CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

High fibrin/fibrinogen degradation product and D-dimer levels for the diagnosis of invasive group A streptococcal infections during pregnancy

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Summary

Objective: Invasive group A streptococcal (GAS) infections during pregnancy are uncommon, and, thus, their early diagnosis remains challenging. The present study was performed to assess fibrin/fibrinogen degradation product (FDP) and D-dimer levels in pregnant women with invasive GAS infections and establish whether they contribute to a diagnosis. *Materials and Methods:* Laboratory data, including FDP and D-dimer levels, measured between fulmination and just before delivery in 46 cases, consisting of 45 previously published cases and the present case, were examined. *Results:* Fetal/neonatal and maternal mortality rates were 61 and 28%, respectively. Laboratory data obtained from 24 cases just before delivery were as follows: white blood cell count $\geq$ 12,000/μL, 46% of cases; platelet count $\leq$ 100,000/μL, 55% of cases, and C-reactive protein (CRP) level $\geq$ 10 mg/dL, 40% of cases. These variables showed no sensitivity for the diagnosis of invasive GAS infections. However, 100% of cases were positive for FDP ($\geq$ 10 μg/dL) and D-dimer ($\geq$ 2 μg/dL), the levels of which were extremely high in many cases. *Conclusion:* FDP and D-dimer levels may contribute to the diagnosis of invasive GAS infections during pregnancy.

Key words: Antepartum; Disseminated intravascular coagulation; Sepsis; *Streptococcus pyogenes*; Toxic shock syndrome.

Introduction

Perinatal invasive group A streptococcal (GAS) infections, which include perinatal GAS-induced toxic shock syndrome, mainly occur in puerperal women. Although these infections are rare in antenatal women, poorer outcomes have been reported for antenatal cases than for puerperal cases [1]. Therefore, early awareness and the rapid initiation of therapy are important for the management of pregnant women with invasive GAS infections [2]. However, since the primary symptoms appear to be flu-like, an early diagnosis remains challenging for clinicians.

We herein describe a case of invasive GAS infection during pregnancy, in which the baby and mother both survived [3]. In brief, the patient was 41 years old, para 1, and on her 39^{th} week of pregnancy. She presented with chills and a fever (38 °C). Fetal tachycardia was noted and, thus, she was admitted for observation. Her laboratory data on admission were as follows: white blood cell count of 8,200/μL, C-reactive protein (CRP) level of 0.52 mg/dL, and normal levels in other tests, except for very high plasma fibrin/fibrinogen degradation product (FDP) and D-dimer levels of 193 and 75 μg/dL, respectively. Intravenous antibiotics were administered for the febrile condition with no detected infection. Although the patient was not in a state of shock, cardiotocography indicated that the condition of the fetus was deteriorating. Emergency cesarean section was performed, and the baby was born without neonatal asphyxia or any infection. Although the patient developed septic shock after the procedure, she was successfully treated and, as a result, fully recovered. Since her blood culture indicated GAS infection, she was diagnosed with invasive GAS infection during pregnancy.

This case prompted speculation on FDP and D-dimer levels in other patients with similar conditions. Therefore, the present study investigated FDP and D-dimer levels in pregnant women with invasive GAS infections and whether they may contribute to a diagnosis.

Materials and Methods

Forty-five cases of invasive GAS infection during pregnancy from studies published in English or Japanese between 2000 and 2017 were identified [4-40]. Cases in which individual clinical data were not available were excluded. The literature search included PubMed, the Japana Centra Revuo Medicina, and reference lists of previously published cases. The search terms used included: 'group A streptococcus', '*Streptococcus pyogenes*', 'infection', 'pregnancy', 'perinatal', 'peripartum', 'antenatal', 'antepartum', 'intrapartum', 'delivery', 'labor', 'abortion', 'toxic shock', 'bacteremia', 'sepsis', and 'disseminated intravascular coagulation'.

The criteria for invasive GAS infections during preg-

Table 1. — *Summary of categorical data for clinical background, symptoms, outcomes and therapies from the 46 cases.*

Factor	n	%
Maternal age (y)		
Teens	1	2.2
Twenties	9	19.6
Thirties	32	69.6
Forties	4	8.7
Parity		
Nulliparous	8	19.4
Multiparous	37	80.6
NA	1	
Maternal complications		
Yes	10	24.4
No	31	75.6
NA	5	
Week of pregnancy at fulmination		
Abortion period (< 22 weeks)	5	10.9
Second trimester (22-27 weeks)	4	8.7
Third trimester before term (28-36 weeks)	18	39.1
Term (≥ 37 weeks)	19	41.3
Fulmination period		
Antenatal (before the onset of labor)	45	97.8
During labor	1	2.2
Mode of delivery		
Emergency cesarean	22	47.8
Vaginal delivery	17	37
Abortion	4	8.7
None (maternal death before delivery)	3	6.5
Mortality		
Fetal/neonatal death	28	60.9
Maternal death	13	28.3
Fetal/neonatal asphyxia (including death)		
Yes	34	91.9
No	3	8.1
NA	9	
Symptoms at fulmination period (some are overlapping)		
Fever (>38 °C)	44	95.7
Respiratory symptoms	20	43.5
Abdominal pain	32	69.6
Gastrointestinal symptoms	17	37
Abnormally strong uterine contractions	20	43.5
Unconsciousness	5	10.9
Administration of antibiotics		
Yes	40	88.9
No	5	11.1
NA	1	
Administration of immunoglobulin		
Yes	20	44.4
No	25	55.6
NA	1	
Blood transfusion		
Yes	24	58.5
No	17	41.5
NA	5	

NA, not available.

Table 2. — *Summary of laboratory test values in the 24 available cases whose laboratory tests were carried out during fulmination and just before delivery.*

Item	n	%	Median	Range
White blood cell count (/μL)			12,490	1,970-45,200
≥ 12,000	11	45.8		
< 12,000	13	54.2		
NA	0			
Hemoglobin concentration (g/dL)			11.4	6.7-13.4
≤ 8	1	7.1		
> 8	13	92.9		
NA	10			
Platelet count (/μL)			96,000	5,000-421,000
≤ 100,000	11	55		
> 100,000	9	45		
NA	4			
AST (U/L)			44.5	15-198
≥ 80	3	37.5		
< 80	5	62.5		
NA	16			
Serum creatinine (mg/dL)			0.87	0.57-1.77
≥ 1.2	4	36.4		
< 1.2	7	63.6		
NA	13			
C-reactive protein (mg/dL)			6.2	0.3-28.2
≥ 10	8	40		
< 10	12	60		
NA	4			
Fibrinogen (mg/dL)			130	18-720
≤ 100	4	44.4		
> 100	5	55.6		
NA	15			
FDP (μg/mL)			352	31-1,920
Strong positive (≥ 40)	6	85.7		
Positive (≥ 10)	7	100		
Negative (< 10)	0	0		
NA	17			
D-dimer (μg/mL)			75	2.0-444
Strong positive (≥ 10)	3	60		
Positive (≥ 2)	5	100		
Negative (< 2)	0	0		
NA	19			

AST, aspartate aminotransferase; FDP, fibrin/fibrinogen degradation product; NA, not available.

nancy were as follows. Each case needed to have GAS infection that was identified through a bacterial culture or rapid antigen detection test (RADT) at some time point during the clinical course. The fulmination period needed to be before delivery or abortion. Cases had to have the criteria for streptococcal toxic shock syndrome [41] or a similar clinical course to that defined by Udagawa [42]. Udagawa advocates and defines invasive GAS infection during pregnancy (perinatal-type invasive GAS infection) as a rapidly progressive infectious and septic condition that causes severe morbidity and mortality of the mother and fetus/neonate through abnormally strong uterine contractions and rushed delivery induced by uterine myometrial hematogenous infection from a remote original GAS infectious focus, such as the upper respiratory tract.

Forty-six cases, including the present case, were reviewed. The clinical background, morbidity and mortality, administration of antibiotics and immunoglobulin, and laboratory data measured between fulmination and just before delivery were extracted and analyzed to assess sensitivity for the disease. Disease fulmination was defined as the period in which fever develops (38 °C or higher, in principle). In two cases [23, 34], both of whom died as a result of the disease, fulmination was regarded as the period of

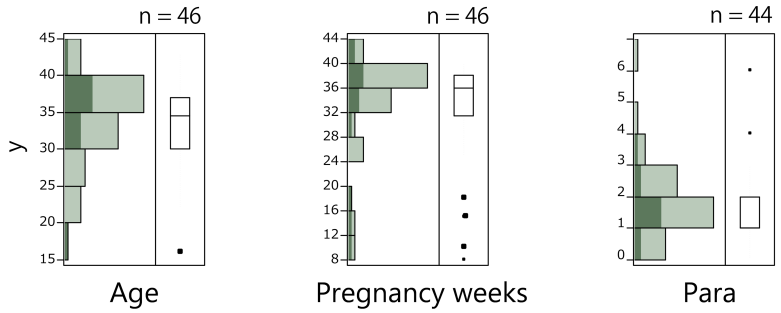

Figure 1. — Histograms of continuous clinical background data from 46 cases of invasive group A streptococcal (GAS) infections during pregnancy. The mean maternal age was 34.5 years, the mean week of pregnancy at fulmination was 36 weeks, and mean parity was 1. (Areas with a deep color indicate maternal death).

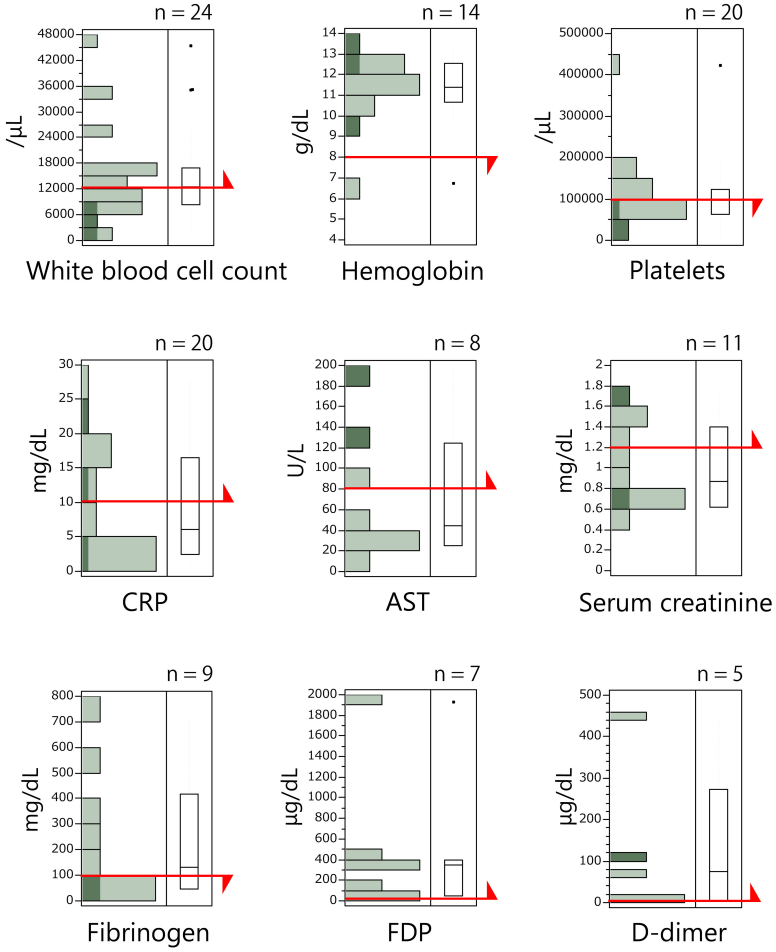

Figure 2. — Histograms for laboratory data from 24 available cases in which laboratory tests were performed between fulmination and just before delivery. Positive fibrin/fibrinogen degradation product (FDP) ($\geq$ 10 μg/dL) and positive D-dimer ($\geq$ 2 μg/dL) each had 100% sensitivity. Strong positive FDP ($\geq$ 40 μg/dL) and strong positive D-dimer ($\geq$ 10 μg/dL) had sensitivities of 86 and 60%, respectively. (Each red horizontal bar indicates the cut-off value defined as an apparently abnormal level that needs clinical intervention. Each arrow indicates an abnormal direction. Areas with a deep color indicate maternal death).

abnormally strong uterine contractions (no body temperature data were available for these cases in the literature). During the analysis of laboratory data, cut-off values for each item were defined as apparently abnormal levels that need clinical intervention. FDP and D-dimer cut-off values were defined as two steps. Accordingly, two cut-off values were defined for FDP ($\geq$ 10 μg/dL and $\geq$ 40 μg/dL) and D-dimer ($\geq$ 2 μg/dL and $\geq$ 10 μg/dL) based on the literature for normal ranges from maternal laboratory data [43, 44], disseminated intravascular coagulation (DIC) diagnos-

tic criteria by the Japanese Ministry of Health, Labour and Welfare [45, 46], and obstetrical DIC scoring [47].

Results

The mean maternal age was 34.5 years (range, 16 to 43 years), the mean week of pregnancy at fulmination was 36 weeks (range, 8 to 40 weeks), and mean parity was 1 (range, 0 to 6) (Figure 1). The duration from fulmination to maternal death was one day or less in eight (67%) cases, two days in two (17%), and three days or more in two (17%). Clinical backgrounds, symptoms, therapies, and fetal/neonatal and maternal mortalities are categorically summarized in Table 1. There were more multiparous than nulliparous women, while the majority of women (76%) had no maternal complications. Among the cases included, 80% developed GAS infection in the third trimester and 41% at term, whereas 11% developed GAS infection during the abortion period. The fulmination period in all cases was before the onset of labor, except in one case in which the disease fulminated during labor. Among the cases included, 7% died before delivery or abortion. Maternal and fetal/neonatal death rates were 28% and 61%, respectively. Despite the exclusion of abortion cases, fetal/neonatal asphyxia or fetal/ neonatal deaths were frequently observed, such that only 8% of cases presented with no fetal/neonatal asphyxia. The majority of cases (89%) received antibiotics, whereas only 44% received immunoglobulin.

Laboratory data measured between fulmination and just before delivery were available for 24 cases [6, 8, 10-12, 15, 17, 18, 22, 25, 26, 28-30, 32, 35, 37-40]. A summary of the data obtained and histograms to assess distributions are shown in Table 2 and Figure 2, respectively. Regarding laboratory data, 46% of cases had a white blood cell count $\geq$ 12,000/μL, 7% had a hemoglobin concentration $\leq$ 8 g/dL, 55% had a platelet count $\leq$ 100,000/μL, 38% had an aspartate aminotransferase level $\geq$ 80 U/L, 36% had a serum creatinine level $\geq$ 1.2 mg/dL, 40% had a CRP level $\geq$ 10 mg/dL, and 44% had a fibrinogen level $\leq$ 100 mg/dL. On the other hand, positive FDP ($\geq$ 10 μg/dL) and positive D-dimer ($\geq$ 2 μg/dL) both had 100% sensitivity for detecting invasive GAS infections during pregnancy with minimum scores of 31 μg/dL and 2.0 μg/dL, respectively. Moreover, strong positive FDP ($\geq$ 40 μg/dL) and strong positive D-dimer ($\geq$ 10 μg/dL) had sensitivities of 86% and 60%, respectively, for detecting invasive GAS infections during pregnancy. Furthermore, in many cases, the levels of these parameters were extremely high, as shown in Figure 2.

Discussion

The present study provides a summary of clinical backgrounds, symptoms, therapies, and severe outcomes among pregnant women with invasive GAS infections. The results of laboratory tests performed between fulmination and just before delivery showed that FDP and D-dimer may be supportive laboratory tests for an early diagnosis of invasive GAS infections during pregnancy in clinical practice.

Severe outcomes of invasive GAS infections during pregnancy were identified and consistent with previous findings [2]. The epidemiological finding of multiparous women being dominant and the results of the present case indicated that a patient's children may be one of the factors affecting the spread of GAS infection. The fulmination period was commonly observed during the third trimester, including term, but was also observed during the early weeks of pregnancy in several cases. The majority of cases (89%) had received antibiotics. However, in almost 40% of reviewed cases (17 out of 43 cases in which the period of antibiotic initiation was known) [4, 7-12, 14-17, 19, 21, 23-25, 27, 29, 31-33, 37, 39], the initiation of antimicrobial therapy was considered to be late. The present results indicated that inadequate management was attributed to circumstances wherein clinicians initially misdiagnosed patients with a viral infection, such as influenza, while occasionally lacking the insight to anticipate the probability of any bacterial infectious conditions, including GAS infections.

In the present study, laboratory data from tests performed between fulmination and just before delivery were available for 24 cases. However, the interpretation of these data was associated with the following limitations. The condition of patients upon blood sampling varied from febrile to almost septic and/or DIC. Furthermore, data availability was limited, such that only seven cases for FDP [3, 10, 11, 15, 22, 37] and five for D-dimer [3, 11, 18, 22, 30] were available for analysis. In addition, negative data may have been omitted from each publication. Therefore, laboratory data were analyzed and interpreted in consideration of these limitations. Moreover, data for pregnant women with febrile conditions, except for those with GAS infections, were unavailable. Therefore, the sensitivity of each laboratory test item was only estimated. The percentages of items over the cut-off value, which affects sensitivity, are shown in Table 2. Accordingly, positive FDP ($\geq$ 10 μg/dL) and positive D- dimer ($\geq$ 2 μg/dL) each had 100% sensitivity, while strong positive FDP ($\geq$ 40 μg/dL) and strong positive D-dimer ($\geq$ 10 μg/dL) had sensitivities of 86% and 60%, respectively. Moreover, high sensitivity implies a high negative predictive value. Therefore, strong positive FDP/D-dimer test results indicate invasive GAS infections in pregnancy, whereas negative FDP/D-dimer test results suggest their absence. Based on these results, high FDP/D-dimer levels may alert clinicians to the possibility of GAS infections during pregnancy.

FDP and D-dimer are both small fibrin-containing molecules that may be measured in blood plasma. Since D-dimer is the final product of fibrin degradation, it is smaller than FDP. These clinical laboratory tests are frequently used to diagnose DIC, deep vein thrombosis (DVT), and pulmonary embolism (PE). Moreover, D-dimer is especially regarded as a marker of DVT and PE. Therefore, high D-dimer levels necessitate further testing in order to rule out DVT and PE. In perinatal medicine, DVT is not uncommon. Moreover, since leg DVT and PE generally present with

obvious symptoms, they are harder to overlook. However, rare types of perinatal DVT, such as ovarian vein thrombosis and internal iliac vein thrombosis [48], are uncommon and may be asymptomatic. Therefore, the early diagnosis of these conditions remains challenging. Moreover, in perinatal medical practice, bacterial infections have been shown to pathophysiologically induce DVT [49] and DIC. Thus, when examining a febrile maternal patient with high FDP and/or D-dimer levels, clinicians need to rule out DVT and DIC, including invasive GAS infections.

The RADT for GAS infections of the throat is a diagnostic test that rapidly identifies the presence of GAS infections. The RADT has a fairly high sensitivity of approximately 85% [50]. However, since the primary infectious focus of invasive GAS infections during pregnancy is not always the throat, negative RADT test results do not always rule out invasive GAS infections during pregnancy.

The results of laboratory tests performed between fulmination and just before delivery in 24 cases showed that FDP and D-dimer may contribute to the diagnosis of invasive GAS infections during pregnancy. Despite some limitations inherent to the present study, the results obtained are of potential clinical significance, particularly for the diagnosis of invasive GAS infections during pregnancy. Nevertheless, further studies are needed to confirm the results presented herein.

Ethics Approval and Consent to Participate

The subjects of our case gave her informed consent for inclusion before she participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Matsumoto Women's Health Clinic (approval number: 202001).

Acknowledgments

A summary of this research was presented at the 71^{st} Academic Conference of the Japan Society of Obstetrics and Gynecology, Nagoya, Japan, 2019.

Conflict of Interest

The authors declare no conflict of interest.

Submitted: June 27, 2019
Accepted: September 23, 2019
Published: August 15, 2020

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