How could we suspect life-threatening perinatal group A streptococcal infection?

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Abstract

**Aim:** Perinatal group A streptococcal infection is a rare but life-threatening condition. Few reports have focused on its clinical characteristics and how to prevent deterioration. We report our experience with two antenatal fatal cases and reviewed 96 cases in the literature to assess the clinical characteristics of group A streptococcal infection.

**Methods:** English-language clinical reports of antenatal and postnatal group A streptococcal infection in 1974–2019 were retrieved and examined. Relationships between clinical characteristics and maternal outcomes were assessed.

**Results:** Univariate analysis revealed that antenatal group A streptococcal infection was significantly associated with an age of ≤19 or ≥35 years, cesarean section, sore throat as an initial symptom, positive throat culture, maternal death and fetal death. Multivariate analysis revealed that antenatal onset (odds ratio = 7.922, 95% confidence interval = 1.297–48.374; P = 0.025) and a quick sepsis-related organ-failure assessment score (qSOFA; low blood pressure, high respiratory rate or altered mental status) of ≥2 (odds ratio = 6.166, 95% confidence interval = 1.066–35.670; P = 0.042) were significantly related to maternal death.

**Conclusion:** Per our findings, antenatal group A streptococcal infection was significantly associated with maternal and fetal death. Further, the antenatal infection was revealed as a more critical risk factor. We suggest that the presence of any sign related to the qSOFA is a potential clue suspecting perinatal group A streptococcal infection in primary obstetric facilities.

**Key words:** group A streptococcal infection, maternal sepsis, perinatal mortality.

Introduction

Perinatal group A streptococcal (GAS) infection is a rare disease, occurring in six of every 100 000 births according to a North American report.1 The largest case study worldwide included only 67 cases.2 Even in the current age, in which hygienic conditions, antibiotics and intensive care settings have undergone significant advances, perinatal GAS infections can induce sudden septic shock (toxic shock syndrome3), resulting in the death of the mother and/or infants. Due to the rarity of the condition, detailed pathophysiology and its clinical characteristics have not been understood. Characteristics of vulnerable pregnant women, that is, important information for clinician, have also been unknown. We report two fatal cases, possibly due to GAS infection and analyzed the clinical features of perinatal GAS infection by reviewing the literature.

Case Reports

**Case 1**

*Patient:* A 26-year-old woman.

*Past obstetric history:* Gravida 2, para 1. Three years prior, the patient was transported to our hospital due
to the rupture of membranes and labor with no pre-
natal care. An emergency cesarean section due to
breach presentation was performed and a 2214 g
healthy male was delivered.

Past medical history: Nothing remarkable.

History of present illness: At 13 weeks’ gestation, the
patient presented to a clinic with abdominal pain. She
was diagnosed with a potential threat of miscarriage
because of vaginal bleeding. Despite the offer of hos-
pitalization, she refused and returned home. Six hours
later, she experienced a rupture of the membranes
and spontaneous abortion at home and thus returned
to the clinic. The transvaginal ultrasound revealed a
retained placenta; she decided to be admitted and
undergo surgical treatment. However, she experi-
enced sudden shortness of breath on admission,
followed by altered mental status. Since her systolic
blood pressure dropped to 60 mmHg, and peripheral
capillary oxygen saturation (SpO2) also dropped to
60%, she was provided artificial ventilation. Despite
the initial treatment, she went into cardiopulmonary
arrest. She was transported to our tertiary medical
center while being resuscitated. On arrival, she was
still under cardiopulmonary arrest, and the resuscita-
tion was continued. Her laboratory findings showed
the following: white blood cell (WBC) count, 35
dice; hemoglobin, 9.0 g/dL; platelet count, 113
000 cells/μL; D-dimer, 32.0 μg/mL; fibrinogen,
<70 mg/dL; blood urea nitrogen, 26.0 mg/dL; creati-
nine, 1.62 mg/dL; aspartate aminotransferase, 3993 U/
L; alanine aminotransferase, 3041 U/L; C-reactive
protein, 8.4 mg/dL and procalcitonin, 9.5 mg/mL. GAS
was later detected from a culture of a vaginal sample
taken at this time. Transthoracic echocardiography rev-
ealed no right ventricular dilatation or pericardial effu-
sion. Because she did not respond to resuscitation, percutaneous cardiopulmonary support was started.
An enhanced computed tomography scan revealed no
pulmonary embolism but diffuse infiltration in the
lungs. She died 11 h and 36 min after the initial exami-
nation at the clinic.

Case 2

Patient: A 37-year-old woman.

Past obstetric history: Gravida 1, para 0.

Past medical history: Acute hepatitis at 24 years
of age.

History of present illness: The patient had regular
prenatal check-ups at a clinic. At 21 weeks’ gestation,
she presented with a fever of 38.0°C. Because she was
suspected of having an influenza viral infection, she
was prescribed oseltamivir and went home. Hypogastric
pain appeared, and she returned to the clinic 6 h
later. Upon arrival, her body temperature was 39°C,
blood pressure was 91/62 mmHg and heart rate was
107 beats per minute. Intrauterine fetal death was
diagnosed with transabdominal ultrasound. As the
influenza point-of-care test result was negative and
her WBC count elevated to 13 600/μL, intravenous
flomoxef was initiated. Labor started after that, and
she had a spontaneous abortion. The placenta was
delivered simultaneously, revealing bloody amniotic
fluid. Directly after the delivery, significant bleeding
was noted, and the patient appeared to be drowsy.
At this time, her blood pressure was 83/56 mmHg,
heart rate was 124 beats per minute and postnatal
hemorrhage had reached 1272 g. Therefore, she was
transferred to a secondary medical center. Labora-
tory findings on arrival showed the following: WBC
count, 32 800 cells/μL; hemoglobin, 8.1 g/dL; plate-
let count, 67 000 cells/μL; D-dimer, 907.3 μg/mL;
fibrinogen, <25 mg/dL; blood urea nitrogen, 31.0
mg/dL; creatinine, 2.28 mg/dL; aspartate aminotransferase, 146 U/L; alanine aminotransferase, 22 U/L and C-reactive protein, 9.3 mg/dL. GAS was
later identified from vaginal discharge taken at this
hospital. She went into cardiopulmonary arrest, and
cardiopulmonary resuscitation was provided. She
restored spontaneous circulation 2 min later and
was transferred to our tertiary medical center. She
again went into cardiopulmonary arrest during the
transfer. After arrival, she did not respond to contin-
ued attempts of cardiopulmonary resuscitation. She
died 21 h and 46 min after the initial visit to the
clinic.

Our two cases suspected of perinatal GAS infec-
tion had severe maternal outcomes with an astonish-
ingly acute clinical course. Several studies have
addressed the clinical characteristics of perinatal GAS infection. Of these, Hamilton et al. reported
the largest number of cases (67 patients, including
10 antenatal) from the literature review. However,
limited evidence is available on the clinical features
indicative of perinatal GAS infection and, particu-
larly, which patients require heightened attention.
On the basis of the severe outcome of our cases, we
hypothesized that antenatal GAS infection was asso-
ciated with the outcome. To test this hypothesis, we
compared the clinical characteristics of GAS infec-
tion between antenatal and postnatal onsets. We
then assessed the clinical characteristics that affected
the maternal outcome.
Table 1 Clinical cases of GAS infection reviewed in this study

| Age        | Onset of symptoms | Mode of delivery | Maternal outcome | Fetal outcome | Reference | Publication year |
|------------|------------------|-----------------|------------------|---------------|-----------|-----------------|
| Antenatal onset (n = 25) |                  |                 |                  |               |           |                 |
| Time of onset unknown (n = 1) |                  |                 |                  |               | [6]       | 1993            |
| 22         | NG               | Vaginal delivery| Survived         | Died          |           |                 |
| Time of onset 1st trimester (n = 3) |                  |                 |                  |               |           |                 |
| 40         | GW 7            | Vaginal delivery| Survived         | NG            | [7]       | 1991            |
| 40         | GW 10           | Vaginal delivery| Died             | Died          | [8]       | 2015            |
| 26         | **GW 13**       | **Vaginal delivery** | Died         | Died          | **Case 1** | **2020**       |
| Time of onset 2nd trimester (n = 5) |                  |                 |                  |               |           |                 |
| 32         | GW 15           | Vaginal delivery| Died             | Died          | [8]       | 2015            |
| 35         | GW 18           | NG              | Died             | Died          | [8]       | 2015            |
| 37         | **GW 21**       | **Vaginal delivery** | Died         | Died          | **Case 2** | **2020**       |
| 21         | GW 27           | NG              | Survived         | NG            | [9]       | 1996            |
| 19         | GW 27           | Vaginal delivery| Survived         | Survived      | [10]      | 2013            |
| Time of onset 3rd trimester (n = 16) |                  |                 |                  |               |           |                 |
| 37         | GW 28           | Cesarean section| Died             | NG            | [11]      | 2001            |
| 24         | GW 32           | Cesarean section| Survived         | Survived      | [12]      | 2016            |
| NG         | GW 34           | Cesarean section| Survived         | Survived      | [13]      | 1990            |
| 43         | GW 34           | Cesarean section| Died             | Died          | [14]      | 1996            |
| 29         | GW 34           | Vaginal delivery| Died             | Died          | [15]      | 1997            |
| 42         | GW 34           | Cesarean section| Died             | Died          | [15]      | 1997            |
| 31         | GW 34           | Cesarean section| Survived         | Survived      | [16]      | 2001            |
| 38         | GW 34           | Vaginal delivery| Died             | Died          | 8         | 2015            |
| 35         | GW 34           | Vaginal delivery| Survived         | Survived      | [17]      | 2017            |
| 36         | GW 35           | NG              | Died             | Died          | 8         | 2015            |
| 32         | GW 36           | Cesarean section| Died             | Died          | [18]      | 1995            |
| 36         | GW 36           | Vaginal delivery| Died             | Died          | [19]      | 2001            |
| 36         | GW 36           | Vaginal delivery| Survived         | NG            | [20]      | 2007            |
| 16         | GW 37           | Vaginal delivery| Died             | Died          | [21]      | 2010            |
| 35         | GW 37           | NG              | Died             | Survived      | [22]      | 2015            |
| NG         | GW 40           | Vaginal delivery| Survived         | Survived      | [13]      | 1990            |
| Postpartum onset (n = 73) |                  |                 |                  |               |           |                 |
| Time of onset unknown (n = 12) |                  |                 |                  |               |           |                 |
| 29         | NG              | NG              | Died             | NG            | [23]      | 1989            |
| 34         | NG              | NG              | Survived         | NG            | [23]      | 1989            |
| 29         | NG              | Cesarean section| Survived         | NG            | [24]      | 2004            |
| NG         | NG              | Vaginal delivery| Survived         | Survived      | [25]      | 2005            |
| NG         | NG              | Vaginal delivery| Survived         | Survived      | [25]      | 2005            |
| NG         | NG              | Vaginal delivery| Survived         | Survived      | [25]      | 2005            |
| NG         | NG              | Vaginal delivery| Survived         | Survived      | [25]      | 2005            |
| 25         | NG              | NG              | Survived         | NG            | [26]      | 2008            |
| 36         | NG              | NG              | Survived         | NG            | [26]      | 2008            |
| 25         | NG              | NG              | Survived         | NG            | [26]      | 2008            |
| 19         | NG              | NG              | Survived         | NG            | [26]      | 2008            |
| Time of onset 0–24 h (n = 21) |                  |                 |                  |               |           |                 |
| NG         | Immediately     | Vaginal delivery| Survived         | Survived      | [13]      | 1990            |
| 31         | Immediately     | Vaginal delivery| Survived         | Survived      | [27]      | 1993            |
| 32         | Immediately     | Vaginal delivery| Survived         | Survived      | [30]      | 2018            |
| 19         | 25 min          | Cesarean section| Died             | Survived      | [29]      | 1974            |
| 20         | 1 h             | Vaginal delivery| Died             | Survived      | 6         | 1994            |
| 33         | A few hours     | Vaginal delivery| Survived         | NG            | [22]      | 2017            |
| 27         | 8 h             | Vaginal delivery| Survived         | Survived      | [30]      | 2008            |
| 24         | 12 h            | Vaginal delivery| Survived         | Survived      | [31]      | 2005            |
| 27         | 12 h            | Vaginal delivery| Survived         | Survived      | [32]      | 2011            |
| 32         | 16 h            | Cesarean section| Survived         | Survived      | [19]      | 2001            |
| Age | Onset of symptoms | Mode of delivery | Maternal outcome | Fetal outcome | Reference | Publication year |
|-----|------------------|-----------------|-----------------|--------------|-----------|-----------------|
| 33  | 18 h             | Vaginal delivery | Survived        | Survived     | [19]      | 2001            |
| 28  | 20 h             | Vaginal delivery | Died            | Survived     | [33]      | 1993            |
| 25  | 20 h             | Vaginal delivery | Survived        | Died         | [27]      | 1993            |
| 21  | 24 h             | Vaginal delivery | Died            | Survived     | [34]      | 1996            |
| 17  | 24 h             | Vaginal delivery | Survived        | Survived     | [35]      | 1999            |
| NG  | 24 h             | Vaginal delivery | Survived        | NG           | [19]      | 2001            |
| 26  | 24 h             | NG               | Survived        | NG           | [26]      | 2008            |
| 34  | 24 h             | Cesarean section | Died            | Survived     | [37]      | 2008            |
| 26  | 24 h             | NG               | Died            | Survived     | 8         | 2015            |
| 28  | 24 h             | Vaginal delivery | Survived        | NG           | [38]      | 2017            |

**Time of onset 1–2 days (n = 14)**

| Age | Onset of symptoms | Mode of delivery | Maternal outcome | Fetal outcome | Reference | Publication year |
|-----|------------------|-----------------|-----------------|--------------|-----------|-----------------|
| 28  | 29 h             | Vaginal delivery | Survived        | Survived     | [39]      | 2008            |
| 39  | 30 h             | Vaginal delivery | Died            | Survived     | [40]      | 2013            |
| 34  | 36 h             | Vaginal delivery | Survived        | NG           | [22]      | 2017            |
| 27  | 2 days           | Vaginal delivery | Survived        | Survived     | [41]      | 1992            |
| 36  | 2 days           | Vaginal delivery | Survived        | Survived     | [42]      | 1995            |
| 29  | 2 days           | Vaginal delivery | Survived        | Survived     | [43]      | 1996            |
| 26  | 2 days           | Vaginal delivery | Survived        | Survived     | [44]      | 2003            |
| 31  | 2 days           | Vaginal delivery | Survived        | NG           | [45]      | 2005            |
| 35  | 2 days           | Cesarean section | Survived        | Survived     | [47]      | 2009            |
| 24  | 2 days           | Vaginal delivery | Survived        | NG           | [10]      | 2013            |
| 27  | 2 days           | Vaginal delivery | Survived        | NG           | [10]      | 2013            |
| 31  | 2 days           | Vaginal delivery | Survived        | NG           | [48]      | 2013            |
| 28  | 2 days           | Vaginal delivery | Survived        | NG           | [38]      | 2017            |

**Time of onset 3–4 days (n = 14)**

| Age | Onset of symptoms | Mode of delivery | Maternal outcome | Fetal outcome | Reference | Publication year |
|-----|------------------|-----------------|-----------------|--------------|-----------|-----------------|
| 36  | 3 days           | Vaginal delivery | Survived        | Survived     | [49]      | 1993            |
| NG  | 3 days           | Vaginal delivery | Survived        | Survived     | [50]      | 2002            |
| NG  | 3 days           | Vaginal delivery | Died            | Survived     | [50]      | 2002            |
| 22  | 3 days           | Vaginal delivery | Survived        | NG           | [51]      | 2009            |
| 29  | 3 days           | Cesarean section | Died            | Survived     | [40]      | 2013            |
| 22  | 3 days           | Vaginal delivery | Survived        | NG           | [38]      | 2017            |
| 37  | 3 days           | Vaginal delivery | Survived        | NG           | [22]      | 2017            |
| 25  | 4 days           | Vaginal delivery | Survived        | Survived     | [52]      | 1991            |
| 14  | 4 days           | Vaginal delivery | Survived        | Survived     | [53]      | 1993            |
| 27  | 4 days           | Vaginal delivery | Died            | NG           | 9         | 1996            |
| 30  | 4 days           | Vaginal delivery | Survived        | NG           | [54]      | 2001            |
| NG  | 4 days           | Vaginal delivery | Survived        | Survived     | [36]      | 2001            |
| 29  | 4 days           | NG               | Survived        | NG           | [26]      | 2008            |
| 37  | 4 days           | Vaginal delivery | Survived        | Survived     | [55]      | 2015            |

**Time of onset 5–7 days (n = 6)**

| Age | Onset of symptoms | Mode of delivery | Maternal outcome | Fetal outcome | Reference | Publication year |
|-----|------------------|-----------------|-----------------|--------------|-----------|-----------------|
| 39  | 5 days           | Vaginal delivery | Survived        | Survived     | [56]      | 2001            |
| 30  | 5 days           | Vaginal delivery | Survived        | NG           | [57]      | 2008            |
| 35  | 5 days           | Vaginal delivery | Died            | NG           | [22]      | 2017            |
| 37  | 6 days           | Vaginal delivery | Survived        | NG           | 9         | 1996            |
| 22  | 7 days           | Vaginal delivery | Survived        | Survived     | [41]      | 1992            |
| 27  | 7 days           | Vaginal delivery | Survived        | NG           | [10]      | 2013            |

**Time of onset ≥8 days (n = 6)**

| Age | Onset of symptoms | Mode of delivery | Maternal outcome | Fetal outcome | Reference | Publication year |
|-----|------------------|-----------------|-----------------|--------------|-----------|-----------------|
| 20  | 8 days           | Vaginal delivery | Survived        | NG           | [19]      | 2001            |
| 26  | 13 days          | Cesarean section | Survived        | NG           | [58]      | 2003            |
| 23  | 14 days          | Vaginal delivery | Survived        | Survived     | [59]      | 1990            |
| 36  | 22 days          | NG               | Survived        | NG           | [26]      | 2008            |
| 23  | 3 weeks          | Cesarean section | Survived        | Survived     | [60]      | 1984            |
| 27  | 5 weeks          | Vaginal delivery | Survived        | Survived     | [61]      | 2005            |

Bold characters indicate cases that we experienced. and GAS, group A streptococcal; GW, gestational weeks; NG, not given.
| Characteristics of GAS infection                                      | No. (%) of patients with the indicated feature | P-value |
|---------------------------------------------------------------------|-----------------------------------------------|---------|
|                                                                      | Antenatal (n = 25)                             |         |
|                                                                      | Postnatal (n = 73)                             |         |
| Age, ≤19 or ≥35 years                                               | 15 / 23 (65.2)                                 |         |
|                                                                      | 15 / 63 (23.8)                                 | 0.000*  |
| Multiparous                                                         | 13 / 17 (76.5)                                 |         |
|                                                                      | 35 / 45 (77.8)                                 | 0.580   |
| Onset during hospitalization                                        | 1 / 25 (4.0)                                   |         |
|                                                                      | 26 / 65 (40.0)                                 | 0.001†   |
| Mode of delivery                                                    |                                               |         |
| Vaginal delivery                                                    | 13 / 20 (65.0)                                 |         |
|                                                                      | 54 / 62 (87.1)                                 | 0.034** |
| Cesarean section                                                    | 7 / 20 (35.0)                                  |         |
|                                                                      | 8 / 62 (12.9)                                  |         |
| Initial symptoms                                                    |                                               |         |
| Fever, chills, full-like symptoms                                   | 16 / 24 (66.7)                                 |         |
|                                                                      | 45 / 60 (75.0)                                 | 0.439   |
| Nausea, vomiting, diarrhea                                          | 7 / 24 (29.2)                                  |         |
|                                                                      | 5 / 60 (8.3)                                   | 0.020** |
| Abdominal pain                                                      | 6 / 24 (25.0)                                  |         |
|                                                                      | 8 / 60 (13.3)                                  | 0.165   |
| Clinical features                                                   |                                               |         |
| Fever (≥38.0°C)                                                     | 11 / 19 (57.9)                                 |         |
|                                                                      | 26 / 57 (45.6)                                 | 0.354   |
| Hypotension (systolic pressure ≤ 90 mmHg)                          | 10 / 19 (52.6)                                 |         |
|                                                                      | 26 / 57 (45.6)                                 | 0.596   |
| Tachycardia (≥100 beats per min)                                    | 11 / 19 (57.9)                                 |         |
|                                                                      | 31 / 57 (54.4)                                 | 0.790   |
| Leukocytosis (WBC count >11,000/mm³)                                | 4 / 19 (21.1)                                  |         |
|                                                                      | 20 / 57 (35.1)                                 | 0.254   |
| Uterine tenderness                                                  | 3 / 19 (15.8)                                  |         |
|                                                                      | 17 / 57 (29.8)                                 | 0.229   |
| Abnormal vaginal discharge                                          | 2 / 19 (10.5)                                  |         |
|                                                                      | 20 / 57 (35.1)                                 | 0.041†   |
| Erythema                                                           | 3 / 19 (15.8)                                  |         |
|                                                                      | 15 / 57 (26.3)                                 | 0.273   |
| Extremity pain                                                      | 2 / 19 (10.5)                                  |         |
|                                                                      | 13 / 57 (22.8)                                 | 0.207   |
| Sore throat + CENTOR, ≥2                                            | 4 / 11 (36.4)                                  |         |
|                                                                      | 4 / 6 (66.7)                                   | 0.247   |
| Pharmacological interventions                                       |                                               |         |
| Antibiotic treatment                                                | 19 / 21 (90.5)                                 |         |
|                                                                      | 67 / 68 (98.5)                                 | 0.137   |
| Immunoglobulin (IVIG)                                               | 4 / 21 (19.0)                                  |         |
|                                                                      | 4 / 68 (5.9)                                   | 0.085   |
| Surgical interventions                                              |                                               |         |
| Debridement, drainage and/or amputation of extremities              | 1 / 21 (4.8)                                  |         |
|                                                                      | 11 / 43 (25.6)                                 | 0.041** |
| Exploratory surgery (laparotomy)                                    | 5 / 21 (23.8)                                 |         |
|                                                                      | 26 / 43 (60.5)                                 | 0.006*  |
| Hysterectomy                                                        | 4 / 21 (19.0)                                  |         |
|                                                                      | 20 / 43 (46.5)                                 | 0.033*  |
| Surgical findings                                                   |                                               |         |
| Ascites or pus in the peritoneal cavity (included peritonitis)      | 3 / 5 (60.0)                                  |         |
|                                                                      | 8 / 12 (66.7)                                  | 0.793   |
| Necrosis, inflammation, or exudate present in the uterus, ovaries   | 4 / 6 (66.7)                                  |         |
| and/or fallopian tubes                                              | 20 / 22 (90.9)                                 | 0.191   |
| Normal placenta, uterus and/or pelvic organs                        | 2 / 6 (33.3)                                  |         |
|                                                                      | 2 / 22 (9.1)                                   | 0.191   |
| Bacterial sources                                                   |                                               |         |
| Urine                                                               | 0 / 22 (0.0)                                  |         |
|                                                                      | 9 / 72 (12.5)                                  | 0.080   |
| Cervix, vagina, lochia                                              | 9 / 22 (40.9)                                 |         |
|                                                                      | 40 / 72 (55.6)                                 | 0.229   |
| Peritoneum (ascites)                                                | 2 / 22 (9.1)                                  |         |
|                                                                      | 11 / 72 (15.3)                                 | 0.368   |
| Oropharynx or respiratory system                                    | 5 / 22 (22.7)                                 |         |
|                                                                      | 4 / 72 (5.6)                                   | 0.030** |
| Blood                                                               | 16 / 22 (72.7)                                 |         |
|                                                                      | 45 / 72 (62.5)                                 | 0.379   |
| CNS system                                                          | 1 / 22 (4.5)                                  |         |
|                                                                      | 1 / 72 (1.4)                                   | 0.415   |
| Maternal outcome                                                    |                                               |         |
| Survived                                                            | 10 / 25 (40.0)                                 |         |
|                                                                      | 61 / 73 (83.6)                                 | 0.000†  |
| Died                                                                | 15 / 25 (60.0)                                 |         |
|                                                                      | 12 / 73 (16.4)                                 |         |
| Fetal outcome                                                       |                                               |         |
| Survived                                                            | 7 / 25 (33.3)                                  |         |
|                                                                      | 41 / 43 (95.3)                                 | 0.000†  |
| Died                                                                | 14 / 25 (66.7)                                 |         |
|                                                                      | 2 / 43 (4.7)                                   |         |

A two-tailed paired Pearson’s chi-square test with α = 0.05, yielded a statistically significant P-value. Actual values were noted in the table. A one-tailed paired Fisher’s exact test with α = 0.05 yielded a statistically significant P-value. Actual values were noted in the table. 

Data were extracted as follows:

1. A valid negative finding was recorded when at least one other positive or negative finding was reported for a specific category.
2. Data were recorded as missing when there were no findings reported for the category.
3. Cases in which a vasopressor was administered were recorded as having a ‘systolic pressure <90 mmHg’.
4. When numerical values were reported, the terms were defined as follows: fever, body temperature ≥ 37.5°C; hypotension, systolic pressure < 90 mmHg; tachycardia, heart rate ≥ 100 beats per minute; tachypnea, respiratory rate > 20 breaths per minute; shock, systolic pressure < 90 mmHg and heart rate ≥ 100 beats per minute.
5. Thus ‘fever’ could not be stratified as either ≥38.0°C or ≥39.0°C.; 6. Missing data were excluded from the analysis. They were also excluded from each denominators.

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Materials and Methods

Data extraction

English-language clinical reports describing antenatal and postnatal GAS infection between 1974 and 2019 were examined according to a PubMed database search using ‘pregnancy’ and ‘group A streptococcus’ as search terms.

Because data were incomplete in some of the published reports, we used the following definitions: Data were defined as a valid ‘negative’ finding when at least one finding, whether positive or negative, was reported for another item in the same category. Conversely, data were defined as ‘missing’ when no findings were reported for the category as a whole. For example, if abdominal pain was not reported as an initial symptom in a clinical report, abdominal pain was defined as ‘negative’ if at least one other initial symptom was reported, while abdominal pain was defined as ‘missing’ if no initial symptoms were reported. Missing data were not included in the analysis. Among the data collected, quick sepsis-related organ failure assessment (qSOFA) score and CENTOR score (Cough absent, Exudate, Nodes, Temperature, young OR old modifier: a widely used diagnostic score for GAS pharyngitis) were dependent variables, whereas the other variables were independent variables. Cases in which vasopressor information was given were defined as ‘systolic pressure <90 mmHg’. In the absence of actual numerical values, these terms were defined as follows: fever, body temperature ≥37.5°C; hypotension, systolic pressure <90 mmHg; tachycardia, heart rate ≥100 beats per minute; tachypnea, respiratory rate >20 breaths per minute; shock, systolic pressure <90 mmHg and heart rate ≥100 beats per minute. Therefore, only the definition of the term ‘fever’ itself was not clearly achieved either as ≥38.0°C or ≥39.0°C. Cases in which the indicated clinical feature was not reported (i.e. missing) were not included in subsequent calculations.

Table 3 Clinical risk factors for perinatal GAS infection (univariate analysis)

| Characteristics                  | Maternal outcome | P-value |
|----------------------------------|------------------|---------|
|                                  | Survived (n = 71) | Died (n = 27) |
| Antenatal onset                  |                  |          |
| Age, ≤19 or ≥35 years            | 10 (14.1)        | 15 (55.6) | 0.000* |
| Multiparous                      | 33 (76.7)        | 15 (78.9) | 0.015* |
| Cesarean section                 | 8 (13.1)         | 7 (33.3)  | 0.045**|
| Onset during hospitalization     | 20 (31.3)        | 7 (26.9)  | 0.685  |
| Sore throat + qSOFA, ≥2          | 6 (60.0)         | 2 (28.6)  | 0.218  |
| qSOFA score, ≥2                  | 11 (19.3)        | 10 (58.8) | 0.003**|
| No surgical intervention         | 14 (28.6)        | 12 (63.2) | 0.008  |
| Positive blood culture           | 43 (62.3)        | 18 (72.0) | 0.385  |

*A two-tailed paired Pearson’s chi-square test (α = 0.05) performed on this data yielded a statistically significant P-value. Actual values were noted in the table.*

| Characteristics                  | Maternal outcome | OR     | 95% CI | P      |
|----------------------------------|------------------|--------|--------|--------|
|                                  | Survived (n = 71) | Died (n = 27) |
| Antenatal onset                  |                  |        |        |        |
| qSOFA score, ≥2                  | 10 (14.1)        | 15 (55.6) | 7.922  | 1.297–48.374 | 0.025* |
| No surgical intervention         | 11 (19.3)        | 10 (58.8) | 6.166  | 1.066–35.670 | 0.042* |
| Age, ≤19 or ≥35 years            | 14 (28.6)        | 12 (63.2) | NG     | NG     |
| Cesarean section                 | 8 (13.1)         | 7 (33.3)  | NG     | NG     |

*Logistic regression analysis (α = 0.05) identified that antenatal onset and a qSOFA score of ≥2 were to be independent risk factors associated with maternal death in perinatal GAS infection. Numerical values were defined as n (%), and cases in which the indicated feature was not reported were not included in calculations. and CI, confidence interval; GAS, group A streptococcal; qSOFA, quick sequential organ failure assessment.

Statistical analysis

The above data were analyzed with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp.). The following tests were used for comparison: Shapiro-Wilk test for the distribution of variables, Student t-test for normally distributed variables, Mann–Whitney U test for non-normally distributed variables; two-tailed Pearson’s chi-square test and one-tailed Fisher’s exact test for categorical variables; multivariate logistic
regression analysis for regression analysis. The level of significance adopted was 5% (α = 0.05).

Ethical approval
This study was approved by the ethical board at Saitama Medical Center (registration number: 2233).

Results
We included a total of 98 patients reported over a long time period (45 years) (Table 16-61). Patient characteristics were compared between antenatal and postnatal GAS infection groups (Table 2). Of the 98 patients included, 25 were antenatal and 73 were postnatal infections. On univariate analysis, the antenatal GAS infection had a significant association with an age of ≤19 or ≥35 years, cesarean section, sore throat as an initial symptom, positive throat culture, maternal death and fetal death. In contrast, the postnatal GAS infection had a significant association with onset during hospitalization, abnormal vaginal discharge and any surgical interventions.

Univariate analysis was used to test the relationship between the maternal outcome and several clinical characteristics assumed to be potential risk factors (Table 3). Five clinical characteristics: antenatal onset, age of ≤19 or ≥35 years, cesarean section, qSOFA score of ≥2 and no surgical interventions were significantly associated with maternal death on univariate analysis. Next, multivariate analysis was performed with the abovementioned five clinical characteristics (Table 4). Antenatal onset and a qSOFA score of ≥2 were significantly and independently associated with maternal death (odds ratio [OR] = 7.922, 95% confidence interval [CI] = 1.297–48.374; P = 0.025, and OR = 6.166, 95% CI = 1.066–35.670; P = 0.042, respectively).

Discussion
Antenatal onset and a qSOFA score of ≥2 were significantly associated with maternal death in our study. In the literature, Hamilton et al. reported the largest number of cases of perinatal GAS infections (67 patients, including 10 with antenatal infection) and noted that GAS infection during the third trimester was associated with maternal and fetal death, whereas we reported a total of 98 patients, including 25 with antenatal infection. Of particular interest is the comparison between clinical characteristics and maternal outcome by multivariate analysis, which was not attempted in previous reports. Furthermore, few reports have included CENTOR criteria, defined as Cough absent, Exudate, Nodes, Temperature, young OR old modifier, and the qSOFA score as a clinical characteristic. Only Tanaka et al. examined the qSOFA score in maternal death cases.

Why was antenatal GAS infection associated with poor maternal outcomes? Compared with postnatal cases, antenatal infections had initial symptoms outside of the hospital and the initiation of treatment might have been delayed. Generally, potentially invasive surgical treatment often makes physicians hesitant to operate upon pregnant patients.

Second, we assume there may be several types of perinatal GAS infection depending on the infection route, as well as the initial infection site. However, as is mentioned in previous article, it is difficult to elucidate the route of infection of GAS, and we were not able to extract valid data from articles.

We next investigated potential indicators of risk that could be used to suspect a perinatal GAS infection in pregnant women. Although the CENTOR criteria is a diagnostic criterion for GAS pharyngitis and the qSOFA score is that for sepsis, we assumed that these criteria can be used for the detection of perinatal GAS infection. However, because of the limited data availability, we were not able to examine the sensitivity in this study. In antenatal cases, all the criteria in the qSOFA score (systolic pressure < 100 mmHg, respiratory rate > 22 breaths per minute and altered mental status) were available in 15 cases. Of these, 13 cases (86.7%) satisfied one or more criteria in qSOFA. Thus, we suggest that medical resources should be provided earlier to pregnant women who feel ill, and medical providers should triage using the qSOFA score. If a patient is positive for any of the qSOFA criteria, she should be immediately referred to a critical care medical center. Further study should be done because of the limited number of cases in this study.

There were some other limitations to our study that should be considered. Because patients from a wide time period were included, patients from a more recent chronological timeframe may have experienced better outcomes than those from an earlier chronological period. However, the maternal outcome was not related to the published year of the case report (P = 0.363, Mann Whitney U test). Since most cases did not fully describe all the data we required.
(respiratory rate, in particular) for the study, we were not able to exclude the possibility of selection bias. In addition, our two cases are not definite cases, but probable cases according to the definition of Streptococcal toxic shock syndrome. Likewise, our analyses included the other 28 probable cases extracted from past articles.

In conclusion, antenatal GAS infection is more critical than postnatal GAS infection, and a qSOFA score of ≥2 is also potentially critical. We suggest that the presence of any of the qSOFA signs may represent a useful clinical marker for antenatal GAS infection among patients presenting at primary obstetric facilities.

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Disclosure

The authors report no conflict of interest.

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