FODs and Pregnancy Research

To the FOD Family Support Group,

Firstly, let me say what an honor it is to work with families with Fatty Acid Oxidation defects. I really appreciate Deb Lee Gould giving me the opportunity to tell you about some of the research we presented this year at the American College of Medical Genetics and the Society for Inherited Metabolic Disorders Meetings in Orlando, Florida.

We recently looked, with great detail, at pregnancies that gave rise to a child with a fatty acid oxidation defect. We followed these pregnancies to see if they evolved into maternal liver disease (MLD). Generally speaking, MLD's are a category of liver problems that occur during pregnancy such as Acute Fatty Liver of Pregnancy or HELLP syndrome (hemolysis , elevated liver enzymes, and low platelets). These liver conditions are very rare, and can cause the maternal liver to stop working properly, and if not recognized, can put both mom and baby at risk.

What we did was to look at the pregnancies of ALL FAODs, not just the ones with long chain defects. What we found was all categories of FAOD are at *some* risk of developing these problems; roughly 16% of all infants with FAOD had a pregnancy complicated by one of these maternal liver conditions. Although this may not seem like a large percentage, it is in comparison to the general population, where it occurs *less* than 1% of the time.

Although our research is far from done, we hope to look in more detail at the biology of why this happens. Perhaps the most important concern is for patient advocacy. When the rare occurrence of HELLP Syndrome and/or Acute Fatty Liver of Pregnancy occurs, the suspicion for a potential fatty acid oxidation defect should be immediately raised. This is especially critical in states that are not currently performing expanded newborn screening for FAODs. Good communication with the pediatric care provider should occur from the obstetric team to ensure that this follow up assessment of the newborn infant occurs.

The clinical collaborators at the different locations during the initial part of this project have been:
Dr. Vivian E. Shih, Massachusetts General Hospital Neurology Service, Chief of Metabolism
Dr. Harvey L. Levy, Children's Hospital Boston, PKU Program
Dr. Louise E. Wilkins-Haug, Brigham and Women's Hospital Maternal/Fetal Medicine Clinic,
Dr. Cecilia Larson, New England Newborn Screening Program

We are very interested in checking the fatty acid intermediates in pregnant women who have had a child with a FAOD in the past. If you are interested in participating, or would like to know more, please contact me at:

Laboratory/Research Office: (617)-726-3884 (Massachusetts General Hospital Amino Acid Lab)
Clinical Appointments: (617) 355-4695 (Children's Hospital Boston)

I can also be reached via email at mfearing@partners.org

Sincerely,
Marsha Fearing, M.D., M.P.H.

Abstract

Maternal Liver Diseases in the Pregnancies of Infants with the Spectrum of Fatty Acid Oxidation Defects Compared to Matched Population Controls.

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Background: Infant fatty acid oxidation defects (FAOD) are rare inborn errors of metabolism, occurring in 1:12,000 births. Common clinical features of long-chain FAOS include hypoglycemic and hypoketotic encephalopathy, hypotonia, cardiomyopathy, and sudden death. Increasingly, fetal long chain FAODs are associated with rare maternal pregnancy complications affecting the liver. These include acute fatty liver of pregnancy (AFLP); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; and pre-eclampsia evolving into HELLP syndrome. This relationship was initially described in the long chain FAODs, specifically Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD). A few isolated case reports emerged implicating the shorter chain defects, but the true prevelance among fetuses affected with the entire spectrum of FAOD is unknown. Maternal liver disease (MLD) in the general population has a low prevalence rate estimated at 0.1-1.5% for AFLP and 0.6-1.0% for HELLP syndrome. Given the paucity of these conditions, elucidating the true epidemiological relationship is difficult. The lack of literature comparing the entire spectrum of FAOD and pregnancy outcomes compared to the population led us to perform the following study.

Method: 50 case infants with fatty acid oxidation defects (FAOD) were identified in the New England region, either clinically or by expanded panel tandem mass spectrometry (MS/MS) newborn screening. A conditional logistic regression model was established, paring each infant affected with a FAOD to 25 unaffected controls for each case. Infants were matched by date of birth and hospital setting, generating a total of 1300 infant-mother pairs. Primary outcome analysis compared pregnancies affected by a fetal FAOD to controls for outcomes of MLD (AFLP, HELLP syndrome, and pre-eclampsia that evolved into HELLP syndrome). Isolated pre-eclampsia was not included in MLD. The pairs were phenotyped for secondary outcomes in antenatal, intrapartum and neonatal characteristics. Subgroup analysis was performed comparing the fetuses with long chain FAO defects to fetuses with medium/short chain FAOD defects. A Bonferroni correction was applied where appropriate to establish cutoffs for significance for the primary outcome.

Results: Case and control infants analyzed were similar with respect to mean gestational age (case = 38.2 ? 2.1 weeks; controls = 37.8 ? 3.6 weeks), mean birth weight (3264 ? 577 grams; 3308 ? 446 grams), and maternal age (30.2 ? 5 years; 28.4 ? 6 years) for the FAOD and control infants respectively. Primary outcome analysis revealed MLD occurred in 16% of all FAOD pregnancies (equally represented in long versus short-medium chain defects) compared to 0.88% in the general population (OR=20.4; 95% CI = 7.8-53.2). Secondary analysis of isolated pre-eclampsia without hepatic involvement was not significantly different between the case (6%) and control pregnancies (6.1%); gestational diabetes mellitus was not significantly different in cases (10.0%) and controls (6.8%). However, post-natal results included elevated rates of clinical neonatal jaundice that was significantly higher in case versus control [FAOD 36%, control 8% (OR 6.25; CI= 3.42-11.4)] infants.

Of the fetuses affected with FAOD, 32% (n = 16) had a defined long chain defect, and 68% (n = 32) had a medium or short chain defect. There was no demographic difference among maternal age, but groups differed slightly on birthweight (long chain =3.410 ±0.52 Kg; short/medium chain =2.940 ±0.57 Kg). Subgroup analysis comparing fetal long chain FAOD to controls and fetal medium-short chain FAOD and maternal liver disease demonstrated significance in both groups (long chain FAOD OR = 50.0 $p<0.001$; short/medium chain FAOD OR = 12.3 $p<0.001$; Bonferroni correction $p < 0.025$).

Conclusions: MLD is significantly higher across the entire spectrum of FAOD demonstrating an 18.1 fold increase in the pregnancies of FAOD neonates compared to our control population. Notably, the prevalence is equally high in the pregnancies of infants with short and medium chain defects and not isolated to those infants with long chain FAOD. This implicates the entire spectrum of the acylcarnitine intermediates. Future studies, in considering pregnancies affected with fetal fatty acid oxidation defects, should examine the relationship of all FAOD with respect to the pathophysiology of the maternal liver disease for improved future health outcomes.