Group A streptococcal toxic shock syndrome developing in the third trimester of pregnancy

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**Background:** Group A streptococcal (GAS) toxic shock syndrome (TSS) is an uncommon, but life-threatening infection during pregnancy and should be considered in rapid onset of shock. Most cases described in the literature have occurred in the puerperium. We report a case of GAS TSS occurring during the third trimester of pregnancy in a previously healthy woman.

**Case:** A 31-year-old female, who was 34 weeks pregnant, presented with fevers and a prodromal ‘flu-like’ illness. She rapidly developed shock and multiorgan failure. Blood cultures revealed GAS bacteremia and the patient met criteria for streptococcal TSS. Despite her eventual recovery, her infant died on postpartum day 15 as a consequence of the mother’s TSS.

**Conclusions:** This case is unusual in that there were no identifiable initiating events or source of the streptococcal infection, and the TSS developed during pregnancy rather than after delivery. Early recognition of GAS infections is important given the rapid onset and high morbidity and mortality associated with these infections. This is the first reported case utilizing intravenous immunoglobulin for GAS TSS in the puerperium.

Key words: Puerperal Infection; Septic Shock; Intravenous Immunoglobulin; Streptococcus pyogenes
these symptoms. On presentation, she was ill-appearing with a temperature of 38.6°C, pulse of 127 beats/minute and blood pressure of 104/64 mmHg. Physical findings included diffuse lower abdominal pain with mild rebound tenderness and uterine tenderness. The cervix was dilated 1 cm with no effacement, no evidence of ruptured membranes and no discharge. The skin and mucosal surfaces were unremarkable and without abrasions; there was no rash. Her chest and throat exams were unrevealing. The patient was suspected of having chorioamnionitis and was admitted to the labor and delivery unit. On admission, blood cultures, vaginal culture, urinalysis, and urine culture were performed before the initiation of antibiotics. Laboratory values on admission included a white blood cell count of 9700/mm$^3$, hematocrit of 34%, platelet count of 124 000/mm$^3$, and differential of 93% segmented neutrophils and 5% band forms. The patient was empirically treated with gentamicin, clindamycin, and vancomycin, as she reported a penicillin allergy. Despite antibiotics and intravenous fluids, the patient continued to have increasing lower abdominal pain. External fetal monitoring revealed periodic pulse decelerations to 90 beats/minute. An obstetric ultrasound showed a fetus with an estimated weight of 2216 g and adequate fluid. Further decelerations were noted to 60 beats/minute prompting an emergency Cesarean section. The fetus had Apgar scores of 0/0 and was pulseless for 20 minutes during the resuscitation. The infant was admitted to the neonatal intensive care unit in critical condition on ventilatory and circulatory support.

Following the Cesarean section, the mother developed respiratory insufficiency requiring intubation. A chest radiograph revealed diffuse pulmonary infiltrates and bilateral pleural effusions consistent with acute respiratory distress syndrome. Within 4 hours of the Cesarean section, bleeding at the wound site was noted as well as hypotension. The patient was rushed to the operating room where a hemoperitoneum was discovered. The patient was noted to have disseminated intravascular coagulation (DIC) with a platelet count of 54 000/mm$^3$, fibrinogen of 61 mg/dl, prothrombin time of 19.7 seconds, INR 1.9, partial thrombin time 73.9 seconds, and more than 20 fibrin split products. During the following 24 hours, the patient required 11 units of packed red blood cells, 19 units of fresh frozen plasma and 36 units of platelets. The patient remained hypotensive despite fluids and packed RBC transfusions requiring vasopressor support with dopamine and phenylephrine.

On hospital day 2, two blood cultures from admission were positive for GAS, sensitive to penicillin, clindamycin, erythromycin, and vancomycin. In addition, the placenta was noted to have abundant Gram-positive cocci in pairs and chains on histopathology. Tissue culture of the placenta was positive for GAS. The urinalysis was unremarkable, and urine and vaginal cultures were negative. Because the patient remained in septic shock, intravenous immunoglobulin (IVIG) at 150 mg/kg daily for a 5-day duration and intravenous clindamycin and ceftriaxone were administered for the diagnosis of streptococcal TSS. No skin or other lesions were noted on repeated examinations. A throat culture was negative for GAS. Repeated postoperative exams and ultrasound evaluations failed to reveal ongoing pelvic infection. The infant was empirically treated with ampicillin and cefotaxime; all cultures from the infant remained negative.

Also on hospital day 2, the mother continued to have abdominal distension and was returned to the operating room where 1 l of intraperitoneal blood was evacuated. Further bleeding near the right fallopian tube was noted, and a right salpingectomy was performed. The uterus appeared atonic, but there was no evidence of necrosis or active infection. The patient remained on ventilatory support, with a peak end expiratory pressure (PEEP) of 15 and paO$_2$ of 70–100%, and vasopressor support.

On day 3, the patient developed oliguric renal failure requiring continuous veno-venous hemodialysis (CVVHD). In addition, liver dysfunction was noted with an alanine aminotransferase (ALT) of 92 units/l, total bilirubin of 8.2 mg/dl, and direct bilirubin of 5.4 mg/dl. On hospital day 4, an exploratory laparotomy was performed revealing a myometrial hematoma without necrosis. During this procedure a feeding jejunostomy tube and a gastric tube were placed for nutritional support. Due to persistent thrombocytopenia despite resolution of the DIC, ceftriaxone was discontinued on
hospital day 5. The patient remained in critical condition over the next week, but no further major surgical intervention was required.

On day 11, a cholecystostomy drain was placed due to persistent biliary sludging with a total bilirubin of 19.3 mg/dL. On day 12, the patient developed a rash, and antibiotics were changed to cefotaxime and levofloxacin, which she continued to complete a 14-day course. The patient was extubated after 19 days of ventilatory support. On hospital day 25, hemodialysis was discontinued, and the patient was discharged from the hospital. Her laboratory values subsequently normalized with a new baseline creatinine level of 1.4 mg/dL. The patient remains in good health and has returned to work.

Despite aggressive supportive care, the infant died on postpartum day 15 with stage III hypoxic brain damage due to asphyxia at delivery, grade IV intraventricular hemorrhage, hydrocephalus, and brainstem herniation. There was no evidence of infection in the infant.

**DISCUSSION**

This case emphasizes that clinicians should consider GAS in life-threatening infections occurring during pregnancy. Our patient’s presentation with high fevers and chills after a ‘viral-like’ prodrome is characteristic of GAS infections. GAS pelvic infections may have a paucity of symptoms or signs related to the genital tract with non-specific symptoms or gastrointestinal manifestations predominating. Our patient’s fulminant clinical course demonstrates several features of streptococcal TSS, including the rapid onset of acute respiratory distress syndrome, septic shock requiring vasopressors, oliguric renal failure, liver dysfunction, and disseminated intravascular coagulation. The criteria for the diagnosis of streptococcal TSS have been previously published. The pathophysiology of streptococcal TSS is related to the production of pyrogenic exotoxins, particularly exotoxin A, an exotoxin closely related to the Staphylococcus endotoxin responsible for staphylococcal TSS. Exotoxin A, a superantigen, can directly stimulate T-cells to release massive amounts of inflammatory cytokines resulting in rapid clinical sequelae.

The primary site of infection or introduction of the invasive streptococci is typically the skin, throat, or vagina. In up to 45% of cases, the primary site may be unapparent. In most described cases of puerperal GAS infections, organisms ascend the genital canal, and the infection occurs shortly after completion of the pregnancy. Silver reported two cases occurring 2–14 days after normal vaginal deliveries. Another case occurred after a spontaneous abortion, while other cases of GAS infection have been linked to vaginal or abdominal hysterectomy, Cesarean section, genital tract abscesses, and intrauterine contraceptive devices. Definite cases of GAS TSS in the intrapartum or puerperium reported since 1990 in the English literature located by a MEDLINE search (using the terms ‘group A streptococci’, ‘Streptococcus pyogenes’, ‘shock’, ‘pregnancy’, and ‘puerperal’) are shown in Table 1. Most GAS puerperal cases occur sporadically with the patients’ endogenous flora; however, outbreaks have been reported due to nosocomial spread and require prompt isolation and identification of the source of the infection.

Recently, a case of streptococcal TSS has been described after vagal delivery in which GAS was isolated during routine surveillance cultures performed to detect group B streptococci (GBS), suggesting that colonization may be a subsequent risk factor for invasive disease. The same authors also presented a second case of GAS endometritis occurring in a patient with a positive surveillance culture. One recent study showed that vaginal or rectal colonization with GAS during pregnancy is rare, with a prevalence of 0.03%, suggesting that screening specifically for GAS is not warranted. Studies on the usefulness of treating GAS colonization found incidentally during 35- to 37-week screens in pregnancy are needed. Our patient developed invasive disease before surveillance cultures for GBS were collected; however, vaginal cultures for streptococci were negative on admission.

In contrast to puerperal infections that typically arise from colonization or infection of the genital tract, most cases of streptococcal TSS in non-pregnant adults have a primary site of infection in the soft tissues or skin. Cases of streptococcal necrotizing fasciitis of the extremities occurring
### Table I  Definite cases of streptococcal toxic shock syndrome (TSS) during pregnancy or the puerperium (1990-present)

| First author/reference | Publication year | Age | Para | Time TSS developed | Complicating factors | Cultures with GAS | Antibiotics | Use of IVIG | Surgeries performed for the delivery of the infant and control of infection | Duration of hospitalization | Maternal outcome | Fetal outcome |
|------------------------|------------------|-----|------|-------------------|----------------------|-------------------|-------------|------------|---------------------------------------------------------------|-----------------------------|----------------|-------------|
| POSTPARTUM             |                  |     |      |                   |                      |                   |             |           |                                                               |                             |                |             |
| Whittet                | 1990             | 23  | NP   | 2 weeks           | NP                   | Blood, throat     | Penicillin   | No         | Chest tubes for empyema 15 days                             | 15 days                     | Survived       | NA          |
| Martens                | 1991             | 25  | I    | 4 days            | Episiotomy           | NP                | Imipenem, then penicillin and metronidazole | No         | Radical hysterectomy                                        | 81 days                     | Survived       | NA          |
| Dotters                | 1991             | 40  | I    | After spontaneous abortion | Septic abortion | Blood, peritoneal | Ampicillin/gentamicin/ clindamycin | No         | Hysterectomy, bilateral salpingo-oophorectomy               | 22 days                     | Survived       | NA          |
| Silver                 | 1992             | 22  | I    | 14 days           | NP                   | Blood, pleural, peritoneal, lochia | Ampicillin/gentamicin/ metronidazole | No         | Hysterectomy, left salpingo-oophorectomy                   | 42 days                     | Survived       | NA          |
| Silver                 | 1992             | 27  | I    | 2 days            | NP                   | Blood, lochia     | Ampicillin/gentamicin/ clindamycin | No         | Hysterectomy, bilateral salpingo-oophorectomy               | 14 days                     | Survived       | NA          |
| Snubes                 | 1993             | 14  | I    | 3 days            | Episiotomy repair with sutures | Blood, endometrial | Nafcillin/gentamicin/ metronidazole | No         | Curettage                                                  | 10 days                     | Survived       | NA          |
| Nathan                 | 1993             | 28  | NP   | 1 day             | NP                   | Blood             | NP           | No         | Hysterectomy, bilateral salpingo-oophorectomy               | 21 days                     | Died           | NA          |
| Nathan                 | 1993             | 22  | NP   | After stillbirth  | History of stillbirth at home | Blood             | Ampicillin/cefotaxime/ clindamycin | No         | Hysterectomy, bilateral salpingo-oophorectomy               | 2 days                      | Survived       | NA          |
| Rowan                  | 1995             | 36  | 3    | 4 days            | Use of NSAIDs       | Blood, vaginal, shoulder swabs | Penicillin/aztreonam/ fluoxacillin | No         | Hysterectomy, right shoulder debridement                    | 2 days                      | Died           | NA          |
| Noronha                | 1996             | 21  | I    | 1 day            | Induction of labor attempted 1 week before delivery | Blood, urine, endometrium | Ampicillin/gentamicin/ clindamycin | No         | None                                                       | 2 days                      | Died           | NA          |
| Antebay                | 1999             | 24  | 3    | 2 days            | Cesarean section at 32 weeks | Blood, cervical, abdominal | Ampicillin/gentamicin/ metronidazole | No         | Exploratory laparotomy                                      | 14 days                     | Survived       | NA          |
| Stofonek               | 2001             | NP  | multiple 4 days | Episiotomy         | Blood, peritoneal, vaginal | Ampicillin/cultbactam/ clindamycin | No         | Hysterectomy, bilateral salpingo-oophorectomy               | 35 days                     | Survived       | NA          |
| Barnham                | 2001             | 33  | 2    | 2 days            | Forceps delivery after 4 hours of labor | Blood, perineal tissues | NP           | No         | NP                                                          | 36 hours                    | Died           | NA          |
| Barnham                | 2001             | 36  | 3    | 1 day            | Stillbirth with induced delivery | Blood, amniotic fluid | NP           | No         | NP                                                          | 36 hours                    | Died           | NA          |
| Christie               | 2001             | 30  | NP   | 4 days            | NP                   | Vaginal swabs, infant's hands | Imipenem/clindamycin | No         | NP                                                          | 4 days                      | Survived       | NA          |

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Table 1  Continued

| First author/ reference | Publication year | Age | Para | Time TSS developed | Complicating factors | Cultures with GAS | Antibiotics | Use of IVIG | Surgeries performed for the delivery of the infant and control of infection | Duration of hospitalization | Maternal Fetal outcome |
|-------------------------|----------------|-----|------|-------------------|-----------------------|------------------|-------------|-------------|-------------------------------------------------|--------------------------|-----------------------|
| INTRAPARTUM             |                |     |      |                   |                       |                  |             |            | Delivery of 2 stillborn fetuses                | 7 days                   | Died                  |
| Ooe23                   | 1997           | 29  | NP   | 34 weeks' gestation| None reported         | Blood            | Piperacillin | No          | Cesarean section and hysterectomy              | < 1 day                  | Died                  |
| Ooe23                   | 1997           | 42  | NP   | 34 weeks' gestation| None reported         | Blood, pharyngeal, myometrium | Ampicillin | No          | Cesarean section only                           | 7 hours                  | Died                  |
| Ichiyama24              | 1997           | 43  | NP   | 34 weeks' gestation| Unclear (stillbirth at Cesarean delivery) | Blood           | Not reported | No          | Cesarean section only                           | 9 hours                  | Died                  |
| Hirose25                | 2001           | 37  | NP   | 29 weeks' gestation| History of premature labor 12 days prior | Blood, various tissues on autopsy | NP          | No          | Cesarean section only                           | 25 days                  | Survived Died         |
| Current Case            | 2002           | 31  | I    | 34 weeks' gestation| None known            | Blood, placental | Vancomycin/gentamicin/clindamycin | Yes – 5 days | Cesarean section only                           | 25 days                  | Survived Died         |

NA, not applicable; NP, not presented; GAS, group A streptococcus
during pregnancy or postpartum have been reported\textsuperscript{17,32}, but the genital tract is typically the source for infections in pregnancy. Other cases in non-pregnant adults have been linked to GAS pneumonia, meningitis, peritonitis, pharyngitis, endophthalmitis, and joint infection\textsuperscript{33}.

In our case, the source of the bacteremia was unclear. We were suspicious of a genital tract source because: (1) our patient was in her third trimester of pregnancy; (2) she presented with lower abdominal pain; and (3) there was no evidence for infection of the skin or pharynx. Placental histopathology and cultures revealed GAS, but it is unclear if the placenta was seeded from maternal bacteremia or if it was primarily infected. There was no evidence of vaginal infection or involvement of the uterus after delivery. This case is unusual in that sepsis developed before delivery and the source of the infection was unclear. Four additional intrapartum cases were found in our literature search\textsuperscript{23–25}. In all these cases, a pharyngeal source for the GAS was proven or strongly suspected. Four of five cases, including our case, developed at 34 weeks' gestation during a previously unremarkable pregnancy. In all four other cases, the mother and fetus died when the outcome was noted. A small case series from Japan showed that TSS developing before or within 12 hours of delivery, when compared with puerperal cases, have a higher rate of both fetal and maternal mortality\textsuperscript{34}.

Cases of GAS infection associated with pregnancy have often required hysterectomy. The adnexa may be preserved if active infection in these sites is absent\textsuperscript{11}. In cases in which the uterus is clearly involved, hysterectomy is generally indicated. In our case, it was debated whether a hysterectomy was indicated since necrotizing streptococcal infections typically require debridement of the involved tissues. Repeated radiologic and intraoperative examinations of the uterus did not reveal necrosis, abscess or other signs of active infection. Therefore, the patient was treated without hysterectomy and subsequently recovered.

In the treatment of GAS infections, antibiotic therapy should include a β-lactam agent and clindamycin. Clindamycin is advocated because of its effectiveness despite a high inoculum of bacteria (the ‘Eagle effect’) and its reduction of toxin production by inhibition of protein synthesis\textsuperscript{7,35}. The use of IVIG has been shown to reduce mortality in cases of invasive GAS infection that are complicated by shock. Case-control studies show a reduction of mortality from 67 to 34\%\textsuperscript{36}. Although a randomized clinical trial has never been conducted, most experts advocate the use of IVIG – preferably early in the disease course – for patients with shock due to invasive GAS infections\textsuperscript{37–39}.

This case represents the first report utilizing IVIG in GAS TSS occurring in the puerperium and reminds clinicians to include invasive GAS in the differential diagnosis of a puerperal infection when a patient presents with the rapid onset of septic shock. Most postpartum cases result from ascending genital tract infection, whereas cases developing intrapartum may have a pharyngeal or occult primary source. GAS TSS occurring in association with pregnancy has a high morbidity and mortality, especially in cases occurring intrapartum.

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