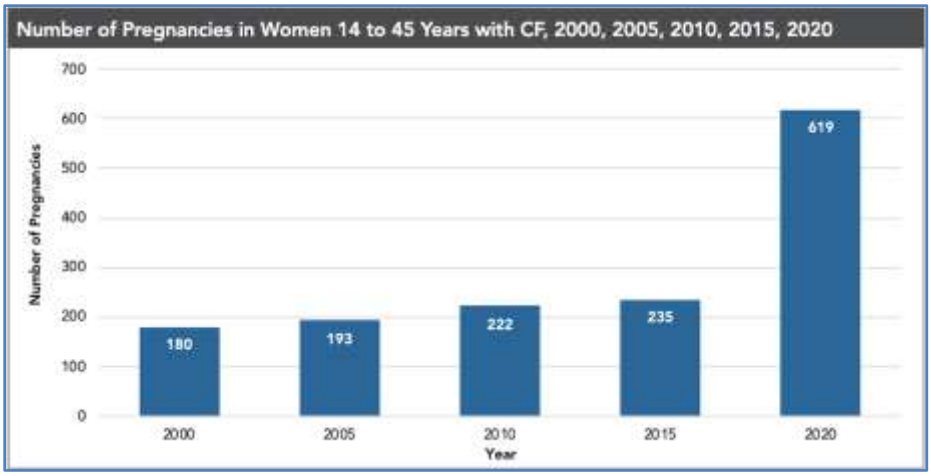
CYSTIC FIBROSIS FOUNDATION®

Clinical Considerations: Fertility and CFTR Modulators

The Cystic Fibrosis Foundation suggests the following considerations as CF care teams coordinate care with obstetrics and pediatrics to counsel their patients about pregnancy and lactation. These considerations are made in light of the marked increase in pregnancies, likely due to the availability of elexacaftor/tezacaftor/ivacaftor (ETI), that have been reported to the CF Foundation Patient Registry for 2020 and 2021 (final number pending).



https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf, page15.

This document is NOT a clinical care guideline. Care decisions should be made based on recommendations and the associated benefit-risk assessment of treatment options from the clinical teams and the goals and preferences of the patients and families they serve.

I. Family Planning

a. Consider proactive discussion with women of childbearing age about increased fertility on ETI, birth control options, and interest in pregnancy.[1]

b. Refer to obstetrics & gynecology (OB-GYN), as needed.

II. Pregnancies

a. Assess risk of newborn having CF

- Test father for all known CF-causing CFTR variants and consider referral to genetic counselor which may be required/advantageous for insurance coverage of genetic testing.

  a. Given the risk of a false negative newborn screen (NBS) [immunoreactive trypsinogen (IRT) in normal range] with maternal ETI use;[2] consider genetic testing of fetus with amniocentesis/chorionic villous sampling during pregnancy if father is a known/possible carrier.
  b. Consider working with state NBS coordinator to flag the risk of missing CF diagnosis due to maternal ETI use.
  c. Encourage close follow-up of newborn by a pediatrician who is knowledgeable about CF.
  d. Collaborate with Pediatric CF program if father is a known carrier or carrier status is unknown to:
     i. Help interpret NBS given confounding effect of ETI
     ii. Consider early genotype and/or sweat testing of infant if not done with amnio/chorionic villous sampling during pregnancy
  e. Manifestations of CF in the newborn may be delayed due to continued ETI exposure via breast milk which could have therapeutic benefit but may delay diagnosis; consider repeating infant sweat test after breastfeeding is completed.

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b. Counsel mother on unknown risks to fetus and tangible maternal benefits of continuing ETI through pregnancy

- Weigh risks and benefits of stopping ETI on mother's health based on the mother's pre-pregnancy clinical status.
- Consider potential ETI-related adverse events for the newborn related to *in-utero* exposure to ETI (animal reproductive models suggest no toxicity at normal human doses, but very limited human data is available *to inform a drug-associated risks during pregnancy*).[1, 3]
    a. Risk of cataracts for ivacaftor-containing products based on juvenile animal models[3]
    b. Risk of hepatotoxicity based on the known metabolism of ETI[3]
- Encourage surveillance for adverse events including cataracts and hepatoxicity.

c. Discuss breastfeeding while on ETI

- ETI has maternal benefits on nutritional status and lung health during post-partum period.
- ETI has been shown in animal models and in humans to be present in breastmilk.[3-5]
- Consider possible ETI-related adverse events for newborn exposure via breast milk (there are limited data available on the use ETI during lactation in human women *to inform a drug-associated risk*).[1-5]
    a. Risk of cataracts for ivacaftor-containing products based on juvenile animal models[3]
    b. Risk of hepatotoxicity based on the known metabolism of ETI.[3]
- Encourage surveillance for adverse events including cataracts and hepatoxicity as long as mother continues to breastfeed on ETI.

Report adverse events of ETI to Vertex to enable reporting to the FDA.

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Encourage pregnant women with CF to consider enrollment in the MAYFLOWERS study to systematically evaluate ETI-related pregnancy/lactation events and build collective knowledge.
https://apps.cff.org/Trials/Finder/details/618/MAYFLOWERS-Study-of-pregnancy-in-women-with-cystic-fibrosis

Additional Resources:

For CF Clinicians:

1. Jain R, Taylor-Cousar JL. Fertility, Pregnancy and Lactation Considerations for Women with CF in the CFTR Modulator Era. J Pers Med. 2021 May 15;11(5):418. doi: 10.3390/jpm11050418.
2. 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 Sep;20(5):835-836. doi: 10.1016/j.jcf.2021.03.018.
3. Prescribing Information for TRIKAFTA, provided by Vertex on pregnancy and lactation can be found on pages 6-7 at: https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf.
4. Collins B, Fortner C, Cotey A, Jr CRE, Trimble A. Drug exposure to infants born to mothers taking Elexacaftor, Tezacaftor, and Ivacaftor. J Cyst Fibros. 2021 Dec 22:S1569-1993(21)02161-5. doi: 10.1016/j.jcf.2021.12.004. Epub ahead of print. PMID: 34952795.
5. NACFC 2021: W03: Hey Baby: Pregnancy in the Era of Highly Effective Modulator Therapy. https://www.youtube.com/watch?v=Di85_5ZvwBU

For your Patients and their Families:

1. Information on planning for a safe pregnancy with CF, provided by the CF Foundation, can be found at https://www.cff.org/managing-cf/pregnancy-and-cf
2. Information on modulator therapies as part of CF care, provided by the CF Foundation, can be found at https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/

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