Offering CFTR modulators in pregnancy to prevent cystic fibrosis-related organ damage before birth: Case series with insights from infants with CFTR variants of varying clinical consequence

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With the advent of highly effective CFTR modulator therapy (HEMT), the prognosis and quality of life for those with cystic fibrosis (CF) has drastically improved with significant improvements in lung function, increased life expectancy, and reduced number of lung transplants performed.[1,2] However, CF complications begin to manifest in utero, including meconium ileus and pancreatic dysfunction, and current FDA approval for HEMT such as elexacaftor/tezacaftor/ivacaftor (ETI) is only for those 2 years and older. Despite this, there are several documented cases of women taking HEMT during pregnancy with promising results of potential CFTR correction in utero, with reversal of developing meconium ileus and preservation of pancreatic function, though with substantial variation between cases.[3-10]

In this study, eight mother and infant dyads were recruited, with each infant having the potential of being born with CF. Each mother was offered HEMT (to treat the fetus) and counseled on the potential benefits and risks. Records from routine care from prenatal, birth, and perinatal period were collected. While much current data on prenatal HEMT use has been reported on CFTR disease causing variants, we showcase its consideration in the context of three cases that have CFTR variants of varying clinical consequence (VCCs), G622D, Y1032C, and F1052V.

Of the eight mothers, three intended to take HEMT, however only two were initiated on ETI due to complications with insurance approval. In one case of maternal ETI use, the infant was homozygous F508del with initial concerns of bowel obstruction on ultrasound, but after starting HEMT at 27 weeks, he was born without obstruction, though was pancreatic insufficient. However, after starting direct dosing of ETI at 12 weeks of age, his fecal elastase increased above threshold for pancreatic sufficiency, allowing him to stop pancreatic enzyme supplementation. In the other case with prenatal ETI treatment, the infant carried a CFTR VCC variant, Y10332C. Here, there was evidence of bowel obstruction, however after initiation of ETI at 26 weeks, the ultrasound findings resolved and there was no meconium ileus at birth. This patient had a more variable course after birth, being initially pancreatic sufficient, but then losing pancreatic function when administration of ETI through breastmilk (while the mother continued taking ETI) was stopped. However, when direct dosing of ivacaftor was initiated, the infant ultimately regaining pancreatic function. The third family who intended to use prenatal ETI but was unable due to insurance coverage, also had a child with a VCC variant, G622D. While this infant had signs of bowel obstruction on ultrasound and we were concerned this infant would be born with meconium ileus, the infant delivered without signs of bowel obstruction. The infant had an intermediate sweat chloride and was diagnosed with CFTR related metabolic syndrome.

These cases demonstrate that prenatal HEMT use is complex, with phenotype variability, insurance coverage, and potential risks and benefits all factoring into decision making. Outcomes

of these cases ranged from successful reversal of developing meconium ileus to pregnancy termination. Further work is needed to collaborate with regulatory bodies and determine long-term outcomes.

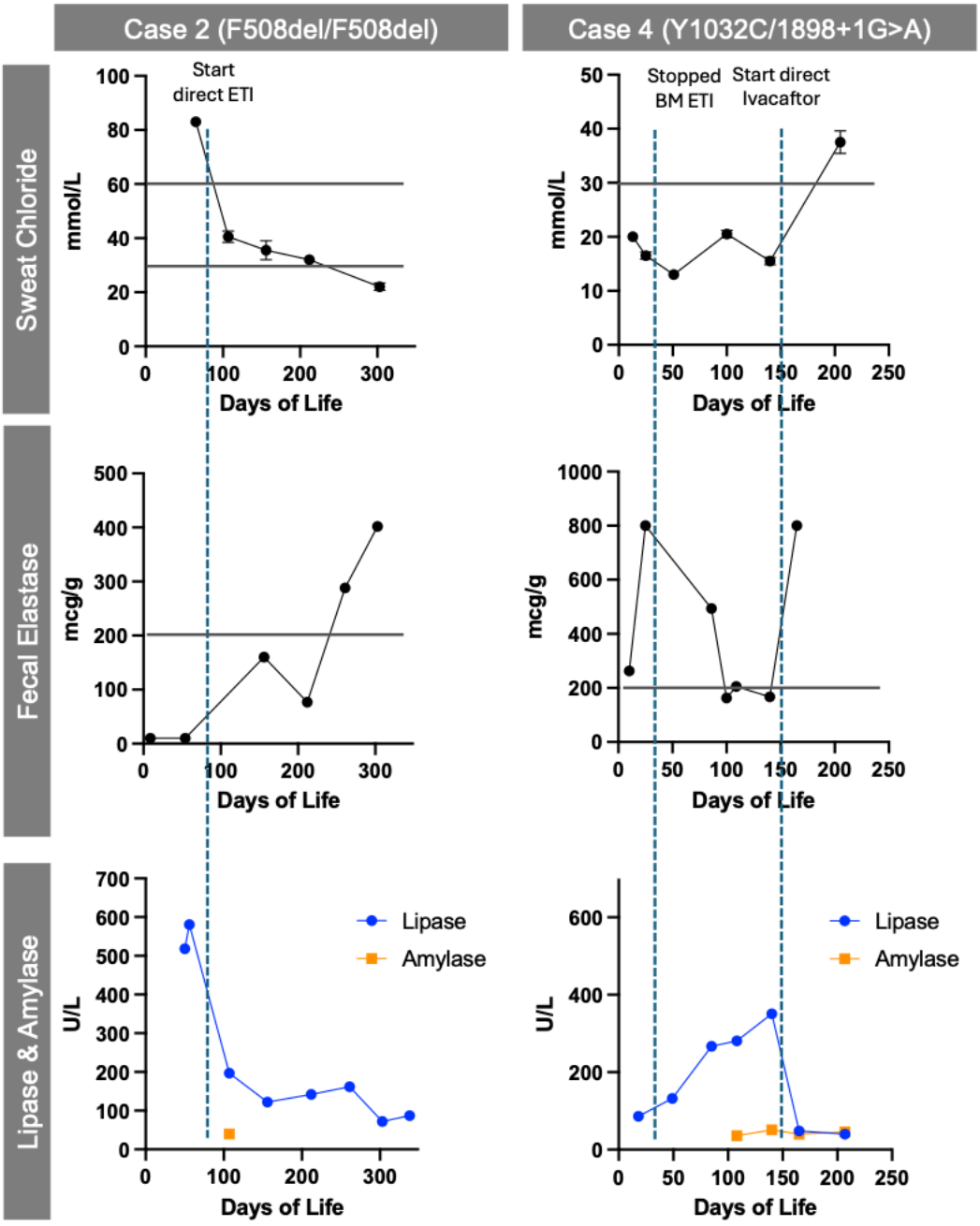

Figure 1. Laboratory Evaluation of Infants Who Received Prenatal HEMT. Change in sweat chloride, fecal elastase, lipase, and amylase plotted from birth until present with changes in HEMT dosing and administration noted by dotted lines.

Dyad	Race/ethnicity of parents	Parental Mutations	US findings	ETI initiation	Resolution of US findings	Clinical outcome	ETI postnatally
1	Non Hispanic, Black (Chinese Irish Jamaican)/ Caucasian (English)	F508del / 1898+5G>T	None	-	-	+ NBS, + sweat chloride, pancreatic insufficient.	-
2	Hispanic (Mexican)/ Hispanic (Mexican, Argentinian)	F508del / F508del	Bowel dilation & echogenicity at 23 weeks	27 weeks	No change	Delivered at 35 weeks. No meconium ileus. + NBS, + sweat chloride. Pancreatic insufficient until direct dosing ETI.	Via breast milk then direct dosing ETI at 12 weeks
3	Hispanic (Mexican)/ Hispanic (Mexican)	F508del / G622D	Bowel dilation & echogenicity at 21 weeks	-	Worsened at 34 weeks	Delivered at 38 weeks. No meconium ileus. +NBS, intermediate sweat chloride. Pancreatic sufficient. Diagnosis of CRMS.	-
4	Caucasian (German, Polish)/ Caucasian (Swiss)	Y1032C / 1898+1G>A	Bowel dilation & echogenicity at 22 weeks	26+4/7 weeks	Resolved by 35 weeks	Delivered at 39 weeks. No meconium ileus. – NBS, sweat chloride <30mmol/L. Initially pancreatic sufficient but lost pancreatic function (then regained with ivacaftor initiation).	ETI via breast milk no HEMT (5 weeks – 3 mo age) direct ivacaftor dosing
5	Caucasian (Portuguese, Italian, German) / Caucasian (Polish, German)-Asian (Japanese)	F508del / 2789+5G->A	None	-	-	Negative amniocentesis. Lost to follow up.	-
6	Caucasian/ Caucasian	D110H / F508del	None	-	-	Termination.	-
7	Hispanic (Mexican)/ Caucasian (Scottish, Irish)	F508del / F311del	None	-	-	Cell Free DNA screen of low risk. Healthy baby.	-

8	Caucasian (Armenian) / Caucasian (Armenian)	F1052V/ F1052V	None	-	-	Healthy baby. Negative NBS. Sweat chloride <30 mmol/L.	

Table 1: Summary of 7 mother-infant dyads presented with option of prenatal HEMT.

+ = positive, NBS = newborn screen, CRMS = CFTR related metabolic syndrome, ETI = elexacaftor / tezacaftor / ivacaftor, CF = cystic fibrosis

References:

1. Middleton, P. G., Mall, M. A., Dřevínek, P., Lands, L. C., McKone, E. F., Polineni, D., ... & Jain, R. (2019). Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *New England Journal of Medicine*, *381*(19), 1809-1819.
2. Heijerman, H. G., McKone, E. F., Downey, D. G., Van Braeckel, E., Rowe, S. M., Tullis, E., ... & Majoor, C. (2019). Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*, *394*(10212), 1940-1948.
3. Fortner, C. N., Seguin, J. M., & Kay, D. M. (2021). Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking CFTR modulator therapy during pregnancy. *Journal of Cystic Fibrosis*, *20*(5), 835-836.
4. Sun, X., Yi, Y., Yan, Z., Rosen, B. H., Liang, B., Winter, M. C., ... & Engelhardt, J. F. (2019). In utero and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis. *Science translational medicine*, *11*(485).
5. Gómez-Montes, E., Salcedo Lobato, E., Galindo Izquierdo, A., García Alcázar, D., Villalain González, C., Moral-Pumarega, M. T., ... & Luna-Paredes, C. (2023). Prenatal cystic fibrosis transmembrane conductance regulator modulator therapy: a promising way to change the impact of cystic fibrosis. *Fetal Diagnosis and Therapy*, *50*(2), 136-142.
6. Blumenfeld, Y. J., Hintz, S. R., Aziz, N., Barth, R. A., Spano, J. M., El-Sayed, Y. Y., & Milla, C. (2023). Treatment of fetal cystic fibrosis with cystic fibrosis transmembrane conductance regulator modulation therapy. *Annals of Internal Medicine*, *176*(8), 1015-1016.
7. Szentpetery, S., Foil, K., Hendrix, S., Gray, S., Mingora, C., Head, B., ... & Flume, P. A. (2022). A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus. *Journal of Cystic Fibrosis*, *21*(4), 721-724.
8. Szentpetery, S., Riva, D., Blumenfeld, Y. J., Engelhardt, J. F., Luna-Paredes, C., Milla, C., ... & Taylor-Cousar, J. L. (2025). PRenatal mOdulator treatment to PrEvent CF complicaTions (PROTECT) workshop report. *Journal of cystic fibrosis*.
9. Metcalf, A., Martiniano, S. L., Sagel, S. D., Zaretsky, M. V., Zemanick, E. T., & Hoppe, J. E. (2025). Outcomes of prenatal use of elexacaftor/tezacaftor/ivacaftor in carrier mothers to treat meconium ileus in fetuses with cystic fibrosis. *Journal of Cystic Fibrosis*, *24*(3), 466-468.
10. Kowalik, A., Roberts, E., Harris, A. H., Sund, M., Wird, S., Kvist, O., & Hjelte, L. (2024). Clinical outcomes of two infants with cystic fibrosis, including presence of the vas deferens, born to a woman with cystic fibrosis taking CFTR modulators during both pregnancies. *Journal of Cystic Fibrosis*, *23*(5), 1027-1030.

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