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PATIENT SAFETY NETWORK

Shortcuts to Acetaminophen-induced Liver Failure

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The Case

An 18-year-old woman, 27 weeks pregnant, presented to the emergency department (ED) after a week of respiratory congestion, nausea, and fever. She was diagnosed with a viral upper respiratory infection, given IV fluids and acetaminophen, and discharged home with advice to continue taking acetaminophen as needed to control the fever. Thirty hours later, the patient returned to the ED with continued symptoms and new abdominal cramps. She was diagnosed with gastroenteritis and discharged with ondansetron and bismuth subsalicylate. Two days later, she presented again to the ED, this time with shortness of breath and abdominal pain. She was admitted to the ward and physical examination revealed lethargy, tachycardia, tachypnea, and generalized abdominal tenderness. Influenza B polymerase chain reaction was positive and Oseltamivir was started. Laboratory tests revealed leukocytosis, transaminitis in the thousands, and lactic acidosis. The patient was admitted to the hospital and given broad-spectrum antibiotics and a diagnosis of "influenza/possible sepsis." Further questioning revealed the patient had taken 1 g of acetaminophen every 4 hours since her initial ED visit. However, despite evidence of acute fulminant hepatitis due to chronic acetaminophen overdose, the antidote, N-acetylcysteine, was held for 10 hours because acetaminophen levels were less than 10 mcg/mL, deemed to be below the toxic level. The patient recovered over the next 24 hours with conservative management and N-acetylcysteine.

The Commentary

by Stephen Bacak, DO, MPH, and Loralei Thornburg, MD

Cognitive errors or biases are flaws or distortions in judgment and clinical decision-making that account for up to 28% of diagnostic errors and are major contributors to safety events.(1,2) Many are unconscious errors based on heuristics, which are shortcuts or educated guesses that humans use to guide clinical decision-making. Factors that increase the risk of cognitive error may be personal (e.g., fatigue), patient-related (e.g., multiple comorbidities), or systems-based (e.g., work environment).(2) This case of acute liver failure in pregnancy highlights several of these cognitive errors.

The cognitive error of *premature closure* (rush to diagnosis without consideration of alternatives) likely contributed to the patient's missed influenza diagnosis. Additionally, both *availability bias* (the first recalled information is deemed the most important) and *anchoring bias* (the first piece of information received is deemed the most important) played a role in the initial diagnosis of uncomplicated upper respiratory infection (URI) (anchoring to URI vs. other etiologies) and in the subsequent diagnosis of gastroenteritis (availability of pregnancy or gastrointestinal illness as etiology vs. other options). The fast-paced nature of the clinical environment undeniably contributed to these cognitive errors.

Respiratory infections are common in pregnancy. However, knowledge of pregnancy-specific changes in respiratory and immune physiology should have led to consideration of other potential serious diagnoses. For example, patients who are pregnant are at additional risk from respiratory disease, as evidenced by the excess maternal mortality related to the H1N1 pandemic.(3) The combination of respiratory symptoms and fever should have prompted a more extensive initial evaluation in this patient. There was also failure to recognize that pregnancy-related metabolic demands and limited physiologic reserve results in increased risk for sudden, rapid collapse.

Acute liver failure is rare, but life-threatening.(4) While liver disease complicates 3% of pregnancies, the incidence of acute liver failure in pregnancy remains unknown. Most cases are related to pregnancy-related conditions such as such as the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) or acute fatty liver of pregnancy, but acute deterioration in liver function may also be caused by nonpregnancy-related conditions including drug overdose (e.g., acetaminophen), viral infection, and exacerbation of underlying liver disease. The metabolic demands of pregnancy likely make these diseases more prone to acute liver failure than in nonpregnant patients.

Acetaminophen toxicity accounts for more cases of acute liver failure (42%) than any other in the United States.(5,6) Most are unintentional overdoses caused by doses exceeding 4 grams/day.(6,7) Acetaminophen is generally considered safe and routinely used in pregnancy for management of fever and pain; however, overdose is quite common. Nausea and vomiting are common symptoms of acetaminophen overdose, but the nonspecific nature of these symptoms and their common occurrence in pregnancy can delay diagnosis. Other symptoms include metabolic acidosis, coagulopathy, acute renal failure, pancreatitis, and coma. Some patients may have no symptoms prior to the onset of acute liver failure. Acetaminophen is also known to easily cross the placenta and ingestions of large doses may also lead to fetal liver injury and even death.

Evaluation and treatment for acetaminophen overdose is similar for pregnant women and nonpregnant women. Acetaminophen levels and liver function tests (LFTs) should be evaluated. Acetaminophen levels should be checked 4 hours or more after ingestion to allow for peak levels to be reached, while LFT levels usually peak 72 hours after ingestion.(8) Early treatment with N-acetylcysteine will reduce the risk of adverse outcomes.(9) Acetaminophen causes liver damage through its toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI), which reacts with hepatic enzymes leading to cellular hepatic damage.(10) Gluathione conjugates and inactivates NAPQI, but in an overdose is quickly depleted. N-acetylcysteine is a prodrug that is a converted to cysteine, providing this key constituent to glutathione replenishment, which in turn detoxifies NAPQI and prevents liver damage. In this patient's case, the levels were low, which may have falsely reassured clinicians. Falsely low levels can be seen when testing is conducted too early in

ingestion (less than 4 hours after overdose) or in patients with heterophile antibodies. Additionally, depending on the amount of time from ingestion, the treatment threshold varies and is much lower at 20 hours (10 mg/dL) postingestion than at 4 hours (150 mg/dL).(11) This is because the measured concentration will fall in the hours postingestion, even though the toxic NAPQI metabolite is still present. The interpretation of levels is further complicated in a patient with chronic, repetitive excessive intake versus single overdose. In this case, with symptoms, signs of liver damage, and levels that were at toxic threshold for 20 hours postingestion, therapy was warranted without delay, as the potential benefit even with low-level overdose strongly outweigh any risks of N-acetylcysteine in pregnancy (i.e., none). Intravenous (vs. oral) administration may increase the amount of medication crossing the placenta and aid in fetal treatment. Liver transplants after acetaminophen overdose during pregnancy have been reported.(12)

One cognitive error unique to medical care of pregnant women is the pervasive bias to nonintervention and nontherapy. Although limited data exist, the prevailing culture of medicine is toward nonintervention during pregnancy to avoid potential harm to the developing fetus, for example from imaging studies, surgery, or medications that might routinely be used in the care of nonpregnant patients. This bias may have contributed to the delay in the administration of N-acetylcyteine in this case. While the goal of avoiding potential teratogenic agents and interventions in pregnancy is laudable, medical or surgical risks need to be balanced against not just the risk of the treatment to the fetus, but also against the risks to the mother and fetus of nonintervention or nondiagnosis. A great example of this risk is imaging. Despite statements from both the American College of Obstetricians and Gynecologists (ACOG) and American College of Radiology on safety of chest radiograph and CT head/chest in pregnancy, and the high risks of a missed stroke or pulmonary embolism, these scans are often avoided or delayed due to concerns about radiation exposure.(13,14) This bias fails to take into account the risks for pregnancy of nonintervention, especially in the nonviable or periviable pregnancy, in which death of the mother would also result in loss of the fetus. In this case of acetaminophen overdose, the bias of nonintervention (delay) regarding antidote medication treatment could have resulted in ongoing acute liver failure with catastrophic outcomes for both mother and child.

This case highlights the need for implementing processes to improve care for pregnant women. Incorporating strategies to increase the recognition and minimize the risks associated with cognitive bias in health care environments are warranted. Some examples include simulation training, morbidity and mortality reviews, critical thinking training, and an organizational culture that optimizes provider cognition and decision-making.(2) Transferring the patient to an obstetric triage or labor and delivery unit, where providers are potentially more experienced with evaluation and medication use in pregnancy, as well as consultation with the obstetrician or maternal–fetal medicine physician, may have prompted a more extensive evaluation during the first two ED visits, or earlier administration of N-acetylcysteine.

A final consideration is the implementation of a checklist specific to the evaluation, treatment, and discharge of pregnant patients. Checklists are document-based tools that link current evidence to clinical practice and have repeatedly shown an improvement in patient care and safety. Both ACOG and the Society for Maternal–Fetal Medicine have endorsed and published obstetrical checklists.(15) In this case, a checklist or patient instruction care map regarding the use of acetaminophen with maximum daily dosing may have prevented the overdose.

Take-Home Points

- Acetaminophen overdose is common in pregnancy. Treatment with N-acetylcysteine is safe and recommended in pregnant women with acetaminophen overdose.
- Nonintervention bias in pregnancy is a serious concern, and providers must balance the risk not only of the medications and procedures, but also the risk of failure to treat or diagnose.
- Implementation of strategies to increase the recognition and minimization of cognitive bias are needed to improve care among pregnant women.
- Cognitive errors in clinical decision-making are a major contributor to patient safety events.
- Use of checklists may prevent cognitive errors and lead to more rapid evaluation and treatment.

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