Fetal Fatty Acid Oxidation Defects and Maternal Liver Disease in Pregnancy

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OBJECTIVE: The objective was to evaluate the relationships between all types of fetal fatty acid oxidation defects and maternal liver disease, including acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

METHODS: This was a case–control study comparing fetal fatty acid oxidation defects to the outcome of maternal liver disease. Fifty case infants with fatty acid oxidation defects were identified, with 25 matched controls collected per case. This generated a total of 50 case infants and 1,250 control infants. Pregnancies were evaluated for the presence of maternal liver disease (comprised of acute fatty liver of pregnancy, HELLP syndrome, and preeclampsia evolving into HELLP syndrome) using a conditional logistic regression model. Subgroup analysis compared long chain to short and medium chain fatty acid defects.

RESULTS: Maternal liver disease was noted in 16.00% of all fatty acid oxidation defect pregnancies compared with 0.88% in the general population (odds ratio 20.4, 95% confidence interval 7.82–53.2). These pregnancies demonstrated an 18.1-fold increase in maternal liver disease when compared with our matched population controls with unaffected fetuses. All classifications of fatty acid oxidation defects were at high risk of developing maternal liver disease. Long chain defects were 50 times more likely than controls to develop maternal liver disease and short and medium chain defects were 12 times more likely to develop maternal liver disease.

CONCLUSION: Maternal liver disease is significantly higher across the entire spectrum of fatty acid oxidation defects pregnancies compared with the matched control population. Notably, there is significant risk to the pregnancies with fetuses affected with short and medium chain defects, not just those with fetal long chain fatty acid oxidation defects as previously reported. Future studies should examine the pathophysiology of all infant fatty acid oxidation defects and its implications for maternal liver disease for improved future health outcomes.

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LEVEL OF EVIDENCE: II-2

Acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome are both relatively rare disorders of pregnancy, occurring in the third trimester.1–7 Each occurs in less than 1.00% of pregnancies, with acute fatty liver of pregnancy in 0.01%8–9 and HELLP syndrome in 0.60–1.00% of pregnancies.10 Acute fatty liver of pregnancy presents with abdominal pain, nausea, and vomiting and can rapidly progress to hepatic failure with coagulopathy, encephalopathy, and death. A microvesicular hepatic steatosis is present.2–8 Before presentation, HELLP syndrome may or may not have a prodrome of preeclampsia but clinically may present with abdominal pain, edema, and edema with the onset of hemolysis, elevated liver enzymes, and a low platelet count.9–11 In both scenarios the pregnant woman and the fetus are at risk of death if the fetus is not delivered quickly. The estimate for maternal mortality is 2% and for fetal mortality is 33% for...
HELLP syndrome; maternal mortality is estimated at 18% and fetal mortality at 23% for acute fatty liver of pregnancy. This association was first reported in 1991 by Schoeman and colleagues with a case of long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) and acute fatty liver of pregnancy. Since then, LCHAD has been associated with both maternal liver diseases at a significantly higher rate than the general population from an empiric standpoint. Uniform study of long chain defects compared with a control population, or examination of different carbon chain length defects for other fatty acid oxidation defects (FAODs) has not been demonstrated in the literature. Fatty acid oxidation defects are a category of inborn errors of metabolism that are inherited in an autosomal recessive pattern. Patients affected with this disease do not have sufficient mitochondrial β-oxidation of the fatty acids for ketogenesis as a secondary source of energy mobilization once the glycogen stores are depleted. A key symptom is critical hypoglycemia during times of catabolic stress. This can severely affect the brain, heart, liver, and skeletal muscle that rely on this energy source.

A key difficulty in characterizing the relationship between fetal fatty acid oxidation defect (FAOD) and maternal liver disease is that maternal liver disease states in the general population have a low prevalence rate. Additionally, the fetal and infant fatty acid defects are also rare conditions, occurring in 1:10,000–12,000 births for all FAODs combined. To accommodate these very low frequencies, we performed an epidemiologic study powered to determine whether a uniform statistical relationship between fetal FAOD and maternal liver disease exists. Our objective was to establish the broad scope of different FAODs associated with devastating maternal liver disease states.

MATERIALS AND METHODS
This was a case–control study. The inclusion criterion for cases was the presence of an infant fatty acid oxidation defect. Infants with an FAOD from the New England region were ascertained by the New England Consortium of Metabolic Centers and through the New England Newborn Screening Program from August 1999 to October 2003 by newborn screening. Fifty case infants were confirmed to have a subtype of an FAOD by a follow-up metabolic evaluation. Confirmation was made by diagnostic biochemical analytes and, when possible, confirmation by molecular mutation analysis. This confirmation was consistent with screening expectations. The FAOD classification groups were designated as a “long chain defect,” consisting of the following disorders: LCHAD, trifunctional protein deficiency, very long chain acyl-CoA dehydrogenase deficiency, and carnitine palmitoyltransferase I and II deficiency. The second FAOD classification group was as the “short and medium chain defects” and consisted of the following disorders: short chain acyl-CoA dehydrogenase deficiency (SCAD) and medium chain acyl-CoA dehydrogenase deficiency. Nonviable gestations or spontaneous abortions were not ascertained as cases. For each case, 25 unaffected infants who were confirmed by a normal newborn screening, were selected and linked to that case infant. Control infants were randomly selected and matched by date of birth and hospital setting. Controls were matched to the birth hospital of the ascertained case when possible; additionally, ethnicity and age was matched as closely as possible to the index case with date of birth having priority over ethnicity.

Cases and controls were then evaluated for maternal liver disease as the primary outcome measure. Maternal liver disease was considered as HELLP syndrome, preeclampsia evolving into HELLP syndrome, or acute fatty liver disease of pregnancy. For diagnostic inclusion, HELLP syndrome was required to have signs of hemolysis, elevated liver enzymes with aspartate transaminase more than 70 U/L, and a platelet count less than 100,000/μL. Acute fatty liver of pregnancy diagnostic inclusion criteria included abdominal pain, nausea or vomiting, signs of hepatic failure including aspartate transaminase more than 70 U/L, signs of coagulopathy, and if available, pathology documenting microvesicular hepatic steatosis or mitochondrial disruption. If available, ultrasound evidence of steatosis was included (62.5% of cases). Isolated preeclampsia was not considered a maternal liver disease state. These diagnoses were confirmed by medical review using electronic medical review if available after appropriate institutional review board process. The umbrella institutional review board review was approved through Partners Health Care system, Children’s Hospital Boston, and South Shore Hospital. Permission from medical directors was obtained if the respective hospital did not have an institutional review board.

The mother–infant pairs were analyzed comparing cases with controls using a conditional logistic regression model. Subgroup analysis was performed comparing the subgroup of “long chain FAOD” and the subgroup of “short and medium chain FAOD”; each subgroup was compared with its matched control population with regard to the outcome of mater-
nal liver disease using a Bonferroni correction for significance. Additional secondary outcome measures were obtained, including other antenatal characteristics such as maternal gestational diabetes and isolated preeclampsia. Gestational diabetes was defined by local hospital policy, but at a minimum inclusion of a 100-g glucose load and a resultant serum glucose concentration fasting of 95 mg/dL, 1 hour at 180 mg/dL, 2 hours at 155 mg/dL, and 3 hours at more than 140 mg/dL, with 2 or more of venous plasma concentrations meeting or exceeding these levels for diagnosis. Isolated preeclampsia was defined as new onset of hypertension, not superimposed on chronic hypertension, with blood pressure values more than 140/90 mm Hg after 20 weeks of gestation in a previously normotensive woman, and proteinuria reflective of a 24-hour urinary protein more than 300 mg or a spot dipstick of 30 mg/dL (1+).

Postnatal relationships, including infant demographics, general health and anthropometrics, and physical characteristics, were noted. Neonatal jaundice was diagnosed on clinical observation by the respective health care provider on physical examination. Jaundice was not uniformly evaluated by laboratory assessment, causing study limitation of the interhospital standard of practices. Due to study limitations, gravida and para information could not be uniformly ascertained and were not included in the statistical model.

RESULTS

Fifty case infants with FAOD were ascertained, 1,250 matched control infants (Table 1). Primary outcome analysis revealed maternal liver disease occurred in 16.00% of all pregnancies with a fetus affected by FAOD (equally represented in long compared with short and medium chain defects) as compared with 0.88% in the general population (odds ratio [OR] 20.4, 95% confidence interval [CI] 7.82–53.2) (Table 2). The specific disorders with each associated maternal liver disease and the prevalence by diagnosis are listed in the box and Table 3. The infant genotypes associated with the pathogenic outcome of maternal liver disease are represented in Table 4. Of note, infant 5 with SCAD did not have a classic mutation for this disorder, but was a compound heterozygote for the disease variant polymorphisms. The diagnosis of SCAD in the patient was based on reduced SCAD activity in skin fibroblasts, elevation of butyryl carnitine (C4) in plasma acylcarnitines, and persistent elevations of ethylmalonic acid in urine. This is a similar presentation to the report of a fetus with SCAD whose perinatal course was complicated by maternal acute fatty liver of pregnancy and was homozygous for the disease variant polymorphism, 625G>A.

Subgroup analysis of the 50 affected infants revealed that 32% had long chain fatty acid oxidation defects and 68% had a medium or short chain fatty acid oxidation defect. Intragroup analysis of the infants with medium or short chain defects compared with those with the long chain defects demonstrated no differences in maternal age between the 2 subgroups, but small differences in birth weight (short and medium chain 2.94 kg compared with long chain 3.41 kg, \(P < .05\)) and gestational age (short and medium chain 39.2 weeks gestational age compared with long chain 37.3 weeks gestational age, \(P < .05\)) existed between the subgroups by analysis of variance. There were no differences in demographics between the case infant group as a whole and the control infant group population relative to maternal age, birth weight, or gestational age.

Analysis of risk for maternal liver disease during pregnancy in the subgroups compared with population controls was performed using a Bonferroni correction (\(P < .025\)). Both groups, the short and medium chain defects and the long chain defects, had significantly higher rates of maternal liver disease than in the matched control population. The fetuses who had a long chain defect were 50 times more likely to have a maternal liver disease outcome than

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>N (%)</td>
</tr>
<tr>
<td>Maternal age (y)</td>
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<tr>
<td>Birth weight (kg)</td>
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<tr>
<td>Gestational age (wk)</td>
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FAOD, fatty acid oxidation defect. Values are mean (± standard deviation) unless otherwise specified.

* Represents intragroup statistical difference.
the matched control population by conditional logistic regression (OR 50.0, \( P < .001 \)). The fetuses with a short or medium chain FAOD were 12 times more likely to have a maternal liver disease outcome as compared with controls by conditional logistic regression (OR 12.3, \( P < .001 \)).

Secondary endpoint analysis did not reveal statistically significant differences in clinical features of pregnancies between fetuses with FAOD and their matched unaffected controls, with the exception of incidence of neonatal jaundice. Clinical jaundice was significantly higher in infants with fatty acid oxidation defects (FAOD 36% compared with control 8%; OR 6.25, 95% CI 3.42–11.4) than in the control population. The remainder of the secondary endpoints were not significantly different, including the incidence of isolated preeclampsia and the incidence of gestational diabetes mellitus.

**DISCUSSION**

Frequency of maternal liver disease morbidity was significantly higher in pregnancies carrying a fetus affected with an FAOD. These pregnancies demonstrated an 18.1-fold increase in maternal liver disease when compared with our matched population controls with unaffected fetuses. Notably, a significant
risk was present in the pregnancies of fetuses affected with short or medium chain defects, and not isolated simply to those infants with long chain FAOD. This implicates the entire spectrum of the FAOD disorders, not just the previously detailed LCHAD.

Although LCHAD remains the most frequently documented FAOD occurring with maternal liver disease, there is no explanation for a specific relationship between LCHAD and maternal liver disease. Reasonable speculation has considered that increased fetal 3-hydroxy fatty acid acylcarnitine intermediates accumulate in utero and detrimentally target the maternal host liver. Fetal FAOD disorders at a more distal end of the mitochondrial β-oxidation spiral than LCHAD have not been consistently implicated with maternal liver disease. Isolated case reports of 1 case of medium chain acyl-CoA dehydrogenase deficiency and 1 case of SCAD deficiency have suggested that these fatty acid intermediates may also be implicated in this pathway of maternal liver disease and have been represented in this study. Overall, the prevalence of maternal liver disease was 16% across the spectrum of all FAOD disorders, posing a significantly higher risk than in the general population. Previous studies noting a higher rate of maternal liver disease complications were clinically ascertained and perhaps confounded by the severity of the index cases. Our study, in ascertaining the infant and extrapolating the diagnosis retrograde to the pregnancy, avoids this prior ascertainment bias and includes fatty acid defects found presymptomatically by newborn screening.

All mothers of affected infants are obligate carriers of the FAOD by definition of an autosomal recessive inheritance pattern, but why only 16% of these pregnancies develop complex maternal liver diseases of pregnancy is unknown. Simple genotype and phenotype correlation models may not be enough to explain the phenomenon of this disease; environmental variables are also likely given the relationship of this disorder to dietary intake. One potential explanation for the variability in expression of this pregnancy complication may be that carnitine demands during the third trimester of pregnancy cause a “functional” carnitine deficiency stressing the maternal and fetal β-oxidation pathway past a critical threshold and producing higher levels of acylcarnitine intermediates that accumulate in the milieu. Other possibilities are that these acylcarnitine intermediates may have more of a “priming” effect on the maternal host liver, rendering it susceptible to catabolic insult toward the end of gestation. Why some obligate carriers of FAOD become more susceptible to maternal liver disease than others remains unknown. Interestingly, the microvesicular fatty infiltration of maternal liver that occurs during maternal liver disease in the obligate carrier is a similar presentation to a homozygous affected child with a long chain FAOD.

We suggest that pregnant women with a history of maternal liver disease should be followed up carefully with liver function tests, blood glucose levels, and low platelets; TFP, trifunctional protein deficiency; SCAD, short chain acyl-CoA dehydrogenase deficiency; MCAD, medium chain acyl-CoA dehydrogenase deficiency; AFLP, acute fatty liver of pregnancy.

Table 4. Mutation Analysis of Fatty Acid Oxidation Defect With Maternal Liver Complications

<table>
<thead>
<tr>
<th>Infant No.</th>
<th>Fetal FAOD</th>
<th>Infant Mutations/Polymorphisms</th>
<th>Maternal Disease</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>LCHAD</td>
<td>G1528C/G2027A</td>
<td>HELLP</td>
</tr>
<tr>
<td>2</td>
<td>TFP</td>
<td>IVS5+1G&gt;A/?</td>
<td>HELLP</td>
</tr>
<tr>
<td>3</td>
<td>LCHAD</td>
<td>G1528C/ G1528C</td>
<td>Preeclampsia → HELLP</td>
</tr>
<tr>
<td>4</td>
<td>LCHAD</td>
<td>Unknown*</td>
<td>Preeclampsia → HELLP</td>
</tr>
<tr>
<td>5</td>
<td>SCAD</td>
<td>625G&gt;A/511C&gt;T</td>
<td>HELLP</td>
</tr>
<tr>
<td>6</td>
<td>SCAD</td>
<td>505A&gt;C/505A&gt;C</td>
<td>Preeclampsia → HELLP</td>
</tr>
<tr>
<td>7</td>
<td>MCAD</td>
<td>985A&gt;G/504A&gt;C</td>
<td>AFLP</td>
</tr>
<tr>
<td>8</td>
<td>MCAD</td>
<td>985A&gt;G/985A&gt;G</td>
<td>AFLP</td>
</tr>
</tbody>
</table>

FAOD, fatty acid oxidation defect; LCHAD, long chain 3-hydroxyacyl-CoA dehydrogenase deficiency; HELLP, hemolysis, elevated liver enzymes, and low platelets; TFP, trifunctional protein deficiency; SCAD, short chain acyl-CoA dehydrogenase deficiency; MCAD, medium chain acyl-CoA dehydrogenase deficiency; AFLP, acute fatty liver of pregnancy.

* Declined molecular testing.
vigilant approach entering the third trimester of pregnancy. In addition, in states that are not currently screening for fatty acid oxidation defects by expanded newborn screening, the infant born to a mother with a maternal liver disease should have close observation after delivery for cardinal signs of an FAOD. We recommend these infants be followed up for signs of hypoglycemiam and hyperbilirubinemia. Future management should consider the entire pathway of β-oxidation in fatty acid defects with respect to maternal liver disease for improved future pregnancy health outcomes.

REFERENCES