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Narrative Review

Pregnancy in People With Cystic Fibrosis Treated With Highly Effective Modulator Therapy

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With improvements in overall health attributable to newly available medications called highly effective modulator therapy, an increasing number of people with cystic fibrosis (CF) are pursuing pregnancy. However, the safety of these medications for pregnant people with CF and the fetus remains largely unknown. Limited data demonstrate a decline in patients' health and well-being after withdrawal of highly effective modulator therapy during pregnancy; however, both animal and human studies suggest an association between highly effective modulator therapy and cataracts in the offspring that requires further investigation. Use of highly effective modulator therapy can also affect the results of newborn screening and may influence fetal outcomes among fetuses affected by CF as a result of transplacental passage of highly effective modulator therapy. An ongoing prospective cohort study will likely provide more information for pregnant people with CF. Until then, multidisciplinary counseling continues to be critical for people with CF who are of reproductive age.

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Cystic fibrosis (CF) is an autosomal recessive genetic disorder affecting the production and function of the CF transmembrane conductance regulator (CFTR) protein. Morbidity and mortality from CF are related primarily to the lungs, with chronic inflammation and infection leading to progressive bronchiectasis, mucus plugging, and ultimately death from respiratory failure. In recent years, the manufacturing and marketing of highly effective modulator therapy targeting specific pathogenic variants in CF transmembrane conductance regulator (Fig. 1) have had profound effects on the health of people with CF.

As shown in Figure 1, many different CF-causing genetic variants lead to absent or malfunctioning CF transmembrane conductance regulator protein on the epithelial cell surface. This protein functions as an ion channel, and in its absence, cells are unable to regulate the ionic transport of chloride and sodium. This lack of regulation leads to a dehydrated airway mucus layer, which is a nidus for chronic infection and inflammation. Highly effective modulator therapies work by potentiating the open-channel probability of the CF transmembrane conductance regulator protein in the cell membrane, rescuing the malformed CF transmembrane conductance regulator protein from recycling within the cell, or a combination of both mechanisms.[1]

Two commercially available drugs classified as highly effective modulator therapy are the CF transmembrane conductance regulator potentiator ivacaftor (Kalydeco), available in the United States since 2012, and the combination CF transmembrane conductance regulator corrector–potentiator drug elexacaftor/

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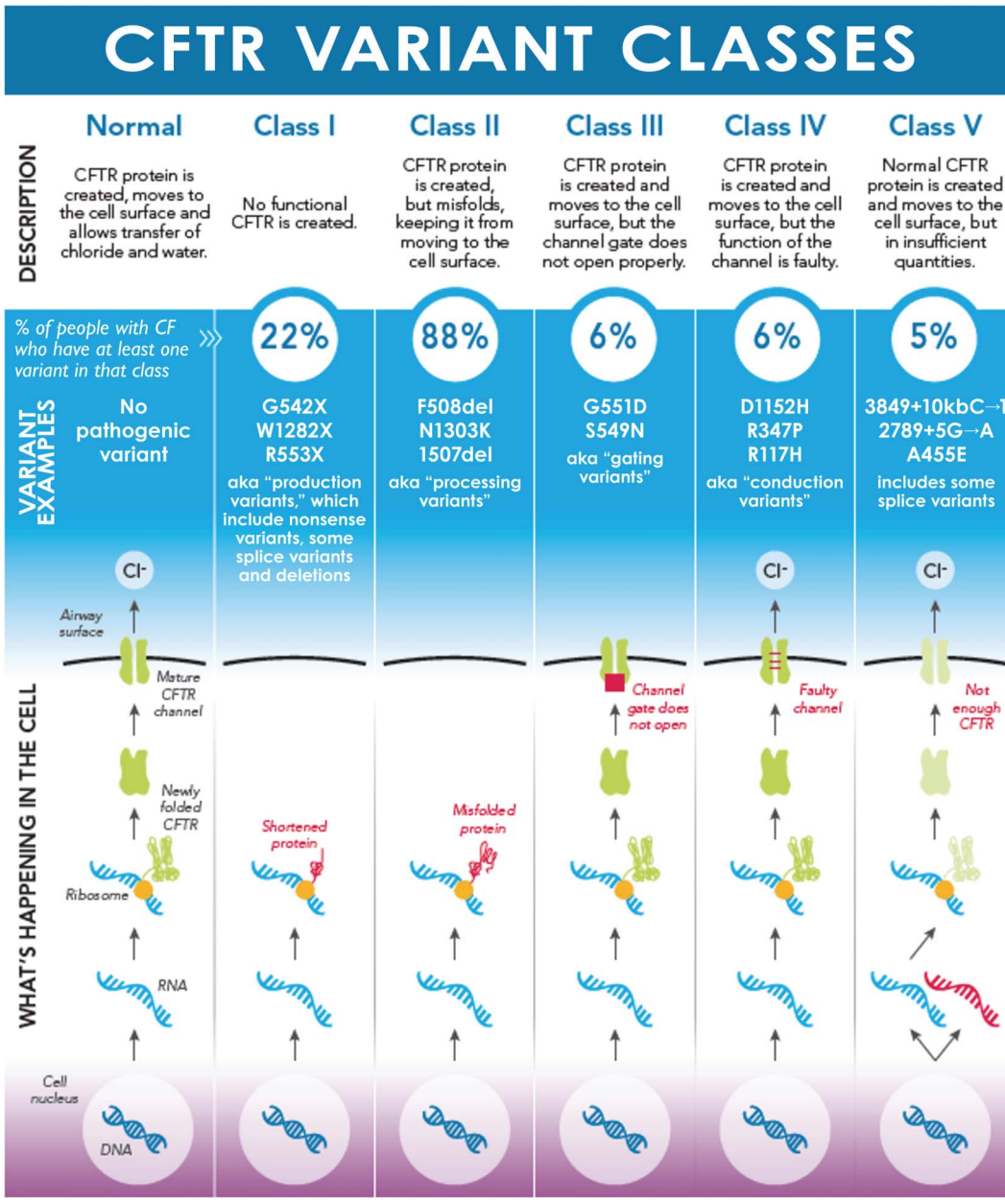

Fig. 1. Cystic fibrosis transmembrane conductance regulator (CFTR) variant classes. Infographic describing the different types of CFTR pathogenic variants, the relative percentage of people with cystic fibrosis (CF) with each type of pathogenic variant, and examples of common variants in each class. Adapted from the Cystic Fibrosis Foundation. Used with permission.

Goralski. Pregnancy in People With Cystic Fibrosis. Obstet Gynecol 2024.

tezacaftor/ivacaftor (Trikafta), which was approved by the U.S. Food and Drug Administration for commercial use in 2019. These medications have resulted in a marked improvement in lung function, body mass index (BMI), and patient-reported outcomes,[2–6] making highly effective modulator therapy the standard of care for eligible people with CF. It is important to note that although ivacaftor was an available treatment option for only about 5% of people with CF in the United States (eligibility determined based on genetic variants), elexacaftor/tezacaftor/ivacaftor approval expanded this eligibility to nearly 90% of people with CF. Two other CF transmembrane conductance regulator modulators, lumacaftor/ivacaftor (Orkambi)[7,8] and tezacaftor/ivacaftor (Symdeko),[9] are also commercially available but generally excluded from the

designation of highly effective modulator therapy because of their comparatively reduced efficacy.[2]

In this review, we focus mainly on the two commercially available CF transmembrane conductance regulator modulators that are classified as highly effective modulator therapy, ivacaftor and elexacaftor/tezacaftor/ivacaftor. Two factors generally guide the selection of the most appropriate CF transmembrane conductance regulator modulator: age of the patient and the class of CF transmembrane conductance regulator variants (Fig. 1) present in the patient. These orally available agents are taken twice a day with a high-fat meal for enhanced absorption. Dosing is fixed if the patient is at least age 12 years and weighs more than 30 kg; lower doses are available for pediatric patients based on weight. Monitoring recommendations include quarterly checks of liver transaminases because hepatic toxicity, including one case of fulminant liver failure requiring liver transplantation, has been reported.[10] For patients younger than age 18 years, baseline and follow-up eye examinations are recommended given reports of noncongenital lens opacities and cataracts.[10] Although conflicting reports exist,[11–13] there is ongoing concern for the propensity of these drugs to contribute to worsening mental health symptoms, including depression, anxiety, and decreased executive functioning skills.[14–16] Although dose adjustments to highly effective modulator therapy are sometimes considered when adverse events are encountered,[17–20] these adjustments are deemed off-label use and are inconsistently applied between different CF centers.

Data from the Cystic Fibrosis Patient Registry suggest that pregnancy rates increased quickly after the 2019 approval of elexacaftor/tezacaftor/ivacaftor, up to 38.04 pregnancies per 1,000 women with CF.[21] Reasons for the increase in pregnancies are speculative, but some experts theorize that thinning of the cervical mucus allows enhanced sperm penetration or improvements in maternal health, leading to increased libido and fewer early spontaneous abortions.[22,23] Some people with CF are choosing to continue use of elexacaftor/tezacaftor/ivacaftor despite experiencing undesirable side effects such as weight gain or brain fog in the hopes of improving their fecundity.[24,25] The increase in pregnancy rates supports the importance of preconception counseling for reproductive-aged people with CF, particularly as they begin using highly effective modulator therapy. This counseling may include optimizing CF disease control, contraception and pregnancy timing, risks of pregnancy, and establishing care with an obstetric team who has experience caring for people with CF. Such discussions should be initiated by a CF health care clinician or through referral to an obstetrician–gynecologist who can help guide reproductive decision making.[26,27] Because of the increasing incidence of pregnancy among people with CF, it is critical to review both new data and existing guidelines for optimal management of this population.[26,28]

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR MODULATOR USE DURING PREGNANCY AND LACTATION

As with many newly approved drugs, discerning safety and efficacy during pregnancy is difficult, and most of the data are generated from animal studies and retrospective case series.[29] Preclinical teratogenicity studies in rats exposed to ivacaftor from gestational day 7 through lactation day 20 demonstrated no adverse effects on growth and development of the offspring at up to three times the maximal human recommended dose.[30] Of special interest, in utero administration of ivacaftor to ferrets harboring two ivacaftor-responsive CF transmembrane conductance regulator variants (G551D/G551D) prevented the development of pathology in the intestine, pancreas, and male reproductive tract, suggesting the potential for fetal effects from maternal highly effective modulator therapy ingestion.[31] Moreover, postnatal withdrawal of ivacaftor therapy in newborn ferrets led to pancreatic insufficiency, fasting glucose impairment, and decline in body weight.

Case reports in humans have also demonstrated that highly effective modulator therapy can cross the placental barrier and lead to measurable levels in cord blood and in the infant.[32,33] Retrospective international data published in 2020[34] described 64 pregnancies in 61 women with CF taking ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor. No fetal or infant complications were deemed to be related to the modulator exposure, either in utero through the placenta or while breastfeeding. Subsequently, a retrospective analysis of 45 elexacaftor/tezacaftor/ivacaftor–exposed pregnancies in the United States showed a generally reassuring safety profile[35]; infant complications were deemed to be unlikely related to elexacaftor/tezacaftor/ivacaftor (15 events in 15 infants) or unknown if related to maternal use of elexacaftor/tezacaftor/ivacaftor (three events in three infants). Of note, two of the three infants in the latter category were born to a pregnant person with diabetes, which is an independent risk factor for fetal malformations. A subsequent case series by Jain et al[36] demonstrated bilateral congenital cataracts in 3 of 23 neonates exposed to elexacaftor/tezacaftor/ivacaftor while in utero. The cataracts were small and did not cause clinically significant impairment; however,

there is biological plausibility for this phenomenon, with studies in rats similarly demonstrating the possibility of cataract formation associated with early-life exposure.[37]

It is important to note that discontinuing highly effective modulator therapy in a pregnant person with CF may have deleterious effects on parental health.[38] Among a cohort of people with CF who became pregnant while taking elexacaftor/tezacaftor/ivacaftor, six elected to stop the medication on learning of their pregnancy, with five of them subsequently resuming treatment after a brief interlude because of intolerable clinical deterioration.[35] The MAYFLOWERS study (Prospective Study of Pregnancy in Women With Cystic Fibrosis; ClinicalTrials.gov, NCT04828382)[39] is gathering prospective health data from parent–child dyads during pregnancy and the first year of life to better understand outcomes after in utero exposure. This study will be important for people with CF and their physicians because elexacaftor/tezacaftor/ivacaftor is a new medication with limited data on immediate or long-term outcomes after in utero exposure and relatively little clinical experience in pregnancy.

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR MODULATOR USE DURING LACTATION

Data on lactating individuals using CF transmembrane conductance regulator modulators are less abundant. Trimble et al[32] established the presence of lumacaftor and ivacaftor in breastmilk using mass spectrometry and noted that, although the levels of each drug were low, they were sufficient to result in measurable levels in the infant's plasma. This was later determined to also hold true for elexacaftor/tezacaftor/ivacaftor.[33,40] A valuable summary[41] of the ongoing risks for transaminitis and lens opacities in breastfed infants has led to some physicians recommending ongoing investigations for these side effects in infants exposed to elexacaftor/tezacaftor/ivacaftor through breastmilk. The aforementioned MAYFLOWERS study[39] is also examining the clinical implications of lactation and breastfeeding, so additional data are expected soon.

PREGNANCY MANAGEMENT OF PEOPLE WITH CYSTIC FIBROSIS ON HIGHLY EFFECTIVE MODULATOR THERAPY

Although maternal management of CF before pregnancy is improved with highly effective modulator therapy, there are limited data guiding how pregnancy management should change for people with CF on highly effective modulator therapy compared with those who are not taking these medications. Because CF is a well-characterized genetic condition with high carrier frequency, details on screening, diagnosis, and management of pregnant people with CF have recently been updated elsewhere. This includes a 2022 expert consensus by Jain et al,[42] health care professional and patient information on pregnancy and identification of CF Centers of Excellence provided by the CF Foundation (www.cff.org), and The CF Reproductive and Sexual Health Guide (https://cfreshc.org/), a collaborative effort by patients, clinicians, and researchers working to improve the sexual and reproductive health of those with CF. Additional data such as those that will be generated by MAYFLOWERS[39] will be pivotal for the development of best practices for care of reproductive-aged people on highly effective modulator therapy but remain a critical knowledge gap at this time. Table 1 offers a summary of commonly used medications in CF, including potential adjustments that may be needed during pregnancy.

POTENTIAL EFFECTS OF HIGHLY EFFECTIVE MODULATOR THERAPY ON NEWBORN SCREENING

Newborn screening has revolutionized the diagnosis and early treatment of infants with CF,[43–45] with improvements in nutritional status and time to chronic pseudomonas infection. Although newborn screening protocols vary from state to state[46] and internationally,[47] the unifying feature of newborn screening programs for CF is immunoreactive trypsinogen, a precursor enzyme for pancreatic inflammation detectable through dried blood spot analysis. Although not specific for CF, immunoreactive trypsinogen is highly sensitive and is used as the basis of the screening program in all 50 states. Some newborn screening programs use a fixed-value cutoff for immunoreactive trypsinogen, whereas others use a "floating" cutoff based on higher than the 96th percentile of the values recorded for the specimens obtained in that review cycle. After an elevated immunoreactive trypsinogen value, some states perform a second verification of the immunoreactive trypsinogen value, and others move directly to a *CFTR* variant panel obtained on the same blood spot. Still other states will use full *CFTR* sequencing if only one variant is detected on the screen.

The method of communication of abnormal results (to parents, pediatricians, or state-designated CF centers) also varies among programs.[44,48] Because newborn screening is a screening test only, diagnosis

Table 1. Commonly Used Medications in People With Cystic Fibrosis

Class of Medication	Examples of Frequently Used Medications	Adjustments to Consider in Conjunction With Primary CF Clinician
CFTR modulators	Ivacaftor (Kalydeco) Lumacaftor/ivacaftor (Orkambi) Tezacaftor/ivacaftor (Symdeko) Elexacaftor/tezacaftor/ivacaftor (Trikafta)	Discussion with patients about the uncertain safety profile in pregnancy.
Vitamins	MVW complete formulation ADEKs	Standard doses of fat-soluble vitamins can lead to vitamin A toxicity in pregnancy. CF health care professionals frequently reduce dose of fat-soluble vitamins by 50% during pregnancy and advise the concurrent use of a prenatal vitamin.
Pancreatic enzyme replacement therapy	Pancrealipase (Creon, Zenpep, Pertzye, Pancreaze)	Dose adjustment is rarely needed in pregnancy. Although prior recommendations were for the exclusive use of Pancreaze because of the presence of potentially toxic phthalates in other enzyme preparations, all enzyme preparations currently available in the United States are phthalate free.
Antibiotics	Fluoroquinolones (ciprofloxacin, levofloxacin) Macrolides (azithromycin, doxycycline) Aminoglycosides (tobramycin, gentamycin)	*Pseudomonas aeruginosa* is a common respiratory pathogen in people with CF and is frequently a cause of CF pulmonary exacerbations. Fluoroquinolones are the only orally available antibiotic class that treats pseudomonas; thus, they are used frequently in combination with inhaled aminoglycosides to treat pulmonary exacerbations that do not require hospitalization. Patients planning pregnancies should be counseled by all clinicians about the need to avoid fluoroquinolones in pregnancy. Discussion between the treating CF team and obstetrics team about the safety profile and risk/benefit ratio for antibiotic use during pregnancy is recommended.

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

of CF is confirmed or refuted by quantitative pilocarpine iontophoresis, or the "sweat test." In this test, a sweat chloride value below 30 mmol/L is inconsistent with CF, a value of 60 mmol/L or higher is consistent with CF, and a value of 30–59 mmol/L falls into the intermediate range and requires further testing.

Despite differences in newborn screening programs, the CF community relies on this early identification strategy to improve early intervention and outcomes in people with CF.[49] However, recent case reports have challenged our confidence in newborn screening in the offspring of people with CF using elexacaftor/tezacaftor/ivacaftor.[50] Fortner et al[51] report a case of a false-negative newborn screen in a child born to a mother homozygous for the F508del variant who used elexacaftor/tezacaftor/ivacaftor throughout pregnancy. The father was a known carrier for the F508del variant, and, when a 20-week ultrasonogram showed possible echogenic bowel, suspicion was high for the fetus to have CF. However, a repeat ultrasonogram at 32 weeks of gestation showed no evidence of echogenic bowel, and a healthy neonate was delivered at 39 weeks. Newborn screening showed an immunoreactive trypsinogen below the cutoff value, but, at the request of the CF center, the state laboratory performed CF transmembrane conductance regulator DNA testing and demonstrated that the child indeed carried two copies of the F508del variant. This case draws attention to the possibility of a false-negative CF screen using immunoreactive trypsinogen in a child born to a pregnant person using highly effective modulator therapy. Biologically, this is likely secondary to the beneficial effect of transplacental elexacaftor/tezacaftor/ivacaftor exposure on the fetal–neonatal pancreas, decreasing early pancreatic inflammation associated with CF. Thus, for a child in whom there is prenatal suspicion for CF based on parental carrier status, prenatal imaging, or DNA screening or for whom transplacental exposure to elexacaftor/tezacaftor/ivacaftor was present, further genetic testing should be conducted.

Szentpetery et al[52] subsequently reported a case of a carrier pregnant person treated with elexacaftor/tezacaftor/ivacaftor during the gestation of an F508del homozygous fetus with meconium ileus diagnosed at 23 weeks of gestation. Treatment of the maternal–fetal

dyad with elexacaftor/tezacaftor/ivacaftor began at 32 weeks of gestation to benefit the fetus, with resolution of ultrasound findings by 35 weeks of gestation. The neonate was delivered spontaneously at 36 1/7 weeks of gestation and passed multiple stools on the first day of life. Newborn screening showed an immunoreactive trypsinogen value of 104.6 ng/mL, suggestive of a diagnosis of CF. Subsequent testing, with ongoing exposure to elexacaftor/tezacaftor/ivacaftor through breastmilk, showed sufficient pancreatic function and sweat chloride values of 64 and 62 mmol/L. Although these values are diagnostic for CF, they fall well below the values typically seen in an infant with two F508del variants. Several ethical challenges to this approach cited by the authors included possible maternal harm, cost of therapy, resource allocation, unknown fetal efficacy, and limited safety data on placental transfer of drug.[52] An accompanying editorial[53] highlighted the ethical concerns about a person's autonomy in regard to treatment of their pregnant body. Notably, this publication provides one of the first reports of using genetic modulator therapies in pregnancy to treat a fetus with an affected condition.

Another case was subsequently reported in Spain of an F508del homozygous neonate born to a CF carrier who used elexacaftor/tezacaftor/ivacaftor starting at 31 1/7 weeks of gestation. After maternal treatment for 8 weeks, bowel echogenicity resolved, and the neonate was delivered after spontaneous prelabor rupture of membranes and labor induction at term.[54] These reports raise several important research, clinical, and ethical questions; remain a novel area of future study; and are particularly valuable for couples at risk of having a child with CF. However, this approach remains experimental and is not recommended in routine clinical practice for a carrier pregnant person and affected fetus at this time. Clinicians considering this approach should discuss risks and benefits thoroughly, particularly emphasizing the unknown effects on neurocognitive development.

The timing of the use of highly effective modulator therapy in pregnancy may contribute to the varied presentations demonstrated in these case studies. In the first example, the drug was initiated for maternal benefit before conception and led to a scenario in which the neonate's newborn screening was a false negative. In the second scenario, the fetus was at 32 weeks of gestation at the time of highly effective modulator therapy treatment onset, and, although resolution of the meconium ileus was documented, the neonate's CF diagnosis was captured by newborn screening. Thus, a high index of suspicion for CF remains necessary when there is prenatal exposure to highly effective modulator therapy.[50] The potentially affected infants may never come to the attention of a pediatric pulmonologist (the traditional CF liaison to state newborn screening laboratories). The diagnostic possibility of CF may be dismissed on the basis of a false-negative newborn screening conducted in the context of maternal CF transmembrane conductance regulator modulator use. Awareness of the possibility of a false-negative newborn screening result by all clinicians involved with the care of a pregnant person is thus important.

CONCLUSION

Harmonizing efforts among obstetricians, maternal–fetal medicine specialists, geneticists, the state newborn screening laboratory, neonatologists, pediatricians, and adult and pediatric pulmonologists is necessary to provide expert care to the parent–child dyad with CF, whether CF is diagnosed in the parent or suspected in the child. Therefore, reproductive-aged people who are started on highly effective modulator therapy should have counseling with their CF clinicians and an obstetrician with experience caring for people with CF on highly effective modulator therapy in pregnancy. The ideal timing of such conversations is in the preconception period, reinforcing the importance of family planning options for these patients. Additional important counseling points include the 1) timing of pregnancy relative to disease stability; 2) risks of pregnancy; 3) plans for partner carrier screening and, if applicable, fetal or neonatal diagnosis; and 4) maternal and fetal risks and benefits of continuing highly effective modulator therapy with up-to-date clinical information.

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