

CASE REPORT

Successful Treatment with Drotrecogin alfa (activated) in a Pregnant Patient with Severe Sepsis

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Sepsis remains one of the leading causes of mortality during pregnancy. Because of the inherent limitations of conducting scientific investigations during pregnancy, a great deal of clinical decision making is based on observational reports, an understanding of the physiologic changes of pregnancy, and consideration for risk to the fetus. We describe a 20-year-old pregnant woman at 20 weeks' gestation who was admitted to an obstetric ward for dehydration and a urinary tract infection. Approximately 36 hours later, the patient's clinical status deteriorated, with the development of mental status changes, acute respiratory failure, and renal failure. Drotrecogin alfa (activated) was started, as the patient's Acute Physiology and Chronic Health Evaluation II score was 27 (> 25 is the typical score required for drotrecogin alfa [activated] therapy); within 48 hours the patient's clinical status dramatically improved. The patient completed 96 uninterrupted hours of therapy and was subsequently discharged after a 15-day hospitalization, with no apparent sequelae. Approximately 17 weeks later, the patient gave birth to a 3.42-kg female infant with no congenital abnormalities. To our knowledge, this represents the second case report to describe the use of drotrecogin alfa (activated) along with the status of the mother and fetus both after completion of therapy and after subsequent delivery. Because of the threat of mortality from sepsis during pregnancy, combined with the inherent limitations associated with clinical research during pregnancy, further reports and investigation into the treatment of sepsis in the pregnant patient are warranted.

Key Words: drotrecogin alfa (activated), pregnancy, sepsis, septic shock. (Pharmacotherapy 2011;31(3):50e–55e)

Sepsis remains a serious threat to patients worldwide, causing considerable morbidity and mortality. In the United States, sepsis is the leading cause of mortality among noncardiac critically ill patients.¹ Despite the growing body of evidence in the treatment of sepsis over the

past 10 years, including improved definitions allowing for identification of the disease, the estimated annual rate of diagnosed cases of sepsis in the United States continues to increase. Combined with the staggering costs of health care associated with the hospitalization and treatment of sepsis, the disease continues to be a great concern among the health care community. Despite the ever-increasing body of information on the treatment of sepsis, many barriers and challenges remain in the treatment of this disease state. Among these challenges, increasing antimicrobial resistance, an aging population, and immunocompromised patients add a significant layer of complexity to treatment decisions.² Although these subsets of clinical conditions add

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Table 1. Laboratory, Hemodynamic, and Clinical Values During the Patient's Hospitalization

Parameter	Normal Range	ED Visit	Hospital Day							
			1	2 ^a	3	4	5	6	11 ^b	15 ^c
Sodium (mEq/L)	137–145	132	—	133	135	135	133	133	138	—
Potassium (mEq/L)	3.6–5.0	3.5	3.4	3.0	3.4	3.7	4.5	4.7	3.8	—
Serum creatinine (mg/dl)	0.7–1.2	0.7	—	1.2	1.0	1.1	0.7	0.6	0.6	—
White blood cell count (x 10 ³ /mm ³)	4.5–11.5	12.5	12.7	9.8	7.7	6.6	6.2	6.1	7.6	—
Hemoglobin (g/dl)	12–15	10.1	8.7	9.6	10.4	11.2	11.7	11.4	11.4	—
Hematocrit (%)	36–48	29.3	25.0	27.7	30.4	33.1	33.9	33.3	33.8	—
Platelet count (x 10 ³ /mm ³)	150–400	117	98	92	90	105	147	181	425	—
Prothrombin time (sec)	9.7–12.3	—	—	10.2	10.6	10.0	9.9	—	—	—
International normalized ratio	—	—	—	1.01	1.05	0.99	0.98	—	—	—
Arterial pH ^d	7.35–7.45	—	—	7.43	7.40	7.42	7.41	7.39	—	—
Partial pressure of carbon dioxide (mm Hg) ^d	35–45	—	—	30	31	35	39	41	—	—
Partial pressure of oxygen (mm Hg) ^d	80–100	—	—	91	167	164	97	88	—	—
Mean arterial pressure (mm Hg)	70–100	50	53	45	58	68	72	74	78	86
Heart rate (beats/min)	60–100	108	114	128	116	106	110	100	92	88
Maximum body temperature (°F)	97.6–99.4	102.6	104.9	103.6	102.5	99.9	100.6	99.9	97.6	97.3

ED = emergency department.

Drotrecogin alfa (activated) was started on hospital day 2.

^bFinal laboratory results obtained from patient.^cDay of discharge.^dObtained from arterial blood gas.

a level of difficulty to the identification and successful treatment of sepsis, there is another population of patients in whom the data on sepsis is somewhat difficult to elucidate—the pregnant patient.

Although sepsis during pregnancy is a rare occurrence, with a reported incidence of 7.5 cases/1000 admissions annually, it is one of the leading causes of death in pregnancy.³ The study of sepsis during pregnancy presents several significant clinical dilemmas, and prospective studies are rare.² The challenges inherent in clinical evaluation of this patient population include ethical concerns of this high-risk population, the potential for harm to a developing fetus, and the significant physiologic changes that accompany normal pregnancy.² Therefore, many treatment decisions are based on observational case reports and an understanding of the physiologic changes that occur during pregnancy, combined with consideration for risk to the fetus.³

In this case report, we describe the successful treatment of sepsis in a pregnant patient at 20 weeks' gestation who received a full treatment course of drotrecogin alfa (activated) for severe sepsis and recovered fully, and who later

delivered a healthy female infant at term without complications.

Case Report

A 20-year-old Caucasian woman (gravida 3, para 2) came to the emergency department at 20 weeks' gestation complaining of a 3-day history of nausea, vomiting, diarrhea, and fever. Twenty-four days before this visit, she had been seen and treated in the emergency department for a *Klebsiella pneumoniae* urinary tract infection. Her medical history was significant for frequent urinary tract infections, anemia, and depression. Her drug therapy consisted of a prenatal vitamin with iron once/day and acetaminophen as needed for pain or fever.

The patient's initial vital signs were a blood pressure of 114/57 mm Hg, heart rate 135 beats/minute, respiratory rate 20 breaths/minute, oxygen saturation 99% on room air, and body temperature 102.6°F (orally). The fetal heart rate was recorded at 175–180 beats/minute. The patient denied pain or discomfort on urination; however, urinalysis was significant for the presence of nitrites, protein, ketones, and blood, and quantitatively revealed the presence of greater than

51 white blood cells/high-power field, 25 red blood cells/ μ l of urine, and a large quantity of bacteria. The results of her laboratory analyses are summarized in Table 1.

The patient was admitted to the obstetric ward for intravenous hydration and antibiotic and antiemetic therapy. She was given intravenous cefazolin 2 g every 8 hours, ondansetron for nausea, and acetaminophen as needed for fever. Fifteen hours after admission, the patient remained febrile and developed hypotension (mean arterial pressure 53 mm Hg) and shortness of breath, necessitating transfer to the intensive care unit with a diagnosis of sepsis secondary to pyelonephritis. Resuscitation was started in the intensive care unit and consisted of intravenous boluses of crystalloids and 2 units of packed red blood cells. To facilitate resuscitation and monitoring, a central venous catheter was placed. The infectious diseases service was consulted because of the patient's history of recurrent urinary tract infections. Cefazolin was then discontinued, and intravenous piperacillin-tazobactam 3.375 g every 6 hours and intravenous vancomycin 1 g every 12 hours were started.

At 5:45 A.M. on hospital day 2, approximately 36 hours after initial presentation, the patient developed acute respiratory failure and altered mental status that required endotracheal intubation. A chest radiograph revealed widespread opacity in the middle and lower lobes of the right lung as well as pulmonary edema; intravenous bumetanide was administered. Blood, urine, and sputum cultures were obtained, including human immunodeficiency virus (HIV) serology. Her antimicrobial regimen was continued with the addition of intravenous azithromycin 500 mg every 24 hours.

The patient remained febrile (with a maximum temperature of 103.6°F), hypotensive (mean arterial pressure 45 mm Hg), and tachycardic (mean heart rate 128 beats/min), despite resuscitation efforts, and subsequently developed acute renal failure. Aggressive fluid resuscitation and further transfusion of 2 units of packed red blood cells were administered. An Acute Physiology and Chronic Health Evaluation (APACHE) II score of 27 was calculated (> 25 is the typical score required for drotrecogin alfa [activated] therapy). At this point, consideration was given for the administration of drotrecogin alfa (activated). Palliative care service was consulted for family support. The patient's family was informed of the poor prognosis of both the patient and the fetus, and education on

the potential risks and benefits of drotrecogin alfa (activated) therapy were discussed. The patient's family provided consent, and intravenous drotrecogin alfa (activated) 24 μ g/kg/hour (patient weight 54 kg) for 96 hours was started at 12:09 P.M. on hospital day 2. Near the start of the infusion, a repeat chest radiograph revealed worsening pulmonary edema. Additional doses of bumetanide were administered. Subsequently, an echocardiogram was obtained, revealing global hypokinesis of the left ventricle and a left ventricular ejection fraction of 45%.

On hospital days 2 and 4, repeat urine cultures were negative. The sputum culture revealed greater than 25 white blood cells/high-power field, but no pathogen was isolated. The remaining microbiologic examinations and HIV serology were negative. The patient's renal function, urinary output, vital signs, and chest radiograph all showed improvement, with the exception of continued bibasilar pulmonary edema. On completion of 96 uninterrupted hours of drotrecogin alfa (activated) therapy, the patient's status continued to improve, and the patient was extubated on hospital day 7. In total, the patient received a 7-day course of vancomycin, a 10-day course of azithromycin, and a 14-day course of piperacillin-tazobactam. Two days later, the patient was transferred back to the obstetrics ward and was subsequently discharged on hospital day 15 after full recovery and no apparent sequelae. Throughout the hospitalization, including during and after completion of the drotrecogin alfa (activated) infusion, there were no reported bleeding events.

The patient's pregnancy continued to full term without any complications noted during routine obstetric visits. Approximately 17 weeks after hospital discharge, the patient came to the birthing center at the same institution in active labor at 38 weeks' gestation. A 3.42-kg female infant was delivered vaginally, without any maternal complications. On delivery, the infant demonstrated an initial Apgar score of 8 (scores of 7–10 indicate good health), which increased to 9 within 5 minutes postpartum. No congenital abnormalities or complications were noted at delivery or in the 48 hours after birth. The placenta was spontaneously delivered with no abnormalities noted and minimal bleeding (estimated blood loss of 400 ml) associated with the delivery. The patient and newborn were discharged home from the obstetrics unit 24 hours after delivery without complications.

Table 2. Case Reports of Treatment of Sepsis with Drotrecogin alfa (activated) in Pregnant Women

Age (yrs)	Gestational Age	Origin of Infection	Drotrecogin alfa Dose ($\mu\text{g}/\text{kg}/\text{hr}$) ^a	Duration of Infusion (hrs)	Adverse Effects
32 ¹²	27 wks	Urinary tract infection, pyelonephritis	24	Not reported ^b	Significant bleeding requiring extensive transfusion and multiple doses of recombinant factor VIIa
34 ¹³	33 wks	Urinary tract infection, bacteremia, and acute fatty liver of pregnancy	Not specified	144 ^c	Thrombocytopenia; no bleeding events noted
31 ¹⁴	22 days after in vitro fertilization	Bacteremia and ovarian hyperstimulation syndrome	24	96	None reported
19 ¹⁵	18 wks	Urinary tract infection	24	96	None reported

^aContinuous infusion.

^bInfusion interrupted multiple times for surgery; total duration of therapy not reported.

^cInfusion started postpartum.

Discussion

There are several critical considerations for the pharmacologic treatment of sepsis in the pregnant patient. Early goal-directed therapy, which has successfully reduced mortality in patients with sepsis, is generally recommended in pregnancy.² The initial approach to therapy is focused on resuscitation with intravenous fluids and is tailored to central venous and mean arterial pressure goals.⁴ During pregnancy, however, both the central venous pressure and the pulmonary artery wedge pressure may not be reliable markers for resuscitation, and to our knowledge, there have been no trials evaluating the appropriate central venous pressure goal for resuscitation specific to the pregnant patient.² In addition, there are several antimicrobial agents that should be avoided during pregnancy, including the fluoroquinolones, tetracyclines, and erythromycin. In general, antimicrobial therapy may be adversely affected by an increased volume of distribution and enhanced renal elimination, as well as alterations in absorption and distribution.

If sepsis progresses and the patient is at high risk for mortality, drotrecogin alfa (activated) may be considered. Drotrecogin alfa (activated) has been classified as pregnancy risk category C.^{5,6} It is not known whether the drug crosses the human placenta, although research indicates that endogenously produced protein C does not cross the placenta.⁵ In addition, the size of the drotrecogin molecule (molecular weight 55,000

kD) likely prohibits transport across the placental membrane.^{5,7} However, pregnancy was an exclusion criterion in the clinical evaluation of drotrecogin alfa (activated) in sepsis.⁸ Drotrecogin alfa (activated) has been recommended for the treatment of preeclampsia during early pregnancy (e.g., < 33 wks' gestation), as well as for the treatment of disseminated intravascular coagulation associated with placental abruption, although the doses used for this condition are significantly lower than those used in the treatment of sepsis.^{5,7,9,10} One particular concern associated with the use of drotrecogin alfa (activated) that is worthy of mentioning is the risk for maternal bleeding, which may threaten the pregnancy.⁷ A thorough assessment for the risk of bleeding in all patients receiving this drug, regardless of whether they are pregnant or not, remains key.¹¹

A review of the literature was conducted to identify reports of the use of drotrecogin alfa (activated) for the treatment of sepsis during pregnancy. Five case reports describing treatment of sepsis in pregnant patients were identified,¹²⁻¹⁶ with four patients receiving drotrecogin alfa (activated) therapy (Table 2).¹²⁻¹⁵ Two of these four patients underwent emergency cesarean delivery, one before initiation of drotrecogin alfa (activated)¹³ and one 9 hours after the start of the infusion.¹² In one case, drotrecogin alfa (activated) was not given,¹⁶ and in another case, the patient received the drug 22 days after in vitro fertilization, but the outcome of the pregnancy was not reported.¹⁴ In another

Table 2. (continued)

Outcome of Mother	Outcome of Fetus
Survived to discharge from intensive care unit; final outcome not reported	Emergency cesarean section required 9 hrs after start of infusion; final outcome not reported
Survived to hospital discharge	Emergency cesarean section required before start of therapy; healthy boy survived to hospital discharge
Survived to hospital discharge	Not reported
Survived to hospital discharge	Cesarean section at 39 wks due to fetal distress; healthy girl survived to hospital discharge

case, the patient received drotrecogin alfa (activated) 24 µg/kg/hour for 96 hours and later underwent urgent cesarean delivery due to fetal distress, which the authors state was not a result of the sepsis.¹⁵ Therefore, we believe our case to be only the second complete case report describing the successful use of drotrecogin alfa (activated) and reporting not only on the status of the mother after completion of a 96-hour course of therapy, but also the outcome of the mother and the fetus after subsequent delivery.

In pregnant patients, the APACHE II score is not a reliable predictor of mortality from sepsis and has been found to overestimate the risk for mortality in these patients.² Therefore, in addition to assessing an APACHE II score, it has been recommended that clinicians weigh the risks and benefits of treatment decisions against an assessment of gestational age and viability, and the presence of maternal organ dysfunction, comorbid disease states, and available treatment options.^{2, 3, 17} Although the patient's APACHE II score in this case was greater than 25, the patient had developed multisystem organ failure, including acute renal failure and acute respiratory failure requiring endotracheal intubation. Based on the rapidly declining status of the patient, and after a discussion of the risks and benefits with the family, drotrecogin alfa (activated) therapy was commenced with a resultant positive outcome.

Conclusion

Sepsis remains the leading cause of mortality in pregnant patients and presents a significant

threat to both the mother and developing fetus. Minimal research is available to evaluate the use of drug therapy in the pregnant patient with sepsis, and most information is deduced from case reports and clinical experience. This case report details the successful use of drotrecogin alfa (activated) in a pregnant woman at 20 weeks' gestation who later completed a normal vaginal delivery of a healthy, full-term, female infant. Because of the threat of mortality from sepsis during pregnancy, combined with the inherent limitations associated with clinical research during pregnancy, further reports and investigation into the treatment of sepsis in the pregnant patient are warranted.

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