

Recombinant Factor VIIa to Successfully Manage Disseminated Intravascular Coagulation From Amniotic Fluid Embolism

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BACKGROUND: Amniotic fluid embolism (AFE) is a rare syndrome that can complicate pregnancy and labor. It often has debilitating and lethal consequences. One serious sequela of AFE is disseminated intravascular coagulation (DIC).

CASE: This report describes an atypical presentation of AFE manifested by sudden fetal bradycardia and complicated by maternal DIC. The DIC was eventually successfully treated with the use of recombinant activated factor VIIa.

CONCLUSION: The use of recombinant activated factor VIIa in cases of massive hemorrhage, such as in our patient, is controversial but has been shown, in some cases, to reverse DIC and be successful. The use of recombinant activated factor VIIa should be considered in patients with massive obstetric hemorrhage in whom standard measures of stabilization are unsuccessful.

(*Obstet Gynecol* 2007;109:524–5)

Amniotic fluid embolism (AFE) was first described in the English language by Steiner in 1941.¹ Currently, this condition is responsible for about 10% of maternal deaths in the United States with a reported incidence of 1 in 8,000 to 80,000 pregnancies. The classic presentation is that of a sudden, profound cardiovascular collapse, followed by maternal bleeding due to disseminated intravascular coagulopathy (DIC). We describe a case of AFE in which fetal bradycardia was the initial presentation.

CASE

A 43-year-old woman, gravida 8, para 5, was admitted at 40 weeks and 5 days gestation in early labor. On admis-

sion, her vital signs were stable. Epidural anesthesia was placed without hypotension. Oxytocin was used for labor augmentation. Amniotomy performed at a cervical dilatation of 4 cm revealed thick meconium-stained fluid. A fetal scalp electrode and an intrauterine pressure catheter were placed. Three minutes later, the fetal heart rate dropped to the 70s (beats per minute) for 3 minutes. Fetal resuscitation was performed by maternal positioning and administration of oxygen with recovery to baseline. One hour later, terminal bradycardia was noted into the 50s (beats per minute) with no response to further resuscitative measures.

An emergency low-transverse cesarean delivery was performed via vertical skin incision under epidural anesthesia. A viable male infant weighing 3,490 grams was delivered with Apgar scores of 6 and 7 at 1 and 5 minutes, respectively. The arterial cord pH was 6.99 with a base excess of -8 . No evidence of placental abruption was noted. Profuse bleeding was noted in the uterine incision and broad ligaments. Hemostatic stitches were placed. Intraoperative laboratory evaluation of the mother revealed a severe coagulopathy with a fibrinogen level of 45 mg/dL, international normalized ratio of 1.9, activated partial thromboplastin time (aPTT) of 150 seconds, and prothrombin time (PT) of 21 seconds. Platelets were 95,000/ μ L and hemoglobin was 3 g/dL (admission hemoglobin had been 12.7 g/dL). Maternal arterial blood gas showed a pH of 7.26 on 50% inspired oxygen.

Aggressive correction of the coagulopathy was attempted with blood products. The patient received 6 units of packed red blood cells (RBCs), 6 units of platelets, 2 units of fresh frozen plasma, and 2 units of cryoprecipitate intraoperatively. There was minimal improvement in the bleeding. After 2 hours of replacement with blood products, the decision was made to give recombinant activated factor VII at a dose of 60 mcg/kg. Within 10 minutes of recombinant factor VIIa infusion, a significant improvement in the bleeding was noted and the surgery was completed. Within 2 hours of giving the recombinant factor VIIa, laboratory values improved significantly, with an aPTT of 43 seconds, PT of 10.4 seconds, and an international normalized ratio of 1. The patient was transferred to the intensive care unit in stable condition. The estimated intraoperative blood loss was 6,000 mL. In the immediate postoperative period, the fibrinogen level was 41 mg/dL. The patient still continued to have oozing from the skin incision and needed replacement with more blood products for the correction of fibrinogen and platelets levels, which finally normalized on postoperative day 3.

During the next 4 days, the patient developed multiple-organ failure including renal failure. There was never any evidence of pathologic thrombosis. Postoperatively, she received a total of 6 units of fresh frozen plasma, 24 units of platelets, 6 units of packed RBCs, and 2 units of cryoprecipitate. She was extubated on postoperative day 4 and made a complete recovery, including recovery of normal renal function. She was discharged home in stable condition on postoperative day 11.

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COMMENT

Amniotic fluid embolism is a catastrophic and potentially fatal disease, and its mechanism of injury is poorly understood. The pathophysiology of AFE is believed to be humoral. When amniotic fluid gains entry to the maternal bloodstream, the pulmonary vasculature is exposed to immunologically active fluid. This results in intense vasoconstriction, leading to the release of inflammatory materials, including histamines, prostaglandin, and leukotrienes, in the lung. The onset of AFE is said to be abrupt, manifested by sudden dyspnea, hypoxemia, and cyanosis. Eighty percent of patients experience cardiopulmonary arrest. Of the survivors, about 45% will develop severe coagulopathy 30 minutes to 4 hours later, usually accompanied by uterine atony.

The cause of coagulopathy from AFE is probably multifactorial. Amniotic fluid has a procoagulant effect; its addition to plasma accelerates clotting by activating factor X. The rate of acceleration along the intrinsic clotting cascade correlates directly with both gestational age and phospholipid content of the amniotic fluid. Although amniotic fluid lacks plasmin and plasmin activator, it contains plasmin proactivator. Weiner² speculated that thrombin generation in the pulmonary beds leads to plasmin and kinin production, which in the absence of antiplasmin, perpetuate their own generation. When thrombin generation occurs in an environment of excess plasmin proactivator, a coagulopathy composed of fibrin-fibrinolysis-yielding fibrin split products may follow. Excessive production of fibrin split products is implicated in decreased uterine contractility, which often occurs in cases of AFE.

Recombinant activated factor VIIa has been successfully used to prevent and control bleeding in hemophilic and nonhemophilic patients. For normal hemostasis, tissue factor and factor VIIa activate factors IX and X at the site of vascular injury to generate thrombin and form fibrin. When pharmacologic doses of recombinant factor VIIa are given, there is a burst in thrombin formation.³ This increase in the rate of thrombin formation permits the formation of a fully stabilized fibrin plug with a tight fibrin structure, making it resistant to premature lysis.

There is limited literature on the use of recombinant factor VIIa in obstetrics. In our reported case, the hemostatic effectiveness of recombinant factor VIIa was dramatic. There has been one report of

successful management of DIC associated with AFE using recombinant factor VIIa in the literature (Ovid, English language only, January 1980 to December 2005, search terms “amniotic fluid embolism” and “disseminated intravascular coagulation”).⁴ Recommended dosing depends on the severity of coagulopathy. The dose that has been used in the treatment of bleeding ranges from 20 to 120 mcg/kg every 2 to 3 hours until bleeding stops. Further studies are needed to determine the optimal dose and timing of administration in postpartum hemorrhage. In all cases, the PT and aPTT have been shortened markedly after treatment with recombinant factor VIIa. Factor VIIa is not, however, a cure all, as multiple controlled trials have demonstrated no advantage to wide-scale off-label use, and some situations are clearly futile. For example, one series of patients documented reduced bleeding but still 70% final mortality when recombinant factor VIIa was administered after transfusion of more than 10 units packed RBCs to patients in shock.⁵ Furthermore, with more off-label use, more reports of thromboembolic events are being reported, with more than 50 fatalities reported thus far to the US Food and Drug Administration.⁶ As clinical use and experience increase and cost of the drug decreases, recombinant factor VIIa may become the treatment of choice in selected cases of massive obstetric hemorrhage unresponsive to conventional treatments. Caution will be important as the morbidity and mortality associated with the use of recombinant factor VIIa in these very ill patients continues to be common.

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Retained Fetal Parts After Elective Second-Trimester Dilatation and Evacuation

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BACKGROUND: Extrusion of fetal parts into the abdomen after second-trimester pregnancy termination is rare.

CASE: We report a case of extrusion of fetal parts into the broad ligament at the time of second-trimester pregnancy termination that remained undetected for 10 days.

CONCLUSION: In cases of perforation during second-trimester pregnancy termination, meticulous evaluation of the abdomen and pelvis with ultrasonography or computerized tomography should be performed if complete fetal evacuation cannot be confirmed.

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Uterine perforation during second-trimester dilatation and evacuation is a rare complication occurring in only 0.2% to 0.4% of such procedures.¹ Extrusion of fetal parts into the abdomen after such a complication is even less common.² We report a case of extrusion of the fetal parts into the broad ligament at the time of dilatation and evacuation that was not recognized until 10 days later.

CASE

A young woman, after elective abortion at approximately 19 weeks of gestation, was referred from a local physician's office after an ultrasound examination revealed findings consistent with fetal parts outside the uterus. Ten days before presentation, the patient had undergone an elective dilatation and evacuation in another state after laminaria placement the night before. The procedure was performed by a physician experienced in second-trimester termination procedures. A dating ultrasound examination before the procedure confirmed the patient's stated gestational age. The procedure was complicated by severe hemorrhage that resulted in hospitalization and transfusion. The patient was

admitted and cared for during her hospitalization by the operating surgeon. A limited ultrasound examination to document an empty uterus was performed before transfer to the hospital, but no further diagnostic testing was performed during the hospitalization. She was discharged on a course of oral antibiotics.

Because of the hospitalization, the patient's parents became aware of the termination. They subsequently arranged follow-up with their personal physician 1 week after discharge. During the bimanual examination at this follow-up visit, a hard mass was noted in the patient's right lower quadrant. With the exception of minimal vaginal spotting, the patient was asymptomatic. Pelvic ultrasonography showed evidence of fetal skull and spine within the uterus. At this time, the patient was transferred to the Regional Medical Center at Memphis for management. Upon arrival, the patient was afebrile and had a normal white blood cell count. Repeat ultrasound examination showed a possible extrusion of the fetal parts through the uterine wall. Computed tomography confirmed the presence of the fetal calvarium and spine outside the uterus (Fig. 1). The fetal parts were located in a fluid collection that appeared to be in continuity with the endometrial cavity. Based on these findings, the patient was scheduled for exploratory laparotomy with removal of fetal parts and repair of uterine perforation. At the time of laparotomy, the uterus had contracted to 12-week gestational size. The anterior broad ligament was opened revealing fetal parts that had been completely extruded into the broad ligament (Fig. 2) Additionally, the fetal spine extended into the uterus through a 3-cm laceration. The right uterine artery was clearly visible at the base of the laceration. The fetal parts were removed, and the laceration of the right lateral uterine wall was repaired using 1–0 chromic suture in a running, locking fashion. The peritoneum of the broad ligament was not closed to prevent possible abscess formation. The

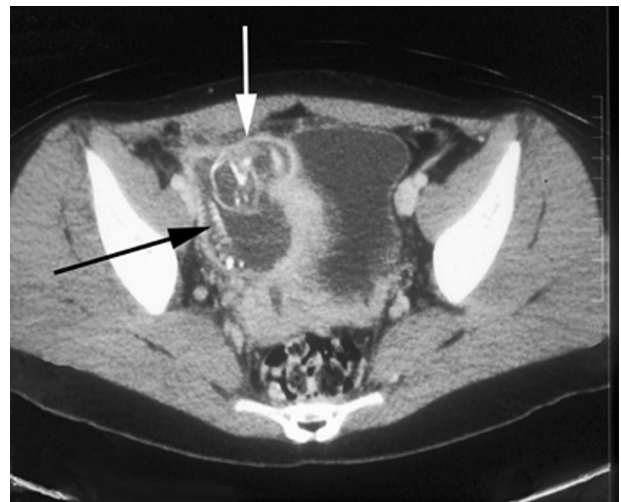


Fig. 1. Computerized tomography showing fetal calvarium (white arrow) and spine (black arrow) outside uterus. Givens. *Retained Fetal Parts*. *Obstet Gynecol* 2007.

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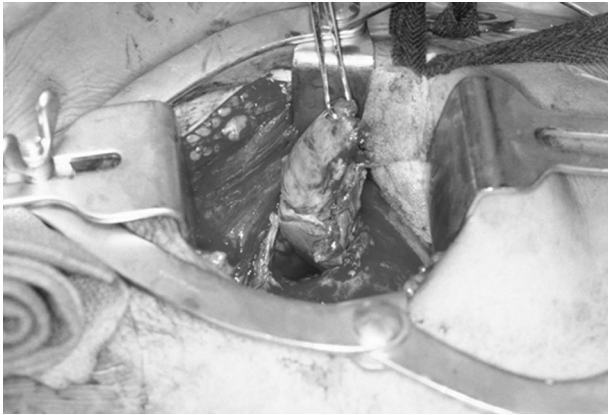


Fig. 2. Fetal parts being removed from broad ligament.
Givens. Retained Fetal Parts. Obstet Gynecol 2007.

patient's postoperative course was unremarkable, and she was discharged home on postoperative day 3.

COMMENT

Retained products of conception and uterine perforation are known complications of both first- and second-trimester termination procedures. However, extrusion of fetal parts into the abdomen is an uncommon complication of second-trimester terminations. In most cases, patients become acutely ill if this complication is not discovered and treated. This case is particularly unusual in that the patient remained asymptomatic despite fetal parts extruding into the broad ligament. This may have been partially due to the isolated location of the fetal parts, the use of oral antibiotics postoperatively, and the near miss of the uterine artery that was immediately adjacent to laceration.

Counting of fetal parts and reconstruction of the aborted fetus to eliminate the possibility of retained

fetal parts after second-trimester procedures is a common precaution. This step had been omitted in this case because of the occurrence of hemorrhage. However, this step could have been performed even after the patient had been transported to the hospital and the information reported to the treating physician. A limited ultrasound examination to ensure the uterine cavity was empty had been used instead. This case illustrates the necessity of ensuring that all fetal parts are removed after second-trimester terminations. Because ultrasonography is generally available in settings where pregnancy terminations are performed, it is the most common study used to identify retained fetal tissue in cases where all fetal parts cannot be verified. Whenever perforation is a consideration (ie, bleeding more than expected, passage of instrument beyond perceived uterine length, or retrieval of suspected extrauterine tissue), ultrasonography may be considered for further evaluation. Failure of a limited ultrasound examination during an acute emergency to identify major fetal parts should prompt suspicion of extruded products and further evaluation performed to exclude this possibility; evaluation in these circumstances should include imaging of the entire pelvis to exclude extrusion of fetal parts into the broad ligament or abdomen. Alternatively, computerized tomography can be performed to more completely evaluate the pelvis and abdomen.

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Diffuse Uterine Leiomyomatosis With Uterine Rupture and Benign Metastatic Lesions of the Bone

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BACKGROUND: We report a case of diffuse uterine leiomyomatosis in pregnancy complicated by uterine rupture and dissemination to the bone.

CASE: A 35-year-old nulliparous woman with a history of uterine leiomyoma presented at term with fetal demise. Failed induction of labor and hemodynamic instability due to uterine rupture resulted in a cesarean hysterectomy. A free-air series performed postoperatively to confirm paralytic ileus revealed multiple lytic bone lesions. The diagnosis of diffuse uterine leiomyomatosis with metastasis was made on histology of the resected uterus and fine-needle aspiration biopsy of the bone. She was managed conservatively, and the lesions are now regressing.

CONCLUSION: Diffuse uterine leiomyomatosis should be considered in pregnant women with a history of uterine fibroids and peripartum hemorrhage.

(*Obstet Gynecol* 2007;109:528–30)

Although uterine leiomyomata are the most common benign internal tumors in humans, there are other smooth-muscle proliferations that are generally accepted as qualifying for the designation of leiomyomatosis. These may be divided into intrauterine and extrauterine variants. The latter includes disseminated peritoneal leiomyomatosis and lymphangioliomyomatosis, which have a predilection for the lungs in women of childbearing age.^{1,2} The former includes intravenous leiomyomatosis and diffuse uterine leiomyomatosis.^{3–5} These unusual, but benign, lesions are distinguished histologically from leiomyosarcoma by their lack of sufficient nuclear atypia, mitotic activity, and necrosis.¹

We present a patient with diffuse uterine

leiomyomatosis who experienced uterine rupture during labor and was found to have bony metastases, diagnostic of benign metastasizing leiomyomatosis.

CASE

A 35-year-old white female, gravida 2, para 0010, presented at 38 weeks of gestation reporting vomiting, abdominal pain, and decreased fetal movements. Her medical history was significant for chronic hypertension. Ultrasound examination performed at 13 weeks of gestation confirmed the gestational age. This also showed a 6-cm tumor at the fundus of the uterus, reported as a fibroid.

On admission the patient was afebrile, blood pressure 152/92 mm Hg, respiratory rate 20 breaths per minute, and pulse rate 120 beats per minute. Her abdomen was diffusely tender. The cervix was dilated 1 cm, and uterine contractions were irregular. Ultrasonography confirmed fetal death and oligohydramnios.

Laboratory studies done on admission showed a white blood cell count of $28.5 \times 10^3/\mu\text{L}$, hemoglobin 9.4 g/dL, platelet count $97.5 \times 10^3/\mu\text{L}$, creatinine of 1.1 mg/dL, normal liver function test, fibrinogen of more than 1,000 mg/dL, and normal prothrombin and activated partial thromboplastin times.

Labor was induced using misoprostol for cervical ripening, followed by pitocin. Over the next 24 hours after the patient's admission, the clinical findings were suggestive of placental abruption, and her cervix failed to dilate beyond 4 cm. After receiving 2 units of packed red blood cells and adequate volume replacement with crystalloids, the decision was made to perform a cesarean delivery.

Approximately 1.5 liters of dark red blood and clots were found in the peritoneal cavity. A 2,190-g stillborn fetus was delivered. The placenta was completely detached from its posterior location, and a large uterine rupture was noted on the posterior uterine wall. A cesarean hysterectomy was performed after unsuccessful attempts to repair the uterus. The patient received a total of 10 units of packed red blood cells and 22 liters of crystalloids.

On postoperative day 2, a free-air series confirmed an ileus and, incidentally, revealed multiple lytic rib lesions. Computerized tomography scan showed multiple lytic lesions involving the iliac bones (Fig. 1A) and vertebral bodies (Fig. 1B). The patient was managed conservatively and discharged home on postoperative day 5.

After extensive outpatient evaluation, a diagnosis of diffuse uterine leiomyomatosis with benign metastasizing lesions was made. Histology of the uterus (Fig. 2A and Fig. 2B) along with fine-needle aspiration of the iliac crest lesion (Fig. 2C) confirmed the benign nature of this neoplasm. Tumor cell nuclei were positive for progesterone and estrogen receptors.

At 2 months postpartum computerized tomography scan revealed a spontaneous decrease in size and numbers of the lytic bone lesions. A whole-body scan done at 1 year revealed complete resolution of lesions previously seen in

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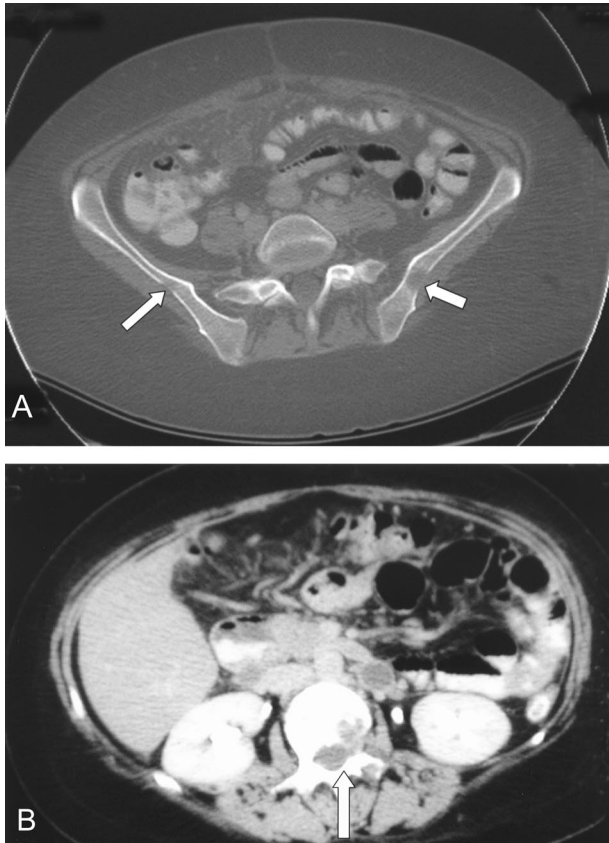


Fig. 1. **A.** Computerized tomography scan showing lytic lesions of the iliac bones. *Arrows* point to lesions of the iliac crests. **B.** Computerized tomography scan showing lytic lesions of the lumbar vertebral bodies. *Arrow* points to lesion of the lumbar spine.

Thomas. *Metastasizing Leiomyomatosis in Pregnancy*. *Obstet Gynecol* 2007.

the skull, right scapula, and pelvis. The patient continues to do well clinically.

COMMENT

Diffuse uterine leiomyomatosis is quite rare and affects women who are reproductive-aged.^{3,4} In this condition, innumerable smooth-muscle nodules (less than 1 cm) result in a diffuse and massively enlarged uterus. Although the uterus is extensively infiltrated by tumor, the condition is benign because it lacks mitosis, necrosis, and nuclear atypia seen in leiomyosarcoma.^{3,4} Menorrhagia, infertility, and antepartum hemorrhage are typical presentations, and it is often mistakenly diagnosed as multiple uterine myomata.^{3,4}

Benign metastasizing leiomyoma is also a rare condition.⁶⁻⁸ It can occur in any age group but most commonly occurs between the ages 30 and 74. It is a benign smooth-muscle tumor whose origin remains

controversial; however, the uterus may be the primary site.^{7,8} In many cases, it has been erroneously labeled as metastasizing leiomyomatosis.^{7,8} With metastasizing leiomyoma, metastatic lesions are usually identified several years after uterine surgery in a woman with a history of fibroids.⁷ The growth of the tumor is thought to be hormone dependent with progesterone and estrogen receptors identified in both the primary tumor and the disseminated lesions.^{1,6,7} The usual sites of dissemination are the lungs, lymph nodes, and the abdomen.⁵

In our review of the literature “benign metastasizing leiomyomata” were found in association with benign uterine leiomyoma (metastasizing leiomyoma) and intravenous leiomyomatosis of the uterus (metastasizing leiomyomatosis) but not with diffuse uterine leiomyomatosis.^{1,5,7,8} Almost all cases previously reported as metastasizing leiomyomatosis were actually metastasizing leiomyoma by modern standardized criteria.^{1,7,8}

At the time of surgery, the structure that had appeared as a fundal uterine fibroid on ultrasound examination was not seen. Instead, this was the site of the uterine perforation. Furthermore, the entire uterine fundus was replaced by a diffuse, multinodular, infiltrating spindle cell proliferation, diagnostic of diffuse uterine leiomyomatosis.¹ We believe the diffuse uterine leiomyomatosis resulted in the posterior uterine rupture and placental abruption causing intrapartum hemorrhage and fetal death.

Tumor found in the uterus and bone metastases were similar; this was interpreted as benign metastasizing leiomyomatosis. The etiology of benign metastasizing leiomyomatosis remains controversial, but recent cytogenetic studies were consistent with a monoclonal origin of both uterine and pulmonary tumors, supporting the concept of “benign” metastatic pulmonary lesions.¹ As demonstrated in this case, the hormone-dependent nature of the metastatic lesions was confirmed by the presence of estrogen and progesterone receptors on histology of the uterine nodules and regression of the bony lesions postpartum. Treatment with gonadotropin-releasing hormone analog resulting in significant reduction in uterine size has also been documented.³

In conclusion, obstetricians need to consider diffuse uterine leiomyomatosis as a part of their differential diagnosis in a pregnant woman who has a history of uterine fibroids and develops peripartum hemorrhage. Also, in patients with uterine fibroids and metastatic lesions, including lytic bone lesions, benign metastasizing leiomyoma, or metastasizing leiomyomatosis should be considered.



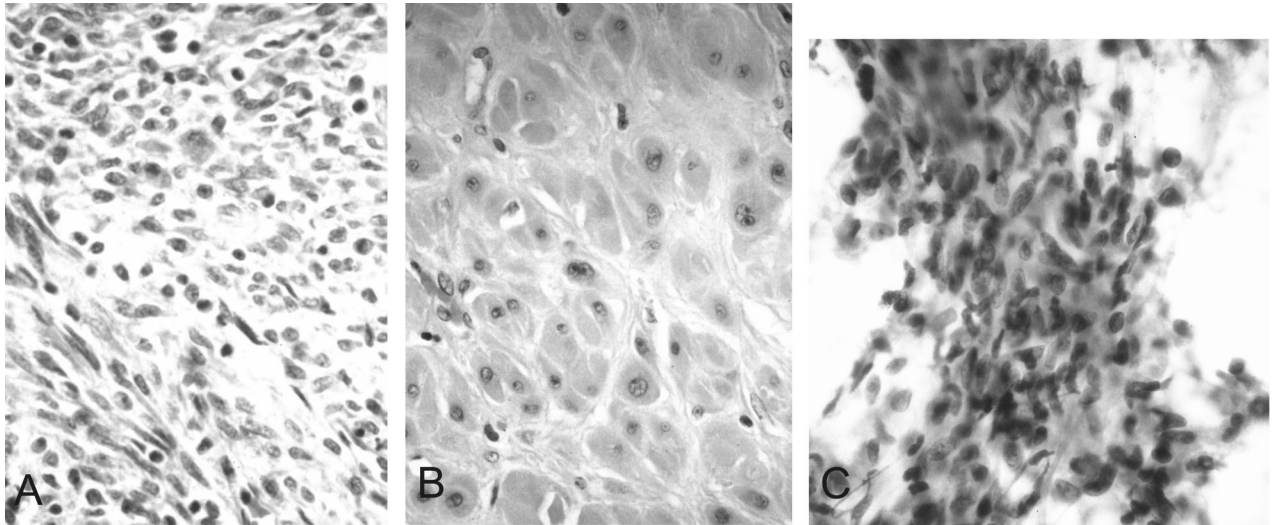


Fig 2. A. Diffuse uterine leiomyomatoses with high cellularity, oval-to-spindle-shaped tumor cell nuclei, increased nuclear cytoplasmic ratio, and no significant nuclear atypia or mitotic activity. Hematoxylin-eosin-stained section at 100× original magnification. B. Normal hypertrophic pregnant myometrium. Hematoxylin-eosin-stained section at 100× original magnification. C. Fine-needle aspirate from the lytic bone lesions. The tumor cells are similar to those found in the uterus (Fig. 2A). Papanicolau-stained aspirate at 200× original magnification.

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Alport Syndrome and Pregnancy

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BACKGROUND: Alport syndrome is a disorder associated with mutations in the type IV collagen gene and manifested by progressive glomerulonephritis. Little is known about the effect of Alport syndrome on pregnancy outcome.

CASE: We report a patient with Alport syndrome whose pregnancy was complicated by rapidly progressive severe preeclampsia, fetal growth restriction, and acute renal failure. At 25 weeks of gestation, termination of pregnancy was performed. The patient's renal function was well controlled before pregnancy, but had not recovered at 6 months postpartum, requiring ongoing hemodialysis.

CONCLUSION: Alport syndrome in pregnancy has the potential for disease acceleration with rapid parallel progression of vasculopathy in the placental and renal circulations.

(Obstet Gynecol 2007;109:531–2)

Alport syndrome is the result of a range of mutations in the type IV collagen gene and manifested by progressive glomerulonephritis. Involvement of the renal glomerular basal membrane leads to progressive glomerulonephritis presenting with hematuria, proteinuria, and renal failure in early adulthood.¹ Although women in their reproductive years are affected by this syndrome, little is known about the effect on pregnancy outcome. We report on a patient with Alport syndrome complicating pregnancy with significant effects on placental and renal function.

CASE

A 29-year-old primigravida was referred to Labor and Delivery at 25 2/7 weeks of gestation for evaluation of severe hypertension (230/130 mmHg) and proteinuria (15g/24 h). She had Alport syndrome since age 11 years, diagnosed after a screening urinalysis revealed proteinuria. She had mild proteinuric renal insufficiency (serum creatinine 1.0–1.2mg/dL, 24-hour urine protein 1.0–2.0 g, cre-

atinine clearance 57.8 mL/m²) when she naturally conceived. A singleton intrauterine pregnancy consistent in size with her last menstrual period was noted at 12 weeks of gestation by prenatal sonogram.

Her blood pressures had initially been well controlled (140–90 mmHg) on methyldopa 200 mg and atenolol 50 mg daily. By 20 6/7 weeks, serum creatinine had increased to 1.8 mg/dL, whereas proteinuria was unchanged (0.9 g/24 h). Ultrasound assessment at 21 2/7 weeks showed an estimated fetal weight at the 16th percentile (293g) and elevated uterine and umbilical artery blood flow resistance. The patient was commenced on aspirin 81 mg/d and atenolol was switched to labetalol due to concerns about the effect on fetal growth. At 23 2/7 weeks, methyldopa and labetalol were increased to 3 g and 2 g daily, respectively, to control accelerating hypertension. At this time increasing serum creatinine (4.5 mg/dL) and urea nitrogen (43 mg/dL) were noted, whereas potassium was high normal (5.3 meq/L). Two weeks later the patient presented to the office with shortness of breath, palpitations, progressive leg swelling, blurry vision with scotoma, and general fatigue. She was significantly hypertensive (242/109 mmHg), tachypneic, obese (body mass index of 38.7), had retinal cotton wool spots on funduscopy, and 3+ pitting edema in all extremities. Her hematocrit was 27.0%, platelet count 149,000/mm³, serum creatinine 6.6 mg/dL, potassium of 5.8 mN, aspartate transaminase/alanine transaminase of 89/62 units/mL, uric acid 6.4 mg/dL, lactate dehydrogenase of 2,699 units, and 24-hour proteinuria was 15 g. The fetal heart rate was 140 beats per minute. Ultrasound-estimated fetal weight was 466 g (less than 5th percentile), the amniotic fluid index 10.6 cm (10th percentile), umbilical artery end diastolic velocity was reversed, and the biophysical profile score and amniotic fluid volume were normal (score 8/10). Based on the combination of these findings, severe preeclampsia with early onset severe fetal growth delay and acute renal failure was diagnosed at 25 2/7 weeks of gestation. After a detailed discussion including the managing perinatologists, nephrologists, and neonatologists, delivery for worsening maternal condition was advised. At our institution survival and intact survival rates for severely growth restricted fetuses at this gestational age are 30% and 12% respectively even after the administration of antenatal steroids. Accordingly, no obstetric intervention for fetal indication was agreed upon after detailed multidisciplinary counseling. Magnesium sulfate was immediately started for seizure prophylaxis. Intracervical laminaria were placed and labor was induced with misoprostol 400 mcg per vagina, followed by intravenous oxytocin augmentation started 4 hours later. Intrapartum serum creatinine and potassium peaked at 7.3 mg/dL and 6.0 meq/L, respectively. Hyperkalemia was corrected with intravenous furosemide. Blood pressure in labor was controlled by intravenous labetalol and ranged between 104–242/55–131 mmHg. The patient's urinary output ranged between 80–100 mL per hour. After 19 hours of labor induction, the patient delivered a normal-appearing stillborn, 400 g (less

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than 1st percentile), female infant; the placental weight was 55 g.

Although serum potassium normalized by postpartum day 1, serum creatinine remained elevated at 8.3 mg/dL, with urea nitrogen of 78 mg/dL. After initial removal of 6 liters of fluid by dialysis in the first 48 hours after delivery, the patient required long-term therapy with furosemide 480 mg/d and hemodialysis. Her hypertension was controlled with methyldopa 2,250 mg, labetalol 1,600 mg and amlodipine 10 mg daily. Six months postpartum, the patient still required hemodialysis.

COMMENT

We present the clinical course of a patient with Alport syndrome complicating pregnancy. Notable was the rapid progression of renal disease coupled with severe early onset of placental disease in the form of preeclampsia and fetal growth restriction, as well as the long-lasting effect on renal function. This clinical presentation and our knowledge about the basic features of Alport syndrome suggests a synergistic interaction between placental and renal vascular factors that may be responsible for this complicated course during pregnancy.²

Successful placental vascular development requires adequate trophoblast invasion and dissolution of the spiral artery media to convert the maternal compartment of the placental circulation into a low-resistance, high-capacitance vascular bed. In the fetal compartment successive branching of the villous vascular tree results in a progressive decline in umbilical artery blood flow resistance and increased surface area for maternofetal gas, fluid, and nutrient exchange. In the mid trimester the presence of bilateral uterine artery notching and umbilical artery end-diastolic blood flow reversal documents the failure of this physiologic process as the basis for the development of severe preeclampsia in the mother and growth restriction of the fetus and placenta. There are several plausible explanations to link the features of Alport syndrome to placental maldevelopment and progressing renal disease in pregnancy.

The early onset of placental disease suggests

interference with trophoblast invasion and placental angiogenesis. Type IV collagen is located in the basal lamina of placental and renal vessels and if mutated at both sites would be subject to the same destructive process. Acceleration of disease could be due to placental oxidative stress, one of the products of normal placental growth that has been proposed as a mechanism for basal membrane damage.^{1,3-6} Finally, a common antigen between placental and glomerular basal membrane may be responsible for disease acceleration.⁷ Although Alport syndrome is not an autoimmune disease like Goodpasture's syndrome, a connection between the two diseases was suspected for many years.¹ In this model enhanced autoantibody production triggered by placental antigen exposure may accelerate renal disease by cross-reaction with the basement membrane. However, further research into the distribution of $\alpha3(IV)$, $\alpha4(IV)$, or $\alpha5(IV)$ collagen in the maternal spiral artery, decidual membrane, or chorionic villi in pregnant women will be necessary to delineate this process. Although the pathophysiology remains speculative, the practitioner needs to be aware of the potential for rapidly progressive deterioration of placental and renal functions in pregnant women with Alport syndrome.

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Methicillin-Resistant *Staphylococcus aureus* Necrotizing Pneumonia Arising From an Infected Episiotomy Site

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BACKGROUND: We report a case of methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis and pneumonia in a postpartum patient.

CASE: A 21-year-old gravida 1 para 1 presented on postpartum day 9 with persistent elevated fever, dyspnea, cellulitis of the upper extremities, and an infected episiotomy site. Computed tomography of the chest revealed multiple widely distributed nodules and bilateral infiltrates with central cavitations. Sputum, blood, urine, and episiotomy site cultures grew MRSA, subsequently demonstrated by molecular fingerprinting and antibiotic susceptibility to be community acquired. A magnetic resonance imaging of the pelvis demonstrated pelvic thrombophlebitis.

CONCLUSION: Community-acquired MRSA is an emerging problem, which may present as skin and soft tissue infections or sepsis. Seeding from an infected episiotomy site seems to be a potential route of systemic infection. The use of empirical treatment with β -lactam agents may fail. Appropriate cultures should be obtained and if MRSA is diagnosed, vancomycin should be employed.

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For several decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has been known to cause infections in patients with well-described risk factors, including hospitalization, surgery, and residence in chronic care facilities. Recently, MRSA has been diagnosed in patients lacking traditional risk factors.¹ Many of these infections have occurred in the community and have affected children, young adults, and pregnant and postpartum women, and some have been associated with substantial morbidity.^{2,3}

We report a case of MRSA sepsis and pneumonia

in a postpartum patient who developed septic pelvic thrombophlebitis due to an infected episiotomy site. Septic emboli arising from the thrombosed pelvic veins apparently underwent hematogenous spread, resulting in necrotizing pneumonia and soft tissue infection.

CASE

A 21-year-old gravida 1 para 1 was sent to the emergency room by her obstetrician on postpartum day 9 because of persistent fever, difficulty in breathing, and back pain of moderate intensity. The patient had had a normal spontaneous delivery over a second-degree median episiotomy of a female infant with 1-minute and 5-minute Apgar scores of 9 and 9. Her postpartum course was significant for a temperature of 38.4°C on the day of delivery, with no obvious site of infection, and she did not receive any antibiotics.

The patient thereafter remained afebrile and asymptomatic and was discharged on postpartum day 2. Two days after her discharge she felt weak and experienced increased pain at the site of the episiotomy. That triggered a visit to her private obstetrician who noted that the episiotomy site was slightly erythematous and separated, and prescribed amoxicillin-clavulanic acid. Over the following 2 days the patient continued to have low-grade fever but also experienced progressively increasing difficulty in breathing. On postpartum day 8 the back pain made her breathing more difficult and she started having blood-tinged sputum. The same day she developed a temperature of 40.0°C and noticed erythema and swelling of her left forearm and the dorsal area of the distal phalange of her right index finger. She called her physician and was referred to the emergency room.

On presentation she had a temperature of 39.0°C and her blood pressure was 120/70 mm Hg. On physical examination she was diaphoretic and in mild respiratory distress. She had tachycardia with normal cardiac sounds and no murmurs or rubs. Decreased breath sounds were appreciated at both bases with coarse crackles bilaterally. There was an erythematous-based macular rash on the upper inner surface of the left forearm that was tender to palpation and that was consistent with cellulitis (Figure 1). A similar rash was noted on the dorsal area of the distal phalange of the right median and index fingers. On pelvic examination the episiotomy site was separated, grossly infected and moderately tender. On pressure a minimal quantity of pus was noted. The uterus and the adnexa on bimanual examination were not tender. Both lower extremities were non tender, and there were no clinical signs of deep venous thrombosis. The laboratory workup was significant for severe leukocytosis, with a white blood cell count of 32,400/UL with 26% bands. The C-reactive protein level was 20,890 mg/dL (normal range 0.012– 0.500). A chest X-ray was performed that revealed left upper lobe infiltrates, diffused increased interstitial markings bilaterally, as well as pleural effusions. A chest computed tomog-

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Fig. 1. Picture of the inner surface of the left forearm of the patient demonstrating cellulitis after antibiotic treatment. *Rotas. Postpartum Sepsis From an Infected Episiotomy. Obstet Gynecol 2007.*

graphy scan that followed was remarkable for the presence of innumerable small, widely distributed nodules measuring up to 9 mm in size. In addition there was a rounded, pleural-based infiltrate anterolaterally in the left upper lobe measuring 4 cm, with a central cavitation (Fig. 2). Similar consolidations were seen posteriorly in the left upper lobe as well as at the right base and in a small area in the right upper lobe. There was also a loculated right pleural effusion.

The overall appearance was suggestive for bloodborne pneumonia and sepsis from septic emboli. Sputum, blood, urine and episiotomy site cultures were obtained and the patient was placed on broad-spectrum antibiotic coverage that included vancomycin, ampicillin-sulbactam, and gentamicin. The episiotomy site was cleaned and débrided.

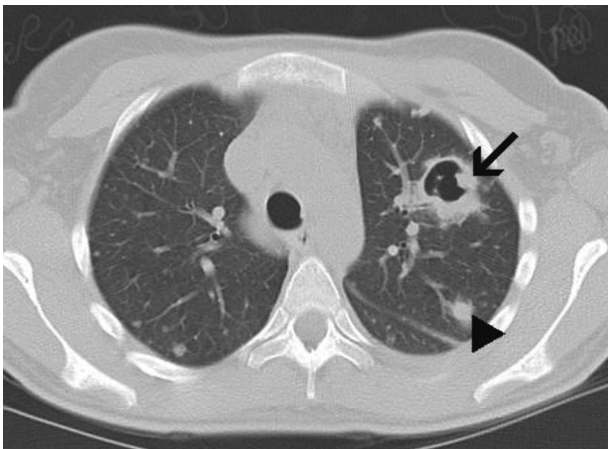


Fig. 2. Computed tomography of the chest illustrating the multiple septic emboli (*black arrowhead*) and the cavitory lesions (*black arrow*) consistent with necrotizing pneumonia. *Rotas. Postpartum Sepsis From an Infected Episiotomy. Obstet Gynecol 2007.*

The patient's skin lesions started to resolve after taking broad-spectrum antibiotics for 48 hours. The workup for the origin of the septic emboli included a transthoracic echocardiogram and Doppler of the lower extremities, which were both negative, as well as a computed tomography scan of the abdomen and pelvis, which failed to demonstrate any abscess in the pelvis or any sign of pelvic thrombophlebitis. Magnetic resonance imaging of the pelvis performed on hospital day 2 demonstrated a collection located in the perineum within the fat immediately lateral to the rectum on the right measuring 5.2×2.9×4.7 cm. In addition, there was excessive thrombosis of the pelvic veins surrounding the uterus, especially the cervix (Fig. 3), and a loculated collection in the pelvic floor that could represent an abscess. A rectal examination that was performed on hospital day 3 did not elicit any pain at the site of the suspected collection seen in the magnetic resonance imaging, and no further consideration was given to draining that collection. The patient was placed on intravenous heparin. The blood and sputum culture as well as the culture from the episiotomy site grew MRSA. Molecular fingerprinting (pulsed-field gel electrophoresis pattern and ribotype) of the strain isolated indicated that it differed from typical nosocomial isolates and was community acquired. This was also supported by a review of the antibiotic susceptibility of MRSA strains isolated at our institution over the last 5 years. The specific strain was highly susceptible to vancomycin, tetracyclines, and trimethoprim-sulfamethoxazole, and the antibiotic coverage was narrowed down to those antibiotics. The patient, though, continued to have low-grade fever until hospital day 7 when her pleuritic pain became also worse. A repeat chest computed tomography scan showed an increase in the size of the right pleural and the cavitory lesions. An aspiration of the right pleural effusion was performed which yielded 600 mL of exudates that grew MRSA. After the drainage of the pleural effusion the patient improved dramatically. She was discharged home on hos-

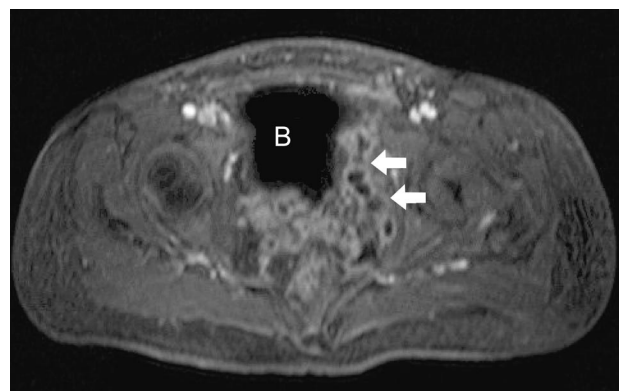


Fig. 3. Axial enhanced volumetric interpolated breath-hold examination image reveals multiple distended serpiginous low signal structures (*arrows*) with high signal borders representing multiple thrombosed pelvic veins. B, bladder. *Rotas. Postpartum Sepsis From an Infected Episiotomy. Obstet Gynecol 2007.*



pital day 10 after she had been afebrile for 48 hours and the repeat blood cultures were negative. She went home on intravenous vancomycin for 3 weeks and therapeutic doses of low-molecular heparin for at least 4 to 6 weeks. The patient had a human immunodeficiency virus test at the beginning of her pregnancy as well as a repeat test during her hospitalization, with both being negative. She did not have any other evidence of immunosuppression.

COMMENT

We report a case of systemic infection with MRSA in the postpartum setting, attributable to an infected episiotomy site. This case demonstrates that community-acquired MRSA infections in pregnant and postpartum patients, even those who lack traditional risk factors for MRSA infections, are becoming more common and can result in severe maternal morbidity.

Humans are a natural reservoir for *Staphylococcus aureus*, and asymptomatic colonization is far more common than infection, with carriage rates ranging between 25% and 50%.⁴ Colonization of the nasopharynx, perineum, or skin, particularly if the cutaneous barrier has been disrupted or damaged, may occur shortly after birth and may recur anytime thereafter. Transmission occurs by direct contact to a colonized carrier, and colonization may be transient or persistent and can last for years.⁴

Methicillin-resistant *Staphylococcus aureus* was first isolated in England in 1961.^{1,4} In the past two decades, the prevalence of MRSA strains among *Staphylococcus aureus* carriers has steadily increased in hospitals in the United States and abroad. National Nosocomial Infections Surveillance data collected by the Centers for Disease Control and Prevention indicated that by the end of 1992, MRSA carriage rates had increased to 40% and approached 50% in intensive care units by the end of 1998. It is probable that the prevalence rate of MRSA in many U.S. hospitals has now reached 50%.¹ Given these high rates, it is reasonable to anticipate that correspondingly high rates of MRSA strains are now also found in the community. However, because no systematic, population-based surveillance of community isolates of *Staphylococcus aureus* exists, the true prevalence of MRSA in the community cannot be determined.¹ One hospital-based study found that up to 40% of MRSA infections in adults were acquired before admission to the hospital.⁵ Even less is known about vaginal colonization with MRSA. In a study that was performed in our hospital from November 2004 to May 2005, of a total of 305 vaginal specimens collected randomly at the onset of labor, two cultures were positive for MRSA. (personal communication

Chunhua Liu, MD, June 1, 2005). The prevalence of MRSA cultures among *Staphylococcus aureus* cultures in our institution is 31% and is 52% in our intensive care units.

In early reports of MRSA infections, investigations usually revealed a history of risk factors such as previous antimicrobial-drug therapy or recent hospitalizations, close contact with a person who had been hospitalized, or other hospital-associated factors, such as ventilatory support, dialysis, indwelling catheters, or other medical devices as well as residence in long-term care facilities.^{3,4,5} More recently, community-acquired MRSA has been described in injection drug users, prisoners,⁶ and children and in otherwise healthy people lacking the historic, hospital-associated risk factors.¹ A recent study of methicillin-resistant *Staphylococcus aureus* carriage in children attending two day-care centers in Dallas showed that 40% of the colonized children had had no contact with a health-care facility, or a household member with such contact, within the previous 2 years, which suggests that sustained transmission and colonization of MRSA in children was occurring in the community and that the epidemiology of *Staphylococcus aureus* is changing.²

Community-acquired MRSA strains have a genotype and a phenotype that are distinct from those of hospital-acquired MRSA.⁷ Unlike hospital strains, which typically are resistant to multiple antibiotics and can be shown by typing schemes to be related to other hospital strains, community-acquired MRSA strains are susceptible to numerous antimicrobial agents, which may include clindamycin, fluoroquinolones, and trimethoprim-sulfamethoxazole and often are resistant only to β -lactam antibiotics.⁷ Importantly, there are therapeutic options available other than vancomycin, levofloxacin (Levaquin, Ortho McNeil Pharmaceutical, Raritan, NJ), and tetracycline, which because of potential fetal side effects are not recommended for use in pregnancy. Additionally, community-acquired MRSA strains, unlike hospital-acquired MRSA strains, have been found to carry virulence genes encoding a leukocyte-killing toxin called the Pantone-Valentine leukocidin determinant.^{4,8} Skin and soft-tissue infections, as well as necrotizing pneumonia, have been associated with Pantone-Valentine leukocidin-producing community-acquired MRSA⁸ which most likely was responsible for the sepsis in our patient. The origins of these community-acquired strains are subject to debate. One possibility is that they are feral descendants of hospital isolates that have undergone considerable change to lose resistance to multiple antibiotics.¹ Another possibility is that the community isolates arose as a consequence of horizontal



transfer of the methicillin-resistance determinant into a formerly susceptible background.^{4,7}

Community-acquired MRSA is an emerging problem in obstetric populations and should be considered in the differential diagnosis of antepartum and postpartum infections.³ Most commonly, it presents in pregnant women as a skin or soft tissue infection that involves multiple sites and recurrences.^{8,9} In a case series recently reported from Parkland Hospital, skin and soft tissue infections accounted for 96% of cases.³ The most common sites for infection were an extremity (44%), buttock (25%), breast (23%), vulva or groin (21%), and abdomen (21%). Soft tissue infections ranged in size from 1 cm to 10 cm. In that series there were no cases of pneumonia or sepsis. An outbreak of a hospital-acquired and transmitted community-acquired MRSA strain among postpartum women was also recently reported.⁹ This outbreak involved postpartum women who developed skin and soft-tissue infections caused by MRSA at a mean time of 23 days (range, 473 days) after delivery. Infections included four cases of mastitis (three of which progressed to breast abscess), a postoperative wound infection, cellulitis, and pustulosis.

Our case is highly unusual in that sepsis was secondary to an infected episiotomy and pelvic thrombophlebitis, which generated septic emboli that resulted in necrotizing pneumonia and soft tissue infection. Our patient was initially treated with outpatient oral amoxicillin-clavulanic acid, which failed to cover the strain isolated from the different culture sites, and she eventually required intensive care monitoring because of the severity of the infection. Whether a patient should be admitted for intravenous antibiotics or allowed to remain outpatient on oral therapy should be decided by the clinician based on the site and severity of the infection. In cases where an abscess is present, incision and drainage with adjunctive antibiotic therapy is recommended. This is supported by a recent study from Young et al⁶ who reported that with adequate surgical drainage, MRSA skin and soft tissue infections severe enough to warrant hospitalization resolved, regardless of whether the antimicrobial agent given to the patient had in vitro activity.

The emergence of MRSA within the community has altered health care practice because it is a major threat with several important clinical implications. Treatment failure with accompanying complications or death may result if an antistaphylococcal β -lactam antibiotic is used and the infecting strain proves to be

resistant. Empirical treatment of community-acquired skin and soft-tissue infections with β -lactam agents without culturing specimens obtained from the infected site may not be appropriate, because such infections may be caused by MRSA.⁹ Empirical treatment of serious infections with vancomycin while awaiting culture results may be warranted.¹ However, that approach may generate a vicious cycle, because the increasing prevalence of MRSA will inevitably increase vancomycin use, adding further to the problem of antibiotic-resistant gram-positive bacteria.¹

Although active surveillance for community-acquired MRSA infection and colonization and molecular studies of virulence factors and drug resistance are critical, the fundamental forces driving resistance are unchanged. The question is not whether resistance will occur, but how prevalent resistance will become. Minimizing the antibiotic pressure that favors the selection of resistant strains is essential to controlling the emergence of these strains in the hospital and the community, regardless of their origins.

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