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Genetics Corner: A Premature Infant with Meconium Peritonitis Inspires an Update on the First Cases of In Utero Therapy for Meconium Ileus Due to Cystic Fibrosis

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Case Summary:

A six-day-old male infant with meconium peritonitis was born prematurely by C-section for breech presentation at 28 weeks 4 days gestational age after spontaneous onset of labor. Polyhydramnios, fetal ascites, and echogenic bowel were noted at the 21-week fetal ultrasound examination. The mother, a 21-year-old primigravida, had Graves' disease that was untreated until the last two months of pregnancy when she was evaluated by a maternal-fetal medicine specialist, who prescribed methimazole. She had normal CFTR gene sequencing, normal maternal serum AFP, and a low-risk result on a cell-free DNA screening test for aneuploidy. An amniocentesis was performed with normal fetal chromosome microarray and negative CMV and toxoplasma studies. Amniotic fluid was meconium-stained. The placenta was large (760 grams, disc, 97th %ile) with abnormal histology: patchy villous edema, fetal vascular malperfusion (multiple foci of avascular villi, occasional stem villous obliteration), and no significant inflammation. The BW was 1.741 kg (99th %ile), Length 37.5 cm (54th %ile), and HC 28.5 cm (94th %ile). The baby had two laparotomies in the first days of life without bowel resection because the bowel was matted, consistent with an in utero perforation and meconium pseudocyst. The family history was negative for cystic fibrosis or consanguinity. The baby's post-operative status limited physical examination, but there were no dysmorphic features.

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Discussion:

Meconium ileus, peritonitis, and in utero bowel perforation have many causes. Over half of newborns with meconium ileus (MI) have cystic fibrosis (CF), which is unlikely in this case but will be pursued with CFTR gene analysis in the newborn. Other common causes are in utero infections, including syphilis (1) and congenital atresia of the intestine or bowel mediated by vascular hypoperfusion of the gut, which seems to be the most likely cause in this case. Interestingly, maternal Graves' disease does not seem to increase the chance of meconium ileus, and methimazole therapy cannot be implicated in this case, as the drug was started after the GI anomalies were recognized at 21 weeks gestation.

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Although this infant would likely not benefit, the first issue of Neonatology Today in the new year seems like an auspicious time to bring our readers some good news about advances in therapy for MI due to CF. All of us could use some good news in 2024.

First, let us discuss some background about CF and MI. CF exerts its first effects on the pancreas during fetal life: in ~85% of individuals with CF, fibrosis of the pancreas begins in utero. About 12-20% of infants with CF present with meconium ileus. Reduced secretion of pancreatic enzymes also causes exocrine pancreatic insufficiency, malabsorption, and failure to thrive in patients with CF. Cystic fibrosis therapy has been vastly improved by the recent development of CFTR modulator drugs designed to overcome specific defects in different types of abnormal CFTR proteins. The FDA now approves these drugs for the treatment of cystic fibrosis in children as young as two years old but not, as

yet, in the newborn.

There is evidence that early pancreatic damage in CF may not be irreversible. Early treatment with Ivacaftor, a CFTR modulator drug, increased fecal elastase, with a more significant effect in younger children of 12–24 months and 2–5 years compared to older children (2). CFTR modulator drugs cross the placenta and appear in cord blood and breast milk. When pregnant CF mothers continue their CFTR modulator treatment during gestation, their exposed infants do not experience any harmful effects (3). At least one affected fetus with CF seems to have benefited from maternal CFTR modulator therapy. In New York State, a pregnant woman with CF continued CFTR modulator therapy during her pregnancy. She delivered an infant with CF who had preserved pancreatic function to the extent that the newborn screening test was falsely negative for CF. In New York state, the CF newborn screening test algorithm requires a high immunoreactive trypsinogen (IRT) value in the top 5% for that day to proceed to CFTR gene analysis. In this case, the affected infant with CF had an IRT value that was below the threshold for gene analysis, although she was found to have two copies of the F508del variant (4).

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Three recent case reports show the efficacy of maternal CFTR modulator therapy initiated in pregnancy in reversing meconium ileus due to CF detected in fetal life when the mothers were themselves healthy carriers. A case report from Charleston, South Carolina, documented CFTR modulator therapy with lumacaftor-lumacaftor-ivacaftor (ETI) treatment in a F508del carrier mother who was pregnant with an affected F508del homozygous fetus. A 23-week fetal ultrasound established the diagnosis of MI with a dilated, hyperechoic bowel that persisted on subsequent imaging. The mother began ETI at 32 weeks, and by treatment day 27, fetal bowel dilation had resolved by imaging. The female infant was born at 36 weeks gestation without complications. The mother continued ETI while breastfeeding. The authors concluded that "maternal ETI treatment likely led to resolution of the MI, and evidence supports continued infant benefit through breastmilk" (5). Authors in Spain (6) reported a healthy pregnant patient who underwent CFTR modulator therapy with ETI to treat her fetus with CF (F508del homozygous CFTR mutation) and MI. Both parents were carriers of the F508del CFTR variant. Ultrasound findings suggestive of MI were observed at 24 weeks. The fetus was diagnosed with CF by amniocentesis at 26+2 weeks. Maternal ETI therapy began at 31+1 weeks. No dilated bowel was observed at 39 weeks, and there were no signs of bowel obstruction after birth. Maternal ETI treatment was continued during breastfeeding, with normal liver function. A third report from Stanford University in California (7) documented fetal therapy with ETI for CF and MI in a heterozygote carrier mother from 26 weeks gestation. Seven weeks after starting therapy, there was apparent resolution of fetal meconium ileus and microcolon on imaging studies. A healthy infant was delivered at 39 weeks gestation, although her IRT was elevated and fecal elastase level was low, indicating that she had pancreatic insufficiency.

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Although these are only a handful of case reports and more studies are needed, they show the great potential of treating MI in CF during fetal life (8, 9). This is a hopeful sign that a better prognosis for newborns with MI and CF may be on the horizon as we enter this new year.

Practical applications:

1. Recall that CFTR modulator drugs taken by pregnant women with cystic fibrosis (CF) cross the placenta and appear in cord blood and breast milk.
2. Understand how CFTR modulator drugs given to a pregnant woman can improve and preserve fetal pancreatic exocrine function in the fetus affected with meconium ileus (MI) due to cystic fibrosis.
3. Recognize that a newborn screening algorithm for CF that relies on an elevated immunoreactive trypsinogen (IRT) value could give a false negative result for CF in infants exposed to CFTR modulator therapy during their gestation. For this reason, order comprehensive CFTR gene analysis for all infants exposed to CFTR modulator medications during gestation.

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