

Severe Facial Clefts in Acrofacial Dysostosis

A Consequence of Prenatal Exposure to Mycophenolate Mofetil?

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BACKGROUND: Immunosuppressants are teratogenic in mice, rats, and rabbits and cause prenatal growth restriction in humans. As yet, there has been no proven teratogenicity in humans.

CASE: We present a chromosomally normal fetus with severe acrofacial dysostosis and orofacial clefts. These were bilateral transverse and oblique clefts and defects of the midface. In addition, there were preaxial limb anomalies with digitalization of thumbs and internal cardiovascular, gastrointestinal, and urogenital malformations. The mother had been treated with high doses of the immunosuppressant mycophenolate mofetil in early pregnancy for systemic lupus erythematosus.

CONCLUSION: Mycophenolate mofetil may have contributed to or even caused acrofacial dysostosis phenotype and extensive clefting.

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See related editorial on page 479.

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Mycophenolate mofetil is one of the newer immunosuppressant agents used in treatment of autoimmune diseases and in prevention of transplant rejection.¹ Traditional immunosuppressants such as azathioprine have shown no increase in congenital anomalies (Berkovitch M, Goldstein LH, Dolinsky G, Schaefer C, Cohen-Kerem R, Malm H, et al. Pregnancy outcome of women exposed to azathioprine during pregnancy: a prospective multicenter study [abstract]. *Reprod Toxicol* 2005;20:454),² but an apparent increase in prematurity and fetal growth restriction.³ Mycophenolate mofetil may be teratogenic. When treated with mycophenolate mofetil, offspring of rats and rabbits showed increased frequencies of anophthalmia, agnathia, hydrocephaly, ectopia cordis, ectopic kidney, and umbilical and diaphragmatic hernias.^{1,4} There have been reports of possible teratogenic effects in humans focusing on orofacial clefts and ear anomalies.^{1,5–8}

We present a female fetus of 17⁺³ gestational weeks with acrofacial dysostosis and facial clefts of hitherto unreported extension. The fetus had been prenatally exposed to mycophenolate mofetil.

CASE

The case was the first pregnancy of a nonconsanguineous couple (aged 18 years and 24 years). Because of systemic lupus erythematosus involving the kidneys, the mother had been treated with cyclophosphamide (800 mg) and mycophenolate mofetil (250–750 mg twice a day) before conception, with high doses of mycophenolate mofetil until gestational week 8⁺² (750 mg twice a day), and with azathioprine (50 mg twice a day) after recognition of pregnancy. There are no diseases or previously reported congenital abnormalities in either family.

Ultrasound examination at 12, 13, and 17 weeks of gestation revealed nuchal translucency, severe facial defects, microphthalmia, malformation of the brain and heart, and a single umbilical artery (Fig. 1). Chorionic villus sampling showed a 46,XX-karyotype. Maternal testing revealed abnormal values for pregnancy-associated plasma protein A (0.600 International Units/L [0.3319 multiples of the median]) and free β -hCG (107.40 International Units/L [2.1437 multiples of the median]) at 11⁺² weeks of gestation by ultrasonography (12⁺⁰ weeks of gestation by last menstrual period). Termination of the pregnancy was carried out at 17 weeks of gestation.

At autopsy, the female fetus (99 g; 11.5/18 cm crown-rump/crown-heel length) displayed a large square skull with facial clefts that included bilateral transverse clefting of the mouth causing severe macrostomia and bilateral



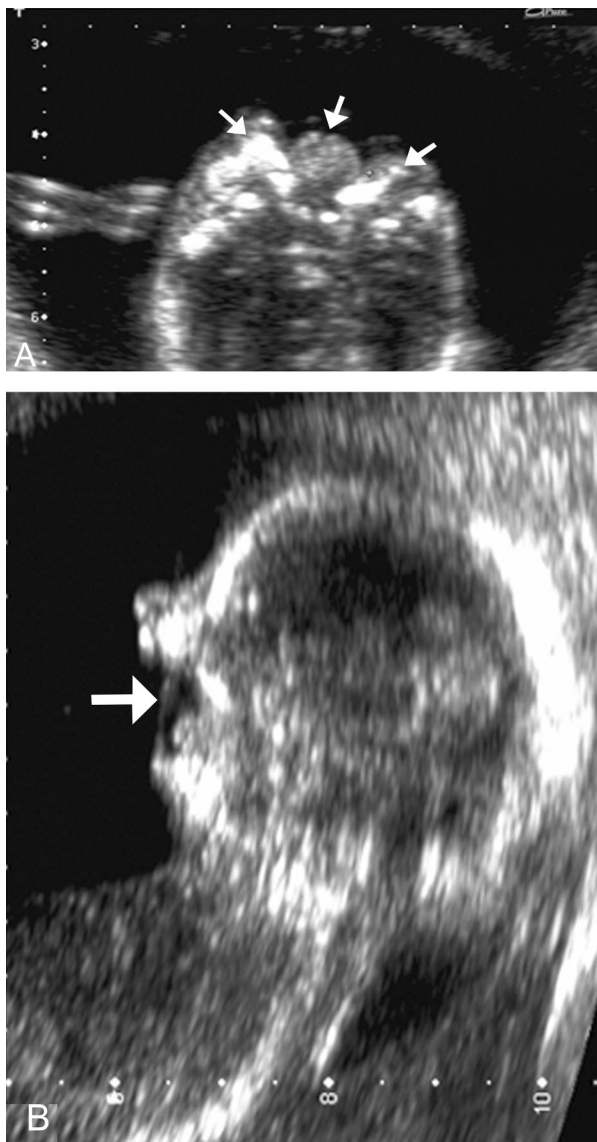


Fig. 1. Ultrasound image at 17⁺³ gestational weeks showing nuchal translucency, severe facial defects, (*large arrow*), displaced rudimentary nose, and microphthalmia (*small arrows*) on transverse (**A**) and sagittal (**B**) sections.

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oblique clefts. The latter arose from a pseudomedial bilateral cleft lip and palate involving the nostrils, the orbital and suborbital bones, and the median two thirds of the lower eyelids and extending to the upper eyelid border. The nose was extremely short, displacing the hypoplastic rudimentary premaxilla to eye level. This resulted in an almost complete defect of the midface with uncovered orbital, nasal, and oral cavities and exposed eyeballs, palatal shelves, and tongue. Orbital findings included down-slanting palpebral fissures, eyelid colobomas, and small, anophthalmic eyeballs with inferior colobomas of the iris, dislocation of the lenses into the

anterior chambers, cataracts, and in association with retinal colobomas chondral metaplasia and hamartomatous retinal dysplasia. Severe mandibular hypoplasia resulted in excessive microretrognathia. There were low-set, rudimentary auricles and atretic auditory canals (Fig. 2) and radial deviation of the right hand. The distally inserting thumbs showed incomplete dermal syndactyly, with the index finger on the right. Internal findings included hypoplasia of thymus and lungs, with incomplete lobulation on the left, subaortic ventricular septal defect with overriding common truncus arteriosus of the heart, aberrant right subclavian and single umbilical artery, esophageal atresia with tracheo-esophageal fistula, and left renal agenesis with ipsilateral streak gonad. There was agenesis of the corpus callosum and mild hydrocephaly.

X-ray revealed scoliosis, hemivertebra Th 11, left-sided rib defect, and slight shortening of the right radius with radioulnar synostosis. Both first metacarpals were thin but elongated. The phalangeal bones of the thumb were thin with significant elongation of the interphalangeal distances indicating triphalangy with not yet ossified middle phalanges (Fig. 3). Lower limbs were normal. Reconstructive computed tomography showed severe facial midline defects. The median two thirds of the maxillary and zygomatic processes were missing, as were bones of the median orbital cavity. There was severe shortening of the nasal bone and hypoplasia of premaxillary bone and mandible.

COMMENT

We present a fetus with an association of facial clefts of hitherto unreported extension in the presence of especially severe mandibulofacial dysostosis and of preaxial limb and internal malformations. This condition is reminiscent of “Nager acrofacial dysostosis (NAFD)—with severe facial clefts,” as defined by the London Dysmorphology Database.⁹

Although azathioprine has been shown not to be teratogenic in man, there are three case reports on possible teratogenic effects of mycophenolate mofetil. They concern a preterm infant with hypoplastic nails and short fifth fingers (mycophenolate mofetil given after renal transplantation to the mother during pregnancy at 6–7 weeks of gestation); a fetus with cleft lip and palate, hypertelorism, ear anomalies, micrognathia, and absent corpus callosum (mycophenolate mofetil after renal transplantation until 14 weeks of gestation), in which the possibility of an underlying autosomal-recessive hypertelorism-microtia-clefting syndrome had not been considered; and a newborn with unilateral ear malformation and meatal atresia and with fetal hydrops due to severe anemia (mycophenolate mofetil after renal transplantation throughout pregnancy).^{5–7,10} In a study on pregnancy outcomes after maternal organ transplantation from Sweden, seven congenital birth defects were



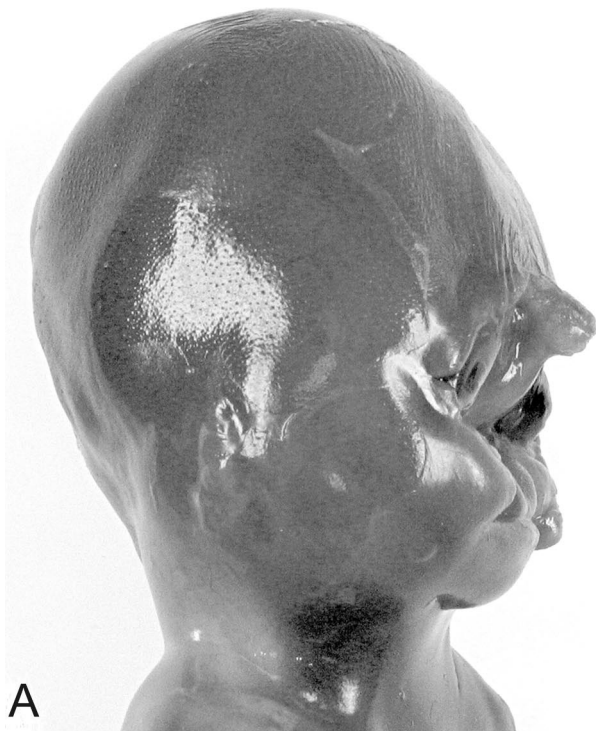
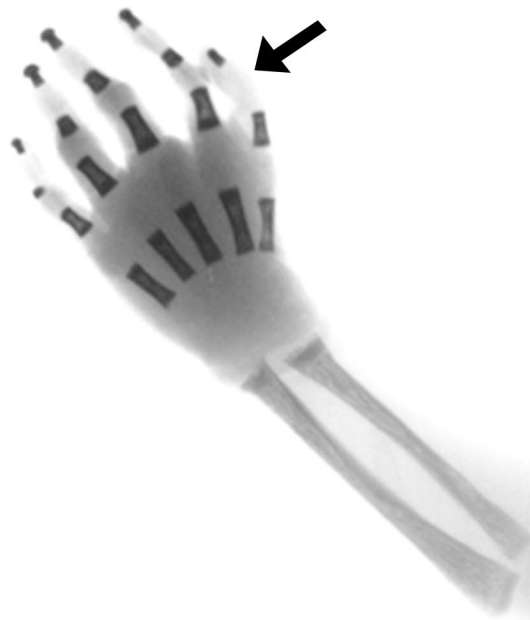
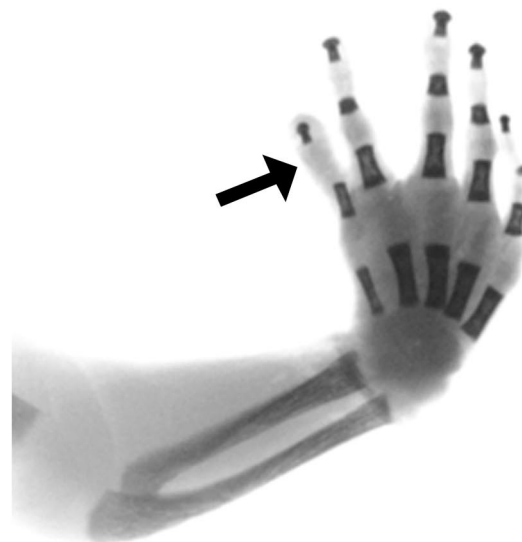


Fig. 2. Fetal profile (A) and face (B) displaying transverse and oblique clefts into the oral, nasal, and orbital cavities and lack of a midface. B. Note defects (arrows) of median upper and lower eyelids (median eyelid border).

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A



B

Fig. 3. X-ray of fetal left (A) and right (B) hands showing digitalization of thumbs (nonopposed, triphalangeal thumbs) with unossified middle phalanges (arrows), elongation, and thinning of the first metacarpals and right radioulnar synostosis.

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identified among 149 infants, but only one of the 149 infants—presenting with esophageal atresia, complex cardiac defect, and iris anomaly—had been prenatally exposed to mycophenolate mofetil.⁸ However, in a report from the National Transplantation Pregnancy registry from Philadelphia, four cases of birth defects among 18 liveborn infants prenatally exposed to myco-



phenolate mofetil were listed,¹ including two cases already cited above^{5,7} and two additional cases of cleft lip and palate and microtia.¹ Because of additional diaphragmatic hernia and cardiac defect, Fryns syndrome had been suspected in one of the two.¹ Not considering questionable underlying syndromal disorders, there are now five cases—including ours—of orofacial clefts or ear anomalies after exposure to mycophenolate mofetil. Given the rare exposure and rare outcome, this raises concern about the teratogenicity of mycophenolate mofetil in humans.

However, none of the above-mentioned cases has been so severely affected by orofacial clefts, ear anomalies, and limb and internal malformations as with our case. This might be due to the exceptionally high doses of mycophenolate mofetil given during early pregnancy (750 mg twice a day compared with 250–500 mg twice a day after organ transplantation).¹ On the other hand, one might argue that mycophenolate mofetil alone did not cause this exceptional phenotype, but that it is responsible for the especially severe facial manifestation in the presence of a pre-existing genetic predisposition or syndromal disorder, in that it furthered blasteme hypoplasia of facial bones as the basic disturbance of mandibulofacial dysostosis and thus caused Nager acrofacial dysostosis-phenotype with extensive facial clefting.

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Cardiac Troponin I Elevation After Orogenital Sex During Pregnancy

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BACKGROUND: Venous air embolism due to orogenital sex in pregnancy is an uncommon clinical event.

CASE: A previously healthy, 29-week pregnant woman presented to the emergency room unconscious 1 hour after engaging in orogenital sex with her partner. The cardiology service was consulted due to troponin elevation. Assessment was that the patient had likely suffered an air embolism with associated troponin leak.

CONCLUSION: Although a rare clinical event, air embolism from air insufflation of the vagina can result in troponin elevation and should be considered in the differential diagnosis in pregnant patients with a history of orogenital sex.

(*Obstet Gynecol* 2008;111:487–9)

Venous air embolism is an infrequent complication of pregnancy but may occur if air is blown into the vagina during orogenital sex.¹ Air passes beneath the fetal membranes and into the circulation of the subplacental sinuses, frequently resulting in death to both mother and fetus. Although pulmonary edema,² acute respiratory distress syndrome,³ and cerebral air embolism⁴ have been reported in this setting, to the best of our knowledge, elevated cardiac troponin has not been reported. We report a case of air embolism from air insufflation of the vagina complicated by troponin elevation in a pregnant patient.

See related editorial on page 481.

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CASE

A previously healthy woman (gravidity 2, para 1-0-0-1) at gestational age of 29 weeks 2 days, presented to the emergency room after collapse. The patient was at home 1 hour before admission engaging in orogenital sex with her partner. The patient's partner forcibly blew air into her vagina. The patient began to complain of abdominal pain and nausea. She then became lightheaded and lost consciousness. Her partner related that during this time the patient began to tremble and then seize. Emergency medical services were called and the patient was brought to the emergency room. The patient awoke in the ambulance complaining of shortness of breath.

In the emergency room, the patient's temperature was 98.6°F (37°C); respiratory rate was 23; pulse rate 113 bpm; and blood pressure 119/78 mm Hg. On physical examination, the patient was alert and oriented to person, place, and time; cardiac examination revealed regular tachycardic rate with a systolic flow murmur; lung examination had bibasilar crackles; the abdominal and extremity examination were normal. Fetal wellbeing was established with a biophysical profile of 8/8 done in the emergency room.

The patient continued to complain of shortness of breath and subsequent chest pain. The chest pain was exacerbated by deep breathing. The woman denied any previous symptoms of chest pain, dyspnea on exertion, shortness of breath, nausea, or vomiting. The differential diagnosis at that time included pulmonary embolus, eclampsia, and myocardial infarction.

Electrocardiogram on admission revealed sinus tachycardia with T wave inversions in leads III and AVF (Fig. 1). Arterial blood gas was obtained on 13 L of oxygen, which demonstrated a pH of 7.41 (normal range 7.4–7.45), Pao₂ 53 mm Hg (normal range 95–105 mm Hg), Paco₂ 33 mm Hg (normal range 28–32 mm Hg), hydrogen carbonate HCO₃ 15 mEq/L (normal range 18–31 mEq/L). Admission laboratory data revealed whole blood count of 10,100/mm³, hemoglobin of 12.6 g/dL, hematocrit of 36.2%, and platelets 144,000/mm³. Basic metabolic panel was unremarkable. Initial troponin was elevated at 2.2 ng/mL (expected 0.0–1.4 ng/mL). Urine drug screen was negative for cocaine metabolites and other illicit drugs. Chest X-ray showed moderate pulmonary edema with small bilateral pleural effusions (Fig. 2). A spiral chest computed tomography with contrast was obtained to rule out pulmonary thromboembolism. The patient was treated with heparin for anticoagulation and magnesium sulfate for potential eclampsia until results of these studies were known. Although there was no evidence of pulmonary embolism, diffuse edema could be seen throughout the mediastinum. Fetal wellbeing was reassuring throughout this time.

Cardiology was consulted due to troponin elevation. Initial assessment was that the patient had likely suffered an air embolism with secondary troponin leak due to orogenital sex. A two-dimensional echo was obtained, which demonstrated normal left ventricular and right ventricular size and systolic function with mild mitral regurgitation and



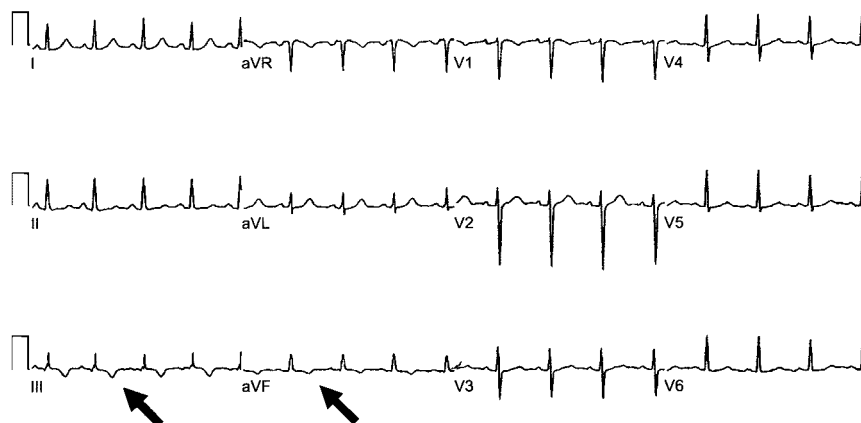


Fig. 1. Electrocardiogram on admission revealed sinus tachycardia with T wave inversions in leads III and aVF illustrated by arrows.

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mild tricuspid regurgitation. The patient then underwent hyperbaric oxygen treatment. Cardiac magnetic resonance imaging (MRI) was obtained, which illustrated mild cardiomegaly without focal wall motion abnormality. There was no evidence of patent ovale or other intracardiac shunt. Normal origins and course of all coronary arteries were noted. Troponin I peaked at 3.9 ng/mL and decreased in 2 days to a normal range of 0.5 ng/mL.

Four days after presentation the patient began to complain of painful contractions. The patient also was noted to have symptoms of preterm labor throughout her hospital stay, and she received dexamethasone for fetal lung maturity. The decision was made to perform a cesarean delivery secondary to breech position and preterm labor. The pathology report on the placenta was significant for severe chorioamnionitis but did demonstrate signs of abruption. Mother did well and was able to be discharged 4 days after delivery on room air with normal oxygen saturation. Because of prematurity, the infant was transferred to the neonatal intensive care unit and was discharged home approximately 2 months after admission.

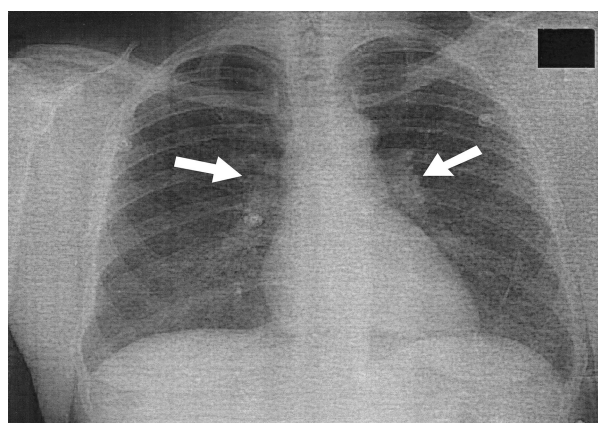


Fig. 2. Chest X-ray showed moderate pulmonary edema illustrated by arrows with small bilateral pleural effusions.

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COMMENT

Acute venous air embolism due to insufflation of the vagina during pregnancy was first described in 1936 by Peirce⁵ Most case reports of air embolism in pregnancy are postmortem. Anoxic death usually results from outflow obstruction by the air bubble in the right ventricle or pulmonary artery.¹

The vagina becomes highly distensible during pregnancy and can contribute to the pathophysiology of this process. Approximately 1.5–2 L of air may be forced through the cervical canal, and the air can then separate the amniotic membrane from the uterine wall and pass into the venous circulation via the subplacental sinuses. Air in the venous circulation can then cross into the arterial circulation via septal defects present in as many as 25% of adults.⁵

Cardiac troponin I elevation in acute pulmonary embolism and submassive pulmonary embolism have been described.⁵ A mechanism of troponin elevation for venous air embolus in the absence of patent foramen ovale or septal defect has not been described in the literature. The mechanism of troponin leak in this case may be an intracardiac shunt that could not be seen under MRI imaging, transient hypotension during the event, or severe right ventricular strain in the setting of pulmonary venous air embolism. Given the high sensitivity of troponin to minor myocardial injury, which occurs in unstable angina in patients who are hemodynamically stable,⁵ it is theoretically plausible for a pulmonary air embolus to result in elevated cardiac troponin.

Further questions as to whether pulmonary air embolisms can result in the release of troponin due to right ventricular strain may require further study, but conservative management remains a reasonable strategy. Air embolism with troponin elevation



should be considered in the differential diagnosis of pregnant patients with a history of orogenital sex and acute onset of shortness of breath and chest pain.

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Venous Air Embolism After Using a Birth-Training Device

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BACKGROUND: This case describes a birth-training device used by a pregnant woman to stretch the perineum.

CASE: A primigravida suffered near cardiovascular collapse and subsequent acute respiratory distress syndrome after using the device at home. Her symptoms and clinical course of disease revealed a high likelihood of venous air embolism.

CONCLUSION: The patient likely suffered a venous air embolism in association with the use of the birth-training device. The complications suffered by this patient should give caution about use of such devices.

(*Obstet Gynecol* 2008;111:489–91)

Air embolism in pregnant women has been recognized as a serious consequence of vaginal insufflation during orogenital sex play. Numerous cases in the literature describe death of the mother or fetus or both. The Epi-No birth and postnatal training device (Tescana, Munich, Germany) consists of an inflatable vaginal dilator attached to a hand pump. Some mod-

els come with a pressure gauge intended for “biofeedback.” The device is recommended by the manufacturer for women at 37 weeks of gestation onward for no more than 30 minutes twice per day until the onset of labor to stretch the perineum. The user inserts the silicone balloon into the vagina and over multiple training sessions increases the balloon’s diameter with air up to an optimal diameter approximating the size of the fetal head (roughly 10 cm). According to manufacturer’s instructions, she then performs what would appear to be a modified Kegel exercise by “gradually relaxing and contracting her vaginal muscles against the balloon, which provides resistance” and then expelling the device to simulate delivery of the fetal head.

CASE

A young primigravida at 37 weeks of estimated gestational age presented to the emergency room via ambulance after appearing to have had a seizure at home. She had received her prenatal care with a private attending at an outside institution and had enjoyed an uncomplicated prenatal course. Her husband reported that she had been at home using the birth-training device (Epi-No), which was being inflated while in her vagina. The woman’s husband was assisting her by managing the hand pump. As he found that it was not adequately maintaining pressure, he continued to attempt to inflate the device. After approximately 5 to 10 minutes of attempted insufflation, the woman began to complain of vaginal pain and dizziness and the device was immediately removed. Her husband left the room to get her a glass of water and, upon his return, found his wife experiencing full body shaking. Following convulsive activity, she appeared unresponsive.

Emergency medical services arrived in response to a call to the local volunteer ambulance service and found the patient unresponsive, cyanotic, and having seizure-like activity. The paramedics then intubated her and noted

See related editorial on page 481.

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suspected aspiration of gastric contents. She received intravenous midazolam, diazepam, and etomidate for muscular relaxation to facilitate endotracheal intubation, and a bolus of magnesium sulfate for presumed eclampsia. She was then transferred via ambulance to the emergency room. Subsequent examination of the birth-training device, which was procured by the paramedic, revealed an air leak in the vaginal balloon.

Obstetric and emergency medicine teams met the patient in the ambulance bay. On presentation to the hospital, the patient's husband provided the history to the medical staff as she herself was unresponsive. On presentation, the patient's heart rate was in the 130s with systolic blood pressures in the 90s and diastolic pressures in the 50s. Her oxygen saturation was 98% while intubated and receiving 100% oxygen. Vomitus was evident around the endotracheal tube, and decreased breath sounds were noted at both lung bases. Her abdomen was soft and nontender with a fundal height approximately appropriate for gestational age. Her cervix was 2 centimeters dilated, 70% effaced with the fetal vertex at 0 station. Ultrasound revealed a live fetus in cephalic position with a heart rate of approximately 100 beats per minute (bpm).

The differential diagnosis included eclampsia, air embolism, and cerebrovascular accident. With both maternal and fetal instability, a decision for emergency cesarean delivery was made, and a cesarean delivery using a low transverse uterine incision was performed in the main operating room. A live female newborn weighing 2,620 grams was delivered under general anesthesia. Apgar scores at 1 and 5 minutes were 8 and 8, respectively. The infant had an uncomplicated course and did not require admission to the neonatal intensive care unit. Attempts to obtain a sample for umbilical cord gas measurement were unsuccessful as the main operating room staff, who were unfamiliar with the practice of cord gas sampling, removed the clamps from the length of cord set aside for that purpose.

From the operating room, the patient was transferred to the postanesthesia care unit. There, she remained tachycardic with a heart rate of 133 bpm. Her blood pressure had increased to 145/100, and she had become increasingly difficult to ventilate mechanically. She required a positive end-expiratory pressure of 18 mm Hg. Her oxygen saturation on 100% oxygen was 92%. To prevent seizures, she was continued on an infusion of magnesium sulfate due to the uncertainty of the diagnosis. Intravenous piperacillin-tazobactam and metronidazole were also started for suspected aspiration pneumonia.

A computed tomography scan of her head was obtained immediately postoperatively and revealed no evidence of ischemia or hemorrhage. The radiologists recommended magnetic resonance imaging as a more sensitive imaging study for detecting a vascular event such as thrombosis or ischemia, particularly sagittal venous thrombosis, but this too was negative.

A computed tomography scan of the patient's chest

obtained at the same time revealed extensive air space disease compatible with pneumonia or acute respiratory distress syndrome. Additionally, bilateral lower lobe atelectasis and pleural effusions were noted. A chest radiograph, performed to aid in following the progression of pulmonary disease, showed similar findings. A transesophageal echocardiogram showed no discernable evidence of pulmonary embolus, normal-to-borderline pulmonary arterial pressure, trace pericardial effusion, and mild pleural effusion.

In the surgical intensive care unit, the patient was continued on magnesium sulfate for 24 hours. She was maintained in a special rotating bed which allowed prone positioning for better oxygenation. She required progressively lower positive end-expiratory pressure, was able to tolerate supine positioning on postoperative day 7, and she was extubated 1 day later.

As she was intubated and sedated during the majority of her early hospital course, the patient could not recall many events of that time period, nor could she recall the events immediately preceding and after her seizure. Her memory and mental status were otherwise normal on discharge from the hospital on day 11. Her only remaining neurological deficit was a slight tremor of the body, most notable in the upper extremities and worse on the left. Repeat magnetic resonance imaging of the brain and serial electroencephalographs failed to show any focal abnormalities. Neurological consulting physicians felt these to be multi-focal diffuse tremors that would improve or resolve on their own in time. These resolved during the following 2 months; she is currently without neurologic sequelae. The patient was counseled regarding the risk of uterine rupture in future pregnancies and was told to discuss the issue of possible vaginal birth after cesarean delivery with her physician.

COMMENTS

Air embolism from vaginal insufflation was first reported in 1936,¹ and subsequent reports in recent years have dealt primarily with incidents related to orogenital intercourse²⁻⁵ and other forms of sexual play.⁶ Although other etiologies for the serious medical complications suffered by the patient are possible, the diagnosis of venous air embolism from vaginal insufflation with the vaginal dilator device was the most likely diagnosis for several reasons.

First, the pathognomonic presentation of air embolism due to vaginal insufflation includes cardiovascular collapse in close proximity to the insufflation event, and this was seen in our patient. Second, there was no evidence of headache, scotoma, or other early neurological signs, nor was there a history of elevated blood pressure at the patient's weekly prenatal visits with her physician as might be suspected in pre-eclampsia. In fact, her blood pressure on the scene as recorded by emergency medical services and on



arrival to the hospital was low, as opposed to elevated. Last, although it is possible that the acute lung injury she suffered was due to aspiration of gastric contents alone, as opposed to embolic insult, air embolism is well known to cause this complication. This is especially true in pregnant women whose dilated vasculature leaves them at risk when air traverses venous plexuses either vaginally or at times of uterine manipulation and instrumentation, such as cesarean delivery⁷ or pregnancy termination.

The mechanism of delivery of an air embolism in this case would be direct insufflation of the vagina due to a leak in the device inside it. The proposed mechanism of entry of air into the venous circulation itself is via the vagina, up through a slightly dilated cervix (2 cm) and between the membranes and decidua. This mechanism would not require rupture of membranes. The force necessary to cause such dramatic tissue disruption is plausible because the air delivered by the hand pump was pressurized.

Evaluations of the Epi-No birth-training device in the medical literature are few⁸⁻¹¹ and deal primarily with its role in reducing risk of perineal injury or episiotomy as opposed to evaluating its safety in large study populations. Although manufacturers' instructions recommend consulting a physician or midwife before use and inflating and deflating the device prior to insertion in the vagina, there is no warning of risk to the user of any serious consequences should the device fail and vaginal insufflation result.

Caution is therefore recommended in evaluating birth-training devices with balloons as tools for patients desiring to decrease their chances of episiotomy and vaginal lacerations through the use of vaginal and perineal stretching methods. Even if device failures are rare, the consequences to both mother and fetus may be so severe as to suggest caution. Our recommendation is that midwives and obstetricians who

recommend the use of these types of devices or who agree to their use specifically instruct patients to test the device for leaks before each use.

The Epi-No birth-training device is currently not approved for use by the U.S. Food and Drug Administration. We have reported the device failure to the MAUDE database. A thorough evaluation of the safety of this type of device is therefore recommended to prevent similar outcomes in pregnant women.

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Major Venous Hemorrhagic Complication During Transvaginal Cystocele Repair Using the Transobturator Approach

C. Touboul, J. Nizard, A. Fauconnier, and G. Bader, MD

BACKGROUND: New approaches to pelvic organ prolapse have been evolving rapidly with few reports on safety and efficacy. This case describes the management of a severe intraoperative venous hemorrhage when performing this minimally invasive surgery.

CASE: A postmenopausal woman experienced a life-threatening hemorrhagic complication during transvaginal cystocele repair using a transobturator approach procedure. The bleeding appeared after the posterior left needle insertion. Immediate imaging revealed that bleeding came from a terminal anterior branch of the left internal hypogastric vein. Embolization of the left hypogastric artery partially reduced the hemorrhage. Local packing was the most efficient hemostatic technique. Pelvic varicose veins were the major risk factor found in this case.

CONCLUSION: Although the transobturator technique is considered minimally invasive surgery, morbidity can be severe and require specific management.

(*Obstet Gynecol* 2008;111:492–5)

Development of suburethral synthetic tapes for treating stress urinary incontinence (SUI) generated an increasing interest in the use of synthetic meshes,¹ which are widely used for transvaginal surgical repair of pelvic organ prolapse. Since the diffusion of transobturator suburethral tapes, the transobturator approach has been developed for prosthetic transvaginal surgical repair of cystocele.² The Anterior Prolift System (Ethicon Women's Health and Urology, Johnson & Johnson, Issy Les Moulineaux, France) is a synthetic low-weight, macroporous,

monofilament polypropylene mesh which is implanted by transobturator route.³ The results concerning a large retrospective multi-centric series including 687 patients were recently published.⁴ Organ prolapse recurrence incidence ranged from 0% to 10.9% (mean 5.3%). Intraoperative complications were rare (1.3%). Short-term postoperative complications were also uncommon (2.5%), and only 1.3% required surgical treatment. Most of these complications were minor, with most being hematomas (1.7%), and no major hemorrhage. The first case report of a major arterial hemorrhage during the transvaginal placement of an Anterior Prolift mesh was reported in October 2006.⁵ This complication was successfully managed with pelvic artery embolization and blood transfusion. We recently experienced a case of hemorrhagic complication during an Anterior Prolift procedure.

Our objective is to describe the management of a severe intraoperative venous hemorrhage when performing this minimally invasive surgery.

CASE

The 64-year-old patient had an isolated stage III cystocele with Ba point at +3 cm to the hymeneal ring according to the pelvic organ prolapse quantification. She had three previous normal vaginal deliveries 38, 36, and 28 years earlier. She had a history of varicose veins stripping 12 years before and had multiple vein sclerosis for varicose recurrences. She was under postmenopausal hormonal therapy for 10 years. She had important bilateral subcutaneous vulvar varices before surgery. Their median diameter was 5 mm. The varices were central, and none spread to the inner thigh. The technique proposed for cystocele repair was the Anterior Prolift procedure under general anesthesia. Right and left superior insertions of the cannula-equipped guides were uneventful. During left inferior transobturator passage, a major continuous bleeding occurred. Placement of hemostatic clips was attempted but unsuccessful. The hemorrhage was uncontrollable and required resuscitation and blood transfusion regardless of local packing. Peroperative imaging was performed to identify the origin of bleeding. The arterial time of the angioscan did not show contrast agent extravasation, confirmed by an angiography performed before arterial embolization. It was deduced that the hemorrhage was of venous origin. On the late venous time of the angioscan, bilateral varicose pelvic veins were visible, including the left internal iliac vein and its terminal divisions. The internal iliac vein diameter was 12.6 mm on the left side and 11.7 mm on the right. The terminal branch of the internal iliac vein diameter was 9 mm on the left side and 6 mm on the right. Ovarian vein diameter was 7 mm on the left side and 4 mm on the right, for a normal range 1–4 mm.⁶ Sagittal view showed a media agent extravasation from a dilated anterior terminal branch

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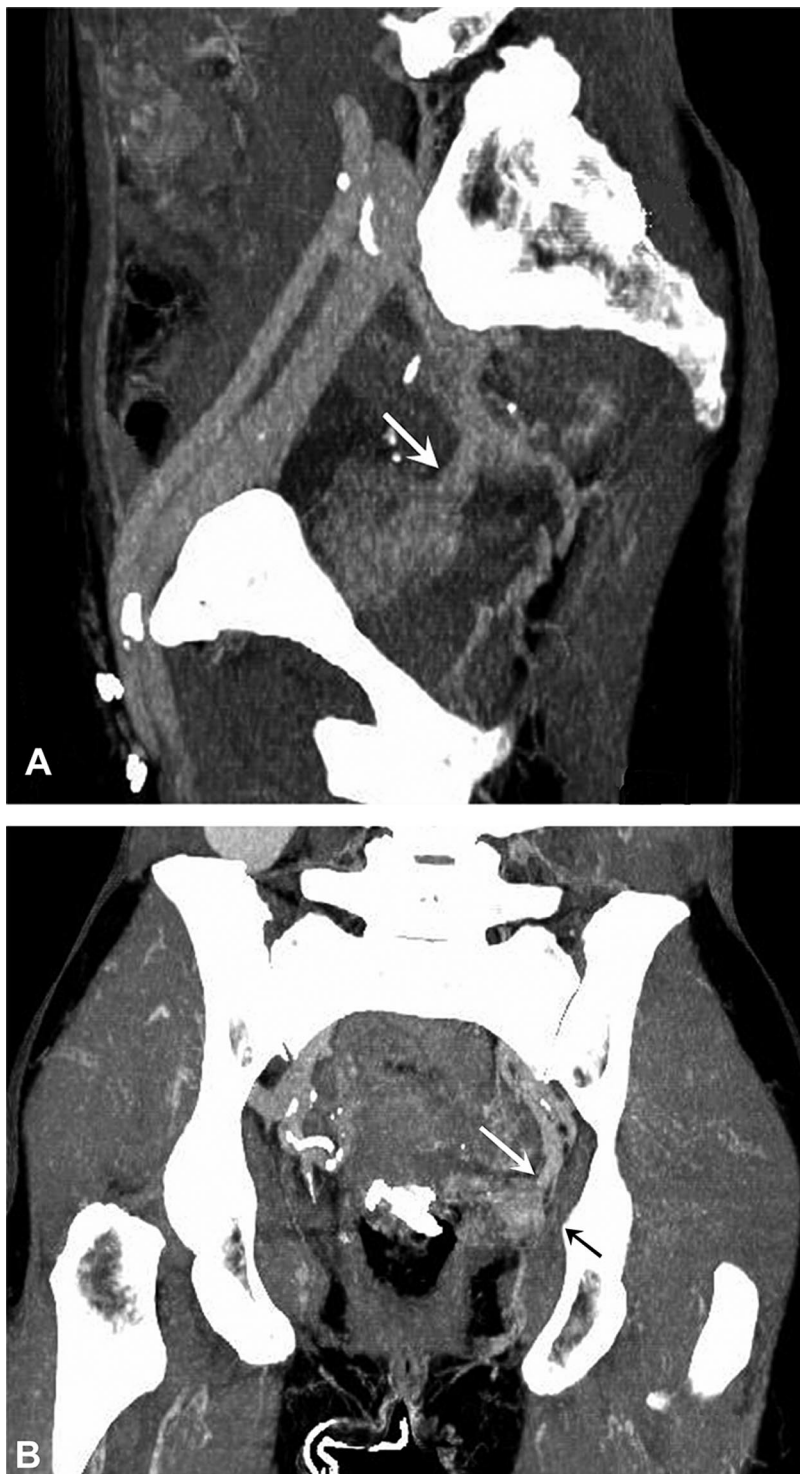


Fig. 1. Pelvic scan during surgery, venous time. On the sagittal view (A), media product extravasation from a dilated anterior branch of the left internal hypogastric vein (arrow). On the coronal view (B), media product extravasation from a dilated branch of the left hypogastric vein (white arrow). Bleeding is located inward left ischial spine (black arrow), which is on the posterior needle trajectory.

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of the left internal iliac vein (Fig. 1). On coronal view, media agent was visible around a terminal branch of the left internal iliac vein above and inside the ischial spine, which corresponded to the obturator vein (Fig. 1B).

We subsequently embolized the left internal iliac artery,

which partially reduced the hemorrhage. The patient remained hemodynamically unstable after embolization with a major hypotension (less than 80/40 mm Hg) and tachycardia above 150 beats per minute. A new attempt at surgical vaginal hemostasis was a failure. Bleeding was



controlled by left lateral paravesical space packing and adequate resuscitation. The total blood loss was estimated at more than 3,000 mL. The hemoglobin level dropped from 131 g/L before surgery to 75 g/L during bleeding estimated by capillary hemoglobin measurement, and finally at 81 g/L 5 hours after the beginning of surgery with 5 red cell packs already infused. The following day, the patient had a hemoglobin level of 101 g/L. Overall, resuscitation required a total of 8 red cell packs, 6 fresh frozen plasma, and 5,000 mL of other fluids, and dopamine during the first hours. Packs were removed 48 hours after surgery and anterior colporrhaphy completed under general anesthesia. The postoperative period was uneventful. The total duration of stay was 7 days: 2 days in the intensive care unit and the 5 remaining days in the gynecologic surgery unit. Cystocele repair was not performed due to the hemorrhage. The patient maintained her demand for surgical treatment and is scheduled for laparoscopic sacrospinous fixation.

COMMENT

We experienced a case of major venous hemorrhagic complication during Anterior Prolift procedure for cystocele repair by vaginal transobturator approach. The origin of the bleeding was an anterior terminal division of the left internal iliac vein. Late venous time of the angiogram confirmed the presence of pelvic varicose veins.

Our patient may have a mild pelvic congestive syndrome which is associated with chronic pelvic pain or "heaviness," superficial varicosities of the vulva, and pelvic varicosities.⁶ Hemorrhagic complication may therefore be explained by size and fragility of her pelvic varicosities.

The other published case of hemorrhage in the literature during Anterior Prolift procedure was related to secondary arterial bleeding⁵ requiring embolization of the anterior division of the left internal iliac artery. In that case, angiography showed a contrast media extravasation in the left pelvic area from a vessel branching from the anterior division of the left internal iliac artery. In our case report, no extravasation was observed on the arterial time angioscan or angiography. Local stitching was inefficient and only packing of the left paravesical space permitted control of the hemorrhage.

Other unpublished reports of vascular injuries are described in the U.S. Maude database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.cfm). These include two arterial injuries at the time of trocar placement (one internal iliac artery and one obturator artery), one venous injury occurring during the vaginal dissection, and one hematoma of unknown origin. Manage-

ment of venous injury required vaginal packing and embolization of the right hypogastric artery. Embolization has also been successful in the case of internal iliac artery injury whereas obturator artery bleeding was diagnosed and stopped by laparotomic ligature.

We believe that pelvic arterial embolization should be attempted even if bleeding is apparently from venous origin. Arterial embolization could reduce venous flow and facilitate other hemostatic techniques. This management had also been recommended in case of severe pelvic hemorrhage during sacrospinous vaginal vault suspension.⁷ Prognosis depends on how rapidly a correct diagnosis is made and specific treatment applied. The case we describe could help rapid diagnosis and management when such situation presents. Acute bleeding requires a multidisciplinary staff with surgeons, radiologists, and anesthesiologists. If a lesser staff is available, we believe surgery necessary, with eventually hypogastric artery ligature associated to the described packing technique.

A recent study about the anatomical position of the Prolift system was performed on three pelvic dissections.⁸ It describes a safe distance between lateral arms of the implant and major neighboring neurovascular structures. This description lacks details on the posterior passage of the mesh. However, the Prolift technique seems promising with regard to functional and anatomical results.^{3,4}

Varicose venous pathology with vulvar varicose veins is a possible risk factor for the hemorrhagic complication we observed. Would other similar experiences be described, varicose venous pathology might become a contraindication for cystocele repair by transobturator approach. Until then, further anatomical studies are necessary to study the exact needle trajectory during the posterior transobturator passage.

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Adrenal Insufficiency After Laparoscopic Hysterectomy in a Patient With Primary Antiphospholipid Syndrome

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BACKGROUND: We report a case of bilateral adrenal hemorrhage and subsequent adrenal insufficiency after a laparoscopic hysterectomy in a patient with anticardiolipin antibody syndrome.

CASE: A 55-year-old woman with a history of anticardiolipin antibody syndrome presented with nausea and vomiting 1 week after laparoscopic hysterectomy and staging for endometrial adenocarcinoma. Based on a diagnosis of adrenal insufficiency, the patient was started on oral hydrocortisone 20 mg in the morning and 10 mg in the afternoon, and fludrocortisone 0.05 mg twice daily on day 5. Her symptoms resolved completely within 24 hours of beginning steroids.

CONCLUSION: The diagnosis of adrenal insufficiency should be entertained in any patient with a history of thrombophilias presenting with general abdominal complaints.

(*Obstet Gynecol* 2008;111:495–8)

Adrenal insufficiency is rarely seen in obstetrics and gynecology practice, but it is a potentially serious complication of surgery in compromised individuals. We report a case of bilateral adrenal hemor-

rhage and subsequent adrenal insufficiency after laparoscopic hysterectomy in a patient with anticardiolipin antibody syndrome. This case emphasizes the importance of maintaining adrenal insufficiency in the differential diagnosis of a patient with general postoperative abdominal complaints.

CASE

A 55-year-old woman underwent a total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and lymph node sampling for stage IC endometrial adenocarcinoma. She had an uncomplicated postoperative course and was discharged to home on the second postoperative day with pain well controlled and tolerating a regular diet.

Six days after surgery, the patient presented to the emergency department with nausea, vomiting, diarrhea, and two days of anorexia. She noted worsening back pain for approximately 3 days. She denied dizziness, fever, chills, abdominal pain, or urinary symptoms. She was afebrile with stable vital signs. Physical examination was within normal except for a mildly tender abdomen without rebound, guarding, or distension. The basic metabolic panel was only significant for a potassium level of 3.2. Other laboratory values included a normal liver function test results, amylase, and lipase. She had a stable hematocrit and a white blood cell count of 6.6. Abdominal x-ray revealed a paucity of bowel gas, consistent with her history of vomiting. There was no evidence of obstruction or ileus.

The patient's medical history was significant for three deep vein thromboses (DVTs). Her first DVT was in 1979 in the immediate postpartum period for which she was treated with warfarin for 6 months. In 1993, she developed a spontaneous DVT and testing revealed positive anticardiolipin antibodies. She was treated first with warfarin and then aspirin. When she developed another DVT, the decision was made to chronically anticoagulate her with warfarin to achieve a target international normalized ratio of 2.0 to 3.0. Medication was changed to low-molecular-weight heparin 7 days before her surgery. Her low-molecular-weight heparin was restarted on postoperative day one, and she restarted her usual dose of 6 mg of warfarin every night upon discharge to home. At the time of her readmission to the hospital, she was therapeutically anticoagulated on warfarin with an international normalized ratio of 2.18.

On hospital days one and two after readmission, the patient tolerated a clear diet with intermittent episodes of

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vomiting. She reported persistent nausea despite ondansetron. Her back pain was partially controlled with oxycodone, acetaminophen, and ibuprofen. When she continued to have small episodes of emesis, a computed tomography (CT) scan of the abdomen and pelvis was ordered to rule out bowel obstruction. The CT scan showed no evidence of bowel pathology but demonstrated bilateral adrenal masses consistent with adrenal hemorrhage (Fig. 1).

Endocrinology consult recommended a cosyntropin stimulation test which revealed a baseline level of cortisol of 1.42 mcg/dL (normal values, 4.5–23 mcg/dL), and adrenocorticotrophic hormone (ACTH) level of 479 pg/mL (normal values, 6–58 mcg/dL) at time zero. At 30 minutes, her cortisol level was 1.39 mcg/dL and it remained 1.29 mcg/dL after 60 minutes. The studies reflected an absence of appropriate response to ACTH and were indicative of abnormal adrenal function. Her dehydroepiandrosterone sulfate level was low and aldosterone was also unresponsive to ACTH stimulation (Table 1).

Based on a diagnosis of adrenal insufficiency, the patient was started on oral hydrocortisone 20 mg in the morning and 10 mg in the afternoon, and fludrocortisone 0.05 mg two times per day on day 5. Her symptoms resolved completely within 24 hours of beginning steroids. She tolerated a regular diet, and her back pain and fatigue improved. She was discharged to home to follow up with endocrinology in approximately 1 month to evaluate return of adrenal function. She was seen in the outpatient setting 1

Table 1. Laboratory Values

	Patient Values (at 0, 30, and 60 min)	Normal Values
Cortisol (mcg/dL)	1.42, 1.39, 1.29	4.5–23
Aldosterone (ng/dL)	<1.6, <1.6, <1.6	4–31
Dehydroepiandrosterone sulfate (mcg/dL)	4, 3, 3	26–200
Adrenocorticotrophic hormone (pg/mL)	479	6–58

week after discharge; she continues to show improvement with only some residual fatigue consistent with her original surgery. A follow-up set of laboratory results at 3 months showed no return of adrenal function and so was maintained on adrenal hormone therapy.

COMMENT

Bilateral adrenal hemorrhage is a rare but serious and often fatal condition. The presenting signs and symptoms are a result of primary adrenal insufficiency and are often vague, requiring a high index of suspicion for timely diagnosis and treatment. Symptoms include nausea and vague abdominal pains as well as fatigue, anorexia, fever, weakness, and weight loss.¹ Signs include fever, hypotension, orthostasis, and abdominal tenderness with de-

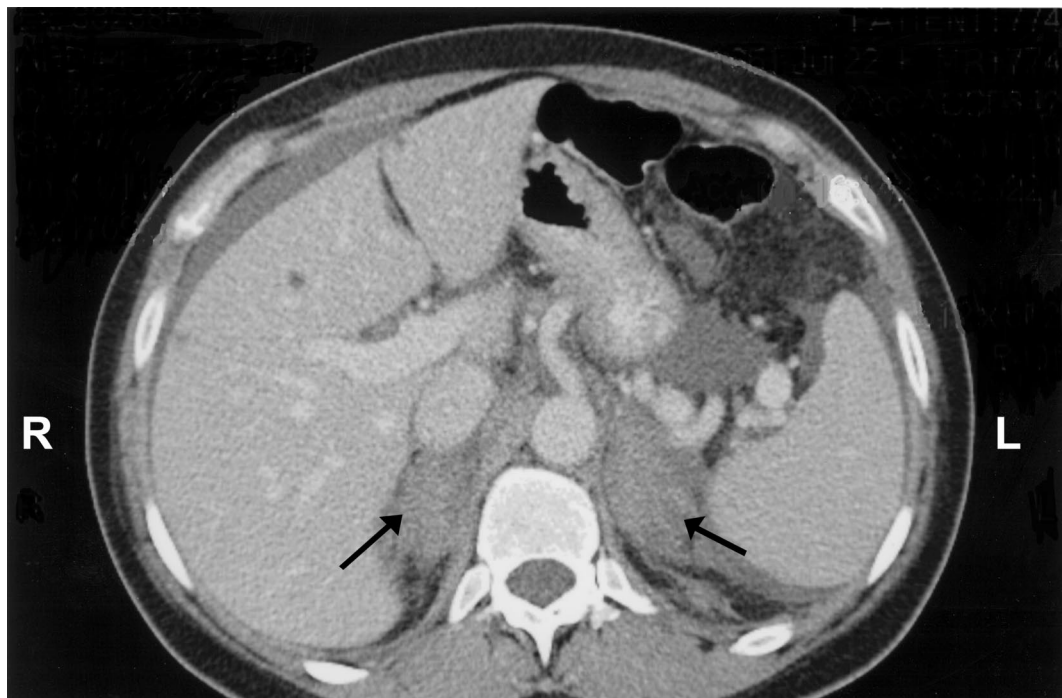


Fig. 1. Computed tomography scan of the abdomen and pelvis, demonstrating bilateral adrenal hemorrhage. Arrows indicate the location of the adrenal glands. R, right; L, left.

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creased bowel sounds. While hypotension is one of the classic signs and is frequently present, its absence does not preclude the diagnosis as evidenced by this case. Biochemical abnormalities of primary adrenal insufficiency include hyponatremia and hyperkalemia. Interestingly our patient did not exhibit these laboratory abnormalities.

Adrenal insufficiency may or may not be present in the setting of adrenal hemorrhage and needs to be confirmed. A low cortisol level at the time of emergency is suggestive but not definitive. The standard cosyntropin stimulation test measures blood levels of cortisol 0, 30, and 60 minutes after intravenous administration of 250 mcg ACTH. Peak cortisol levels of between 18 and 25 mcg/dL, with an increment of at least 8 mcg/dL, have been proposed as indicating adequate adrenal function. Once the diagnosis of adrenal insufficiency has been made, the next step is to evaluate the level of hypothalamic–pituitary–adrenal axis defect, since this guides the use of mineralocorticoid and/or glucocorticoid replacement therapy. Plasma levels of ACTH, dehydroepiandrosterone sulfate, and aldosterone may also be of value in identifying the location of the defect.² Usually, more than 90% of the adrenal cortical tissue needs to be destroyed to have symptomatic Addison's disease.³

The diagnosis of adrenal hemorrhage can be made using abdominal imaging or on postmortem examination of the adrenals. Computed tomography scans demonstrate nontraumatic hematomas as adrenal enlargement that is round to oval in shape, with blood infiltration leading to surrounding induration and perinephric "stranding." By using a combination of changing T1- and T2-weighted images, magnetic resonance imaging can differentiate among acute, subacute, and chronic hematomas. In addition, magnetic resonance imaging can show if there is a coexisting tumor.⁴ Ultrasonography is a modality that can be performed at the bedside, but it does not adequately image the adrenal gland in most adult patients.⁵

The antiphospholipid syndrome puts patients at special risk of developing adrenal insufficiency. Indeed, about 36% of patients with this syndrome first present with Addison's disease.⁶ Additional risk factors for the development of adrenal hemorrhage in this syndrome include anticoagulation therapy, including subcutaneous prophylactic heparin or its withdrawal, pregnancy, surgery, trauma, spontaneous bleeding, and infection.⁷

Espinosa and colleagues³ reported on 86 cases of adrenal insufficiency due to antiphospholipid syndrome. Of these, only 62.8% had evidence of hemorrhage or hemorrhagic infarction, so there may be

other etiologies of adrenal dysfunction in this syndrome, such as autoantibodies. Adrenal hemorrhage may be primary or secondary. Primary hemorrhage may occur spontaneously (ie, without thrombosis). Secondary hemorrhage occurs when a clot forms in the adrenal veins and eventually results in hemorrhage within the gland itself. It has been proposed that the unique structure of the adrenal gland, with three arteries and only one vein, may result in limited drainage of the organ's blood supply and therefore predispose to thrombosis.⁸

Other causes of adrenal hemorrhage include trauma, septicemia, burns, hypotension, and tumors, especially those metastatic to the adrenal glands and pheochromocytomas. The largest series of adrenal hemorrhages was reported in 2001 by Vella et al⁹ from the Mayo Clinic. They found 141 patients aged more than 25 years who presented with either unilateral or bilateral adrenal hemorrhage. In their series, antiphospholipid syndrome consistently caused bilateral destruction, although there is a later case report by Mo et al⁶ of unilateral hemorrhage in this syndrome.^{6,9} It is interesting to note that even patients with unilateral disease may acutely present with adrenal insufficiency, although they eventually recover.⁶

Little data exist on the long-term endocrinologic follow-up or prognosis of patients with adrenal hemorrhage. Jahangir-Hekmat et al¹⁰ followed four patients for 6 to 19 years. In their small case series, they suggest that long-term mineralocorticoid replacement may not always be necessary, but that resumption of glucocorticoid production generally does not occur. However, patients with unilateral adrenal disease related to phospholipid antibodies can generally be treated without steroid hormone therapy, except in times of stress, although they need continued anticoagulation therapy.⁶ Patients must additionally be counseled about carrying an emergency card detailing their medications and recommendations for emergency treatment. Our case highlights the importance of considering adrenal insufficiency in the differential diagnosis of a postoperative patient with generalized abdominal complaints, especially if there is a history of antiphospholipid syndrome or anticoagulation therapy.

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Spontaneous Ovarian Hyperstimulation in a Naturally Conceived Pregnancy With Uncontrolled Hypothyroidism

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BACKGROUND: Spontaneous ovarian hyperstimulation syndrome is a rare occurrence in pregnancy. This is a case of pregnancy with spontaneous ovarian hyperstimulation syndrome, uncontrolled hypothyroidism, elevated human chorionic gonadotropin (hCG), deep vein thrombosis, and Rh isoimmunization.

CASE: An African-American woman in her mid-30s, gravida 3 para 0, with hypothyroidism presented with abdominal pain, hCG 291,206 milli-International Units/mL, thyroid stimulating hormone 41.7 milliunits/L, hematocrit 12.8%, and Anti-D titer 1:256. Pelvic ultrasonography revealed a pregnancy at 10 weeks of gestation with enlarged adnexal masses. Doppler images demonstrated a right, lower extremity, deep vein thrombosis. Conservative maternal treatment involved levothyroxine and heparin with regression of the ovaries by 22 weeks of gestation after adequate thyroid repletion. Fetal surveillance was with serial ultrasound examinations of the estimated fetal weight, amniotic fluid index, and the fetal

middle cerebral artery Doppler images. Cesarean delivery of a nonhydriopic 1,400-gram newborn occurred at 35 weeks of gestation. Although born prematurely, the newborn required only 2 liters of oxygen through nasal cannula initially, received only 2 blood transfusions, advanced to oral feeds quickly, had good urine output throughout the hospitalization, and had a normal hearing examination upon discharge. The bilirubin levels remained stable with some phototherapy, so exchange transfusion was not necessary.

CONCLUSION: Spontaneous ovarian hyperstimulation syndrome can occur in pregnant women with severe hypothyroidism or extremely elevated hCG and present with enlarged adnexal masses and acute abdominal pain. Accurate diagnosis and continuation of pregnancy with conservative management is a viable option, once ovarian malignancy is ruled out.

(*Obstet Gynecol* 2008;111:498–501)

Ovarian hyperstimulation syndrome most commonly occurs iatrogenically in association with assisted reproductive technologies, but it has been seen to develop spontaneously without ovulation induction therapies. While extremely rare in naturally conceived pregnancies, spontaneous ovarian hyperstimulation syndrome tends to present later in the first trimester at 8 to 14 weeks of gestation, while iatrogenic ovarian hyperstimulation syndrome usually presents earlier at 3 to 8 weeks of pregnancy.¹ In severe ovarian hyperstimulation syndrome, patients may present with ascites, dyspnea, adnexal masses, electrolyte imbalance, hemoconcentration, and oliguria. Both the hemoconcentration and the hypercoagulable states associated with elevated estrogen levels increase the risk of thromboembolic events.

Vascular endothelial growth factor (VEGF), an angiogenic cytokine, has been identified as a causative factor for the development of ovarian hyperstimulation syndrome and is responsible for the increased capillary permeability seen in this clinical

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entity.² Elevated serum and follicular VEGF have been detected in women with ovarian hyperstimulation syndrome, and the VEGF levels correlate with the severity of the ovarian hyperstimulation syndrome.³ This clinical presentation, along with enlarged adnexal masses, mandates that ovarian hyperstimulation syndrome be differentiated from ovarian malignancy, to avoid unnecessary surgical exploration.

New insights into the pathogenesis of recurrent and familial spontaneous ovarian hyperstimulation syndrome point to mutations in the follicle-stimulating hormone (FSH) receptor. These mutations cause increased sensitivity to endogenous hCG or thyroid-stimulating hormone (TSH).⁴ Follicle-stimulating hormone receptor mutations provide molecular basis for the pathophysiology of some spontaneous ovarian hyperstimulation syndrome and support conservative management in spontaneous ovarian hyperstimulation syndrome.

CASE

An African-American woman in her mid-30s, gravida 3 para 0, presented to the emergency department reporting general malaise, abdominal pain, bloating, and constipation for approximately 1 week. She denied any emesis, diarrhea, hematochezia, weight loss, or vaginal bleeding. The patient reported a history of irregular menstrual cycles with the last one being 3 months before presentation. Her medical history was significant for hypothyroidism and vitiligo, and she reported two previous first-trimester pregnancy losses without Rho(D) immune globulin administration. She admitted to chronic noncompliance with her thyroid medication. Her family history was noncontributory.

On presentation, the patient was sluggish but oriented, and her vital signs revealed tachycardia with a pulse rate of 112 beats per minute. Significant laboratory values were hemoglobin 3.9 g/dL, hematocrit 12.8%, mean corpuscular volume 64.7 fL, white blood cell count 16,800/microliter, platelets 287,000/microliter, hCG 291,206 milli-International Units/mL, TSH 41.7 milliunits/L. The hemoglobin electrophoresis was normal. Peripheral smear demonstrated spherocytes, microcytes, and fragmented red cells consistent with iron-deficiency anemia. The patient's blood type was B-negative, and the antibody screen returned positive with Anti-D titer 1:256 and Anti-C titer 1:1.

Pelvic ultrasonography demonstrated a single live intrauterine pregnancy at 10 1/7 weeks of gestation, bilateral large complex adnexal cystic masses measuring 10×14×7 cm and 10×12×8 cm without evidence of ovarian torsion, and a small amount of free fluid. No solid components or papillary projections were seen. CA 125 was 901 units/mL, and gynecologic oncology was consulted secondary to the concern for malignancy. Magnetic resonance imaging of the pelvis confirmed bilateral cystic structures without solid

components or metastatic lesion. Incidental finding of calf asymmetry prompted right lower extremity Doppler ultrasound, which revealed an acute deep vein thrombosis (DVT). The patient was admitted to the hospital and treated with heparin anticoagulation, blood transfusion, levothyroxine 200 mcg daily, analgesics, and conservative monitoring of the bilateral ovarian masses.

After stabilization, the patient was followed up with close maternal and fetal surveillance at the high-risk obstetrics clinic. Adequate repletion of thyroxine resulted in normalization of TSH to 1.01 milliunits/L. Serial assessment for fetal growth and middle cerebral artery peak systolic Doppler velocimetry was performed secondary to the Rh isoimmunization. An amniocentesis was performed at 17 weeks of gestation for advanced maternal age and returned normal karyotype 46XX. The patient declined Rh genotyping of the fetus. At 22 weeks of gestation, the ultrasound examination of fetal anatomy was normal with adequate fetal growth, and the ovaries had decreased to approximately 5 cm. At 26 weeks of gestation, the patient was diagnosed with gestational diabetes and maintained good blood sugars on diet alone. At that time, medications included levothyroxine 200 mcg daily, iron sulfate 325 mg 3 times daily, stool softener 100 mg twice daily, prenatal vitamin daily, and heparin 17,000 units subcutaneously twice daily.

Serial Doppler studies of the fetal middle cerebral artery peak systolic velocity were normal until 34 weeks of gestation, when the peak systolic velocity became elevated at 1.91 multiples of the median and a small pericardial effusion had developed. At that time, estimated fetal weight was 1,443 grams with intrauterine growth restriction at the third percentile and oligohydramnios, with amniotic fluid index of 4 cm. The patient was admitted for continuous fetal monitoring, steroid administration, neonatology consult, and planned induction. At 34 3/7 weeks of gestation, a primary cesarean delivery was performed secondary to nonreassuring fetal heart tracing. The newborn weighed 1,400 grams (third percentile) with Apgar scores of 8 and 9, and the hemoglobin was 6.3 g/dL, hematocrit 20.4%, bilirubin 5.2 mg/dL, reticulocyte count 24.6%, and blood type was B-positive. Although born prematurely, the neonate required only 2 liters of oxygen via nasal cannula initially, received only 2 blood transfusions, advanced to oral feeds quickly, had good urine output throughout the hospitalization, and had a normal hearing examination upon discharge. The bilirubin levels remained stable with some phototherapy, so exchange transfusion was not necessary. The newborn remained hemodynamically stable throughout the hospital course and was discharged from the neonatal intensive care unit on the 20th day of life.

The newborn was followed up at the Cedars-Sinai Medical Center infant progress follow-up clinic and at 8 months appeared to be neurodevelopmentally appropriate. The maternal postoperative course was further complicated by intraabdominal hematoma and anemia. Another maternal blood transfusion was required to stabilize the hemat-



ocrit. The anticoagulation was restarted, and the patient was discharged on postoperative day 10 with warfarin and levothyroxine. She was followed up closely in the outpatient clinic for continued management of the hypothyroidism, right-sided lower extremity DVT, and resolving abdominal hematoma.

COMMENT

Spontaneous ovarian hyperstimulation syndrome has been reported on rare occasions in the literature. A search of MEDLINE (1966–2005) and PubMed (1950–2005) with the terms “spontaneous ovarian hyperstimulation syndrome,” “hypothyroidism,” and “deep vein thrombosis” revealed no report of spontaneous ovarian hyperstimulation syndrome complicated by both severe hypothyroidism and acute DVT. Cardoso et al⁵ described a case of consistent regression of large bilateral ovarian cysts in a hypothyroid patient after the institution of thyroid hormone replacement therapy, suggesting the causal relationship between primary hypothyroidism and spontaneous ovarian hyperstimulation syndrome. Nappi et al⁶ presented a case of untreated hypothyroidism associated with spontaneous ovarian hyperstimulation syndrome. In their patient, thyroid replacement therapy and fluid administration also led to prompt resolution of the spontaneous ovarian hyperstimulation syndrome. Similarly, our patient responded to thyroid hormone replacement with regression of the ovarian cysts by 22 weeks of gestation.

Todros et al⁷ reported a case of spontaneous ovarian hyperstimulation syndrome involving DVT in pregnancy, but their patient had genetic thrombophilia involving factor V Leiden mutation and Antithrombin III deficiency. In contrast, our patient had a negative thrombophilia work-up initially upon presentation. The thrombophilia work-up was then repeated again postpartum because in pregnancy, the Protein S decreases and so it is not valid to test antenatally. The final results postpartum were negative for antibodies for anti-cardiolipin, anti-DNA, β -2 glycoprotein, lupus anticoagulant, anti-thrombin III, and factor V Leiden. However, both the functional Protein C and Protein S were found to be decreased. The homocysteine and the lipoprotein A were elevated, indicating increased risk of coronary artery disease. This also supports poor placentation and possible small arteriolar disease in the mother leading to intrauterine growth restriction. Her thromboembolic event is most likely secondary to the combined hypercoagulable states of ovarian hyperstimulation syndrome and pregnancy.

Various mechanisms have been proposed for spontaneous ovarian hyperstimulation syndrome.

Follicle-stimulating hormone, luteinizing hormone, hCG, and TSH are four glycoprotein hormones that share a common alpha subunit. Their β subunits, albeit distinct, share greater than 40% amino acid homology.

Each glycoprotein hormone receptor counterpart also shares a 40% concordance in their hormone binding domains. Mutations in the receptors may lead to promiscuous ligand recognition and cross-stimulation of end-organs. De Leener et al⁴ proposed to classify spontaneous ovarian hyperstimulation syndrome into three types, based on clinical presentation and FSH receptor mutation. Identification of the four FSH receptor mutations has allowed for creation of a pathophysiological classification of spontaneous ovarian hyperstimulation syndrome. Type I involves mutated FSH receptor with a hyperreactivity to normal hCG and TSH levels. Type II corresponds to spontaneous ovarian hyperstimulation syndrome that occurs secondary to high levels of hCG, with wild-type FSH receptor. Type III is related to hypothyroidism, with TSH greater than 100 milli-units/L, in the face of wild-type FSH receptor irrespective of pregnancy status.⁴

The case presented here, we believe, falls under De Leener Type II because of the extremely elevated hCG at initial presentation and that Type II is noted to be the most frequent cause of spontaneous ovarian hyperstimulation syndrome. In a rat model, severe hypothyroidism with high TSH triggers rapid follicular growth and spontaneous ovarian hyperstimulation syndrome. It is suggested that the accelerated 16 α -hydroxylation of estradiol results in increased formation of estriol, causing an inadequate feedback inhibition on the pituitary, and uninhibited release of gonadotropins. The hyperstimulated ovaries subsequently respond with massive luteinization and severe cystic reaction.⁶

Although bilateral adnexal masses with increased hCG and CA 125 are concerning for malignancy in a 36-year-old patient, the likelihood was low for several reasons. The pelvic ultrasonography demonstrated a normal intrauterine pregnancy without any placental abnormalities, so a molar pregnancy was excluded. In addition, the patient presented with amenorrhea and not vaginal bleeding. The magnetic resonance imaging and subsequent chest x-ray were both negative for retroplacental lymphadenopathy or metastatic disease, making ovarian malignancy doubtful. Our gynecology–oncology colleagues agreed with conservative management and followed her closely with us antepartum and postpartum.

Women with severe hypothyroidism experience greater perinatal complications including prematu-



rity, preeclampsia, impaired intrauterine growth, stillbirth, nonreassuring fetal heart tracings, and cesarean delivery.⁸ In our case, the delivery of a premature, growth-restricted infant requiring a cesarean delivery for a nonreassuring fetal heart tracing is consistent with the above findings. It is noted that during early gestation, fetal thyroid hormone requirement is dependent on maternal supply. The consequences of suboptimal thyroid status during pregnancy to the growing fetus are grave and include low birth weight and possible long-term neurodevelopmental impairments.⁸ Additionally, in this patient, the physiological anemia of pregnancy is compounded by poor maternal nutrition, iron deficiency anemia, and chronic disease of hypothyroidism which all lead to a low birth weight infant. These known morbidities of hypothyroidism, in addition to the development of spontaneous ovarian hyperstimulation syndrome with DVT, gestational diabetes, and incidental Rh isoimmunization, presented an extremely challenging clinical case.

To conclude, spontaneous ovarian hyperstimulation syndrome can occur in pregnant women with severe hypothyroidism or extremely elevated hCG levels and present with enlarged adnexal masses and acute abdominal pain. Accurate diagnosis and continuation of pregnancy with conservative management is a viable option, once ovarian malignancy is ruled out.

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Advanced Abdominal Pregnancy Resulting From Late Uterine Rupture

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BACKGROUND: Advanced abdominal pregnancy is rare, and one that occurs after uterine rupture with delivery of a viable fetus is exceptional.

CASE: A multiparous patient was admitted at 29 weeks of gestation for conservative management of placenta previa. She complained of intermittent abdominal pain, but repeated assessment suggested that both the patient and the fetus were doing well. At 36 weeks, an abdominal pregnancy was diagnosed with radiological features suggestive of uterine rupture. Laparotomy was performed and a healthy infant was delivered.

CONCLUSION: Fetal viability was achieved in this case of abdominal pregnancy secondary to uterine rupture after close maternal and fetal surveillance.

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Abdominal pregnancy is rare, and this is even more so for advanced abdominal pregnancy. The incidence is estimated to vary approximately between 1:400 and 1:50,000 deliveries. This condition is associated with high maternal and perinatal mortality.

CASE

A woman (gravida 11 para 7) was seen at a tertiary hospital for further management of asymptomatic placenta previa at 29 weeks of gestation. The patient had a history of three previous spontaneous miscarriages and one previous dilation and curettage. The earliest scan at 23 weeks of

gestation revealed an intrauterine pregnancy, and she was admitted for conservative management. One week after admission, she complained of abdominal pain. Clinical assessment showed stable vital signs, and abdominal examination revealed a uterine size corresponding to 32 weeks of gestation. The abdomen was soft and nontender, and there were no contractions. A single fetus was lying in an oblique breech position. The cardiotocograph showed a reactive fetal heart rate (FHR) pattern.

There were no episodes of vaginal bleeding, but the patient complained of intermittent abdominal pain especially when the fetus moved. Repeated clinical assessment with the differential diagnoses of abruptio placenta, gastritis, diverticulitis, and appendicitis could not detect any obvious problem. She had urinary tract infection and was given a course of antibiotics. The nonspecific pain was eventually felt to be possibly musculoskeletal in origin, and she was treated symptomatically.

She also had an ultrasound assessment every 2 weeks as the clinicians searched for an underlying problem that might explain the abdominal pain. Although the fetus remained in an abnormal lie, the growth of the fetus was found to be satisfactory, with good liquor volume. At 36 weeks of gestation, she was referred to the fetal-maternal unit to rule out morbid adherence of the placenta. A transabdominal sonography (PowerVision; Toshiba, Tokyo, Japan) revealed a mass adjacent to the cervical os that was thought to be the placenta previa (Fig. 1). However, the fetal head was seen next to the maternal liver. There was an irregular mass seen protruding out of the fundus of the uterus, alongside which was the umbilical cord (Fig. 2). The fetus was in transverse lie, and the parameters corresponded to 38 weeks of gestation. The estimated fetal weight was 3.2 kg, with normal amount of liquor. The authors failed to find an intact uterus surrounding the fetus. In view of these suspicious findings, magnetic resonance imaging (MRI) was performed.

Magnetic resonance imaging confirmed the uterine rupture and an extrauterine pregnancy (Fig. 3). At the emergency laparotomy, the peritoneal cavity was covered with a thick layer of dense tissue that looked like a large omental cake. Beneath that was a viable fetus encased in a “pseudosac” on a bed of small bowels. The infant boy weighing 3.16 kg was delivered with Apgar scores of 5 at 1 minute and 9 at 5 minutes. The liquor was stained with stale meconium and old blood.

At the uterine right lateral fundal region, there was a large area of rupture measuring about 10 cm in diameter, through which protruded the umbilical cord and about 25% of the placenta that looked infarcted and unhealthy. There was no active bleeding from the edges of the rupture. Hysterectomy was performed, and the estimated blood loss was 1,800 mL. The patient was discharged well.

Histopathologic examination revealed that the rest of the placenta within the uterine cavity was healthy and covering the os. There was no evidence of morbidly adherent

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Fig. 1. Placenta (P, P) within the uterus (arrows), thought to be placenta previa.

Naim. Uterine Rupture With Abdominal Pregnancy. Obstet Gynecol 2008.

placenta. In summary, this was an interesting case of secondary abdominal pregnancy due to a late rupture of the uterus that resulted in a viable extrauterine pregnancy.

COMMENT

The risk of uterine rupture during a trial of labor is 0.7%¹ in patients with a previous cesarean scar. A review of the few cases of early uterine ruptures did not reveal any common underlying risk factors.² As in this patient, the risk factor was probably her grand

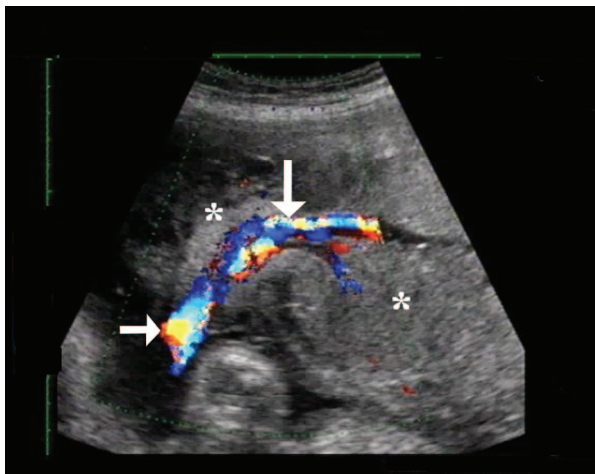


Fig. 2. Mass (placenta [asterisks]) protruding through the defect in the uterus and color Doppler revealing the umbilical cord (arrows) originating from within the uterus and coming through the defect to join the fetus in the abdominal cavity.

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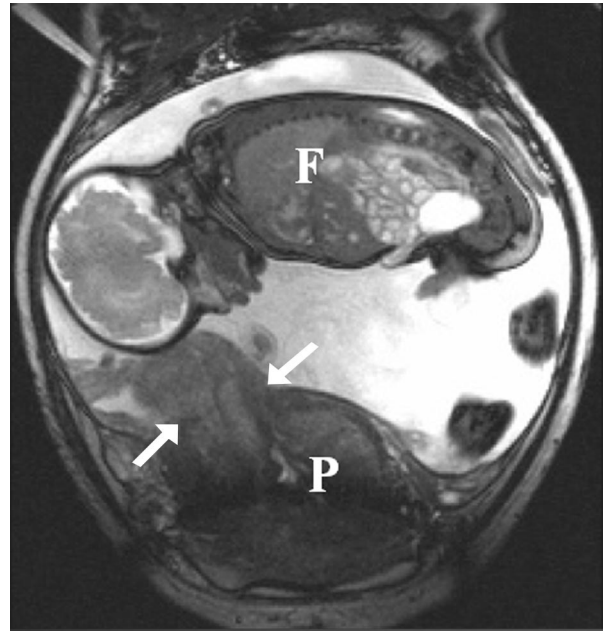


Fig. 3. Magnetic resonance imaging reveals the defect at the uterus (arrows), with part of the placenta (P) protruding, and the extrauterine pregnancy (F).

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multiparity and a previous dilation and curettage. The interesting aspect of this case was that the rupture was postulated to have occurred at about 30–31 weeks of gestation when the patient started to complain of abdominal pain.

However, despite the intermittent abdominal pain, the patient had always remained stable, and the fetus was growing well. All the other biochemical results were also normal. There was a drop of 1 g/L in her hemoglobin level, but this was thought to be due to her physiological anemia. There was no evidence of maternal or fetal compromise during her stay in the ward. In fact, at birth the fetus was large for gestational age (90th percentile). Although there are probably a few hundred cases of secondary abdominal pregnancy cited in the literature, a secondary abdominal pregnancy as a result of a late and chronic uterine rupture is so extremely rare that this diagnosis would hardly be considered in this patient. Furthermore, there have been very few reports of similar cases in the literature.^{3–6}

Although the uterine rupture had resulted in an abdominal pregnancy, fetal growth and the liquor index were good as opposed to the expectation in an abdominal pregnancy. This is not surprising because the fetus was still deriving its blood supply from the uterus, and the pseudosac formation was mimicking a



normal amniotic sac. As the policeman of the abdomen, the omentum had moved over to cover the fetus like a blanket and the ruptured site, thus isolating the "foreign body," ie, the fetus. These formed a pseudosac and radiologically presented like a normal amniotic sac. This pseudosac gave rise to some confusion because one would expect oligohydramnios in an abdominal pregnancy.

Once there was suspicion of uterine rupture with abdominal pregnancy, delivery was expedited. In some cases, the defect in the uterus can be repaired, but the risk of another rupture in subsequent pregnancies can be as high as 19%. In this case, however, hysterectomy was done because the defect was large and the patient had completed her family. In this particular case, fortunately, there was no dilemma with regard to the management of the placenta because it was located still within the uterine cavity. Most reports in the literature discussed at length whether to leave the placenta or deliver it, with the increased risk of massive hemorrhage, because the placenta is usually located in the abdomen, attached to the surrounding organs.

Diagnostic error is high in this type of case, and the literature has shown that the diagnosis was missed in approximately 50–90% of cases.⁷ The ability to make the correct diagnosis is based on the level of skill of the medical care provider and a high index of suspicion in patients complaining of abdominal pregnancy, especially with a fetus in an abnormal lie. In this case, all the earlier scans were performed by trainees, and none of them suspected the diagnosis until the patient was reviewed by the fetal-maternal team. As obstetricians, one must always bear in mind that when a pregnant patient presents with repeated and persistent abdominal pain, especially with the fetus in an abnormal lie, it is important for an experienced sonographer with good equipment to search for an intact uterus around the fetus to minimize the risks to both mother and fetus.

Advanced abdominal pregnancy is rare and associated with high fetal and maternal morbidity and mortality. Maternal mortality has been reported to be about 0.5–18%⁸ in such cases. The chance of fetal survival is reported to be dismal, with the mortality ranging from 40% to 95%.⁸ There is also a high rate of congenital malformation of 30–90%.⁸ Most case reports of abdominal pregnancy as a result of uterine rupture have reported fetal demise.

Fortunately, in this case the outcome was good for both mother and infant. If the diagnosis was made much earlier, the delivery may have been at a stage where fetal viability was poorer. Advanced abdominal pregnancy remains a diagnostic and therapeutic challenge for every obstetrician. This case reiterates that there may be a role for conservative management, even after uterine rupture, provided that there is no maternal or fetal compromise.

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Uterine Artery Embolization Followed by Dilation and Curettage for Cervical Pregnancy

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BACKGROUND: Cervical pregnancy can be a life-threatening condition due to the risk of severe hemorrhage. Progression of ultrasonographic diagnostic technology has allowed the early detection of cervical pregnancy. However, a standard treatment protocol for fertility preservation has not yet been established.

CASE: Two women with cervical pregnancy presented with cardiac activity at 6 and 7 weeks of gestation. They were treated with transfemoral uterine artery embolization followed by dilation and curettage with minimal bleeding. One patient gave birth to a healthy neonate 20 months after the procedure.

CONCLUSION: Early cervical pregnancies were treated with dilation and curettage after uterine artery embolization. This treatment can be considered as conservative management for patients who desire to preserve their fertility.

(*Obstet Gynecol* 2008;111:505–7)

Cervical pregnancy can be a life-threatening condition due to the risk of severe hemorrhage. Cervical pregnancy is the implantation of a developing conceptus in the endocervical mucosa. Diagnosis and treatment of cervical pregnancy has changed dramatically in recent decades. Before 1980, the diagnosis was commonly made when dilation and curettage (D&C) for presumed incomplete abortion resulted in unexpected catastrophic hemorrhage. Emergency hysterectomy usually ensued.¹ Cervical pregnancy is now commonly diagnosed on a routine transvaginal ultrasound tomography examination in first-trimester pregnant patients without bleeding. However, a protocol for

conservative management in early cervical pregnancy patients has not been established, as yet.

Below, we present two cases of cervical pregnancy in which uterine artery embolization was performed as a prophylactic procedure before D&C. According to our experience and review of published reports written about the management of cervical pregnancy, new suggestions are made regarding the potential role of uterine artery embolization before D&C in the treatment of cervical pregnancy.

CASE 1

A 27-year-old, gravida 2, para 0, with an ultrasonographic diagnosis of cervical pregnancy at the sixth week of gestation was referred to our hospital in 2005. She presented with painless fresh vaginal bleeding. Transvaginal ultrasonography showed a yolk sac with a positive fetal heart beat in a 13.2-mm-sized gestational sac located within the cervical canal (Fig. 1.). The urine human chorionic gonadotropin (hCG) was 3,951 milli-International Units/mL. Her vital signs were stable, and findings from a general physical examination were unremarkable. In the uterine cavity, there were no endometrial signs of an intrauterine pregnancy. As the patient expressed a strong desire to preserve her fertility and presented a moderate amount of flesh uterine bleeding, conservative management with uterine artery embolization followed by D&C was planned with informed consent. Under fluoroscopic control, each uterine artery was embolized with minced gel foam. After the procedure, uterine bleeding was immediately decreased. To avoid severe postembolization ischemic pain, continuous epidural analgesic reagent injection was started before uterine artery embolization. Twenty-four hours after the uterine artery embolization, D&C of the cervical pregnancy was performed under general anesthesia. The estimated blood loss was 20 mL. After the evacuation, no uterine bleeding occurred. Three days after D&C, a ultrasound examination showed a normal structure of the uterine cervix and body. Pathological examination of the intracervical curettage specimen confirmed the products of conception. The urinary hCG titer was decreased to normal range within 4 weeks. Seventy-six days after the procedure, the patient resumed regular menstrual cycles.

A natural intrauterine pregnancy was confirmed 12 months after the procedure. The course of pregnancy was unremarkable except the patient received prophylactic cervical cerclage for suspected cervical incompetency with a wedge-shaped cervix detected by transvaginal ultrasound tomography at 19 weeks of gestation on routine screening. At 36 weeks of gestation, her membranes ruptured spontaneously, the cerclage was removed, and she gave birth to a healthy neonate after a spontaneous labor. The newborn (male, weight 3,016 g, Apgar scores 8 and 9) and the mother's course were uneventful after delivery.

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Fig. 1. Sagittal transvaginal ultrasonographic view of the uterus in case 1 showed gestational sac in the cervical canal. Yolk sac was also noted (arrow).

Nakao. *Conservative Treatment for Cervical Pregnancy. Obstet Gynecol* 2008.

CASE 2

A 41-year-old, gravida 2, para 1 with a sonographic diagnosis of cervical pregnancy at the seventh week of gestation was referred to our hospital in 2006. The vaginal examination revealed no uterine bleeding. The transvaginal ultrasonography demonstrated a gestational sac and a fetus with a positive fetal heartbeat located in the mid portion of the endocervical canal. The crown-rump length was 12 mm, corresponding to 7 weeks of gestation. The patient expressed a strong desire to maintain her fertility. After providing informed consent, she agreed to undergo conservative treatment with uterine artery embolization followed by D&C. At day 1, angiographic embolization of the bilateral uterine arteries was successfully performed with gel foams under continuous epidural anesthesia using fentanyl and ropivacaine hydrochloride hydrate. On the following day, D&C was carried out without unexpected bleeding. The urinary hCG titer was 25,700 milli-International Units/mL on the day of the operation. Within 48 hours, the urinary hCG decreased to 3,340 milli-International Units/mL, and the patient was discharged. Histological examination of the curettaged specimen confirmed the products of conception. She resumed a normal menstruation cycle 4 weeks later.

COMMENT

Various conservative methods for cervical pregnancy termination have been suggested in an attempt to avoid hemorrhage, preserve the uterus and maintain fertility, such as D&C followed by intracervical tamponade, cervical cerclage, or operative ligation of uterine arteries, and antitrophoblastic chemotherapy.¹

Dilation and curettage with subsequent tamponade of the defect in the cervical canal used to be the

orthodox method for management of cervical pregnancy. Various procedures have been tried to avoid uncontrollable massive postevacuation bleeding. For many years, cervical or vaginal packing with gauze has been the primary method used to control such bleeding. As the packing device, a Foley catheter was also used. Other methods for local control are transvaginal ligation of the descending branches of the uterine arteries, cervical cerclage, and intracervical injection of vasoconstrictors like vasopressin or prostaglandins.² However, these procedures showed uncertainty.

Systemic and/or local instillation of methotrexate (MTX) has become one of the main choices among fertility-preserving therapies for cervical pregnancy because it is convenient to perform and has a high success rate in selected cases. Since Oyer et al³ reported the first successful case of cervical pregnancy treated with MTX, many patients have been treated by various systemic or local chemotherapeutic agents or both. Most cases were treated with an MTX protocol similar to those used in gestational trophoblastic disease.^{1,4} During the treatment, unexpected massive bleeding was sometimes observed, and additional procedures were necessary for hemostasis. The effectiveness of MTX for the treatment of cervical pregnancy is reduced with β -hCG levels of greater than 10,000 milli-International Units/mL, gestational age greater than 9 weeks, and positive fetal heart activity.⁵ Kim et al⁶ reported that concomitant procedures with the MTX treatment were required in 54% of cases with positive fetal heart beat and in 50% of cases of greater than 6 weeks of gestation in their series. These results suggest that MTX treatment cannot be considered a criterion standard for the treatment of cervical pregnancy.

Bilateral internal iliac artery ligation is performed in patients refractory to local treatment after evacuation of cervical pregnancy. However, the high complication rate of general anesthesia and emergency surgery in patients who are already hemodynamically unstable should be taken into consideration. Recently, uterine artery embolization has been shown to be effective for the treatment of acute pelvic hemorrhage and obstetric emergencies including postpartum hemorrhage, postabortion hemorrhages with placenta accrete, and cervical pregnancy. Uterine artery embolization is now widely accepted as an alternative treatment for uterine fibroids. Although rare serious complications related to uterine artery embolization for fibroids are presented in recent case reports, including endometrial atrophy with permanent amenorrhea, uterine necrosis, and fatal sepsis, cases of



pregnancy after uterine artery embolization even for uterine fibroids have recently been reported. As to the treatment tool for cervical pregnancy, uterine artery embolization was initially used after surgical evacuation to reduce postoperative blood loss and preserve fertility, instead of surgical internal iliac artery ligation. Uterine artery embolization was secondarily used when uncontrollable bleeding occurred after chemotherapy. Recently, prophylactic use of uterine artery embolization before D&C was also applied to avoid massive intraoperative bleeding.^{7,8} We experienced two successful cases of patients treated by uterine artery embolization before D&C, one of which was followed by a successful pregnancy without adverse events. Furthermore, for both cases, no additional chemotherapy was needed. This conservative method should be applied at least during the first trimester because the blood flow of the ovarian arteries will increase in the second trimester. Therefore, early and correct diagnosis of cervical pregnancy is necessary.

In conclusion, D&C after uterine artery embolization was shown to be effective for patients with cervical pregnancy during the first trimester, especially for those with massive vaginal bleeding. This therapy has potential to minimize the patient's discomfort and recovery time to and preserve fertility.

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Pregnancy After Microinsert Sterilization With Tubal Occlusion Confirmed by Hysterosalpingogram

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BACKGROUND: Introduced to the U.S. market in late 2002 as a permanent method of contraception, a microinsert device is placed hysteroscopically into the fallopian tubes, not requiring incisions or general anesthesia. This report describes a case of pregnancy more than 6 months after a hysterosalpingogram (HSG) confirming bilateral occlusion after microinsert sterilization.

CASE: A 30-year-old gravida 1 para 1 woman desired permanent sterilization. The patient underwent microinsert device placement and 6 months later had an HSG that confirmed bilateral tubal occlusion. More than 6 months after the confirmatory HSG, the patient became pregnant and delivered a term infant by cesarean birth. Cornual perforation was noted at surgery.

CONCLUSION: This case illustrates pregnancy after microinsertion sterilization and an HSG confirming bilateral tubal occlusion, despite perforation. A microinsert device continues to be a viable option for sterilization.

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Permanent sterilization is one of the most commonly used options for family planning and contraception. Approximately 700,000 tubal sterilizations are performed annually and more than 10 million women rely on this procedure currently in the United States.⁸ Conversely, an estimated half (48%) of pregnancies that occur in the United States each year are unintended, translating to an estimated 3 million unplanned pregnancies in the United States each year.¹

Introduced to the U.S. market in late 2002, Essure

(Conceptus, Mountain View, CA) permanent birth control is a method of contraception that does not require incisions or general anesthesia. The device is a microinsert designed to be placed into the fallopian tubes hysteroscopically. It causes an intended benign, occlusive tissue response, resulting in tissue in-growth that permanently anchors the insert and occludes the fallopian tubes.⁵ A second form of birth control is necessary for 3 months until a hysterosalpingogram (HSG) can provide evidence of tubal occlusion. This is an extremely attractive option for those women seeking a form of permanent birth control who would like to avoid the risks of anesthesia and transabdominal surgery. Additionally, this option is available to women whose medical conditions preclude the use of general anesthesia.

The device showed very compelling results in the studies conducted to achieve U.S. Food and Drug Administration approval. Studies have proven over time that the procedure is well tolerated, provides high patient satisfaction, and is a very effective means of preventing pregnancy. We report a case in which a patient became pregnant after a microinsert device procedure and an HSG confirming bilateral tubal occlusion.

CASE

A 30 year old gravida 1 para 1 morbidly obese woman presented to our clinic desiring permanent sterilization. The patient's surgical history was significant for a cesarean delivery at term secondary to failure to progress. Her postoperative course was complicated by pulmonary edema and a wound infection requiring long-term wound vacuum placement. After being presented with several options for permanent sterilization, the patient decided to proceed with microinsert device placement.

The patient underwent the microinsert sterilization without complication. Findings at the time of hysteroscopy included a normal endometrial cavity and normal tubal ostia bilaterally. Expanded coils were trailing into the uterine cavity bilaterally after placement. Before discharge from the hospital, the patient received depomedroxyprogesterone acetate for contraception.

The patient was seen for her 6-week postoperative visit and was without complaints. A 3-month HSG was scheduled. The patient presented as scheduled for her HSG, which was performed using CooperSurgical (Trumbull, CT) surgical hysterosonography and hysterosalpingography catheter with a 1.5-mL balloon. Twenty milliliters of sonografin 38% organically bound iodine (diatrizoate meglumine and iodipamide meglumine) contrast media was used. The report was read as right tubal occlusion and left tubal patency with spillage of contrast into the peritoneal cavity. The patient was seen again in

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Fig. 1. June 2006 hysterosalpingogram showing bilateral placement and occlusion.

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clinic, and the results were explained to her. Per the microinsert company's guidelines, depomedroxyprogesterone was continued, and a repeat HSG was performed 3 months later. The interpretation was bilateral tubal occlusion (Fig. 1). A nonsteroidal anti-inflammatory drug was not given at the time of either HSG.

More than 6 months later, the patient missed her menstrual cycle and performed a pregnancy test at home, and the result was positive. The patient presented to the emergency department because of this, and a sonogram was performed. The patient was noted to have an intrauterine pregnancy at 7 weeks of gestation with fetal cardiac activity.

The patient had a routine prenatal course. The patient presented in active labor and, given her history of prior cesarean delivery, desired a repeat cesarean delivery, with a bilateral tubal ligation. At the time of surgery, the microinsert was found to have perforated the uterus in the left cornual area. A tubal ligation was then performed.

COMMENT

This case report is one of only two found reporting pregnancy after microinsert hysteroscopic sterilization and bilateral occlusion confirmed by HSG. We searched Ovid/Medline and PubMed using the following search terms in English: "microinsert device," "permanent birth control," "hysteroscopic sterilization," and "conceptus." Between January 2000 and July 2007, there is only one other case reporting pregnancy after microinsert device tubal sterilization with confirmed occlusion on HSG. This study by Moses et al⁹ reports a patient who became pregnant despite an HSG showing tubal occlusion. This patient was ultimately found to have a microinsert perforating the uterine wall. There is another case report of

failed tubal occlusion using the microinsert device permanent birth control hysteroscopic sterilization procedure; however, that report resulted in a patent tube by HSG, but pregnancy did not occur.⁶ In a reported case from Australia, the device was appropriately placed and retained; however, the device never occluded the right fallopian tube. In a follow-up editorial, the author questions the interpretation of the follow up HSG and plain film x-ray.⁷ The author states that the microinsert was lodged above the wall of the fallopian tube, most likely subserosal, and that two tracts can be seen on the x-ray.

Upon review of the early studies and phase II and III trials, complications were very limited. These included inability to place the device bilaterally due to anatomic, procedural, and device-related events, uterine wall or tubal perforations, some of which were thought to be due to a support catheter that has since been discontinued, and microinsert expulsion.^{2,3,4} In an early study, the device was placed bilaterally in 85% of women with no pregnancies reported, and the procedure was tolerated very well.⁴ In phase II trials, bilateral placement was successful in 88% of cases.³ There were no pregnancies reported in this trial. There was unsatisfactory placement in 4% of cases including one microinsert expulsion, six perforations, and two unsatisfactorily placed devices. At 3-month HSG, 96% showed bilateral occlusion, 3% had unilateral occlusion, and 1.5% had an "equivocal" HSG. At 6 months postprocedure HSG, all women who had at least one patent fallopian tube at the 3-month HSG showed bilateral occlusion.

During the phase III study, bilateral placement was achieved in 92% of cases.² Of those with bilateral placement, HSG at 3 months showed bilateral occlusion in 92% of women. As in the phase II study, all women who did not have occlusion at 3 months had a 6-month postprocedure HSG, which showed bilateral occlusion. Complications included a 3% expulsion rate, a 0.9% perforation rate, and an unsatisfactory placement rate of 0.6%. Including all phases as of January 8, 2003, there were no pregnancies after 9,620 woman-months of exposure.² In our case, the HSG was interpreted as showing bilateral tubal occlusion. The patient then became pregnant 6 months after the confirmatory HSG, nearly 1 year after her initial procedure. Some hypotheses as to how this could occur are suggested.

The first is that there was unsatisfactory placement with only two trailing coils into the uterine cavity. Ideally, there should be three to eight expanded coils. The microinsert device company recommends if there are fewer than 3 or more than 8



coils seen that the device should be left in place and the patient should be evaluated as planned by HSG at 3 months postprocedure. Our case followed this recommendation, and the device showed bilateral tubal occlusion at 6 months.

Another possibility is that at the time of HSG, tubal spasm occurred causing a false evaluation of tubal occlusion. An important consideration might be to give a nonsteroidal anti-inflammatory drug 30–60 minutes before the HSG, as is done at the time of the procedure. Another way to reduce tubal spasm is to slowly inject the contrast at the time of HSG. This, however, was not done during this case. Another theoretical explanation for pregnancy after microinsert device could be assisted reproductive techniques; this, however, was not the case in this patient. Last, as in the case by Moses et al⁹ uterine perforation by the microinsert device in the proximity of the tubal ostia may mimic proper microinsert placement and bilateral tubal occlusion. As we later found out, this was the case in this patient.

This case illustrates pregnancy after microinsert device hysteroscopic sterilization and an HSG showing bilateral occlusion. As of the end of July 2007, the microinsert device website reports 130,000 procedures have been done. Our case and the case by Moses et al⁹ are the only two that can be found, using our search criteria, that have had microinsert device with bilateral occlusion on HSG and a subsequent pregnancy. We now know that, as in the other case by Moses et al,⁹ there was a uterine perforation. In the context of knowing all sterilization procedures have a

failure rate, a microinsert device continues to be a viable option for permanent sterilization. We continue to offer this procedure to our patients. We contend, however, that as with all medical procedures, failures do occur.

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Persistent Pain After Hysteroscopic Sterilization With Microinserts

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BACKGROUND: Hysteroscopic sterilization using tubal microinsert devices is an increasingly common method of contraception. Postprocedure pain is typically minimal and brief, adding to the popularity of this method. This report describes a case of intractable pain after placement of microinserts, ultimately requiring removal of the inserts.

CASE: A 31-year-old gravida 4 para 4 woman underwent an uncomplicated office hysteroscopic tubal occlusion for permanent birth control. Subsequent to the procedure, she had significant bilateral pelvic pain that failed all attempts at conservative management and required removal of the microinserts for pain relief.

CONCLUSION: Hysteroscopic placement of tubal microinserts for sterilization may occasionally be associated with intractable pelvic pain requiring removal of the devices.

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Hysteroscopic sterilization using tubal microinsert devices, known as the Essure (Mountain View, CA) procedure, has become increasingly common as an outpatient office procedure for permanent birth control. Advantages of performing sterilization in the office using the transcervical hysteroscopic approach for interval procedures include elimination of the need for general anesthesia associated with laparoscopy, avoidance of abdominal incisions and entry into the peritoneal cavity, rapid placement time, no need for hospitalization, decreased postoperative pain, high efficacy rates when bilateral devices are successfully placed,^{1,2} and lower healthcare costs.³ Potential disadvantages include the need for a follow-up hysterosalpingogram to confirm tubal occlusion, inability to successfully place bilateral

microinserts, and specialized hysteroscopic skills necessary to perform the procedure.⁴

CASE

A gravida 4 para 4 woman requested permanent sterilization 8 months after the delivery of her fourth child. She did not use oral contraceptives before the procedure and had no significant history of chronic pelvic pain. She underwent an in-office transcervical Essure procedure with placement of bilateral microinsert devices. The first microinsert was placed in the proximal right tube with the tip, but no trailing coils, visible hysteroscopically after placement. The second microinsert was placed in the proximal left tube with three trailing coils visible hysteroscopically in the uterine cavity. The patient tolerated the procedure well and reported only minimal cramping postprocedure. She required no additional pain medication after the procedure. Two days after the procedure, the patient reported right-sided cramping pain and was treated with nonsteroidal anti-inflammatory pain medications. Twenty days after the procedure, the patient was evaluated in the office for ongoing bilateral pelvic pain, which she described as a fairly constant “poking” pain that was associated with a tingling sensation radiating into her right leg. Physical examination was unremarkable, and there was no fever, discharge, or vaginal bleeding. She was given additional nonsteroidal anti-inflammatory pain medications and underwent a plain radiograph and ultrasound examination of the pelvis. The radiograph revealed appropriately located bilateral microinserts. The ultrasonogram was notable for devices appropriately located in the bilateral adnexae and a small amount of fluid within the right fallopian tube suggesting a hydrosalpinx. Subsequently, the patient was treated with doxycycline for 10 days for presumed salpingitis without relief in pain; at this time she required narcotic pain medication for relief of her constant pelvic pain. Ten weeks after the sterilization procedure, the patient underwent laparoscopy for evaluation and treatment of her persistent pain. At laparoscopy, the pelvis appeared normal and there was no visible hydrosalpinx or adhesive disease (Fig. 1). In addition, there was no evidence of tubal or uterine perforation or pathology. Before the procedure, the patient requested removal of the devices in combination with bilateral salpingectomies in the event that normal anatomy was encountered. Accordingly, the devices were removed and salpingectomies performed without difficulty at the time of laparoscopy. Final tissue pathology showed no diagnostic abnormality and grossly unremarkable microinsert devices. The patient’s postoperative course was unremarkable, and she had resolution of her pain postoperatively.

COMMENT

In the 2003 phase II study by Kerin et al⁴ of the Essure permanent birth control device, there were no cases of postprocedure pain lasting more than 2 weeks. The phase III study also reported no cases of persistent pain

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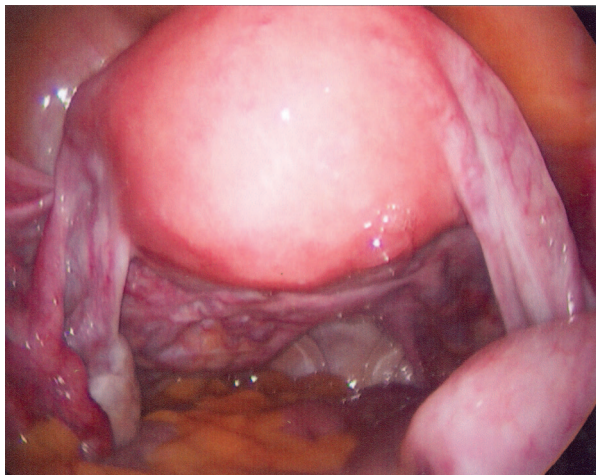


Fig. 1. View of uterus and tubes at laparoscopy. Uterus, tubes, and ovaries appear grossly normal. No adhesions or hydrosalpinges are seen. No evidence of misplacement or perforation of either microinsert is visible.

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after the procedure.¹ Various reported complications include perforation and expulsion,^{1,4} failure of a properly located device to occlude the tubal lumen,⁵ and pregnancy.⁶ Using OVID search engine to search English language articles from 1996 to 2007 utilizing search terms “Essure, tubal sterilization/hysterectomy,” and “hysteroscopic sterilization,” no additional case reports of persistent pain lasting more than 2 weeks were encountered.

This is a case report of significant ongoing pelvic pain after uncomplicated placement of the Essure microinsert devices for hysteroscopic sterilization that required removal of devices for pain relief. In this patient, there was no evidence of grossly abnormal location or placement of the devices or of tubal pathology to account for the onset of pelvic pain after the Essure procedure. Although placement of the

right coil was not ideal in that only the tip was visible hysteroscopically rather than the recommended minimum of three coils, there was no perforation or laceration of the right tube visible at laparoscopy, and the device was nonetheless maintained in the proper uterotubal junction region. Furthermore, the patient's reports of pain, although more significant on the right, were bilateral. The postprocedure pain failed to respond to all conservative attempts at management and required removal of the devices for relief of pain. While cases of persistent pain have been noted after tubal sterilization with laparoscopic and open procedures, hysteroscopic sterilization using tubal microinsert devices has generally been reported to be well tolerated in terms of procedure-related pain.^{1,7} Continued monitoring for persistent pain after the Essure hysteroscopic tubal occlusion procedure is appropriate, and consideration may be given to microinsert device removal in cases of intractable pain.

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Hysteroscopic Tubal Occlusion Sterilization After Failed Laparoscopic or Abdominal Approaches

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BACKGROUND: When tubal ligations cannot be performed because of dense postoperative adhesions, options for female sterilization are very limited. As the incidence of cesarean delivery rises and the occurrence of peritubal adhesions increases, tubal ligation using abdominal or laparoscopic surgery may become increasingly technically difficult. Hysteroscopic tubal occlusion provides a method of permanent sterilization when an abdominal or laparoscopic approach is unsuccessful.

CASES: Three patients with failed tubal ligations by abdominal or laparoscopic approaches were referred to our institution. Their cases were complicated by technically difficult surgeries with dense intraabdominal adhesions. Hysteroscopic tubal occlusion was successfully performed in each patient.

CONCLUSION: Hysteroscopic tubal occlusion can be used for permanent sterilization when abdominal or laparoscopic approaches are not possible.

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Tubal ligation remains a popular form of female contraception.¹ Pregnancy rates after tubal ligations are well documented,¹ but there is little information on attempts at tubal ligation which are not successfully completed because of difficulties such as excessive adhesions. The only option for female permanent sterilization, if still desired, has been another attempt at tubal ligation via repeat laparoscopy or laparotomy or both. However, the difficulties encountered at the first attempt may prevent a successful result with a second attempt.

The Essure tubal occlusion device (Conceptus, Mountain, CA; <http://www.essuremd.com>) is an alterna-

tive for women who desire permanent sterilization. The device is a micro-insert made of a flexible stainless steel inner coil, an outer coil made from a nickel-titanium alloy, and a layer of polyethylene fibers. This micro-insert is placed into the cornual portion of the fallopian tubes at the time of transcervical hysteroscopy under local anesthesia. Two separate clinical investigations have evaluated the safety and efficacy of this system. In a cohort of 745 women, the reported success rate is 99.8%, with a rate of expulsion between 0.5% and 2.9%, and a rate of uterine perforation between 1.1% and 2.9%. Because the tubal occlusion device is placed without entry into the peritoneal cavity, it may be particularly useful in patients with abdominal or pelvic adhesions from prior surgery.

We present three patients in whom a tubal ligation could not be performed and placement of a tubal occlusion device proved to be an effective and minimally invasive technique to produce permanent sterilization.

CASES

A woman, gravida 3 para 2-1-0-4, presented at 13 weeks postpartum for an elective sterilization. The patient had undergone three previous cesarean deliveries. Her most recent twin pregnancy ended in a repeat cesarean delivery at 34 weeks of gestation. During her prenatal care, the patient requested a tubal ligation. At delivery, dense intraabdominal adhesions were noted. Despite attempts to dissect the adhesions, neither fallopian tube could be visualized. Plans to perform a tubal ligation were abandoned out of concern of causing unintended bladder or bowel injury. Postpartum, the patient was offered a hysteroscopic tubal occlusion.

The patient had an uncomplicated hysteroscopic tubal occlusion performed under local anesthesia and sedation. The total operating time was 18 minutes, and total blood loss was less than 50 mL. She was discharged the same day. The patient used alternative contraception until her follow-up hysterosalpingogram (HSG). Approximately 3 months after the procedure, an HSG confirmed correct placement of the inserts and occlusion of her fallopian tubes.

The second patient, a gravida 6 para 4-0-2-4, presented for an elective postpartum sterilization. She had previously had four term cesarean deliveries. Her last pregnancy was a repeat cesarean delivery at 39 weeks of gestation, at which time a tubal ligation was planned. Similarly to the previous patient, her cesarean delivery was complicated by dense intraabdominal adhesions, which prevented adequate visualization of her fallopian tubes. The attempt at sterilization was abandoned. Postpartum, the patient was scheduled for an open laparoscopy and tubal ligation via fulguration. During the procedure, the patient's fallopian tubes could

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not be visualized adequately. The case was converted to laparotomy; however, the surgeon was still unable to identify the fallopian tubes, and the procedure was abandoned again.

Approximately 3 months after these procedures, this patient sought a second opinion at our institution. We successfully performed a hysteroscopic tubal occlusion. The total operating time was 20 minutes, and total blood loss was less than 50 mL, without complication. This patient used oral contraceptives until her follow-up HSG, which, four months later, confirmed tubal occlusion.

The third patient, a gravida 2 para 1-0-0-1, presented for elective sterilization after a failed laparoscopic attempt. The patient's surgical history was significant for bowel resection and gastric bypass. During the laparoscopic attempt, the surgeon was unable to enter the peritoneal cavity because of dense adhesions. The laparoscopy was converted to a laparotomy, which was unsuccessful, and the procedure was abandoned. Due to excessive bleeding, the patient was admitted to the hospital for several days of observation. She presented to our institution and had a successful hysteroscopic micro-insert placement. Total operating time was 18 minutes with less than 50-mL blood loss and no complications. This patient had an HSG that confirmed bilateral tubal occlusion 3 months after her procedure.

COMMENT

Rates of cesarean deliveries continue to rise, from 20.7% in 1996 to a rate of 27.5% in 2003,² as do those for other abdominal surgeries such as bariatric surgery.³ Patients who undergo such procedures will result in a growing number of women who present for sterilization with an already significant surgical history. Although the impact of cesarean delivery on a physician's ability to perform subsequent procedures is not known, prior surgery may prevent abdominal or laparoscopic attempts for tubal ligation. In women who still desire sterilization after failed conventional approaches to tubal ligation, an alternative approach would be of great value. While there is much information on why tubal ligations fail,¹ there are scant data available discussing aborted tubal ligation procedures. We performed a literature search using Medline and the Cochrane database from 1950 to January 2007, with the terms "failed tubal ligation," "aborted tubal ligation," and "failed laparoscopic tubal ligation." This report is the first with a series of patients in whom a tubal ligation could not be performed secondary to dense intraabdominal adhesions and successful sterilization was later performed.

In patients with prior abdominal surgery, abdominal or laparoscopic sterilization poses a diffi-

cult challenge. Alternatives to sterilization, particularly in women who are not ideal surgical candidates, include vasectomy, oral contraception, intrauterine device or Implanon (Organon USA, Roseland, NJ), and vaginal approaches for sterilization; each method has its own advantages and limitations. Not all women have the option of relying upon a male partner's vasectomy, which is simple, safe, and highly effective. Oral contraceptives are popular, but there are large groups of women where use is contraindicated. Side effects, cost, or compliance issues may make them a less desirable form of contraception, especially in older patients.⁴ While a vaginal approach for tubal ligation was once utilized, the technique has fallen out of favor in the United States due to technical difficulty and higher morbidity compared with present laparoscopic techniques.⁵ The intrauterine device (IUD) is available for long-term contraception, but is frequently unpopular with patients because of bleeding, pain, or expulsion.⁶ The public concern about safety of the IUD since the Dalkon Shield has further dampened enthusiasm for the newer safer IUDs.

Hysteroscopic tubal occlusion provides many advantages over traditional methods for tubal sterilization. In contrast to tubal ligation techniques, an often overlooked advantage of this device is that it allows the operator to completely bypass the peritoneal cavity. This minimally invasive approach offers shorter operating times, little or no hospital stay, local anesthesia, and rapid return to work. In most patients desiring sterilization, these potential benefits may be counterbalanced with the need for adequate contraception for 3 months after the procedure, as well as the requirement for a HSG to demonstrate successful occlusion. Even with proper placement, tubal occlusion does not occur in approximately 5% of cases at the 3-month postoperative mark (see <http://www.essuremd.com>). In the pivotal trial of the device, at 6 months after microinsert placement, all of these initial nonoccluded patients subsequently had full tubal occlusion. It remains unknown whether peritoneal peritubal adhesions, such as those seen in our patients, will distort the tubes sufficiently to affect proper placement and occlusion. However, we were reassured by the finding of occlusion on postoperative HSG in all three cases.

Our three cases serve as a useful reminder that a tubal ligation cannot always be accomplished. As shown with our third case, even when the attempt is abandoned, complications such as severe hemorrhage can occur. Indeed, larger studies of laparoscopic tubal ligation show complication rates of 1–2%.⁷ In a pro-



spective multicenter study of 9,475 women, prior abdominal or pelvic surgery and dense abdominal or pelvic adhesions were both associated with an increased risk of complications, with an odds ratio (95% confidence interval) of 2.3 (1.4–2.9) and 3.3 (2.3–4.7), respectively. As shown with our cases, the advantage of avoiding the peritoneal cavity is invaluable in patients with prior surgery and dense adhesions. Based on our experience, we believe that hysteroscopic tubal occlusion, when available, should be strongly considered as an initial approach to sterilization in women who have previously undergone abdominal or pelvic surgery or who have had documented abdominal or pelvic adhesions.

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Failure of Sterilization After Clip Placement

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BACKGROUND: Tubal sterilization is a common method of contraception used worldwide. The Filshie clip is a device designed to occlude the fallopian tubes. It is common practice to apply the clips across the isthmus using laparoscopy. It is often suggested that failures occur due to problems with the technique used to occlude the fallopian tubes.

CASE: After insertion of an intrauterine device, a patient experienced an unplanned pregnancy and subsequent abortion. The intrauterine device was removed, and bilateral Filshie clips were applied by an experienced surgeon. After this procedure, the patient experienced a second unplanned pregnancy and subsequent abortion. A partial salpingectomy was performed after the fallopian tubes were examined, and it was confirmed that the Filshie clips were applied appropriately.

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CONCLUSION: It is important to understand why sterilization clips lead to contraceptive failure and to inform patients of this risk. Contraceptive failure after female sterilization remains a medical issue.

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Tubal sterilization is a common method of contraception used worldwide. The most common surgical approaches used to perform tubal sterilization include either an abdominal approach (laparotomy or laparoscopy) or a vaginal approach (hysteroscopy). There are several different techniques used to occlude the fallopian tubes: electrocoagulation or ligation with or without a transection, or insertion of (Yoon) rings or (Filshie [Avalon Medical Corporation, VT] or Hulka [Richard Wolf Medical Instruments Corporation, Vernon Hills, IL]) clips.² The Filshie Clip is a hinged titanium clip with an inner silastic rubber lining that gently compresses the tissue as the clip locks onto the isthmus portion of the tube.

Many studies compare the efficacy and safety of each technique. For example, The Collaborative Review of Sterilization (CREST), a multi-center, prospective study compares these different techniques.³ However, the reasons why contraceptive failure occurs after tubal sterilization remains unknown.⁴ It is often suggested that failures occur due to a problem with the technique used to occlude the fallopian tubes. Additionally, no literature uses histology to report the application of Filshie clips after contraceptive failure.

Overall, it is important to understand why con-



traceptive failure occurs after tubal sterilization, especially as this may potentially have legal implications.

CASE

A patient presented with an antenatal history of two normal pregnancies. Both were uncomplicated vaginal deliveries and healthy babies.

After the birth of her last child, her choice of contraception was a copper intrauterine device (IUD). Despite the presence of the IUD, an unplanned pregnancy occurred in November 2003. An abortion was then carried out with removal of the IUD.

At that time, a patient requested tubal sterilization. In May 2004, after gaining informed consent, the procedure was performed using laparoscopy and bilateral Filshie clips were inserted. The procedure was conducted by an experienced surgeon who reported no difficulties when applying the Filshie clips. The surgeon also reported that he felt and saw both Filshie clips lock appropriately.

In October 2004, 5 months after the insertion of the Filshie clips, the patient presented with amenorrhea and pelvic pain. An ultrasound scan was thus performed, which unexpectedly revealed an intrauterine pregnancy. At the time, it was possible to measure the crown-rump length and date the pregnancy at 8 weeks of gestation. Another abortion was later carried out.

In May 2005, the patient requested another method of female sterilization. Laparoscopy was performed, and the fallopian tubes were carefully examined, and it was confirmed that Filshie clips were appropriately applied (Fig. 1). The decision was therefore made in favor of a partial salpingectomy, removing the isthmus portion of the fallopian tubes at the site where the Filshie clips had been applied.

During the procedure, microdissection of the clips allowed the surgeons to confirm that the Filshie clips had been correctly applied and that the whole circumference of

each fallopian tube was contained within the Filshie clip. Microscopic examination on serial sections revealed a small channel remaining within each fallopian tube. These channels presented normal portions covered with ciliated epithelium, and other portions contained within the clips that had a compacted surface epithelium (Fig. 2).

To date, more than 2 years after the procedure, the patient has not had any further pregnancies.

COMMENT

This case report documents histologic evidence that confirms the correct application of Filshie clips after contraceptive failure. The search strategy was ascertained using PubMed with the following key words: "sterilization," "sterilization," "Filshie," "clips," "failure," and "pregnancy." The search strategy included both English and French articles from 1985 to October 31, 2006. According to various studies, the failure rate after tubal sterilization, including all techniques, varies between 0.3% and 1.8%.⁴ These failure rates include all types of pregnancy whether intrauterine or extrauterine. The failure rates vary according to the technique used, the length of follow-up, and the patient's age.^{5,6} Several studies show that the failure rate using Filshie clips is between 0.1% and 0.4%.^{7,8}

The clinical case mentioned above confirms that, even if a sterilization procedure is correctly carried out, it may fail. The chronology of events excludes any possibility of a pregnancy existing during the preoperative or perioperative period. Macroscopic examination confirmed that the clips were correctly applied and properly closed. Additionally, microscopic examination showed normal epithelium replaced by simple surface epithelium with small chan-



Fig. 1. Laparoscopic view of the Filshie clips confirming their appropriate location.

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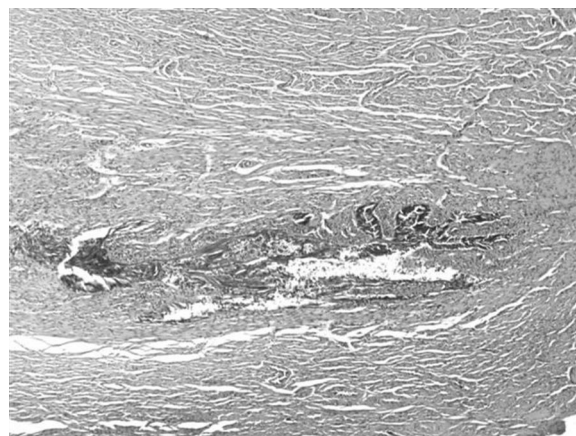


Fig. 2. Microscopic cross-section of the fallopian tube confirming the presence of a remaining small channel.

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nels. Therefore, it is likely that the channels were large enough for an ovum to slide through.

It is important that each patient is given the appropriate information before a procedure. In conclusion, gynecologists managing patients who desire tubal sterilization using Filshie clips should inform all patients of the risk of contraceptive failure.

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Transient Severe Fetal Heart Rate Abnormalities in a Pregnancy Complicated by Thrombotic Thrombocytopenic Purpura

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BACKGROUND: Thrombotic thrombocytopenic purpura is a rare disease. However, in pregnant women it occurs more frequently. Thrombotic thrombocytopenic purpura may be a severe condition for both mother and fetus.

CASE: This is a case of severe but temporary fetal heart rate abnormalities in a pregnancy complicated by thrombotic thrombocytopenic purpura. There was a remarkably good outcome despite indications of an impaired fetal condition for a period of at least 48 hours.

CONCLUSION: Based on the literature regarding transient severe neurological symptoms in adults with thrombotic thrombocytopenic purpura, we hypothesize that the transient fetal heart rate abnormalities were most

likely due to reversible microthrombi in the placenta. (*Obstet Gynecol* 2008;111:517-21)

Thrombotic thrombocytopenic purpura is a rare form of thrombotic microangiopathy resulting in vascular occlusion of terminal arterioles and capillaries by hyaline microthrombi.¹ The diversity of symptoms occurring in patients with thrombotic thrombocytopenic purpura is a result of microvascular thrombi in multiple organs.² Before the introduction of plasmapheresis as therapy, the diagnosis of thrombotic thrombocytopenic purpura was based on the appearance of thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurologic and renal abnormalities. To allow rapid initiation of this therapy, the diagnosis is now based on thrombocytopenia and microangiopathic hemolytic anemia, without an alternative cause.² Despite improved therapy, thrombotic thrombocytopenic purpura remains a severe condition for both mother and fetus during pregnancy.¹ Thrombotic thrombocytopenic purpura is a rare cause of thrombocytopenia in pregnancy, with an incidence of 1 in 25,000 pregnancies.³ The incidence of thrombotic thrombocytopenic purpura in the general population in the United States is four to 11 cases per million people.² However, in studies of thrombotic thrombocytopenic purpura, 10-25% of patients were pregnant or in the postpartum period.⁴

To our knowledge, fetal heart rate abnormalities have not yet been described in the literature on thrombotic thrombocytopenic purpura and pregnancy. A MEDLINE search for "Purpura, Thrombotic Thrombocytopenic" (MeSH) AND "fetal monitoring" (Title/Abstract) OR "fetal heart rate" (Title/

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Table 1. Laboratory Data

	Day 1	Admission	Day 2			Day 3	Day 4	Day 5	Day 6	Day 7
			1:30	6:00	12:12					
Hb (g/dL)		10	9.8	8.7	8.4	7.3	6.6	8.7	9.4	9.7
Platelets ($\times 10^9/L$)	8	2	8	8	10	36	64	131	156	202
AST (units/L)	60	116		59		45		90		27
ALT (units/L)	35	37		27		33		118		39
LDH (units/L)		10,780		3,495	3,625	1,344		1,305	889	
Creat (mg/dL)	1.2	1.2		1.2		1.2	1.2	1.1		0.9
Bili indirect/Bili direct (mg/dL)					4.9/2.4	2/0.4		1.3/0.2		

Hb, hemoglobin; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; Creat, serum creatinine; Bili, bilirubin.

Abstract) OR “fetal assessment” revealed one article.⁵ In this article, fetal heart rate pattern was not described. No limits for language were used, and the search dates were January 1966 to May 2007.

CASE

A 29-year-old, healthy, nulliparous woman presented to her general practitioner with hematuria at 34 weeks of gestation. Until then her pregnancy had developed uneventfully. She was treated for a urinary tract infection, but 3 days later the clinical situation deteriorated with gingival bleeding and progressive confusion, whereupon she was admitted to the hospital. Laboratory data showed thrombocytopenia (platelets $8 \times 10^9/L$), mild increase of liver enzymes (aspartate transaminase [AST] 60 units/L and alanine transaminase [ALT] 35 units/L), and mild increased serum creatinine (1.2 mg/dL). Contractions were observed without signs of cervical dilation. The fetal heart rate (FHR) recording showed late decelerations.

Because of the severe thrombocytopenia and complex clinical condition, the patient was admitted to the intensive care unit. At arrival she was confused and was not able to obey simple instructions. She had a blood pressure of 110/75 mm Hg and a pulse rate of 90/min and was febrile (temperature 100.4°F [38°C]). Laboratory testing disclosed thrombocytopenia (platelets $2 \times 10^9/L$), mild anemia (hemoglobin 10 g/dL), a normal white cell count (leukocytes $16 \times 10^9/L$), normal coagulation factors (activated partial thromboplastin time 40 seconds, control activated partial thromboplastin time 34 seconds +6 seconds; prothrombin time 14 seconds, control prothrombin time 12.2 seconds), normal fibrinogen (5.1 g/L), mild increased creatinine (1.2 mg/dL), severely increased lactate dehydrogenase (LDH) (10,780 units/L), mild increase of liver enzymes (AST 116 units/L, ALT 37 units/L), absent von Willebrand factor (vWF) cleaving proteases (ADAMTS-13 0% with positive autoantibodies), and negative direct Coombs' test. The patient was diagnosed with thrombotic thrombocytopenic purpura. Laboratory data of subsequent days are shown in Table 1. Fetal heart rate recordings (Fig. 1) showed

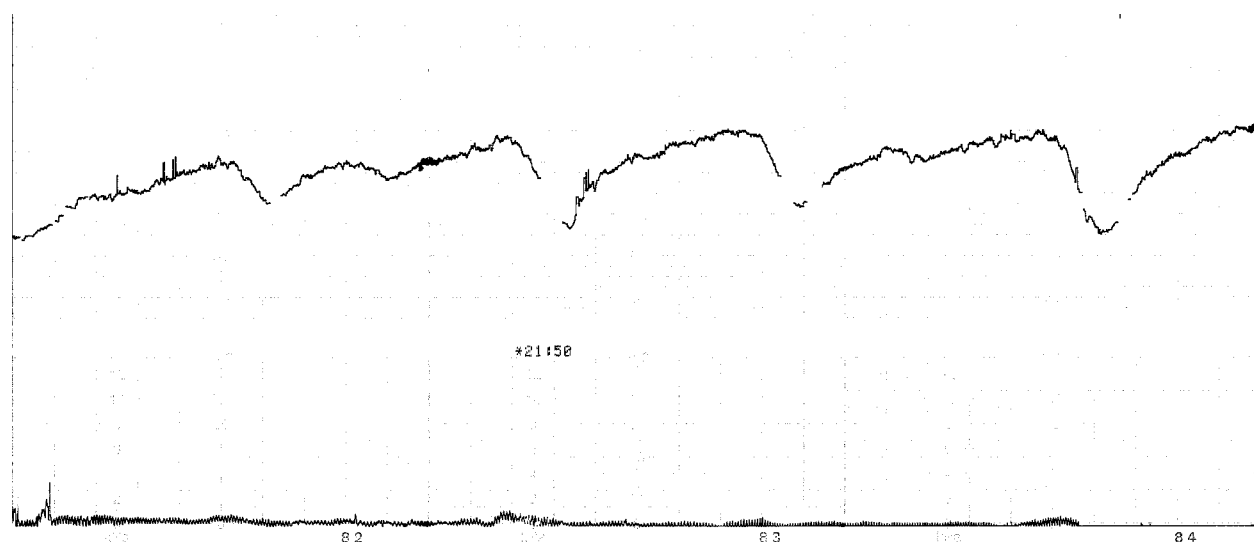


Fig. 1. Fetal heart rate recording at admission (paper speed 2 cm/min).

Strasser. Fetal Heart Rate Abnormalities in Pregnancy. *Obstet Gynecol* 2008.



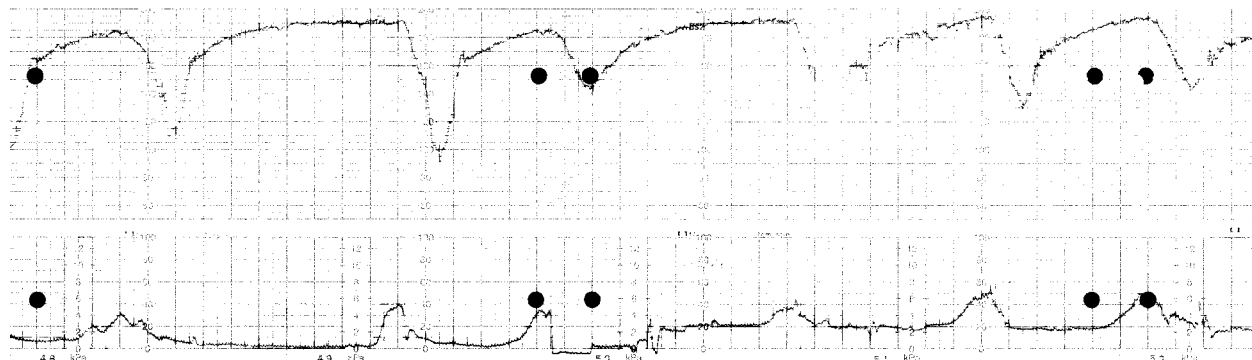


Fig. 2. Fetal heart rate recording at day 2 (paper speed 2 cm/min).
 Strasser. *Fetal Heart Rate Abnormalities in Pregnancy. Obstet Gynecol* 2008.

repeated spontaneous late decelerations and a poor variability with less than 5 beats per minute.

Both the severe clinical condition and the expected poor prognosis for the fetus were discussed with the partner. Considering the clinical condition and the accompanying risk for the mother, it was decided not to perform an emergency caesarean delivery.

Plasmapheresis of 4 L daily was started. After two plasmapheresis sessions, the patient responded to painful stimuli. The platelet count had increased to $10 \times 10^9/L$. Her blood pressure was 110/70 mm Hg. Contractions were still present every 10 minutes without cervical dilation, and intravenous nifedipine was administered for tocolysis. The FHR continued to show a lack of variability, with deep late decelerations and tachycardia developing (190 beats per minute) (Fig. 2). On the third day of plasmapheresis, the platelet count rose to $36 \times 10^9/L$, and the patient became completely conscious. The FHR recording was improving (Fig. 3), despite a low maternal blood pressure of 90/40 mm Hg. Because of concern for a relapse, termination of the pregnancy was considered beneficial, and tocolysis was stopped. Ultrasonographic evaluation of fetal growth and amniotic fluid was normal for the time of gestation. Umbilical, middle cerebral artery, and maternal uterine artery Doppler studies were normal.

Four days after admission, the FHR pattern showed a

normal pattern, with normal variability and accelerations (Fig. 4). Three days later, induction of labor was possible, and by uncomplicated vaginal delivery, a healthy male infant of 2,365 g with an Apgar score of 10/10 was delivered. The infant had a normal platelet count ($185 \times 10^9/L$). The pH in the umbilical artery was 7.34, base excess -5.5 . Only elevated liver enzymes (AST 53 units/L, ALT 167 units/L, LDH 4,230 units/L) indicated evidence of antenatal hypoxia. On the first day of life cerebral function monitoring demonstrated a normal cycling pattern and no convulsions; cranial ultrasonography showed flare densities. One month after birth, magnetic resonance imaging showed no cerebral ischemic lesions or other abnormalities. The placenta was macroscopically normal. Microscopic examination showed no evident ischemic pathology and only diminutive infarction in the subchorion and no thrombosis.

Plasmapheresis was continued for 2 weeks. The patient relapsed with a decrease in platelet count on day 8 postpartum. With prolonged plasmapheresis for another 2 weeks, the platelet count remained normal, and no relapses occurred. The patient and child were both discharged in a good condition. At the age of 1½ years, the motor and mental development of the child were normal.

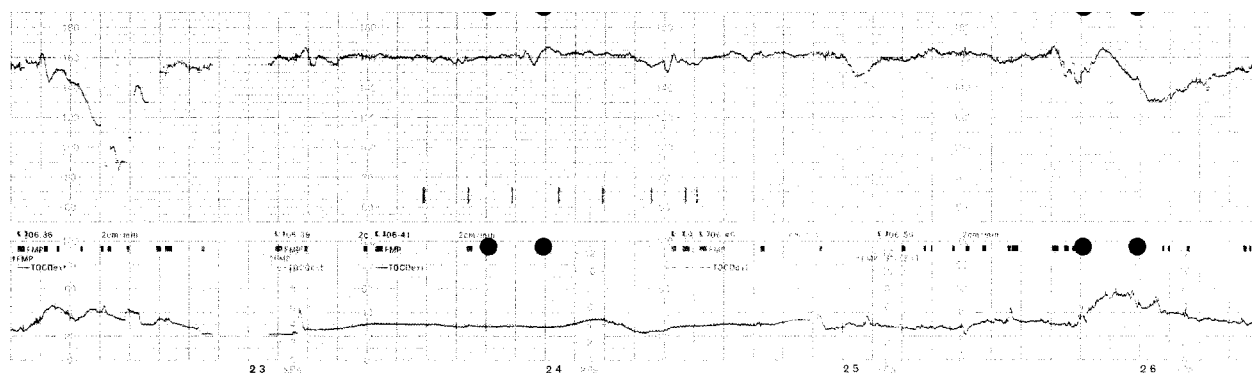


Fig. 3. Fetal heart rate recording at day 3 (paper speed 2 cm/min).
 Strasser. *Fetal Heart Rate Abnormalities in Pregnancy. Obstet Gynecol* 2008.



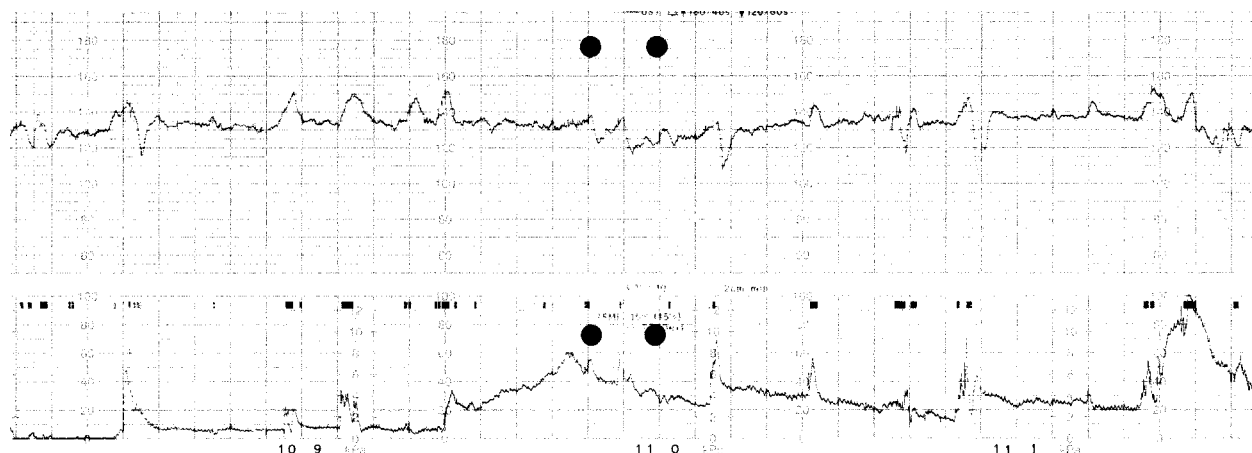


Fig. 4. Fetal heart rate recording at day 4 (paper speed 2 cm/min).
Strasser. Fetal Heart Rate Abnormalities in Pregnancy. Obstet Gynecol 2008.

The ADAMTS-13 remained severely decreased in the patient (4% with the presence of high titer autoantibodies). The patient and her partner were informed of the significant risk of maternal and fetal complications in a future pregnancy. The patient and her husband decided to abstain from a second pregnancy, fearing recurrence of thrombotic thrombocytopenic purpura.

COMMENT

Based on the classic pentad of deep thrombocytopenia causing a hemorrhagic diathesis, fluctuating neurologic symptoms, mildly impaired renal function, fever, and Coombs' negative hemolytic anemia, our patient was diagnosed as having thrombotic thrombocytopenic purpura.⁶

In most adults with thrombotic thrombocytopenic purpura, complete or partial deficiency of the vWF cleaving protease ADAMTS-13 is found. Almost all of these patients have autoantibodies against ADAMTS-13 inhibiting the cleavage of vWF. Inhibition of ADAMTS-13 leads to extraordinarily large multimers of vWF and spontaneous intravascular platelet aggregation with microangiopathy.⁷ Clotting factors are not affected in thrombotic thrombocytopenic purpura.⁸ The high incidence of thrombotic thrombocytopenic purpura during pregnancy may be a consequence of the association of pregnancy with higher concentrations procoagulant factors, decreasing fibrinolytic activity, loss of endothelial cell thrombomodulin, and decreased activity of ADAMTS-13.⁹ The results of laboratory tests in the patient, with the absence of ADAMTS-13 activity and the presence of antibodies observed in this case, correspond to these findings. The long-term absence of ADAMTS-13 seen in our patient without signs of thrombotic thrombo-

cytopenic purpura has been observed in other patients as well. In almost 50% of the patients with a thrombotic thrombocytopenic purpura in the past, ADAMTS-13 levels remain low to undetectable. The long-term absence of ADAMTS-13 is a risk factor for relapsing disease.¹⁰ In future pregnancies there is also a significant risk of relapse of thrombotic thrombocytopenic purpura, although most subsequent pregnancies seem to be unaffected.² Nevertheless, our patient did not have further pregnancies, and no relapses occurred.

Before plasma infusion and plasma exchange were introduced, thrombotic thrombocytopenic purpura had a mortality rate of 90–95%.^{2,11} During pregnancy maternal survival was low, and fetal mortality was approximately 80%.⁶ Thrombotic thrombocytopenic purpura has now become a curable disease, with a response rate to therapy of 80–90%.^{1,11} A study of 40 articles investigating pregnant women suffering from thrombotic thrombocytopenic purpura before introduction of this therapy as preferred treatment reported a maternal mortality rate of 58% and a fetal loss rate of 80%.¹² Recent studies, in which plasma-pheresis is administered, report a maternal mortality rate of 25% and a fetal mortality rate of 25% in pregnancies complicated by thrombotic thrombocytopenic purpura.¹ Fetal death is considered to be due to infarction of the placenta as a result of thrombotic occlusion of the decidual arterioles.¹¹ Other causes of fetal loss are preterm termination of pregnancy because of worsening maternal clinical condition and spontaneous preterm labor.¹ Growth restriction is frequently seen in pregnancies complicated by throm-



botic thrombocytopenic purpura, but surviving infants generally do well, with no thrombocytopenia.^{3,8}

Transient neurologic symptoms occur frequently in patients with thrombotic thrombocytopenic purpura. In the literature the temporary character is presumed to be due to transient small vessel occlusions. Rapidly reversible microvascular occlusive changes are typical of thrombotic thrombocytopenic purpura.⁶ Bakshi et al¹³ investigated neuroimaging of thrombotic thrombocytopenic purpura patients with neurologic involvement and showed that neurologic recovery was associated with disappearance of edematous lesions. Poor neurologic outcome is associated with infarcts or hematomas.

In the present case, intrauterine death or severe perinatal cerebral injury was expected to occur, based on the nonreassuring FHR tracings. Surprisingly, the neonate was healthy and was not suffering from irreversible damage caused by hypoxia. In previous studies on thrombotic thrombocytopenic purpura and pregnancy, the actual fetal assessment was not described in detail.^{1,4,8,11,14}

Because a substantial proportion of the fetuses with abnormal FHR tracings are not known to suffer from asphyxia at birth, FHR monitoring has a high false-positive rate. However, this concerns mainly intrapartum FHR traces and not antenatal recordings. Moreover, a false-positive registration also seems unlikely considering the severe abnormalities and persistence of the abnormalities during several days.

Nonreassuring FHR tracings can be caused by maternal hypotension. In the present case, the patient only suffered from hypotension on the third day of admission, when the FHR recording started to improve, despite the hypotension at that time. This contradicts the assumption of hypotension as the cause of the FHR abnormalities.

The most likely explanation for the transient abnormal FHR recordings in our case is the presence of transient occlusive microthrombi in the arterioles and reversible villous edema of the placenta. These presumed microthrombi and the edema probably resolved in response to therapy similar to the process in other organs involved in thrombotic thrombocytopenic purpura. The minimal infarction of the placenta matches this hypothesis. It remains remarkable that, despite observations of an impaired fetal condition lasting for at least 48 hours, no persistent cerebral defects developed in the neonate. This corresponds to symptoms observed in adults with thrombotic thrombocytopenic purpura in whom EEG patterns show diffuse slowing with complete recovery after treatment.⁶

This case demonstrates that an impaired fetal

condition in a pregnancy complicated by thrombotic thrombocytopenic purpura is not always followed by a poor outcome of the neonate. However, one single case is insufficient to conclude that continued observation would be safe in case of a stable maternal condition. If possible, early intervention is preferred.

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Glutaric Aciduria Type II and Narcolepsy in Pregnancy

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BACKGROUND: Glutaric aciduria type II is a rare disorder affecting the metabolism of fatty acid oxidation and several mitochondrial dehydrogenase enzymes. Narcolepsy and cataplexy is a disorder affecting sleep cycles and rapid eye movement activity. There is little information on outcome or management for either disorder in pregnancy.

CASE: This is a case of a 16-year-old with glutaric aciduria type II and narcolepsy with cataplexy, treated with L-carnitine, riboflavin, fluoxetine, and modafinil during pregnancy. Intrapartum management included intravenous carnitine administration, and the patient underwent cesarean delivery at term without complication.

CONCLUSION: This inborn error of metabolism and sleep disorder can be effectively treated during pregnancy with nutritional supplementation and stimulants. Because of the risk of cataplexy during labor, cesarean delivery is recommended to minimize the patient's risk. (*Obstet Gynecol* 2008;111:522–4)

Glutaric aciduria type II, also known as multiple acyl-CoA dehydrogenase deficiency, is a rare disorder of metabolism that can have a variety of manifestations. There is a mild form requiring nutritional supplements of riboflavin, L-carnitine, and glycine, a diet that is low in fat and protein and high in carbohydrates, and avoidance of fasting. There is also a severe neonatal form with congenital anomalies, and this form is usually lethal in the first weeks of life. Narcolepsy with cataplexy is a disorder of excessive daytime sleepiness with atonic episodes often brought on by strong emotions. We present a case of a pregnant patient with both disorders and the management of her case during pregnancy.

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CASE

This is a 16-year-old primigravid who presented for prenatal care at 19 weeks of gestation. She was first diagnosed with glutaric aciduria type II 4 months before pregnancy. At that time, she had presented with altered mental status and a concurrent urinary tract infection. Laboratory evaluation revealed mild metabolic acidosis (carbon dioxide [CO_2] 17, base excess -10.8), hyperammonemia ($209 \mu\text{mol/L}$), and elevated acetone. She underwent extensive testing for inborn errors of metabolism, and based on the acylcarnitine profile and the urine organic acids, the diagnosis of glutaric aciduria type II was established. This was further confirmed with an enzyme assay on fibroblasts for electron transfer flavoprotein (ETF) and electron transfer flavoprotein coenzyme Q-oxidoreductase (ETF-QO). The results of this testing showed a slight deficiency in the ETF assay. She was started on L-carnitine and riboflavin supplementation and advised to follow a low-fat, low-protein diet. The abnormal metabolites seen in the urine organic acids slowly resolved with treatment and the patient's mental status returned to normal.

The patient's medical history was also significant for narcolepsy and cataplexy, which were diagnosed at the age of 13 and treated with fluoxetine 20 mg daily and modafinil 200 mg daily. She continued to have cataplectic episodes infrequently, especially with periods of laughter. Of note, her family history was significant for narcolepsy in her father, paternal aunt, and paternal grandfather.

The patient continued to take L-carnitine, riboflavin, fluoxetine, and modafinil during pregnancy. The results of an obstetric ultrasound examination and fetal echocardiography were normal. Electrolytes remained normal during pregnancy, but the ammonia level peaked at $39 \mu\text{mol/L}$ (normal range $11\text{--}35 \mu\text{mol/L}$). Carnitine levels dropped during the third trimester, and the dose was increased to 500 mg three times daily. As she approached 37 weeks of gestation, the episodes of narcolepsy and cataplexy increased in frequency, so she underwent an elective cesarean delivery under spinal anesthesia at 38 weeks (infant weight 2,360 g, Apgar scores of 7, 8, and 9). Before the delivery, she received 250 mg of intravenous carnitine, and this dose was continued every 6 hours until she could tolerate oral medication. Intravenous hydration was given at rates of 150–250 mL/h before delivery and throughout the immediate postoperative period. Modafinil, fluoxetine, and riboflavin were continued as previously prescribed. Electrolytes and ammonia levels remained normal. The infant was monitored for signs of withdrawal from fluoxetine and remained hemodynamically and clinically stable, with no abnormalities in vital signs or behavior. Acylcarnitine profile was negative. The patient and the infant were discharged after 3 days.

COMMENT

Narcolepsy is a condition that is thought to have a frequency of approximately 1 in 2,000 in the gen-



eral population. It typically presents in adulthood and is characterized by excessive sleepiness and frequent daytime naps. It is often associated with abnormalities of rapid eye movement (REM) sleep, such as cataplexy, visual hallucinations, and sleep paralysis. It is thought to be caused by loss of neurons that produce orexin A and B (also known as hypocretin 1 and 2). Orexin neurons, located in the posterior and lateral hypothalamus, have been implicated in wakefulness and motor function. Loss of function could lead to inhibition of the motor excitatory systems or loss of arousal systems. The process that causes this is unknown but is postulated to be autoimmune or neurodegenerative, although there are no consistent neuroimaging abnormalities or identified autoantibodies.¹

Narcolepsy is usually sporadic but has been reported to run in families. Genetic studies have shown associations with human leukocyte class II antigens, DR2 and DQ1, with some subtypes increasing susceptibility, while others are protective.^{1,2} A diagnosis can be made with an overnight polysomnogram and a multiple sleep latency test. Key features are rapid onset of REM sleep and spontaneous awakenings. During the multiple sleep latency test, which typically follows the overnight polysomnogram, patients with narcolepsy will fall asleep within 5 minutes (normal is 10–15 minutes) and have sleep-onset REM periods.¹

Cataplexy is specific to narcolepsy, characterized by an abrupt loss of muscle tone, which may manifest as a fall with the potential for injury. These episodes are often associated with strong emotions, such as laughter or stress. Cataplexy is a manifestation of inappropriate REM, usually not associated with loss of consciousness. A case of status cataplecticus during labor has been reported, and the patient underwent subsequent cesarean delivery.³ Because of the risk of cataplectic episodes during labor, we proceeded with elective cesarean delivery in this case.

Treatment options for narcolepsy and cataplexy include selective serotonin-reuptake inhibitors (SSRIs), sodium oxybate, methylphenidate, pemoline, modafinil, or dextroamphetamine sulfate. Modafinil is pregnancy category C, with a half life 15 hours and minimal adverse effects. It is not known if modafinil crosses the placenta, but it is considered to be low risk in pregnancy.⁴ Fluoxetine is also listed as a pregnancy category C medication, but questions have been raised regarding the safety of SSRIs in pregnancy. A recent study reports a risk of neonatal pulmonary hypertension when exposed to SSRIs.⁵ Transient withdrawal is also of concern, and neonates may experience vomiting, irritability, and other neurologic manifestations.⁴

Glutaric aciduria type II is an autosomal recessive inborn error of metabolism involving fatty acid oxidation and dehydrogenases of several amino acids metabolism. It is caused by deficiency of electron transport flavoprotein or deficiency of electron transport flavoprotein coenzyme-Q oxidoreductase.⁶ Manifestations range from a mild form diagnosed in late adolescence or adulthood to a severe, lethal form diagnosed in the neonatal period that may be associated with congenital anomalies. Late onset may present with recurrent episodes of vomiting, hypoglycemia, metabolic acidosis, hepatic dysfunction, and muscle involvement. One case report describes an infant diagnosed in the neonatal period, with associated cardiomegaly, who died of cardiac arrest after 7 days.⁷ Clinical manifestations also include acidosis, hypoglycemia, polycystic/dysplastic kidneys, and a strong odor of urine and other bodily fluids described as a “sweat-sock odor.” Diagnosis can be made with specific acylcarnitine profile (elevations of C4–C18) and urine organic acids (lactic, glutaric, 2-hydroxyglutaric, ethylmalonic, dicarboxylic acids) and confirmed by enzyme studies.⁶ The urine organic acids may be abnormal only during acute episodes. Treatment for the severe neonatal presentation is usually not effective. For the mild/late onset presentation, treatment involves nutritional management and supplements, along with avoidance of fasting, a diet low in fat and protein and high in carbohydrates, and supplementation with riboflavin, L-carnitine, and glycine.

We report a case of a woman with narcolepsy and cataplexy and recently diagnosed with glutaric aciduria type II. She continued her medications and supplements during pregnancy and had an unremarkable course. Perioperative management included continuing riboflavin and intravenous supplementation of carnitine with intravenous hydration. We recommend electrolyte and ammonia levels every trimester, with consideration for monthly testing in the third trimester or more frequently as clinically indicated. Cesarean delivery is recommended to minimize the patient’s risk. Prenatal diagnosis may be possible, and because glutaric aciduria type II is autosomal recessive, patients should be counseled regarding risk of this disorder in their offspring.⁸

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Resolution of Hydrops Secondary to Cytomegalovirus After Maternal and Fetal Treatment With Human Cytomegalovirus Hyperimmune Globulin

Katherine Moxley, MD, and Eric J. Knudtson, MD

BACKGROUND: Congenital cytomegalovirus (CMV) is a common infection with limited treatment options. Vertical transmission can lead to fetal death or long-term neurologic injury. We present a case wherein fetal hydrops resolved after maternal and fetal intravenous administration of CMV hyperimmune globulin.

CASE: A 20-year-old gravida 3, para 0 was referred for Level II ultrasonography secondary to hydrops fetalis. Amniocentesis demonstrated in utero CMV infection. Resolution of hydrops occurred after the administration of CMV hyperimmune globulin to the patient and then to her fetus.

CONCLUSION: Resolution of hydrops secondary to congenital CMV was temporally related to the administration of maternal and fetal hyperimmune globulin.

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Cytomegalovirus (CMV) is the most common cause of congenital infection in humans, affecting 0.5% to 3% of liveborn neonates worldwide.¹ The majority of severe fetal infections result from primary CMV infections. Primary infection carries up to a 50% risk of vertical transmission. Vertical transmis-

sion can result in fetal death or cytomegalic inclusion diseases, a severe form of infection which may be fatal in up to 30% of neonates.² Current treatment options for this problematic infection are limited, but ganciclovir and CMV hyperimmune globulin have been investigated.^{3,4} Recently, a nonrandomized study using CMV hyperimmune globulin showed promise in the prevention and treatment of fetal infection.⁴

CASE

A 20-year-old African-American female, gravida 3 para 0, was referred to the Maternal-Fetal Medicine service after a 17 week ultrasound study performed in the community revealed multiple fetal abnormalities. Ultrasonography at our facility found oligohydramnios, echogenic bowel, placentalomegaly, cardiomegaly, a pericardial effusion, and ascites. A maternal antibody screen was performed, which was negative, and the patient was diagnosed with nonimmune hydrops.

After appropriate counseling, the patient underwent evaluation for nonimmune hydrops, including amniocentesis. Results showed a karyotypically normal male fetus with greater than 2,500,000 cytomegalovirus DNA copies/mL. The remainder of the patient's laboratory evaluation was unremarkable.

The results were reviewed and the patient was counseled in part as to the possibility of stillbirth or a neurologically impaired neonate. Pregnancy termination was discussed and declined. The limited information regarding in utero treatment was reviewed. After discussion of the risks, alternatives, and options, the patient opted for a plan of maternal treatment with CMV hyperimmune globulin, with salvage therapy given to the fetus if lack of response was detected.

Due to a manufacturing shortage, the medication was unable to be procured and given until the 28th week of pregnancy. Continued fetal deterioration was noted with worsening ascites. The last ultrasonography before treatment was performed at 28 1/7 weeks. A transverse view of the abdomen demonstrated marked ascites (Fig. 1). At 28 6/7 weeks, a weight-based maternal dose of CMV hyperimmune globulin (150 mg/kg) was administered. Both mother and fetus tolerated this well and were discharged home.

Continued fetal evaluation demonstrated persistent hydrops, and cordocentesis was undertaken at 31 4/7 and 32 3/7 weeks of gestation. At both procedures, CMV hyperimmune globulin was administered according to estimated

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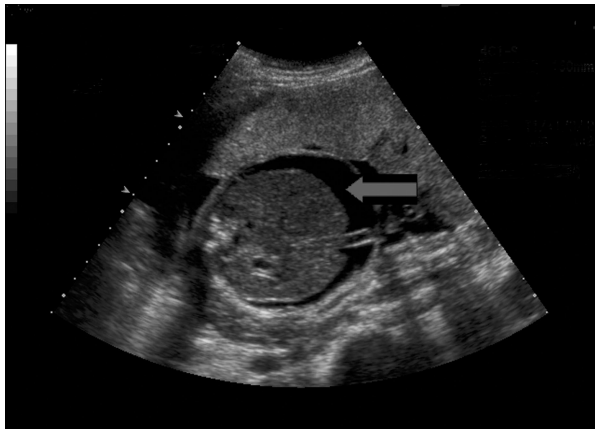


Fig. 1. Abdomen with ascites (arrow).

Moxley. Hydrops Secondary to Cytomegalovirus. *Obstet Gynecol* 2008.

fetal weight (150 mg/kg). Because CMV can cause thrombocytopenia, we sampled a platelet count before the administration of medication, and were prepared to transfuse platelets to minimize the risk of serious fetal bleeding. At 31 4/7 weeks of gestation, the platelet count was 26,000 and 30 mL of platelets were administered. The posttransfusion platelet count was 70,000. At 32 3/7 weeks of gestation, the sampled platelet count was 30,000. Thirty-five milliliters of platelets were administered, raising the platelet count to 77,000. No serious bleeding was encountered during either procedure.

At 37 1/7 weeks of gestation, complete resolution of hydrops was documented on ultrasonography (Fig. 2). However, oligohydramnios with breech presentation was noted. A 2,246-g infant was delivered by cesarean procedure, with Apgar scores of 9 and 9. Cord blood gases revealed a normal pH and base excess. The infant was small for gestational age with symmetric measurements and



Fig. 2. Abdomen with resolution of ascites (arrow).

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required a 1-week admission to the Special Care Nursery for temperature instability.

Neonatal evaluation revealed the presence of CMV in the infant's urine and periventricular calcifications on computed tomographic scan consistent with congenital CMV infection. Initial auditory brainstem responses were normal. At nine months of age, the infant was noted to be reaching appropriate developmental milestones and demonstrated appropriate neurologic development for his age.

COMMENT

Congenital CMV infection occurs in up to 3% of pregnancies worldwide. Maternal antibody status does not prevent congenital CMV infections but seems to confer protection from the more severe sequelae of congenital CMV, such as cytomegalic inclusion disease.² Although associated with significant morbidity, screening of pregnant women is not routinely performed in this country.⁴

Several off-label treatment modalities have been used, largely as an extension of our experience with adult patients. Specifically, CMV-specific hyperimmune globulin has been investigated, and several reports using ganciclovir have been published.^{3,4} Cytomegalovirus hyperimmune globulin consists of enriched CMV-specific immunoglobulin G antibodies and is used widely in the prevention of posttransplant CMV prophylaxis.⁵ One recent nonrandomized study showed promise in the prevention and treatment of in utero infection.⁴ Administration of CMV immune globulin was typically given to the mother, but several fetuses in that series received intra-amniotic and intra-umbilical infusions. No hydropic fetus received an intra-umbilical administration. An additional case report has described the treatment of CMV-related hydrops with immune globulin, but that fetus received injections intraabdominally.⁶

Short-term outcome has thus far been promising, with normal developmental milestones documented up to 9 months of age. Although spontaneous resolution of hydrops secondary to parvovirus has been noted to occur, there is limited evidence that this occurs with CMV.⁷ Spontaneous resolution is a possibility in our case, but deterioration was noted up to, and resolution was temporally related to the administration of medication. Although encouraging, causality cannot be assumed. Clinicians should also be mindful that each cordocentesis carries risk, and this was an off-label use of CMV immune globulin. These risks were known to the patient and treatment team, but given the bleak prognosis, we felt offering treatment was reasonable.



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Medical Treatment of Uterocutaneous Fistula With Gonadotropin-Releasing Hormone Agonist Administration

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Bilhan Sidal, MD, and Bulent Urman, MD

BACKGROUND: Uterocutaneous fistula is a rare complication of uterine surgery. All published cases have been surgically treated with hysterectomy and excision of the fistulous tract. We report a case of uterocutaneous fistula that was successfully treated with gonadotropin-releasing hormone agonist administration.

CASE: A 25-year-old woman reported bloody discharge during her periods from a previous Pfannenstiel incision. A fistulous tract leading from the incision scar to the uterus was diagnosed. Leuprolide acetate depot was administered twice subcutaneously at a dose of 11.25 mg. The fistulous tract closed spontaneously, and the patient was symptom free thereafter.

CONCLUSION: Medical treatment with gonadotropin-releasing hormone agonists should be considered before resorting to surgery for treatment of uterocutaneous fistulae.

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Uterocutaneous fistula is a very rare complication of uterine surgery. Successful treatment of uterocutaneous fistulae with total abdominal hysterectomy together with excision of fistulous tract has been reported.^{1,2} We herein report a case of a woman treated with gonadotropin-releasing hormone (GnRH) agonist administration. Medical treatment may provide an option that may avoid costs and risks associated with major surgery.

CASE

A 25-year-old, gravida 4, para 4 woman was admitted to our clinic reporting bloody discharge from a small opening in her abdominal scar that was due to a fourth repeat cesarean delivery performed 4 months ago. The gestational and puerperal periods were unremarkable. The discharge had started simultaneously with the first postpartum menstrual period and continued to occur during subsequent periods. She had three menstrual periods since the delivery, the first being at the eighth postpartum week. She had declined to breastfeed her baby. She had poorly controlled type I diabetes.

On physical examination, there were brown granular deposits surrounding a very small opening, approximately 2 mm in size on the Pfannenstiel incision scar. On pelvic examination, the uterus was anteverted and adherent to the anterior abdominal wall. Palpation of the scar and uterine movements caused pain. A suspicious fistulous tract between the uterine cavity and abdominal scar was visualized during transvaginal ultrasound examination. A fistulogram was planned to demonstrate the fistula tract, but it was not possible to inject the contrast material through the very small opening in the skin. An hysterosalpingogram was performed. Although the contrast material filled the uterine cavity and spilled through the fallopian tubes, it did not fill the fistula tract. Finally, a contrast-enhanced magnetic resonance imaging was performed, and the diagnosis of a uterocutaneous fistula was confirmed (Fig. 1). There was no clinical or radiographic evidence of a fascial dehiscence accompanying the fistula.



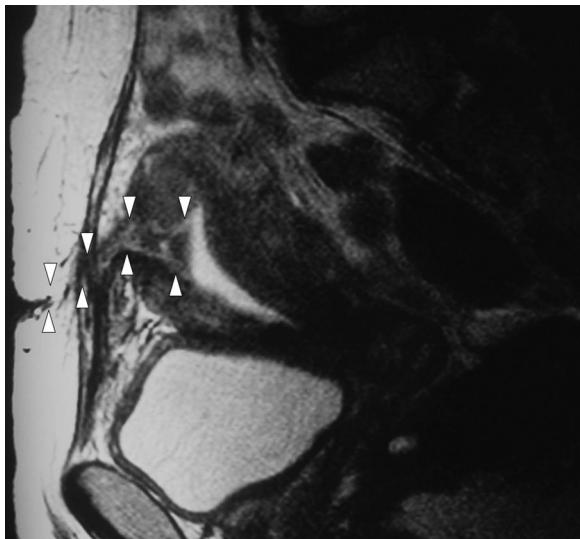


Fig. 1. Contrast-enhanced magnetic resonance image; arrows show the fistula tract between the endometrial cavity and skin.

Seyhan. Uterocutaneous Fistula. Obstet Gynecol 2008.

Leuprolide acetate depot suspension at a dose of 11.25 mg was administered subcutaneously and repeated after 3 months. The patient exhibited prompt symptomatic response to the medication. She was amenorrheic during the treatment period, and the lesion on the skin was closed spontaneously at the follow-up visit 3 months after the first injection. She is currently free of disease and experiences regular menstrual cycles.

COMMENT

The major symptom of uterocutaneous fistula is bloody discharge from an opening in the skin. The discharge occurs simultaneously with menstrual periods. Symptoms may resemble scar endometriosis. However, it may not be possible to differentiate scar endometriosis and uterocutaneous fistula by physical examination alone, because both may present with pain and accompanying bloody discharge during menstrual periods.

Demonstration of the fistulous tract is necessary for a definitive diagnosis. It may not always be possible to demonstrate a fistulous tract with ultrasonography; contrast studies such as fistulogram might be helpful in those cases. We failed to demonstrate the fistulous tract with either a contrast fistulogram or a hysterosalpingography. High resistance to flow of the contrast material within the narrow fistulous tract might have caused the failure of these methods. We established the diagnosis by contrast-enhanced magnetic resonance imaging, which clearly demonstrated the fistula tract.

Fistula formation in this case may be related to multiple uterine and abdominal incisions due to previous cesarean deliveries. Moreover, poorly controlled type-1 diabetes might have led to impairment of the wound healing process and thus facilitated the formation of a fistula.

Total abdominal hysterectomy with excision of the fistulous tract has been reported to be the treatment of choice, however, considering our patient's age and the presence of dense intraabdominal adhesions noted during the cesarean delivery, we preferred medical treatment with GnRH agonist administration. Her glycemic control was also optimized to improve wound healing.

Patency of vesicouterine fistula tract is reported to be dependent on hormonal changes such as cessation of breastfeeding and commencement of menstrual periods.³ Additionally, presence of endometrium like glandular epithelium-bearing sex hormone receptors has been demonstrated in vesicouterine fistulae.⁴ A similar epithelial lining can be expected to cover the lumen of uterocutaneous fistulae. Successful treatment of fistulae communicating with the uterus with GnRH agonists supports these observations.⁵ In addition to cessation of menstrual flow through the fistula tract, GnRH agonist administration may induce atrophic changes in this endometrium-like epithelium further causing closure of fistulous tract. Fistulae communicating with the uterus may be regarded as a different manifestation of endometriosis. This hypothesis might explain menstrual flow through the fistula. The second dose of GnRH agonist was administered to decrease the chance of endometriosis recurrence. The patient has been asymptomatic for 2 years since the last injection.

In conclusion, cessation of menstrual flow and inducing atrophy in the endometrium-like lining of the fistula tract by medical therapy with GnRH agonists or other hormonal manipulations should be considered before resorting to surgical treatment for uterocutaneous fistulae. This may obviate additional cost and risks associated with surgery.

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Pregnancy-Induced Hemolytic Anemia With a Possible Immune-Related Mechanism

Shinji Katsuragi, MD, Hiroshi Sameshima, MD, Mitsuhiro Omine, MD, and Tsuyomu Ikenoue, MD

BACKGROUND: Pregnancy-induced hemolytic anemia is a rare maternal complication that occurs during pregnancy and resolves soon after delivery. The mechanism is unclear, and the disease is often referred to as unexplained hemolytic anemia associated with pregnancy.

CASE: We report a case of life-threatening hemolytic anemia that occurred during pregnancy and resolved spontaneously soon after delivery. Direct and indirect Coombs test results were negative. Several possible causes were investigated, but all were ruled out. However, an increased immunoglobulin G level was observed in maternal red blood cells throughout pregnancy when the patient was severely anemic. The immunoglobulin G level decreased after delivery and was close to the control level on postpartum day 5.

CONCLUSION: These observations suggest that the hemolytic anemia in this patient had an immune-related etiology.

(*Obstet Gynecol* 2008;111:528–9)

Unexplained hemolytic anemia associated with pregnancy is a rare maternal complication that resolves soon after delivery.^{1–3} An immunological mechanism is currently considered the most likely pathology, since the clinical characteristics of the condition include homologous destruction of red blood cells, response to steroid therapy, and transient anemia in infants. Identification of an immune

mechanism or intracorporeal and extracorporeal defects has been attempted in several studies, with a particular focus on detecting anti-erythrocyte antibody.² A direct Coombs test result may be negative in 1–4% of patients with autoimmune hemolytic anemia.^{4,5} Here, we report a case of hemolytic anemia in which an increased immunoglobulin G (IgG) level on maternal red blood cells was observed throughout pregnancy.

CASE

A 30-year-old woman, primigravida came to our hospital at 8 weeks of gestation. Her hemoglobin (Hb) level was 9.7 g/dL and dropped to 7.8 g/dL at 12 weeks of gestation. A raised reticulocyte count (10.3%), increased serum indirect bilirubin (1.7 mg/dL), and reduced serum haptoglobin (2 mg/dL) confirmed hemolytic anemia. At 15 weeks of gestation, indirect and direct Coombs test results (using anti-IgG, anti-IgM, anti-IgA, and anti-complement [C3, C4] sera) were negative. Ham and Donath-Landsteiner test results (test for paroxysmal nocturnal hemoglobinuria and paroxysmal cold hemoglobinuria, respectively) were negative, and screening for red blood cell (RBC) enzymes and abnormal hemoglobins revealed no abnormalities. As the Hb level dropped to 3.9 g/dL at 23 weeks of gestation, we started administration of prednisolone (30 mg/d) and increased the dose to 60 mg/d at 30 weeks of gestation, and that showed slight effectiveness. We transfused 44 units of RBCs until 35 weeks of gestation to maintain the Hb level 8 g/dL or higher. After 22 weeks, the biophysical profile score was 10/10, and no signs of fetal anemia were detected on ultrasound examination. Continuation of pregnancy would have required further transfusion, and therefore birth was induced at 36 weeks of gestation. A healthy girl weighing 2,422 g was delivered vaginally. Maternal Hb levels of 8.5 g/dL and 10.2 g/dL were present 1 month and 2 years after delivery, respectively.

At 30 weeks of pregnancy, to detect IgG on the surface of RBCs, RBCs were reacted with anti-human IgG antibody-labeled with fluorochrome and assayed using flow cytometry. The flow cytometry peak was shifted to the right compared with healthy control blood (Fig. 1A). Blood was also tested at 34 and 36 weeks of gestation, with the same results (data not shown). On day 1 postpartum, the flow cytometry peak was still shifted to right, but on postpartum days 5, results were similar to control data (Fig. 1B). The neonate was not anemic at birth; the Hb level was 15.8 g/dL. Direct and indirect Coombs test results were negative, and Ham and Donath-Landsteiner test results were normal. No irregular antibodies were found. The Hb level was 16.6 g/dL on day 5 and 13.5 g/dL on day 13. However, on day

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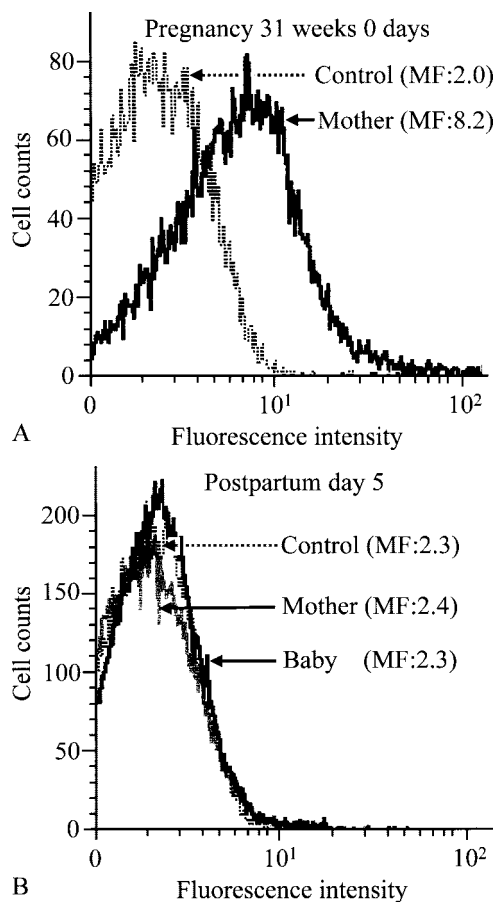


Fig. 1. Results of an anti-immunoglobulin G test against red blood cells, using flow cytometry. Cell counts and fluorescent intensity are shown on the vertical and horizontal axes, respectively. MF denotes mean fluorescence and corresponds to the peak of the curve. At 31 weeks of pregnancy, the mean fluorescence shifted to the right (**A**). On postpartum day 5, mean fluorescence was similar to that for the control (**B**).

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20, the Hb level had dropped to 4.3 g/dL, and a blood transfusion of 20 mL/kg was given. The Hb level of the infant was 11.5 g/dL at 3 months and 12.0 g/dL at 2 years old.

COMMENT

The mechanism of “unexplained hemolytic anemia associated with pregnancy” has been studied widely, including use of sensitive techniques such as the complement-fixation antibody consumption test,¹ but a free or surface-associated anti-erythrocyte antibody has not

been detected. Our report is the first to show longitudinal changes of IgG on maternal RBC. The results of flow cytometry were correlated with changes in maternal hemolytic anemia, since the peak shifted to the right when the patient was severely anemic, and this indicates the involvement of an immunological mechanism.

Flow cytometry provides a sensitive method for IgG detection than the standard direct Coombs test. Although we are unable to state with certainty the number of molecules required for positive results in assays used in previous studies, it is possible that in these cases the amount of IgG was below the serological test limit but over the level required for a biological effect, or there may have been another factor promoting hemolysis. In addition, the homologous destruction of RBCs that occurs in this disease may make it hard to detect stable IgG on RBCs in some assays.

We note that the disorder in our case is not necessarily the same as “unexplained hemolytic anemia associated with pregnancy” because in such cases anemia has been reported to be mild in early pregnancy, and neonatal anemia is usually mild. These clinical differences suggest caution in using the current report to explain all previous cases of unknown pathology.² However, we speculate that an unknown fetus-derived factor (an antigen itself or a molecule that promotes an immune reaction on the surface of RBCs) may attach to maternal RBCs to cause hemolytic anemia, but soon after delivery this factor is lost, leading to recovery of maternal anemia. Late-onset transient anemia in a newborn makes it difficult to conclude that the cause of anemia is only due to transplacental movement of IgG.

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Complete Fetal Transection After a Motor Vehicle Collision

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BACKGROUND: Motor vehicle collisions are the leading cause of fetal death related to maternal trauma, with rupture of the gravid uterus being one potential grave outcome.

CASE: We present a case of a woman at 22 weeks of gestation who presented to the emergency department after a "high-speed" motor vehicle collision. On initial presentation, she was hemodynamically stable, and the examination was significant for midabdominal transverse ecchymosis from seatbelt trauma. A computed tomography scan identified a probable uterine rupture. Laparotomy revealed a 1,500-mL hemoperitoneum and a completely ruptured uterus requiring hysterectomy. The fetus was completely transected at the level of the midabdomen.

CONCLUSION: Uterine rupture is possible for gravid women involved in motor vehicle collisions.

(*Obstet Gynecol* 2008;111:530–2)

Trauma is known to be the leading nonobstetric cause of death in pregnant women. Motor vehicle collisions are the leading cause of fetal death related to maternal trauma.¹ Although rarely encountered (only approximately 0.6% of traumatic events), one potential grave outcome of blunt abdominal trauma associated with motor vehicle collision is rupture of the gravid uterus. Most uterine ruptures occur at the fundus (likely due to anatomic position) and are believed to occur from sudden deceleration causing hyperflexion of the uterus. There are approximately 25 reports of uterine rupture after a motor vehicle collision in pregnant patients, and while maternal mortality from traumatic uterine rupture is only ap-

proximately 10%, fetal mortality approaches 100%.² Most fetal trauma after uterine rupture includes injuries consistent with blunt trauma such as closed head injury (subdural and subarachnoid hemorrhage), skull fracture, and hepatic or splenic rupture/hemorrhage.³ We present a case of uterine rupture in the second trimester with subsequent expulsion and complete abdominal transection of the fetus.

CASE

A gravida 2 para 0010 woman with a pregnancy of unknown dates presented to the emergency department after a motor vehicle collision at "high speed." Exact details of the accident were unknown; however, it was known that the patient was the restrained driver of a vehicle unequipped with airbags and had been hit by another vehicle on the front, driver's side corner at approximately 40–50 miles per hour. The patient denied any significant medical history with the exception of mild-to-moderate asthma. The patient reported one prior pregnancy with subsequent elective termination of pregnancy and was uncertain as to dates (last menstrual period, gestational age, etc.) for her current pregnancy.

Upon presentation to the emergency department, the patient had stable vital signs. An initial fetal acoustic stimulation testing was performed in the emergency department and reported as normal; however, it was noted that she was reporting lower abdominal pain. An initial obstetric ultrasound (abdominal) examination performed in the emergency department (by the emergency department physician) revealed no fetal cardiac activity, and no intrauterine pregnancy was identified at this time. Abdominal computed tomography was performed, which identified significant hemoperitoneum and a pregnancy of approximately 22 weeks of gestation, which appeared to be outside the uterus in the pelvis (Fig. 1).

The obstetrics service was consulted at this time, and at the time of evaluation the patient's vital signs had become ominous with a pulse in the range of 110–119 beats per minute and blood pressure in the range of 70–79/40–49 mm Hg. Physical examination revealed ecchymosis of the lower abdomen (below the umbilicus) consistent with seatbelt trauma. The abdomen was protuberant but soft with diffuse tenderness to palpation. Pelvic examination was not performed; however, vaginal ultrasonography was attempted by the obstetrics team and showed only blood in the pelvis.

The patient was emergently taken to the operating room for laparotomy. After general endotracheal anesthesia, a vertical skin incision was made, and upon entering the abdominal cavity approximately 1,500 mL of blood was irrigated from the abdomen. Upon exploration of the abdomen/pelvis, the fetal vertex (approximately 22-week fetus) was found to be extrauterine. The fetus was then delivered through the abdominal incision at which time it was discovered that the fetus had been completely

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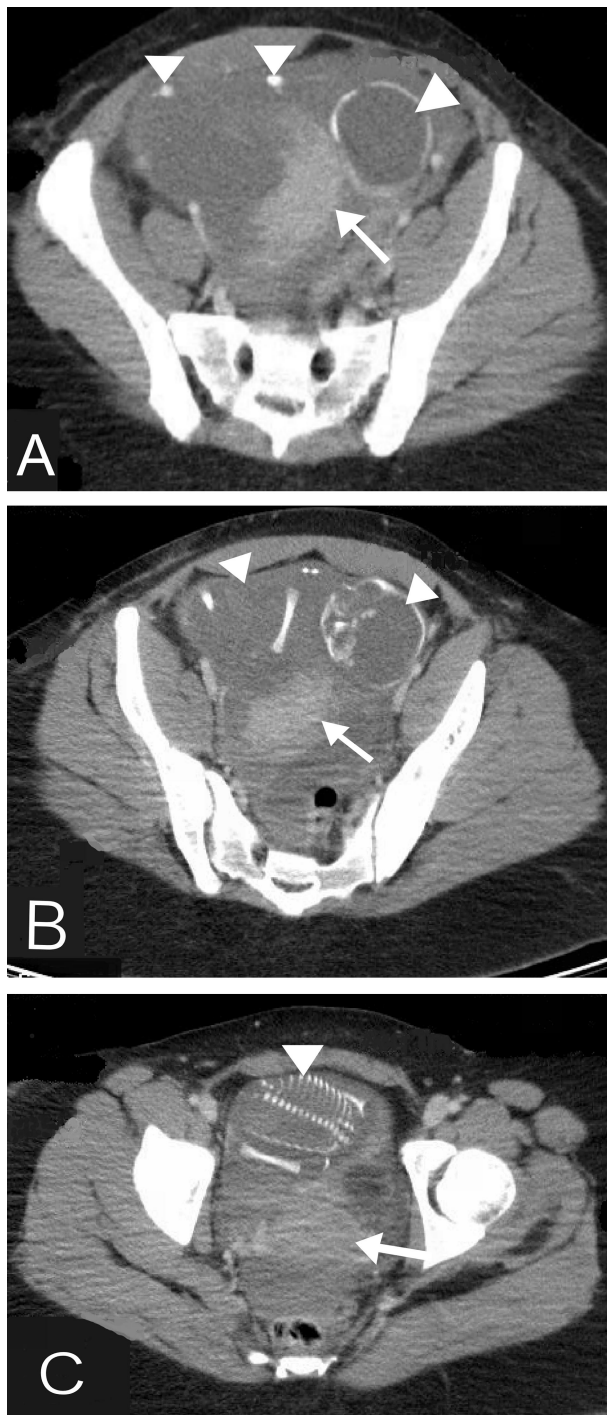


Fig. 1. Computed tomography images showing significant hemoperitoneum, uterus, and fetal parts evident outside of the uterus. **A** and **B** reveal the fetal skull and limbs in the mid pelvis directly adjacent to the exterior of the uterus (arrow: uterus; arrowheads: fetal parts). **C** shows the fetal thoracic cavity in the lower pelvis anterior to the lower uterine segment (arrow: lower uterine segment; arrowhead: fetal parts).

Weir. Complete Fetal Transection. *Obstet Gynecol* 2008.

transected at the mid-abdominal level. The abdominal/pelvic cavity was re-examined, and the lower half of the fetus was found in the maternal right lower pelvis (also extrauterine). The remainder of the fetus was delivered through the abdominal incision.

Attention was then turned to the uterus, which was noted to be completely ruptured with only approximately 2 cm of the posterior lower uterine segment holding the uterus together. The uterine arteries were completely avulsed bilaterally with significant bleeding from these sites. Due to the severity of the injury to the uterus and broad ligaments (the broad ligaments were almost entirely torn open with bowel protruding through them) and the significant bleeding, the decision was made to perform a supracervical hysterectomy. The ovaries appeared undamaged and were left in situ.

General surgery then performed a complete abdominal exploration finding only a small retroperitoneal hematoma, which was easily controlled. After surgery, the patient was taken to the surgical intensive care unit for close postoperative monitoring and further evaluation of orthopedic injuries. Including resuscitation initiated in the emergency department, she received 5,000 mL of lactated Ringers solution and 4 units packed red blood cells. During and after the procedure, there was no evidence of coagulopathy or disseminated intravascular coagulopathy. The patient recovered acutely and was transferred to a civilian hospital on postoperative day 4.

COMMENT

Pregnant women hospitalized after a motor vehicle collision are at increased risk of adverse pregnancy outcomes regardless of the presence or severity of their own injuries. Proper use of seatbelts in pregnant patient has been shown to decrease risk associated with motor vehicle collisions, such that in one retrospective study pregnant women wearing seatbelts were not at significantly greater risk of adverse fetal outcomes than pregnant women not in collisions.⁵ Similarly, pregnant women who do not wear seatbelts were 1.3 times more likely to have a low-birth-weight infant, 2.0 times as likely to have excessive maternal bleeding, and 2.8 times more likely to experience fetal death.⁵ It is important to keep in mind that death of the mother is the main cause of perinatal death, and use of seatbelts significantly decreases maternal mortality from motor vehicle collisions.

The key point illustrated in this case is the importance of proper seatbelt wear in pregnant women as improper seatbelt use can be dangerous. A comparison of properly restrained pregnant women to improperly restrained women showed an increased risk of adverse fetal outcome (including fetal loss, placental abruption, extreme preterm delivery or fetal injury) in lower severity crashes in those who were



improperly restrained.⁶ With specific regards to uterine rupture, it was initially thought that use of seatbelts may predispose to uterine rupture. While use of lap belt alone may increase risk of uterine rupture (increase the deceleration concentrated in the abdomen therefore increasing uterine hyperflexion), the use of lap and shoulder belts worn appropriately (shoulder belt above and lap belt below the “bump”) does not appear to contribute to such injury. Proper wear of seatbelts in pregnancy includes placement of the lap belt under the uterus with the shoulder belt placed lateral to the uterus, between the breasts and over the mid portion of the clavicle. Pearlman and Viano⁴ specifically examined force transmission through the gravid uterus (28 weeks of gestation) from a variety of seatbelt placements during simulated collisions. They revealed a threefold to fourfold increase in force through the uterus with improper seatbelt placement (placement of the lap belt over the body of the uterus). Additionally, when comparing proper lap belt and shoulder belt placement with proper and improper use of lap belt only, forces transmitted through the uterus were highest with lap belt only. The ecchymosis on the lower abdomen of the patient described above indicates possible improper positioning of the lap belt, or displacement of the belt during initial impact, followed by further impact. The role of airbags in motor vehicle collisions involving pregnant patients is unclear. Although there are few reports of airbag associated fetal mortality, one case report indicates possible airbag involvement in a uterine rupture.⁷

Also well demonstrated in this case is the need for a high index of suspicion for uterine rupture in gravid patients involved in motor vehicle collisions. The classic presentation of uterine rupture includes severe uterine pain, profound shock, palpation of fetal parts outside of the uterus, and vaginal bleeding. However, as illustrated by the above case, and as documented in other case reports, this constellation of symptoms may not initially be present after a motor vehicle collision, therefore delaying the diagnosis. Normal, physiologic changes of pregnancy can additionally obscure the diagnosis of intrauterine rupture. Not only can a pregnant patient tolerate an approximate 30–35% loss of blood volume before a change in vital signs (both maternal blood pressure and pulse are poor predictors of maternal stability and fetal viability⁸),

the stretched abdominal wall changes the normal pain response from intraperitoneal irritation.³ In addition to a fetal mortality approaching 100% from traumatic uterine rupture, maternal morbidity can be quite significant as well. Previous series have shown that more than half of women require 5 or more units of blood after uterine rupture, and hysterectomy rates range from 26% to 83%⁷ with traumatic rupture resulting in approximately 80% or greater hysterectomy rates.

Maternal trauma is a significant morbidity in pregnancy, with maternal vehicle collisions specifically contributing the highest number of fetal deaths associated with maternal trauma. Traumatic uterine rupture, although rare, can be a significant cause of fetal mortality and maternal morbidity. Instruction regarding proper seat belt use in pregnancy is imperative and may help prevent such injury. A high index of suspicion for uterine rupture is required in pregnant women who present following a high speed motor vehicle collision even with initially stable vital signs and lacking the classic signs and symptoms. Most importantly, in all traumas involving pregnant patients, the first priority of management is resuscitation and stabilization of the mother as the majority of fetal mortality is a result of maternal death.

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Necrotizing Cervical and Uterine Infection in the Postpartum Period Caused by Group A *Streptococcus*

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BACKGROUND: Group A *Streptococcus*, once the most common causes of puerperal sepsis, is now a rare cause of postpartum fever.

CASE: A term 27-year-old woman presented after spontaneous membrane rupture. After an uncomplicated vaginal delivery, she became febrile without a source of infection. Despite two different antibiotic regimens, she remained febrile for 3 days. A computed tomography scan showed a wedge-shaped discontinuity in the anterior uterus suggesting uterine infection with early abscess formation. The patient underwent exploratory laparotomy and hysterectomy, with an uneventful postoperative course. Uterine pathology revealed a necrotizing infection within the uterus and cervix from Group A *Streptococcus*.

CONCLUSION: Puerperal sepsis from Group A *Streptococcus* can be a cause of necrotizing infection following delivery. Physicians should be aware of the resurgence of this potentially fatal pathogen.

(*Obstet Gynecol* 2008;111:533–5)

In the past, Group A *Streptococcus* was the most common cause of puerperal sepsis. With the development of hand-washing policies by Semmelweis in the late 1840's, the incidence of Group A streptococcal puerperal sepsis significantly decreased.¹ However, since the mid-1980s, a resurgence of Group A streptococcal infections has been documented. These include a streptococcal toxic shock syndrome, bacteremia, and invasive skin and soft tissue disease that are associated with a high degree of morbidity and mortality.² Several reports have documented how

rapidly this pathogen can cause multi-organ system failure and ultimately death.^{3–6}

We report a case of a pregnancy complicated by a necrotizing infection of the uterus and cervix due to Group A *Streptococcus*. This report serves to emphasize the need for early diagnosis and treatment of this severe and potentially lethal organism.

CASE

A 27-year-old woman (gravida 4, para 1-0-2-1) was admitted to labor and delivery at 38 6/7 weeks of gestation after spontaneous rupture of membranes. Her prenatal course was complicated by A1 gestational diabetes. Approximately 4 hours after membrane rupture, the patient had an uncomplicated spontaneous vaginal delivery of a viable male neonate, 3,551 g, with Apgar scores at 1 and 5 minutes of 8 and 9. A small first-degree perineal laceration was repaired for hemostasis.

Eight hours after delivery, the patient developed a temperature of 38.8°C. Evaluation at that time failed to find a source of infection. She continued to have a fever, with a white blood cell count 20,600. Gentamicin and ampicillin/sulbactam were empirically started 1 day after delivery. Chest X-ray results were negative for disease. On the second postpartum day, the patient remained febrile to 39.9°C. She was without any focal complaints with a benign physical examination. Urine culture grew Group A *Streptococcus*, at which time an infectious disease consult was obtained, and antibiotics were changed to penicillin and clindamycin. A computed tomography (CT) scan of the abdomen and pelvis was ordered to evaluate for possible septic pelvic thrombophlebitis or pelvic collection. The CT scan reported a moderate amount of ascites and a wedge-shaped discontinuity within the anterior portion of the uterus that extended into the endometrial canal, suggesting an area of infection with early abscess formation (Fig. 1).

The patient was reevaluated and noted to have developed an acute onset of pelvic pain in the suprapubic region. At that point, she was febrile at 40.2°C and tachycardic at 130 beats per minute. Her abdomen was soft, with tenderness to palpation suprapubically. Sterile speculum examination revealed a well-healing perineal laceration without erythema or drainage. Her cervix was large and edematous, without purulent discharge. Bimanual examination confirmed an enlarged, edematous cervix, 1–2 cm dilated, with the uterine fundus palpable at the umbilicus. Blood culture results were positive for Group A *Streptococcus*. Her white blood cell count was 27,200 with 35% neutrophils and 60% bands. The CT scan findings, coupled with the patient's persistent febrile illness and increased pelvic pain prompted surgical exploration of the abdomen and pelvis.

Exploratory laparotomy revealed an enlarged, boggy uterus at the level of the umbilicus, and approximately 200 mL of straw-colored ascites. There was purulent exudate over the uterus and ovaries bilaterally. The anterior uterine wall and the cervix were intact, although edematous. The

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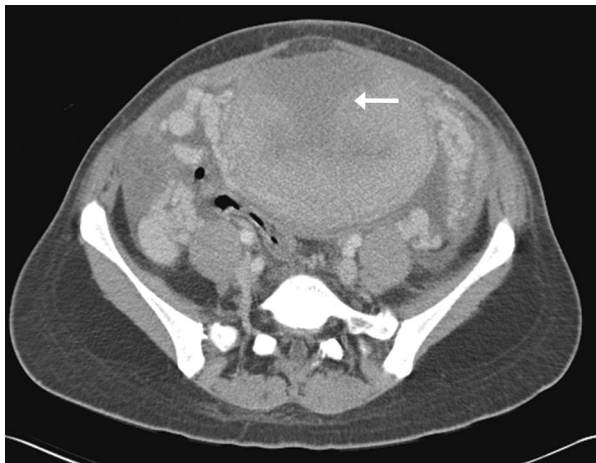


Fig. 1. Computed tomography scan imaging demonstrating a wedge-shaped area (arrow) within the anterior uterine wall suggestive of early abscess formation.

Castagnola. Group A *Streptococcus Necrotizing Cervicitis*. *Obstet Gynecol* 2008.

clinical and intraoperative findings were consistent with sepsis. Given the patient's desire for permanent sterilization and the presumptive source of infection being the uterus, a total abdominal hysterectomy was performed. Postoperatively, the patient did well, and she was afebrile by the first postoperative day. She was discharged home after 4 days with 1 week of penicillin and clindamycin via a peripherally inserted central catheter.

Grossly, the uterus measured 15×15×6cm, and weighed 1,016 grams. The exocervix measured 6×5 cm, and the epithelium was nodular and hyperemic. The endometrium and myometrium were both thickened and hemorrhagic. Microscopic examination revealed extensive acute necrotizing inflammation with reactive changes in the cervix and endometrium. Septic thromboemboli were present in both the cervix and uterine fundus.

COMMENT

Group A *Streptococcus*, or *Streptococcus pyogenes*, is a gram-positive bacterial pathogen responsible for a wide array of infections. These include bacterial pharyngitis, scarlet fever, impetigo, and postinfection sequelae such as acute rheumatic fever, acute glomerulonephritis, and reactive arthritis.² Less common, more severe manifestations include streptococcal toxic shock syndrome and invasive skin and soft tissue infections, making it known as the “flesh-eating” bacterium.² Recently, there have been several case reports documenting streptococcal toxic shock syndrome and invasive soft tissue infection as a cause of postpartum morbidity.^{3–6} The severity of these infections is due to the exotoxin A that is produced by the M1 and M3 serotypes of the bacteria.^{1,2}

Patients with Group A Streptococcal sepsis most commonly present within the first 24 hours after delivery, with fever, tachycardia, hypotension, leukocytosis, hemolysis, and disseminated intravascular coagulation. These patients rapidly progress to multi-organ failure, and occasionally, death. Frequently, patients are without identifiable pelvic disease.⁶ Although our patient became febrile with leukocytosis within 24 hours of delivery, she remained stable for 3 days before showing signs of overt sepsis.

In many of the cases described, the patients clinically improved over several days with appropriate antibiotics. Nathan et al³ and Stefonak et al⁷ both document cases that required laparotomy and hysterectomy. Both noted significant ascites and enlarged, edematous uteri. Pathologic examination of each uterus showed foci of hemorrhagic necrosis in the myometrium associated with thrombi of pelvic vessels.^{3,7} Our findings were consistent with those previously described; however, our patient had significant tissue necrosis in the cervix as well. This is important to note because performing a hysterectomy of an enlarged, edematous, postpartum uterus can be challenging, and providers may elect to perform a supra-cervical hysterectomy for this reason. Had we not removed the cervix in our patient, we would not have removed the nidus of infection.

Our case is unique in that there was an abnormality in the uterus noted on CT scan that aided in the decision to proceed with surgical exploration. The CT scan showed a wedge-shaped discontinuity in the anterior portion of the uterus that extended into the endometrial canal. This finding was felt to be most consistent with an area of infection with early abscess formation. This prompted the performance of a total abdominal hysterectomy after surgical exploration failed to reveal other pathology. Needle aspiration of the possible early abscess was not considered since there was not clear evidence of a drainable fluid collection. Although this may be a feasible option for most abscess collections, the treatment of Group A Streptococcal infections requires antibiotics followed by prompt surgical debridement of necrotic tissue if infections persist.

This case serves to remind practitioners of the presence of this severe and potentially fatal pathogen. Although Group A *Streptococcus* is not the most common cause of puerperal sepsis today, one must remember it as a possible source of infection, especially in cases with febrile morbidity and no evidence of pelvic disease. It is also imperative to recognize the symptoms of developing streptococcal toxic shock syndrome, so as to rapidly institute treatment with intravenous antibiotics and possible surgical intervention.



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Postpartum Thrombosis of the Superior Mesenteric Artery After Vaginal Delivery

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BACKGROUND: Several causes of severe and acute postpartum abdominal pain (pelvic infection, complications of pelvic thromboembolism, arterial ischemia) require early diagnosis and prompt therapy.

CASE: Eight days after a normal vaginal delivery, a 38-year-old woman presented with severe acute abdominal pain that had been going on for 3 days. Abdominal computed tomography showed a superior mesenteric artery thrombosis with suggested ileal wall ischemia. An emergency thrombectomy associated with ileal resection and ileostomy were performed. No identifiable source of embolism, hemostatic disorder, systemic vasculitis, or systemic disease associated with thrombosis was found.

CONCLUSION: Even after a vaginal delivery, the postpartum period is associated with an increased risk of complications of thromboembolism. In the case of acute abdominal pain, abdominal contrast-enhanced com-

puted tomography may be necessary to exclude mesenteric arterial ischemia.

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Postpartum is a period of risk requiring careful monitoring. In the case of severe acute postpartum abdominal pain, pelvic infection, thrombophlebitis, ovarian venous thrombosis, or acute urinary retention are systematically investigated after a vaginal delivery and should be rapidly cared for and treated. We describe an unusual case of acute bowel ischemia due to a superior mesenteric thrombus 8 days after an uncomplicated vaginal delivery.

CASE

A 38-year-old woman, gravida 3, para 3, presented with acute and increasing abdominal pain for 3 days. Eight days before, she had given birth by vaginal delivery without complications. Her previous pregnancies ended in normal vaginal deliveries. She smoked (more than 15 cigarettes per day). Body mass index was 19.5 kg/m². She had been an intravenous drug-addict (heroin) 15 years before, and hepatitis C had been recently diagnosed. She had no fever, and her blood pressure was 140/90 mm Hg. The clinical examination showed spasmodic abdominal pain located in the epigastrium and right hypochondrium, with no antalgic posture. The patient had no mouth ulcers. No gynecologic abnormalities were detected during a vaginal or pelvic ultrasound examination. Blood cell count and liver and pancreatic test results were normal. No drug toxicology study was performed on admission or during the prenatal course. The patient was treated with acetaminophen, which decreased abdominal pain for about 24 hours.

Twenty-four hours later the patient returned to hospital with severe abdominal pain and agitation requiring nalbuphine, diclofenac sodium, and acetaminophen, which were administered by intravenous injection. Blood pressure was normal, and the abdominal examination was unchanged. Blood cell count and albumin, creatinine, and C-reactive protein blood levels were normal, and proteinuria was negative. A contrast-enhanced abdominal computed tomography (CT) scan showed thrombosis in the proximal

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portion of the superior mesenteric artery extending 3 cm with suggested ileal wall ischemia (Fig. 1).

The patient was immediately transferred to the department of vascular surgery. Emergency laparotomy showed no blood and a normal uterus and adnexa for 10 days postpartum. The intestines and the mesentery were edematous with nonpulsatile vessels and necrosis of an ileal segment. A thrombectomy of the superior mesenteric artery with a saphenous patch angioplasty and a 45-cm ileal resection with a protective loop ileostomy was performed. An arterial biopsy was possible by longitudinal rather than transversal arteriotomy. Angioplasty was performed with autologous material because of the risk of sepsis associated with bowel resection. The postoperative course was uneventful. Pathological examination showed a normal arterial wall, and analysis of the thrombus did not reveal any malignant cells.

Hemostatic tests were normal including antithrombin III, protein C, homocystein level, anticardiolipin antibodies, factor V Leiden, G20210A prothrombin, and Janus-kinase 2 (JAK2)-V617F gene mutations. Venereal disease research laboratory, rheumatoid factor, hepatitis C virus-RNA, cryoglobulinemia, and paroxysmal nocturnal hemoglobinuria results were negative. Serum autoantibody tests showed positive antinuclear antibodies at 1/640 with a nucleolar aspect, with no double-strand DNA antibodies. Blood cell count, transesophageal echocardiography, and Holter-elec-

trocardiogram results were normal. There were no signs of Behcet's disease. Thoracoabdominal CT, breast echography, and magnetic resonance breast imaging did not suggest cancer. The loop ileostomy was closed 4 months later. The patient's condition was normal with no complications 7 months after the initial diagnosis.

COMMENT

Acute mesenteric ischemia is an unexpected and extremely rare postpartum complication whose final stage is intestinal necrosis. It is a surgical emergency whose prognosis is very poor mainly because of a long delay between diagnosis and surgical treatment.¹ A Medline search with no time limit was performed using "acute bowel ischemia," "postpartum," and "mesenteric thrombus" identified only one case of acute mesenteric ischemia immediately after a caesarean delivery.² This case concerned acute mesenteric ischemia diagnosed 6 hours after an emergency caesarean delivery for breech in India. The authors reported that they performed an abdominal paracentesis, which was negative. No abdominal CT scan was performed. Due to worsening of the patient's condition (pain and low blood pressure), an exploratory

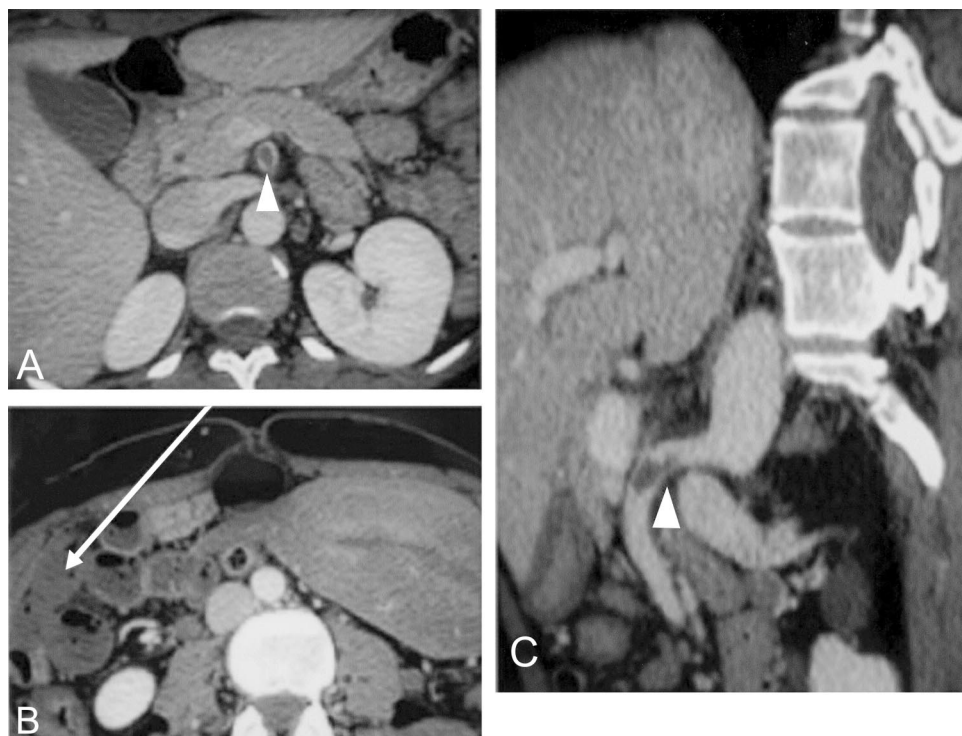


Fig. 1. Contrast-enhanced computed tomography scan showing thrombosis of the proximal portion of the superior mesenteric artery (arrowhead in **A** and arrow in **B**) and nonenhancement of the ileal wall (arrowhead in **C**).

Ducarme. Postpartum Thrombosis. Obstet Gynecol 2008.



laparotomy was performed. Acute mesenteric ischemia was diagnosed, but the patient went into cardiac arrest and could not be resuscitated.

This case highlights the importance of early diagnosis, care, and specific treatment of this pathology. Acute mesenteric ischemia occurs as the direct result of thrombosis in 25% or embolism in 50% of mesenteric vessels.³ Ischemic times as short as 6 hours can produce significant damage to the bowel (necrosis), initiating a cascade of events, such as reperfusion injury, acute inflammatory response, hypovolemia, and multi-system organ dysfunction. In absence of prompt therapy, the mortality rate is high in such situations, mainly because of the risk of peritoneal infection. The diagnosis is very difficult, mainly because pain is not specific, so it is usually made at a late stage when digestive necrosis and peritonitis have developed. When suspected early, imaging such as arterial CT and arterial mesenteric arteriography should be used.³ Moreover, contrast-enhanced abdominal CT scan is very useful for differential diagnosis of acute abdominal postpartum pain (pelvic abscess or thrombophlebitis).

The goals of therapy include restoration of superior mesenteric artery blood flow and resection of nonviable bowel. Methods to restore blood flow to the superior mesenteric artery are dependant on operative findings and on the preoperative CT scan or arteriogram. In the case of emboly, the artery is opened and Fogarty catheters are passed proximally and distally in the artery to extract the embolic material and thrombus. A bypass to the artery is required if there is poor inflow. If the patient is hemodynamically stable, without signs of peritonitis and a small thrombus burden, thrombolysis therapy may be an option. However, this endovascular treat-

ment may expose the patient to the risk of ongoing ischemic damage during the wait for the thrombolytic therapy to have an effect, and it usually does not preclude evaluation of bowel integrity by laparotomy or laparoscopic procedure.¹

Pregnancy, as well as the postpartum period, is associated with an increased risk of thromboembolism complications.⁴ In our case, extensive hemostatic test results were negative. Initial thrombosis leading to mesenteric ischemia was probably triggered by the association of tobacco abuse, hypoalbuminemia, and variations in the hemostatic system during the postpartum period corresponding to increased coagulation and regional compressions.⁴

In the case of acute and persistent abdominal pain in postpartum, contrast-enhanced abdominal CT scan may be necessary to diagnose an acute bowel ischemia due to a superior mesenteric thrombus. After this event and if there is no risk factor for arterial thrombosis, an assessment of predictive factors for thromboembolism is often required even through results are often normal. Duration of anticoagulant therapy in these cases is debatable even if hemostatic tests are normal.

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Diagnosis and Treatment of Human Seminal Plasma Hypersensitivity

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BACKGROUND: Human seminal plasma hypersensitivity is a rare disorder that is often misdiagnosed. While this disorder is well described in the allergy and immunology literature, few cases exist in the gynecologic literature.

CASE: A young woman presented to our allergy clinic with recurrent vaginal burning, swelling, and itching occurring approximately 10 minutes postcoitally. Semen allergy was suspected. Using her partner's semen, intradermal testing produced 1.6-cm wheal and 6.0-cm flare. The patient underwent intravaginal desensitization, and she and her partner were instructed to have intercourse every 48 hours to maintain desensitization. At 5-month follow-up, they were practicing coitus interruptus with success.

CONCLUSION: Human seminal plasma hypersensitivity may mimic chronic vaginitis. The intravaginal graded challenge, a form of immunotherapy used by allergists, remains a mainstay in treatment, but is only effective if maintained correctly.

(*Obstet Gynecol* 2008;111:538–9)

Despite being well described, human seminal plasma hypersensitivity remains a misdiagnosed disorder. A history of postcoital vaginal symptoms and relief of symptoms with a condom should introduce the possibility of this diagnosis. Greater awareness among the gynecologic and general medical community for correct diagnosis and potential treatment is essential. The intravaginal graded challenge, whereby the female is intravaginally desensitized to her partner's sperm, is safe and effective if maintained properly.

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CASE

A 24-year-old woman presented to our allergy clinic with the suspicion that she had semen allergy. Her symptoms consisted of recurrent vaginal burning, swelling, and itching that occurred approximately 10 minutes postcoitally. The symptoms did not occur when her partner used a condom. She also had an episode of general hives 10 minutes after oral sex. She reported no shortness of breath, wheezing, throat closing, faintness, or blister formation. The patient reported sexual activity with three partners with one successful pregnancy. She reported no vaginal symptoms with her former partners. She had been in a monogamous relationship with her current partner for a total of 4 years. Her vaginal symptoms began 2 years into the relationship. For the past 2 years, she sought treatment by a gynecologist who evaluated her for sexually transmitted diseases and treated her for chronic vaginitis with metronidazole gel multiple times without relief. Her medical history was significant for food allergy and atopy. She reported no surgical history. The physical examination, including a genital examination, was normal. A complete blood count with differential, basic chemistry, Complement 1 esterase level, and functional assay were normal. Her IgE level was elevated at 135 kilo-Units per liter. A radioallergen sorbent test result for latex allergy was negative.

Seminal fluid allergy was suspected, and skin testing to her partner's semen was performed. Fresh seminal plasma was collected in a sterile cup the morning of the testing. Skin-prick testing and intradermal testing were performed with undiluted semen, normal saline as a negative control, and histamine 1.0 mg/mL as a positive control. Prick testing gave a negative response but intradermal testing produced a 1.6 cm wheal and a 6.0 cm flare.

Treatment options were discussed and she elected to undergo intravaginal graded challenge. The challenge was performed using the protocol described by Matloff.¹ Diluted semen 1:1000, 1:100, 1:10, and undiluted semen were prepared. Two milliliters of incremental concentrations of semen were placed intravaginally every 20 minutes until the patient tolerated 2 mL of undiluted semen. The patient's vital signs and respiratory status were monitored throughout the procedure. The patient tolerated the procedure without complications. She and her partner were instructed to have intercourse at least every 48 hours to maintain the desensitization. She remained symptom free for 1 month. Her gynecologist, during a routine visit, unfamiliar with the desensitization protocol, advised her not to engage in such frequent coitus and her symptoms returned. She and her partner declined to undergo repeat intravaginal desensitization. At a 5-month follow up, they were practicing coitus interruptus with success.

COMMENT

The Dutch gynecologist Specken² first described human seminal plasma hypersensitivity in 1958. Ap-



proximately 80 cases exist in the medical literature, primarily published in the allergy and immunology journals. A PubMed literature search (from 1962 to 2007) using the keywords “human seminal fluid plasma protein hypersensitivity,” “sperm allergy,” “hypersensitivity,” “chronic vaginitis,” and “burning semen syndrome” and review of relevant bibliographies revealed only 10 articles in the English gynecologic literature referring to human seminal plasma hypersensitivity. Patients with human seminal plasma hypersensitivity often seek gynecologic attention for symptoms related to human seminal plasma hypersensitivity before the diagnosis of their allergy. Many of these patients are unsuccessfully treated for chronic vaginitis and vulvovaginitis.^{3,4} Common causes of vaginitis, including bacterial and candidal infection, contact dermatitis, and latex allergy, should be eliminated.^{4,5} Both history of postcoital, local and/or systemic allergic symptoms, and treatment failure for chronic vaginitis should raise the question of human seminal plasma hypersensitivity and warrant an allergy workup.⁶ While the exact prevalence of this syndrome is unknown, it is more common than previously suspected.⁵ Most individuals present in their 20s to 30s⁴ with a majority of women developing symptoms after their first coitus; some report history of food allergy.^{4,7} The mechanism of disease is typically an immunoglobulin E-mediated hypersensitivity response, presumably against multiple allergens contained within the seminal fluid. Diagnosis is supported by clinical history, positive skin testing, and cessation of symptoms with condom use. Prophylactic usage of antihistamines and intravaginal cromolyn 8% cream may alleviate local symptoms but is often ineffective. First-line treatment entails allergen avoid-

ance through abstinence, coitus interruptus, or condom use. While effective, these methods rarely provide acceptable solutions.^{1,3,8} Other treatments include intravaginal graded challenge and subcutaneous immunotherapy followed by frequent coitus every 48 hours. Women with human seminal plasma hypersensitivity experience anxiety and lack of spontaneity with their partner because of their inability to engage in unhindered sexual intercourse. This often causes problems within their sexual relationship and worry regarding their ability to conceive. They are decidedly motivated to maintain this highly effective, safe, and natural, notwithstanding intensive, treatment.⁸ There are no long-term data regarding resolution of human seminal plasma hypersensitivity, and more long-term studies are necessary. However, allergies, including food, can change or even dissipate over time.

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Acute Esotropia After Epidural Anesthesia

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BACKGROUND: Cranial nerve palsy after dural puncture is an uncommon complication. The sixth cranial nerve is the most commonly affected because of its long intracranial course. We report a case of acute comitant esotropia that occurred after unintentional dural puncture.

CASE: A young woman presented with acute onset comitant esotropia 1 week after epidural anesthesia for a normal vaginal delivery during which the dura was unintentionally punctured. Magnetic resonance imaging revealed diffuse pachymeningeal enhancement, typically seen after dural puncture. Resolution was spontaneous.

CONCLUSION: Puncture of the dura should be considered when acute strabismus is diagnosed shortly after epidural anesthesia.

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The onset of comitant strabismus occurs in most cases during early infancy and childhood. These cases are usually not related to any serious underlying neurologic abnormality. In contrast, the onset of acute esotropia and diplopia in adults should prompt a careful consideration of whether the strabismus is a sign of an underlying neurologic pathology.^{1,2}

CASE

A young woman, gravida 2, para 2, was referred to our neuro-ophthalmologic service due to acute bilateral diplopia that occurred 1 week after an unremarkable vaginal delivery at 39 weeks of gestation after a normal pregnancy. Before labor, the patient underwent an epidural anesthesia at the T12 to L1 level. An 18-gauge needle was used, no cerebrospinal fluid or blood return was noted, and the procedure was uncomplicated. One day later, she reported a severe frontal throbbing headache that worsened with postural change. Dural perforation was suspected, and epidural blood patching using 20 mL of autologous blood

was performed. The headache improved and subsequently resolved 2 days after blood patching. Several days after the procedure, the patient reported blurry vision and difficulty in reading, which gradually worsened; she reported double vision 1 week after the epidural anesthesia.

Examination revealed normal visual acuity (20/25) and refraction in both eyes. Ocular versions were normal, and the slit-lamp examination of the anterior and posterior segments was normal. Ocular alignment tests demonstrated a comitant esotropia of 32 prism diopters and bilaterally symmetric abducens palsy.

On follow-up examination 2 weeks later, the patient reported gradual improvement of symptoms. A cover test measured 14 prism diopters of esotropia, and the patient was symptom free with no detectable movement on cover testing at examination after 2 more weeks. Magnetic resonance imaging (MRI) was performed 5 weeks after the initial symptoms, and demonstrated diffuse pachymeningeal enhancement as is typically seen after dural puncture.³ The MRI was otherwise normal and did not show any downward shift of the brainstem.

COMMENT

Cranial nerve palsy after dural puncture is a rare complication. The incidence of accidental dural puncture complicating epidural anesthesia varies from 0.19% to 4.4%.⁴ The sixth cranial nerve is the most commonly affected because of its long intracranial course.⁵ Nearly 80% of the cases are unilateral.⁶ Nerve dysfunction is thought to be caused by intracranial hypotension and descent of the brain, causing stretching of the nerve which results in nerve damage.⁷ Arcand et al⁸ recently published a report describing bilateral sixth nerve palsy after unintentional dural puncture in a woman who underwent anesthesia for surgical management of a neurogenic bladder.

Extraocular muscle paralysis usually presents 4–7 days after dural puncture but can appear as early as 1 day and as late as 3 weeks after the procedure.⁷ Previous reports show that most of the cranial nerve paresis after spinal anesthesia show complete resolution within 6 months after diagnosis, but that the paresis can persist for more than 8 months in 10% of the cases; these cases are usually found to be permanent and warrant further investigation and treatment.^{7,9}

We described a case of acute comitant esotropia secondary to unintentional puncturing of the dura during epidural anesthesia. This case represents an uncommon complication of a common procedure. It is well recognized in the anesthesiology community but less familiar to ophthalmologists and obstetricians. Acute esotropia in an otherwise healthy adult can cause marked distress both for the patient and the doctor and can result in costly investigations for an

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acute neurologic illness. Early correct diagnosis and reassurance of the patient and the family can prevent unnecessary stress and expenditure. Acute esotropia after spinal or epidural anesthesia/analgesia, accompanied by postdural headache should alert to the possibility of this unusual and benign diagnosis. Suspicion of this condition should arise when a patient reports double vision days or few weeks after dural puncture. Usually, there are no other symptoms, besides the postdural headache, which almost always precedes the strabismus. Referral to an ophthalmologist or neuro-ophthalmologist is advised for comprehensive work-up and proper diagnosis of the strabismus. We recommend MRI of the brain and orbits to rule out other less-benign conditions such as neoplasm, ischemia, or multiple sclerosis. Blood patching, although an affective treatment for postdural puncture headache, has been proved to be noneffective for treatment of abducens nerve palsy.¹⁰ No treatment is required besides supervision and support. Occasionally, temporary patching of one eye can alleviate symptoms of diplopia and nausea. Puncturing of the dura should be considered when acute strabismus is diagnosed shortly after epidural anesthesia.

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Recurrent Ectopic Pregnancy in a Cesarean Scar

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BACKGROUND: Ectopic pregnancy in a cesarean scar is a rare but well-recognized potential complication of cesarean delivery. Multiple risk factors exist, including prior uterine surgery, a history of uterine infections such as endomyometritis, and a brief interval between uterine surgery and subsequent conception. It is important to recognize such cases early, due to the risk for uterine rupture and catastrophic hemorrhage at early gestational ages.

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CASE: This patient presented for a dating ultrasound examination at 4 6/7 weeks of gestation. Her history was significant for an ectopic pregnancy in her cesarean scar 3 years prior that was managed by surgical resection. The initial ultrasound examination was suspicious for a recurrent ectopic pregnancy in her cesarean scar. The diagnosis was confirmed on repeat ultrasonography at 6 weeks of gestation. She was treated with methotrexate, and the pregnancy resolved without complication.

CONCLUSION: Ectopic pregnancy in a cesarean scar is an important diagnosis to consider in a woman who has had a history of cesarean delivery and whose early ultrasonography shows a thin, lower uterine segment or a low implantation site. If the diagnosis is not clear on initial ultrasound examination, the patient should be followed up with serial ultrasound examinations. Once recognized, patients with this complication may be treated either surgically or medically as indicated by the clinical situation.

(Obstet Gynecol 2008;111:541–5)

Ectopic pregnancy in a prior cesarean scar is a rare but well-recognized potential complication of cesarean delivery. Risk factors that have been suggested for the occurrence of ectopic pregnancies in this location include multiple prior surgeries (either cesarean delivery or myomectomy), a brief interval between such surgery and subsequent conception, and infections such as en-



domyometritis. Despite their rarity, it is important to be able to recognize these cases early due to the risk for uterine rupture and hemorrhage, even in early gestation. Historically, such cases have been treated in a surgical fashion, either with hysterotomy or hysterectomy; however, more recently conservative strategies have been attempted, including methotrexate administration and uterine artery embolization.

CASE

A 40-year-old para 1041 with a history of a prior ectopic pregnancy in a cesarean scar presented to ultrasonography for a routine examination to confirm dates. Although her last menstrual period was uncertain, she was thought to be approximately 4 weeks pregnant. She was without complaints at the time of her examination. Her obstetric history was significant for two spontaneous abortions, one immediately before this pregnancy; a low transverse cesarean delivery 7 years before presentation; and an ectopic pregnancy in the prior cesarean scar which had been surgically resected 3 years before presentation. Her gynecologic history was notable for a history of myomectomy within the anterior lower uterine segment. At the time of her previous ectopic pregnancy, she had presented with lower abdominal cramping but no other symptoms. The ultrasonography performed at that time had shown an 8-week gestational sac bulging from the anterior lower uterine segment into the vesico-uterine pouch, with only a thin rim of myometrium visible anterior to the sac (Fig. 1A and 1B). She was referred to the gynecologic oncology service and underwent exploratory laparotomy, evacuation of a lower uterine segment ectopic pregnancy and uterine reconstruction. A left hypogastric artery ligation was performed as well at the time of that surgery, due to excessive bleeding from the placental bed after removal of the ectopic pregnancy.

The patient's initial ultrasonography during this pregnancy showed a gestational sac measuring 4 6/7 weeks of gestation, located in the anterior lower uterine segment. There was 6 mm of myometrium between the gestational sac and the posterior wall of the bladder (Fig. 2). At this point, concerns were raised as to the likelihood of a recurrent ectopic pregnancy in her cesarean scar; however, as this was a desired pregnancy, the decision was made to follow the patient closely with serial ultrasound examinations. A repeat ultrasound examination performed at 6 weeks of gestational age showed only 2.1 mm of myometrium remaining between the gestational sac and the posterior bladder, thus confirming the diagnosis of ectopic pregnancy in the location of her previous scar. She was counseled regarding the option of surgery versus conservative management. As the ectopic pregnancy had not yet eroded completely through the uterine wall, fetal heart motion was not visible, her human chorionic gonadotropin (β -HCG) level was less than 10,000 (7,619 units/mL), and her laboratory values were within normal limits, it was decided to offer her methotrexate. After appropriate in-

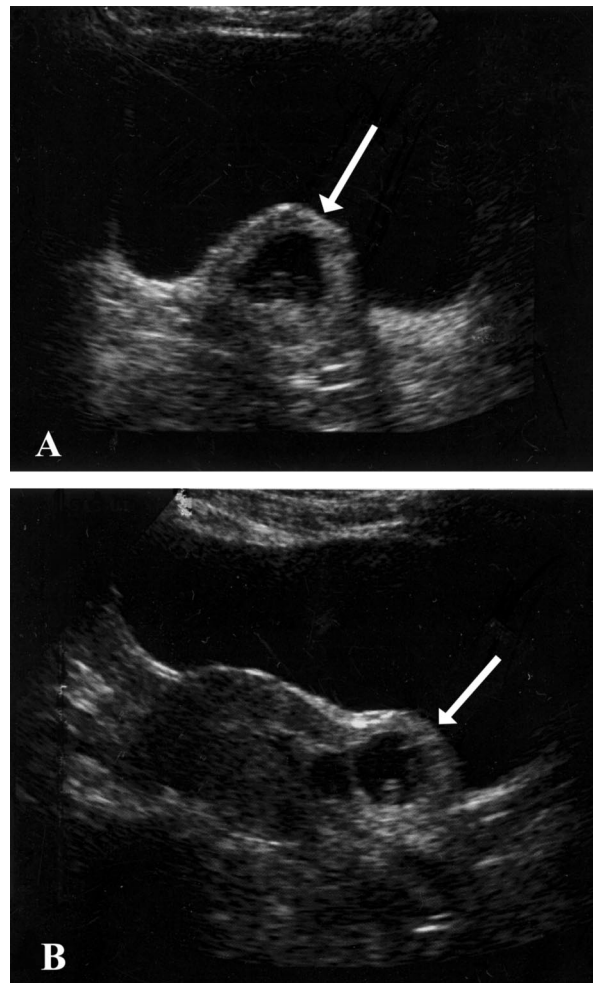


Fig. 1. Ultrasonograph of the patient's uterus in transverse (A) and sagittal (B) views during her first ectopic pregnancy, showing it protruding into the bladder with only a thin area of myometrium (arrows) surrounding the gestational sac.

Holland. Ectopic Pregnancy in a Cesarean Scar. *Obstet Gynecol.* 2008.

formed consent was obtained, she was given 100 mg of methotrexate (50 mg/m^2) (Figs. 3 and 4).

Over the course of the next 2 months, the patient's β -HCG level decreased steadily to zero. She did report some intermittent vaginal bleeding during this time period, for which an ultrasound examination was performed. This was significant only for a heterogeneous mass measuring $2.9 \times 3.1 \times 2.2 \text{ cm}$ within the upper cervix that was felt to be consistent with a blood clot. The bleeding resolved spontaneously, and as of the time of this report, she had been without complaints for more than 6 months.

COMMENT

Pregnancy implantation within a prior cesarean scar is the rarest of all forms of ectopic pregnancy. While the exact incidence is unknown, fewer than 50 cases were





Fig. 2. Initial ultrasonography of the patient's second ectopic pregnancy, showing a thinned lower uterine segment (arrow) measuring 0.62 mm in the region of the uterine scar.

Holland. Ectopic Pregnancy in a Cesarean Scar. *Obstet Gynecol.* 2008.

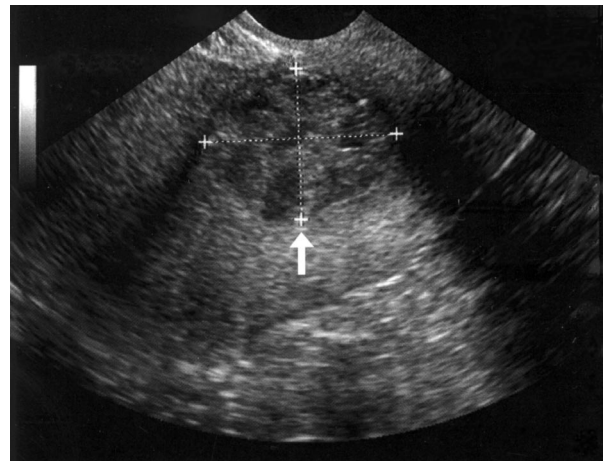


Fig. 4. Ultrasound image of the ectopic pregnancy 6 weeks after administration of methotrexate, showing a blood clot in the area of the previous gestation (arrow).

Holland. Ectopic Pregnancy in a Cesarean Scar. *Obstet Gynecol.* 2008.

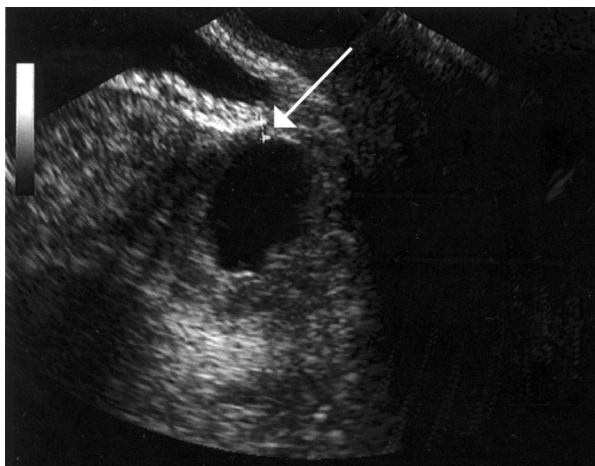


Fig. 3. Image from the follow-up ultrasonography of the second ectopic pregnancy, showing the progressive erosion of the myometrium (arrow); at this point, only 0.21 cm of myometrium separates the gestational sac from the bladder.

Holland. Ectopic Pregnancy in a Cesarean Scar. *Obstet Gynecol.* 2008.

reported in the English-language literature between 1966 and January 2006. An argument can be made that the incidence appears to be increasing, because before 2001 only 18 such cases had been reported, whereas between 2001 and 2003, there were 33, 18 of which came from a single institution.¹ Whether this is a true increase in frequency, perhaps related to an increase in frequency of cesarean delivery, or simply an increase in frequency of diagnosis as transvaginal ultrasonography has become more widely used is

uncertain. Regardless, the condition is one that all practitioners should be aware of given the risk of uterine rupture and subsequent catastrophic hemorrhage, which can occur as early as the first trimester in these cases.

The etiology of ectopic pregnancies in prior cesarean scars is likely to be multi-factorial. It is well known that any sort of endometrial and myometrial disruption increases the risk of abnormal implantation; for example, the increased risk of placenta accreta with multiple cesarean deliveries. However, in the latter case, the gestation is completely encased by the myometrium and is separate from the endometrial cavity. It has been suggested that the early pregnancy actually travels through a defect in the endometrium and outer myometrium to reach its intramural location.^{1,2} Risk factors for such defects include uterine surgery, such as cesarean delivery, myomectomy, or curettage. A shorter time interval between the insult and conception may be important as well; several case reports have concerned pregnancies occurring less than 1 year from the time of the cesarean delivery.³ Presumably this is related to incomplete healing of the defects within such a short period of time. One could therefore extrapolate that causes of incomplete or prolonged healing of the scar are important as well; such causes could include postoperative infections, decreased blood flow due to scar tissue, a history of multiple prior surgeries, or medical conditions such as diabetes that predispose to poor wound healing. In the case described above, the patient had had three procedures to the anterior lower uterine segment by the time



of her second ectopic pregnancy: her initial cesarean delivery, a hysteroscopic myomectomy, and the excision of her initial ectopic pregnancy with subsequent repair of the lower uterine segment. She had also undergone hypogastric artery ligation at the time of her first ectopic pregnancy.

Diagnosis of an ectopic pregnancy within a cesarean scar is usually made by transvaginal ultrasonography. However, even with a skilled ultrasonographer, it can be difficult to differentiate between similar diagnoses, such as a spontaneous abortion or cervico-isthmic pregnancy. In 2002, Fylstra² laid out the following guidelines for ultrasound diagnosis of an ectopic pregnancy within a cesarean scar:

- 1) An empty uterine cavity and cervical canal.
- 2) Development of the gestational sac in the anterior portion of the lower uterine segment.
- 3) Absence of healthy myometrium between the bladder and the gestational sac.

In particular, it is this last criterion that helps distinguish the ectopic pregnancy in a cesarean scar from a cervico-isthmic pregnancy. The use of Doppler flow techniques can help to ascertain that the myometrium does in fact surround the posterior (uterine) side of the pregnancy. In cases in which the diagnosis remains unclear after transvaginal ultrasound examinations, magnetic resonance imaging may be useful.

Treatment is, in part, dependent on the timing of diagnosis. If the pregnancy is early and there are no signs of rupture, conservative management can be attempted. However, if the gestational sac is large and there is evidence of dehiscence, surgical management is clearly indicated. Surgical management in the past has involved laparotomy, with resection of the pregnancy and repair of the uterine scar. However, there are now multiple case reports of successful endoscopic management. Most recently, Wang et al⁴ published a series of 11 cases, four of which had been managed via laparoscopy, and six via hysteroscopy. The remaining case used a combination of laparoscopy and hysteroscopy. There were no surgical complications and minimal blood loss, and all of the patient's β -HCG values declined to zero within 4 weeks postoperatively. The success of the cases reported in this study suggest that endoscopic management is a reasonable alternative to laparotomy in cases in which the patient's condition is stable, there is no indication of uterine rupture, and the physician is comfortable in the use of endoscopic techniques. A reasonable suggestion as to which endoscopic technique to attempt was made by Chao et al,⁵ namely that hysteroscopic resection is more appropriate for the

ectopic pregnancy which is growing toward the uterine cavity, while laparoscopy is appropriate for a deep implantation which is adjacent to the posterior bladder wall. One caveat to attempting a hysteroscopic resection is that it may be difficult to visualize the pregnancy if the patient has significant vaginal bleeding.⁶

With regard to medical management, the most common treatment chosen is methotrexate, administered either intramuscularly or directly into the gestational sac under ultrasound guidance. Some authors have suggested that, due the fact that this type of ectopic pregnancy is implanted in an area of scar tissue, intramuscular methotrexate may not reach the ectopic pregnancy at the same concentration seen in other ectopic pregnancies, causing slower absorption and thus predisposing to methotrexate failures. It has therefore been argued that direct injection of methotrexate into the gestational sac is more effective.^{2,7,8} Other ultrasound-guided injections, such as potassium chloride and hyperosmolar glucose have also been found to be effective.⁸ When pursuing medical management, the same guidelines that apply to tubal or other forms of ectopic pregnancies should also be followed for ectopic pregnancies in a cesarean scar, namely, that the gestational sac size and quantitative β -HCG be appropriate, and a comprehensive metabolic profile must be within normal limits. Presence of fetal heart motion should be regarded as a relative contraindication as well, as it is in other forms of ectopic pregnancies. It is also important to counsel the patient regarding risk of failure and need for possible surgical intervention, particularly as some literature suggests the risk of failure may be increased in these types of ectopic pregnancies. Once methotrexate or another medical treatment has been given, close clinical follow-up is needed, including serial β -HCG evaluations. The values should decrease at the same rate as seen in other forms of ectopic pregnancy; if this does not occur, a repeat transvaginal ultrasound examination is indicated, and the risks of a repeat methotrexate injection weighed against that of surgical intervention.

In summary, ectopic pregnancy in a cesarean scar is a rare, but well-recognized, complication of cesarean delivery that appears to be increasing in frequency. Left untreated, it can lead to uterine rupture with catastrophic hemorrhage within the first trimester. Therefore, early diagnosis is key, and any suspected case must be followed up carefully with serial transvaginal ultrasound examinations. Ultrasound criteria for diagnosing an ectopic pregnancy within a cesarean scar currently include an empty uterine cavity and cervical canal, implantation of the pregnancy within the anterior portion of the lower uterine segment, and extreme thinning or absence of myo-



metrium between the gestational sac and the bladder. If the diagnosis is not clear on initial ultrasound examination, the patient should be followed up with serial ultrasound examinations. Multiple treatment modalities have now been reported in the literature, and the type of treatment should be chosen based on the clinical picture. Clearly, laparotomy with hysterotomy or hysterectomy or both is indicated for those cases that present with active hemorrhage. Recent case reports of endoscopic techniques suggest that laparoscopy or hysteroscopy by an experienced physician are viable alternatives to laparotomy in a stable patient. Finally, medical management such as intramuscular methotrexate or intra-amniotic injections can also be pursued in appropriate patients, although these strategies require close clinical follow-up and may have a higher risk of failure than usually seen in other forms of ectopic pregnancy.

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Spinal Cord Stimulator for the Treatment of a Woman With Vulvovaginal Burning and Deep Pelvic Pain

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BACKGROUND: Vulvodynia is a chronic pain disorder of the vulva that occurs in the absence of visible infectious, inflammatory, neoplastic, or neurological findings. Multiple treatment modalities are used, often with insufficient results. We report the successful use of a spinal cord stimulator to treat vulvodynia symptoms in a patient who had unsuccessful prior conservative therapies.

CASE: A postmenopausal woman presented with 15 years of treatment for vulvar and vaginal burning and deep pelvic

pain. She had been taking multiple pain medications with inadequate relief. After successful test stimulation, a permanent spinal cord stimulator was implanted. At 10 months posttreatment, her pain improved by 80%, and the patient no longer requires oral medication.

CONCLUSION: The use of spinal cord stimulation was successful in a patient with vulvodynia and unsuccessful multiple prior therapies and whose symptoms were diffuse in nature.

(*Obstet Gynecol* 2008;111:545-7)

Vulvodynia is a condition of vulvar discomfort that affects millions of women in the United States each year.¹ It is most often described as burning pain, occurring in the absence of visible infectious, inflammatory, or neoplastic findings or a specific, clinically identifiable neurological disorder.² Other symptoms include stinging, irritation, itching, and feeling of rawness anywhere from the mons to the anus. Vulvodynia may be generalized or localized, involving a portion or component of the vulva. It may be provoked by sexual and/or non-sexual contact, unprovoked, or both.

These symptoms may cause physical, sexual, and psychological distress.^{3,4} Current modalities of treatment include vulvar care measures; topical, oral, and injectable medications; dietary modifications; physical therapy; sexual counseling; surgery; and referral to pain management specialists if all other measures are ineffective.^{1,4} Despite these multiple treatment op-

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tions, therapy is often ineffective. We report the use of a spinal cord stimulator to treat a patient with refractory vulvodynia and deep pelvic pain.

CASE

A 57-year-old woman was referred by her gynecologist in March of 2005 for treatment of severe vaginal pain due to vulvodynia. The pain was described as constant burning in the vulvovaginal area with pain that radiated deep inside the pelvis for the past 15 years (visual analog scale [VAS] 10 of 10). The pain would increase with sitting for prolonged periods of time as well as with any strenuous activity. Intermittent severe exacerbations resulted in numerous trips to the emergency department for immediate pain relief. The degree of pain resulted in avoiding intercourse for 15 years and had forced her to quit her employment 8 years ago. Prior treatments included topical estrogen/steroids, amitriptyline 25 mg, and physical therapy. Recent treatments with oxycodone continuous release 80 mg taken every 12 hours, oxycodone 10 mg every 4 hours, and methadone 30 mg taken three times per day did not improve her pain score.

Spinal cord stimulator trial was performed on July 2006 involving percutaneous placement of two Advanced Bionics (Advanced Bionics, Inc., Sylmar, CA) 8 contact leads (Fig. 1). The leads were implanted via a 14-gauge introducer that was used to access epidural space at L3–4 level. Then two leads were guided down under fluoroscopy to reach right and left S4 nerve roots. The proximal ends were secured with silk suture to the skin. On day 2 of the trial, the patient noted a 90% improvement of pain to a VAS score of 1 of 10. After removing the trial leads on day 8 in the office, her pain increased to 9 of 10.

In September 2006, the patient had a permanent implant of the spinal cord stimulator that involved making a 2-cm incision at L3–4 level, dissecting down to the supraspinous ligament, and implanting two Advanced Bionics 8 contact leads via a 14-gauge introducer used to access epidural space. Two leads were guided down under fluoroscopy to reach right and left S4 nerve roots and were then secured to the supraspinous ligament. A 4-cm incision was made above the left buttock to create a pocket for the rechargeable, implantable pulse generator (volume 22 mL, weight 33 g). The leads were tunneled to the pocket and connected to the generator. The generator was programmed and activated,

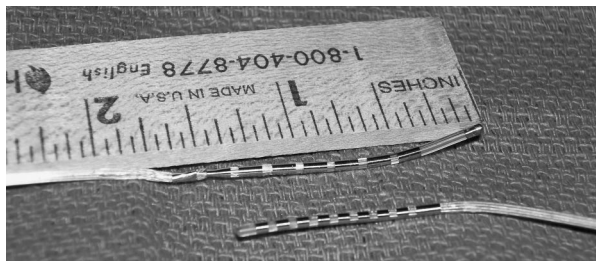


Fig. 1. Microcurrent spinal cord nerve stimulator.
Nair. Spinal Cord Stimulator. Obstet Gynecol 2008.

incisions were closed, and the patient was discharged home 30 minutes later. On postoperative day 7, her pain had improved to a VAS score 1 of 10. Three weeks postoperative, she no longer needed methadone. Currently, she is 10 months posttreatment with a pain score of 2 of 10, off all oral pain medications with no adverse effects of the implanted stimulator.

COMMENT

It is estimated that more than 2 million women have vulvodynia.³ Causes may include changes in estrogen concentration, immunologic factors, and neuropathic factors. Alterations in estrogen levels change vulvar nerve density and sensory nociceptors, which may explain why vulvodynia may occur at the onset of menopause.⁵ In addition, long-term tissue damage may cause local accumulation of chemical mediators that activate nociceptors, resulting in the perception of pain.⁶

Vulvodynia may be diffuse or focal, unilateral or bilateral, constant or sporadic. Dyspareunia and pain with light touch may or may not be a feature. Symptom-free periods lasting days or weeks or transient symptoms have been reported.

Diagnosis of vulvodynia is largely one of exclusion. Other causes of pain must be ruled out. Current modalities of treatment include vulvar care measures; topical, oral and injectable medications; dietary modifications; physical therapy; sexual counseling; surgery; and referral to pain management specialists if all other measures are ineffective. There are no large randomized trials to guide therapy of these patients, with most reports involving case series or retrospective studies.

All chronic pain disease states are expressed at the cellular level with changes in metabolism, neurotransmitters release, and electrical discharge. In order for any therapy to be successful, there has to be a return of electric balance. Spinal cord stimulators are devices that use neurostimulation to treat chronic pain of neurogenic origin with demonstrated long-term efficacy.⁷ An adjustable electrical generator, which must be replaced every 15 years, delivers an electrical pulse to a specific targeted spinal cord area via electrodes that are placed in and around nerves involved in the transmission of pain. The mechanism of action of electrical stimulation has been the subject of debate. Most interestingly, a recent study has shown that the electric stimulation, when successful, changes metabolic activity within the thalamus. This, in turn, alters release of neurotransmitters, effecting intrinsic electrical activity associated with pain, with the end result being a reprogramming of the central nervous system.⁸

In the initial phase of therapy, a temporary lead is connected to an external pulse generator. If patient has a 50% improvement of her pain during the trial period, she



is considered a candidate for a permanent spinal cord stimulator implant. During permanent placement, a new lead is positioned similar to the test lead and connected to a rechargeable implanted pulse generator. The frequency and amplitude of the current are modified to achieve the optimal relief of pain. In our patient, pain scores improved from 9 of 10 to 1 of 10 with the test stimulation. After permanent placement of the stimulator, the current pain score is 2 of 10. In addition, she no longer requires oral pain medication and has obtained a satisfactory functional result with a return to an active lifestyle.

Spinal cord stimulators are now being used to treat a variety of chronic pain syndromes with demonstrated efficacy. This is an early report of a spinal cord stimulator successfully used for the treatment of vulvodynia and deep pelvic pain in a patient who had unsuccessful prior therapies.

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Progression of Atypical Endometrial Hyperplasia to Adenocarcinoma Despite Intrauterine Progesterone Treatment With the Levonorgestrel-Releasing Intrauterine System

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and B. J. Van Voorhis, MD

BACKGROUND: Intrauterine progesterone therapy has been proposed as a potential uterine-sparing treatment for atypical endometrial hyperplasia and adenocarcinoma.

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CASE: We present a case of an infertility patient with atypical endometrial hyperplasia who was treated with the levonorgestrel-releasing intrauterine system for 6 months. At follow-up, she was noted to have an increasing endometrial thickness on ultrasonography, and biopsy revealed progression of her lesion to adenocarcinoma.

CONCLUSION: Although there is a need for uterine-sparing treatment for atypical endometrial hyperplasia and early adenocarcinoma, especially in the setting of desired fertility, caution should be exercised. We do not recommend using the levonorgestrel-releasing intrauterine system as a treatment for atypical hyperplasia or adenocarcinoma until further studies demonstrate the efficacy of this treatment.

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Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 40,000 cases to be diagnosed in 2007.¹ Seventy-five percent of endometrial cancers are the endometrioid histologic cell type. This is the cell type also found in precancerous hyperplastic lesions of the endometrium. Hysterectomy is the recommended treatment for both atypical endometrial hyperplasia and endometrial adenocarcinoma.

While most endometrial cancers occur in postmenopausal women, 2–14% of cases occur in those less than 40 years of age.² Preserving fertility is often a priority for these women, and this requires uterine-



sparing treatment options. In such cases, progestins such as megestrol acetate and medroxyprogesterone acetate have been used to treat atypical endometrial hyperplasia and endometrial adenocarcinoma with some success.^{3,4}

More recently, the levonorgestrel-releasing intrauterine system has been suggested as an alternative uterine-sparing option, often with fewer side effects than oral progestins.^{5,6} We describe the case of a 41-year-old infertility patient with hysteroscopic biopsy-proven atypical endometrial hyperplasia that progressed to grade I endometrial adenocarcinoma during the 6 months that a levonorgestrel-releasing intrauterine system was in utero.

CASE

Our patient was a 41-year-old gravida 0 woman referred to the reproductive endocrinology and infertility clinic with a diagnosis of primary infertility. Her medical history was significant for polycystic ovarian syndrome with insulin resistance, hypertension, hyperlipidemia, and obesity (body mass index 33). Several years before presentation to our clinic, she had undergone hysteroscopic resection of endometrial polyps and was found to have concurrent complex endometrial hyperplasia without atypia. After 6 months of hormone treatment with oral Megace, hysteroscopic-guided endometrial sampling revealed no residual evidence of hyperplasia.

We subsequently assumed her care and treated her infertility with a cycle of in vitro fertilization and embryo transfer. This was unsuccessful, and the patient was planning to undergo transfer of remaining cryopreserved embryos when she was found to have a recurrence of endometrial polyps on ultrasonography. Embryo transfer was cancelled, and she was taken for a second hysteroscopic polypectomy with focused endometrial sampling and curettage. Pathology revealed complex endometrial hyperplasia with atypia.

Although she was counseled that the definitive treatment for this pathology is hysterectomy, the patient was interested in alternative treatment options that would preserve childbearing potential. The patient was not enthusiastic about taking megestrol acetate again, since she developed significant weight gain and mood lability on this medication in the past. After counseling regarding the limited data on the effectiveness of the levonorgestrel-releasing intrauterine system for endometrial hyperplasia, the patient elected to proceed with levonorgestrel-releasing intrauterine system placement.

Three months after placement, the patient was seen in follow-up and reported regular, light menses and no side effects. Transvaginal ultrasonography revealed a hyperechoic endometrial lining measuring 9 mm in thickness. If the lining had thinned after 3 months, the plan had been to resample the endometrial lining and remove the levonorg-

estrel-releasing intrauterine system once the hyperplasia had resolved. Since the 9-mm lining was thicker than we had hoped, the decision was made to leave the levonorgestrel-releasing intrauterine system in place and re-image in 3 months. Unfortunately, repeat transvaginal ultrasonography 3 months later revealed a secretory endometrium measuring 12 mm. Again the patient reported regular, light menses. Because of the increased thickness of the lining, Pipelle endometrial biopsy was done at that visit with the levonorgestrel-releasing intrauterine system in place. Pathology returned showing International Federation of Gynecology and Obstetrics classification grade I endometrial adenocarcinoma.

The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with staging, as recommended by our gynecologic oncologists. Pathology review of the specimen revealed stage Ib grade I endometrial adenocarcinoma. Postoperative course was uncomplicated. The patient and her husband have two cryopreserved embryos that may be used in the future with the assistance of a gestational carrier.

COMMENT

In patients desiring future childbearing with a diagnosis of atypical endometrial hyperplasia or grade I endometrial cancer, alternative treatment options to hysterectomy are necessary. Oral progestins have been studied and shown to be a safe, and usually effective, alternative. Randall and Kurman³ examined oral progestin treatment of atypical hyperplasia in 17 women and noted complete histologic regression of the atypical hyperplasia in 16 of 17. In another study, 13 women aged 23–40 years with a diagnosis of grade I endometrial carcinoma were treated for at least 3 months with oral progestins. The patients were followed for an average of 18 months. Mean response time was 3.5 months for complete histologic regression. Six of the 13 were found to have a recurrence of disease, and three of those six had a histologically complete response to a second course of progestins.⁴

While oral progestins may be successful in treating most cases of atypical endometrial hyperplasia, undesirable side effects and the question of adequate oral dosing in morbidly obese women suggest the need for a local delivery system. Limited recent literature supports the use of the levonorgestrel-releasing intrauterine system as such a delivery system. One case series followed eight women with atypical hyperplasia who were treated with the levonorgestrel-releasing intrauterine system for 12 months. Follow-up ranging from 14–90 months revealed complete regression of hyperplasia in all but one patient.⁵

Importantly, other case reports suggest that the levonorgestrel-releasing intrauterine system is not al-



ways successful in treating these precancerous and cancerous lesions. In one case series, the levonorgestrel-releasing intrauterine system was used to treat one patient with atypical endometrial hyperplasia and two patients with adenocarcinoma because they were poor surgical candidates. The levonorgestrel-releasing intrauterine system was in place for 6 months for all three patients, and follow-up sampling revealed complete regression in the patient with hyperplasia, but persistence of adenocarcinoma in the remaining two patients.⁶ A different case series that looked at 6–36 months of levonorgestrel-releasing intrauterine system treatment for early endometrial cancer noted that one patient had complete histologic regression of disease within 6 months while the remaining three patients had persistent disease at 6, 12, and 18 months respectively.⁷

We describe the case of an infertile, obese woman with polycystic ovarian syndrome in whom careful hysteroscopic-guided biopsy at the time of polypectomy showed atypical endometrial hyperplasia. Despite treatment with the levonorgestrel-releasing intrauterine system for 6 months, follow-up revealed progression of her lesion to grade I endometrial adenocarcinoma. Although other studies have shown promising results for treating atypical hyperplasia with the levonorgestrel-releasing intrauterine system in those desiring uterine preservation, in this case the precancerous hyperplastic lesion apparently progressed to a cancerous one.

Alternatively, this case may be an example of the difficulty inherent in differentiating the spectrum of hyperplastic endometrial lesions under the microscope. As an example of this, a cohort study looked at 289 community hospital–diagnosed specimens of atypical endometrial hyperplasia and asked for a consensus diagnosis from three gynecologic pathologists. Twenty-nine percent of the specimens actually showed evidence of endometrial carcinoma, and hysterectomy specimens revealed concurrent endometrial carcinoma with atypical endometrial hyperplasia in 43% of the 289 cases. Because biopsy or curettage may not sample the entire endometrial cavity, hysteroscopic-guided biopsy may decrease the possibility of missed diagnoses.⁸ Although in our case the endometrium was well-sampled during hysteroscopy and therefore most likely represents true disease progres-

sion, it is possible that our patient's adenocarcinoma may represent a failure of pathologic diagnosis.

There is undoubtedly a role for uterine-sparing treatments for atypical endometrial hyperplasia and, perhaps, well-differentiated adenocarcinoma, particularly in those patients who are poor surgical candidates or who desire future childbearing. At this time, however, there are no randomized controlled trials comparing the levonorgestrel-releasing intrauterine system with oral progestins for the treatment of these lesions, and variability in diagnosis is an important reality. As the incidence of obesity continues to rise, and older women increasingly seek infertility treatment, there will be an increase in the diagnosis of endometrial hyperplasia and adenocarcinoma in patients such as ours. Thus, while the levonorgestrel-releasing intrauterine system may prove to be a viable treatment option for some patients, until further studies demonstrate its efficacy in treating atypical endometrial hyperplasia and adenocarcinoma, we cannot recommend its use for treatment of these lesions.

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Extrapulmonary Tuberculosis in Pregnancy Masquerading as a Degenerating Leiomyoma

Andrea R. Moore, MD, Francesca M. Rogers, MD, Donovan Dietrick, MD, and Samuel Smith, MD

BACKGROUND: Tuberculosis (TB) is an increasingly common infectious complication of pregnancy. The diagnosis of extrapulmonary TB in pregnancy is hampered by many factors and thus often delayed, and that has the potential of increasing morbidity and mortality.

CASE: This case involves a gravida with extrapulmonary TB, which was originally diagnosed as a degenerating leiomyoma. Diagnosis did not occur until lesions were discovered and biopsied at the time of cesarean delivery.

CONCLUSION: With proper identification, diagnosis, and treatment of pregnant women infected with all types of tuberculosis, the morbidity and mortality can be significantly decreased for mother and infant, and a public health emergency can be prevented.

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Worldwide, tuberculosis (TB) infects approximately 646 million women, and it is responsible for more than 1 million female deaths annually.¹ Tuberculosis was once believed to be controlled in the United States as a result of effective antituberculosis drugs, which resulted in a steady annual decline in the number of TB cases reported between 1953 and 1984.² According to the Centers for Disease Control and Prevention (CDC), however, a 20% increase in the number of reported cases of TB occurred between 1985 and 1992.³ This resurgence in the late 1980s was attributed to the human immunodeficiency virus (HIV) epidemic, immigration from countries with high rates of TB, transmission in congregate settings such as prisons, the deterioration of public health services previously in place to treat TB, and the development of multi-drug resistant-TB.

More than 90% of new active TB cases arise in

patients with a prior latent TB infection.⁴ Furthermore, the prevalence of extrapulmonary TB is increasing worldwide, likely secondary to its frequent associated comorbidity with HIV. Several recent U.S. series have reported a high frequency of extrapulmonary disease in recent nonwhite immigrants.⁵ It is important that today's health care providers maintain proficiency in recognizing, diagnosing, and treating all types of TB. We, herein, report a case of extrapulmonary TB masquerading as a degenerating fibroid.

CASE

A 36-year-old woman (gravida 2, para 1) registered at 11 weeks of gestation. Her prenatal course was unremarkable with normal routine blood work except for a hematocrit of 30%, consistent with her 2-year history of diagnosed iron deficiency anemia. The patient denied any significant medical or surgical history. Her obstetric history was complicated by an induced termination at 25 weeks of gestation secondary to lethal cardiac anomalies. The patient has lived in the United States for 10 years, having immigrated from Ethiopia. Her last visit to Ethiopia was 3 years before registration. A purified protein derivative (PPD) test was not performed at initial evaluation. Ultrasonography at 11 weeks of gestation was normal except for a right fundal fibroid measuring 5 cm.

At 19 weeks of gestation, the patient reported a 2-day period of waxing and waning febrile illness (39.7°C) and abdominal pain at home. Outpatient evaluation during this time revealed appropriate fetal growth, eutermic maternal state, normal maternal white blood cell (WBC) count, and the previously confirmed anemia. Ultrasonography was normal except for an unremarkable 5-cm fibroid. Diagnosis and treatment centered on nonsteroidal anti-inflammatory drug pain control for a possible degenerating fibroid. The patient, however, continued to report intermittent fevers accompanied by lethargy and abdominal pain.

The patient was hospitalized at 28 weeks of gestation secondary to unresolved generalized abdominal pain, back pain, nausea, vomiting, and fever. Admission lab work was significant for marked leukocytosis (WBC of 26.0×10^9) and anemia with hematocrit of 27%. The hospital course was complicated by temperatures between 33.5°C and 39.2°C, mild hypoxemia (87–90% pulse oximetry), symptomatic anemia (hematocrit of 20%), and ultimately a relative leucopenia (WBC 7.0×10^9). The patient received multidisciplinary consults, including maternal-fetal medicine, neonatology, infectious disease, hematology, gastroenterology, and general surgery. Extensive workup revealed the following results: blood and urine culture results were negative, a ventilation-perfusion (V/Q) scan was low probability, an abdominal ultrasound examination was negative, and an amniocentesis demonstrated only leukocytosis. Significant results included positive stool hemocult and right upper lobe pneumonia on chest radiograph. Further imaging, including a magnetic resonance imaging, was

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deferred until postpartum because of the patient's refusal due to her perception of potential fetal harm. The patient received 3 units packed red blood cells (PRBCs) and antibiotics for atypical pneumonia. The patient's obstetric status remained stable throughout the hospital course, and the patient improved clinically. She was discharged home on nonsteroidal anti-inflammatory drugs for an unchanged diagnosis of a degenerating fibroid and resolved pneumonia. Results of a PPD test, placed on the day of discharge, were negative.

The patient returned again at 32 weeks of gestation with unrelenting severe abdominal pain, back pain, and repetitive fevers up to 40°C. Admission evaluation revealed a temperature of 38.3°C and generalized abdominal tenderness. Laboratory results were again significant for marked leukocytosis, hematocrit of 27%, and negative blood and urine cultures. Maternal-fetal medicine, infectious disease, neurology, and critical care consults were obtained during this admission secondary to hectic temperatures, mild hypoxemia, leucopenia, and severe anemia (hematocrit 16%). The patient was transferred to the intensive care unit (ICU) and received 3 units PRBCs and 1 unit of fresh frozen plasma in preparation for surgery. She was delivered at 32 weeks of gestation via primary cesarean secondary to complete breech presentation, severe anemia, and the suspected maternal development of severe inflammatory response syndrome.

The patient delivered a vigorous female newborn, 1,790 grams, that required only brief bag mask ventilation and transfer to the neonatal ICU. Intraoperative findings revealed several uterine leiomyomata and large, distorting masses on the cecum and transverse colon along with extensive paraaortic and mesenteric lymphadenopathy. Intraoperative gynecologic oncology consultation was obtained, and several biopsies were taken of the mesenteric lymph nodes and sent for frozen section. The placenta was sent to pathology. The patient received 2 units PRBCs and 1 unit of fresh frozen plasma intraoperatively and was transferred to the ICU. The results from the frozen specimens returned as necrotizing granulomatous inflammation suggestive of TB. In the ICU, bronchial brushing and sputum stain results were positive for acid fast bacilli. Initial specimens were sensitive to streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide. There were no bacilli noted in the placenta. The patient received the diagnosis of pulmonary and intestinal TB. She was placed on acid fast bacilli contact isolation and started on rifampin, ethambutol, isoniazid, pyrazinamide, and pyridoxine. Lab work normalized, and the patient showed clinical improvement with resolution of fever. She was discharged home on postoperative day 6 on the anti-TB regimen to follow up with her obstetrician and infectious disease consult. The patient's newborn was not found to be infected and only isoniazid prophylaxis was initiated. The patient and her newborn's treatment course were followed up by the health department. A total of 12 weeks had passed from the date of first symptomatic presentation to diagnosis.

COMMENT

The diagnosis of active TB in pregnancy is often hampered by a low index of suspicion, as in this report. This problem is compounded when the disease is extrapulmonary, as it is in 20% of cases.⁵ Extrapulmonary TB has been shown to be associated with fetal complications such as fetal growth restriction, low Apgar scores, preterm delivery, and occasionally perinatal mortality. A recent series of 13 patients who developed TB in pregnancy noted a 7-week delay in diagnosis from the onset of symptoms.⁵ This delay was felt to be due to multiple factors including nonspecific symptoms such as lethargy, the absence of cough in extrapulmonary cases, the tendency to defer radiologic evaluation in pregnancy, and the reluctance to use biopsy and surgery to establish diagnosis. It is also known that the PPD skin test result is negative in 10–25% of patients with active disease. In addition, a recent study found a significant increase in obstetric morbidity and perinatal mortality in patients whose treatment was started late in pregnancy.⁶

A positive PPD screen during pregnancy is evaluated by chest X-ray after appropriate abdominal shielding of the gravid uterus. Pulmonary TB is characterized by an inflammatory reaction in lung parenchyma and draining lymph nodes (the primary, or Gohn, complex). Progression to these lesions is associated with coughing in 77% of patients, as well as with hemoptysis, weight loss, anorexia, and night sweats. Chest X-ray usually shows active disease with the presence of hilar adenopathy, multinodular infiltrates, cavities in the upper lobe (cavitation), or upward medial retraction of hilar markings.⁷ With positive chest X-ray findings, three sputum samples must be collected on three separate occasions, 8 to 24 hours apart, and sent for tissue sample smear and culture to identify acid fast bacilli. Identification and sensitivities of organisms in culture may take up to 4–6 weeks. With tailored laboratory work and specific imaging, the diagnosis of TB should become more apparent.

There are many diagnoses that must be considered when a pregnant woman presents with nonspecific symptoms of fever, nausea and vomiting, lethargy, abdominal distension, and altered mental status. Those etiologies that can cause an increase in maternal and fetal morbidity and mortality and those presenting with acute illness and pain should be in the forefront. Differential diagnoses include preeclampsia, appendicitis, cholecystitis, ectopic pregnancy, pancreatitis, and placenta abruption. In addition, ex-



trapulmonary TB and degenerating fibroids should be considered high on this list.

Fibroids often enlarge during pregnancy, due to complex mechanisms, and thus require an increased blood supply. Although they are usually asymptomatic, they may cause symptoms due to degeneration caused by hemorrhagic infarction. In mild cases, the patient may only note pelvic fullness or pressure, constipation, lower back pain, or leg pains as the fibroid compresses adjacent structures. In more severe cases, degeneration may be accompanied by severe pain, low-grade fever, leukocytosis, and even symptoms of anemia (fatigue and weakness), as seen in this case report. Uterine fibroids may be associated with a number of obstetric complications such as preterm labor, placental abruption, fetal malpresentation, obstructed labor, cesarean delivery, and postpartum hemorrhage.⁸

The identification and treatment of persons who have active TB remain the first priority in controlling the spread of this disease.³ As it is known that the household remains the primary arena for spread of disease, it is imperative that high-risk persons, as well as their family, have proper evaluation to avoid a public health emergency. Should a pregnant woman become diagnosed with TB, proper treatment with chemotherapy will ensure an excellent prognosis for mother and baby. Several studies have confirmed no adverse affects of pregnancy, birth, the postpartum period, or lactation on the course of TB in women receiving chemotherapy. Neither tuberculin nor the

Bacillus Calmette Guérin vaccine are treatments for tuberculosis, but they play an important role in the management of TB. To date, Bacillus Calmette Guérin vaccine is the most effective means of preventing TB in pregnancy. Vaccination should occur immediately after birth in areas of the world where TB is common. The use of live vaccines during pregnancy, moreover, is not recommended. Until antepartum TB surveillance becomes the standard of care, screening and treatment of high-risk pregnant women should help facilitate the diagnosis of active TB in pregnancy.

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Symptomatic Enterocoele

An Unusual Presentation of Chylous Ascites and Lymphoma

Renée M. Ward, MD, and Charles R. Rardin, MD

BACKGROUND: Chylous ascites is a rare phenomenon caused by extravasation of chyle from the lymphatic system. In Western countries, the majority of adult cases are due to occlusion of the lymphatics secondary to a lymphoma or other malignancy.

CASE: A middle-aged woman with reports of fecal urgency, incomplete bowel evacuation, and recurrent pelvic organ prolapse presented for surgical correction of a posterior vaginal defect. During the repair, a sac filled with milky white fluid was found ventral to the rectum. Further dissection revealed a large enterocoele filled with chylous ascites. Postoperatively, diffuse lymphadenopathy was detected by computed tomography imaging, and a biopsy confirmed follicular lymphoma.

CONCLUSION: Repair of symptomatic pelvic organ prolapse revealed underlying chylous ascites and lymphoma. Ascites may have exacerbated underlying support defects in the pelvic floor.

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Chylous ascites is a rare condition occurring in approximately 1 of every 20,000 hospital admissions.¹ Its prevalence may be increasing due to longer survival times for patients with lymphoma and more aggressive thoracic and retroperitoneal surgery, during which injury to the lymphatic system may occur.² It is usually diagnosed by its characteristic milky white appearance and high triglyceride content. In Western countries, lymphoma is the most common cause among adults, although any malignancy that partially occludes the lymphatics can cause chylous ascites. Nonmalignant causes include a variety of

inflammatory conditions and other disorders that lead to increased lymphatic pressure. Congenital anomalies or direct trauma to the lymphatics can also cause chyle to collect in the abdominal cavity.² In all cases, treatment should be based on treating the underlying condition.

We present a case of recurrent pelvic organ prolapse in which chylous ascites was encountered during a posterior colporrhaphy. Since ascites can exacerbate abdominal defects and cause symptomatic hernias, it is possible that ascites accentuated pelvic floor defects in this case.

CASE

A middle-aged multiparous woman presented with reports of fecal urgency and recurrent pelvic organ prolapse. She had undergone a total vaginal hysterectomy followed by a retropubic needle suspension 30 years prior. Nearly 2 years ago, she underwent a bilateral sacrospinous ligament fixation and anterior colporrhaphy with porcine dermis. Subsequently, she developed a recurrent vaginal bulge as well as fecal urgency. She reported as many as six stools daily, as well as a sensation of incomplete bowel evacuation. Despite multiple dietary changes, the symptoms persisted. She denied splinting or anal incontinence. Her family history was only notable for brain tumors in her father and one sister.

On examination, the patient was mildly obese. There was an eroded polyester suture in the right vaginal apex. Pelvic organ prolapse quantification measurements³ documented a stage I cystocele (Aa, Ba: –1.5), stage I vaginal vault prolapse (C: –5 cm, total vaginal length: 7.5 cm), and a stage III rectocele (Ap, Bp: +2 cm). Digital rectal examination confirmed a defect in the rectovaginal septum. There was good anal sphincter tone. An outpatient cystoscopy was performed, revealing no suture erosions into the bladder. At that visit, the eroded vaginal suture was removed, and the patient was scheduled for a posterior colporrhaphy. Preoperative labs included a complete blood count, electrolytes, and a hepatic panel. These revealed mild lymphocytopenia (20.4% lymphocytes, normal 24–44%) and a mildly increased aspartate aminotransferase of 33 international units/L (normal 12–30), but were otherwise normal.

In the operating room, during the dissection for the posterior repair, nonviscous, milky white fluid began to weep from the posterior defect. Further dissection revealed an opaque white sac adjacent to the rectum, which was fluctuant and reducible. There was no communication with the rectum or the region of the prior vaginal suture erosion. The patient had no signs or symptoms of infection preoperatively, and the fluid was not purulent. No mass was palpable. After extensive dissection, it was apparent that the sac was an enterocoele. Upon sharp entry, 200 mL of chylous ascites was released. Intraperitoneal cultures and washings were obtained. The enterocoele was repaired, and

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a site-specific posterior colporrhaphy was performed with good restoration of vaginal support.

Postoperatively, multiple serum laboratory tests and computed tomography scans of the chest, abdomen, and pelvis were ordered to assist in identifying the underlying cause of the chylous ascites. Postoperatively, the hematologic, metabolic, and hepatic panels, lipase, amylase, albumin, protein, cholesterol, and triglyceride levels were all normal. The computed tomography scan revealed extensive lymphadenopathy with pathologically enlarged nodes (more than 1 cm) in the left axilla, mesentery, paraaortic region, and bilateral iliac and inguinal areas. The largest area of disease was a conglomeration of lymph nodes at the root of the mesentery measuring 9.3 cm in diameter (Fig. 1). There was a small amount of intraperitoneal fluid seen by the liver edge.

Intraoperative peritoneal washings were negative for malignancy, and the cultures showed no sign of infection. Subsequent biopsy of enlarged lymph nodes in the left groin confirmed a grade II/III follicular lymphoma. The patient

has opted for chemotherapy and is currently doing well, with no evidence of disease 12 months out from her diagnosis.

COMMENT

Chylous ascites is a manifestation of an underlying disease, rather than a disease in and of itself, and identification of the cause is imperative. Press et al¹ reported a series of 28 cases of chylous ascites diagnosed at the Massachusetts General Hospital between 1960 and 1980. These patients had a poor overall survival, with a 50% fatality rate among adults at 3 months and 71% fatality at 12 months. The finding is less ominous among children since the majority of these cases are due to a congenital leak in the lymphatics, which is amenable to surgical correction. Despite medical improvements, the underlying pathology for the majority of adult cases of chylous ascites has a grim prognosis. In the presented case of indolent non-Hodgkin's lymphoma, there is a 78% 5-year and 51% 10-year survival rate, given this patient's stage and degree of nodal involvement.⁴

In this case, there were two pelvic floor defects: a rectocele and an enterocele. While enteroceles are common in patients with pelvic organ prolapse, it is possible that the presence of ascites exacerbated the enterocele in this case. Somewhat unique to this enterocele was its large size and distal location, theoretically consistent with ascites pooling at the most dependent portion of the enterocele sac, thus causing stretching and expansion of the peritoneum. Additionally, it is likely that there was more ascites present than seen at the time of surgery since the fasting state is known to decrease the volume of chylous ascites.¹ Furthermore, hernias are more common in patients with ascites. For example, 20% of patients with cirrhosis and ascites will develop umbilical hernias,⁵ and chylous ascites has been associated with recurrent umbilical, inguinal, epigastric, femoral, and obturator hernias.⁶ Perhaps ascites can aggravate defects in the pelvic floor as well.

This patient's initial lymphocytopenia was likely secondary to the chylous ascites. This has been reported in 47% of patients with chylous ascites. High concentrations of lymphocytes, chylomicrons, and proteins are present in chylous ascites, resulting in a depletion of these factors from the serum.¹

Interestingly, 26% of patients with chylous ascites are found to have steatorrhea.⁷ This may be due to lymphatic blockage preventing the uptake of dietary fats out of the gut lumen for transport to the liver and adipose tissue. This patient's presenting reports of

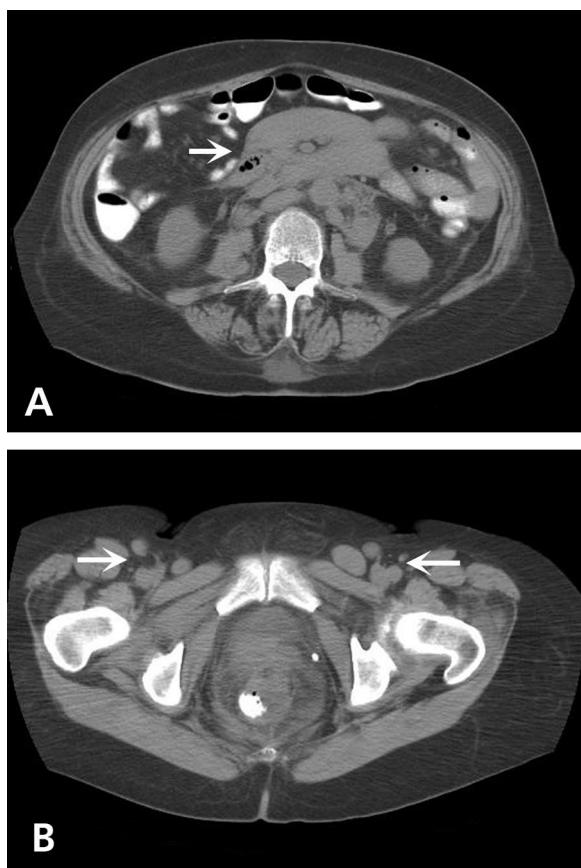


Fig. 1. Computed tomography scan of the abdomen and pelvis revealing diffuse lymphadenopathy. **A.** Conglomeration of lymph nodes at the root of the mesentery (arrow). **B.** Bilateral inguinal lymphadenopathy (arrows).

Ward. Chylous Ascites Presenting as an Enterocele. *Obstet Gynecol* 2008.



fecal urgency and incomplete evacuation were more consistent with steatorrhea than a symptomatic rectocele. Successful management of these symptoms was likely due to drainage of the ascites and chemotherapy, rather than the prolapse repair.

In this case, repair of symptomatic pelvic organ prolapse revealed underlying chylous ascites and lymphoma. In patients presenting with pelvic floor prolapse and a concomitant diagnosis of ascites, it is important to determine the underlying cause of the ascites. The ascites may exacerbate any enterocele that is present, as it exacerbates umbilical and groin hernias. Additionally, while defecatory problems and disorders of bowel function are associated with pelvic organ prolapse, they do not correlate with prolapse severity in the posterior compartment.^{8,9} A thorough evaluation for other factors contributing to a patient's defecatory symptoms is merited before undergoing a rectocele repair.

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Pulmonary Synovial Sarcoma Presenting as a Pneumothorax During Pregnancy

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BACKGROUND: Synovial sarcoma is a clinically rare, but morphologically well-defined neoplasm, which accounts for approximately 10% of all malignant soft-tissue tumors. The diagnosis can be established with clinical and imaging evaluations together with immunohistochemical, electron microscopy, and molecular genetic studies.

CASE: We describe a case of primary pulmonary synovial sarcoma presenting as a pneumothorax in a young woman at 34 weeks of gestation. Her persistent symptomatology ultimately led to a video-assisted thoracos-

copy and thorascopic decortication. The diagnosis was established by pathology and immunohistochemistry of the cells, which were consistent with primary pulmonary synovial sarcoma.

CONCLUSION: Malignancies, even those as uncommon as primary synovial sarcoma, should be considered in the differential diagnosis of pneumothorax during pregnancy. (*Obstet Gynecol* 2008;111:555-8)

Synovial sarcoma is a clinically rare but morphologically well-defined neoplasm, which accounts for approximately 10% of all malignant soft-tissue tumors, mostly arising in the paraarticular deep soft tissues of the extremities of adolescents and young adults.¹ This tumor has also been described in other anatomic locations such as the head and neck area, mediastinum, heart, abdominal wall, mesentery, retroperitoneum, and peritoneal cavity. Primary pulmonary synovial sarcoma is extremely rare, but recently the occurrence of this tumor is increasingly recognized due to the potent diagnostic tools in the form of immunohistochemistry and molecular genetics.²

CASE

A gravida 2, para 1, woman with an intrauterine pregnancy at 34 weeks of gestation presented with progressively severe shortness of breath, dyspnea, and left-sided chest pain that had persisted for about 1 month. She was anemic

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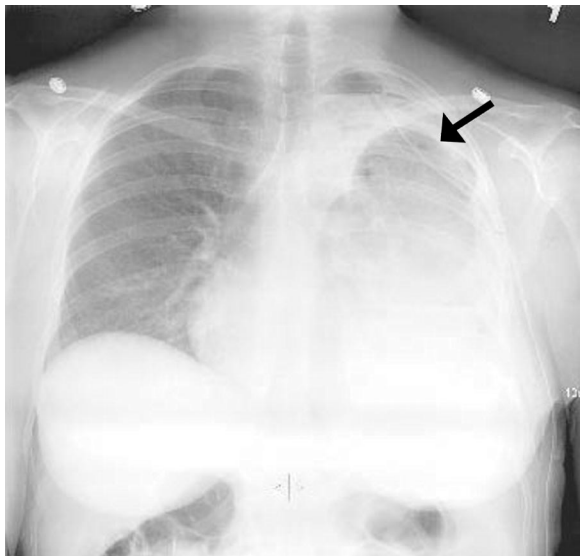


Fig. 1. Chest radiograph showing left-sided pneumothorax (arrow).

Esaka. Pneumothorax in Pregnancy. Obstet Gynecol 2008.

(hemoglobin of 8.7 g/L and hematocrit of 25.4%), but there were no other signs or symptoms of chronic disease. A chest X-ray revealed a left-sided apical pneumothorax occupying 60% of the left hemithorax with collapse of the lung to the base. The patient was a nonsmoker and had no history of a prior pneumothorax or any other underlying pulmonary disease. At presentation she was hemodynamically stable. There were no signs of fetal distress. An obstetric sonogram showed fetal growth at the 53rd percentile. The interventional radiology service was consulted, and a left pigtail chest tube catheter was placed for resolu-

tion of the pneumothorax. A repeated chest X-ray revealed an increased fluid density at the left lung base with a reduction of the apical pneumothorax.

Three days after the initial admission, the patient was transferred to our facility. Upon arrival, the patient was stable. Repeat chest radiography revealed a mass-like opacity of the left anterior aspect of the left thorax. The findings were felt to be suspicious for a neoplastic process such as lymphoma or sarcoma, metastatic disease, or an infectious process (Fig. 1). A computed tomography (CT) scan of the chest revealed a left pneumothorax with a significant complex mass, an infiltrate, and some areas of emphysema within the left lung. The patient was started on piperacillin/tazobactam 3.375 g intravenously every 6 hours as prophylaxis for a possible infectious process. Human immunodeficiency virus (HIV) screening and purified protein derivative antigen testing were negative.

On hospital day 3, a decision was made by the cardiothoracic surgery service to proceed with a video-assisted thoracoscopic surgery with thorascopic decortication, a procedure that further delineated the left-lung process. Before the thoracoscopy, the patient was transfused 2 units of packed red blood cells. The fetal status remained reassuring throughout and after the procedure.

Five days after the initial presentation at our facility, the pathologic evaluation revealed a poorly differentiated synovial sarcoma within the left pleural debris and no neoplasm from the visceral pleura or the parietal pleura biopsies. The tumor consisted of spindle cells in a fascicular growth pattern, while other areas had a more rounded morphology with increased mitotic activity (Fig. 2). The tumor was positive for the mesenchymal marker vimentin. Scattered and clusters of cells were positive for epithelial markers epithelial membrane antigen, AE1/3, CK7, CK56, and K903. This immunostain supported the above diagno-

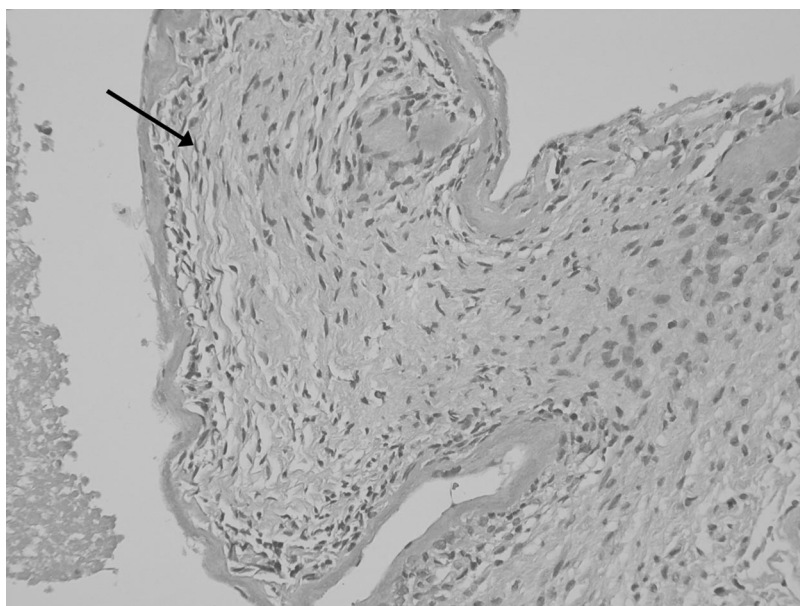


Fig. 2. Hematoxylin-eosin-stained lung biopsy specimen revealing the classic biphasic spindle cells (arrow) in a fascicular growth pattern (40× power).

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sis. The tumor was negative for neurogenic marker S-100 and calretinin, a mesothelial marker.

After review of the findings, early delivery was decided upon to proceed to definitive surgical treatment and subsequent adjuvant chemotherapy. Cervical ripening with cerividal was followed by oxytocin induction. The patient had a vacuum-assisted vaginal delivery after passive descent in the second stage of labor, resulting in delivery of a healthy 2,125-g male neonate.

Before discharge home on day 8, a chest CT scan was repeated that revealed a complex left pleural effusion and a minimal loculated pneumothorax. The patient underwent a left pneumonectomy and received adjuvant chemotherapy; she died 13 months after resection.

COMMENT

“Pneumothorax in pregnancy” and “primary synovial sarcoma” were surveyed via MEDLINE from 1980 to June 2007 in the English language and human literature.

Twenty-four cases have been reported. Most patients develop the pneumothorax in the third trimester, intrapartum, or immediately postpartum. Risk factors most commonly reported were an underlying respiratory infection, asthma, or a history of pneumothorax. Spontaneous pneumothorax is potentially serious for both the patient and the fetus, because any impairment in ventilation during pregnancy leads to hypoxia more readily than in the nonpregnant patient.

Both X-rays and CT scans of the chest may be used to assist in treatment decisions. In our case, the chest CT scan was particularly useful in defining the anatomic abnormality. Initial management is drainage with tube thoracostomy. Our neonatology consultants counseled the patient that the risk of delaying maternal treatment outweighed the risk of prematurity at 34 weeks of gestation. Delivery was therefore planned. Vaginal delivery is well tolerated.³ A cesarean delivery should be reserved for obstetric indications. The administration of epidural anesthesia with a passive second stage prevents increased intrathoracic pressure during the second stage of labor.⁴ Definitive treatment of the pneumothorax can be approached after delivery. The optimal time of treatment for maternal disease is during the second trimester, after the period of organogenesis and before the pregnancy is advanced. This is not always possible, as was demonstrated in our case; the patient presented at 34 weeks of gestation and required a left video-assisted thoracoscopy. The traditional approach to recurrent pneumothorax has been thoracotomy with bleb or bulla resection and pleurodesis. Starting more than a decade ago, thoracoscopy has increased as an alternative to thoracotomy.⁵

The clinical course of primary pulmonary sarcoma is largely unknown. Among malignant lung tumors, leiomyosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, fibrosarcoma, and hemangiopericytoma are common.⁶ Primary pulmonary synovial sarcoma is being increasingly recognized; Zeren et al⁷ reported 25 cases. Fifty-four cases have been reported in the English literature.

The patient population affected by this tumor ranges in age from 16 to 77 years without any predilection for either sex. In the 25 cases reported by Zeren et al,⁷ most patients had complaints related to pulmonary pathology such as chest pain, cough, hemoptysis, or shortness of breath. There was no predilection of this tumor for any particular side or lung segment. The tumor may also present as a parenchymal or endobronchial mass.

Special techniques, including clinical and imaging evaluations, immunohistochemistry, electron microscopy, and cytogenetics are often helpful in making the diagnosis of synovial sarcoma. Immunohistochemical staining patterns classically found in synovial sarcomas include S100 protein negativity and positivity for vimentin, cytokeratin, and epithelial membrane antigen. Our case was positive for vimentin, epithelial membrane antigen, AE1/3, CK7, CK56, and K903. Immunoreactivity for bcl-2 protein can be particularly helpful in separating synovial sarcoma from other possibilities in the differential diagnosis including leiomyosarcoma, malignant peripheral nerve sheath tumor, and fibrosarcoma. A highly consistent and specific chromosomal aberration, t(X; 18) (p11.2; q11.2), and its molecular sequence, the SYT-SSX fusion gene, are identified in more than 90% of cases of synovial sarcoma.⁸

The prognosis for patients with primary pulmonary synovial sarcoma is poor with an overall 5-year survival rate of 50%. Factors predicting a worse prognosis for patients with synovial sarcomas include tumor size (larger than 5 cm), male gender, older age (more than 20 years), extensive tumor necrosis, high-grade cellular changes, large number of mitotic figures (more than 10 per 10 high-powered fields), neurovascular invasion, and the identification of the SYT-SSX1 variant.⁹ The main poor prognostic factor is an inability to achieve a complete resection.

There is no standardized therapy. As with their soft tissue counterparts, surgical resection appears to be the treatment of choice for these tumors. Clear evidence of preoperative and adjuvant chemotherapy or radiotherapy efficacy is not reported in the literature as patients treated have been selected and not randomly assigned. However, patients who present



with incomplete resection, invaded margins, lymph node involvement, high-grade morphology, and large bulky tumors should undergo adjuvant chemotherapy using ifosfamide and doxorubicin.¹⁰ Metastasis is primarily via the hematogenous route, followed by lymph nodes and, in rare cases, by bone marrow. Malignancies, even those as uncommon as primary synovial sarcoma, should be considered in the differential diagnosis of pneumothorax during pregnancy.

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Catamenial Appendicitis

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BACKGROUND: Reproductive-aged women undergoing appendectomy for suspected appendicitis have twice the rate of negative histology as age-matched men. The reason for this discrepancy is unknown.

CASES: Three patients with peritoneal endometriosis and recurrent symptoms of acute appendicitis coincident with menses underwent resection of a noninflamed appendix with long-term symptom resolution. Standard pathological evaluation failed to demonstrate evidence of appendiceal endometriosis or appendicitis. Additional evaluation demonstrated a marked increase in number of

mast cells in the appendiceal muscularis compared with normal appendices.

CONCLUSION: The term “catamenial appendicitis” has been coined to describe these cases, and a mechanism of pathogenesis of right lower quadrant pain and nausea in patients with histologically confirmed endometriosis is proposed.

(*Obstet Gynecol* 2008;111:558–61)

Endometriosis is a common condition affecting up to 10% of the reproductive-aged women. Many patients with endometriosis experience pelvic pain with a significant decrease in quality of life.¹ At least two studies have confirmed clinical observations that the stage of endometriosis correlates poorly with the degree of dysmenorrhea or dyspareunia, although deep endometriosis and pelvic adhesions are independent predictors of pelvic pain.² The reason for this lack of correlation is unknown, but it may be related to the proportion of active disease.

Acute appendicitis is the most common intraabdominal condition requiring emergency surgery in the United States. A recent report described a discrepancy in the false-positive appendectomy rate between young reproductive women aged 11–30 years (44.2%) and men (21.3%).³ A previous study demonstrated a similar gender bias by using diagnostic laparoscopy to screen the gross appearance of clinically suspected appendicitis in women. The authors concluded that false positives might be partly explained by gynecologic

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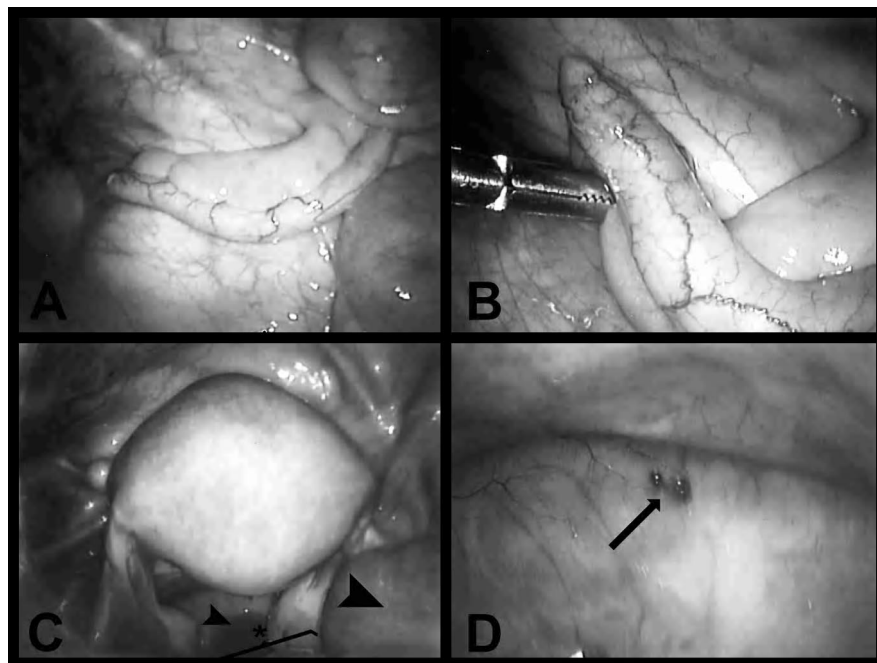


Fig. 1. Photographs of the initial diagnostic laparoscopy from case 1. **A.** Noninflamed vermiform pelvic appendix, elevated to pelvic brim. **B.** Tip of appendix removed from dependent peritoneal fluid. **C.** Cecum (large arrowhead) with appendix (asterisk bracket) draped into dependent peritoneal fluid (small arrowhead). **D.** Minimal peritoneal endometriosis (arrow) in posterior cul-de-sac.

Barrier. Catamenial Appendicitis. *Obstet Gynecol* 2008.

logic pathology such as hemoperitoneum, endometriosis/ovarian cysts (10%), and pelvic inflammatory disease (18%).⁴ “Negative laparoscopy” was reported in 32% of these patients.

CASES

We report three cases involving patients with peritoneal endometriosis and recurrent symptoms of acute appendicitis who underwent resection of a noninflamed appendix with long-term symptom resolution. Standard pathological clinical practice was to sample these normal-appearing appendices in three areas—base, mid-appendix, and ap-

pendiceal tip—and to place all samples in a single block. Step sections were not performed. These blocks were cut by microtome into 4-micron sections and stained using standard hematoxylin and eosin (H&E). None of these appendices had evidence of acute or chronic appendicitis or appendiceal endometriosis by standard H&E stain.

During a secondary exploration for evidence of pathological change in these appendices, increased numbers of mast cells were noted in the muscularis in H&E stained slides. Additional staining with toluidine blue confirmed the presence of significantly increased numbers of mast cells in the appendiceal muscularis in the cases compared with appendices from reproductive-aged females without endometriosis who underwent incidental appendectomy at the time of other surgery (Table 1).

The patient in case 1 is a 24-year-old, gravida 1 para 1, with a 4-month history of worsening right lower quadrant pain during and after menses. The pain was associated with significant nausea and anorexia; effective pain relief was accomplished only with daily narcotic therapy. Due to persistent, lifestyle-limiting pain, despite scheduled nonsteroidal anti-inflammatory medication and cyclic oral contraceptive pills (OCPs), the patient was offered diagnostic laparoscopy.

Intraoperative findings included minimal biopsy-proven endometriosis in the posterior cul-de-sac. The long, vermiform appendix was free floating in peritoneal fluid and was not removed (Fig. 1). Persistent postoperative nausea, anorexia, and right lower quadrant pain presented a diagnostic and therapeutic challenge. The persistence of her symptoms prompted a laparoscopic appendectomy 15 days later. The patient reported an immediate profound improvement in pain and has remained pain free 9 months after the appendectomy. Pathological evaluation of the appendix by

Table 1. Histological Appearance of Appendices and Patient Pain Scores

Case	H&E	No. of Mast Cells	Control	H&E	No. of Mast Cells
1	Normal	82	1	Normal	16
2	Normal	51	2	Normal	29
3	Normal	96	3	Normal	21
			4	Normal	22
			5	Normal	33
			6	Normal	45
Mean±SD		76±17			28±8

H&E, standard light microscopic clinical pathological evaluation of the appendix; SD, standard deviation.

None demonstrated any evidence of acute or chronic appendicitis, fibrosis, endometriosis or other gross abnormality. Mast cells in the muscularis mucosa of the appendix are measured as number of mast cells/10 400× high-power fields. The difference in mean numbers of mast cells between cases and controls is significant based on a one-tailed *t* test (*P*=.001).



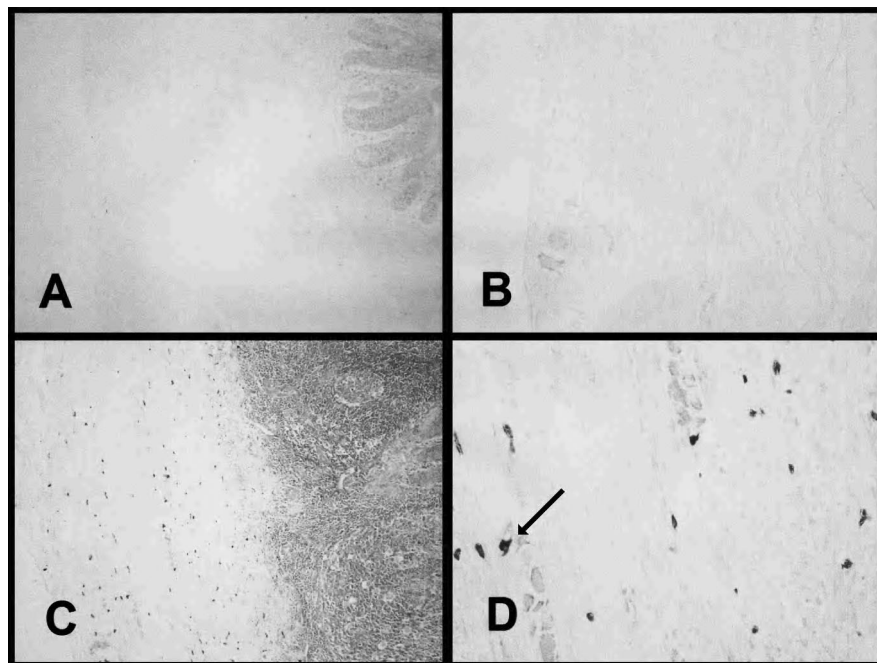


Fig. 2. Representative slides of appendices from case 1 and from an incidental appendectomy control. **A.** Toluidine blue stain of the control appendix at 100 $\times$. **B.** Toluidine blue stain of the control appendix at 400 $\times$ (high power). **C.** Toluidine blue stain of the appendix from case 1 at 100 $\times$. **D.** Toluidine blue stain of the appendix from case 1 at 400 $\times$. Note the many mast cells (arrow) seen in the muscularis of patient 1's appendix.

Barrier. Catamenial Appendicitis. Obstet Gynecol 2008.

H&E stain and light microscopy revealed no evidence of acute or chronic appendicitis, edema, fibrosis, or endometriosis. Interestingly, toluidine blue stain demonstrated 82 mast cells/10 400 $\times$ high-power fields (HPFs) in the appendiceal muscularis (Fig. 2). This finding was abnormally high when compared with incidental appendectomies from reproductive-aged females (Table 1).

The patient in case 2 is a 25-year-old nulligravida with a history of endometriosis proven during two previous laparoscopies. The first laparoscopy at age 19 was followed by 6 months of gonadotropin-releasing hormone agonist therapy, during which her pain resolved. After therapy, she was placed on a continuous OCPs but required subsequent laparoscopy at age 21 with ablation of minimal endometriosis. Her pain returned, and she was treated with danocrine for 1 year with little relief.

Worsening right lower quadrant pain and nausea prompted her to seek care 3 years later. Given her history, she was placed on 1 mg anastrozole and 20 mcg ethinyl estradiol/0.1 mg levonorgestrel daily for 6 months.

On follow-up, the patient demonstrated no improvement. We routinely utilize the McGill Pain Questionnaire in our clinical practice. Her McGill pain score demonstrated a pain rating index of 43. Subsequent laparoscopy demonstrated three brown endometriotic lesions that were sharply excised from the superficial bladder peritoneum. Her appendix was long, vermiform, and pale, with its tip located in 10 mL of clear ruby-colored free fluid in the posterior cul-de-sac. Laparoscopic appendectomy was performed. Hematoxylin and eosin stain and light microscopy revealed no evidence of acute or chronic appendicitis, edema, fibrosis, or endometriosis. Toluidine blue stain revealed 51 mast cells/10 HPFs in the appendiceal muscularis, a finding similar to case 1 (Table 1).

Appendectomy resulted in dramatic improvement in pain. At the time of reevaluation 8 weeks postprocedure, the patient's McGill pain rating index had decreased from 43 to 5 with resolution of all nausea and right lower quadrant pain. She continued on OCPs with nonsteroidal anti-inflammatory drugs and at 6 months postprocedure, her McGill score remained a 5, her greatest pain-free interval to date.

The patient in case 3 is an 18-year-old white female nulligravida with a history of biopsy-proven endometriosis. Her symptoms manifested at age 15 as right lower quadrant abdominal pain. The pain preceded menses, lasting 10–14 days. After ineffective treatment with continuous OCPs, she underwent diagnostic laparoscopy with uterosacral nerve ablation. Her cyclic right lower quadrant pain persisted and worsened. Over the next 2 years, multiple therapeutic modalities were tried, including pelvic physical therapy, antidepressant medication, injectable medroxyprogesterone acetate, propxoxyphene, and gabapentin; all with no significant improvement.

She presented with anorexia and right lower quadrant pain, which prompted laparoscopic appendectomy. At the time of surgery, a moderately long, uninfamed vermiform appendix was noted, as was peritoneal endometriosis. Pathological evaluation by H&E stain and light microscopy revealed no acute or chronic appendicitis, edema, fibrosis, or endometriosis. Toluidine blue stain revealed 96 mast cells/10 HPF in the appendiceal muscularis (Table 1).

Four weeks after surgery, the patient reported that her right lower quadrant pain had completely resolved for the first time in 3 years. Her preoperative McGill pain rating index score was 49, and postoperatively this decreased to 13, reflecting only minor central pelvic cramping.



COMMENT

This small case series illustrates a phenomenon in which symptoms of appendicitis, right lower quadrant pain, and anorexia become acute during menses. In each patient, these symptoms were associated with peritoneal endometriosis, a vermiform appendix, and notable dependent clear fluid in the posterior cul-de-sac. Symptoms always resolved following appendectomy.

In each of these cases, we noted increased numbers of mast cells in the appendiceal muscularis when compared with six incidental appendectomy specimens (Table 1). These specimens were obtained from a cohort of six reproductive-aged control patients undergoing incidental appendectomy at the time of other surgery over the past 3 years at our institution. This case report was not intended for or powered for statistical analysis. However, it is interesting to note that even with these low numbers of cases and controls, the data suggest a significant difference in mean mast cell numbers based on a one-tailed *t* test ($P=.001$).

One possible explanation for the presence of increased numbers of muscularis mast cells could be the presence of appendiceal ischemia with reperfusion. Experimental intestinal ischemia/reperfusion injury leads to a significant increase in the number of mast cells in the intestinal muscularis after 2 weeks of recovery, and the number increases over time.⁵ The mediators of such injury may be found in the peritoneal fluid of women with endometriosis.

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is a mildly acidic, lipid-soluble prostanoid; its vascular effects are well established and could contribute to ischemia of the vermiform pelvic appendix. Elevations of this prostanoid have been previously observed in the peritoneal fluid of patients with endometriosis compared with controls.⁶ The vasoconstrictive effects of $PGF_{2\alpha}$ occur via activation of a Ca^{2+} influx pathway which has properties consistent with those of a receptor operated channel, and at low concentrations, $PGF_{2\alpha}$ causes the release of intracellular Ca^{2+} stores.⁷ A lipid-soluble weak acid, $PGF_{2\alpha}$ is capable of crossing membranes to cause local vasoconstriction of small visceral vessels. We hypothesize that this mechanism or a related causation may be responsible for ischemia of the

pelvic vermiform appendices in our cases of patients with endometriosis and free peritoneal fluid. This series of events may then cause injury and cycle-dependent symptoms such as right lower quadrant pain and anorexia, thus mimicking acute appendicitis.

Despite the absence of neutrophilic infiltration in any appendices in our series, we refer to this constellation of findings as “catamenial appendicitis” because of the temporal relationship of the symptoms of classic appendicitis with menses. The entities common to all cases included 1) a vermiform appendix, histologically normal by standard H&E but abnormal by toluidine blue stain, in a patient with 2) a history of surgically confirmed endometriosis, and 3) symptoms of right lower quadrant pain and anorexia that 4) occurred in close proximity to the onset of menses. The findings of a pale appendix and increased number of smooth muscle mast cells raise the possibility that appendiceal ischemia/reperfusion injury may be causative. It is speculated that cyclic production of peritoneal fluid prostanoids or other vasoactive compounds by endometriotic lesions or retrograde menstruation could account for these changes.

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Luckenschadel Skull

A Forgotten Entity

Marguerite B. Vigliani, MD

BACKGROUND: Luckenschadel skull is an ossification disorder in which the fetal skull appears fenestrated. It is almost always associated with Chiari II malformation and meningomyelocele.

CASE: We report a case of fatal subgaleal hemorrhage occurring in a full-term infant with undiagnosed Chiari II malformation, meningomyelocele, and luckenschadel skull. A cesarean delivery was performed after attempted vacuum and forceps delivery for fetal distress.

CONCLUSION: Obstetricians should be aware that fetuses with antenatal diagnosis of neural tube defects could have luckenschadel skull. Questions are raised concerning the possible clinical significance of this anomaly, especially in the context of a vacuum delivery.

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Luckenschadel skull is an ossification disorder in which the fetal skull appears fenestrated. It is almost always associated with Chiari II malformation and meningomyelocele. A case is presented of a neonate with undiagnosed meningomyelocele, Chiari II malformation and luckenschadel or lacunar skull.

CASE

A 31-year-old woman (gravida 3, para 0) had a positive family history for anencephaly and Down syndrome. She was a smoker and did not take vitamin supplements before pregnancy. Despite counseling, she declined serum screening for prenatal diagnosis.

During the pregnancy, four ultrasonograms were performed, but no neural tube defect was identified. She presented at 39 weeks in advanced labor. The initial fetal heart rate (FHR) was reactive without decelerations, but after administration of a combined spinal-epidural anesthetic, she developed symptomatic hypotension treated with ephedrine. Within minutes the FHR showed deep and long early decelerations with each contraction, suggesting

head compression. These did not respond to oxygen, intravenous fluids, or changes in maternal position. Amniotomy showed meconium. After amniotomy the FHR worsened. Although the baseline FHR continued to show good beat-to-beat variability with accelerations, the magnitude of the decelerations was ominous.

Cesarean delivery was recommended, but the patient refused, requesting to push standing and squatting at the bedside as she was feeling rectal pressure. The FHR continued to deteriorate with each push, so a vacuum delivery was attempted. A Kiwi Omni Cup (Clinical Innovations, Murray, UT) was applied to the fetal head with the patient standing; the suture lines and the fontanelles were easily palpated, and the vertex was in the direct occiput posterior position at +2 station.

The infant's head descended easily to the perineum with the first traction, but the vacuum device popped off forcefully at the end of the contraction. Two further attempts at establishing suction were unsuccessful because the device slipped off with minimal traction. The patient was placed in lithotomy for delivery with what appeared to be the head crowning. Then, an episiotomy was performed. More caput appeared, but the FHR continued to deteriorate. An outlet forceps was attempted to expedite the delivery, but tense thickening of the caput was noted, and a good application of forceps could not be accomplished because sutures and fontanelles could no longer be felt.

An immediate low-transverse cesarean delivery was performed, and a 7-lb (3,175 g) female infant with a large gelatinous head and a meningomyelocele was delivered. The infant was depressed, with Apgar scores of 2, 2, and 5 at 1, 5, and 10 minutes after birth. Hypovolemic shock was diagnosed, and the infant was treated with blood products and pressors until death from disseminated coagulopathy and subgaleal hemorrhage at 63 hours of age.

Skull X-ray and computerized tomography (CT) showed luckenschadel skull. The CT (Fig. 1) also showed Chiari II anomalies as well as subdural, subarachnoid, and intraventricular hemorrhages. Multiple parenchymal punctate hemorrhages were also noted, with "possible bleeding from extensive vascular malformations." By ultrasonography, these were described as "punctate contusions" in the brain parenchyma.

COMMENT

Luckenschadel, also known as lacunar skull deformity or fenestrated skull, is a fetal cranial ossification disorder in which the skull is characterized by deep and shallow pits, or lacunae, in the membranous bones of the skull. Figure 2 shows a three-dimensional CT of luckenschadel, with clustering of lacunae in the hindbrain region. On X-ray luckenschadel has a characteristic honeycomb appearance, with large rounded areas of decreased density outlined by a weblike pattern of thicker bone (Fig. 3). This honeycomb appearance corresponds to the oval, rounded,

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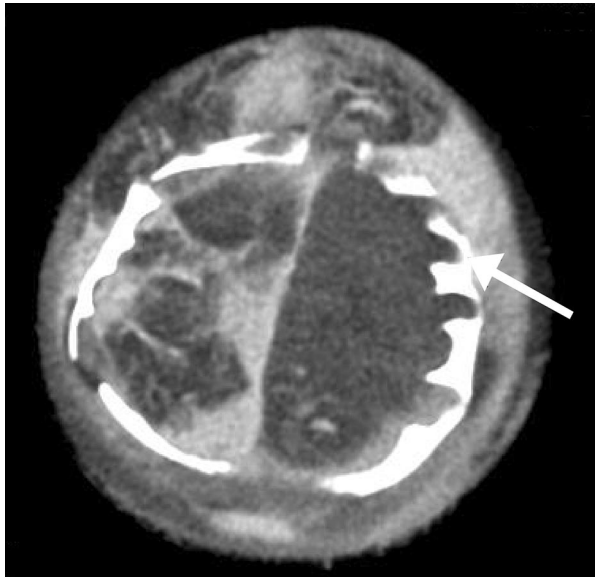


Fig. 1. Computed tomography scan of infant showing luckenschadel, as well as subgaleal hemorrhage and intracranial hemorrhages. The arrow points to a typical lacunar defect of the inner table (craniolacuna) seen in luckenschadel.

Vigliani. *Luckenschadel Skull. Obstet Gynecol* 2008.

or finger-like lacunae that are clearly seen at autopsy (Fig. 4).

When the defects involve only the inner table of bone and are not palpable from the outside of the skull, they are called craniolacunae. Craniofenestrae, however, are palpable and signify more full thickness involvement of the inner table and outer table. In the most severe cases, lacunar defects are covered only by a thin fibrous membrane, and the dura mater may be in direct contact with the periosteum. There may also be thinning of the dura and bulging of the brain and the arachnoid plexus into the bony defects.

Luckenschadel is not found in adults. It is primarily a calvarial development disorder found in fetuses with neural tube defects. Developmentally this anomaly is analogous to myelomeningocele in that there is failure of normal bone induction over the brain. Typical X-ray changes can be seen as early as 7½ months of gestation but begin to fade around the time of birth. In most cases, the radiologic findings are not recognizable by 4–6 months of age.

When X-ray pelvimetry was commonly used, obstetricians were more familiar with luckenschadel as evidenced by older reviews of the obstetric literature.^{1,2} Today luckenschadel is less often recognized because it is primarily a prenatal X-ray finding, and X-ray is rarely used in contemporary obstetric practice. It is possible that the “lemon sign,” which is the hallmark for first-



Fig. 2. Three-dimensional computed tomography scan showing craniolacunae (arrow). From Thamburaj AV. Craniosynostosis. Neurosurgery on the web. Available at: www.thamburaj.com/craniosynostosis.htm. Retrieved August 15, 2007.

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trimester fetuses with severe neural tube defects, is related to luckenschadel. Like luckenschadel, the “lemon sign” resolves in the third trimester.

Although luckenschadel has been reported in association with various congenital anomalies, genetic mutations, inborn errors of metabolism, maternal ingestions, and even in normal newborns, the strong association with spina bifida and meningocele is well established. Early radiologic case series reported an overall 40–60% incidence of luckenschadel among infants with neural tube defects, with a higher incidence associated with more severe lesions.^{3,4} These early case series included many older infants in whom X-ray changes might already have faded after birth. However, among newborns admitted with a diagnosis of meningocele, some degree of lacunar skull deformity is detectable by skull X-ray in 97%,⁵ by CT scan in 92%,⁶ and by neurosonography in 85.7% of cases.⁷ One case series identified luckenschadel by CT in every newborn admitted with a diagnosis of both meningocele and Chiari II anomaly.⁸ A number of authors^{3,5,7} have graded the severity of luckenschadel by X-ray or by CT or by both, but they have been unable to correlate the severity with other parameters.



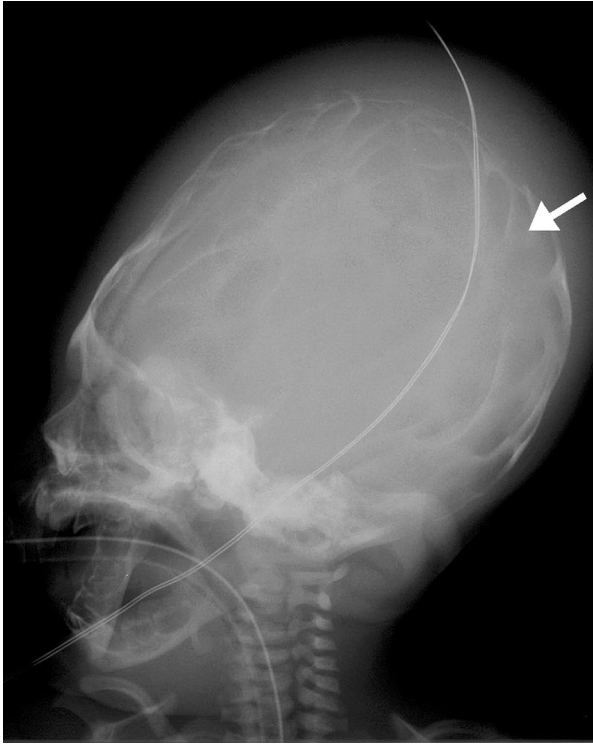


Fig. 3. Skull X-ray of infant showing swelling of the scalp as well as the characteristic honeycomb changes (arrow) seen with craniolacunae or luckenschadel skull.

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Review of the CT scan in this case (Fig. 1) shows severe full thickness cranial defects. In places there is the appearance of open pathways into the brain through the skull. It is possible that the fetal brain suffered compression during contractions leading to the development of FHR changes as soon as the baby's head engaged in the pelvis. Application of the vacuum to a skull with such severe cranial defects could result in the punctate parenchymal intracranial hemorrhages seen both by CT scan and ultrasonography and interpreted to be vascular malformations.

The fatal event in this case was the subgaleal hemorrhage complicated by coagulopathy and intracranial bleeding. Subgaleal hemorrhage is associated with vacuum deliveries,⁹ and the risk is increased when cup detachments occur and when the indication for the delivery is a nonreassuring FHR. Although standing at the bedside is not contraindicated for a vacuum extraction, it might have resulted in either inappropriate axis traction or in excessive force exerting on the fetal cranium from the combined effects of maternal expulsive efforts, vacuum on the scalp, traction toward the ground, and the effects of gravity. Finally, the second stage of labor lasted too long because

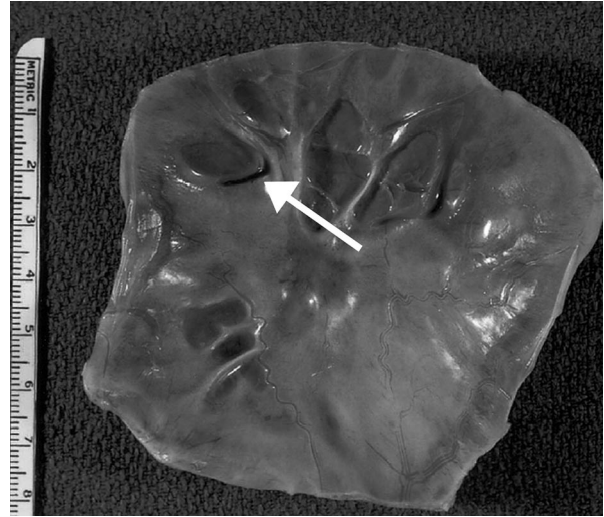


Fig. 4. Lacunar skull in a neonate with lumbar myelomeningocele (arrow). From Glass RB, Fernbach SK, Norton KI, Choi PS, Naidich TP. The infant skull: a vault of information. *Radiographics* 2004;24:507–22.

Vigliani. Luckenschadel Skull. *Obstet Gynecol* 2008.

the expanding hematoma was misinterpreted as progress and imminent delivery, causing further delay.

In fetuses with meningocele and Chiari II anomalies, there is controversy over the optimal method of delivery.¹⁰ If a vaginal delivery is chosen for a infant with meningocele, perhaps further imaging of the cranium should be considered before labor to determine the severity of lacunar skull deformity. Clinicians should be cautious before considering use of a vacuum extractor to assist a vaginal delivery in a fetus with luckenschadel.

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May-Thurner Syndrome Resulting in Acute Iliofemoral Deep Vein Thrombosis in the Postpartum Period

Kimberly D. Zander, MD, Barton Staat, MD, and Henry Galan, MD

BACKGROUND: May-Thurner Syndrome is a congenital anomaly of the right iliac artery, which causes an acquired narrowing defect in the left iliac vein. The artery abnormally compresses the vein causing intraluminal collagen deposition and sluggish venous flow. This syndrome places patients at increased risk of proximal deep venous thrombosis.

CASES: We describe three postpartum patients with May-Thurner Syndrome complicated by iliofemoral deep vein thrombosis and their management. There was no evidence of underlying thrombophilia, yet these women had large proximal thrombi. They were treated with anticoagulation followed by thrombolysis and, in one case, stent placement.

CONCLUSION: May-Thurner syndrome can predispose postpartum patients to large, proximal thrombi and may be treated effectively with a combination of thrombolysis and stent placement. May-Thurner Syndrome should be considered in the differential diagnosis of pelvic thrombosis, especially when thrombophilias are excluded.

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The relative risk of deep venous thrombosis (DVT) is increased fivefold during pregnancy and up to 20-fold higher during the postpartum period.¹ Commonly, postpartum thrombi involve the popliteal or femoral vein and are most often left-sided. However, less than 30% of patients complain of edema, calf discomfort, or pain with flexion. Deep venous thrombosis in the postpartum period may result in postphlebotic syndrome, decreased mobility, and rarely, catastrophic pulmonary embolism. May-Thurner syndrome is a congenital abnormality in which the right iliac artery abnormally overlies the left iliac vein, resulting in extrinsic compression of the vein. Compression, coupled with transmitted arterial pulsation, causes chronic irritation of the vein endothelium. The vein responds by depositing collagen and elastin at that site, forming a callus or “spur” (Fig. 1). We describe the clinical presentation and treatment of three women with May-Thurner Syndrome who experienced extensive pelvic and lower extremity thrombosis during the postpartum period.

CASE 1

After an uncomplicated antepartum and a normal vaginal delivery, a 23-year-old primipara presented 2 months postpartum with difficulty walking. Her left leg had become increasingly swollen, warm, and painful over the past 9 days. Additionally, she reported abdominal pain and chills since delivery. On physical examination, the left lower extremity was edematous, tender, and erythematous. Laboratory tests revealed an elevated white blood cell count with a left shift. Blood cultures were collected. A pelvic ultrasound examination showed a large clot in the left common iliac vein and pelvic sidewall tributaries. Duplex Doppler revealed thrombosis from the iliac vein to the popliteal branch of the femoral which was noncompressible.

Heparin was started and interventional radiology consulted. After blood culture results were negative for 24 hours, mechanical thrombectomy was performed. The left popliteal vein was accessed under direct ultrasound guidance, and hard thrombus occluding the left common iliac vein was traversed with a Hy-wire. Next, multiple passes were made with the Angiojet (Possis, Minneapolis, MN) mechanical thrombectomy device, leaving multiple areas of retained wall thrombus and stenosis in the left common iliac, external iliac, and femoral vein. Those areas were treated with high-pressure balloon angioplasty. Sluggish



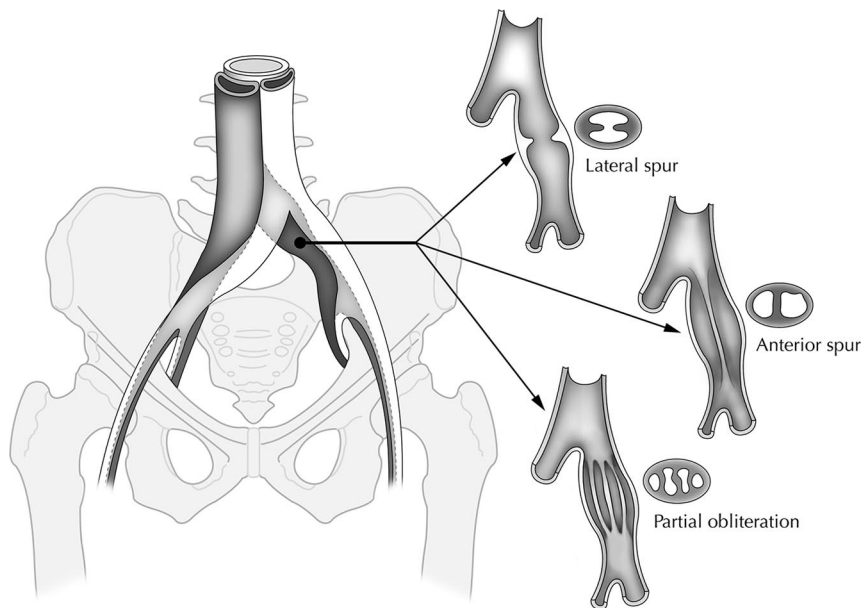


Fig. 1. Schematic diagram showing the relationship of the left common iliac vein and right common iliac artery. The compression results in development of the spur. Reprinted from Patel NH, Stookey KR, Ketcham DB, Cragg AH. Endovascular management of acute extensive iliofemoral deep venous thrombosis caused by May-Thurner Syndrome. *JVIR* 2000;11:1297–1302. Copyright 2000, with permission from Elsevier Zander. *May-Thurner Syndrome. Obstet Gynecol* 2008.

antegrade flow and irregular vessel borders indicated persistent retained thrombus, thus an infusion catheter was placed from the common iliac to the common femoral vein. Tissue plasminogen activator was administered in the intensive care unit overnight, and a repeat venogram was completed 24 hours later. At that time, flow was reestablished in the common iliac vein revealing a defect in flow at the origin of the vessel, consistent with May-Thurner Syndrome. The patient began bleeding around the catheter site and further intervention was halted. Extensive clot remained in the inferior vena cava, extending to the level of the renal veins.

CASE 2

A 28-year-old primipara presented 11 days after a vaginal delivery with left lower quadrant pain, increased with movement. Her vital signs were normal and the physical examination was unremarkable. She was thought to have musculoskeletal pain secondary to increased activity, and ibuprofen was recommended. The next day she returned to clinic with asymmetric swelling and numbness in her left leg, fever, and a tender left inguinal adenopathy. Initial workup in the hospital revealed an elevated white blood cell count and extensive septic pelvic thrombophlebitis on computed tomography scan. Due to a high clinical suspicion of thrombus, a heparin load of 80 units/kg was given intravenously, followed by an 18-units/kg/h drip with a goal partial thromboplastin time of 60–90 seconds. A few hours later, Doppler ultrasonography showed complete occlusion of the common femoral vein without compressibility or Doppler flow.

Interventional radiology physicians performed a venogram with mechanical thrombectomy, venoplasty, and thrombolysis. Thrombus was visualized from the bifurca-

tion of the inferior vena cava to the mid common femoral vein. Critical stenosis at the origin of the left common iliac vein was consistent with May-Thurner Syndrome (Fig. 2). The patient was transferred to the intensive care unit for 24 hours of alteplase therapy through an indwelling popliteal catheter. Alteplase, a tissue plasminogen activator, binds to the fibrin in a thrombus and converts the plasminogen to plasmin. A repeat venogram demonstrated poor flow through the common iliac vein and well-developed collateral vessels, and tissue plasminogen activator therapy was continued for an additional 6 hours. Then she underwent repeat mechanical thrombolysis and deployment of an



Fig. 2. Ascending iliac venogram (case 2) demonstrating poor proximal left iliac vein flow (thin arrow) and well developed collateral blood flow (thick arrow).

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implantable metallic stent across the common iliac vein. Therapeutic dalteparin, warfarin 5 mg, and baby aspirin were started after the procedure, and the patient went home the following day. Anticoagulation with dalteparin was continued until her international normalized ratio was therapeutic on warfarin. Results of a thrombophilia evaluation, including anticardiolipin antibodies, β_2 glycoprotein, antithrombin III, factor V Leiden, prothrombin G20210A mutation, were negative.

CASE 3

A 20-year-old multipara with a history of May-Thurner syndrome and DVT was referred to our high-risk obstetric clinic at 23 weeks of gestation. In a previous pregnancy, she had left iliac DVT, was later delivered by cesarean delivery, and then took warfarin for 6 months postpartum. Unfortunately, she had a second left-sided DVT shortly after discontinuing anticoagulation. During the index pregnancy, she was anticoagulated with enoxaparin 1 mg/kg subcutaneously every 12 hours until 35 weeks of gestation when she was switched to therapeutic unfractionated heparin (14,000 units subcutaneously twice daily) in preparation for delivery. At term, she desired a repeat delivery, and her unfractionated heparin was discontinued for 1 day in preparation. She was therapeutically anticoagulated, again at 14,000 units subcutaneously twice daily postpartum. On postoperative day 2 she had increased perineal incision pain, and a superficial wound hematoma was diagnosed. A venogram was planned for 6 weeks postpartum.

COMMENT

May-Thurner Syndrome is a congenital anomaly of the left iliac vein, resulting from extrinsic compression by an aberrant overlying right iliac artery predisposing to thrombosis. It was first described in 1957 by May and Thurner, who found this anatomic anomaly in 22% of autopsy specimens.² Chronic compression and pulsation transmitted from the overlying iliac artery causes endothelial irritation and extensive intimal hypertrophy in the iliac vein (Fig. 1). Histologically, these lesions are composed of collagen and elastin, not recanalized clot or inflammatory cells. Lateral, anterior, and web-like lesions can occur.³ In the model of Virchow's triad, this partial obstruction creates venous stasis, and vascular (endothelial and intimal) damage, which together with the thrombogenic state of pregnancy increases the risk of iliofemoral deep venous thrombus. Chronic thrombi lead to venous outflow obstruction, valvular incompetence, and subsequently clinical symptoms.

Up to 5% of patients undergoing evaluation for lower extremity venous disorders have May-Thurner syndrome, and three of every four patients affected

are women.⁴ Ilio-femoral DVT comprises 20% of DVTs. Of those with iliofemoral DVT, approximately 18% to 40% have underlying May-Thurner syndrome. Acute iliofemoral DVT presents with sudden onset left leg swelling. Lower extremity pain, a sensation of thigh tightness with exercise (subsiding with rest), and stasis associated skin changes occur with chronic thrombus. Well-developed venous collaterals can diminish these symptoms (Fig. 2).⁵ This syndrome may be more difficult to diagnose during the postpartum period when reports of pain and swelling are common. Furthermore, approximately 90% of DVTs in pregnancy are located on the left side, due to pregnancy-related compression of the left iliac vein. The expected left-sided predominance of DVT in pregnancy further delays recognition of this syndrome.

Contrast venography demonstrating narrowing of the iliac vein at the pelvic brim is the gold standard imaging for May-Thurner syndrome diagnosis (Fig. 3). Other suggestive findings include abnormal iliac vein pressure gradients and tortuous venous collaterals (Fig. 2) draining to the contralateral side on ascending iliac venography.⁴



Fig. 3. Venogram (case 2) before catheter directed thrombolysis demonstrating narrowing of the iliac vein at the pelvic brim (arrow).

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Failure to diagnose or optimally treat DVT can result in both short- and long-term complications. Proximal DVTs are associated with greater morbidity, compared with popliteal thrombi. Extension of proximal thrombi can threaten more clinically significant venous systems or lead to embolization to the pulmonary tree. At least 5–10% of DVT victims progress to postthrombotic syndrome and experience chronic edema, venous claudication, hyperpigmentation, varicosities, and stasis ulcers.³ Iliofemoral DVT should be a part of the differential in postpartum women with lower extremity symptoms since accurate and timely diagnosis is essential for minimizing the risk of fatal and nonfatal pulmonary embolism and chronic sequelae.

Therapeutic goals include symptom relief, clot stabilization, reestablishment of venous flow, avoidance of bleeding complications, and prevention of future complications. Whenever a clot is suspected, a weight-based dosing of therapeutic heparin may be initiated first, recalling that requirements are often higher in pregnancy. Heparin effectively stabilizes clot and prevents pulmonary embolus. Heparinization results in thrombolysis in less than 15% of DVTs; however, obstructive lesions, such as in May-Thurner Syndrome, are the least likely to respond. On adequate heparin, 40% of clots propagate, compounding venous valvular damage.³

In patients with a large, proximal DVT, like the women in our cases, treatment at a tertiary care center with an experienced vascular laboratory, interventional radiology, and intensive care facilities results in optimal outcomes. Ascending venography, followed by placement of an endovascular catheter for local infusion of a thrombolytic agent, such as plasminogen activator or urokinase, can accurately diagnose and rapidly lyse clot.³ Underlying venous stenosis is often present in May-Thurner syndrome and may be treated with concurrent venoplasty. Expedient resolution of thrombi restores flow, alleviates symptoms, preserves venous valve function, and prevents dysfunction of the endogenous fibrinolytic pathway. Some authors believe that rapid removal of thrombi is essential to preventing postthrombotic syndrome. In studies of nonpregnant patients, catheter-directed thrombolytic therapy for lower extremity DVTs had an 85% clinical and technical success rate. Likewise, ten women with May-Thurner syndrome and iliofemoral DVT were treated with local urokinase infusion, followed by venous stenting, which resulted in a 90% resolution of symptoms at a mean follow-up of 15 months.³

Intravenous heparin anticoagulation alone has

long been standard treatment for thromboembolism complications of pregnancy and the postpartum period. Catheter-directed thrombolysis is avoided due to fears of placental abruption, fetal hazards, and uncontrolled bleeding. Closely monitored endovascular treatment of large DVTs is likely safe and lyses thrombus more effectively than anticoagulation alone. Two case reports describe catheter directed thrombolysis during pregnancy with good success.^{6,7} Likewise, in a small pilot study published in Denmark, five postpartum women with proximal DVTs underwent catheter-directed thrombolysis and experienced restoration of flow without complications.⁵ A multi-center registry of 287 nonpregnant patients who underwent catheter-directed thrombolysis found an 11% rate of puncture site bleeding and 1% incidence of pulmonary embolus. Inferior vena cava filters were not routinely used during thrombolysis unless there was free-floating clot or the patient had a history of DVT on therapeutic anticoagulation.³ After thrombectomy, treatment of the left iliac vein compression in May-Thurner syndrome is essential to prevention of future DVT.

In May-Thurner syndrome, adjunctive stent placement improves long-term vessel patency and helps prevent iliofemoral DVT recurrence. Metal stents can easily be inserted in the iliac vessels, re-expanding the vein to its normal size by obliterating intimal lesions and preventing recoil. In a prospective trial of endovascular stent placement, 15 patients with May-Thurner and iliofemoral DVT received catheter-directed thrombolysis, angioplasty, endovascular stent placement and 6 months of warfarin. Patency was assessed by physical examination and duplex ultrasonography at 6-month intervals and found to be 87% at a mean follow-up of 16 months.⁵

Specific guidelines for the management of future pregnancies in women with May-Thurner and iliofemoral DVT do not exist. However, it is reasonable to proceed with therapeutic low-molecular-weight heparin throughout pregnancy. With the arrival of regular contractions or scheduled cesarean delivery, unfractionated heparin can be discontinued until after delivery. Postpartum anticoagulation may be resumed 12 hours postpartum. In either case, warfarin can be started within 24 hours after a vaginal delivery at 5–10 mg once daily. Warfarin anticoagulation may be continued at least 6 weeks postpartum in patients with May-Thurner syndrome and longer for acute or recurrent thrombosis. Warfarin is compatible with breastfeeding. Postpartum monitoring of warfarin is necessary as is re-evaluation for recurrent



thrombosis. Given that May-Thurner Syndrome exists in 5% of patients undergoing DVT evaluation and tends to occur in women, consideration of this syndrome should be given in differential diagnosis of any patient with iliofemoral DVT or with recurrent or refractory DVT.

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Thrombosed Fetal Dural Sinus Malformation Diagnosed With Magnetic Resonance Imaging

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BACKGROUND: Dural sinus malformations are rare congenital forms of dural arteriovenous shunt. Our goal is to describe prenatal ultrasonography and magnetic resonance imaging (MRI) findings of a thrombosed midline dural venous malformation.

CASE: Second-trimester fetal ultrasonography and MRI demonstrated a large T2-hypointense mass centered at the level of the torcular Herophili consistent with complete thrombosis of a dural sinus malformation. A follow-up third-trimester MRI showed decreased thrombus size and no parenchymal injury. A neurologically intact newborn was delivered.

CONCLUSION: Dural sinus malformations can lead to fetal intracranial thrombosis. Prenatal imaging is useful to establish the diagnosis of dural sinus malformations and

to plan perinatal management and treatment options. (*Obstet Gynecol* 2008;111:569–72)

Dural sinus malformations are rare congenital forms of dural arteriovenous shunt. Here we present a case of fetal intracranial thrombosis in a patient with dural sinus malformation diagnosed during the second trimester with ultrasonography and magnetic resonance imaging (MRI) in an otherwise uncomplicated pregnancy.

CASE

A woman was referred to our institution for an abnormal ultrasonogram performed at 20 weeks of gestation. A transabdominal ultrasound examination performed at 22 weeks of gestation documented a large intracranial well-defined hypoechoic area encompassing the posterior fossa and the posterior third of the supratentorial compartment without any detectable vascular flow within or around the mass (Fig. 1A). The differential diagnosis included a dural sinus malformation, an arachnoid cyst, or a cystic extra-axial tumor.

A fetal brain MRI was performed at 23 weeks of gestation on a 1.5 T MR scanner, using a single-shot fast spin-echo T2-weighted sequence (repetition time/echo time/flip angle/slice thickness, shortest/95/90/3; field-of-view, 280×280 mm). A large extra-axial T2-hypointense mass was noted, without flow voids, centered at the level of the torcular Herophili, displacing anteriorly the supratentorial structures and inferiorly the infratentorial structures (Fig. 1B and 1C). The location and appearance of the lesion raised the possibility of a thrombosed dural sinus malformation. The location was not typical for a vein of Galen malformation. Other etiologies, such as arachnoid cyst, dermoid or teratoma, were deemed unlikely.

The poor prognosis of dural sinus malformations and the

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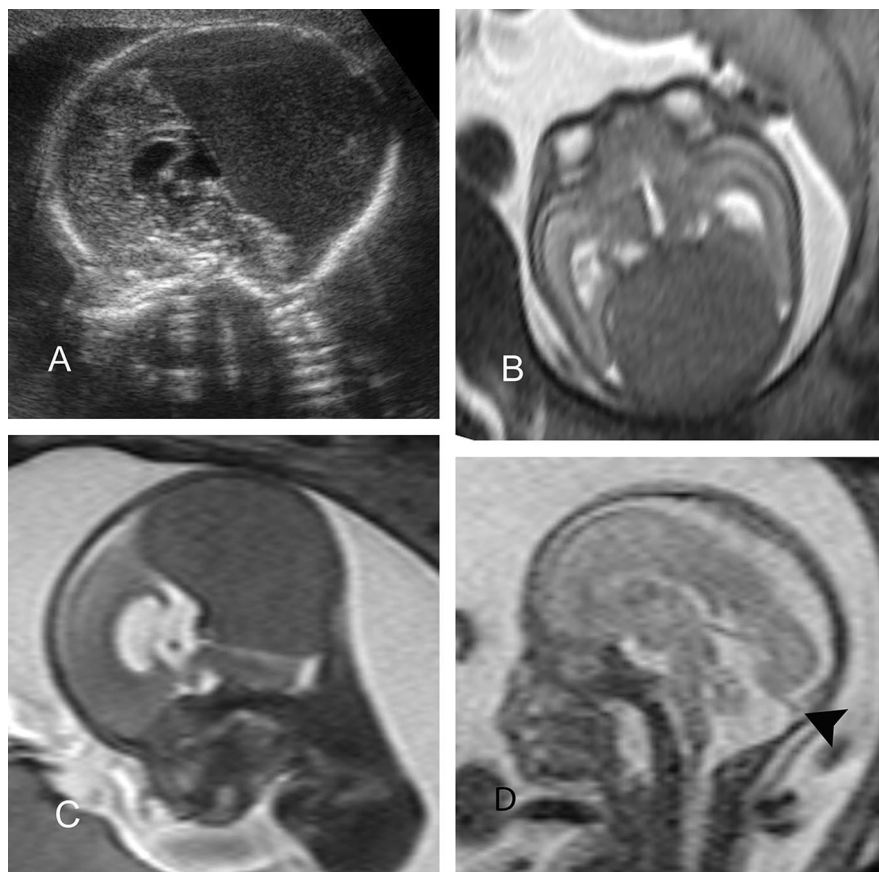


Fig. 1. Fetal thrombosis of the torcular Herophili. Ultrasound (A) sagittal image of the fetal head obtained at 22 weeks of gestation. Axial (B) and sagittal (C) T2-weighted fetal magnetic resonance images obtained at 23 weeks of gestation. A hypoechoic and T2 hypointense mass occupied the majority of the posterior fossa. Sagittal T2-weighted image (D) shows the normal appearance of the torcular Herophili (arrow-head).

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high risk of an unfavorable neurologic outcome based on the existing literature were discussed with the patient. She elected to continue the pregnancy. At this point, the decision was made to obtain follow-up imaging evaluation at 36 weeks of gestation, to determine the optimal modality of delivery, the most appropriate medical center where to deliver the child, and the need for an early angiogram, based on the appearance of the lesion and the presence or absence of brain parenchyma injury. A 36-week ultrasound examination showed grossly normal appearing intracranial anatomy. A fetal MRI was then obtained for further evaluation and confirmed interval resolution of the mass (Fig. 2), with linear flow voids within the superior sagittal sinus and torcular, consistent with a partial recanalization, and no signs of ischemic or hemorrhagic brain lesions. At 37 weeks of gestation, labor was induced after spontaneous rupture of membrane, and the patient delivered a neurologically intact newborn, with head circumference within normal range. A computed tomography scan of the head performed at 10 months of age revealed patency of the torcular and a partially calcified, but patent, superior sagittal sinus (Fig. 3A and 3B). Enlargement of the internal cerebral veins and of the straight sinus and cerebellar developmental venous anomalies were also noted. At age 16 months, the child had a normal somatic and cognitive development. He was followed up at a different institution, and it is

unknown whether he has signs of increased intracranial pressure.

COMMENT

Magnetic resonance imaging has been used to further evaluate and characterize the fetal central nervous system abnormalities after their detection and evaluation on prenatal ultrasonography.¹

Dural sinus malformations account for 57.7% of dural arteriovenous shunts in children and are classified into midline with giant pouches, and lateral, involving the jugular bulb.^{1,2} Dural sinus malformations with giant pouches are characterized by an abnormal development and uncontrolled growth of the posterior sinuses (transverse sinuses, torcular Herophili, and posterior superior sagittal sinus), accompanied by multiple slow-flow arteriovenous shunting within the wall of the malformed sinus, likely secondary to the presence of the dural sinus malformation.² The malformed dural sinus communicates with the other sinuses. Spontaneous thrombosis of the giant venous pouch can occur and, in presence of



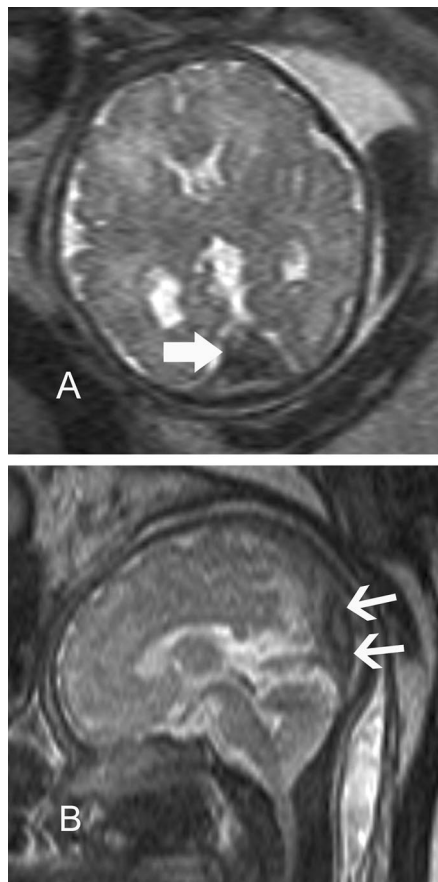


Fig. 2. Fetal thrombosis of the torcular Herophili. Axial (A) and sagittal (B) T2-weighted magnetic resonance images obtained at 36 weeks of gestation. Interval significant decrease in size of the thrombus was noted (arrows).

Spampinato. *Fetal Dural Sinus Malformation*. *Obstet Gynecol* 2008.

occlusion of all the venous outlets, can lead to bilateral venous infarctions.¹ When the draining veins remain initially patent, the clinical presentation of delayed secondary thrombosis consists of seizures and intraparenchymal or subdural hemorrhages. When dural sinus malformations remain undiagnosed and untreated, a focal or diffuse melting-brain syndrome can occur. Dural sinus malformations are rare congenital abnormalities. It is important to differentiate them from other posterior fossa space-occupying lesions.³ Vein of Galen malformations are differentiated from dural sinus malformations based on their location, as they typically involve the region of the choroidal fissure and extend from the interventricular foramen to the pineal gland. Teratomas of the posterior fossa are characterized by heterogeneous signal intensity on MRI. Dandy-Walker malformation and arachnoid cysts have signal intensity analogous to the cerebrospinal fluid on all pulse sequences.

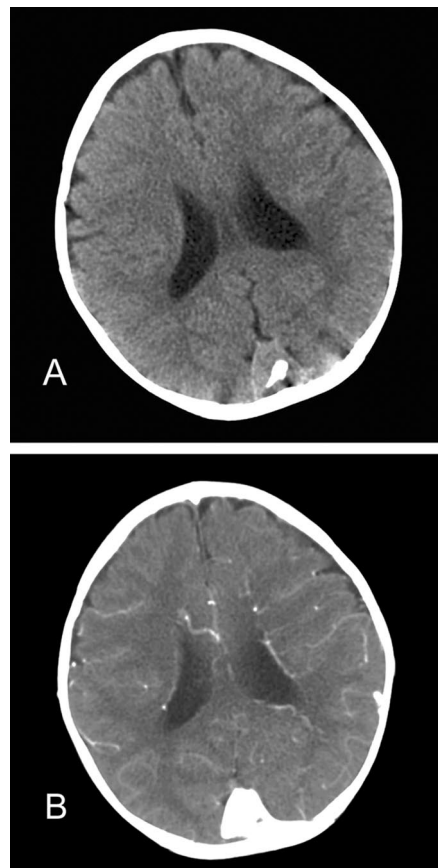


Fig. 3. Noncontrast (A) and postcontrast (B) computed tomography images of the head obtained at 10 months of age. The superior sagittal sinus appeared calcified but patent.

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An unfavorable outcome was reported in 71.4% of cases with dural sinus malformation involving the torcular in a series of 30 patients.² The involvement of the torcular, the absence of cavernous capture (drainage of deep and superficial sylvian veins in the cavernous sinus), the presence of brain damage, and jugular bulb dysmaturation (postnatal occlusion of the jugular bulb) are negative prognostic factors.² In case of an antenatal diagnosis, Barbosa et al² recommend obtaining an MRI of the brain at birth to assess the location of the malformation and the presence or absence of brain damage. In case of large dural sinus malformations involving the torcular, an early angiogram is recommended to evaluate the venous anatomy. Otherwise follow-up MRIs are recommended at 2-month intervals, followed by a cerebral angiogram at 4–5 months (a time when cavernous capture may have already occurred). Depending on the angiographic findings, the management is then conserva-



tive (anticoagulation with low-molecular-weight heparin) or endovascular.

Rossi et al³ previously described a case of dural sinus malformation prenatally diagnosed on fetal MRI, confirmed with a postnatal MRI, which required endovascular treatment at the age of 1 month. Two additional cases of dural sinus malformations diagnosed prenatally with ultrasound at 24 and 35 weeks of gestation, both with in utero cardiac failure at diagnosis, also required multiple endovascular treatment sessions.⁴ In both cases moderate developmental delay and in one case hydrocephalus and mild hemoparesis were noted at follow-up. In our case, the dural sinus malformation appeared thrombosed in the second-trimester and significantly smaller on the third-trimester ultrasound examination and MRI. Despite the large size of the malformation, the involvement of the torcular and the fact that cavernous capture is unlikely until the first months of postnatal life, spontaneous thrombosis of the venous pouch did not lead to brain damage. Differently from the previously reported cases of dural sinus malformations diagnosed prenatally, our patient did not undergo any endovascular treatment and was developmentally normal during his first year of life.

A review of the literature yielded several other cases of thrombosis of the torcular Herophili diagnosed prenatally, with abnormally enlarged appearance on imaging of the thrombosed sinuses.^{5–7} Based on our review of the literature, we believe that also in those cases the primary abnormalities were dural sinus malformations, which underwent spontaneous thrombosis in utero. Spontaneous thrombosis, secondary for example to infections, severe dehydration, or prothrombotic states, would not lead to the extreme dilatation of the sinuses seen in patients with dural sinus malformations, in presence or absence of

thrombosis.^{1–3} Dural sinus malformation involving the torcular is a rare congenital disease which can be diagnosed on prenatal imaging. The occurrence of thrombosis of abnormally enlarged dural sinuses should prompt the suspicion of an underlying dural sinus malformation. After the initial evaluation and diagnosis with fetal ultrasonography and MRI, follow-up fetal MRIs should be performed to evaluate for changes in size and configuration of the venous malformation. A significant decrease in size of the malformation, as seen in our case, is likely associated with higher probability of a positive outcome. It is important to be aware of the imaging features of dural sinus malformation, as prenatal diagnosis of this condition can help optimize the clinical management of affected newborns.

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Late Postpartum Hemorrhage Due to von Willebrand Disease Managed With Uterine Artery Embolization

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BACKGROUND: Von Willebrand disease is the most common inherited bleeding disorder caused by quantitative or qualitative defects of von Willebrand factor, which may lead to postpartum bleeding problems. In such patients, resistant postpartum hemorrhage may be treated effectively by using transcatheter arterial embolization.

CASE: Life-threatening late postpartum bleeding of a patient with von Willebrand disease type 3 unresponsive to traditional medical approaches was successfully managed with selective uterine artery embolization.

CONCLUSION: Selective transcatheter uterine artery embolization may be used to control life-threatening pelvic hemorrhage unresponsive to traditional local measures. Such an intervention may also be used successfully in patients with bleeding disorders as the last chance of uterine preservation.

(*Obstet Gynecol* 2008;111:573–5)

Von Willebrand disease is the most common inherited bleeding disorder with an estimated prevalence of 1% in the general population caused by quantitative (type 1 and 3) or qualitative (type 2) defects of von Willebrand factor (vWF).^{1,2} Epistaxes, mucosal bleedings, hemorrhage after surgery, and excessive menstrual blood loss are the common manifestations of von Willebrand disease.³ Although levels of vWF increase during pregnancy, rapid postpartum decrease may lead to bleeding problems.⁴

Uterine artery embolization under angiographic guidance was reported to be successfully used to control pelvic hemorrhage related with either obstetric or gynecologic procedures.⁵

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Here, a case of late postpartum bleeding seen after a cesarean delivery in a patient with von Willebrand disease type 3 successfully managed by uterine artery embolization is presented.

CASE

A 29-year-old gravida 1 patient who had a diagnosis of von Willebrand disease type 3 was delivered via cesarean delivery due to breech presentation after an uneventful course of pregnancy. She had been diagnosed to have von Willebrand disease after being evaluated for epistaxis when she was 18 months old. During childhood, she had to get fresh frozen plasma support when needed, and she used combined oral contraceptives for menorrhagia after menarche. Also, after menarche, she sometimes had to receive factor 8 for heavy menstrual bleeding episodes. Before cesarean delivery, the level of vWF was 1% and vWF antigen was 2%. She was given an intravenous bolus of 2,000 units of factor 8 just before the operation. She was given 2×1,000 units factor 8 for 4 days after the delivery. Postoperative course was also uneventful, and she was discharged from hospital on fourth postpartum day. Fourteen days after the delivery, she was admitted to outpatient clinics with reporting heavy vaginal bleeding and was started a factor 8 replacement of 500 units/day. She used it for 4 days. However, although the amount of bleeding was reduced, it persisted and she was readmitted to the hospital on the 19th postpartum day. Her hemoglobin level was 6.2 g/dL. She was hospitalized, and 2×1,000 units factor 8 replacements were commenced after an intravenous bolus of 2,000 units. Her vaginal examination was free of any local pathology, but active bleeding originating from the uterine cavity was seen. No acute abdomen was detected, and ultrasonographic evaluation did not show signs of retained products in uterine cavity or fluid collection consistent with intraabdominal bleeding. The bleeding continued despite the increased replacement dose of 3×1,000 units factor 8, and the patient was given a total of 9 units of red blood cell transfusion in 10 days due to impaired hemodynamic status indicated by episodes of tachycardia and hypotension. On the 12th day of hospitalization, uterine artery embolization was decided after an interventional radiology consultation. Pelvic arteriogram and bilateral selective uterine artery catheterizations were performed under local anesthesia using 4F pigtail and Simmons 1 catheters (Terumo, Tokyo, Japan) which showed hypertrophied uterine artery branches and paranchymal staining consistent with the postpartum period. Active bleeding was not seen. The right uterine artery was embolized via a microcatheter (Progreat 2.7F; Terumo) using 250–355-microns polyvinyl alcohol microspheres (Contour; Boston Scientific Cork Ltd., Cork, Ireland) (Fig. 1). Bleeding decreased gradually after embolization and ceased totally on the fourth postembolization day. No transfusion was re-



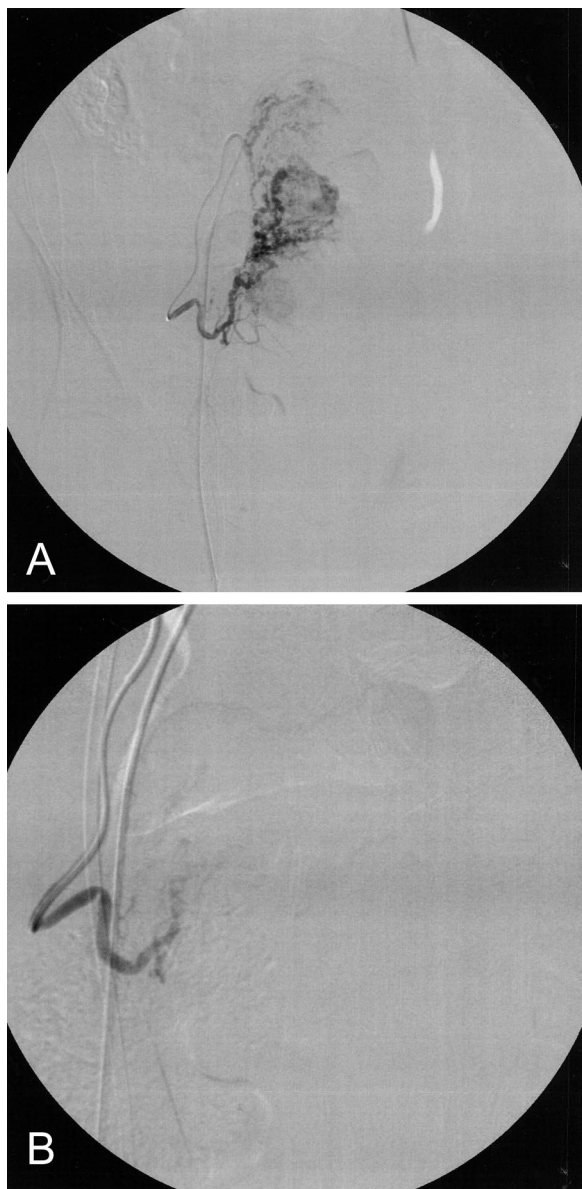


Fig. 1. Right uterine arteriogram shows no active bleeding (A) and postembolization arteriogram shows occlusion of the artery (B).

Salman. Arterial Embolization for Postpartum Hemorrhage. *Obstet Gynecol* 2008.

quired after the embolization, and she was discharged from the hospital 1 week after the intervention. The patient is free of any symptoms nearly 3 months after the delivery and 2 months after the embolization.

COMMENT

von Willebrand factor is needed for fibrin clot formation by means of mediating the adhesion of platelets to the damaged endothelium and carrying the coag-

ulation factor 8.⁶ The qualitative or quantitative defects of vWF cause von Willebrand disease.³ The diagnosis is achieved by obtaining a personal or familial history of excessive bleeding and a laboratory evaluation of vWF.² Among three types of von Willebrand disease, type 1 is the most commonly seen type, while type 3 is the least common and the most severe type.⁷ Our patient was diagnosed to have von Willebrand disease type 3 during evaluations carried out for epistaxis episodes when she was 18 months old.

In the traditional management of von Willebrand disease, desmopressin and blood products are used. Desmopressin causes release of vWF and factor 8 from the stores within the body. Plasma-derived factor concentrates may be used in cases with desmopressin failure.²

During pregnancy, plasma levels of vWF increase, but a rapid decrease may be expected after delivery.^{4,8} The preferred therapy is factor concentrates during pregnancy, and the factor levels should be kept above 50% for 3–4 days after vaginal delivery and for 4–5 days after cesarean delivery to decrease the risk of postpartum hemorrhage.⁴ Our patient did not need therapy during pregnancy, and she was given factor 8 concentrate preoperatively and for 4 days postpartum. Despite such a treatment, she experienced late postpartum bleeding unresponsive to replacement of higher doses. Therefore, a decision of selective transcatheter uterine artery embolization was made.

In patients with postpartum hemorrhage resistant to traditional approaches, transcatheter arterial embolization has recently emerged as an effective technique that controls acute and chronic genital bleeding caused by obstetric and gynecologic conditions. Indications include symptomatic leiomyomata, postpartum and postsurgical bleeding, ectopic pregnancy, trauma, and arteriovenous malformations. Advantages of this intervention are easy identification of bleeding site, preservation of uterus, and the ability of the angiographer to visualize and occlude collateral vessels contributing to bleeding. The success rate was reported to be as high as 95%.^{9,10} Embolization was used as the last conservative approach in our patient, and if the embolization was not successful in controlling hemorrhage, she would have had to have a hysterectomy, destroying future fertility at a relatively younger age.

Pregnancies occurring after uterine artery embolization carry risks for malpresentation, preterm birth, cesarean delivery, postpartum hemorrhage, and abnormal placentation.^{11,12} Therefore, a careful antenatal care is essential. Uterine artery embolization was also implicated in the pathogenesis of myometrial



damage.¹² Therefore, vaginal birth after cesarean delivery should not be attempted in future pregnancies.

As a conclusion, selective transcatheter uterine artery embolization may be used to control life-threatening pelvic hemorrhage unresponsive to traditional local measures. Such an intervention may also be used successfully in patients with severe bleeding disorders, and embolization may be the last chance of uterine preservation in these cases.

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Abetalipoproteinemia Complicating the Puerperium

Andrea B. Palmer, MD, and Eric J. Knudtson, MD

BACKGROUND: Abetalipoproteinemia is a rare, autosomal recessive disease, in which the absence of β -lipoprotein results in the malabsorption of fat-soluble vitamins. There are few reported complications from abetalipoproteinemia during pregnancy. We present a case of untreated abetalipoproteinemia complicating the puerperium.

CASE: A 23-year-old, gravida 3, para 0020 woman presented to an outside facility in labor, and her delivery was complicated by postpartum hemorrhage and a large vulvar hematoma. She was coagulopathic and transferred for suspected disseminated intravascular coagulation.

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Her preexisting medical history was not appreciated by the transferring facility.

CONCLUSION: Abetalipoproteinemia in pregnancy is rare. Untreated disease conveys multi-system organ dysfunction and has ramifications in labor and delivery. Clinicians must elicit a comprehensive medical history to properly manage complications in the puerperium.

(Obstet Gynecol 2008;111:575–7)

Abetalipoproteinemia is an autosomal recessive disease of fat malabsorption. The incidence is less than 1 in 10,000,000 and occurs in diverse ethnic backgrounds. The inability to synthesize β -lipoproteins (β 100 and β 48) results in absent apoprotein B in the plasma, as well as absent lipoprotein fractions (chylomicrons, very-low-density lipoprotein, and transport cholesterol).¹ Diagnosis is confirmed by acanthocytes in the peripheral blood and extremely low plasma levels of cholesterol. Clinical manifestations are related to malabsorption of fat. Children exhibit failure to thrive during their first year of life and have foul-smelling, pale stools. Intellectual development tends to be slow. The intestinal symptoms tend to improve with time; however, neurologic symptoms tend to develop after the first decade of life. Ataxia, loss of deep tendon reflexes, and decreased vibratory/proprioceptive senses occur due to deficient levels of Vitamin E.² In untreated patients, severe neurologic impairments can be debilitating by the fourth or fifth



decade. Vitamin A deficiency can cause a progressive, pigmented retinopathy.³ Vitamin K deficiency can lead to significant coagulopathy and bleeding diathesis. We present a case of untreated abetalipoproteinemia complicating the puerperium.

CASE

A 23-year-old Native American woman, gravida 3 para 0020 delivered a term, healthy infant by spontaneous vaginal delivery at an outside facility. Prenatal care was initiated in the first trimester. No medical problems were elucidated, and her care was uneventful. At delivery, she suffered a postpartum hemorrhage and a second-degree laceration. She was treated with several uterotonic agents immediately after delivery, and uterine bleeding slowed. Late on postpartum day 0, a large vulvar hematoma developed. Laboratory evaluation revealed the patient to be coagulopathic. Her treating physicians felt she was suffering from disseminated intravascular coagulation, and a transfer of care was arranged on postpartum day 1.

On arrival, the patient appeared pale, and her skin was icthyotic. Her fundus was firm, and examination of her perineum revealed an 8×10-cm left-sided vulvar hematoma tracking back into the vagina.

Further questioning of the patient and family members revealed several prolonged hospital admissions as a child, for what appeared to be failure to thrive. More inquiries from the treatment team elucidated a workup and eventual diagnosis of abetalipoproteinemia. The patient had been on high-dose oral supplementation of vitamin A, vitamin E, and vitamin D, along with weekly subcutaneous Vitamin K injections. The patient had stopped these on her own volition and without physician direction at approximately age 16.

The patient's initial laboratory studies were significant for a profound anemia (hemoglobin 5.4 g/dL hematocrit 15.1%), thrombocytopenia (platelet count 89,000/mL), and coagulopathy (prothrombin time 72.4 seconds, international normalized ratio of 7.7, and partial thromboplastin time of 83.6 seconds). Peripheral smear revealed mild polychromasia, marked poikilocytosis, many echinocytes, many acanthocytes, and occasional shistocytes. Lipid panel checked on day of admission was significant for a total cholesterol of 69 mg/dL, triglycerides 17 mg/dL, low-density lipoprotein 39 mg/dL, high-density lipoprotein 27mg/dL, and absent chylomicrons.

Vitamin K therapy was undertaken for replacement and correction of coagulopathy. The patient was transfused with a total of 4 units of packed red blood cells to correct her anemia, 1,500 mL fresh frozen plasma to correct her coagulopathy, and 1 unit of platelets due to the fact that the treatment team felt her vulvar hematoma was expanding.

Computed tomography (CT) angiogram of the patient's pelvis was preformed to fully evaluate the vulvar hematoma and determine if embolization was necessary. The CT angiogram revealed a 10×10×8-cm left vulvar hematoma,

which on delayed imaging had a faint blush, but no active arterial bleeding. Her vulvar wound was managed expectantly with the help of the physical therapy/wound care team. Endocrinology was consulted and helped to reinstitute her vitamin regimen. Slow improvement was noted, and at discharge, her wound was healing well. She remains on her maintenance vitamin therapy of vitamin A 10,000 units orally weekly, vitamin E 800 units orally daily, vitamin K 1 mg subcutaneously weekly, and calcium carbonate 600 mg orally daily. A repeat CT scan 2 weeks postpartum showed a resolving hematoma. No neonatal complications were appreciated. Importance of indefinite compliance with the medications was emphasized with the patient and her family.

COMMENT

There are few published case reports of abetalipoproteinemia in pregnancy. A PubMed literature search using the keywords "abetalipoproteinemia" and "pregnancy" revealed three published reports of the disease in pregnancy from 1950 to May 2007. A case reported by Biemer and McCammon⁴ in 1975 illustrated a case of postpartum hemorrhage leading to a new diagnosis of abetalipoproteinemia. Guadet and colleagues⁵ have reported on two cases of abetalipoproteinemia in pregnancy and contrasted outcomes of treated and untreated disease, as well as potential neonatal complications such as retinal abnormalities.

Postpartum hemorrhage is a significant cause of maternal mortality and morbidity. Severe postpartum hemorrhage complicates 4–6% of all deliveries.⁶ Postpartum hemorrhage is most commonly encountered in the setting of uterine atony, genital tract lacerations, or retained placental tissue. Severe hemorrhage may lead to disseminated intravascular coagulation, adult respiratory distress syndrome, pituitary necrosis, and death.⁶

The patient presented here had postpartum hemorrhage and disseminated intravascular coagulation; however, her case was complicated by her unknown medical condition. Initial appreciation of her vitamin K deficiency and correction of her international normalized ratio in the antepartum period would have potentially avoided the morbidity she encountered post partum. The case presented here highlights the need for comprehensive history taking and the importance of keeping a broad differential diagnosis when faced with common postpartum complications.

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Preoperative Magnetic Resonance Imaging and Antepartum Myomectomy of a Giant Pedunculated Leiomyoma

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BACKGROUND: Antepartum myomectomy is reserved for severe pain and prevention of fetal complications. Magnetic resonance imaging has been useful in nonpregnant women for preoperative management and patient counseling.

CASE: A primigravida was admitted at 12 weeks of gestation in severe acute abdominal pain with a large abdominal mass, confirmed by magnetic resonance imaging to be a pedunculated 30×27×19-cm uterine leiomyoma. An uncomplicated abdominal myomectomy was performed, incorporating a flat cup vacuum device to mobilize the mass without disturbing the gravid uterus. The patient later had an uncomplicated term vaginal delivery and healthy newborn.

CONCLUSION: Magnetic resonance imaging and a flat cup vacuum device were helpful in preoperative planning and performing an uncomplicated abdominal myomectomy during pregnancy, respectively.

(*Obstet Gynecol* 2008;111:577–9)

The true prevalence of uterine leiomyomata in pregnancy is unknown. However, they have been detected by ultrasonography in 2.7% of pregnancies after 24 weeks of gestation.¹ Uterine leiomyomata are associated with pregnancy-related maternal and fetal

complications, including miscarriage, threatened preterm labor, preterm delivery, placental abruption, placenta previa, obstructed labor, cesarean delivery, breech presentation, malposition, and severe postpartum hemorrhage.^{1,2} Massive uterine leiomyomata may be associated with fetal growth restriction and fetal compression syndromes.³ Magnetic resonance imaging (MRI) is often used to complement or clarify equivocal ultrasonography in the evaluation of pelvic masses. In addition, MRI is superior to ultrasonography in defining spatial relationships and characterizing the embedment of uterine leiomyomata in nonpregnant women.⁴ Therefore, MRI has been described as an important tool in preoperative planning for cases in which mapping of uterine leiomyomata is paramount. We describe a case in which MRI aided in the diagnosis and preoperative strategy for a patient who underwent an antepartum myomectomy of a giant pedunculated leiomyoma at 12 weeks of gestation.

CASE

A 22-year-old gravida 1, para 0 woman presented to an outlying emergency department at 7 weeks of gestation with abdominal discomfort and an abdominal mass palpable to just below the xiphoid process. She reported that her abdomen started increasing in girth several months before pregnancy. A giant uterine leiomyoma was suspected by the maternal-fetal medicine consultant, who planned a second-trimester MRI given concern for preterm delivery or severe fetal compression syndrome. Expectant management with oral analgesics (5 mg/325 mg oxycodone/acetaminophen tablets) was recommended until 12.0 weeks of gestation, at which time she was admitted with severe intractable acute abdominal pain. Examination revealed a firm, severely tender abdominal mass unchanged in size. Magnetic resonance imaging confirmed the diagnosis of a 30×27×19-cm giant pedunculated leiomyoma. T1- and T2-weighted images without contrast clearly demonstrated the leiomyoma arising from the right fundus by a 3-cm stalk (Fig. 1). Multiple areas of cystic degeneration within the leiomyoma were appreciated by MRI and felt to be the cause of the patient's symptoms. No ascites or hydronephrosis was noted. Because of the patient's severe pain, failed expectant management, and concern regarding the prognosis of the pregnancy, the patient underwent an uncomplicated abdominal

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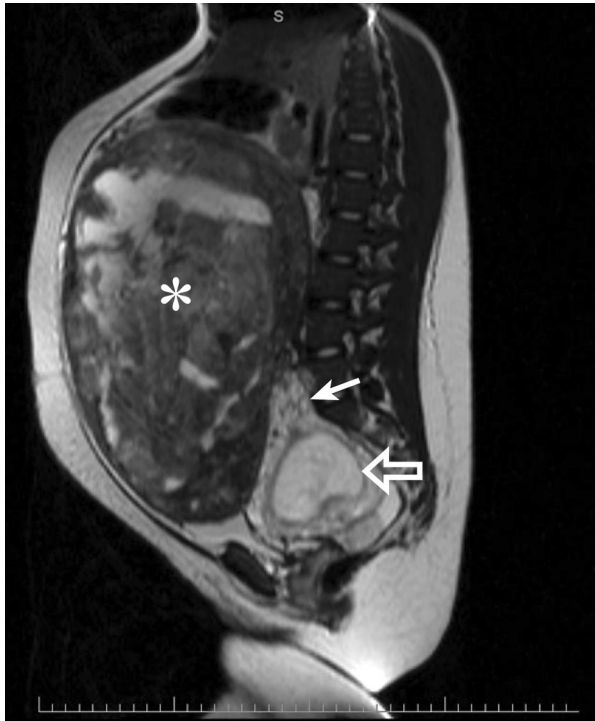


Fig. 1. T2-weighted magnetic resonance sagittal image demonstrating a giant leiomyoma (asterisk) undergoing cystic degeneration and connected to the gravid uterus (open arrow) by a 3-cm stalk (solid arrow).

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myomectomy procedure at 12.1 weeks of gestation via a midline, vertical incision. A Kiwi manual vacuum system (Clinical Innovations, Murray, UT) was used to mobilize the mass out of the peritoneal cavity while minimizing disturbance of the gravid uterus (Fig. 2). A giant, pedunculated

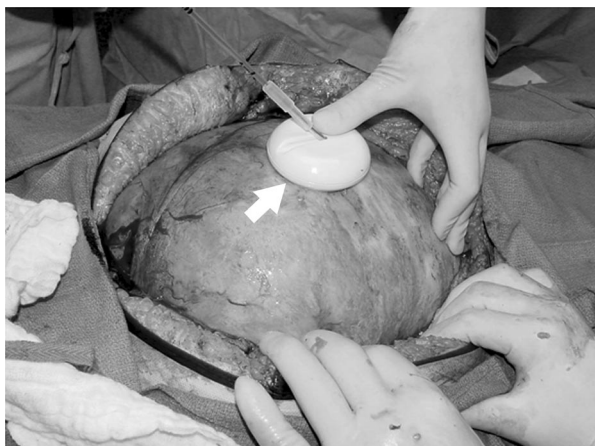


Fig. 2. A manual vacuum cup (arrow) is applied to the anterior surface of the leiomyoma to enable its mobilization while minimizing disturbance of the pregnant uterus.

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7.95-kg leiomyoma was noted to be vascularized by several saprophytic vessels from the omentum and bladder (Fig. 3). The stalk was cross-clamped near its base and over-sewn with a baseball stitch. The myometrium was not incised. Cefazolin 1 gram intravenously was used preoperatively. No perioperative tocolytic therapy was employed. The patient was discharged home on postoperative day 3, and the remainder of her pregnancy proceeded unremarkably. At 38 weeks of gestation the patient went into spontaneous labor followed by a vaginal delivery of a 2,330-gram male neonate. Both the infant and mother were discharged home on postpartum day 2. The patient was diagnosed with preeclampsia on postpartum day 7, which resolved without sequelae.

COMMENT

Antepartum myomectomy has been discouraged in the past over fears of bleeding and pregnancy-related complications. However, Mollica et al⁵ demonstrated that antepartum myomectomy reduced the rate of miscarriage and cesarean hysterectomy in women with recurrent severe pain, large or rapidly-growing leiomyoma, or leiomyomata, which distorted the placental site. Retrospective and observational series document the safety and low risk of antepartum myomectomy in well-selected patients.^{6,7} The most common and important reason for antepartum myomectomy is severe abdominal pain that is not amendable to conservative medical management. Angtuaco et al⁸ reported on the efficacy of MRI in the pregnant patient with an acute abdomen for differentiating degenerating uterine leiomyomata from ovarian torsion, which can be especially difficult in cases with a large pedunculated leiomyoma. Transabdominal ultrasonography could not contribute to the diagnosis in

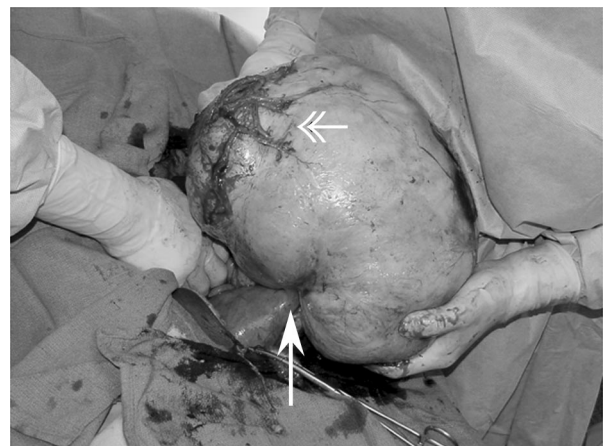


Fig. 3. Saprophytic vessels (double-headed arrow) to the omentum and bladder have been divided, and the narrow stalk can be seen at the base of the leiomyoma where it is connected to the uterus (single-headed arrow).

Alanis. Antepartum Myomectomy. *Obstet Gynecol* 2008.



our patient, because the density and size of the leiomyoma rendered the ultrasound image non-interpretable. The decision to operate was made after MRI confirmed the diagnosis and described the pedunculated nature of the 30-cm leiomyoma nearly 8 kg in weight. The weight of the newborn was small for gestational age. This may have been influenced by several mechanisms, including constitutional factors, maternal smoking, or preeclampsia, although this was not clinically evident until postpartum day 7. Magnetic resonance imaging provides essential topographic information and helps exclude other pathology, making antepartum myomectomy a good option in pregnant patients with large or painful uterine leiomyomata that do not respond to conservative medical management.

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Computed Tomography–Based Radiation Therapy of Ovarian Remnants for Symptomatic Persistent Endometriosis

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BACKGROUND: Endometriosis, a major cause of pelvic pain in women, is driven by estrogen. Ovarian remnant irradiation may alleviate pelvic pain by eliminating estrogen production in appropriately selected women with endometriosis.

CASE: Three patients with endometriosis causing incapacitating pelvic pain received 3D-imaging–based external beam radiation to doses of 1,500 to 2,100 cGy. All had pre-irradiation premenopausal follicle stimulating hormone levels and imaging evidence of ovarian remnants.

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None were candidates for further medical or surgical interventions. By 3 months after radiation, follicle stimulating hormone levels reached postmenopausal levels in all three patients, with complete resolution of the severe pelvic pain.

CONCLUSION: Radiation therapy effectively induced menopause and relieved refractory pain from endometriosis. Careful selection of patients is necessary, given the potential for an increased long-term risk of radiation-related complications.

(Obstet Gynecol 2008;111:579–83)

Endometriosis is the presence of ectopic endometrial glands and stroma outside the endometrial cavity. The prevalence of endometriosis is up to 22% in asymptomatic women.¹ Approximately 80% of women undergoing laparoscopy for chronic pelvic pain carry a diagnosis of endometriosis, and it is the third most common cause of gynecologic hospitalizations.^{2,3}

The pain caused by endometriosis may be multifactorial in causation; reduction in estrogen levels by medical or surgical suppression has been previously reported to relieve the pain. A long-standing precedent exists for administering 16 to 20 Gy of radiation directed to the ovaries to induce menopause in premenopausal women with breast cancer.⁴ Ovarian ablation by radiation has been historically reported in the treatment of endometriosis under rare circumstances when medical and surgical interventions have failed to palliate pain. However, the use of three dimensional (3D) imaging for simulation to target the



specific ovarian remnant tissue has not been previously reported.⁵

This report presents three patients with severe pelvic pain from endometriosis. Each was initially treated both medically and surgically with no resolution of symptoms and was subsequently referred to our department for radiotherapeutic ablation of ovarian remnants for palliative pain relief. This study was approved by the Human Subjects Research Committee of the Brigham and Women's/Dana-Farber Cancer Center.

CASES

We identified all patients with severe refractory pelvic pain due to endometriosis treated with external beam radiation from 2002 to 2006 at Brigham and Women's Hospital. All three identified patients had failed multiple prior interventions and had been referred for consideration of radiation therapy by their primary gynecologic surgeons after all other standard treatment options were exhausted. The three patients were also in a premenopausal state, as determined by serum follicle stimulating hormone (FSH) levels.

Comprehensive discussions were held with all patients regarding all possible surgical and medical options pertinent to their individual cases. The possibilities of acute reactions and long-term serious sequelae associated with radiation, including the risk of radiation-related malignancy, bowel or bladder changes, or radiation-induced fibrosis, were also discussed in detail. Three-dimensional simulation was conducted using a computed tomography (CT) simulator (GE Medical Systems, Waukesha, WI). Computed tomography images were fused to pelvic magnetic resonance imaging (MRI) scans in two patients to aid in identifying ovarian remnants. Target volumes were contoured on a GE Advantage Sim workstation. Patients were treated using 15-MV photons delivered using AP/PA fields or a four-field box (AP/PA and opposed laterals) to a total dose of 1,500 cGy in 10 fractions. The pelvic borders extended superiorly, from the bottom of the sacroiliac joints, inferiorly to the pubic symphysis, and laterally to the pelvic brims. For the lateral fields, the anterior border covered the pubic symphysis, and the posterior border covered the sacrum. In two cases, an additional boost dose of 450 cGy or 600 cGy was delivered to a smaller cone-down volume using either AP/PA fields or six-field conformal radiation to the area of the ovarian remnant.

Patient 1 was a 44-year-old woman with a long history of abdominopelvic pain. She had severe cramping since her menarche at age 12. She used nonsteroidal anti-inflammatory medications with little relief and had dilatations and curettages at ages 24 and 26. Laparoscopy at age 35 established the diagnosis of stage IV endometriosis. Severe pelvic adhesions were detected at that time. The same year, the patient underwent supracervical hysterectomy and unilateral salpingo-oophorectomy. Because of her young age, the left ovary was left intact.

The patient's pain persisted, and she was treated with leuprolide for the next 8 years, from which she gained temporary relief. In the last 3 years of her leuprolide treatments, she developed heavy menstrual bleeding, accompanied by worsening pelvic pain. Neither transvaginal/transabdominal ultrasonography nor abdominopelvic CT scan showed any identifiable ovarian tissue or other abnormality. Leuprolide was discontinued, and 2 months later, her FSH was 2.4 milli-International Units/mL (premenopausal range, 1.7–18.4 milli-International Units/mL), consistent with a premenopausal state. At that time, it was deduced that her bleeding originated from residual endometrial and cervical tissue. Her gynecologic surgeon felt that further surgery was not feasible due to the presence of severe pelvic adhesions and the inability to identify resectable ovarian tissue.

On presentation in our clinic, the patient reported constant, dull left-sided abdominopelvic pain that was not relieved by medications. Abdominal examination revealed a diffuse tenderness, especially over the left hemipelvis. There was no rebound, guarding, or distention. She had pain refractory to narcotics and was reluctant to undertake an extended trial of opioid-based pain medications. She therefore opted to receive radiation. After providing signed informed consent, the patient was simulated. Radiation treatment to the pelvis of 1,500 cGy in 10 fractions was administered with 15-MV photons using AP/PA fields measuring 14.4×11 cm, with the goal of covering the entire pelvic inlet and all possible locations of residual ovarian tissue.

At 2-month follow-up, patient 1 reported near-complete resolution of her pelvic pain. Pain at a level of 1/10 manifested only occasionally during bowel movements, and her abdomen was not tender on physical examination. Three months after completing treatment, her FSH measured 32.8 milli-International Units/mL (postmenopausal range, 32.2–132.4 milli-International Units/mL), consistent with a postmenopausal state. The most recent follow-up 5 years after completing radiation revealed complete resolution of the patient's severe refractory pain; she states that she has had no other complications, including no skin, bowel, or bladder changes.

Patient 2, a 33-year-old woman, underwent menarche at age 12 and began to experience intermittent, severe abdominal pain by age 14. She was diagnosed with endometriosis at age 19 and subsequently underwent multiple ablative therapies. Her pain recurred. Between the ages of 19 and 22, she was treated with multiple hormonal treatments, including oral contraceptives, estrogen, combined estrogen and progesterone, estrogen patch, and medroxyprogesterone. She developed a deep vein thrombosis at age 22, and all hormonal therapies were stopped. She underwent a trial of leuprolide but was allergic to a component of the depot vehicle.

At age 31, patient 2 underwent supracervical hysterectomy and right salpingo-oophorectomy for persistent pelvic pain. One year later, she underwent exploratory laparot-



omy, lysis of adhesions, and left salpingo-oophorectomy. Over the ensuing months, she continued to have worsening left-sided pelvic pain in a cyclical pattern. Two months before presenting to our clinic, she also developed breast tenderness and intermittent vaginal bleeding from the residual cervical tissue. A pelvic MRI at that time revealed two cystic structures measuring 1.2 and 0.6 cm in the left pelvis, which were bright on T2-weighted images with rim-like enhancement after contrast administration, reported to be most consistent with residual ovarian tissue with follicle formation. Her FSH level at that time measured 5.1 milli-International Units/mL, consistent with a premenopausal hormonal state. The gynecologic surgeon felt that she was not a candidate for further surgery.

On presentation in our clinic, the patient reported persistent 10/10 intermittent severe left-sided pelvic pain. By her report, she continued to have apparent cyclical vaginal bleeding. After providing signed informed consent, the patient was simulated. Computed tomography images were fused with MRI images to identify her left ovarian remnants. A radiation dose of 1,500 cGy in 10 fractions was administered to the ovarian remnant with 15-MV photons using a four-field approach with 15.2×11.8-cm AP/PA fields and 19.0×11.8-cm lateral fields. This was followed by treating a smaller cone-down field to 600 cGy in four fractions directed at the left ovarian remnant with 15-MV photons by a six-field conformal technique.

At 3-month follow-up, the patient noted complete resolution of her severe cyclical pelvic pain with some minimal residual noncyclical pelvic pain. Her FSH level at that time was 63.9 milli-International Units/mL, suggestive of a postmenopausal state. At the most recent follow-up, 3.5 years after completing radiation, her FSH level remained in postmenopausal range (47.2 milli-International Units/mL), and she states that she has not had any severe pain since completing radiation. She has had no other complications, including no skin, bowel, or bladder changes.

Patient 3, a 37-year-old woman, was clinically diagnosed with endometriosis at age 21 after presenting with severe pelvic discomfort during menses. At age 24, she underwent a 6-month trial of leuprolide with minimal relief. At age 26, she underwent laser vaporization of endometrial deposits followed by a brief trial of danazol. At age 27, she started ethinyl estradiol and norgestrel, but continued to have intermittent pain and dyspareunia, as well as low back pain. At age 29, she began treatment with nafarelin acetate with minimal improvement in her pain. Oral contraceptives failed to relieve her pain. Repeat laparoscopy revealed endometriosis and a frozen pelvis due to extensive adhesions.

At age 37, the patient underwent supracervical hysterectomy and bilateral salpingo-oophorectomy due to continued severe pelvic pain. However, her pelvic pain continued. Transvaginal and transabdominal ultrasonography revealed a left complex cystic structure. She subsequently developed menstrual-like bleeding from the supracervical stump 7 days per month, at which time her pain became

most severe. Pelvic MRI at that time revealed right- and left-sided cystic masses measuring 3.7 and 2.4 cm with signal characteristics consistent with ovarian remnants (Fig. 1A). Her FSH level measured 12.5 milli-International Units/mL, consistent with a premenopausal state. Her gynecologic surgeon felt that she was not a candidate for further surgery.

On presentation in our department, abdominal examination of patient 3 revealed tenderness to light palpation in all quadrants without rebound or guarding, but dense fibrous tissue was palpable in the left lower quadrant. After

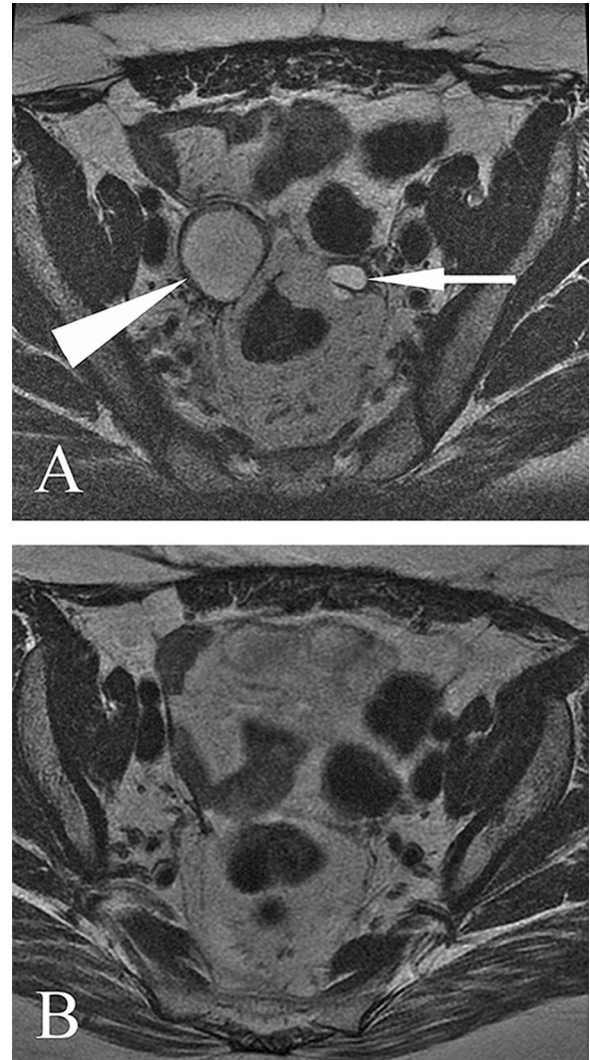


Fig. 1. A. Axial T2-weighted pelvic magnetic resonance images of patient 3 were obtained 2 weeks before radiation treatment. The large arrowhead indicates the 3.8-cm right-sided cystic mass, and the arrow indicates the 2.4-cm cystic mass, both of which were present before radiation treatment. B. Neither cystic mass is evident on axial magnetic resonance images obtained from approximately the same level 8 months after radiation therapy.

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providing signed informed consent, she was simulated. Initial treatment of 1,500 cGy in 10 fractions was administered to the ovarian remnant with 15-MV photons using AP and PA fields measuring 13.2×13.2 cm and 10.6×11.1 cm, respectively. This was followed by treatment to a cone-down field measuring 9.5×6.8 cm AP by 10.5×7.5 cm PA to a total dose of 450 cGy in three fractions (Fig. 2).

Three months posttreatment, the patient's FSH level measured 99.3 milli-International Units/mL, consistent with a postmenopausal state. Upon follow-up at 7 months, she noted some mild residual pelvic pain that had improved significantly since radiation treatment. An MRI of the pelvis at that time showed complete regression of the pelvic cystic structures (Fig. 1B).

None of the three patients developed any acute skin, bowel, or bladder complications of radiation treatment, such as diarrhea, urinary frequency, or skin erythema. All patients used topical moisturizers daily on their skin to prevent skin reddening. Two patients developed mild fatigue by the completion of radiation, which resolved completely by the 3-month follow-up. No long-term complications were noted throughout follow-up, including no proctitis or bowel obstruction.

COMMENT

We describe here the use of 3D imaging to guide radiation for the therapeutic ablation of ovarian remnants in symptomatic refractory endometriosis. Three women with severe, persistent pelvic pain due to endometriosis were successfully managed by ovarian remnant ablation with radiation therapy.

These patients illustrate the difficulties inherent to managing advanced endometriosis. In one case (patient 1), the left ovary was left in place at her initial surgery because of the patient's young age. However, subsequent medical ovarian ablation proved ineffective, and surgical intervention to remove the remaining ovary was felt to be unfeasible due to extensive adhesions and inability to identify the ovarian remnant on imaging. In the other two cases (patients 2 and 3), both ovaries were removed, but ovarian remnants sustained the patients in a premenopausal state, and it was felt that no further surgery could be safely performed. All patients had premenopausal levels of FSH despite having had oophorectomies.

All three patients attained postmenopausal levels of FSH within 3 months of radiation therapy. All patients reported complete relief of the severe, refractory pelvic pain for which they were referred, including one patient who had complete relief of cyclical pain. The latter effect may have been due to interruption of estrogen production by ovarian remnants; however, limited data suggest that ovarian remnants may respond in a cyclical fashion to pituitary gonad-

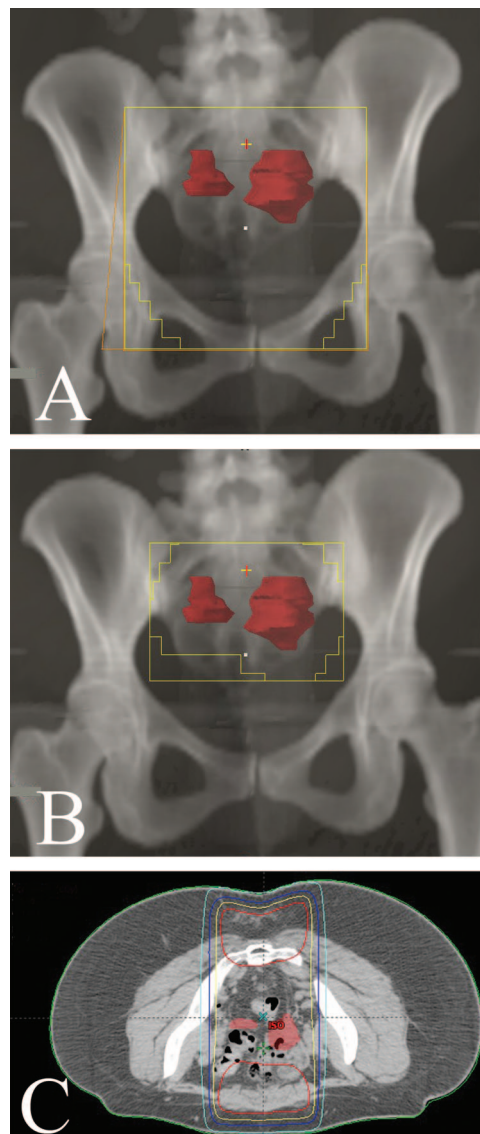


Fig. 2. **A.** Digitally reconstructed AP radiographs of the initial field for patient 3, which was treated with 1,500 cGy. The two central structures overlying the sacrum are contoured outlines of the two cystic structures identified on magnetic resonance imaging in this patient. The solid square indicates the position of the independent jaws. Blocking of the inferior corners was achieved with multi-leaf collimators. **B.** Digitally reconstructed AP radiograph of the cone-down field for patient 3, which was treated with 450 cGy. Contours of the cystic structures are shown, as are the positions of the independent jaws (solid square) with further blocks obtained by multi-leaf collimators. **C.** Planning noncontrast simulation computed tomography obtained in the prone position with corresponding contours of both cystic structures (inner hatched volumes) and the cumulative isodose lines for her prescribed course of 1,950 cGy in 13 fractions. From outermost to innermost, the isodose lines are as follows: 1,000, 1,700, 1,950, and 2,100 cGy. ISO, isocenter.

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otropins. The noncyclical component of low-level chronic pelvic pain that may persist after treatment may be related to pelvic adhesions; radiation therapy may cause fibrosis, thereby contributing to the underlying fibrosis and the attendant risks from adhesions in such patients. The dose used, however, is below the threshold at which either acute or long-term adverse effects on the bowel or bladder could reasonably be expected.

Both multiple surgeries and endometriosis itself are risk factors for the development of ovarian remnant syndrome.⁶ Several studies have shown that ovarian remnants causing pain can be removed successfully by experienced surgeons with minimal complications. Retrospective data from the Mayo Clinic on 180 patients who underwent surgery to remove ovarian remnants (56.8% of whom had endometriosis) showed only a 9% re-exploration rate and a 9.6% intraoperative complication rate.⁷ Another series described 69 laparoscopies to remove ovarian remnants from patients with a mean of four prior surgeries. Only three were found to have residual functional ovarian tissue after a first laparotomy but opted to pursue medical management. An additional five patients underwent a second laparoscopy for residual pain with satisfactory outcomes.⁸

The standard first-line treatment for women with endometriosis that is refractory to surgical intervention is hormonal manipulation. However, in the patients reported here, medical management had failed to relieve their pain. Radiation is a last resort for women with refractory pelvic pain unresponsive to hormonal manipulation because of the increased risk of radiation-related malignancy and other radiation-related side effects. Historically, low-dose ovarian ablation with 16 to 20 Gy of radiation for breast cancer treatment has been tolerated well with few long-term effects.⁴ The normal tissues at risk of radiation-related complications in pelvic radiation are the bowel, rectum, bladder, and soft tissues.

Based on our literature search of MEDLINE for "endometriosis" and "radiation therapy" through December 7, 2007, no prior publications using 3D targeted radiation for endometriosis exist. Two prior studies indicated that radiation was effective at eliminating pelvic pain in endometriosis; one targeted all regions of endometriosis and treated the entire pelvis with 30 Gy⁹; the other treated ovarian remnants as identified on pelvic ultrasonography 1 year before therapy and treated the entire pelvis with 15 Gy.⁵ Neither specifically targeted the ovarian remnant nor reported the use of 3D imaging at the time of radiation treatment planning.

Our results demonstrate the well-known ability of radiation to decrease estrogen production but with an unconventional purpose. The dependence of endometrial deposits upon estrogenic stimulation allows radiation to provide palliative benefit for premenopausal women with persistent pelvic pain from endometriosis who have exhausted all other treatment options. All patients had complete resolution of the severe pelvic pain for which they were referred. Two had complete resolution of all forms of pelvic pain. The persistence of low-level pelvic pain after radiation in one patient highlights the diversity of causes of pelvic pain, including fibrosis, which may be exacerbated by radiation, and the need for all potential outcomes to be addressed appropriately with the patient before embarking on therapy. Long-term severe endometriosis often results in dense pelvic adhesions that, in and of themselves, can cause severe pelvic pain long after elimination of estrogenic stimulation by endometriosis deposits. Carefully selected patients with persistent, severe, refractory, long-standing pelvic pain due to endometriosis who have residual functioning ovarian tissue after oophorectomy, but who have exhausted all other medical or surgical treatment options, may obtain a symptomatic benefit from ovarian ablation with relatively low-dose 3D conformal pelvic radiation.

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