Cystic Fibrosis: Prenatal Testing, Ultrasound and Treatment

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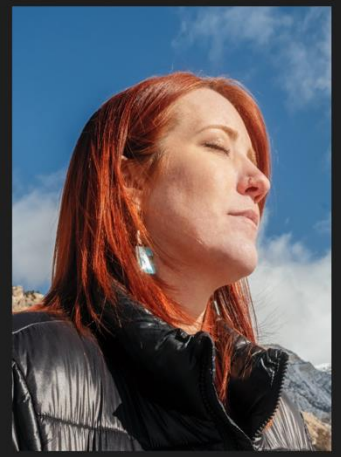
Conflicts of Interest

- I have no financial conflicts of interest
- I am also not a cystic fibrosis expert

THE CYSTIC-FIBROSIS BREAKTHROUGH THAT CHANGED EVERYTHING

The disease once guaranteed an early death—but a new treatment has given many patients a chance to live decades longer than expected. What do they do now?

By Sarah Zhang
Photographs by Fumi Nagasaka



Before she started taking Trikafta, in 2019, Jenny Livingston hoped more than anything to survive long enough to see her daughter graduate from high school.

HEALTH

The Mothers Who Aren't Waiting to Give Their Children Cystic-Fibrosis Drugs

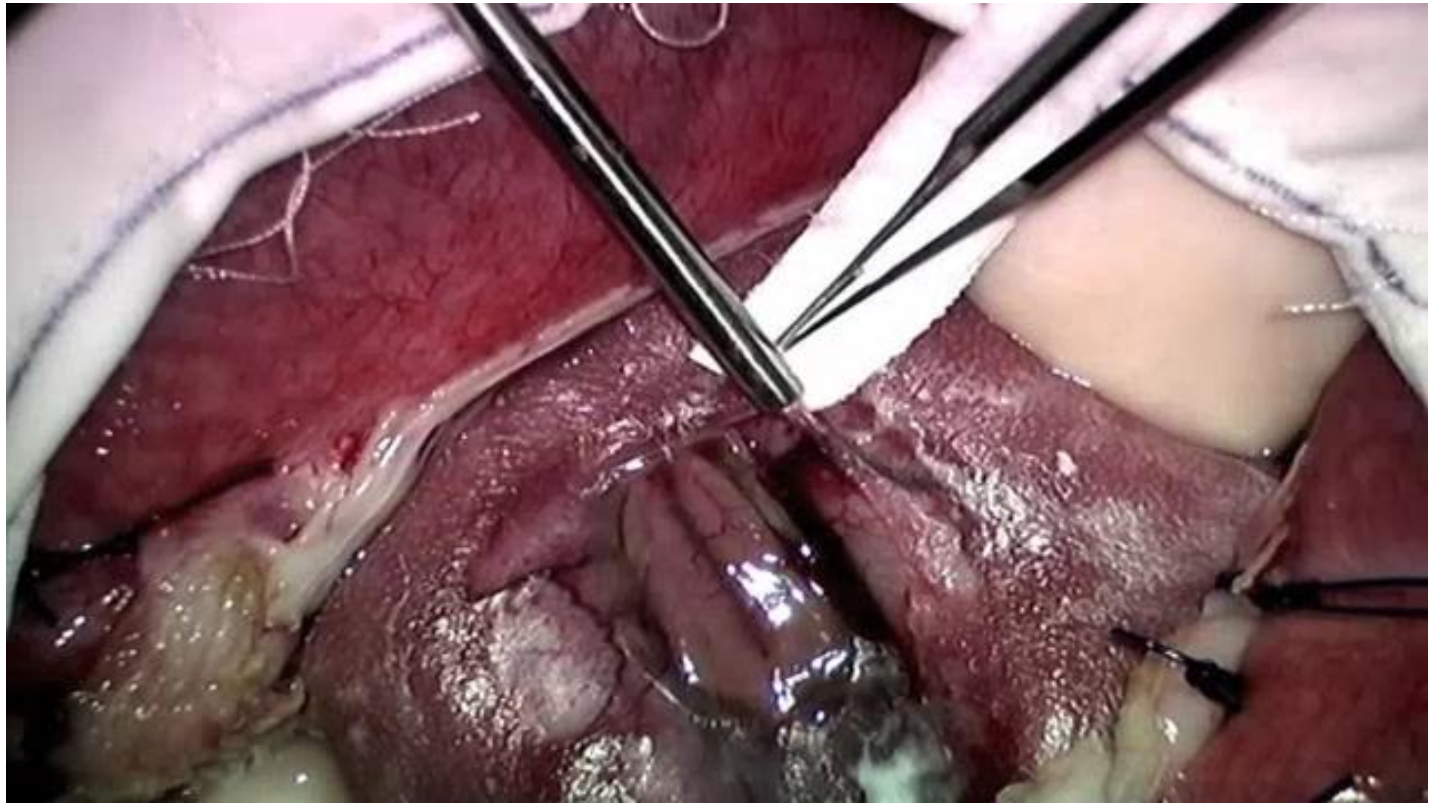
A new treatment can change a person's life, but is not officially approved for anyone under 2.

By Sarah Zhang

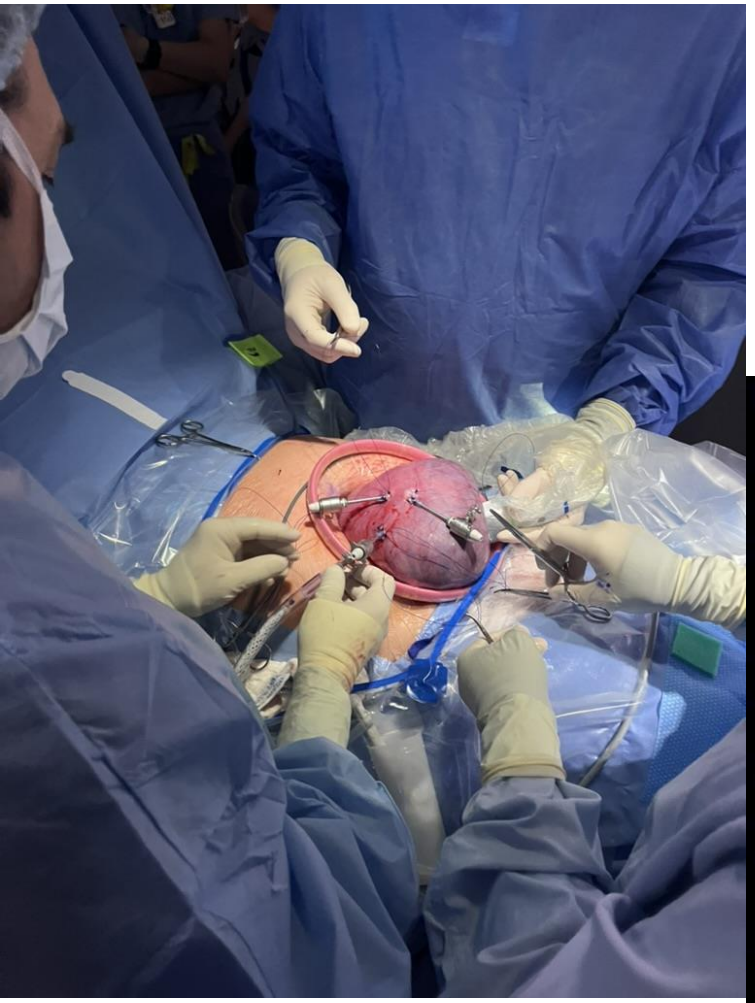
Fetal Therapy

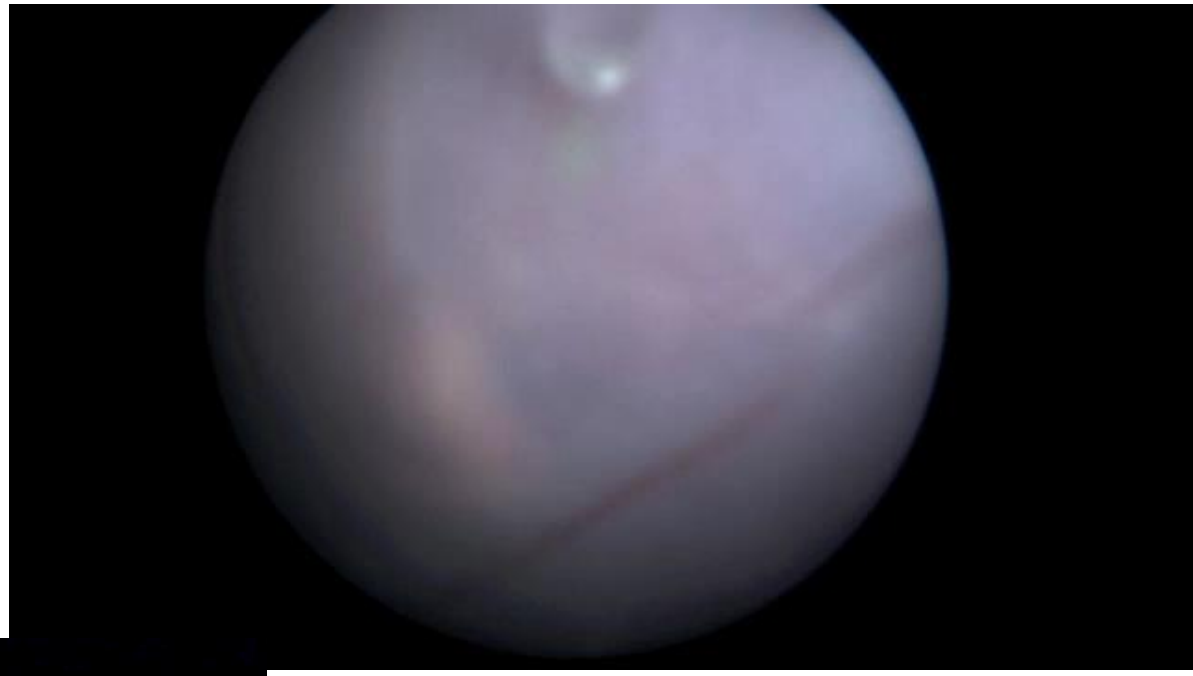
- Invasive
- Minimally Invasive
- Non-invasive

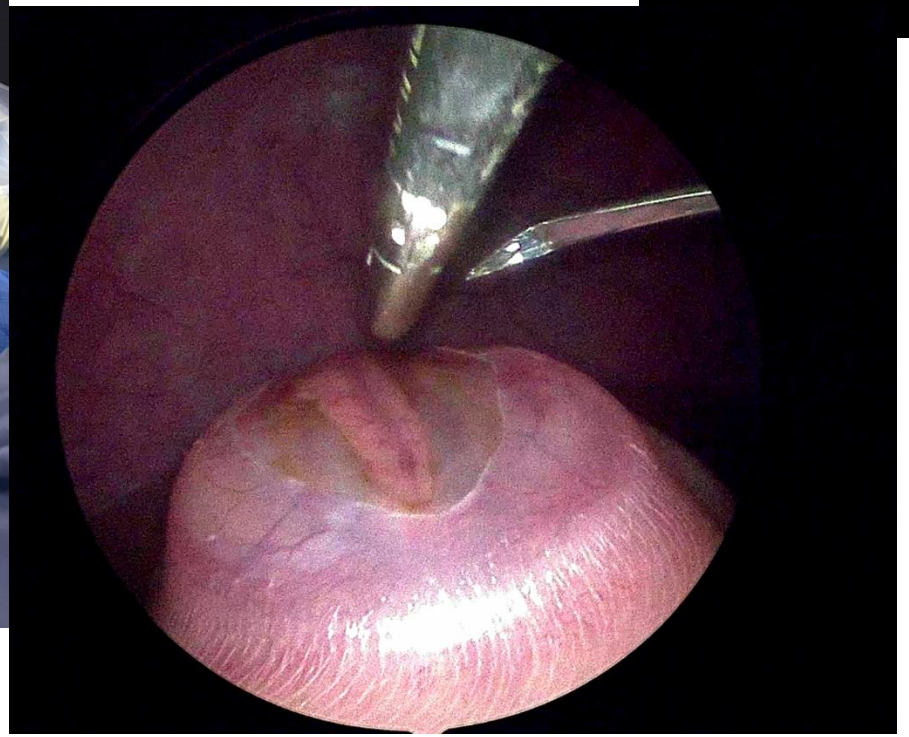
Invasive Fetal Therapy



Minimally Invasive Fetal







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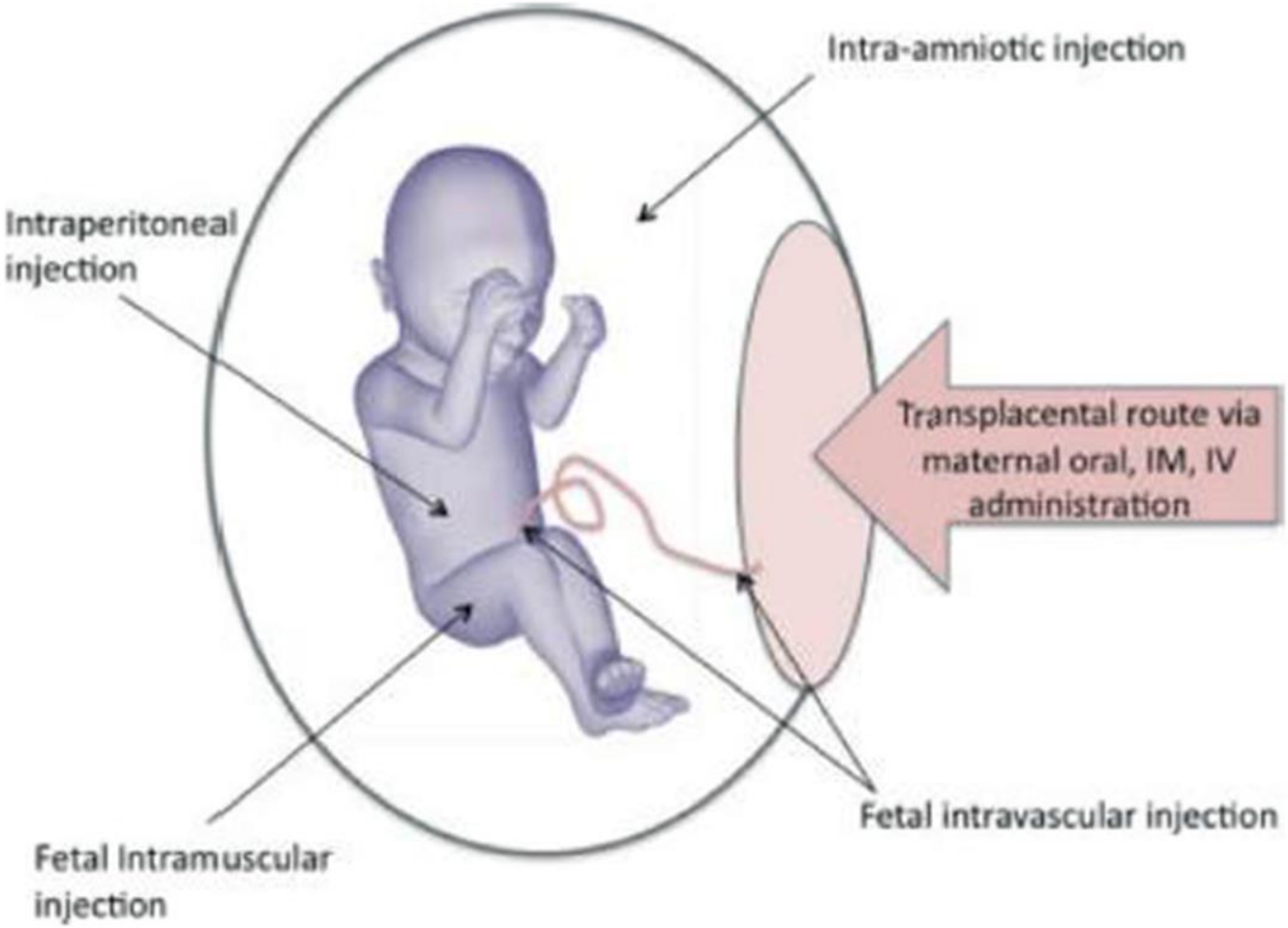
Non-invasive Fetal Therapy

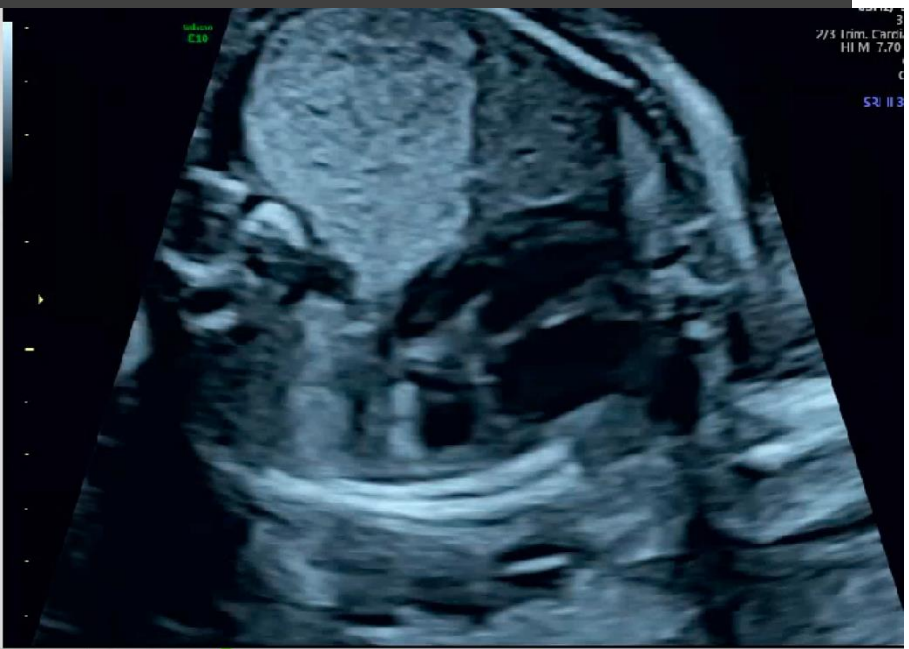
- Requires no physical access to the fetal compartment



Transplacental Route/Maternal- *Common Uses*

- *Corticosteroids* for fetal lung maturity
- *Rhogam* prophylaxis against development maternal alloimmunization
- *Folic acid* to prevent open neural tube defects
- *Vaccination* for passive fetal/neonatal immunity
  - TDAP
  - Influenza
  - Covid
  - RSV
- *Magnesium sulfate* for neuroprotection in premature delivery
- *Antibiotics*
  - PPROM and GBS prophylaxis
  - Hydrops secondary to congenital syphilis

Transplacental Route- *Uncommon Uses*

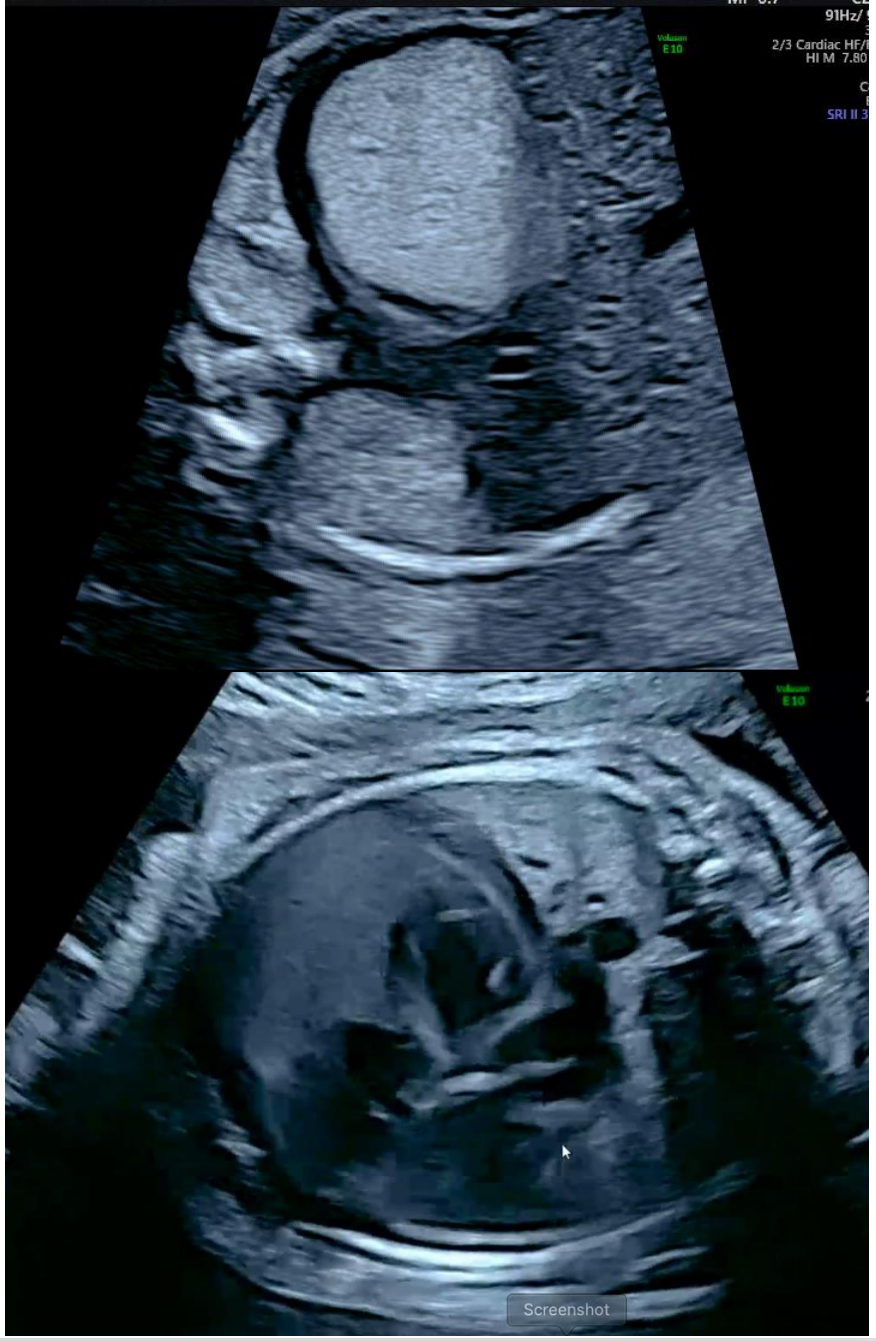


- *Maternal thioamides and levothyroxine*
  - Fetal goiter
- *Indomethacin*
  - Circular shunt in Epstein's cardiac
- *Sulindac*
  - Medical amnioreduction for polyhydramnios

- *IVIG +/- corticosteroids*
  - NAIT
  - Early onset fetal anemia from alloimmunization
  - Fetal Congenital heart block
- *Corticosteroids*
  - *Large Congenital lung lesions*
  - Congenital adrenal hyperplasia
- *Antiarrhythmic* agents for fetal tachyarrhythmias
  - Digoxin, flecainide, sotalol, amiodarone

Transplacental Route- *Uncommon Uses*

- *mTOR inhibitor*
  - Fetal rhabdomyoma
  - Lmph-vascular malformation
- *Bisphosphonates*
  - Generalized arterial calcification of infancy (GACI)
- *Maternal supplementation* for fetal inborn errors of metabolism
  - Eg B12 for methylmalonic acidemia, pyridoxine for pyridoxine dependent seizures, cobalamin C defect
- *High dose valacyclovir* (8 gm/day)
  - Congenital CMV



Cystic Fibrosis

- 1 in 3,000 to 4,000 newborns in the U.S.
- Mutations in CF transmembrane conductance regulator (CFTR) protein, an anion channel expressed at apical membrane of epithelial cells
- CFTR dysfunction
  - Chronic sinopulmonary infections
  - Progressive lung disease
  - Pancreatic insufficiency
  - Gastrointestinal dysfunction
  - Hepatic cirrhosis
  - Diabetes

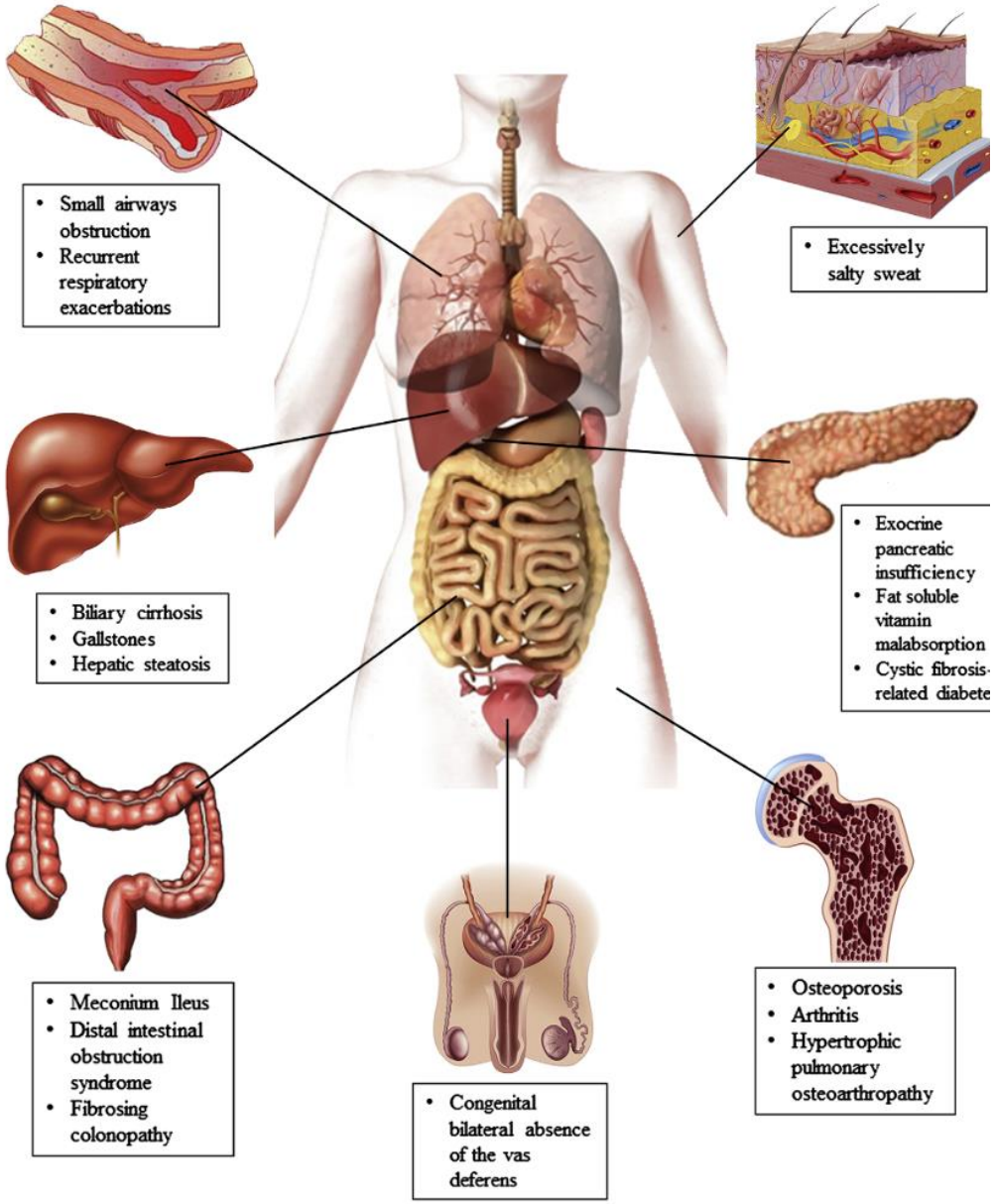


FIGURE 12.1 Common clinical manifestations of cystic fibrosis. While cystic fibrosis is primarily characterized by a progress ob pulmonary disease and exocrine pancreatic dysfunction, many organ systems can be affected. Variations in prevalence of extrapulmonary sy are not completely understood, but evidence suggests some disease manifestations are related to the severity of the underlying CFTR mutation as environmental and genetic modifiers [5].

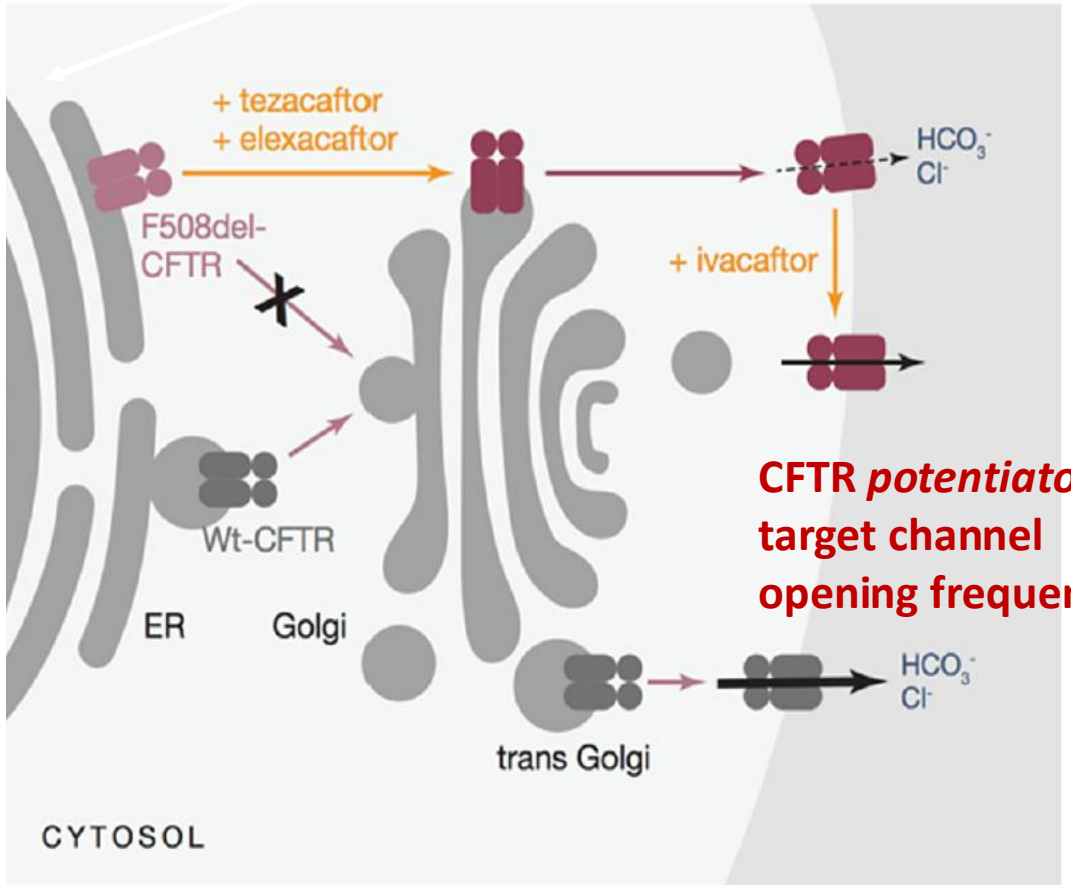
Meconium Ileus (MI)

- Affects up to 20% of newborns with CF
- Can lead to long-term morbidity and can impact mortality.
- Simple MI - viscid meconium obstructing the terminal ileum
- Complex MI - can result in volvulus, ischemic necrosis, atresia, and perforation resulting in meconium peritonitis, meconium pseudocyst
- Most studies report worse growth and lung function, require more nutritional interventions, and are hospitalized more frequently than those without MI

ETI- Trikafta

- CFTR modulators are a key therapeutic for CF
- Elexacaftor and tezacaftor bind sites on CFTR protein, have an additive effect facilitating cellular processing and trafficking for select mutations (i.e., F508del) increasing amount of protein delivered to cell surface
- Ivacaftor potentiates gating of the CFTR protein at the cell surface.
- In 2019, two landmark phase 3 clinical- remarkable clinical benefits of (ETI) triple therapy in people with CF, 12 years of age and older, with at least one copy of the F508del mutation in the CF gene
- Approved down to 6 years in 2021, and 2 years in 2023
- 90% of CF patients are eligible for ETI therapy
- **Costs ~$311,503/yr**

CFTR *correctors* target protein unfolding



CFTR *potentiators* target channel opening frequency

FIGURE 1: Mechanism of action of Trikafta on a cellular level

Figure: Zaher A, 2021, Cureus 13(7):E16144

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ETI and Pregnancy

- Case series- maintains health of patients with CF without known adverse fetal outcomes
  - Concern for development of cataracts, which have been very mild

- Maternal and Fetal Outcomes in the Era of Modulators (MAYFLOWERS; ClinicalTrials.gov identifier: NCT04828382)

ETI and MI

- Ferret model of CF
  - G551D mutation, ivacaftor prevented intestinal pathology in utero, preserve exocrine pancreatic function, and male kits born with preserved vas deferens

Sun X, Yi Y, Yan Z, Rosen BH, Liang B, Winter MC, Evans TIA, Rotti PG, Yang Y, Gray JS, Park SY, Zhou W, Zhang Y, Moll SR, Woody L, Tran DM, Jiang L, Vonk AM, Beekman JM, Negulescu P, Van Goor F, Fiorino DF, Gibson-Corley KN, Engelhardt JF. **In utero and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis**. Sci Transl Med. 2019 Mar 27;11(485):eaau7531. doi: 10.1126/scitranslmed.aau7531. PMID: 30918114; PMCID: PMC6489481

ETI and MI Case Report

- Homozygous F508del infant, born to mother with CF on ETI therapy
  - Ultrasound at 20 weeks echogenic bowel, repeat ultrasound at 32 weeks was normal
  - False-negative newborn screen for CF, normal pancreatic function, and lower-than expected sweat chloride levels

Fortner CN, Seguin JM, Kay DM. **Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking CFTR modulator therapy during pregnancy.** J Cyst Fibros 2021;20(5):835–6 official journ l of the Euro- pean Cystic Fibrosis Society

ETI and MI Case Report

- F508del carrier patient and F508del homozygous fetus
  - Dilated, hyperechoic bowel at 28 weeks gestation consistent with MI
  - Mother requested maternal ETI therapy and ETI initiated at 32 weeks gestation.
  - 36 weeks gestation the bowel dilatation had resolved.
  - After delivery, no evidence of MI.
  - ***ETI continued while breastfeeding***
    - Neonate had preserved exocrine pancreatic function at 2 weeks of age
    - Lower-than-expected sweat chloride levels at one month of age

Szentpetery S, Foil K, Hendrix S, Gray S, Mingora C, Head B, Johnson D, Flume PA. **A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus**. J Cyst Fibros. 2022 Jul;21(4):721-724. doi: 10.1016/j.jcf.2022.04.005. Epub 2022 Apr 11. PMID: 35422395.

ETI and MI Case Report

- Pregnant F508del carrier with fetus CF (F508del homozygous) and had prenatal ultrasound findings concerning for MI at 24 weeks gestation
- Maternal ETI therapy was initiated at 31 weeks gestation and no dilated bowel was observed at 39 weeks
- No signs of bowel obstruction after birth
- Maternal ETI was continued during breastfeeding

Gómez-Montes E, Salcedo Lobato E, Galindo A, García Alcázar D, Villalain C, Moral-Pumarega MT, Bustos Lozano G, Luna-Paredes C. **Prenatal cystic fibrosis transmembrane conductance regulator modulator therapy: A promising way to change the impact of cystic fibrosis**. Fetal Diagn Ther. 2023 Mar 30. doi: 10.1159/000530261. Epub ahead of print. PMID: 36996799.

Risks and Benefits of ETI

Potential Benefits for Fetus/Newborn:

- *Reversal of meconium ileus?*
- Fewer pulmonary exacerbations?
- Fewer hospitalizations?
- Improved lung function?
- Nutritional status improvement?
- Prevention of vas deferens underdevelopment?

Potential Risks Mother and Fetus:

- *Formation of cataracts*
- *Hepatotoxicity*
- Difficulty sleeping
- Hypogogic hallucinations
- Brain fog
- Reduced concentration/attention
- Memory difficulties
- Word finding problems
- Confusion
- Mood/perceptual changes
- Anxiety, agitation

***these side effects occur in up to 24% of those taking ETI, often requiring dose changes*

Bathgate CJ (2023) Pediatr Pulm, 58:2469
Figure: Wesley BD (2021) Am J Obstet Gynecol, 225(1):21-32

How do you obtain ETI in Pregnancy

- Need fetal diagnosis of CF through ***amniocentesis***
  - One allele needs to be ETI responsive (eg dF508)
  - Non-invasive testing for CF is not accepted
- Suspicion for meconium ileus on imaging
  - Future may see just fetal CF as indication
- Maternal carrier completes pulmonary function tests
- Maternal baseline liver function tests
- Submit info through Vertex pharmaceutical portal to attempt approval
- Then submit through insurance providers along with extensive letter stating the justification and evidence for prenatal use

CFCC Cases of MI

Diagnosis of MI

- Presence of echogenic bowel as bright as surrounding bone
- Echogenic mass in the terminal ileum
- Dilated bowel
- Evidence of meconium peritonitis with presence of peritoneal calcification, ascites, and pseudocysts

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2020, VOL. 33, NO. 4, 633–638
https://doi.org/10.1080/14767058.2018.1498837

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Reference curves for the normal fetal small bowel and colon diameters; their usefulness in fetuses with suspected dilated bowel

Chiara C. Lap[a], Charlotte S. Voskuilen[a], Lourens R. Pistorius[a,b], Eduard J. H. Mulder[a], Gerard H. A. Visser[a] and Gwendolyn T. R. Manten[a,c]

[a]Department of Obstetrics, University Medical Center Utrecht, Division Woman and Baby, Utrecht, The Netherlands; [b]Department of Obstetrics and Gynaecology, University of Stellenbosch, Stellenbosch, South Africa; [c]Department of Obstetrics and Gynecology, Isala Women and Children's Hospital, Zwolle, The Netherlands

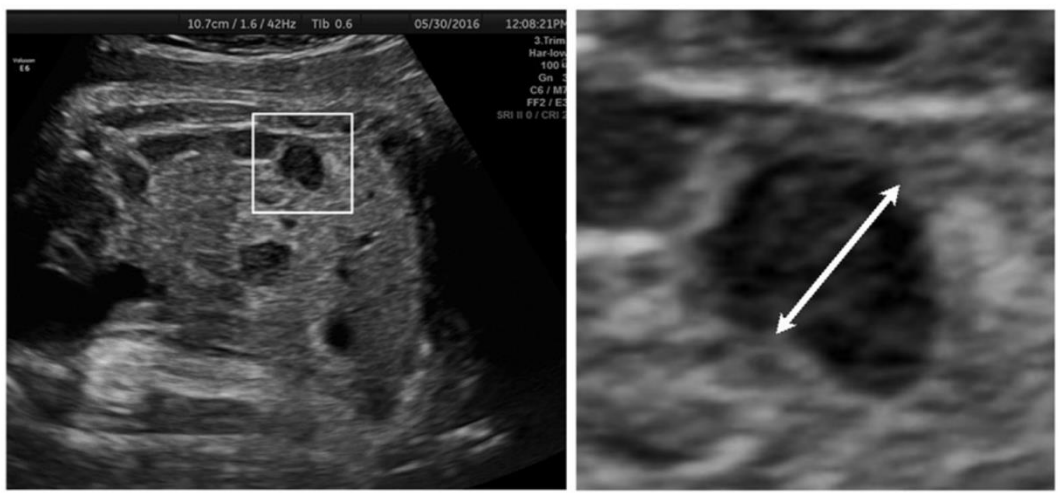
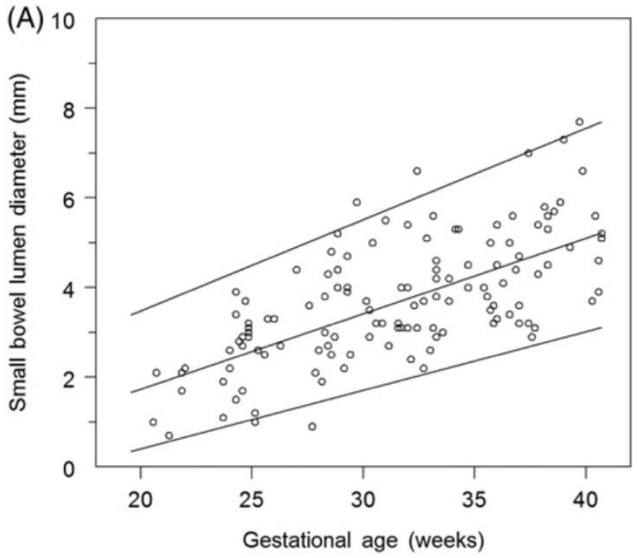


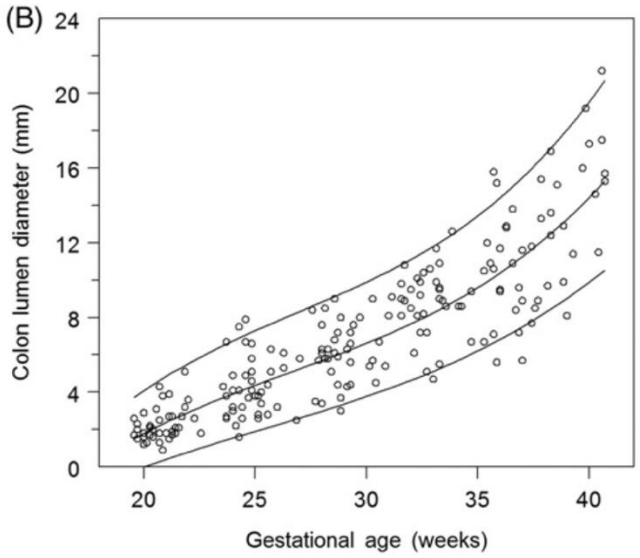
Figure 1. Identification of the largest loop of the colon (coronal plane) at 35 weeks of gestation. Measurement of the short axis of the bowel lumen (inner to inner bowel wall).

Mean and 95% intervals for bowel

Table 1. Small bowel and colon diameters according to gestational age.

	Small bowel diameter (mm)		Colon diameter (mm)	
Weeks of gestation	Mean	95% prediction interval	Mean	95% prediction interval
20	1.7	0.4–3.5	1.8	0.0–4.0
22	2.1	0.7–3.9	2.9	0.8–5.5
24	2.4	0.9–4.3	3.9	1.5–6.7
26	2.7	1.2–4.7	4.8	2.2–7.8
28	3.1	1.4–5.1	5.7	3.0–8.8
30	3.4	1.7–5.5	6.6	3.7–9.8
32	3.8	2.0–5.9	7.7	4.6–11.0
34	4.1	2.2–6.3	8.9	5.6–12.5
36	4.4	2.5–6.7	10.4	6.8–14.3
38	4.8	2.8–7.1	12.3	8.2–16.5
40	5.1	3.0–7.6	14.5	9.8–19.4





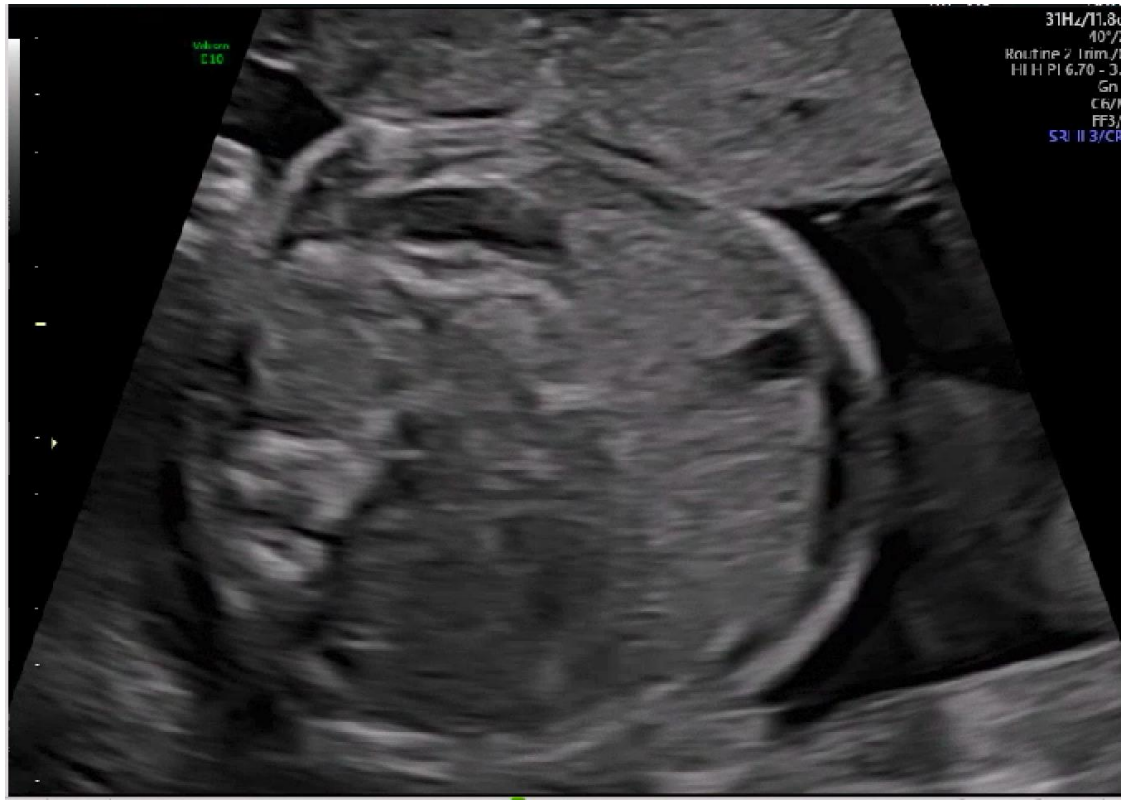
CF Cases Listed

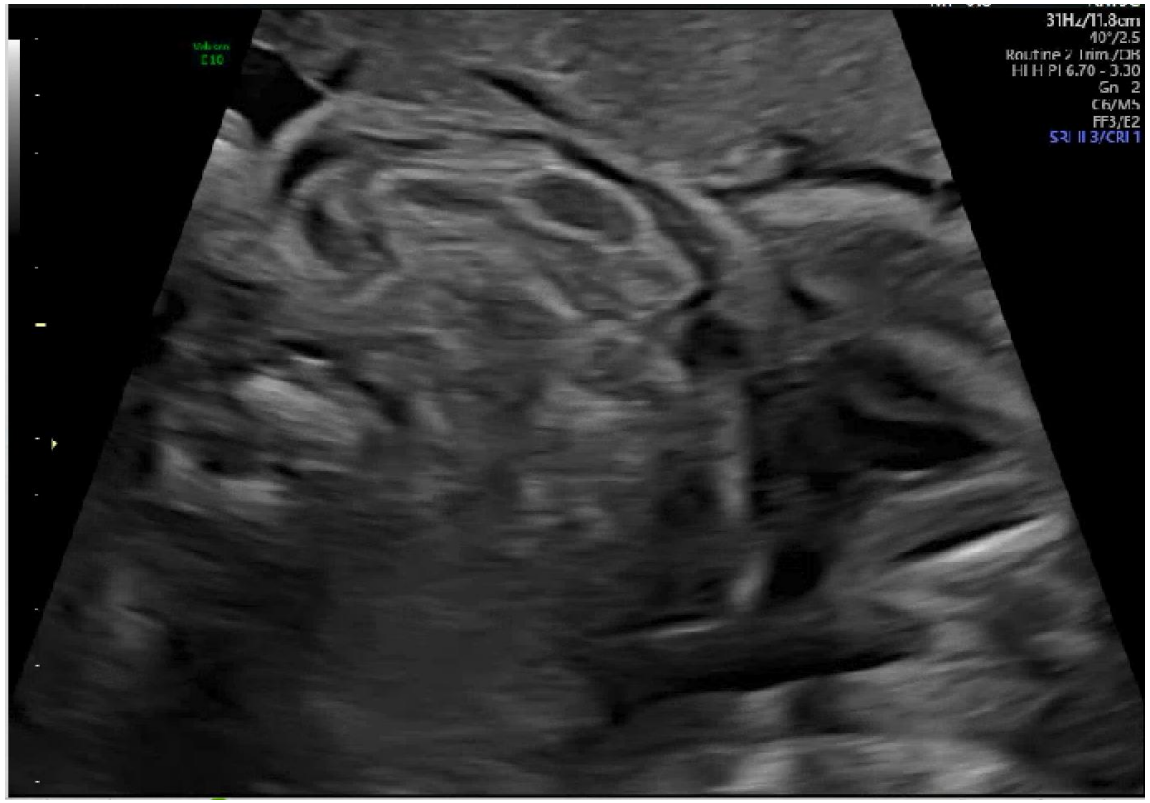
31w 6d	Dilated bowel loops (28 mm)	Meconium ileus, volvulus, small bowel necrosis	Ileal resection, cystic fibrosis
31w 0d	Dilated bowel (12 mm), meconium plug, echogenic bowel, polyhydramnion	Meconium ileus, meconiumperitonitis	Ileal resection, cystic fibrosis

Case 1

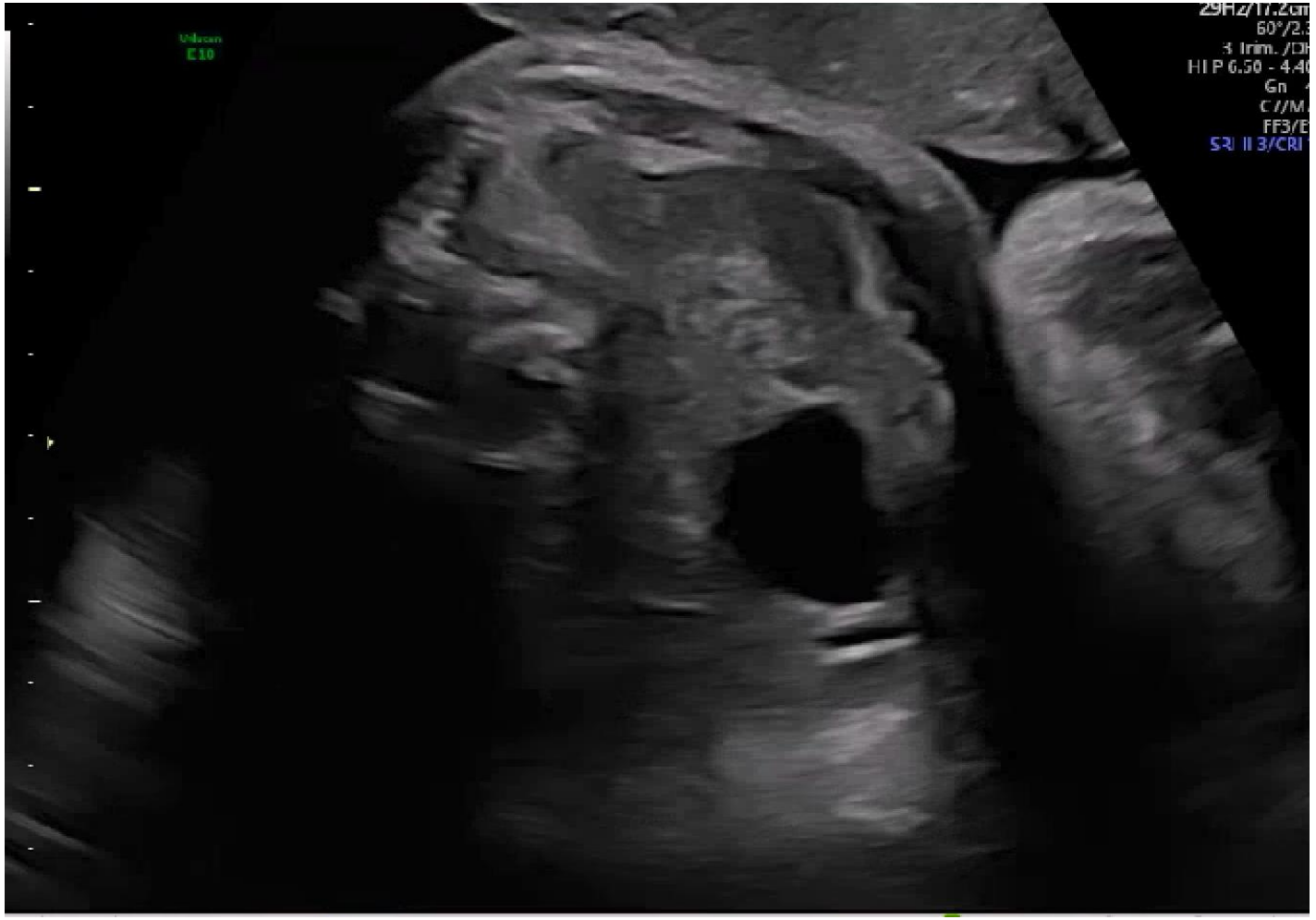
- 30 yo G1
- Both parents CF carriers for dF508
- Referred for diagnosis of fetal cystic fibrosis at 23w3d due to dilated echogenic bowel
- Started ETI at 31w3d
- Several weeks were spent trying to obtain medication
- Ultimately family opted to pay for ETI without insurance coverage
  - **$50K for 2 months**
- Induction at 39 weeks

23 weeks





36 weeks- after a month of ETI



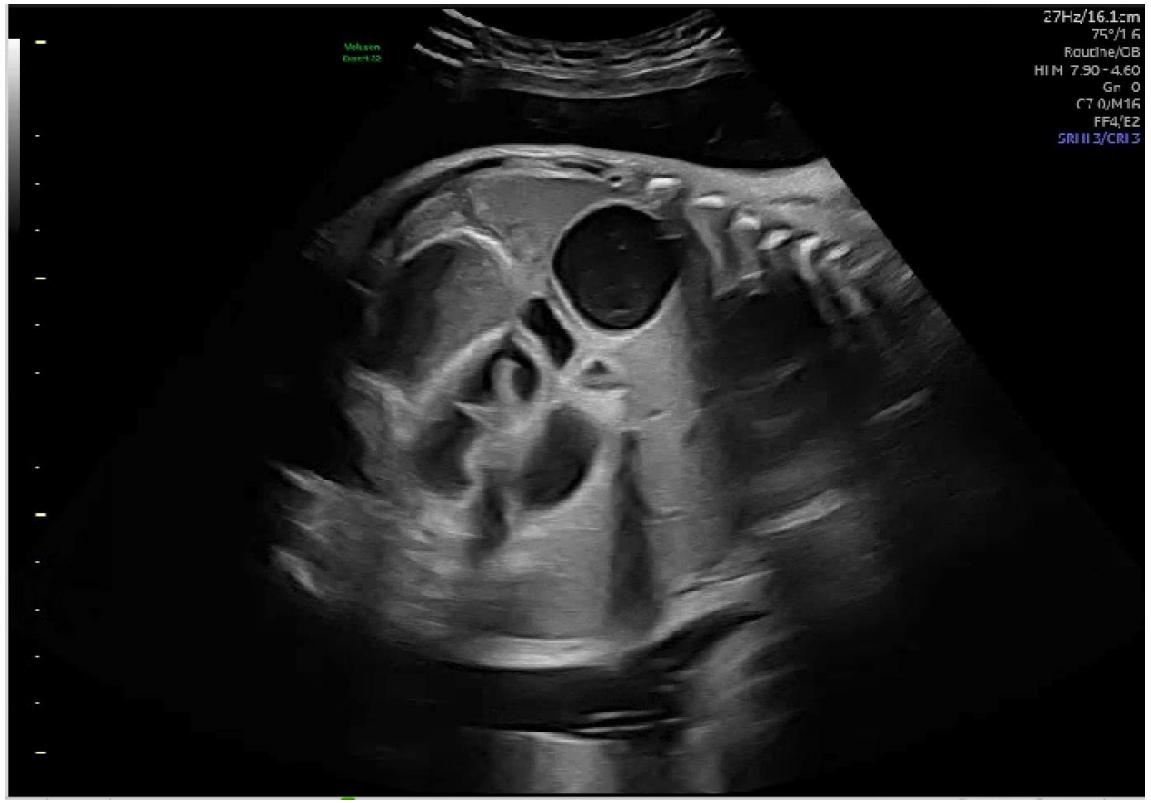
Neonatal Findings

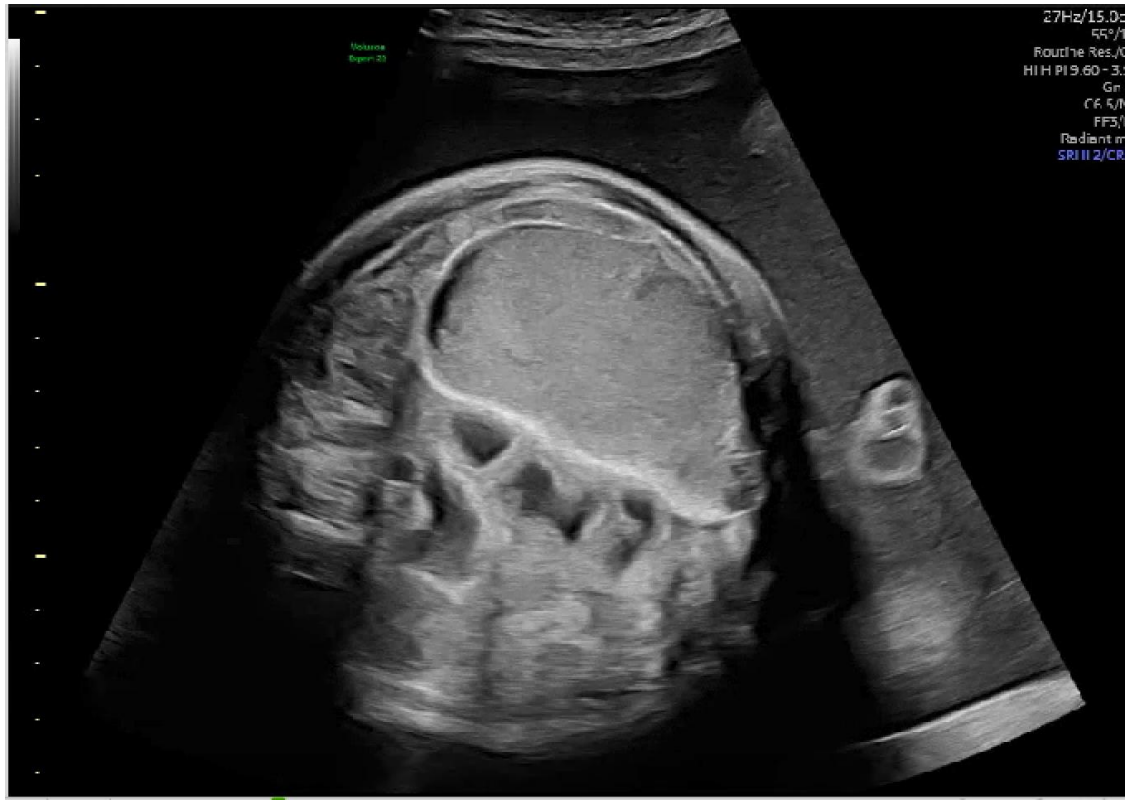
- Induction at 39 weeks, stopped ETI after delivery
- No evidence of MI after delivery
- **Discharge day of life 2**
- Immunoreactive Trypsinogen IRT was elevated on newborn screen
- Borderline pancreatic elastase test (100-200 mcg/g),
  Consistent with slight to moderate pancreatic insufficiency .
- Initial sweat chloride result: Cystic fibrosis unlikely
  - Ultimately turned positive
- Receiving standard therapy with enzyme replacement, nutritional support, regular monitoring, will start lumacaftor/ivacaftor (Orkambi) or tezacaftor/ivacaftor (Symdeko) at age 1 and ETI at age 2

Case 2

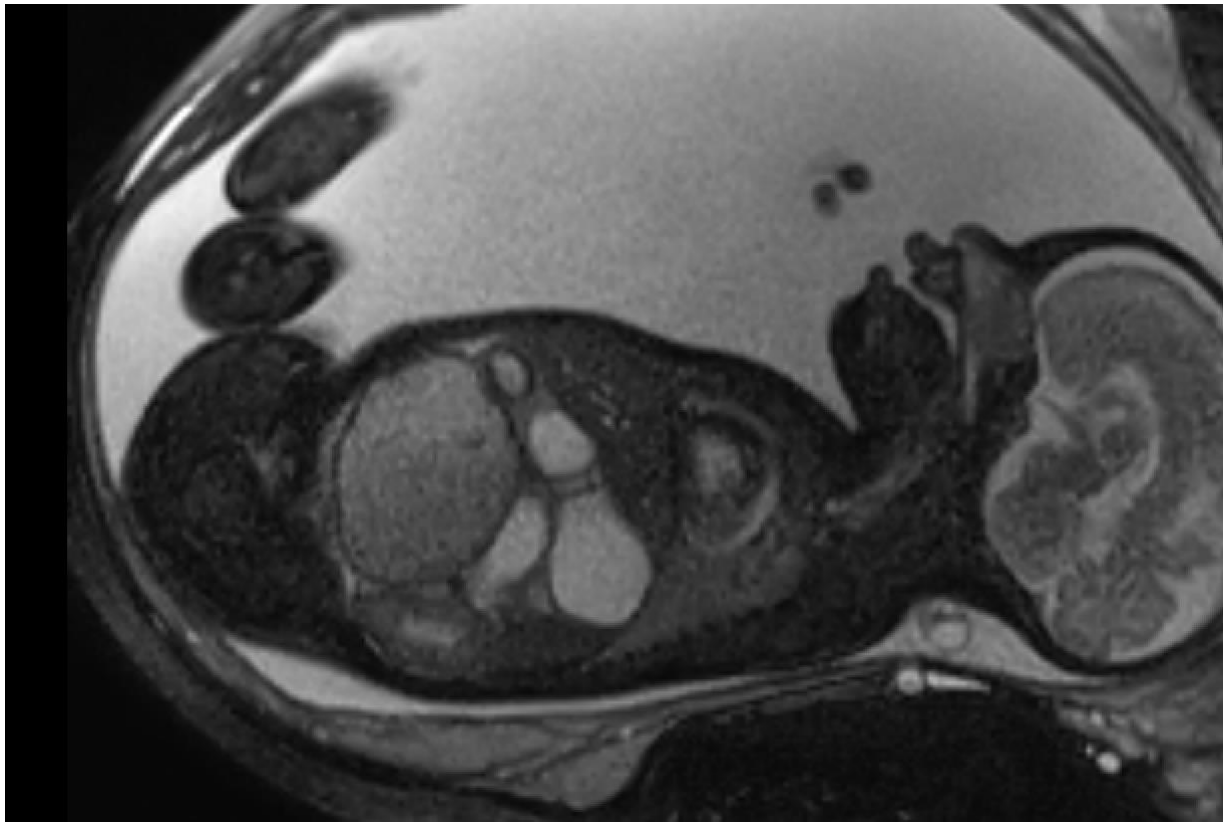
- 32 yo G3P2 referred at 33w6d
- Prior Son with CF and both parents known CF carriers
- Bowel dilated (1.2-1.6 cm) with echogenic walls
- 6.7 x 4.3 x 3.9 cm meconium pseudocyst.
- Polyhydramnios with AFI 40.7 cm.
- 2400 ml amnioreduction completed- genetics sent
- ETI approved and started at 35w5d

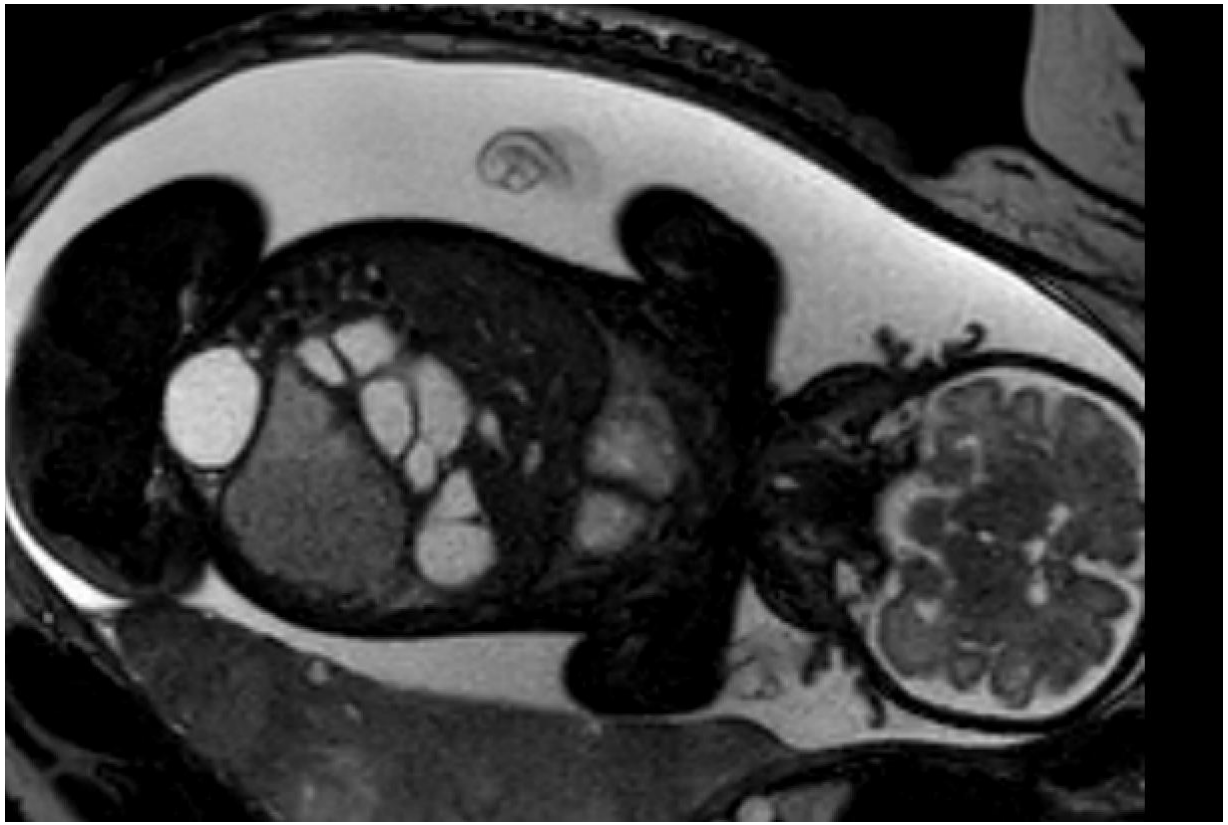
33 weeks 6 days



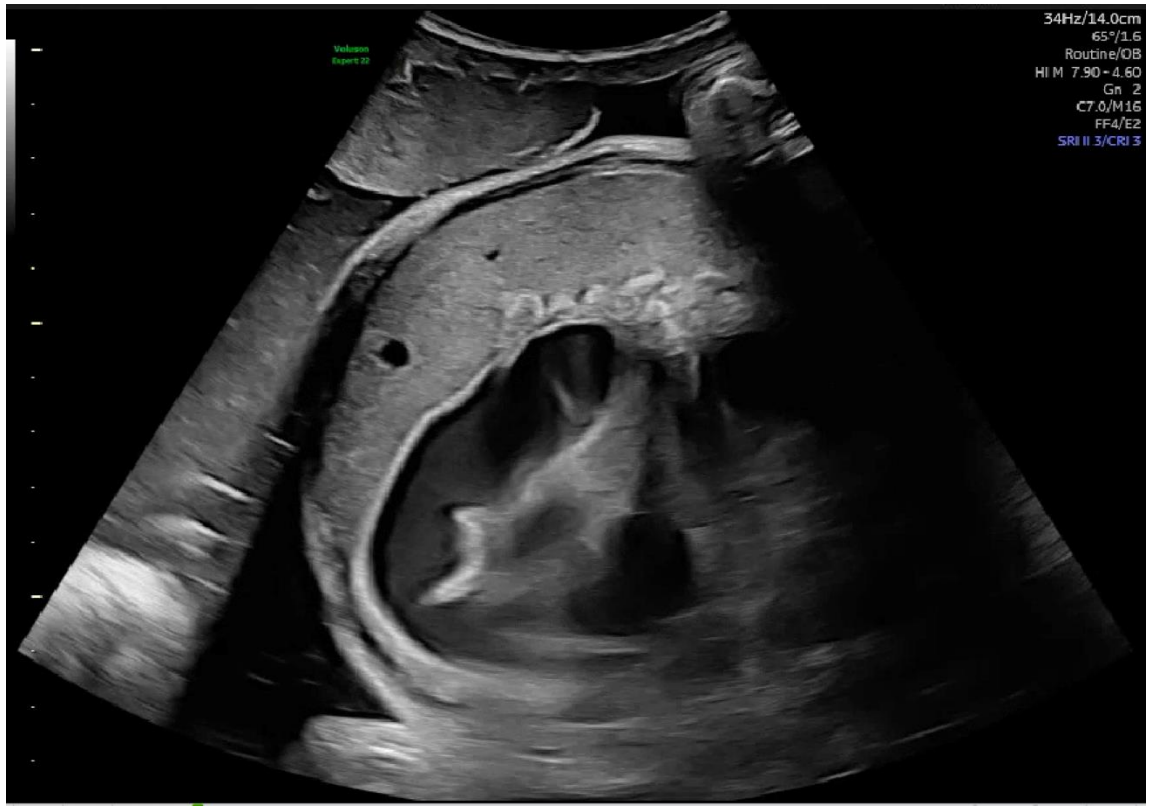


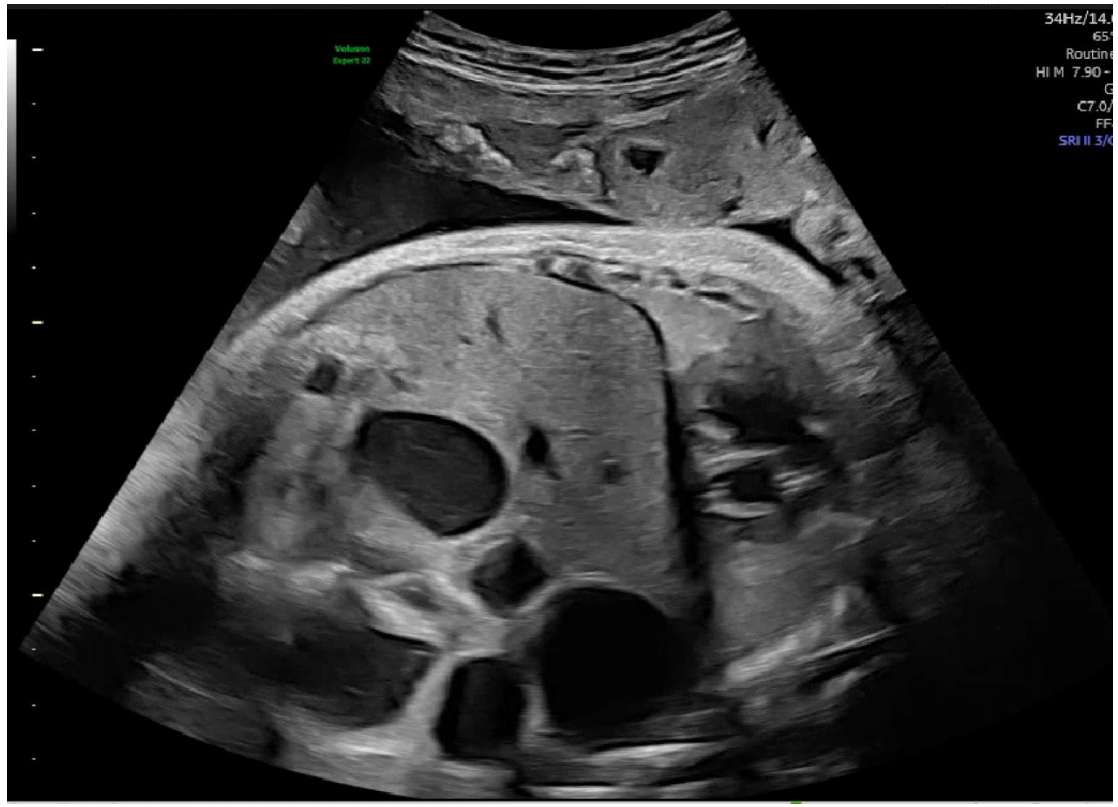
Fetal MRI





37 weeks and 6 days- 2 weeks on ETI





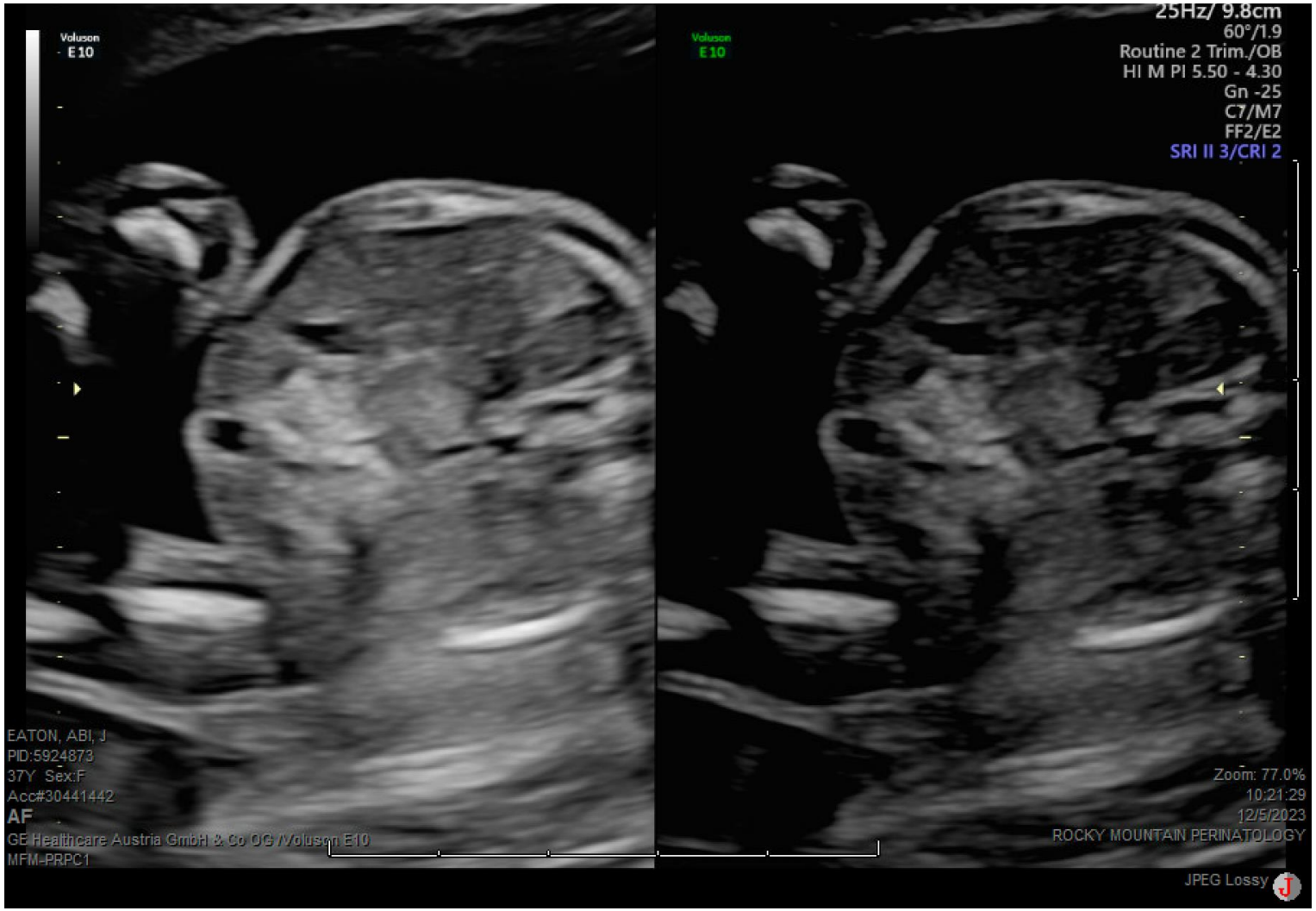
Neonatal Course

- Delivered at 38-39 weeks, stopped ETI after delivery
- MI with pseudocyst
  - Laparotomy with lysis of adhesions.
  - Distal bowel irrigation.
  - Bishop-Koop jejunostomy formation followed by takedown
- IRT newborn screen was negative
- Sweat chloride test was abnormal
- Pancreatic elastase-slight to moderate pancreatic insufficiency
- **LOS 58 days**

Case 3

- 38 yo G4P2 referred to CFCC at 36 weeks for bowel dilatation after being on ETI for a month
- **Prior child with CF and meconium pseudocyst**
- Amniocentesis completed at 28 weeks
- Started on ETI at 32 weeks

20 weeks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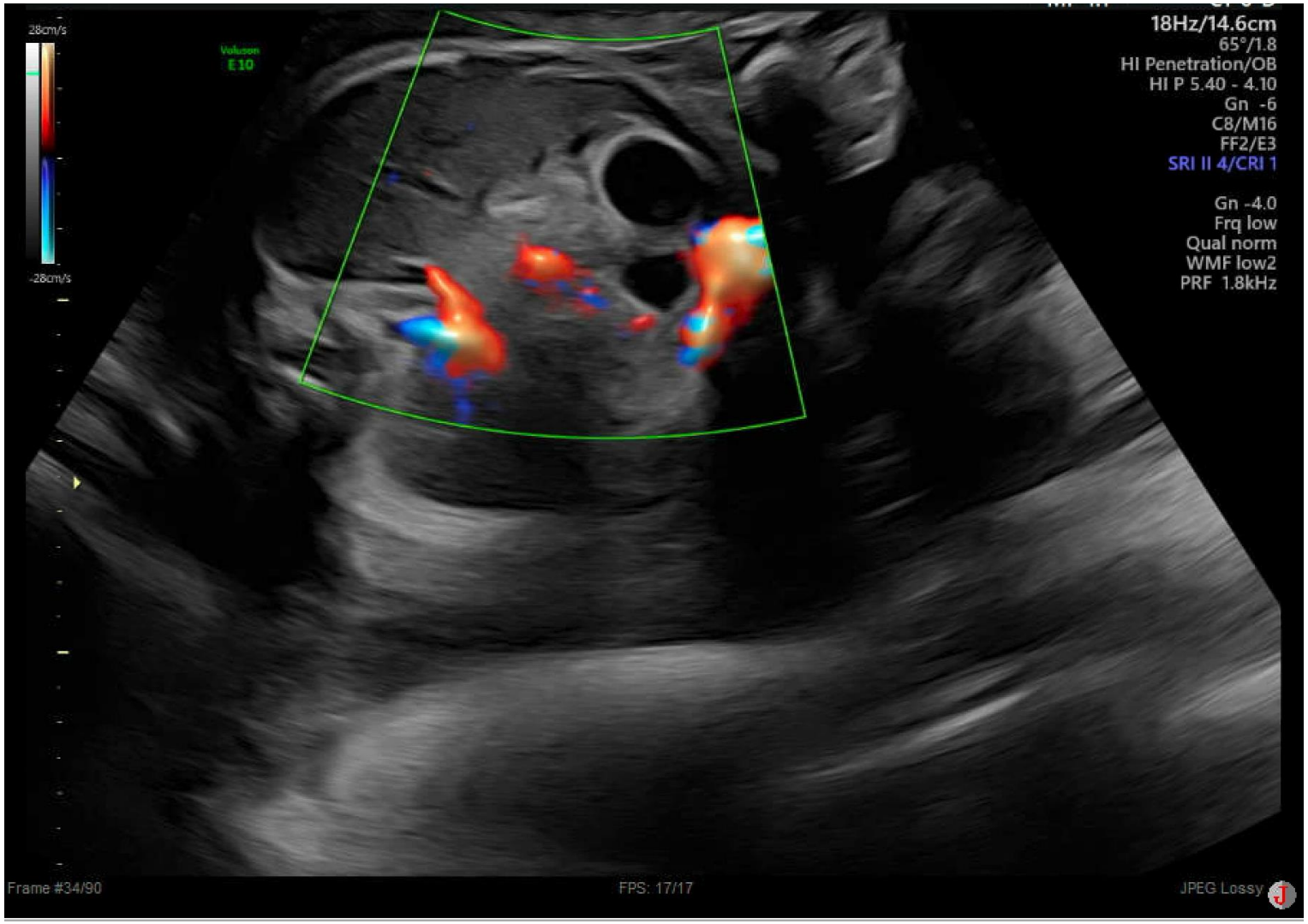
ROCKY MOUNTAIN PERINATOLOGY
JPEG Lossy

28 weeks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HI P 5.40 - 4.10
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C8/M16
FF2/E3
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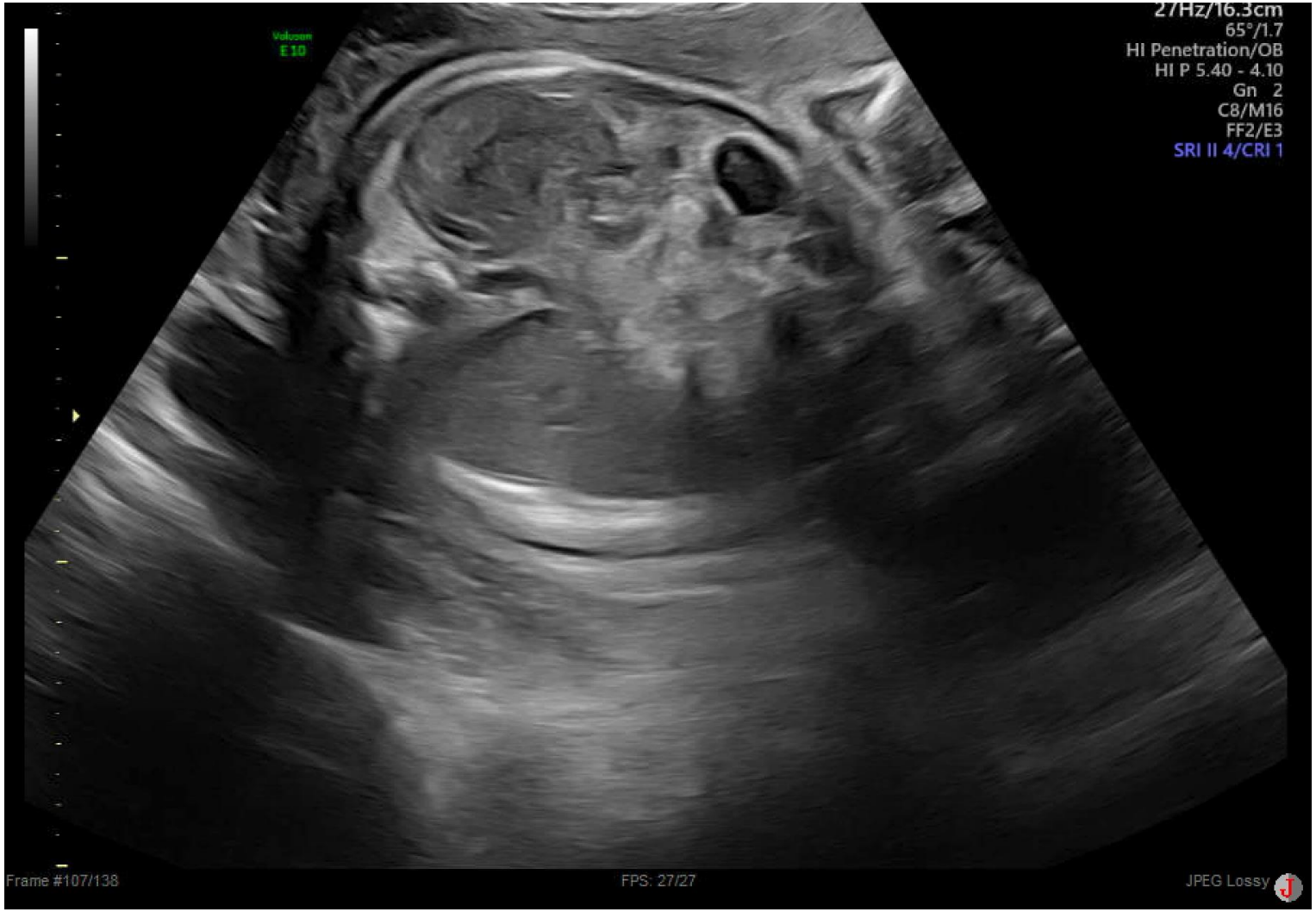
30 weeks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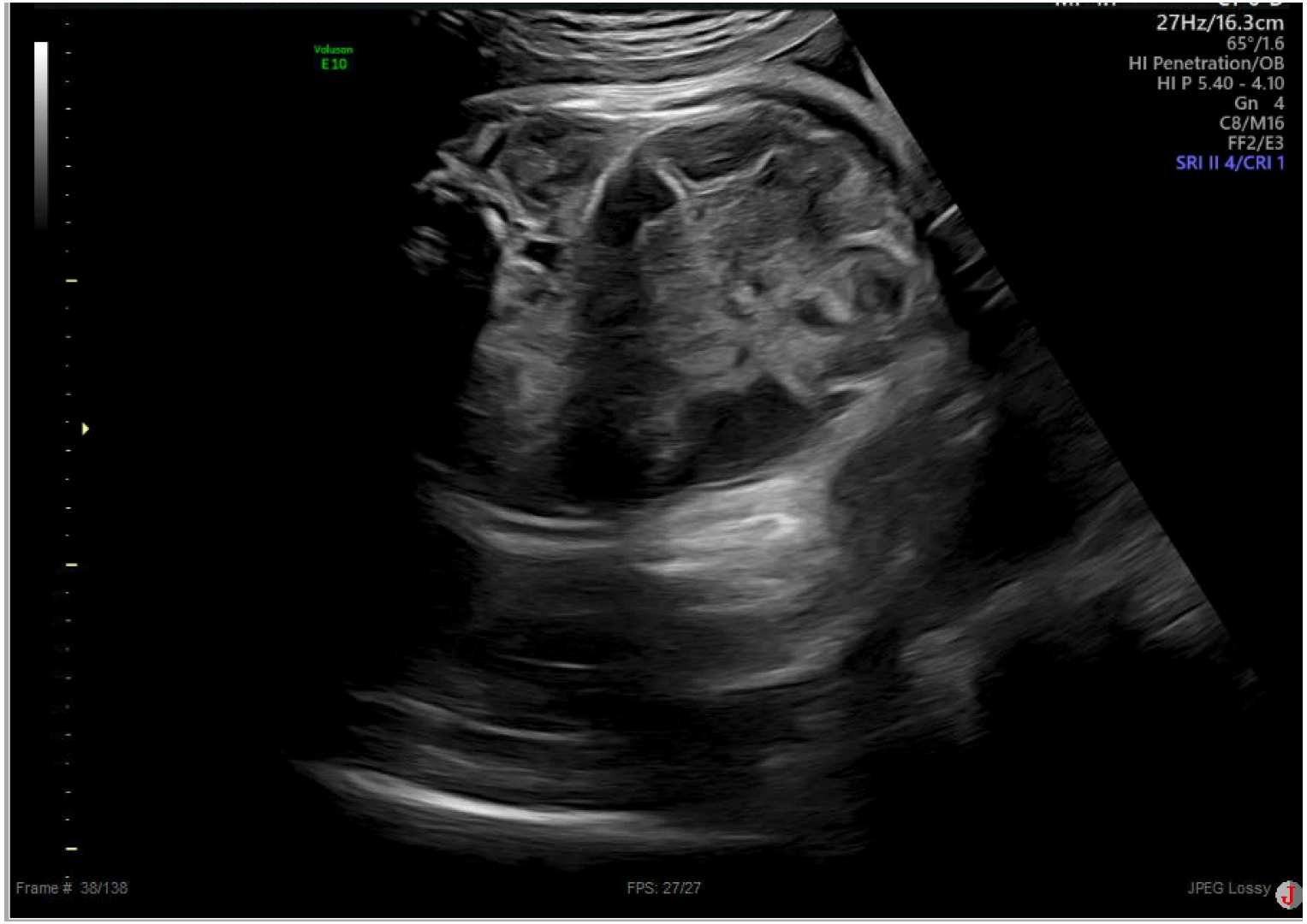
34 weeks


Voluson
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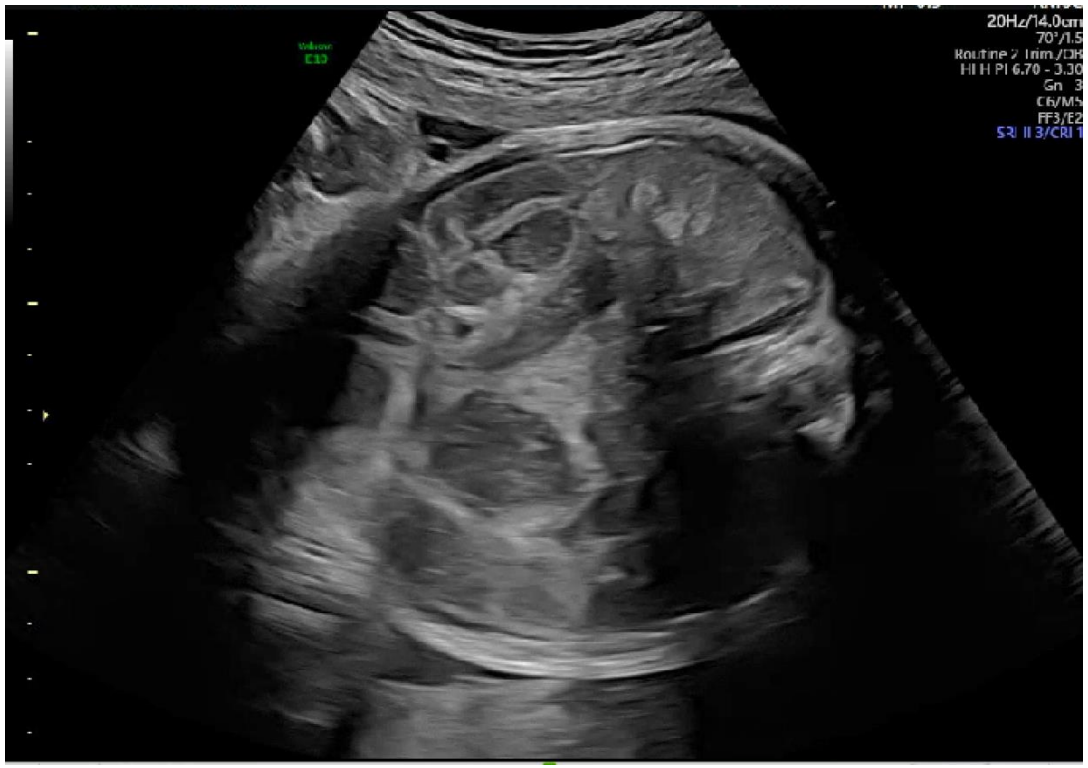
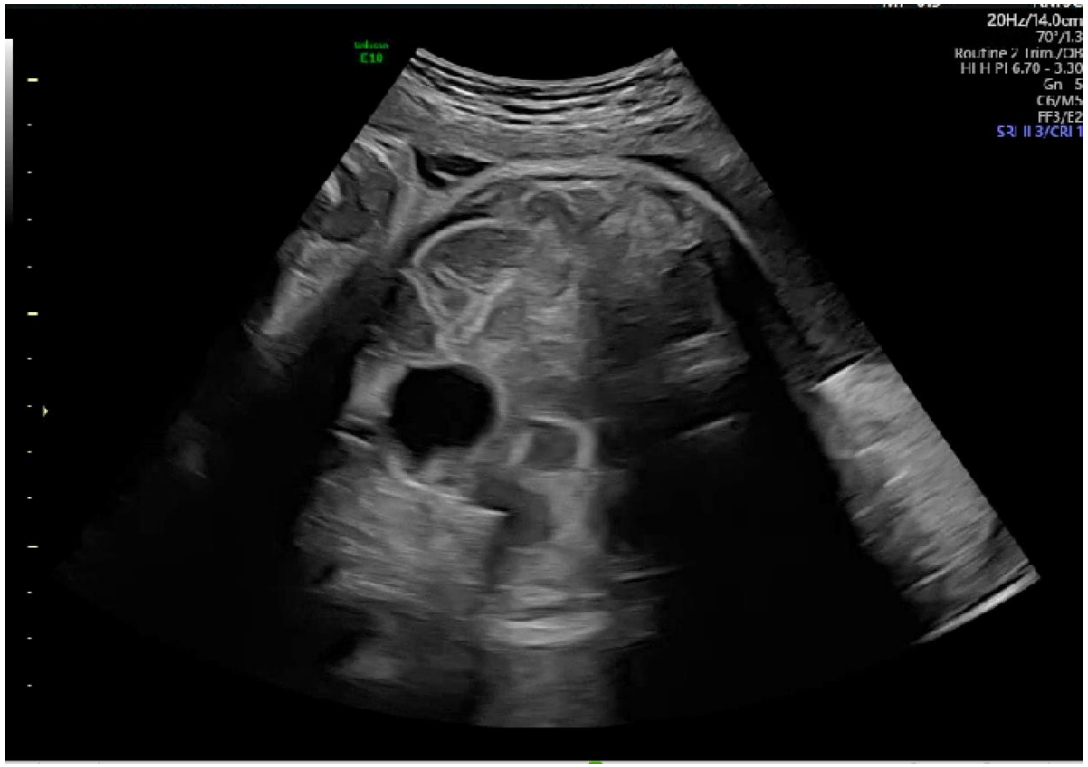
36 weeks





Neonatal Course

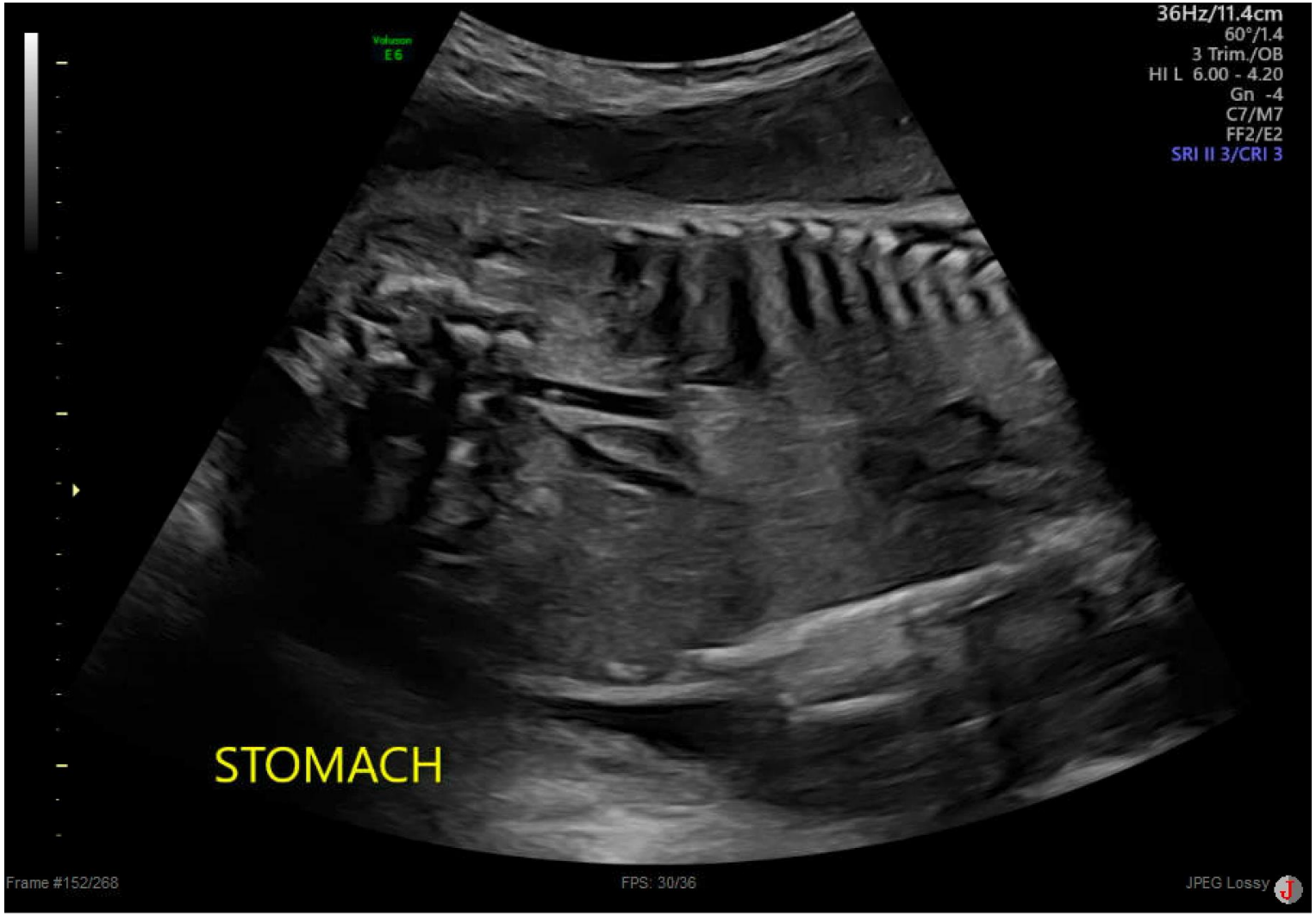
- Delivered at term, mother continued ETI while breastfeeding
- Simple meconium ileus at birth, cleared with gastrografin enemas and rectal irrigations with subsequent normal stooling pattern
- Receiving ongoing exposure via breastmilk.
  - Normal LFTS and eye exams
- Negative IRT initially then slightly above abnormal range
- Pancreatic elastase slight to moderate pancreatic insufficiency
- **LOS 4 days**
- Had subsequent admissions for URI/pneumonia

Case 4

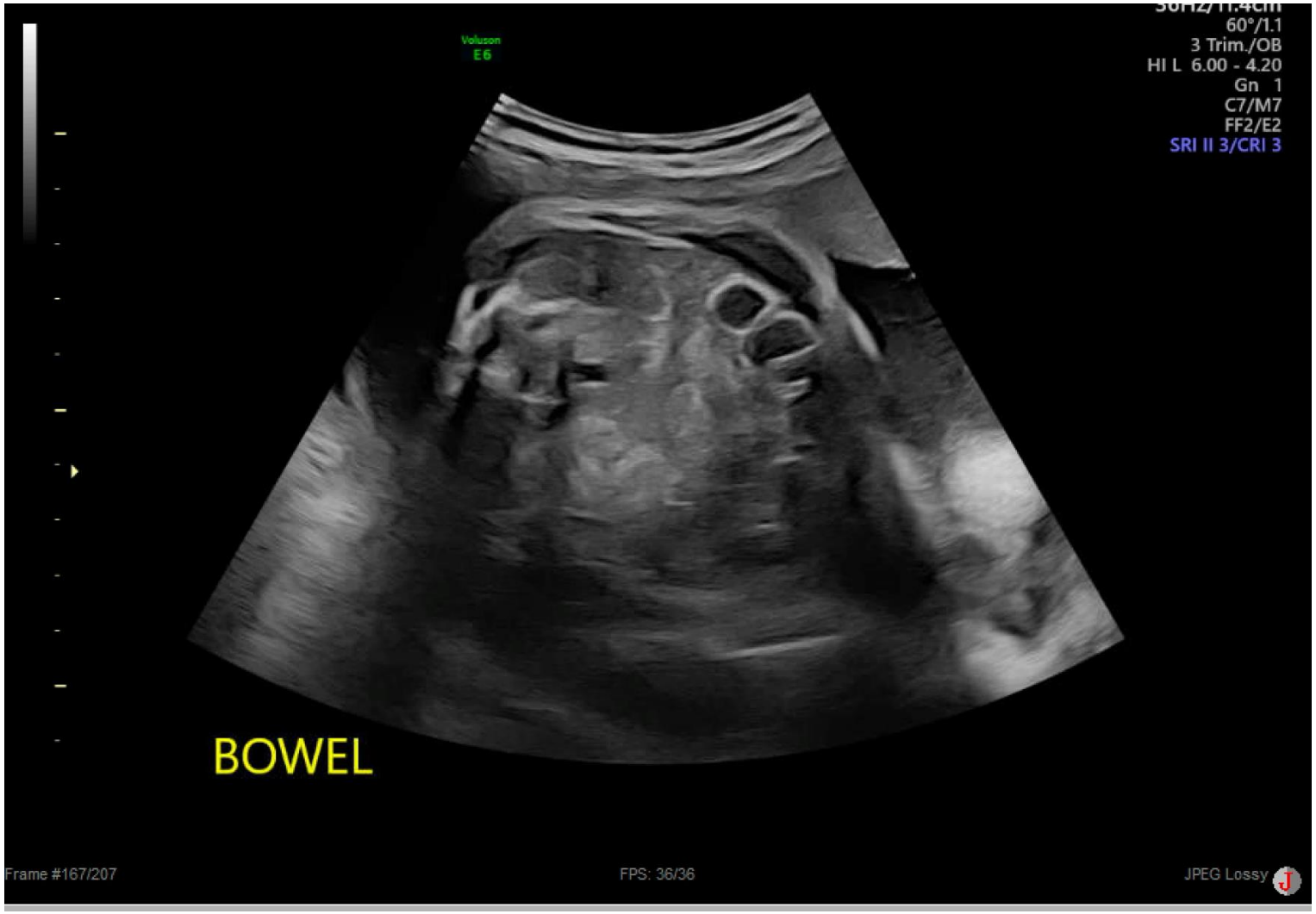
- 22 yo G1
- Both parents CF carriers- c.1006_1007insG and the father is a deltaF508 carrier.
- Referred at 37 weeks 2 days
- Dilated, echogenic bowel. Trace ascites seen throughout abdomen. Findings consistent with simple fetal meconium ileus in the setting of likely fetal CF..

- Unity screen 1:2 risk for Fetal CF- *Declined amnio due to fear of complications!!!*

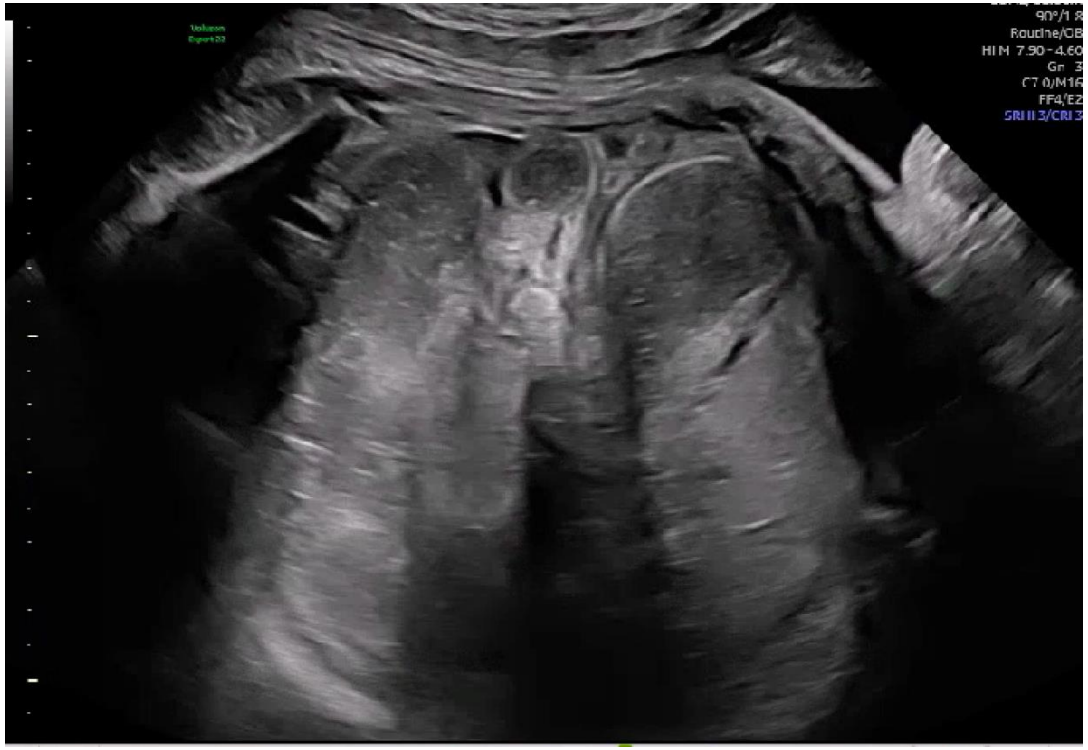
28 weeks

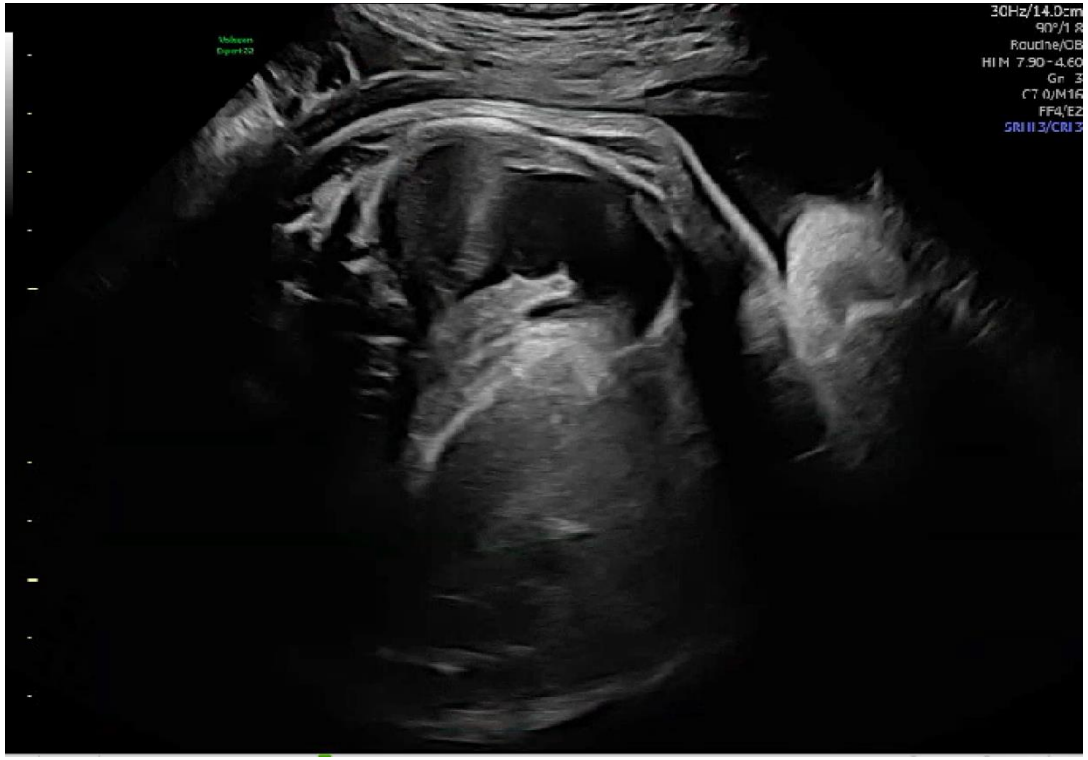

36Hz/11.4cm
60°/1.4
3 Trim./OB
HI L 6.00 - 4.20
Gn -4
C7/M7
FF2/E2
SRI II 3/CRI 3
STOMACH
Frame #152/268
FPS: 30/36
JPEG Lossy

32 weeks


Voluson
E6
60°/1.1
3 Trim./OB
HI L 6.00 - 4.20
Gn 1
C7/M7
FF2/E2
SRI II 3/CRI 3
BOWEL
Frame #167/207
FPS: 36/36
JPEG Lossy

37 weeks





Neonatal Course

- Induction at 39 weeks
- Exploratory laparotomy with evacuation of meconium ileus
  - Suction rectal biopsy
  - Inspissated meconium noted in distal ileum. Enterotomy made about 60cm from ileocecal valve that allowed retrieval of meconium and irrigation with Mucomyst and saline
- IRT well above cut-off on newborn screen
- Pancreatic elastase- Abnormal (<100 mcg/g), Consistent with pancreatic insufficiency
- Positive sweat chloride
- **LOS 20 days**

Summary

- Meconium ileus in setting of fetal CF is a morbid condition
- Prenatal ETI therapy is new, and more data is needed to fully understand its benefits/risks and limitations
- Carrier screening and **early** prenatal diagnosis is critical if ETI is a consideration
- Initiation of ETI prior to marked findings of MI is likely of great importance
- Overcoming barriers to obtaining and shortening time needed to obtain ETI is a necessity for equitable care

- Discussion and Questions