at 32 weeks of gestation. In this case, the neonate' s HPA-5b alloimmunization had substantially less severe manifestations than other HPA-antigen alloimmunizations; the reported incidence of intracranial hemorrhage due to HPA-5b alloimmunization is 0-8% [7]. However, due to the risk of occurrence of NAIT, cordocentesis was performed at 34 weeks of gestation in order to decide the mode of delivery. The platelet count was sufficient for vaginal delivery. The fetus was delivered by vaginal birth, and there were no bleeding complications. The fetal platelet count transiently decreased, but subsequently increased without any treatment.

There must be a 50% risk of feto-maternal incompatibility of HPA-5b about next pregnancy because the patient has anti-HPA-5b antibody and her husband has a HPA-5 (a+b+) antigen. Recently, maternally administrated intravenous immunoglobulin has been the most successful therapy [6] however health insurance adaptation cannot be accepted in our country. In any case, a sufficient counseling about a recurrence of NAIT is important.

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Case Report

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A Case Study of a Pregnant Patient with a Congenital Heart Block Accompanied by Left Isomerism and Uncontrolled Type 2 Diabetes Who Was Treated Successfully with Ritodrine

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Key Words
Congenital heart block · Left isomerism · Ritodrine hydrochloride · Type 2 diabetes mellitus

Abstract
We present a case study of a patient with a congenital heart block associated with a left isomerism that was diagnosed during the 26th week of gestation. The mother had type 2 diabetes mellitus that was difficult to control during the early stages of the pregnancy. A fetal echocardiogram revealed an atrioventricular dissociation, with an atrial rate of 120 bpm and a ventricular rate of 55 bpm. Subsequent examinations also revealed a left isomerism in the fetus. To increase the fetal heart rate, a continuous intravenous infusion of ritodrine was administered. The fetal ventricular rate rapidly increased to 65 bpm. The pregnancy successfully continued until term and a female infant weighing 3,182 g was born via a cesarean section. A subsequent surgery was performed to provide the infant with a permanent cardiac pacemaker, and notably, the child is now 4 months of age and her growth has been within the normal range.

Case Report

A pregnant woman in the 26th week of gestation was referred to the Obstetric Outpatient Clinic of Niigata University Medical and Dental Hospital for close examination of fetal bradycardia and a suspicious left isomerism. She had been diagnosed with type 2 diabetes mellitus, which had manifested when she was 6 years old. The diabetes was poorly controlled and a concerned internal medicine doctor had initially advised against the pregnancy. She had, however, already conceived and desired to continue the pregnancy. The titer of glycosylated hemoglobin (HbA1c) during the early stages of pregnancy was determined to be 10.2%. She was then thoroughly informed that the risk of fetal anomalies significantly increased under such conditions, and ultimately she decided to continue with pregnancy. She underwent prenatal management and care at the hospital near her residence.

Ultrasonographic examinations performed during the first visit indicated that the fetal heart rate was 60 bpm, the atrial rate was 120 bpm and the ventricular rate was 60 bpm. Thus, a two-to-one atrioventricular block (AV block) was diagnosed. We also noted several cardiac abnormalities, a ventricle septal defect, a double outlet of the pulmonary artery and the aorta from the right ventricle, stenosis of the pulmonary valve, and a defect in the inferior vena cava. In addition, the cardiothoracic area ratio (CTAR) was about 30%. The fetus was diagnosed with a second degree AV block further characterized by a left isomerism.

She was hospitalized during the 28th week of gestation, and serial ultrasonographic examinations were performed, which

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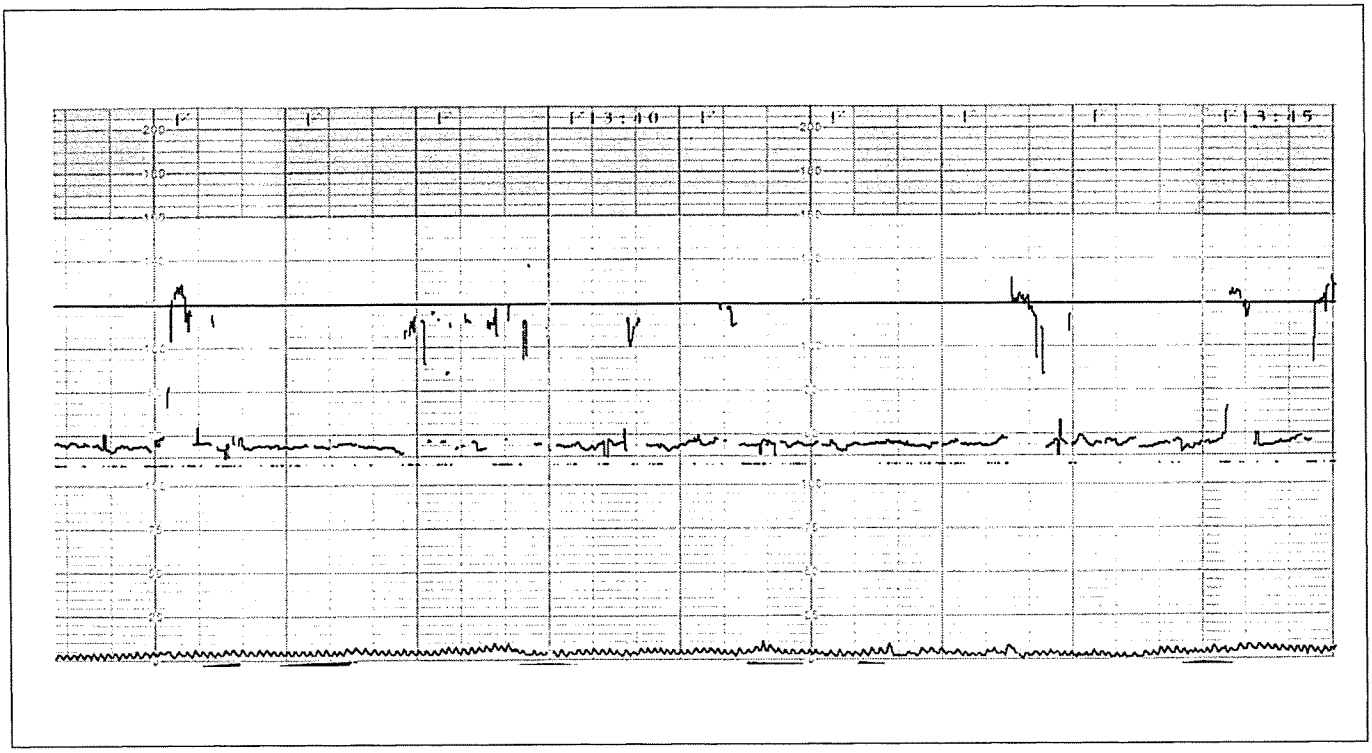

Fig. 1. Nonstress test performed during the 33rd week of gestation. Fetal heart rate was 55 bpm.

showed a stable fetal heart rate of about 60–70 bpm and revealed no cardiac enlargement and no fetal edema. Therefore, she was managed at the outpatient clinic of our hospital. However, during the 33rd week of gestation, the fetal heart rate decreased to 55 bpm (fig. 1), and the CTAR increased to 44%. She was subsequently readmitted to our hospital. Fetuses with a ventricular rate <55 bpm have been found to have a poorer prognosis than those with >60 bpm [1]. Since fetal heart rate had gradually decreased, we started to use the beta mimetic agent (ritodrine hydrochloride) to prevent hydrops fetalis so that it might not be less than 55 bpm. The fetal heart rate increased to 65 bpm upon infusion of ritodrine hydrochloride (fig. 2), and the CTAR was observed to be 30%, which indicated no cardiac failure in the fetus. Administration of ritodrine hydrochloride intravenously was continued until the 37th week of gestation. There were no maternal complications by ritodrine. The blood sugar level was kept from 100 to 150 mg/dl under insulin treatment.

It would be very difficult to evaluate CTG monitor because of fetal advanced bradycardia when the labor was onset. We decided to perform a cesarean section, as a result of consulting with her and her husband about a delivery mode. She underwent elective cesarean section during the 37th week of gestation, and a female infant weighing 3,182 g was delivered with an Apgar score of 6 and 7 at 1 and 5 min postdelivery, respectively. The postoperative course of the patient was fairly uneventful such that she was discharged from our hospital on the 8th day after the operation. Her diabetes mellitus was well controlled using recombinant human insulin administered throughout the second and third trimester. After delivery, the infant was confirmed to have cardiac anomalies such as double outlet of the pulmonary artery and the aorta from the right ventricle, atresia of the pulmonary valve, a defect in the inferior vena cava, and patent ductus arteriosus. In addition, a left isomerism was diagnosed. On the other hand, there were no side effects by ritodrine to the neonate as written in the pharmaceutical references. A permanent pace maker was introduced into the fetus for normalizing the infant's bradycardia, and the heart rate was maintained at 120 bpm after the surgical procedure. The infant's weight gain was observed to be normal.

Disussion

It is generally believed that poorly controlled diabetes during the early stages of pregnancy results in an increased risk of congenital malformations. Fuhrmann et al. [2] reported that there was only one malformation observed in 128 infants (0.8%) of diabetic women who, while planning pregnancy, underwent intensive treatment before conception. They also reported that 22 of 292 diabetic women (7.5%), for whom strict metabolic control was initiated as late as after the 8th week of gestation, de-

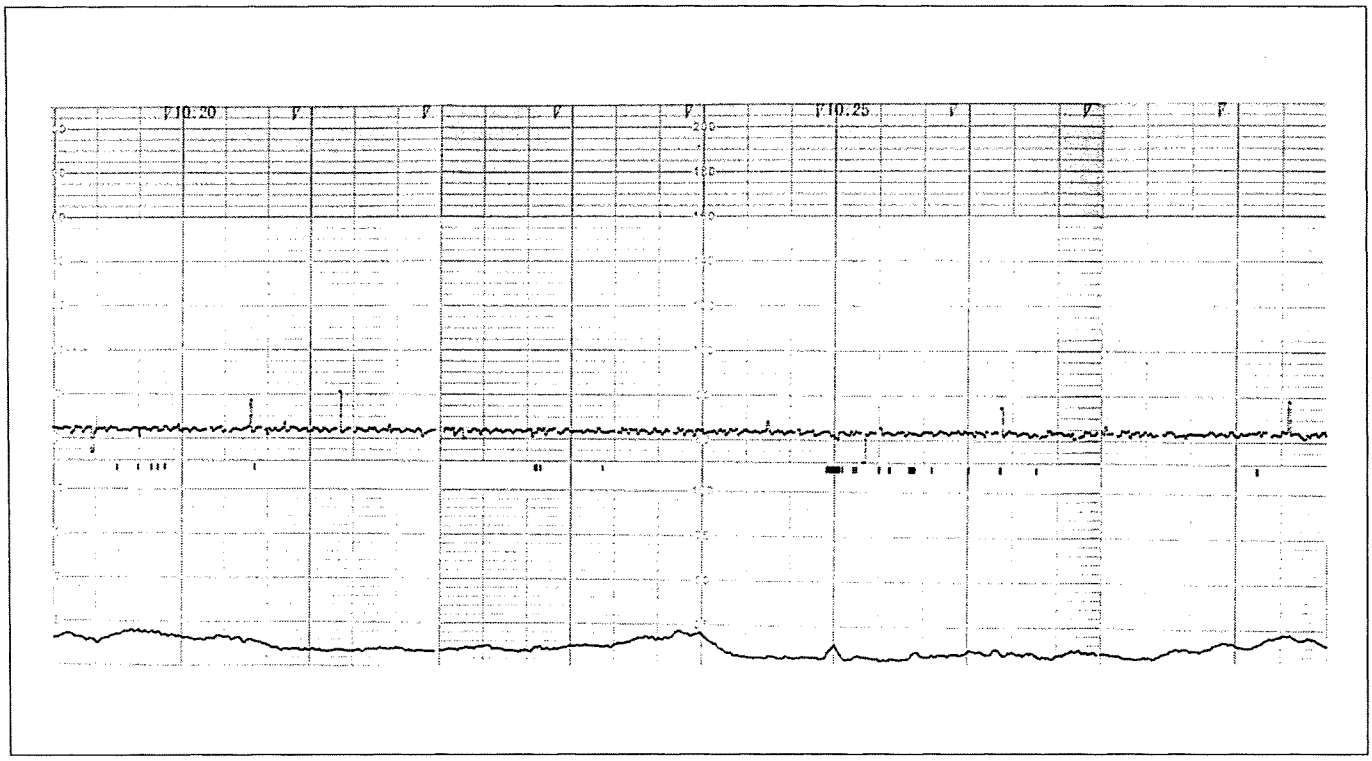

Fig. 2. Nonstress test performed after the administration of ritodrine hydrochloride. Fetal heart rate improved to 65 bpm.

livered infants with congenital malformations, an observation that is suggestive of a close relationship between the generation of congenital malformations and the poor management of diabetic mellitus. In the index case, the titer of HbA1c during the early stage of the pregnancy was 10.2% and as such, poorly controlled diabetes was possibly the cause of the fetal heart malformations. Isomerism sequence, bilateral right-sidedness or left-sidedness, is a rare defect with an estimated birth prevalence of approximately 1 in 24,000 individuals. A specific association between left-isomerism sequence and maternal type 1 diabetes has been suggested [3]. However, the association with type 2 diabetes has not been well established.

The current case demonstrated a complete AV block accompanied by left isomerism and multiple cardiac anomalies. It has been reported that the prognosis of AV block accompanied by structural heart disease is very poor, particularly with atrial isomerism, as a result of the disruption of the early left-right axis determination [4]. In addition, the prognosis of a fetus with congenital heart block is not always favorable. A higher mortality rate has been documented in cases that demonstrated a structural anomaly of the heart, hydrops fetalis, or a ventricular rate less than 55 bpm [1, 4]. We previously reported a case of a congenital heart block associated with the maternal anti-SSA antibody, in which maternal administration of ritodrine hydrochloride was observed to increase the fetal heart rate from 54 bpm to 65 bpm, and the pregnancy successfully continued to term [5]. Maternal administration of beta mimetic agent has been proposed to increase fetal ventricular rate [6]. We started maternal ritodrine infusion because it has been used for the treatment of threatened premature delivery most commonly in our country and we are familiar with the maternal and fetal side effects of ritodrine such as pulmonary edema, arrhythmia, pancytopenia, liver dysfunction, rhabdomyolysis and neonatal hypoglycemia.

Therefore, we administered ritodrine hydrochloride to increase the fetal heart rate in this case. The fetal heart rate was observed to be 55 bpm during the 33rd week of gestation. We consulted with pediatric cardiologists and they said termination of the pregnancy would be desirable when the fetal bradycardia advanced and hydrops fetalis developed, and the fetus at the 33rd week of gestation was too small to embed a pacemaker. They asked us to try ritodrine use for prevention of hydrops fetalis. Ma-

ternal intravenous ritodrine hydrochloride infusion was performed, after which the heart rate rapidly increased to 65 bpm. As we tried to detect side effects of ritodrine with pulse oximeter and examining blood test, no complications were detected. The administration of ritodrine hydrochloride was continued until term because maternal diabetes was controlled well under internal medicine management, and a mature female infant was delivered without neonatal hypoglycemia.

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Original Article

Antibody responses to *Porphyromonas gingivalis* outer membrane protein in the first trimester

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Background: *Porphyromonas gingivalis* (*Pg*) is one of the most harmful periodontal pathogens and it has been reported that *Pg* is associated with preterm birth (PTB), intrauterine growth retardation (IUGR) and pregnancy-induced hypertension (PIH), discovered by animal experiments and clinical research. The relationship between adverse pregnancy outcomes and maternal antibody response to *Pg* is controversial. On the other hand, the serum C-reactive protein (CRP) has been recognised as a reliable serum marker of periodontal disease.

Aims: To determine the significance of antibody responses to *Pg* affecting pregnancy outcomes in the first trimester.

Methods: A case–control study was carried out on women with PTB ($n = 58$), IUGR ($n = 91$), PIH ($n = 32$) and without any complications (control, $n = 98$). The serum level of the CRP and IgG1 against 40-kDa outer membrane protein of *Pg* (anti-40-kDa OMP *Pg*-IgG1) in the first trimester was measured.

Results: The IUGR group, and PTB patients whose placentas were diagnosed as chorioamnionitis or whose vaginal flora included *Lactobacilli*, showed a lower level of anti-40-kDa OMP *Pg*-IgG1 than the control group. There was no difference in the serum CRP level between each case group and control group.

Conclusions: These results suggest that a lack of humoral immunity against *Pg* in early pregnancy is associated with IUGR and some PTB.

Key words: intrauterine fetal growth retardation, periodontal disease, *Porphyromonas gingivalis*, pregnancy-induced hypertension, preterm birth.

Introduction

Periodontal disease is chronic infection of tooth-supporting tissues, which is caused by oral bacteria. For decades, many studies have indicated that periodontal disease is not only a problem of the oral cavity but also is very much related to systemic diseases, such as cardiovascular disease, type 2 diabetes mellitus, osteoporosis and so on.[1] In the obstetrical field, it is suggested that preterm birth (PTB), low birthweight, intrauterine growth retardation (IUGR), pre-eclampsia and miscarriage are associated with periodontal disease, and the mechanisms may be host-immune responses against oral bacterial infection or a direct bacterial assault on the placenta and fetus.[1–3] *Porphyromonas gingivalis* (*Pg*) is one of the most important periodontal pathogens and it is strongly suggested that *Pg* could cause adverse pregnancy outcomes, discovered by animal experiments and clinical research.[4–7] The outer membrane protein (OMP) of *Pg* is a major virulence factor associated with bacteria colonisation in the gingival crevice. Chronic periodontitis patients showed a significantly higher serum level of IgG, especially the IgG1 subclass, against 40-kDa OMP of *Pg* (anti-40-kDa OMP *Pg*-IgG1).[8] The purpose of this study was to determine the relation between pregnancy outcomes and the serum level of anti-40-kDa OMP *Pg* -IgG1 in the first trimester.

Methods

The subjects were selected from Japanese pregnant women who underwent blood sampling during the first trimester between January 1994 and May 2002 and delivered at Niigata University Medical and Dental Hospital. The Ethics Committee of Niigata University approved this study. One hundred and eighty-one women with adverse pregnancy outcomes and 98 control women were enrolled in this study.

The adverse pregnancy outcomes indicated the causes to be PTB, IUGR and pregnancy-induced hypertension (PIH).

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Table 1 Clinical characteristics of each group

	Maternal age, years median (IQR)	Primipara, %	Gestational age, weeks median (IQR)	Birthweight, grams median (IQR)
PTB ($n = 58$)	33.0 (29.3, 36.8)	44.8	35.9 (34.6, 36.4)*	2230 (1828, 2542)*
IUGR ($n = 91$)	33.0 (29.0, 36.0)†	54.1	39.4 (38.6, 40.2)†	2504 (2376, 2639)*
PIH ($n = 32$)	33.0 (29.8, 36.0)†	37.5	39.0 (36.4, 40.5)†	2729 (2043, 3156)*
Control ($n = 98$)	31.5 (28.0, 34.0)	57.1	39.9 (39.0, 40.4)	3068 (2911, 3352)

P-values were determined by Mann–Whitney *U*-test or Fisher exact test. *, $P < 0.01$; †, $P < 0.05$.
CRP, C-reactive protein; IQR, interquartile range; IUGR, intrauterine growth retardation; PIH, pregnancy-induced hypertension; PTB, preterm birth.

PTB is defined as delivery at less than 37 weeks of gestation, as a result of either preterm labour or premature rupture of the membranes (PROM). IUGR is defined as delivery of an infant whose birthweight is less than the 10th percentile of Japanese standards. According to the criteria of the Japanese Society of Obstetrics and Gynecology (2005), PIH is defined as hypertension with or without proteinuria occurring after the 20th week of gestation but being resolved by the 12th post-partum week. It encompasses pre-eclampsia (hypertension plus proteinuria), gestational hypertension (hypertension without proteinuria) and superimposed pre-eclampsia. Superimposed pre-eclampsia is defined as the new onset of proteinuria after the 20th week of gestation in a woman with chronic hypertension and no proteinuria before the 20th week of gestation, or a sudden increase in blood pressure and/or proteinuria after the 20th week of gestation in a woman with both hypertension and proteinuira before the 20th week of gestation, or the new onset of hypertension after the 20th week of gestation in a woman with proteinuria and no hypertension before the 20th week of gestation. Mild PIH was diagnosed where there was systolic blood pressure higher than 140 mmHg but not exceeding 160 mmHg and/or diastolic blood pressure higher than 90 mmHg but not exceeding 110 mmHg, as well as daily proteinuria higher than 300 mg but not exceeding 2 g. Severe PIH was diagnosed where there was systolic blood pressure exceeding 160 mmHg and/or diastolic blood pressure exceeding 110 mmHg, as well as daily proteinuria exceeding 2 g. PIH with an onset earlier than the 32nd week of gestation is defined as being early onset, and PIH with an onset after the 32nd week is defined as being late onset. Patients who experienced PIH and delivered IUGR infants, were classified in the PIH group, and those who delivered IUGR infants as a result of preterm labour or PROM, were classified in the PTB group. The control group consisted of women who delivered appropriate birthweight infants after 37 weeks of gestation without pregnancy-induced hypertension (PIH) or other medical problems.

In the case of PTB patients, vaginal swabs were obtained for bacterial culture tests when they were admitted with preterm labour or PROM, and their placentas were examined for histological chorioamnionitis (CAM) after delivery. CAM was diagnosed if there was acute inflammation with polymorphonuclear leucocytes infiltrating the chorionic membrane. Exclusion criteria included multiple birth, congenital fetal abnormalities and incompetent cervix.

Peripheral venous blood samples were obtained from first trimester women. Serum was collected by centrifugation at 1500 *g* for 20 min and stored at – 20°C until use. Recombinant 40-kDa OMP of *Pg* was purified by the method of Kawamoto *et al.* and anti-40-kDa OMP *Pg*-IgG1 was determined by enzyme-linked immunosorbent assay, as previously described.[8,9] Antibody levels were expressed as percentages of the control serum. The control serum was derived from a patient with periodontitis and with *Pg* detected in her periodontal pockets by polymerase chain reaction (PCR). A CRP assay was performed by Latex Photometric Immunoassay on QUICK TURBO C (SHINO-TEST, Tokyo, Japan).

The statistical differences from the control group were determined by the Mann–Whitney *U*-test or Fisher exact test. All analyses were performed using the R version 2.6.1. and R Commander version 1.3-9.

Results

A total of 279 subjects (58 PTB, 91 IUGR, 32 PIH and 98 controls) were enrolled in the study. The clinical characteristics of each group are shown in Table 1. There were no differences in the percentage of primipara between each case group and the control group. The maternal ages of those in IUGR and PIH groups were significantly higher than those of the control group. As expected, the PTB, IUGR and PIH groups had significantly lower gestational ages and birthweights than the control group. Anti-40-kDa OMP *Pg*-IgG1 of the IUGR group was significantly lower than that of the control group and no differences were observed among the PTB, PIH and control groups (Table 2). However, PTB patients whose placentas were diagnosed as CAM showed a lower tendency ($P = 0.055$), and those who were *Lactobacillus*-positive in vaginal flora showed significantly lower levels than the control group (Table 3). Although there were eight PTB patients who suffered from CAM despite the presence of *Lactobacilli*, they showed very low serum levels of anti-40-kDa OMP *Pg*-IgG1 (median 14.5%, interquatile range: 6.7~37.4%). As shown in Table 4, there were no differences in anti-40-kDa OMP*Pg*-IgG1 between the control group and each subclass of PIH (gestational hypertension, pre-eclampsia, superimposed pre-eclampsia, early onset, late onset, mild

Table 2 Serum level of anti 40-kDa *Pg*-IgG1 and CRP in the first trimester

	Anti 40-kDa *Pg*-IgG1, %		CRP, mg/dL	
	Median (IQR)	*P*-value	Median (IQR)	*P*-value
PTB ($n = 58$)	80.4 (35.0, 166.5)	0.226	0.12 (0.03, 0.28)	0.115
IUGR ($n = 91$)	57.3 (29.4, 151.4)	< 0.01	0.06 (0.02, 0.18)	0.684
PIH ($n = 32$)	82.8 (48.1, 90.7)	0.118	0.06 (0.20, 0.19)	0.315
Control ($n = 98$)	100.3 (54.6, 177.6)		0.06 (0.03, 0.19)	

P-values were determined by Mann–Whitney *U*-test.
CRP, C-reactive protein; IQR, interquartile range; IUGR, intrauterine growth retardation; PIH, pregnancy-induced hypertension; PTB, preterm birth.

Table 3 Relation of CAM and *Lactobacilli* with anti-40-kDa *Pg*-IgG1 and CRP in preterm birth group

		Anti-40-kDa *Pg*-IgG1, %		CRP, mg/dL	
	n	Median (IQR)	*P*-value	Median (IQR)	*P*-value
CAM					
Positive	24	52.6 (22.1, 143.3)	0.055	0.11 (0.05, 0.27)	0.098
Negative (unknown 13)	21	136.7 (63.2, 210.0)	0.334	0.18 (0.02, 0.44)	0.109
Lactobacilli in vaginal flora					
Positive	22	38.1 (8.5, 127.7)	< 0.01	0.08 (0.02, 0.24)	0.849
Negative (unknown 20)	16	144.8 (66.7, 226.3)	0.114	0.20 (0.05, 0.35)	0.077
Control	98	100.3 (54.6, 177.6)		0.06 (0.03, 0.19)	

P-values were determined using Mann–Whitney *U*-test.
CAM; histological chorioamnionitis; CRP; C-reactive protein; IQR, interquatile range.

Table 4 Anti-40-kDa *Pg*-IgG1, CRP and subclasses of pregnancy-induced hypertension

		Anti-40-kDa *Pg*-IgG1, %		CRP, mg/dL	
	n	Median (IQR)	*P*-value	Median (IQR)	*P*-value
Gestational hypertension	9	71.1 (37.3, 85.2)	0.146	0.05 (0.00, 0.08)	0.194
Pre-eclampsia	15	83.6 (67.9, 88.1)	0.206	0.03 (0.02, 0.14)	0.308
Superimposed pre-eclampsia	8	90.4 (67.4, 161.6)	0.910	0.14 (0.04, 0.26)	0.549
Early onset type	11	81.6 (54.6, 120.7)	0.590	0.08 (0.03, 0.22)	0.661
Late onset type	21	83.6 (49.8, 88.9)	0.101	0.03 (0.00, 0.08)	0.108
Mild	18	83.1 (44.7, 90.1)	0.104	0.04 (0.00, 0.08)	0.106
Severe	14	82.6 (73.7, 90.7)	0.507	0.07 (0.02, 0.24)	0.826
Control	98	100.3 (54.6, 177.6)		0.06 (0.03, 0.19)	

P-values were determined using Mann–Whitney *U*-test.
CRP, C-reactive protein; IQR, interquatile range.

and severe PIH). There was also no difference in the serum CRP level between the control group and each case group (Tables 2–4).

Discussion

Periodontal disease is a chronic infection of periodontal tissue by anaerobic Gram-negative rods, which has recently been recognised as a risk factor for PTB, IUGR, pre-eclampsia and so on.[2] *Pg* is one of the most harmful periodontal pathogens and induced IUGR in rodent models. It has been detected in the placenta of patients with pre-eclampsia and in the amniotic fluid of those with preterm labour.[4–7]

There are several studies about serum antibody levels against *Pg* during pregnancy, but the significance has been controversial. Dasanayake *et al.* stated that higher antibody

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levels against *Pg* were associated with low birthweight deliveries.[10] On the other hand, Lin *et al.* reported that low maternal IgG antibody response to *Pg* was associated with an increased risk of PTB.[11] In our results, lower antibody response was observed in the IUGR group and some PTB patients, and these agree with Lin's data. In the previous reports described above, antibody levels were measured by the immunological method using sonicated whole bacteria as the antigen, whereas recombinant 40-kDa OMP was used in this study. 40-kDa OMP plays a role in the progression of periodontal disease caused by *Pg* and it has been suggested that 40-kDa OMP should be the antigen of a vaccination for periodontal disease.[12,13] Patients with chronic periodontitis showed significantly higher serum levels of antibody against 40-kDa OMP, especially the IgG1 subclass, than periodontally healthy controls, however, the antibody level did not have a significant association with the mean probing depth, which is one of the most reliable clinical measurements of periodontal disease.[8] Furthermore, we measured the serum level of anti-40-kDa OMP *Pg*-IgG1 of 14 non-pregnant young individuals who were periodontally healthy and *Pg* could not detected in their periodontal pockets by PCR. The median antibody level was 69.3% (IQR: 44.7~151.8%) and the highest antibody level was 195.2%, which is about twice as high as that of the control serum. Our control serum was derived from a patient with periodontitis and *Pg* was detected in her periodontal pockets by PCR. The positive rate of *Pg* by PCR in periodontal pockets was more than 50% in Japanese pregnant women in the first trimester (our unpublished data). *Pg* is the common oral bacteria in young Japanese women and most of them must have obtained humoral immunity before pregnancy. Serum CRP levels are strongly associated with periodontal status. Meta-analyses have suggested that serum CRP levels in periodontitis patients are elevated, compared with controls, and lowered by periodontal treatment.[14] In early pregnancy, compatible results were also reported.[15] Although periodontal examinations were not performed in this study, there may be no significant differences in the periodontal status between each case group and the control group because the serum CRP levels were similar in each group. These may mean that the risk factor for adverse pregnancy outcome is not periodontal disease itself but the lack of humoral immunity against *Pg* (and other oral bacteria?) in early pregnancy.

There are two hypotheses about the mechanism of periodontal disease worsening pregnancy outcomes. One explanation is intrauterine infection of oral bacteria through maternal circulation.[4–7] Maternal immunoglobulins against periodontal pathogens should protect the mother and fetus from bacterial dissemination into the uterus.[16] The other hypothesis is inflammatory cytokine or prostaglandin production in the oral cavity. Cytokines, like tumour necrosis factor-α and prostaglandin, will reach the uterus through maternal circulation and induce uterine contractions or worsen the condition of the fetus and placenta.[2,3] Boggess *et al.* reported that maternal periodontal disease in early pregnancy was associated with delivery of a small-for-gestational-age infant and hypothesised that it presents an oral microbial challenge that results in a systemic inflammatory response in a subset of women and ultimately results in abnormal placental or fetal development that impacts fetal growth.[17] In our results, it is difficult to speculate on the mechanism suppressing fetal growth, however, it is possible to do so in the case of PTB. In the PTB group, the serum levels of anti-40-kDa OMP *Pg*-IgG1 were low in patients with CAM or without *Lactobacilli* in vaginal flora. Intrauterine infection, which is called CAM pathologically, is one of the most prevalent causes of PTB and it has been suggested that the origin is often ascending infection with bacteria from the vagina and cervix.[18] *Lactobacilli* prevent pathogenic bacteria from growing in the vagina and from invading the uterus, therefore the presence of *Lactobacilli* in vaginal flora is a negative risk factor for PTB.[19] These suggested that haematogenous infection by oral bacteria may be one of the origins of intrauterine infections and occur more commonly in PTB patients who suffer from CAM despite the presence of *Lactobacilli*.

Conclusion

These results suggest that a lack of humoral immunity against *Pg* itself in early pregnancy is associated with IUGR and some PTB.

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Abscess formation due to *Mycoplasma hominis* infection after cesarean section

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Abstract

A 27-year-old female patient underwent cesarean section and a postoperative hematoma occurred at the site of the uterine incision. The patient underwent relaparotomy to remove the hematoma. Four days later she developed a fever of over 39°C and an abscess had formed at the site. Despite therapy with several antimicrobial agents, her fever persisted. Consequently, she underwent transvaginal abscess drainage, after which she promptly became afebrile. *Mycoplasma hominis* was considered to be the primary causative organism. There are two reasons that could explain why the wound infection became serious: (i) *M. hominis* is resistant to several antimicrobial agents that are usually used to treat obstetric infections; and (ii) a long time is required to identify the pathogen. In conclusion, *M. hominis* should be considered as a causative organism if an antimicrobial-resistant infection occurs at the surgical site after a cesarean section.

Key words: cesarean section, *Mycoplasma hominis*, postpartum infection.

Introduction

Mycoplasma hominis usually colonizes the lower urogenital tract. In the context of gynecologic and obstetric infections, there are reports of an association between *M. hominis* and pelvic inflammatory disease, postpartum fever, and preterm labor. Usually, the pathogenicity of *M. hominis* is considered to be relatively low. Although infections caused by the bacteria are often mild, occasionally, they may be serious. We report a case of abscess formation at the uterine incision site after cesarean section, which was caused by *M. hominis* infection.

Case Report

A 27-year-old woman, para 2, underwent emergency cesarean section at a local hospital because of arrest of labor at 38 weeks of gestation. A transverse incision was made at the lower uterine segment. The patient presented with hematuria 5 h after the cesarean section, and ultrasound examination revealed a 5-cm hematoma between the lower uterine segment and the bladder. Subsequently, she was transported to our hospital for further evaluation and treatment of the hematoma.

On admission, the patient's general condition was maintained, and her clinical and laboratory data were as follows: body temperature, 37°C; blood pressure, 103/63 mmHg; heart rate, 137 bpm; white blood cell count, 31 200 cells/mm^3; hemoglobin, 10.8 g/dL; and C-reactive protein (CRP), 2.3 mg/dL. The hematoma measured 8 × 6 cm and had spread into the retroperitoneal space (Fig. 1). Therefore, the patient underwent relaparotomy for hemostasis. The bleeding was identified and stemmed, and the hematoma was removed. A Penrose drain was placed at the site of the hematoma for 2 days.

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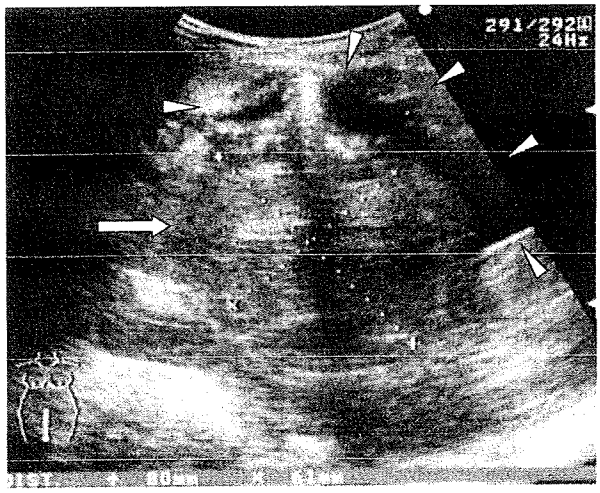

Figure 1 Ultrasonogram on admission. A hematoma was detected between the lower uterine segment and bladder (arrow). The bladder is indicated by arrowheads.

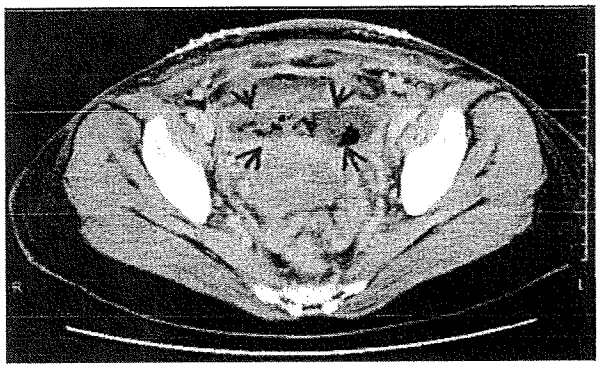

Figure 2 Computed tomography scan obtained on the fourth day. An abscess was detected at the site where the hematoma had formed (arrows).

On the second day after relaparotomy, the patient's leukocytosis and elevated CRP level showed no improvement, and on the fourth day, her body temperature rose to over 39°C. A computed tomography (CT) scan revealed a 9 × 4.5-cm abscess at the site where the hematoma had formed (Fig. 2). Although we administered cephalosporin, carbapenem, clindamycin, and aminoglycoside, the patient's high fever persisted. On the seventh day, an abdominal incisional abscess was also apparent. The removed drain and abdominal incisional abscess were plated onto blood agar and chocolate agar, and incubated at 37°C in a 5% CO_2-containing atmosphere. After 72 h of incubation, pinpoint and translucent colonies were observed on all of the plates, but repeated Gram stains of the colonies were negative. It was difficult to identify the bacterial species and perform antimicrobial sensitivity tests because the bacterial growth was very slow. However, the laboratory personnel of our department suggested that the bacteria might be *M. hominis* on the basis of the features of the colonies.

On the tenth day, the pelvic abscess was drained using the transvaginal approach. A transverse incision was made at the junction of the anterior vaginal mucosa and cervical portion of the uterus, and the bladder was dissected in order to reach the abscess wall. The abscess wall was hard, so it was punctured with a Kelly clamp under the guidance of transabdominal ultrasonography. A Penrose drain was placed in the abscess.

Fluoroquinolone (pazufloxacin mesilate) was administered, and the next day, the patient promptly became afebrile. Pazufloxacin mesilate was administered for a week, and the patient was discharged 14 days after the pelvic abscess was drained.

The Gram-negative bacteria that had been detected in the specimen obtained from the Penrose drain, the abdominal incisional abscess, and the pelvic abscess were later identified as *M. hominis* by a polymerase chain reaction (PCR) assay as described previously.[1] Briefly, bacterial cells were suspended in 300 μL of sterile water and boiled for 5 min; they were then centrifuged and the supernatant was used as the DNA template for the PCR reaction. PCR primers were used to amplify a 334-bp fragment of the *M. hominis* 16S rRNA gene as described previously.[1] A 334-bp amplicon was produced by the species-specific PCR assay. Sequencing of the amplicon demonstrated 100% base-pair identity to those of the *M. hominis* strain.

Discussion

M. hominis is a pathogenic bacterium that usually colonizes the lower urogenital tract, in which colonization is approximately 20–50%.[2–4] In the context of obstetric and gynecologic infections, *M. hominis* has been associated with pelvic inflammatory disease,[5] postpartum fever,[6] and preterm labor.[7] Furthermore, *M. hominis* causes various extragenital infections, such as septicemia,[8] septic arthritis,[9] endocarditis,[10] and brain abscess.[11]

Usually, infections caused by *M. hominis* are self-limiting and cause mild symptoms.[12–14] However, occasionally, the infection becomes serious in patients with risk factors, such as compromised immunity. In serious

cases, therapy with appropriate antibacterial agents and surgery are strongly recommended.

Mycoplasma species do not have a cell wall, which is the target for beta-lactam antimicrobials that are commonly used as prophylaxis agents for post-surgical infections. Furthermore, they do not synthesize folic acid and are resistant to antimicrobials that interfere with folic acid synthesis, such as sulfonamides.[15] Tetracyclines, erythromycin, clindamycin, chloramphenicol, aminoglycosides, and fluoroquinolones have been shown to have activity against one or more mycoplasmal species; however, there are some reports that *M. hominis* is generally resistant to erythromycins and amynoglycosides.[13,15–17] Tetracycline has been considered to be the drug of choice for treating *M. hominis* infections.[18] However, there is an increase in the emergence of tetracycline-resistant strains of *M. hominis*,[19,20] and clindamycin is often used when tetracycline is not effective.[13,15,20]

In the context of wound infection after cesarean section, Gram staining is considered a helpful method for predicting subsequent culture results.[21] However, because they lack a cell wall, mycoplasmas cannot be identified using Gram staining of clinical specimens.[16] In addition, *M. hominis* is a slow-growing bacterium, and its identification and antimicrobial sensitivity test with routine cultural methods are difficult. Therefore, appropriate antibacterial therapy is generally started late in cases of *M. hominis* infection. As noted above, a number of cases have been reported wherein *M. hominis* could not be detected by Gram staining and administration of effective antimicrobials as they were initiated late.[16,22] Furthermore, specific media were required for identification of *M. hominis* in those cases.

Recently, it was reported that compared to culture methods, PCR assay is a simple, rapid, and more sensitive method for the identification of this pathogen.[23] Therefore, a PCR assay should be performed if an *M. hominis* infection is suspected.

There are some reports on the use of surgical procedures to treat *M. hominis* infection.[13,16,20,24] In these reports, the patients underwent drainage and aspiration and received local wound care because antimicrobial therapy with beta-lactam antibiotics, such as penicillin derivatives and cephalosporins was ineffective. Surgery is considered to be a promising treatment for *M. hominis* infection if antimicrobial therapy is ineffective. In our case, antimicrobial sensitivity tests could not be performed, and it was not clear as to which antimicrobials were actually effective. Although clindamycin, which is typically considered to be effective against *M. hominis*, was administered after abscess formation, it showed no clinical effects. Once an abscess develops, antimicrobial therapies only have a limited effect even if the drug shows high *in vitro* activity; in such cases, surgery should be performed promptly.[25]

In conclusion, we present a case of severe wound infection that was caused by *M. hominis* infection after cesarean section. Resistance to beta-lactam antibiotics, which are regarded as the first-line treatment agents for antimicrobial prophylaxis, and difficulty in identification with conventional bacterial culture methods may have made the infection worse.

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RESEARCH LETTER

Prenatal diagnosis of unilateral pulmonary agenesis in a pregnant woman undergoing chronic hemodialysis due to chronic renal failure

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KEY WORDS: pulmonary agenesis; chronic renal failure; hemodialysis; fetal ultrasound

Pulmonary agenesis is a very rare developmental malformation of the lung, in which there is a complete absence or severe hypoplasia of one or both lungs (Bianchi *et al.*, 2000). Prognosis of pulmonary agenesis varies from stillbirth, to neonatal death, to survival without any symptoms (Booth *et al.*, 1967; Maltz *et al.*, 1968; Engellenner *et al.*, 1989). We describe the prenatal diagnosis of unilateral pulmonary agenesis in a woman with chronic renal failure (CRF) treated with hemodialysis.

A 32-year-old woman, para 0, had undergone hemodialysis for 6 months because of CRF, the cause of which was unknown. She conceived spontaneously and was referred to our hospital at 22 weeks' gestation for the management of pregnancy and delivery. She had no family history of any malformation. At sonographic scan, the fetal cardiothoracic area ratio (CTAR) was increased to 38%. No structural cardiac anomalies were observed. The total cardiac dimension was normal (19 mm) and the thoracic circumference/abdominal circumference ratio was low (0.65), which suggested not a cardiomegaly but a small thorax. A mediastinal shift to the right side was present without abnormal intrathoracic mass lesions. The left lung appeared normal, however, the right lung could not be detected (Figure 1a). Therefore, we diagnosed the fetus as having right pulmonary agenesis. Magnetic resonance imaging (MRI) examinations at 26 and 35 weeks' gestation confirmed the absence of the right fetal lung without abnormal intrathoracic masses (Figure 1a and b). Her pregnancy course was uneventful, and preterm labor and polyhydroamnios were not observed. She underwent hemodialysis four times a week and after 24 weeks' gestation, hemodialysis was performed five times a week. Maternal renal function was stable during the pregnant period. Her fetus was healthy and fetal growth was appropriate. At 35 weeks' gestation, MRI was performed again for reevaluation of fetal lungs, and the lack of the right lung was confirmed, as suspected from the MRI examination performed at 26 weeks' gestation (Figure 1b). At 40 weeks' gestation, she delivered a male infant (2834 g) vaginally. The apgar score at 1 min was 4 points, so mask ventilation was performed and the apgar score improved to 8 points at 5 min. A plain chest radiogram showed hyperinflation of the left lung, a mediastinal shift toward the right side, and radiopacity of the right hemithorax. Administration of oxygen and nasal directional positive airway pressure were required for a few days due to cyanosis, retraction, and low oxygen saturation of pulse oximetry, after which no treatment was necessary. Computed tomography (CT) was performed on the fourth day after birth and the results again confirmed the infant's right pulmonary agenesis. No associated anomalies were detected by physical exam, CT, or ultrasound examination of the brain, heart, and abdomen. Mother and child were discharged from our hospital, 14 days after delivery. At pediatric follow-up after 1 year, the child was doing well.

Pulmonary agenesis is defined as the complete absence or severe hypoplasia of one or both lungs (Bianchi *et al.*, 2000). Pulmonary agenesis is considered to be a rare malformation. Schechter *et al.* (1968) estimated an incidence of 1 in 15 000 based on autopsies. There have been some reports on prenatal diagnosis of unilateral pulmonary agenesis (Bianchi *et al.*, 2000; Viora *et al.*, 2002). There has been only one reported case that was diagnosed prenatally during the second trimester at 23 weeks' gestation (Viora *et al.*, 2002). The unilateral pulmonary agenesis of our case was prenatally diagnosed at 22 weeks and may be the earliest such case in the literature. We suspect that prenatal diagnosis of unilateral lung agenesis should be possible even before 22 weeks' gestation. The most important sonographic finding is usually the mediastinal shift to the affected

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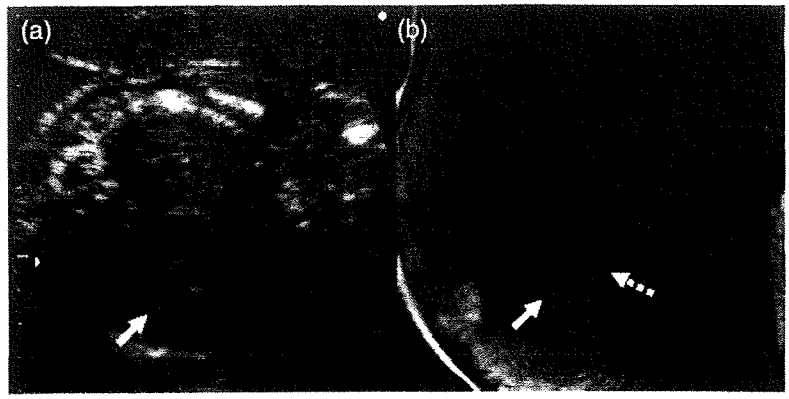

Figure 1—(a) Coronal section of fetal thorax (4-chamber view) at 22 weeks' gestation by ultrasound. The right lung could not be detected and the heart (solid arrow) was shifted to the right side. The cardiothoracic area ratio was increased to 38%. (b) MRI (half Fourier single-shot Turbo spin echo) performed at 35 weeks' gestation. Right lung was absent and the mediastinum (solid arrow) was shifted toward the right side. Dotted arrow indicates left lung

side. Therefore, differential diagnoses have been considered, that is, an abnormal intrathoracic mass lesion, such as a congenital diaphragmatic hernia or a congenital cystic adenomatoid malformation of the lung (Bianchi *et al.*, 2000). In this case, at first we noticed an increase in CTAR, but not a mediastinal shift. If increased CTAR is observed, which was induced by the lack of a unilateral lung in this case, the fetal condition causing increased CTAR, such as a congenital cardiac disease, should be considered as a differential diagnosis. MRI is more useful than ultrasound in identifying fetal thoracic organs. Indeed, MRI, which clearly demonstrated the absence of the right lung and abnormal mass lesions, was helpful in confirming the diagnosis of pulmonary agenesis.

Bilateral agenesis of the lung is incompatible with life. Unlike bilateral lung agenesis, unilateral pulmonary agenesis is not lethal. Some patients may die in the neonatal period because of respiratory failure or pulmonary hypoplasia, others have only modest and transient respiratory distress at birth like our case, or signs of illness may be absent in the newborn. However, even these infants remain at risk for recurrent bronchopulmonary infection, which can be a cause of death (Bianchi *et al.*, 2000; Hansen *et al.*, 2005). About half of the cases have been associated with other malformations, including those of the cardiovascular, gastrointestinal, genitourinary, ocular, and skeletal systems. Another common cause of death is related to associated malformations, primarily cardiac in cause. Without major malformations and problems of the respiratory system, long-term survival is possible (Berkenstadt *et al.*, 1999; Bianchi *et al.*, 2000).

In our case, fetal pulmonary agenesis occurred in a pregnant woman undergoing hemodialysis due to CRF. CRF requiring hemodialysis can be associated with fetal growth restriction (Chao *et al.*, 2002) and with high risk of fetal congenital anomalies (Okundaye *et al.*, 1998). A careful ultrasound examination for evaluating fetal growth and malformations, including pulmonary agenesis, is recommended for pregnant women undergoing hemodialysis.

Unilateral pulmonary agenesis occurs approximately 25 times more commonly than bilateral cases (Booth *et al.*, 1967; Maltz *et al.*, 1968). It is more difficult to diagnose prenatally the absence of one lung compared to that of both lungs by ultrasound. Unilateral pulmonary agenesis presents the possibility of several associated diseases, which need to be distinguished. Neonates with unilateral pulmonary agenesis often have some problems in regard to respiration and associated anomalies (Bianchi *et al.*, 2000). In unilateral pulmonary agenesis, prenatal evaluation of the associated anomalies and early treatment immediately after birth by a neonatologist can improve the prognosis. If prenatal diagnosis is made, management of pregnancy and delivery should be done in a tertiary care center.

In conclusion, we reported here a case of unilateral pulmonary agenesis in a pregnant woman receiving hemodialysis. Prenatal diagnosis is important to improve the prognosis of unilateral pulmonary agenesis.

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INTERNAL MEDICINE

□ CASE REPORT □

HELLP Syndrome, Multiple Liver Infarctions, and Intrauterine Fetal Death in a Patient with Systemic Lupus Erythematosus and Antiphospholipid Syndrome

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Abstract

We report a case of HELLP syndrome, multiple liver infarctions, and intrauterine fetal death in a woman in the 17th week of pregnancy with SLE and APS who had been in remission on a regimen of low-dose prednisolone and aspirin. An increase in the dosage of corticosteroid together with intravenous heparin infusion led to improvement of the clinical symptoms, laboratory parameters, and multifocal low-density liver lesions detected by computed tomography. Early onset and signs of severe organ involvement are the characteristic features of HELLP syndrome associated with APS, and patients that are at risk should be followed up carefully.

Key words: HELLP syndrome, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), multiple liver infarction, catastrophic antiphospholipid syndrome (CAPS)

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Introduction

The syndrome of hemolysis, elevated liver enzyme levels and low platelet count (HELLP) is a multisystemic thrombotic microangiopathy that complicates pregnancy. It is associated with a high maternal death rate and perinatal mortality, and is considered to be a severe form of preeclampsia (1-4). HELLP is estimated to occur in 0.17-0.85% of the general population, and is diagnosed antepartum in 70% and postpartum in 30% of cases. Among cases diagnosed antepartum, 90% are in the third trimester, and the syndrome rarely occurs before 27 weeks of gestation (2). Although the pathogenetic mechanism is not fully understood, it is thought to occur as a result of aberrant placental function, impaired placental vascular perfusion, and ischemia-producing oxidative stress, which stimulate the release of factors that injure the vascular endothelium via activation of platelets, vasoconstrictors, and loss of normal vascular relaxation in pregnancy (3, 4).

Antiphospholipid syndrome (APS) is known to be a major cause of fetal loss due to a thrombotic tendency leading to placental infarction during pregnancy (5, 6), and there is a growing body of evidence that APS may be one of the possible risk factors of HELLP syndrome (7-12).

Here we report a case of HELLP syndrome associated with systemic lupus erythematosus (SLE) and APS in the early second trimester, which was treated successfully with corticosteroid and heparin administration.

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Table 1. **Laboratory Data on Admission to Our Hospital**

Blood count			Serum chemistry		
WBC	23860	/μL	ALT	1049	IU/L
RBC	343 ×10⁴	/μL	AST	1218	IU/L
Hb	10.4	g/dL	LDH	1292	IU/L
Ht	29.1	%	γGTP	209	IU/L
Plt	5.6 ×10⁴	/μL	ALP	442	IU/L
			TB	1.4	mg/dL
Coagulation tests			DB	0.3	mg/dL
APTT	51.1 sec (control 26.2)		IB	1.1	mg/dL
HPT	88	%	ChE	136	IU/L
Fbg	472	mg/dL	Amy	34	IU/L
FDP	91.2	μg/mL	BUN	9	mg/dL
D-dimer	40.5	mg/dL	Cr	0.33	mg/dL
ATIII	60	%	Ferritin	5018	ng/mL
Direct Coombs test	(-)				
Indirect Coombs test	(-)				
Immunological Findings					
CRP	17.62	mg/dL	ANA	66.9	index
IgG	1111	mg/dL	dsDNA	9	IU/mL
IgM	131	mg/dL	LAC	2.33	(+)
IgA	67	mg/dL	(mixing test, cut-off value < 1.3)		
C3	48.4	mg/dL	aCL/β2GPI	<1.2	U/mL
C4	5.4	mg/dL	aCL-IgG	<8	U/mL
CH50	20	U/mL			

Case Report

A 26-year-old woman in the 17th week of pregnancy was transferred to our hospital because of progressive severe liver dysfunction, thrombocytopenia, and elevated levels of acute inflammatory markers. She had a 12-year history of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), which had been in remission for more than 3 years under a treatment of 9 mg prednisolone daily and low-dose aspirin. She had become pregnant in July 2008, and at 17 weeks of pregnancy had developed acute epigastralgia and vomiting. Laboratory examinations had shown no significant abnormality, and famotidine had been prescribed for her symptoms. However, she visited the clinic again because of worsening of her symptoms one week after onset. At that time, severe thrombocytopenia together with liver dysfunction and an elevated level of C-reactive protein were observed, and she was therefore admitted to the emergency ward.

Laboratory examinations showed severe liver dysfunction, and data from coagulation studies met the diagnostic criteria for disseminated intravascular coagulation (DIC). Continuous intravenous infusion of nafamostat methylate together with antibiotics, gamma-globulin, and platelet transfusion did not improve the clinical symptoms or laboratory abnormalities.

When transferred to our hospital, the patient had a fever and persistent severe epigastralgia. Her blood pressure was normal and pulse was 154 min. Blood examination revealed leukocytosis and thrombocytopenia with severe liver dysfunction. Fragmented red blood cells were not observed. Urinalysis showed macroscopic hematuria without proteinuria. Ultrasound examination revealed intrauterine fetal death after transfer to our hospital, and induction of delivery was performed with platelet transfusion. Histopathological examination confirmed multiple placental infarctions with small-vessel thrombosis. Abdominal computed tomography (CT) scan after the delivery showed multiple low-density areas in the patient's liver, suggesting multiple liver infarctions (Fig. 1).

Immediately after the delivery, the dosage of prednisolone was increased to 1 mg/kg body weight, together with continuous intravenous heparin infusion, and the clinical symptoms and laboratory data gradually improved (Table 2). Follow-up abdominal CT scan at 4 weeks demonstrated improvement of the multiple low-density liver lesions (Fig. 2).

Discussion

APS is a well known condition that has a close relationship with pregnancy-related complications (5, 6). Although the most characteristic complication is recurrent spontaneous abortion, recent studies have also indicated APS as a possible risk factor for the onset of HELLP syndrome (7, 8).

HELLP syndrome associated with APS has been reported to have some characteristic features. In a retrospective study, Thuong et al reported that 16 pregnancies (10.6%) with APS

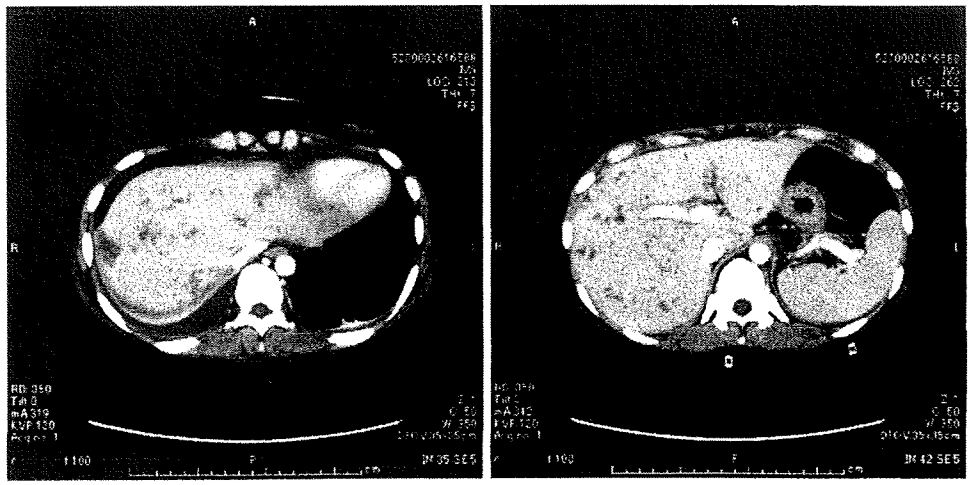

Figure 1. **Computed tomography scan of the upper abdomen, showing multifocal hypodense lesions in the liver and right pleural effusion.**

Table 2. **Clinical Course and Laboratory Findings in This Patient**

Day	8 Sep	12 Sep	14 Sep	22 Sep	14 Oct
Symptoms	epigastralgia fever	epigastralgia fever	epigastralgia fever resolved	no symptoms	no symptoms
Events	emergency hospitalization	transfer to our hospital IUFD	induction of delivery multiple liver LDAs in CT		CT findings improved
Treatment	PSL 9mg, aspirin antibiotics gamma-globurin nafamostat methilate platelet transfusion	PSL 9mg, aspirin antibiotics nafamostat methilate platelet transfusion	PSL 50mg, aspirin antibiotics heparin platelet transfusion	PSL 50mg, aspirin antibiotics heparin	PSL 45mg aspirin warfarin
WBC ($\times 10^3/\mu L$)	14900	23860	24310	8830	9130
Platelet ($\times 10^4/\mu L$)	5.1	5.6	1.9	19.7	19.9
ALT (IU/L)	280	1049	385	51	17
AST (IU/L)	250	1218	892	135	19
CH50 (U/mL)	-	20	-	-	36
CRP(mg/dL)	17.1	17.62	-	0.14	<0.1

IUFD: intrauterine fetal death. PSL: prednisolone. LDAs: low density areas

were accompanied by HELLP syndrome (7). Although the syndrome usually occurs in the third trimester or postpartum, they found that it occurred earlier and was more severe in APS-associated pregnancies than in the general population. Pauzner et al reported the relationship between liver infarction in HELLP syndrome and APS, and described that hepatic infarction during pregnancy was almost always associated with APS (13). Several other case reports have also indicated that patients with HELLP syndrome associated with APS are sometimes refractory to fetal delivery and require further intensive therapy such as corticosteroid administration or plasmapheresis, suggesting the severity of HELLP syndrome associated with APS (9-12).

Another focus of interest has been the similarities between some cases of HELLP syndrome and catastrophic APS (CAPS) during pregnancy (10, 14-17). CAPS is a very rare and life-threatening variant of APS characterized by multiple microvascular thromboses over a short period of time, leading to multiple organ failure and a high mortality rate. Around 50% of cases are thought to have a trigger event before the onset of CAPS, including infections, surgery, malignancy, lupus flares, and pregnancy (15-17). Gomez-Puerta et al reported 15 episodes of CAPS among 255 pregnancies associated with APS. Among these 15 cases, 8 showed overlap with HELLP syndrome, and the authors indicated that a severe form of HELLP syndrome was a major feature of CAPS, based on their own study and other case reports (14). Indeed, in some severe cases of HELLP syndrome, several organs are affected simultaneously, and the features can include liver infarction, acute renal failure, or acute respiratory distress syndrome, which could also meet the preliminary criteria for CAPS. In addition, aggressive immunosuppressive therapies such as high-dose steroid administration, intravenous immunoglobulin, andor plasmapheresis appear to have a beneficial effect on both of these disorders (15-17). This might be attributable to the presence of severe systemic inflammatory response syndrome (SIRS) in both conditions (15, 16).