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Original Article

The most common causative bacteria in maternal sepsis-related deaths in Japan were group A *Streptococcus*: A nationwide survey☆

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ABSTRACT

The present retrospective study provides an in-depth analysis of the maternal sepsis-related deaths reported in Japan, and aims to guide future care regarding maternal sepsis. This is a nationwide, retrospective, descriptive cohort study. Data were retrospectively analyzed on all maternal death cases related to sepsis reported in Japan from 2010 through 2016. A total of 7,347,727 births and 317 maternal deaths were reported during the study period. The cause of maternal death was sepsis in 24 women (7.5%). Causative bacteria were *Streptococcus pyogenes* (54.2%), *Chlamydia psittaci* (8.3%), *Mycobacterium tuberculosis* (8.3%), *Escherichia coli* (4.2%), *Neisseria meningitidis* (4.2%), Epstein-Barr virus (4.2%), and unknown (16.6%). In maternal death due to *S. pyogenes* (13 women), onset periods ware antepartum in 10 women (76.9%) and postpartum in 3 (23.1%); death within 24 h after hospital admission occurred in 7 women (53.8%); and the median time from hospital admission to death was 12 h (6–744 h). The most common causative bacteria in to maternal sepsis-related death were GAS. When encountering severe sepsis during the peripartum period, we recommend considering severe GAS infection and early intervention.

1. Introduction

In pregnancy, infection has an impact on neonatal outcomes, preterm birth due to intrauterine infection, and neonatal sepsis. At the same time, infection also has an impact on maternal prognosis. Recently, the rate of maternal death related to sepsis has increased in the United States [1]. Those maternal death cases related to sepsis in the USA were analyzed, leading to 3 improvements prompted by obstetricians, namely: recognition of sepsis, administration of appropriate antibiotics, and escalation of care [2]. Although sepsis is the most common direct cause of maternal death in the United Kingdom, its rate has been decreasing [3]. Analysis of those maternal death cases in the UK pointed to delayed diagnosis. Because the clinical symptoms of sepsis are nonspecific, bundles such as the "sepsis six" are recommended within 1 h of sepsis diagnosis [3]. The sepsis six comprises the following steps: (1) take arterial blood gas and give high-flow oxygen if required, (2) take blood cultures, (3) commence intravenous antibiotics, (4) start intravenous fluid resuscitation, (5) take blood for hemoglobin and lactate levels, and (6) measure urine output hourly [3]. In Japan, sepsis is the sixth most common cause of maternal death, and is responsible for one-sixth of all maternal death cases [4]. However, analysis of those maternal death cases related to sepsis, as was conducted in the United States and United Kingdom, is still lacking in Japan [4]. The present retrospective study provides an in-depth analysis of the maternal death

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cases related to sepsis reported in Japan from 2010 through 2016 and aims to guide future care regarding maternal sepsis.

2. Materials and methods

2.1. Design and study population

This retrospective study was conducted on all cases of maternal death related to sepsis reported to the Japan Association of Obstetricians and Gynecologists (JAOG) by Japanese healthcare institutions from January 2010 through December 2016. According to the World Health Organization, maternal death is defined as the death of a woman during pregnancy or within 42 days after the end of pregnancy, due to any factor associated with or aggravated by the pregnancy itself or its management but excluding any accidental or incidental causes. The present study also included cases of late maternal death, defined as the death of a woman from direct or indirect obstetric causes occurring >42 days but <12 months after the end of pregnancy. This study was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center of Japan under the title "Research on a model project regarding surveys and evaluations on maternal mortality in Japan" (receipt No. N18-34).

Since 2010, the clinical information on nearly all cases of maternal death occurring in Japan has been recorded by the JAOG. When a maternal death occurs, the local medical facility documents the case using a detailed standard survey that is submitted to the JAOG of each prefecture [5,6]. Each case is then reviewed by the Maternal Death Exploratory Committee (MDEC), which is chaired by Dr. T. Ikeda (principal author of the present manuscript). This committee consists of 15 obstetricians, 4 anesthesiologists, 2 pathologists, and 1 emergency physician. In addition, several specialists attend monthly review sessions to make annual recommendations that aim to reduce the rate of maternal death in Japan. This study constitutes the first investigation of the rate and characteristics of maternal sepsis-related death in Japan that was conducted by the MDEC.

2.2. Outcomes

Demographic, clinical, and pathologic data available on all reported maternal death cases related to sepsis from 2010 through 2016 were collected from the JAOG database [5,6]. We investigated the causative bacteria in each case. Parameters considered in the analysis were maternal age, stage of pregnancy, reason for admission, body temperature on admission, intrauterine fetal death (IUFD) on admission, and cause of maternal death. We also investigated maternal death cases related to group A *Streptococcus* (GAS).

3. Results

3.1. Characteristics of maternal death cases related to infection

A total of 7,347,727 births and 317 maternal deaths (Rates per 100,000 maternities; 4.3 95%Cl 3.8–4.8) were reported in Japan from January 2010 through December 2016. The cause of maternal death was sepsis in 24 women (7.5%). The causative bacteria are shown in Fig. 1. Most causative bacteria were *Streptococcus pyogenes (GAS)*, as in 13 cases (53.4%).

Maternal characteristics, including age, stage of pregnancy, reason for admission, body temperature on admission, IUFD, and cause of maternal death are shown in Table 1. Most patients were aged 25–34 years (58.3%). Fever and lower abdominal pain accounted for approximately half of the reasons for admission; onset during hospitalization comprised one-fourth of all cases. IUFD occurred in 45.8% of cases. Two cases with tuberculosis died due to asphyxia by spitting up blood.

3.2. Characteristics of maternal death cases related to antepartum group A Streptococcus

Characteristics of maternal death cases related to GAS are shown in Table 2. Median maternal age was 33.5 years (range, 27–40 years). Two cases were primipara (20.0%). Delivery mode was equally divided between vaginal and no delivery. Timing at onset was antepartum in 77% and postpartum in 23%. Gestational age at onset was second trimester in 50% of cases and third trimester in 40%. Seven cases had death occur within 24 h from hospital admission (53.8%). Death within 24 h from hospital admission was significantly increased in the GAS group compared with the non-GAS group (1/12; 9.0%). Death in the antepartum period occurred in nine cases in the GAS group and ten cases in the non-GAS group.

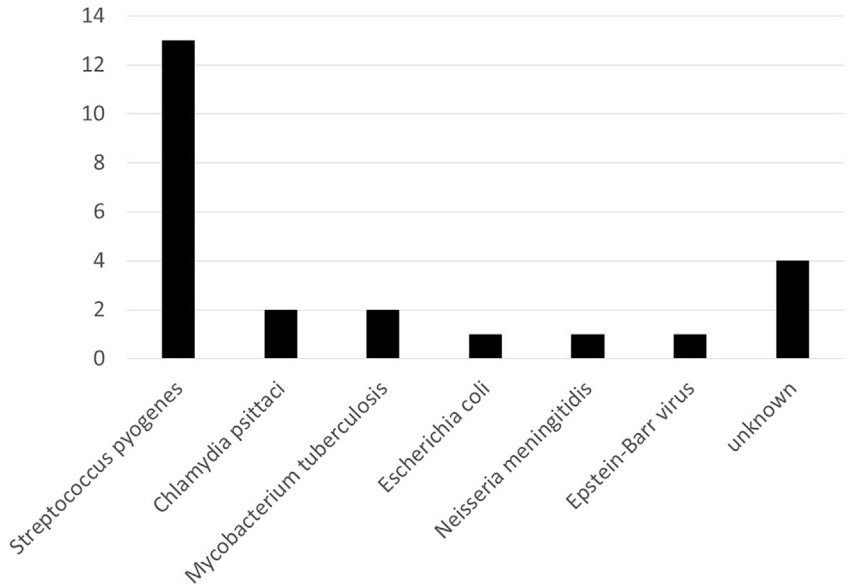

Fig. 1. Causative bacteria of maternal death cases related to infection.

Table 1
Characteristics of maternal death cases related to infection.

Characteristic	N = 24
Age, y	
≤24	1 (4.2)
25–34	14 (58.3)
≥35	9 (37.5)
Stage of pregnancy	
Antepartum	18 (75.0)
Hospitalization for delivery	0 (0)
Postpartum	6 (25.0)
Reason for admission	
Fever	7 (29.2)
Lower abdominal pain	5 (20.8)
Onset during hospitalization	6 (25.0)
Septic shock	1 (4.2)
Disturbed consciousness	3 (8.3)
Respiratory distress	1 (4.2)
Criteria of qSOFA	
Altered mental status	4 (16.7)
Respiratory rate >22 breaths/min	11 (45.8)
Systolic blood pressure <100 mmHg	7 (29.2)
Body temperature on admission	
Normal	6 (25.0)
>38 °C	18 (75.0)
<36 °C	0 (0)
Intrauterine foetal death on admission	11 (45.8)
Cause of maternal death	
Sepsis	22 (91.6)
Asphyxia	2 (8.4)

qSOFA, quick sequential organ failure assessment.
Data are presented as n (%).

In the antepartum GAS group, nine cases experienced IUFD while admitted to hospital (90.0%). In the antepartum non-GAS group, there were two such cases (20.0%).

4. Discussion

We investigated maternal death cases related to sepsis in this study. Three important new findings arose from the present study. First, the most common cause of maternal death related to sepsis was GAS. Second, in more than half of the maternal death cases related to GAS, death occurred within 24 h of hospital admission. Third, the maternal death cases with antepartum GAS had a significantly higher rate of IUFD than did the antepartum non-GAS group.

A recent investigation reported an increased rate of GAS infection in Japan [7]. Average incidence remained at 60 to 70 cases per year but gradually increased in the 2000s to 270 cases in 2014 [7]. In an analysis of genotype, emm 1 was most frequent, while emm 89, emm 12, and emm 28 all increased [7]. GAS genotypes mostly comprise emm 1, emm 89, emm 12, emm 28, emm 3, and emm 9 [7].

Although incidence of GAS infection in Japan has increased compared with the United States during the last 3 decades, it has remained mostly level in recent years [8–12]. In non-pregnant patients, the cause of sepsis is typically *Escherichia coli*, *Staphylococcus aureus*, *Pneumococcal organism*, or *Pseudomonas aeruginosa*. However, the most common cause of sepsis in pregnancy is GAS [13,14]. Interleukins 4, 5, 10, and 13 produced by CD4-positive T lymphocytes increase in pregnancy [15,16]. In streptococcal toxic shock syndrome, the toxin has a direct action on the major histocompatibility complex class II molecule, causing the Th2 cell, as a subtype of CD4-positive T lymphocytes, to activate and increase cytokines [17]. Therefore, T lymphocytes are activated by lower actin levels in pregnancy [17]. This is considered to be the mechanism for having numerous cases of sepsis related to GAS in pregnancy [17].

IUFD during hospital admission was recognized in many maternal death cases in the antepartum GAS group. Fetoplacental circulation is primarily comprised of maternal circulation. Therefore, fetoplacental circulation is greatly influenced by the breakdown of maternal cells, which may cause IUFD. Massive cytokines ("cytokine storm") may cause strong uterine contractions [18]. In streptococcal toxic shock syndrome, massive cytokines are produced by neutrophils and macrophages due to GAS infection, which may lead to strong uterine contractions and subsequent IUFD. Thus, many patients with GAS infection describe symptoms of abdominal pain.

Despite early intervention for GAS infection in pregnancy, most cases deteriorated quickly within 24 h from hospital admission. Therefore, prevention of GAS infection may be essential in decreasing maternal deaths related to GAS infection. One study reported that GAS was isolated from vaginal swabs of adult women in a hospital. However, isolation of GAS from the vaginal swabs of adult females is uncommon [19].

We cannot be certain of the rationale underlying the decisions made in the cases studied here because this study was conducted as a retrospective analysis. Future research should investigate the ratio of GAS sepsis in non-pregnant women to that of pregnant women. In conclusion, GAS was the most common microorganism responsible for maternal sepsis-related death in Japan. When encountering severe sepsis during the peripartum period, we strongly recommend a high index of suspicion for GAS infection.

Table 2
Characteristics of maternal death cases related to group A *Streptococcus*.

Case	Onset Periods	Age	Parity	Mode of delivery	Timing at onset (weeks)	Death within 24 h from visiting hospital	IUFD at visiting hospital
1	antepartum	38	1	VD	34 gestational weeks	No	Yes
2	antepartum	36	2	Undelivery	36 gestational weeks	Yes	Yes
3	antepartum	40	1	Undelivery	9 gestational weeks	Yes	Yes
4	antepartum	35	1	Undelivery	18 gestational weeks	Yes	Yes
5	antepartum	31	0	Undelivery	27 gestational weeks	Yes	Yes
6	antepartum	32	3	D&C	15 gestational weeks	Yes	Yes
7	antepartum	27	0	VD	27 gestational weeks	No	Yes
8	antepartum	37	1	VD	32 gestational weeks	No	Yes
9	antepartum	28	3	Undelivery	22 gestational weeks	Yes	No
10	antepartum	32	2	VD	29 gestational weeks	Yes	Yes
11	postpartum	26	0	VD	Postpartum 2nd day	No	–
12	postpartum	35	1	CS	Postpartum 2nd day	No	–
13	postpartum	38	0	VD	Postpartum 2nd day	No	–

IUFD, Intrauterine foetal death; VD, vaginal delivery; D&C, dilation and curettage; CS, caesarean section.

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Conflicts of interest

No potential conflicts of interest to disclose.

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