonatal deaths (3/427; 0.7%).

In terms of management, 11 studies reported admission to an Intensive Care or High Dependency Unit in 18.5% of invasive

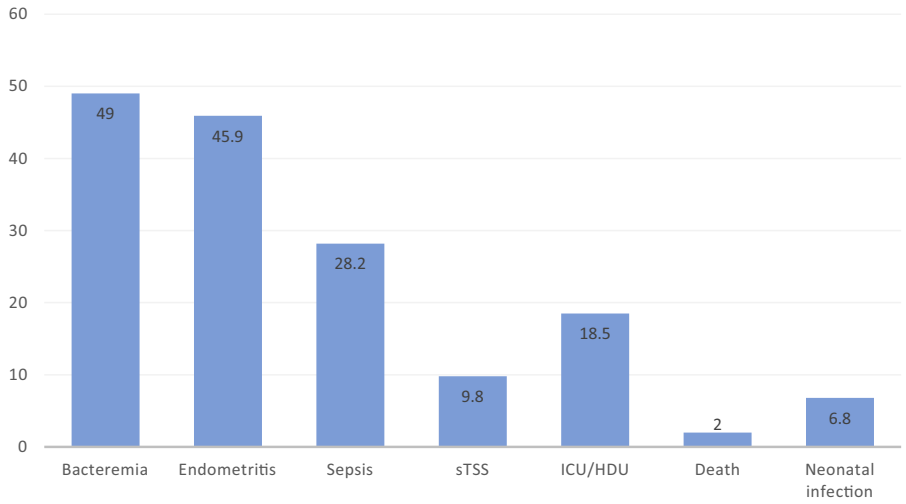

FIGURE 2 Carrier outcomes in puerperal group A streptococcal infections (%). sTSS: streptococcal toxic shock syndrome; ICU, intensive care unit; HDU high-dependency care unit.

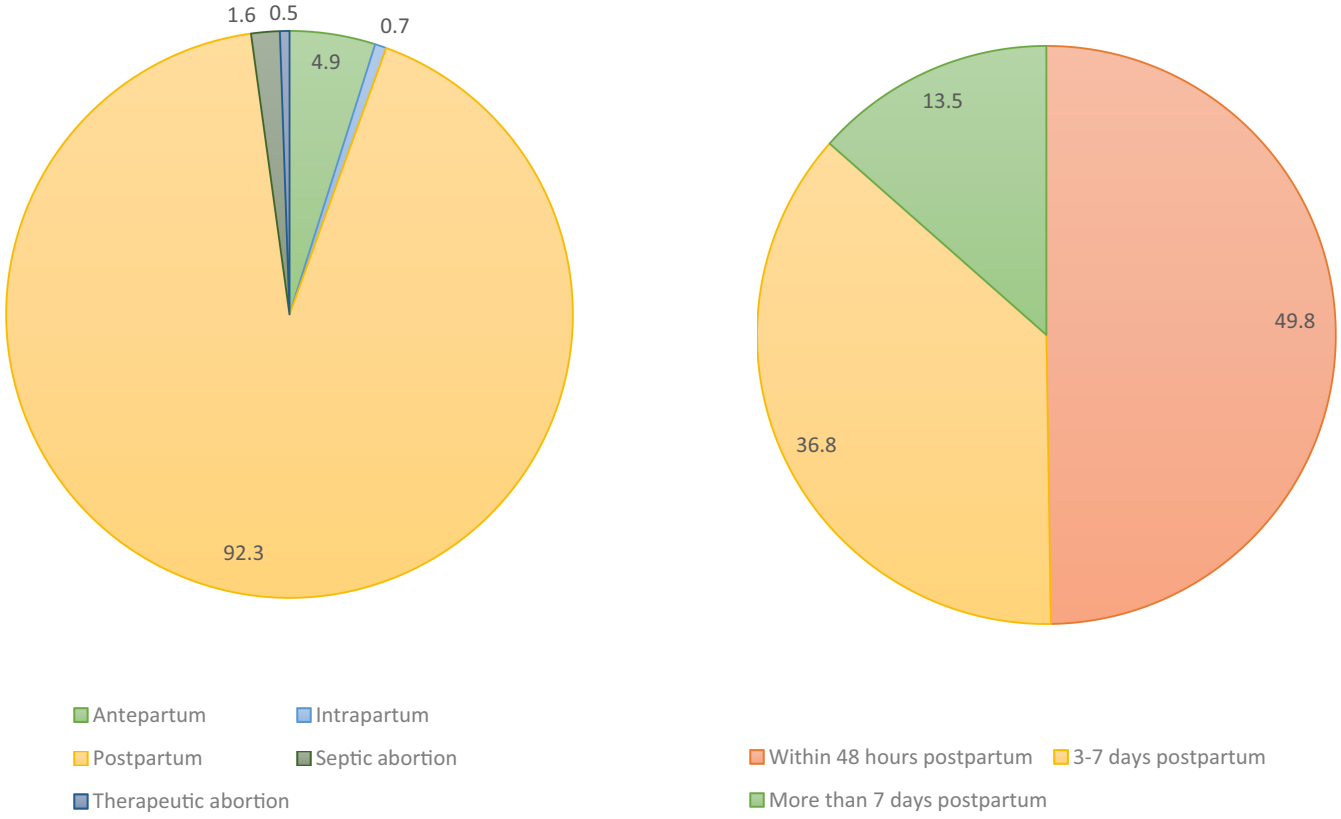

FIGURE 3 Timing of presentation in cases of group A streptococcal infection in pregnancy and postpartum (%).

puerperal GAS (91/492). Antibiotics were given in almost all cases (296/301; 98.3%) when management was described; however, there was a paucity of data on the time when antibiotics were administered, class of antibiotics used, time to clinical response, and duration of antibiotic course. Intravenous immunoglobulin (IVIG) was only employed in seven cases in two studies,[38] with Shinar et al.[38] describing use for the management of cases with severe complications including acute liver failure, acute renal failure, acute respiratory distress syndrome and respiratory failure. The outcomes of these cases were not specifically reported. Transfusion, mechanical ventilation and extracorporeal membrane oxygenation treatment were required in several cases. Surgical exploration occurred in 60 cases with 33 cases of hysterectomy (33/246; 13.4%), often with evidence of tissue necrosis on inspection (Table 2).

Attempts were made to track infection source in less than half of the studies reported (18/40). A community source was reported

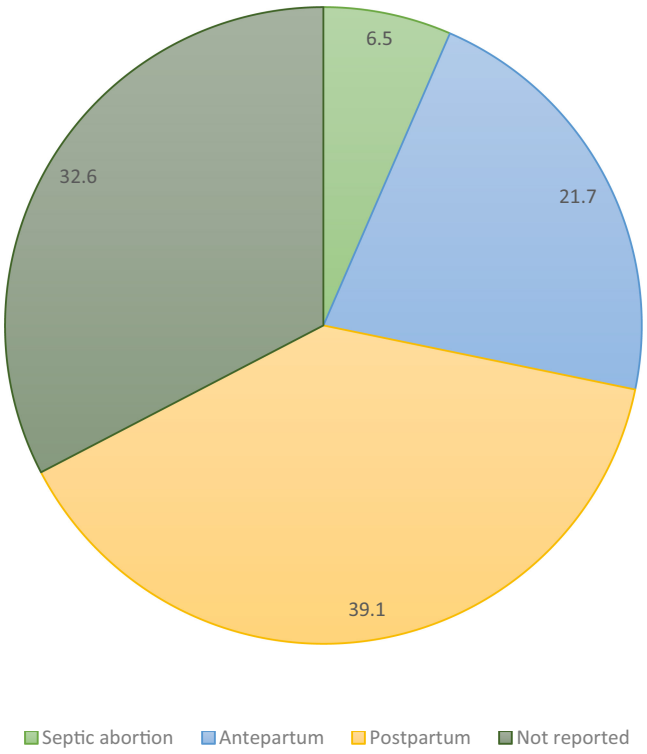

FIGURE 4 Maternal deaths by gestation at presentation (%).

in 43.4% (190/438), nosocomial source was reported in 30.6% (134/438), and unknown source in 26% (114/438).

4 | DISCUSSION

This systematic review aligns with previous literature in that the vast majority of GAS infections occur in the postpartum population following uncomplicated vaginal birth in multiparous carriers at term. Half of the reported cases presented within 48 hours of delivery, with fever and uterine tenderness as common symptoms. Bacteremia (49%) and endometritis (45.9%) were common outcomes, with blood cultures and genital swabs positive in 49.6% and 43.7% of reported cases, respectively. Sepsis developed in 28.2% of patients and a third progressed to sTSS, totaling almost 10% of cases. The case fatality rate in this review (2%) is slightly lower compared with previous population studies from the early 2000s with rates of 3.5%[23] and 4.3%.[8] However, three of the case series detailing a substantial number of fatalities were not included due to unpublished data regarding total number of infections. Although improved recognition and management have likely contributed to better survival, the burden of GAS infection continues to be significant. Historical challenges in surveillance and reporting of GAS puerperal infection at a population level are likely to contribute to an underestimation rather than a fall in case fatality rates.

A third of the deaths were antenatal cases and there was also a disproportionate number of stillbirths in the antenatal infections compared with both postpartum and non-GAS infections in the Tanaka et al. study.[41] These findings are consistent with a review by Hamilton et al.[51] of 10 antepartum case reports from 1974 to 2009 which suggests that infections during the antenatal period result in more devastating consequences than infections occurring postpartum. Rates of septic abortion (pregnancy loss secondary to infection <20 weeks gestational age) and complications from elective therapeutic abortion were low, which as above, could be an underestimation secondary to historical challenges in reporting and labelling.

From a diagnostic perspective, recto-vaginal carriage rates of GAS in pregnant women are low at 0.03%.[52–54] This is compared with skin and throat swabs which reveal colonization of GAS in 5%–30% of the population.[55] At this time, screening for asymptomatic women in pregnancy is not recommended; however, given the excessive risk during this period, further studies on necessity, modality and cost analysis of screening are needed.[56] People presenting with postpartum fever and/or abdominal pain deserve a high level of suspicion for GAS. and investigation with blood and vaginal cultures should be strongly considered and is recommended per the most recent International Society for Infectious Disease in Obstetrics and Gynecology (ISIDOG).[56] Given the potential for severe disease and rapid deterioration, the development of rapid assays for detection of GAS from vaginal specimens could allow for timely diagnosis and appropriate antibiotic therapy. Further studies on the necessity and modality of screening and treatment are needed. Positive swab results should be interpreted seriously and managed swiftly given the potential for severe disease and complications.

The optimal management strategy for puerperal GAS infection remains unclear. Most patients in this review received antibiotics; however, the timing, type and duration were not often reported and cannot be linked to outcomes. The typical regimen for invasive GAS is intravenous penicillin with clindamycin to inhibit protein production in GAS bacteria in order to avoid superantigens and M proteins.[56] Penicillin and first-generation cephalosporins are used routinely in pregnancy for prophylaxis in preterm premature rupture of membranes, group B streptococcus carriage, as well as surgical and instrumental births. However, a prophylactic course of antibiotics for group B streptococcus is insufficient for eradication of GAS (a 10-day course of amoxicillin plus clavulanic acid or a first-generation oral cephalosporin is recommended) and spontaneous clearance occurs in only half of patients.[56] Therefore, this practice is unlikely to change GAS prevalence rates, but it should be considered in future population surveillance studies. At present, resistance to penicillin in GAS organisms is non-existent; however, resistance to macrolides is upwards of 25% in some populations with increased use of these antibiotics.[57] Given that macrolides are used as an adjuvant to penicillin in managing GAS, stewardship should be employed with antibiotic use in this population to avoid developing further resistance.

The benefit of IVIG in cases of sTSS remains unknown as the few studies exploring this intervention have conflicting results.[58–61] In this review, IVIG was employed in seven complicated cases across

TABLE 2 Studies reporting hysterectomy as management in puerperal group A streptococcal infections

Study, Year	Hysterectomy *n* (%)	No hysterectomy *n* (%)	Total patients included in study	Details surrounding procedure
Alexander, 2018	0	5 (100)	5	- No information on specific cases
Anteby, 1999	0	47 (100)	47	- No information on specific cases
Aronoff, 2008	0	7 (100)	7	- No information on specific cases
Bauer, 2015	0	4 (100)	4	- No information on specific cases
Bengner, 2019	0	5 (100)	5	- No information on specific cases
Busowski, 2013	2 (50)	2 (50)	4	- 24yo 2 days postpartum from uncomplicated SVD presenting with sTSS and **NF** requiring ICU admission. Blood and endometrial swab positive for GAS. Hysterectomy completed. Survived with multiple disabilities and limb amputations -27yo 7 days postpartum from uncomplicated SVD presenting with sTSS, **NF**, multi-organ failure, thrombocytopenia and acute liver failure, requiring ICU admission. Hysterectomy on admission day 2. NF to abdominal wall following procedure requiring additional debridement. Survived and discharged after lengthy admission.
Davis, 2010	5 (17.9)	23 (82.1)	28	- No information on specific cases
Dietz, 2003	0	5 (100)	5	- No information on specific cases
Gustafason, 2017	2 (50)	2 (50)	4	- 34yo 36 hours postpartum from SVD. Pregnancy complicated by cardiomyopathy. Presents with sTSS and **NF** requiring ICU admission. Blood and vaginal cultures positive for GAS. Multiple cardiac arrests. Hysterectomy. Survived with brain damage secondary to cardiac arrests - 35yo 5 days postpartum from uncomplicated SVD. Presents with sTSS, **NF** and multi-organ failure. Hysterectomy and resection of external genitalia due to NF. Blood cultures positive for GAS. Cardiac arrest requiring ECMO. Maternal death.
Kaiser, 2018	21 (29.6)	50 (70.4)	71	- Patients undergoing hysterectomy had significantly increased risk of capillary leakage (RR 21.77, 95% CI 3.09–153.54, $p = 0.002$)
Knowles, 2015	0	12 (100)	12	- No information on specific cases
Lev-Sagie 2017	0	11 (100)	11	- No information on specific cases
Shinar, 2016	3 (8.1)	34 (91.9)	37	- Postpartum following uncomplicated SVD, no evidence of NF
Thewessen, 1999	0	6 (100)	6	- No information on specific cases
Total	33 (13.4)	213 (86.6)	246	

Abbreviations: NF, necrotizing fasciitis; sTSS, streptococcal toxic shock syndrome.

two studies; however, different outcomes were reported and therefore results could not be summarized.[36,38] Hysterectomy was not required in the majority of GAS cases (213/246; 86.6%), even in the context of puerperal sepsis and sTSS. In the described cases where hysterectomy was performed, there was often evidence of necrotizing fasciitis in addition to sepsis, sTSS and multiorgan failure. Most experts agree that a confirmed GAS infection in the presence of organ dysfunction should be managed surgically;[7,51,62] however,

severe clinical presentations have not necessarily been shown to be predictive of severe adverse outcome in the literature.[30] In a case report by Dehaene et al., a sharp rise in creatinine kinase was suggested to be a marker of tissue destruction and indicator for hysterectomy.[63] Moving forward, active registries should include initiation and duration of antibiotic administration, adherence to the Surviving Sepsis guidelines,[64] employment of IVIG therapy, and clinical and/or laboratory predictors for risk stratification for escalation to surgical management as well as outcomes following hysterectomy including duration of antibiotics, length of hospital stay, and carrier morbidity and mortality.

Historically, GAS infection has been considered a hospital-acquired infection; however, in our study only 30.5% were confirmed nosocomial infections. Therefore, acquisition of GAS in the community is increasingly important and could be considered a target for prevention, intervention and screening.[65]

The strengths of this review include the extensive search across international databases, inclusion of articles in all languages and combining more than 1000 cases. Further, international definitions for infection and sepsis were employed consistently across all studies (Table S5). Recent studies were often explicit in defining cases; however, older studies may have used common terms such as "puerperal sepsis" more loosely, which would overestimate cases of sepsis. This review was limited by the inability to perform a meta-analysis due to dominant study design and heterogeneity. Further, the specific outcomes of interest were not universally reported across all studies and therefore the denominator for assessment is variable in studies reporting that outcome only. This review is also limited by the quality of the older studies, which were mostly large case series. Lastly, all of the studies included were performed in high-income countries, which limits our ability to generalize the findings and recommendations to low- and middle-income countries. Further study with broader geographical representation is important to guide national and international recommendations for management and public health intervention.

5 | CONCLUSION

GAS infection remains an important contributor to pregnancy and puerperal morbidity and mortality despite advances in infection control protocols. There continues to be a paucity of data to guide management strategies; however, early recognition and diagnosis, aggressive management with fluid resuscitation and antibiotic therapy, and consideration of source control are expected to be important for favorable outcomes given the serious risk of sepsis and progression to sTSS.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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