Case Study

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Acute Fatty Liver Disease of Pregnancy

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When Corinne Warren became pregnant with her first child at the age of 28 in 1995, she was in exceptional physical condition. As an aerobics instructor, her exercise routine included cardiovascular training three to four times per week and weight conditioning five to six times per week. Her pregnancy progressed without complication. Everyone commented on her ability to maintain her fitness level throughout the pregnancy.

As Corinne puts it, "I was the poster child for a healthy pregnancy." Her excellent physical condition made the diagnosis of acute fatty liver of pregnancy (AFLP) after delivery almost unbelievable.

"The diagnosis just didn't fit with me or my lifestyle," says Corinne, reflecting back upon the nearly fatal complication that afflicted her and her newborn son. Although Corinne began having symptoms of AFLP in the 36th week, as a primigravida (as are 80% of diagnosed cases), it was difficult for Corinne to differentiate between "normal" and abnormal pregnancy symptoms. She reported an increased thirst to her practitioner, but was told that women in late pregnancy typically had a variety of odd symptoms. When she developed an unquenchable thirst, followed by uncontrollable shivering, her husband quickly transported her to the hospital. While being tested in the hospital, her water broke and labor quickly ensued. Corinne required a cesarean section. After the delivery of her son, Aiden, Corinne was transferred to the intensive care unit, where her memory of the events begins four days later, on Wednesday, April 24, 1996.

Pathophysiology

Although the exact etiology of AFLP is unknown, recent research points to a correlation between the maternal development of AFLP and a fetal enzyme deficiency called long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD), which prevents babies from processing certain fats (Staff, 2002). Hepatic histopathology reveals pericentral microvessicular fat in the liver, with minimal inflammation or necrosis. This excessive fatty build-up in the liver can result in hepatorenal failure, coagulopathy, and severe infections.

Symptoms

Symptoms most commonly present late in the third trimester, although there are documented cases with symptoms appearing as early as 26 weeks, and as late as after delivery (Buytaert, et al., 1996). Common symptoms include (Samuels & Cohen, 1992):

1. Vomiting (80%)
2. Abdominal pain (52%)
3. Jaundice (93%)
4. Encephalopathy (87%)
5. Polydipsia (80%)
6. Pruritis (60%)
7. Ascites (47%)

Polydipsia with or without polyuria frequently is an early symptom of AFLP. In Corinne's case, she was drinking in excess of 3 liters of fluid per day! This is thought to be a transient diabetes insipidus, and is one of the features that helps differentiate AFLP from HELLP syndrome. It is important to quickly and accurately diagnose AFLP, because the time from onset of symptoms to hepatorenal failure is only approximately two weeks (Blaskiewicz, n.d.).

Diagnosis of AFLP

Most women with AFLP present late in the third trimester with one or more of the above listed symptoms. Clinicians should suspect AFLP when pregnant women exhibit polydipsia, increased transaminase levels, decreased platelet count, and increased prothrombin time (Bacq & Riely, 1993). The differential diagnosis is that of fulminant hepatitis.

Definitive diagnosis of AFLP is through liver biopsy. However, this is rarely feasible in a pregnant woman and therefore, in many cases, it is necessary to rely on the laboratory data without waiting for a histologically proven diagnosis. Ultrasound is helpful in the exclusion of biliary tract disorders, but its value, as well as the value of CT and MRI scan has been limited and has not been considered helpful in the management of patients with AFLP (Abdalla, 1999). Clinical analysis of liver function tests is of paramount importance.

Liver Function

There is no single laboratory test available to assess liver function. Rather, the common phrase "liver function tests" describes a panel of tests, each of which assesses discrete aspects of liver function. Liver cell injury or necrosis is determined by measuring aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) levels. Liver synthetic function is determined by measuring albumin level and prothrombin time. Cholestasis and biliary function are determined by measuring alkaline phosphatase, bilirubin, and 5' nucleotidase or gamma glutamyl transpeptidase levels. In normal pregnancies, alkaline phosphatase levels may be elevated three to four times normal due to placental alkaline phosphatase levels.

During pregnancy, ALT levels can be elevated due to viral hepatitis (easy to diagnose using serologic tests), drug-induced hepatotoxicity, hyperemesis gravidarum, cholelithiasis, HELLP syndrome, or acute fatty liver of pregnancy.

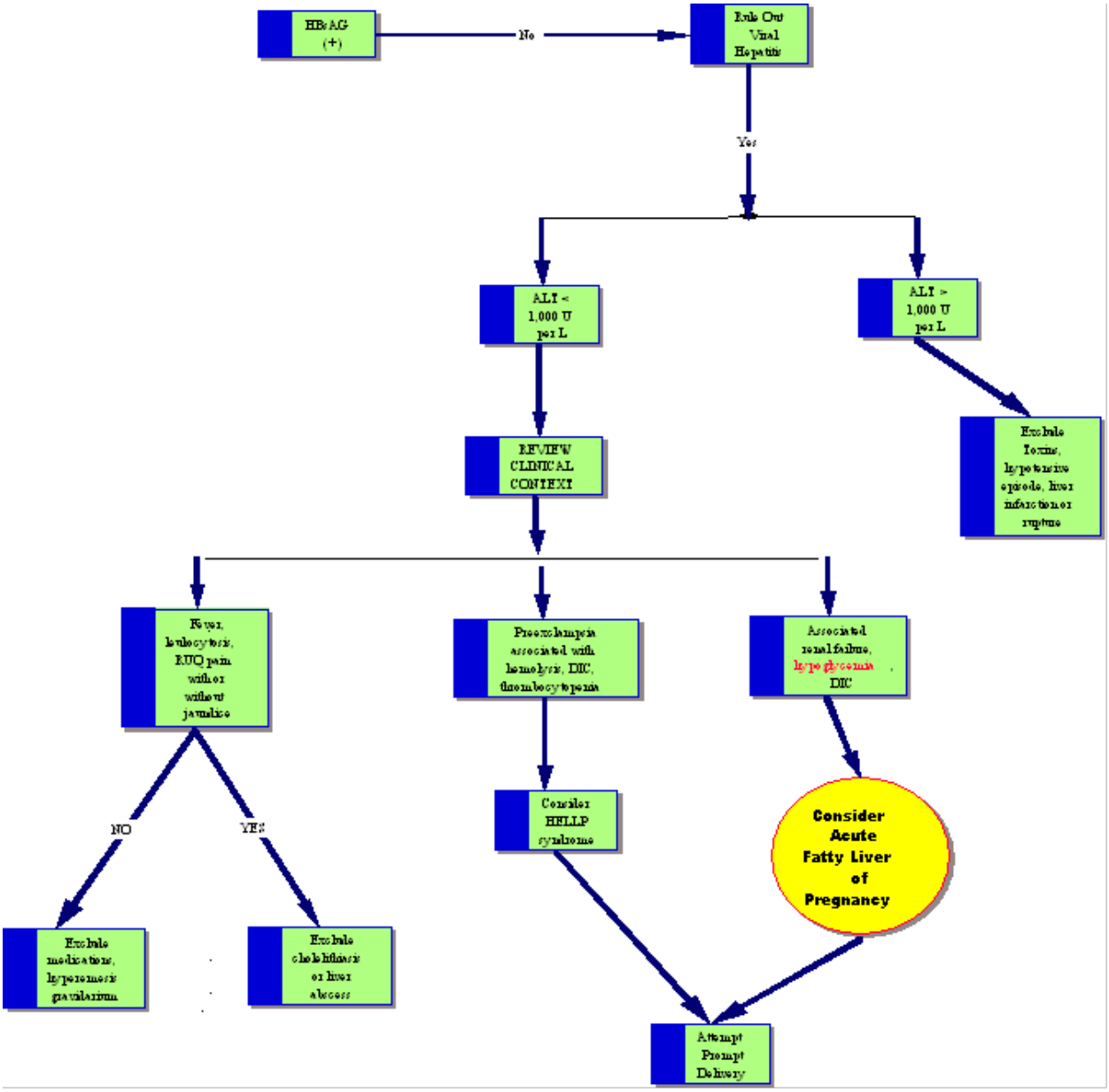
Once hepatitis has been ruled out, the level of ALT elevation is analyzed (normal level is less than 50). If the ALT level is elevated greater than 1,000 U per L, toxins are suspected and excluded. If the ALT level is more moderately elevated (less than 1,000 U per L), this is more suggestive of a triad of disorders, which can affect the liver:

- Cholelithiasis and hyperemesis gravidarum are associated with symptoms such as fever, leukocytosis, and RUQ pain, with or without jaundice.
- HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) is commonly associated with preeclampsia, hemolysis, disseminated intravascular coagulation (DIC), and thrombocytopenia.
- AFLP is commonly associated with renal failure, hypoglycemia, and DIC.

Other test abnormalities associated with AFLP can include:

- Coagulation abnormalities:
    - Hypofibrinogenemia (<300 mg/dl)
    - Prolonged prothrombin time
    - Prolonged partial thromboplastin time
- Conjugated hyperbilirubinemia (usually between 5 and 15 mg/dl)
- Increased alkaline phosphatase (normal is less than 170)
- Hyperuricemia
- Leukocytosis
- Hypoglycemia

The following chart, from Dr. Christine Hunt's "Liver Disease in Pregnancy" provides a visual diagnostic algorithm for the diagnosis of elevated ALT during pregnancy (Hunt & Sharara, 1999):



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As the above diagram illustrates, one major factor differentiating AFLP from HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is the presence of hypoglycemia, which, if untreated, can lead to hypoglycemic coma. Because of this, it has been proposed that women be treated with IV glucose infusion until their condition stabilizes.

Complications

Complications can include renal failure, cerebral edema, coagulopathy, gastrointestinal hemorrhage, severe postpartum hemorrhage, and severe infections. Most maternal deaths are attributable to one or more of the complications from AFLP and not to liver failure alone.

Treatment

All patients should be hospitalized as soon as a diagnosis of AFLP is suspected. Moderately or severely affected patients (those presenting with encephalopathy, deep jaundice, or prothrombin times less than 40% of control) or patients with any extrahepatic complication should be attended to in the intensive care unit. Glucose infusions should be maintained until a full metabolic recovery is achieved due to the risk of sudden hypoglycemia, which can occur at any time, even during clinical recovery. Most patients require platelets and fresh frozen plasma infusions. Prothrombin time and blood glucose levels should be monitored daily or more often. Other supportive care is provided based upon clinical symptoms.

Prognosis

Maternal recovery is slow and generally takes between 4 and 6 weeks. Babies born to mothers who developed AFLP are at increased risk of having a genetic mutation that causes a potentially fatal enzyme deficiency, commonly referred to as LCHAD (Scaglia, 2003). Therefore, it is recommended that all women with AFLP and their infants be screened for this genetic condition. LCHAD is a serious deficiency that usually presents in the latter part of infancy with hypoglycemia, cardiomyopathy, hypotonia, and hepatomegaly. In the majority of cases, the disease is severe and can lead to death during the first few years of life. The chance of recurrence of AFLP in subsequent pregnancies is 15-25% (Tyni, Ekholm & Pihko, 1998).

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Corinne and Aiden at 7 ½ months

Corinne's Recovery

Corinne Warren recovered slowly, as do most women afflicted with AFLP. She was treated in the intensive care unit after the delivery of her son, Aiden, by cesarean section, on April 20, 1996, due to breech presentation. Her complications included DIC, jaundice, hypoglycemia and renal impairment. She remembers being in a lot of pain, and states, "the only area of my body that didn't hurt was the tips of my ears."

Corinne has suffered ongoing medical problems since her diagnosis of AFLP, including a depressed immune system, despite return to normal of her liver function tests. She suffers from chronic migraine headaches, which have been treated with medication. She has been unable to resume her former level of aerobic activity.

Aiden was born with an APGAR score of 2 but quickly recovered. He was readmitted to the hospital less than two weeks after delivery for treatment of dehydration and hypoglycemia. He has since suffered migraine headaches.

Corinne and Aiden have both been tested for LCHAD deficiency, and both are negative. After consulting a perinatologist, Corinne went on to have a second pregnancy, without AFLP complications. Her second child, daughter Elora, was born on August 18, 1998.

When reflecting back upon her diagnosis of AFLP, Corinne states, "I am convinced that I survived AFLP because I was in such great physical shape throughout my pregnancy. I weighed 108 pounds at conception, with only 13% body fat. By the time recovered, my weight was well under 100, and I had almost no muscle left!"

When asked how she feels about her experience with AFLP, Corinne has this to say:

"I never asked 'Why me?' I just felt that the diagnosis was so unexpected. I had had a clinically stable pregnancy, and I had taken good care of my body. I could not believe that any disease would affect me! My advice to other women would be 'Expect the unexpected.' Even if the odds of AFLP are one in nine thousand, that one person could be you! Pay attention to your body and don't ignore symptoms that do not feel right. Pursue

them, even if you are told that they are 'normal.' You know your body better than anyone else."

Potential Medical-Legal Actions

1. Wrongful death (maternal and fetal) due to delayed diagnosis.
2. Birth injury due to delayed diagnosis.
3. Failure to treat the sequelae of AFLP (resulting in maternal or fetal injury or death).
4. Failure to diagnose LCHAD in an infant born to a mother who experienced AFLP (leading to infant mortality or development of neurological, cardiac, ophthalmologic, or other abnormalities).

Legal Nurse Review

Review all medical records, especially the last trimester, for signs and symptoms of AFLP. These can include preeclampsia (elevated blood pressure, edema, and proteinuria), polydipsia, polyuria, nausea, vomiting, hypoglycemia, abdominal pain, jaundice, pruritis, or ascites. Note that mild jaundice and a modest elevation in serum aminotransferase are important signs against the diagnosis of fulminant hepatitis, viral or toxic. The mild increase in blood pressure, hyperuricemia, and intense thirst are uncommon in fulminant hepatitis and they favor the diagnosis of acute fatty liver of pregnancy. AFLP should be suspected when persistent vomiting, malaise, encephalopathy or jaundice appear in the final weeks of pregnancy or in the early puerperium.

If signs and symptoms were present, determine whether appropriate laboratory tests were ordered and analyzed:

- Liver functions tests, especially ALT
- Appropriate analysis of moderately elevated ALT
- PT, PTT
- Bilirubin
- Serum glucose levels
- Serum uric acid levels

Was the patient hospitalized as soon as AFLP was suspected? Was delivery promptly carried out? Were moderately or severely affected patients treated in the intensive care unit? Were sequelae anticipated and treated appropriately (especially coagulopathy, renal failure and serum glucose levels)? Was the mother counseled regarding the potential

LCHAD deficiency and offered appropriate genetic testing? Was the infant screened for LCHAD?

In subsequent pregnancies, was the gravida well informed of the risks of recurrence of AFLP? Were the required tests (liver tests, uric acid, prothrombin time, and possibly antithrombin III) carried out biweekly in the third trimester?

Although rare, the high morbidity and mortality rates associated with AFLP make this diagnosis fraught with medical legal implications. Recent research into the correlation between AFLP and LCHAD may lead to prospective diagnosis of pregnant women sometime in the future. Until then, recognition of symptoms, accurate differentiation, and appropriate medical intervention are critical mitigating factors against potential legal action related to the diagnosis and treatment of this disorder.

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