13° FORUM ITALIANO SULLA FIBROSI CISTICA

Riscrivere il futuro insieme:
nuovi percorsi di vita e di cura.

BARI 15_16 NOV 2025 HOTEL PARCO DEI PRINCIPI

Salute sessuale e riproduttiva in Fibrosi Cistica nell'era dei modulatori di CFTR

Dr. Barbara Messore

LIFC
Lega Italiana
Fibrosi Cistica

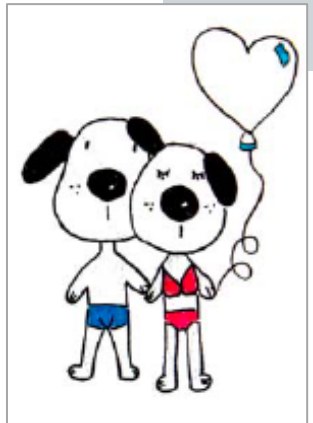
Sexual and Reproductive Health

OMS

- Sexual and Reproductive health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes.

- Sexual and Reproductive health implies that people are able to have a *satisfying and safe sex life* and that they have the capability *to reproduce* and the freedom to decide if, when and how often to do so.

- Both man and female with CF face many sexual and reproductive health concerns



2011

SOCIETÀ ITALIANA DI FIBROSI CISTICA
SIFC

FORUMRS

LIFC
Lega Italiana
Fibrosi Cistica

Sessualità e fibrosi cistica

Sexual and reproductive health in cystic fibrosis: a life-course perspective

Review

Lancet Respir Med 2015; 3:70–86

Katherine B Frayman, Susan M Sawyer

begins little by little, as your patient grows up… …

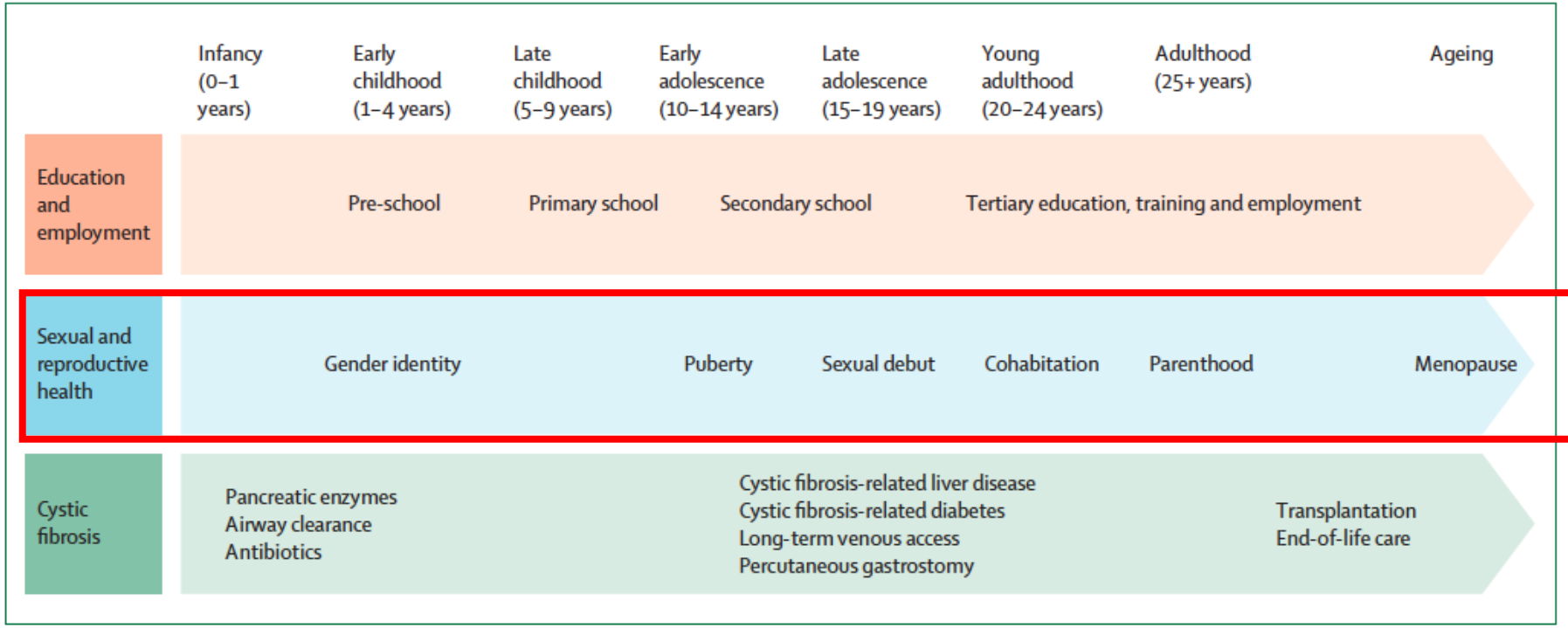


Figure 1: Developmental milestones

Lancet Respir Med, 2015

Optimizing sexual and reproductive health across the lifespan in people with cystic fibrosis

Pediatric Pulmonology. 2022;57:S89–S100.

TABLE 2 Sexual and reproductive health model of health assessment over the lifespan for CF care providers and collaborating care providers

Adolescence	Adulthood	Late adulthood
Assess pubertal development, hormones, and hypogonadism		
Openly discuss gender identity and sexual preferences		
Discuss fertility and contraception		
Counsel on STI prevention		
	Discuss sexual functioning; address any concerns	
	Discuss parenthood and reproductive options	
	Evaluate urinary incontinence	
		Evaluate peri-menopause symptoms

Abbreviation: STI, sexually transmitted infection.

CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

FORUM 2018

LIFC Lega Italiana Fibrosi Cistica

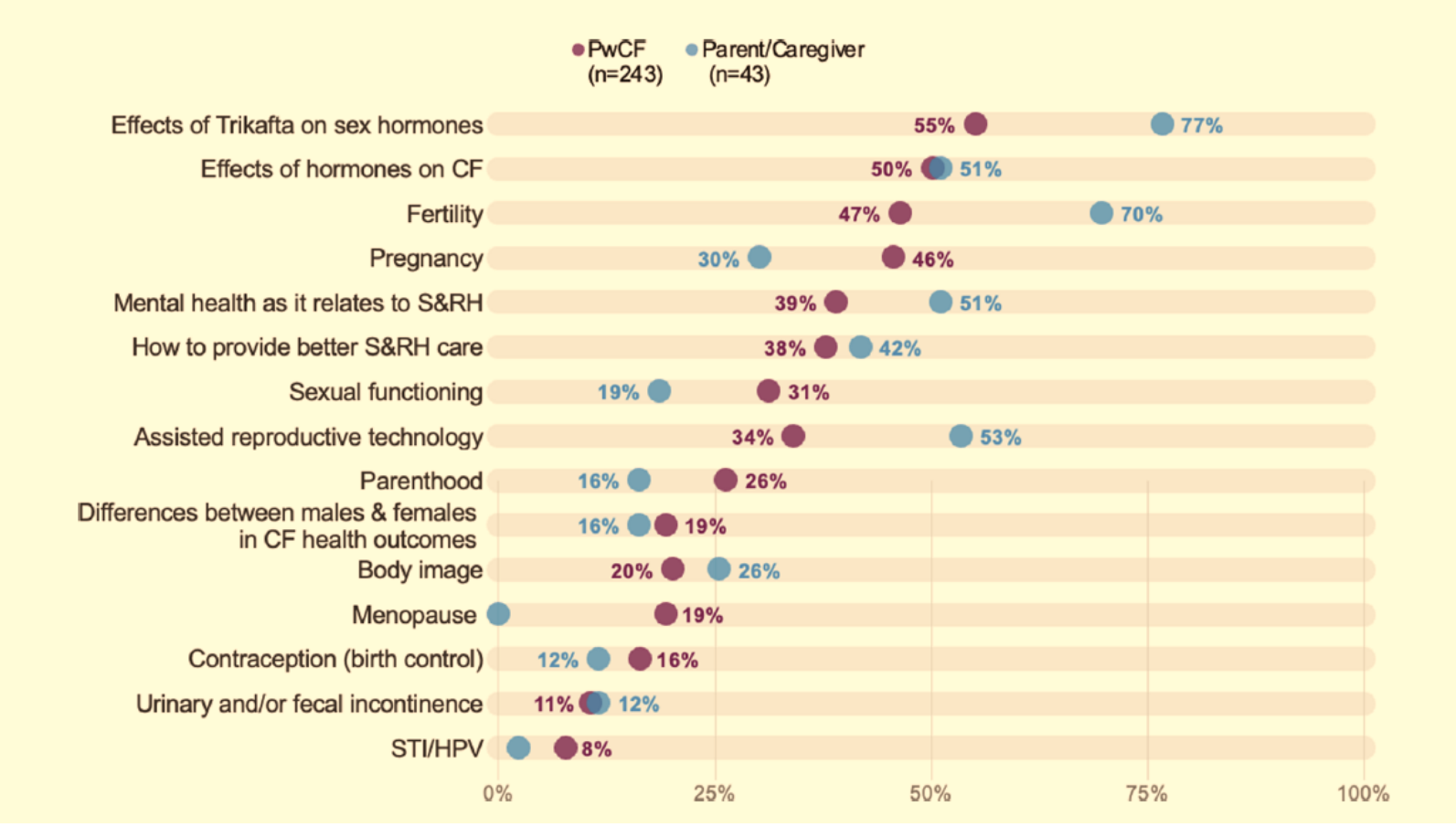
Sexual Health, Reproduction, and Gender (SHARING) Research Working Group

Background: To address sexual and reproductive health (SRH) concerns among people with cystic fibrosis(PwCF),

SRH is an important and emerging area of CF research.

Prioritizing sexual and reproductive health research and care for people with cystic fibrosis: A 2023 workshop report from the Cystic Fibrosis Foundation Sexual Health, Reproduction, and Gender (SHARING) Research Working Group

J Cystic Fibrosis 2024; 23: 639-646



Effects of hormons on CF

SHARING Working Group

Sex hormons implicated as one factors that may contribute to sex disparity in CF

In female with CF:

- respiratory morbility, PEX after puberty correlated with menstrual cycle
- benefit of hormonal contraception
- not studied the impact of menopause

In male with CF:

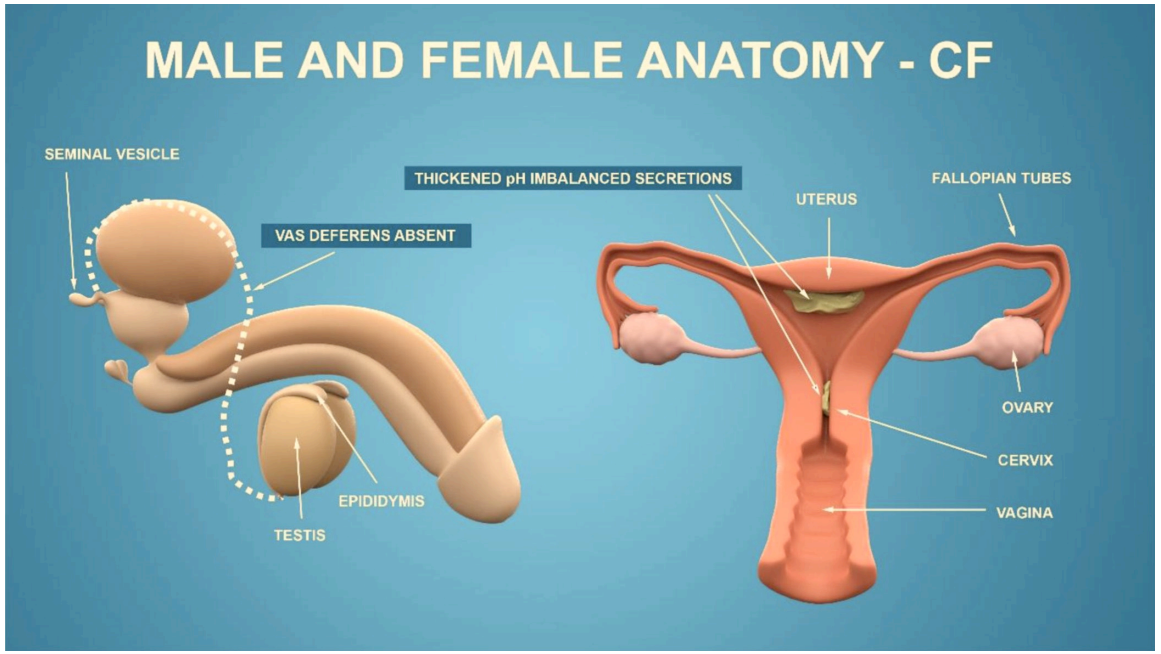
- Low frequency of investigation (testosterone level measured in only 10% → 1/3 hypogonadal→ 1/3 not supplemented)

- **Effect of ETI on sex hormons?**

- **Under study long term effect of ETI on sex disparity in pwCF**

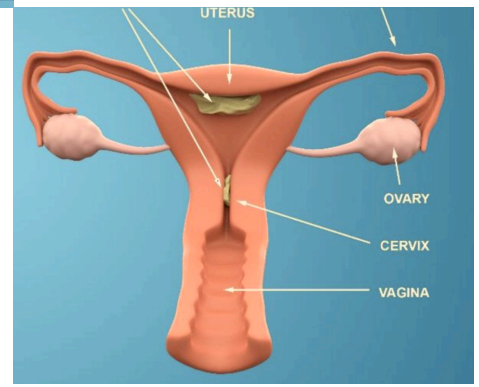
Fertility in CF and impact of CFTRms

SHARING Working Group



Female Fertility and CFTR

THICKENED pH IMBALANCED SECRETIONS



CFTR expression in cervix and uterus

high proportion of WwCF experience **multifactioral subfertility /infertility**
(35% vs 5% general population)

delayed puberty / increased anuvulatory cycles /reduced ovarian reserve

nutritional deficiency

thick acidic reproductive tract **mucus** → physical barrier to sperm entrance into the uterus and impairment of sperm capacitation

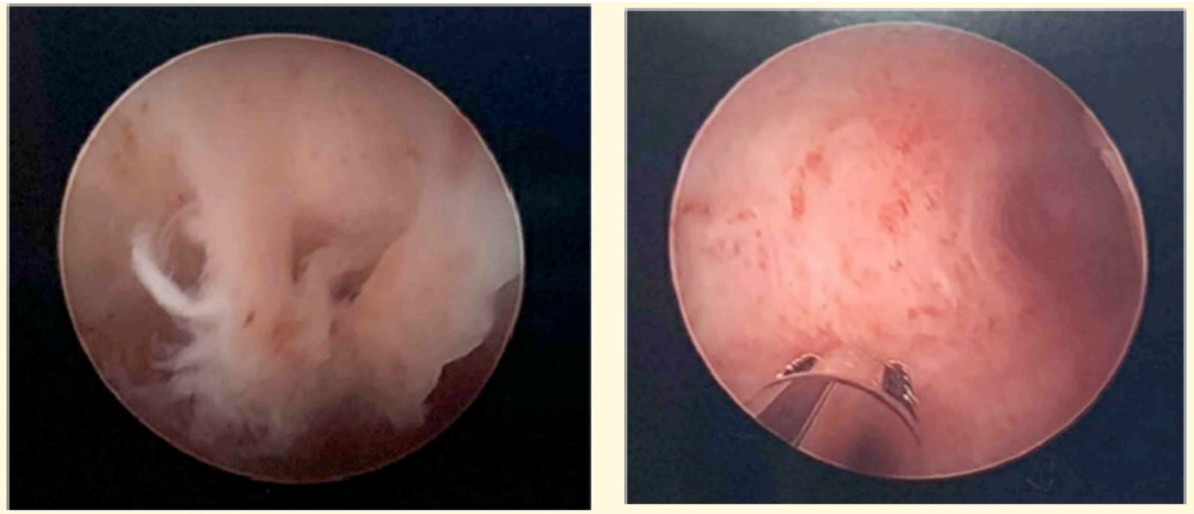
Jain R and Taylor-Coursar A J Pers Med, 2021; 11: 418

Female Fertility and CFTR modulators

31 ys old WwCF

C1021_1022dupTC / c.328G>C
Sweat test: Cl 63

ppFEV1 82
BMI 22



pre ivacaftor

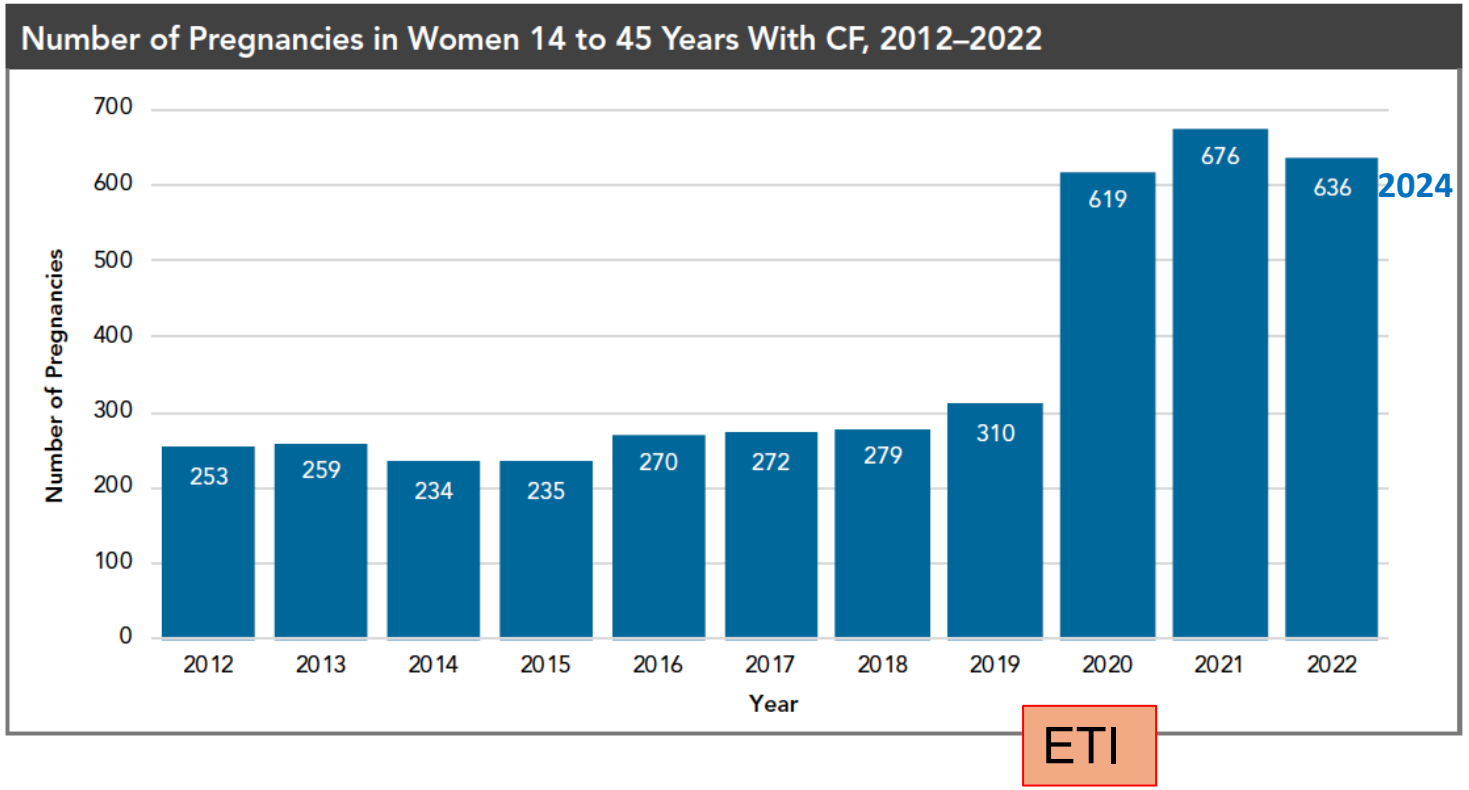
post-ivacaftor

Hysteroscopic image oth the uterus pre and 3 months after initiation of IVA

Female Fertility and CFTR modulators:

Baby Boom !

Pregnancy in Female with CF
age 14 – 45 ys

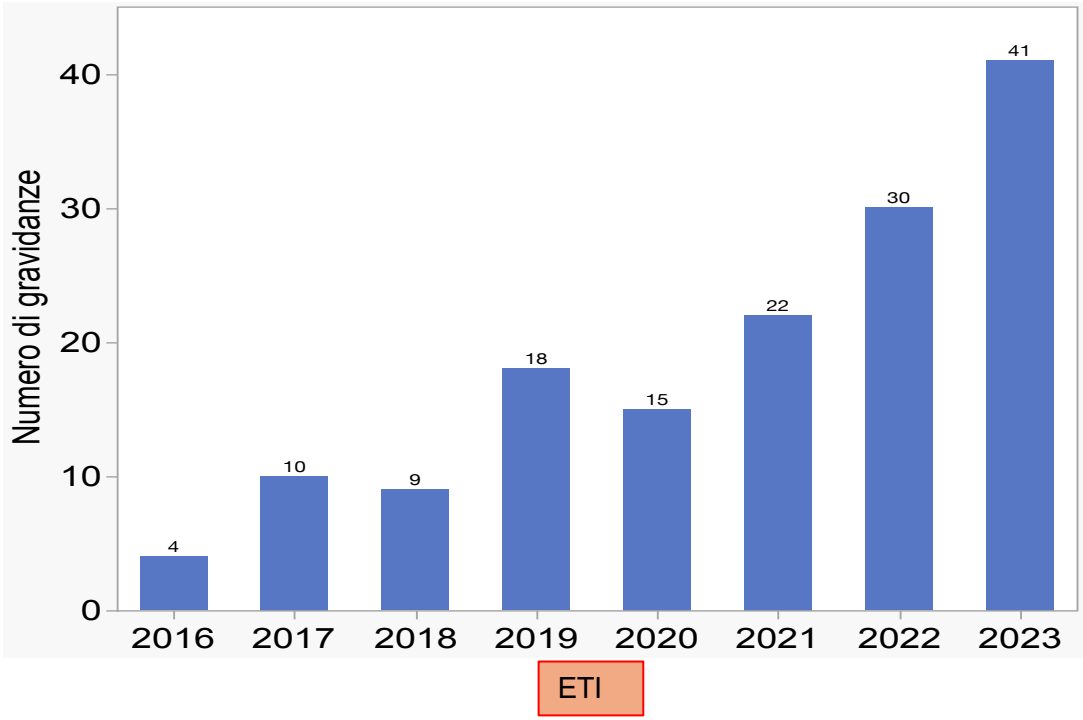


Annual Data Report 2022 *Cystic Fibrosis Foundation Patient Registry*

Female Fertility and CFTR modulators:

Baby Boom !

Registro Italiano Fibrosi Cistica



Amato A[1], Campagna G[1], Fabrizzi B[2,3], Galici V[4], Majo F[1,5], Padoan R[2], Ripani P[6], Salvatore M[2,7], Taccetti G[2,4] & Comitato Tecnico e Scientifico del Registro Italiano Fibrosi Cistica

[1]Comitato Tecnico del RIFC, [2]Comitato Scientifico del RIFC, [3]CRR FC di Ancona, [4]CRR FC di Firenze, [5]CRR FC di Roma Bambino Gesù, [6]CRR FC di Atri (TE), [7]Responsabile Scientifico del RIFC.

Orizzonti FC
Organo della Società Italiana per lo studio della Fibrosi Cistica

2-2024

Gravidanza e parto in donne FC nell'era dei modulatori: i dati del Registro Italiano Fibrosi Cistica (RIFC)

Unplanned pregnancies

Unplanned pregnancies following the introduction of elexacaftor/tezacaftor/ivacaftor therapy in women with Cystic Fibrosis

Dacco V. et al. Archives of Gynecology and Obstetrics. 2023; 308:1657-9

… recommendation on contraception

… perception of subfertility developed over time…

Association between unplanned pregnancies and maternal exacerbations in Cystic Fibrosis

Peng G. et al. J Cystic Fibrosis. 2023. doi.org/10.1016/j.jcf.2023.03.020

226 pregnancies followed in 11 centers US
- *2010-2020*
40% unplanned

No difference change in ppFEV1 from pre- to post-pregnancy

↑ *Pulmonary exacerbations in unplanned group +26%*
PEXs -16 in planned group

ELSEVIER

Journal of Cystic Fibrosis 15 (2016) 133 – 134

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Letter to the Editor

A successful uncomplicated CF pregnancy while remaining on Ivacaftor

Rachel Kaminski [a,b,*], Dilip Nazareth [a,b]

[a] *Bristol Adult Cystic Fibrosis Centre, University Hospitals Bristol NHS Foundation Trust, Upper Maudlin Street, Bristol BS2 8HW, United Kingdom*
[b] *University of Bristol, United Kingdom*

We report the case of a 25-year-old Gravida 1 Para 1 female [Genotype: G551D; 3272-26A > G; BMI 20.8 kg/m^2] colonized with *Achromobacter xylosoxidans*, on Ivacaftor (commenced in 2013) who conceived naturally. Prior to starting Ivacaftor, she had a predicted FEV_1 of 85%. At her first clinic appointment after discovering she was pregnant her FEV_1 was 94%.

To be or not to be on CFTR modulators during pregnancy: Risks to be considered

Journal of Cystic Fibrosis 19 (2020) e7–e8

«withdrawal syndrome»

29ys
F508del / G551 D

ppFEV1 30 pre IVA
46 post IVA + 1ys

P aeruginosa
Pancreatic insufficiency
CF R-diabetes

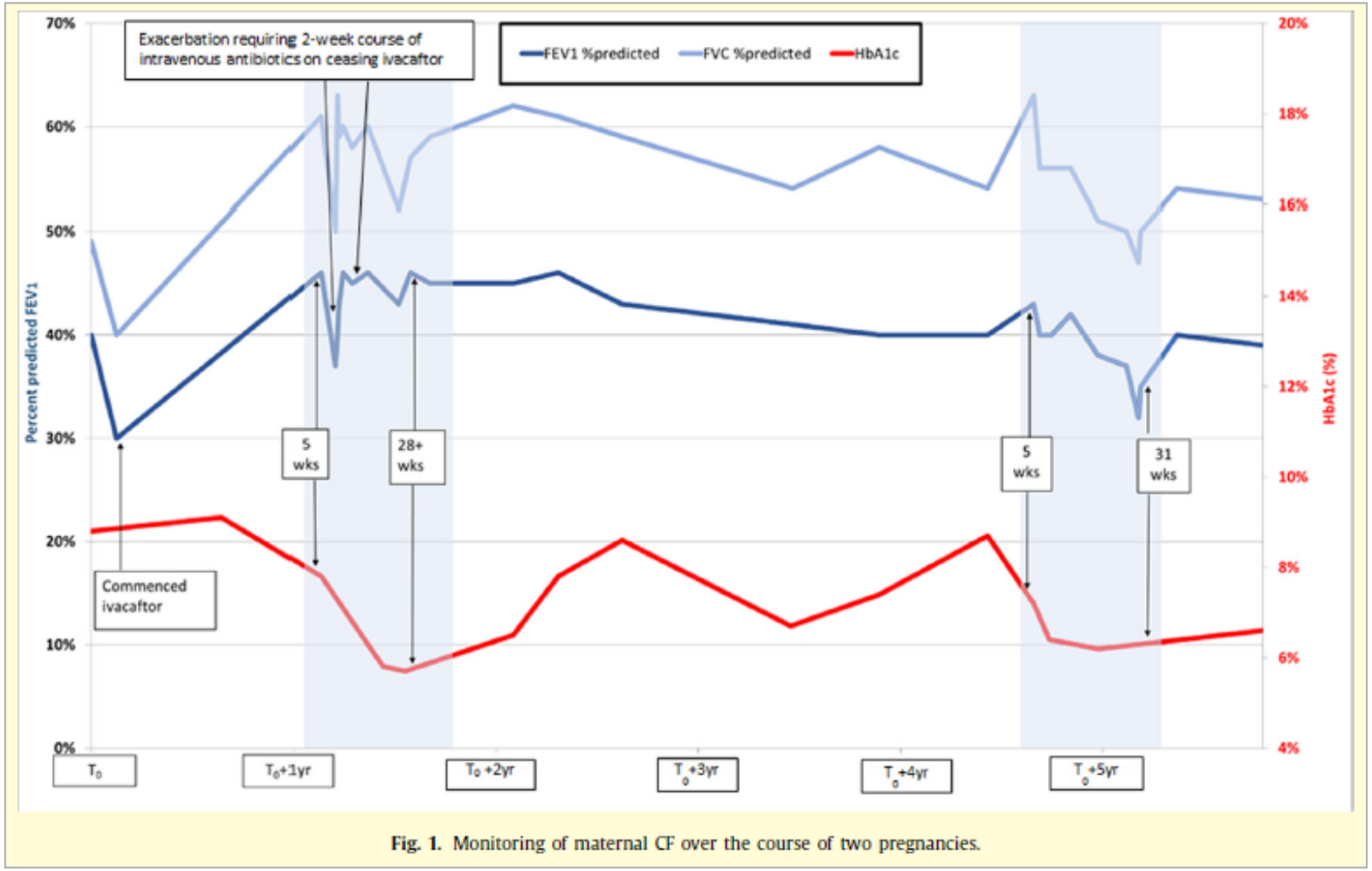


Fig. 1. Monitoring of maternal CF over the course of two pregnancies.

REVIEW

Use of CFTR modulators in special populations, part 1: Pregnancy and lactation

Pediatric Pulmonology. 2023;58:3377–3385.

TABLE 1 Summary of case reports in relation to CFTR modulator use in females with CF during pregnancy and breastfeeding.

References	Treatment	Mutation(s)	Mother's baseline ppFEV$_1$	Trimesters exposed	Infant gestational age (weeks)	Infant health (postnatal)	Mother's health (postpartum)	Breastfed infant
Jones and Walshaw[19]	IVA	F508del/G551D	75	1–3	38	Normal	NR	NR
Kaminski and Nazareth[20]	IVA	G551D / 3272-26A>G	94	1–3	39	Normal	Normal	No
Trimble et al.[18]	LUM/IVA	F508del homozygous	90	1–3	38	Increased aspartate aminotransferase and total bilirubin while being breastfed	Normal	Yes
Mainz et al.[21]	LUM/IVA	F508del	52	1–3[a]	35	Normal	Normal	No
Ladores et al.[22]	LUM/IVA	F508del	NR	1–3	NR	Normal	NR	NR
				1-3[b]	NR	Normal	NR	NR
Vekaria et al.[23]	IVA	F508del/G551D	46	1–3[c]	36	Normal	NR	NR
			43	1–3[d]	34	Normal	NR	NR
Fortner et al.[24]	ELE/TEZ/IVA	F508del homozygous	NR	1–3	39	Liver function test at 5 weeks was notable for elevated unconjugated bilirubin (attributed to resolving hyperbilirubinemia of a breastfed newborn)	NR	Yes
Goodwin et al.[25]	IVA	G551D / 1161 deletion c	86	1–3	38	Normal	Normal	Yes
	ELE/TEZ/IVA	F508del homozygous	50	1–3	35	Apgar score was normal; infant was admitted to NICU for 4 days with neonatal hypoglycemia and jaundice which resolved	Normal	Yes
Balmpouzis et al.[26]	ELE/TEZ/IVA	F508del / Y1092X	40	1–3	36	Normal	Normal	NR
Collins et al.[12]	ELE/TEZ/IVA	F508del homozygous	NR	2–3	NR	Normal	Normal	Yes
		F508del homozygous	NR	1–3	NR	Normal	Maternal cholecystitis requiring cholecystectomoy	Yes
		F508del homozgous	NR	1–3	NR	Normal	Normal	Yes
Chamagne et al.[27]	ELE/TEZ/IVA	F508del homozygous	37	1–3	34.5	Normal	Normal	NR

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ELE/TEZ/IVA, elexacaftor–tezacaftor–ivacaftor; LUM/IVA, lumacaftor–ivacaftor; NR, not reported

[a]Discontinued at 10 weeks gestation due to unknown risk in pregnancy and restarted at 15 weeks due to pulmonary decline following discontinuation.

[b]The woman experienced two separate pregnancies while receiving treatment with LUM/IVA.

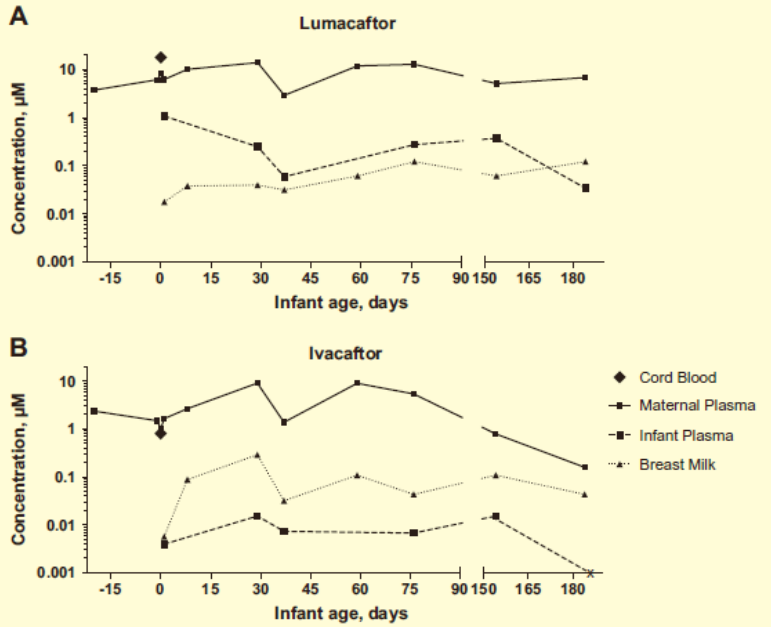
[c]Discontinued at 5 weeks due to unknown risk of pregnancy and reinitiated at 10 weeks due to pulmonary decline following discontinuation.

[d]The woman experienced two separate pregnancies while receiving treatment with IVA.

CF fetus/children ARE exposed to ETI in utero and during breastfeeding

Measured fetal and neonatal exposure to Lumacaftor and Ivacaftor during pregnancy and while breastfeeding

Journal of Cystic Fibrosis 17 (2018) 779–782



Maternal, newborn and breast milk concentrations of elexacaftor/tezacaftor/ivacaftor in a F508del heterozygous woman with cystic fibrosis following successful pregnancy

Pietro Ripani[1*†], Matteo Mucci[2†], Stefano Pantano[1], Maria Di Sabatino[1], Francesca Collini[1], Giulia Ferri[2], Mario Romano[2] and Antonio Recchiuti[2*]

Front. Med. 10:1274303.
doi: 10.3389/fmed.2023.1274303

Drug (ng/mL)	VX-661	VX-445	VX-770
Maternal plasma	1017.57 ± 80.02	1185.2 ± 114.01	1071.5 ± 80.12
Breast milk	761.3 ± 22.62	1049.07 ± 68.77	1794.50 ± 4.95
Child plasma	13.91 ± 2.25	4.66 ± 1.15	23.93 ± 2.95

CFTR modulators in pregnancy

J. Clin. Med. 2023, *12*, 1468.

Use of CFTR modulators in pregnancy according to international surveys.

Modulator	Pregnancies/Modulator Used throughout Preg. (*n*)	Miscarriage	Prematurity	Fetal Complications Related to Modulator *	Fetal Complications Unknown/Not Related	Maternal Complications Related to Modulator *	Maternal Complications Unknown/Not Related
IVA	31/15	2	-	0	3	0	16
LUM/IVA	26/16	0	4	0	8	2	17
TEZ/IVA	7/5	1	-	0	2	0	5
ETI **	47/23	4	5	0	20 [a]	1	30 [b]

fetal multiple severe malformation
forceps delivery
intrauterine groth retardation
large for gestational age
Trisomy 16 with spontaneous miscarriage

cholestasis
cholecystitis
cholecystectomy

gestational diabetes
gestational hypertension
hemoptysys preeclampsia
post partum depression
seizures
nephrolithiasis
wound infection
neck pain after epidural
headache after epidural

CF Pregnancy: outcome pre CFTRm

Mother

- Non survival disavantage
- More need for treatment for PEx
- Some studies decline in ppFEV1
- Higher risk of gestational diabetes
- Higher rates of cesarion section

Infant born to mother with CF

- More likely pre-term (< 37 ws)
- Low birth weight (< 2.5 kg)

WS 07.06 – ECFS Congress 2024

Etherington C. J.Cystic Fibros 23S1(2024),S102

Maternal and foetal outcomes following ETI use in pregnancy: comparison with pregnancy outcome from the pre modulator era

Adult CF Center Leeds- UK
2010-2023 retrospective

ETI group
24 WwCF → 26 babies

27,5 ys FEV1 75%

non ETI group
24 WwCF → 30 babies

28,5 ys FEV1 73%

	ETI group	non ETI group	
↑ **unplanned**	67%	40%	p=0.003
↑ **natural conception**	96%	68%	p<0.001
↑ **baseline BMI**	24.5	21.7	p<0.01
↑ achieved minimun **target weight gain**	76%	36%	p<0.01
GDM	71%	38%	p<0.001
↓ preterm	19%	43%	p=0.03
↑ **breast feeded**	50%	35%	p=0.04
↓ antibiotic (days)			p<0.01
during pregnacy	7	24	
+ 1 ys	0	29	
+ 2 ys	0	17	

CFTR modulators and pregnancy outcomes: Early findings from a nationwide cohort study

Laurent Chouchana [a,b,*], Mathis Collier [b,c], Clémence Martin [d,e], Pierre-Régis Burgel [d,e], Jean-Marc Treluyer [a,b,c]

Journal of Cystic Fibrosis 24 (2025) 469–475

Results: Among 590 pregnancies in fwCF, 148 (24.7 %) were exposed to CFTR modulators, including 136 during first trimester. Of these, 147 (99.3 %) resulted in livebirths. The most common CFTR modulator used was ELX/TEZ/IVA, in 121 (81.8 %) pregnancies. The prevalence of major birth defects was similar between exposed and unexposed fwCF (3.38 % vs. 4.66 %; $p = 0.72$). The rate of small for gestational age (SGA, <10th percentile) was significantly lower in pregnancies exposed compared to unexposed (6.8 % vs. 16.1 %; $p < 0.01$).

Discussion: The study provides early reassurance about the safety of CFTR modulators during pregnancy, particularly in terms of teratogenicity and adverse pregnancy outcomes. While findings suggest potential benefits, such as halved rate of SGA, further research is required to confirm these outcomes and investigate long-term effects on the development of children prenatally exposed to CFTR modulators.

Table 2
Pregnancy outcomes.

	Pregnancies in females living with cystic fibrosis				Pregnancies in general population
	Exposed to CFTR modulators n = 148	Unexposed to CFTR modulators n = 451	Overall n = 599	p-value[a]	Overall n = 3879,601
Obstetrical adverse events					
Gestational diabetes	53 (35.81 %)	74 (16.41 %)	127 (21.2 %)	< 0.001	629,089 (16.22 %)
Preeclampsia	7 (4.73 %)	18 (3.99 %)	25 (4.17 %)	0.87	78,288 (2.02 %)
Outcomes of the pregnancy					
			588 (98.16 %)	0.69	3,849,289 (99.22 %)
			2 (0.33 %)		17,901 (0.46 %)
			9 (1.5 %)		12,411 (0.32 %)
			26 (4.34 %)	0.72	118,363 (3.05 %).
			318 (54.08 %)	< 0.001	2,598,109 (67.5 %)
			166 (28.23 %)		765,181 (19.88 %)
			104 (17.69 %)		485,999 (12.63 %)
			38.07 +/- 2.34	< 0.05	39.12 +/- 1.76
			112 (19.05 %)	0.54	196,091 (5.09 %)
Moderate to late preterm birth 32–36 weeks	28 (19.05 %)	73 (16.55 %)	101 (17.18 %)	–	166,510 (4.33 %)
Very preterm birth 28–31 weeks	3 (2.04 %)	4 (0.91 %)	7 (1.19 %)		18,933 (0.49 %)
Extreme preterm birth < 28 weeks	0 (0 %)	4 (0.91 %)	4 (0.68 %)		10,648 (0.28 %)
Induced preterm birth*	15 (10.2 %)	37 (8.39 %)	52 (8.84 %)	0.61	80,664 (2.1 %)
Birth weight, g*	3122 +/- 495	3024 +/- 640	3049 +/- 608	0.055	3284 +/- 517
Small for gestational age (< 10th percentile)*	10 (6.8 %)	71 (16.1 %)	81 (13.78 %)	< 0.01	376,424 (9.78 %)
Small for gestational age (< 3rd percentile)*	3 (2.04 %)	16 (3.63 %)	19 (3.23 %)	0.50	112,351 (2.92 %)
Large for gestational age (> 90th percentile)*	16 (10.88 %)	40 (9.07 %)	56 (9.52 %)	0.63	374,671 (9.73 %)
Hospitalization in neonatal unit (including intensive unit)*	18 (12.24 %)	55 (12.47 %)	73 (12.41 %)	1.0	160,062 (4.16 %)

Impact of Cystic Fibrosis Transmembrane Conductance Regulator Modulators on Maternal Outcomes During and After Pregnancy

CHEST 2025; 167(2):348-361

2010-2021
11 US adult CF centers

114 pregnancy on CFTRms
(77on ETI)

RESULTS: Among 307 pregnancies, mean age at conception was 28.5 years (range, 17-42 years), before pregnancy $ppFEV_1$ was 74.2, and BMI was 22.3 kg/m^2. A total of 114 pregnancies (37.1%) had CFTR modulator exposure during pregnancy (77 with highly effective modulator therapy [HEMT] and 37 with other modulators). The adjusted mean change in $ppFEV_1$ from before pregnancy to during pregnancy was −2.36 (95% CI, −3.56 to −1.16) in the unexposed group and 2.60 (95% CI, 0.23 to 4.97) in the HEMT group, with no significant change from during pregnancy to 1 year after pregnancy. There was an overall decline in $ppFEV_1$ from before pregnancy to after pregnancy in the no modulator group (−2.56; 95% CI, −3.62 to −1.49) that was not observed in the HEMT group (1.10; 95% CI, −1.13 to 3.34). PEx decreased from before pregnancy to after pregnancy in the HEMT group, and BMI increased from before pregnancy to during pregnancy in all groups but with no significant change after pregnancy. Missing infant outcomes data precluded firm conclusions.

INTERPRETATION: We observed superior pregnancy and after pregnancy pulmonary outcomes in individuals who used HEMT, including a preservation of $ppFEV_1$, compared with those unexposed to HEMT.

CHEST 2025; 167(2):348-361

Expert recommendation on CFTR modulators in pregnancy

ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases

Eur Respir J 2020; 55:

CFTR modulators	Pre/T1	T2/T3	Labour	Breastfeeding	Observations/considerations
Ivacaftor (B3) [–] Lumacaftor and ivacaftor (B3) [–] Tezacaftor and ivacaftor (B3) [–] Elexacaftor and tezacaftor and ivacaftor (B3) [–]	Probably safe				Limited data in humans [56–58]. No evidence of toxicity in animals at usual doses. Modulators are present in breast milk, although potential effects on the fetus are unknown. Maternal benefit may outweigh potential risk during pregnancy and/or breastfeeding, although exact risks are unknown.

The Impact of Highly Effective Cystic Fibrosis Transmembrane Conductance Regulator Modulators on the Health of Female Subjects With CF

the decision to continue versus discontinue HEMT during pregnancy and lactation warrants a clear and comprehensive conversation between **provider and mother/partner** with ***informed shared decision-making***.

data support the need to consider infant monitoring with **routine**
-liver function testing and
-ophthalmologic examinations for cataracts.

… careful in neonatal testing for CF Clinical Therapeutics 2023

Pregnancy in cystic fibrosis: Review of the literature and expert recommendations

Most common therapies used in the chronic treatment of CF.

Medication	Route of Administration	Considerations	Use in Pregnancy	Use in Lactation
CFTR modulators (ivacaftor, tezacaftor/ivacaftor, lumacaftor/ ivacaftor, elexacaftor/tezacaftor/ivacaftor)	Oral	No harm observed of individual components given in animal models, but human data is limited	Yes, if necessary for mother's health	Yes, if necessary for mother's health

Standards for the care of people with cystic fibrosis; establishing and maintaining health

Kevin W Southern [a,*], Charlotte Addy [b], Scott C Bell [c], Amanda Bevan [d], Urzula Borawska [e], Catherine Brown [f], Pierre-Régis Burgel [g], Brenda Button [h], Carlo Castellani [i], Audrey Chansard [j], Mark A Chilvers [k], Gwyneth Davies [l], Jane C Davies [m], Kris De Boeck [n], Dimitri Declercq [o], Michael Doumit [p], Pavel Drevinek [q], Isabelle Fajac [r], Silvia Gartner [s], Anna M Georgiopoulos [t], Sandra Gursli [u], Andrea Gramegna [v], Carina ME Hansen [w], Martin J Hug [x], Elise Lammertyn [y], Edwina (Eddie) C. Landau [z], Ross Langley [aa], Nicole Mayer-Hamblett [bb], Anna Middleton [cc], Peter G Middleton [dd], Monika Mielus [ee], Lisa Morrison [ff], Anne Munck [gg], Barry Plant [hh], Maarten Ploeger [ii], Dominique Pougheon Bertrand [jj], Tacjana Pressler [kk], Bradley S Quon [ll], Thomas Radtke [mm], Zoe L Saynor [nn], Ilan Shufer [oo], Alan R Smyth [pp], Chris Smith [qq], Silke van Koningsbruggen-Rietschel [rr]

Journal of Cystic Fibrosis 23 (2024) 12–28

women with CF. The decision to continue or stop CFTR modulator therapy during pregnancy and breastfeeding should be made considering the risks for the mother and the baby [195,210].

Standards of care for *CFTR* variant-specific therapy (including modulators) for people with cystic fibrosis☆

Kevin W. Southern [a,*], Carlo Castellani [b], Elise Lammertyn [c], Alan Smyth [d], Donald VanDevanter [e], Silke van Koningsbruggen-Rietschel [g], Jürg Barben [h], Amanda Bevan [i], Edwin Brokaar [j], Sarah Collins [k], Gary J. Connett [l], Thomas W.V. Daniels [m], Jane Davies [n], Dimitri Declercq [o], Silvia Gartner [p], Andrea Gramegna [q], Naomi Hamilton [r], Jenny Hauser [s], Nataliya Kashirskaya [t], Laurence Kessler [u], Jacqueline Lowdon [v], Halyna Makukh [w], Clémence Martin [x], Lisa Morrison [y], Dilip Nazareth [z], Jacquelien Noordhoek [aa], Ciaran O'Neill [bb], Elizabeth Owen [cc], Helen Oxley [dd], Karen S. Raraigh [ee], Caroline Raynal [ff], Karen Robinson [gg], Jobst Roehmel [hh], Carsten Schwarz [ii], Isabelle Sermet [jj], Michal Shteinberg [kk], Ian Sinha [ll], Constance Takawira [z], Peter van Mourik [mm], Marieke Verkleij [nn], Michael D. Waller [oo], Alistair Duff [v]

Journal of Cystic Fibrosis 22 (2023) 17–30

The decision to continue or withhold VST during pregnancy should be made between the CF team and the woman with CF, considering the risks for the mother and the baby (Statement 20,

CFTR modulators: fetus-infant exposure risks

What we know

risk : liver health
-early sign of liver stress (elevated transaminases or bilirubin) - usually temporary

monitor :
- liver function tests within one months of birth;
- every three months while breast feeding on ETI

where the follow up for this «healthy» babies?

risk : eye health
-juvenil rats given ivacafator, days 7-35 after birth developed cataracts
-case reports of infant exposed to ETI in utero found to have mild cataracts

monitor :
- eye exam by pediatric ophtalmologisdt within 2 - 3 months of birth
- consider repeat eye examafter one year for infants ongoing exposute to ETI through breast milk breast feeding on ETI

Clinical consideration: Fertility and CFTR modulators. cff.org 2023
Cystic Fibrosis Canada's Heathcare Advisory Council 2023

CF fetus/children exposed to ETI in utero

CF fetus/children exposed to ETI in utero

Journal of Cystic Fibrosis 20 (2021) 835–836

Mother CF
Baby CF

Case report

Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking *CFTR* modulator therapy during pregnancy

Christopher N. Fortner[a,*], Julie M. Seguin[a], Denise M. Kay[b]

Impact on neonatal screening

Mother F/F - Father F carrier
ETI from nov 2019

"infertility"… spontaneous conceiving after 6 ws on ETI

Female **F/F** - birth at 39 ws

Suspicious of echogenic bowel in pregnancy
Pancreatic sufficiency

Neonatal screening (IRT) negative
Sweat Cl 60

exposure to ETI maintained with breastfeeding

Luma/Iva when 2 years old

CF fetus/children exposed to ETI in utero

Kowalik A, J Cystic Fibros 2024; 23: 1027-1030.

Clinical outcomes of two infants with cystic fibrosis, including the presence of
vas deferens, born to a woman with cystic fibrosis taking CFTR modulators during both pregnancies

Mother CF
Babies CF

Mother F/F - Father F carrier
ETI from 2020
FEVpp 25 → 45% post ETI

"infertility" spontaneous conceiving + 3 ms on ETI

concomitant treatment for mioclonic epilepsy (levetiracetam and valproic ac)and intracranial aneurysm

Babies CF

- Female F/F
- Male F/F → **normal vas deferens**

Breastfeeding controindicated

Kowalik A, J Cystic Fibros 2024; 23: 1027-1030.

Mother CF
Babies CF

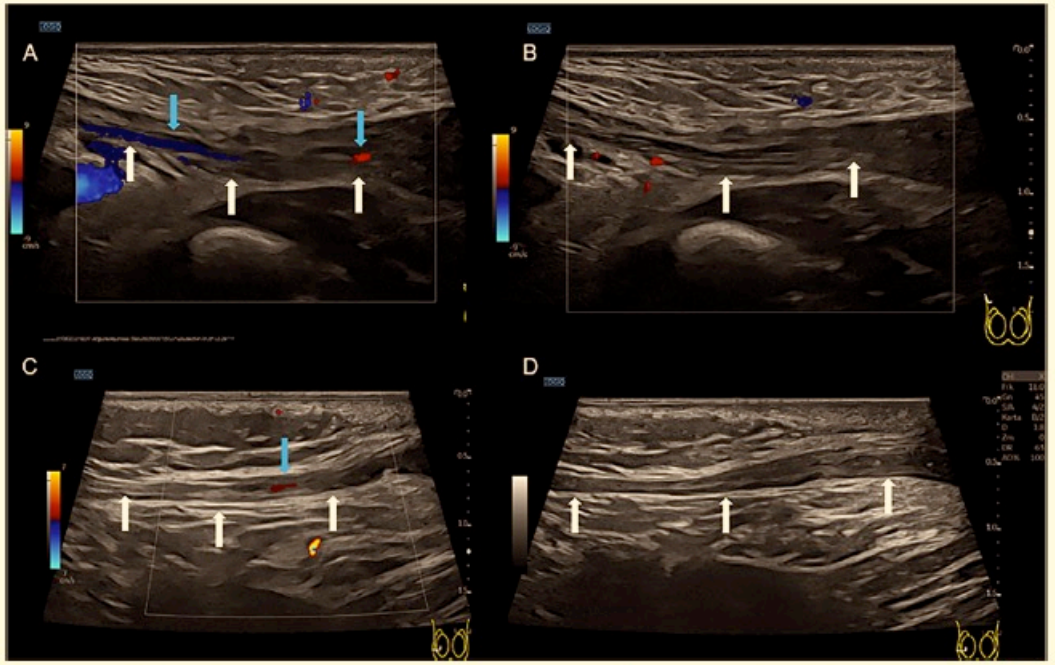


Fig. 1. Spermatic cord was identified with normal appearance when ultrasound was performed at the age of two weeks (A and B) and at the age of three months (C and D). The white arrows indicate the spermatic cord in the inguinal canal. The blue arrow indicates arterial blood flow that can be seen in the spermatic cord in image A and C.

→ **normal develpment of vas deferens**

male F/F exposed to ETI during pregnancy

Kowalik A, J Cystic Fibros 2024; 23: 1027-1030.

Breastfeeding controindicated

→ **rapid development of CF features with cessation of ETI exposure**

Mother CF
Babies CF

Characteristics of both infants.

	Infant 1	Infant 2
Time for diagnosis of CF	Postnatal	Prenatal
Diagnosis by genetic test	The umbilical cord	Amniocentesis
Genotype	F508del homozygous	F508del homozygous
Gestational age, weeks + days	37 + 1	36 + 1
Mode of delivery	Vaginal	Caesarean section
Sex	Female	Male
Birth weight and length	2560 gr, 45 cm	3000 gr, 48 cm
Examination efter partus	Normal	Normal
Meconium ileus	No	No
Breastfeeding	No	No
Hepatic function tests	Day 3, hyperbilirubinemia (neonatal, transient) Week 7, normal	Week 2, normal
Age at first CF Center visit, status	Day 9, normal examination	Week 2, airway infection with respiratory distress
Fecal elastase µg/g, age	602, 9 days 182, 6 weeks	436, 2 weeks 36, 2 months
Age at start with PERT	2 months	2 weeks*
Sweat test, chloride value mmol/l, age	98, 7 weeks	83, 7 weeks
Initiation of airway physiotherapy	3 months	2 weeks
Eye examination, age	No cataract, 1 year	No cataract, 3 months
Airway infections first year	Several mild ones treated with oral antibiotics	Severe infection at the age of two weeks
Airway culture first year	*Staphylococcus aureus*	*Pseudomonas species*, *Staphylococcus aureus*
Age at first intravenous antibiotic course	2 years	2 weeks
Hospitalizations first year	No	Yes
Start of CFTR modulators	iva/luma, 18 months ETI, 2 years	iva/luma, 1 year

* Start with PERT in infant 2 despite normal fecal elastase at admission to the hospital because of insufficient weight gain and airway infection with respiratory distress.

PROTECT

Prenatal Modulator Treatment to Prevent CF Complications

CFF reseach programm Webinar November 15, 2024 9.00 am – 4.00 pm

Mother CF *carrier*
Baby CF

Case Report

A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus

Sylvia Szentpetery*, Kimberly Foil, Sara Hendrix, Sue Gray, Christina Mingora, Barbara Head, Donna Johnson, Patrick A. Flume

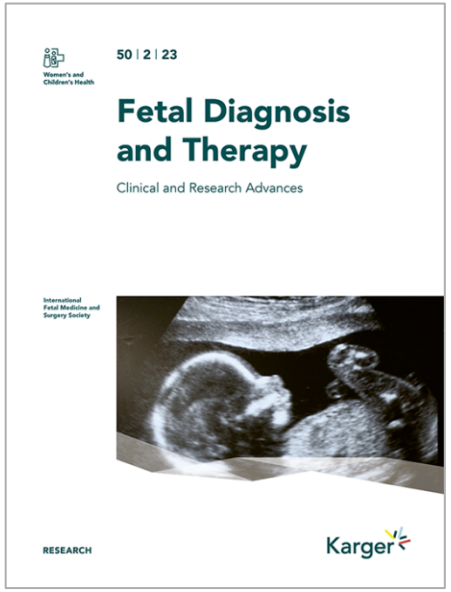
Medical University of South Carolina, Charleston, SC 29424, USA

Journal of Cystic Fibrosis 21 (2022) 721–724

CASE REPORTS

Prenatal Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy: A Promising Way to Change the Impact of Cystic Fibrosis

Fetal Diagn Ther (2023) 50 (2): 136–142.



PROTECT

Prenatal Modulator Treatment to Prevent CF Complications

CFF November 2024

Mother CF *carrier*
Baby CF

Journal of Cystic Fibrosis 21 (2022) 558–559

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

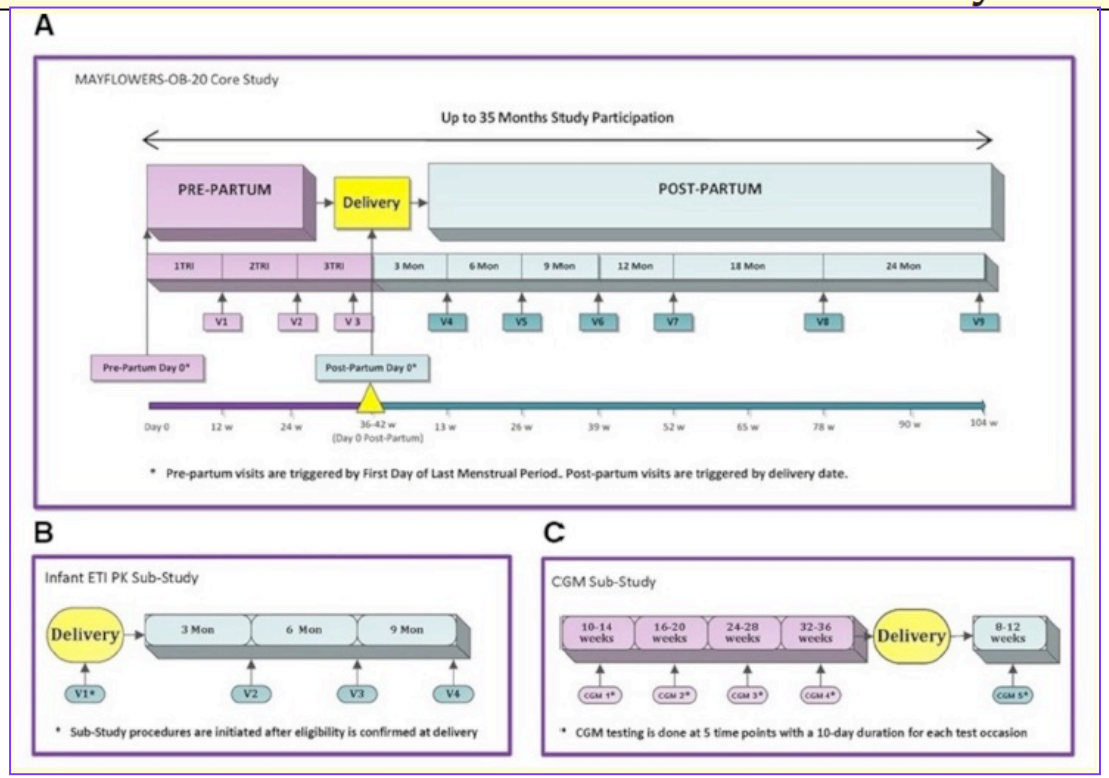
Editorial – The ethical implications of treating a pregnant woman to benefit the fetus

Impact of CFTR modulators on pregnancy and infant *born to mothers with CF*

Open Access — Cystic fibrosis

BMJ Open Respiratory Research

Prospectively evaluating maternal and fetal outcomes in the era of CFTR modulators: the MAYFLOWERS observational clinical trial study design



longitudinal prospective multicentre observational study
40 US TDN CF centres
CFF sponsorized
2021-2025
aims to entroll 285 fwCF

WHAT THIS STUDY ADDS

⇒ The Maternal and Fetal Outcomes in the Era of Modulators (MAYFLOWERS) is the first prospective study of pregnancy in CF. It will also provide the first prospectively collected data on infants born to mothers with CF, and include outcome data for mothers and infants for 2 years following pregnancy.

sub studies: infant ETI PK and maternal Continous Glucose Monitoring

MAYFLOWERS study – 2024 update

NACFC-Boston

WwCF Pregnancies	279
age	30 (17- 41) years
pre - pregrancy ppFEV1	85 (25-123)
diabetes	104 (37%)
assisted reproduction	32 12%
Delivery outcomes	
Live birth	**226** (95%)
Caesarion section	88 (36%)
Weight	3.2 (1.2 – 4.7) kg
Gestational age	38 (27 – 42) weeks
Preterm birth	44 (22%) (extended NICU in 20%)

What we do NOT know

CFTR modulators: fetus-infant exposure risks

Potential effect of ETI in pregnancy on **prenatal** development

Biomedicine & Pharmacotherapy 171 (2024) 116155

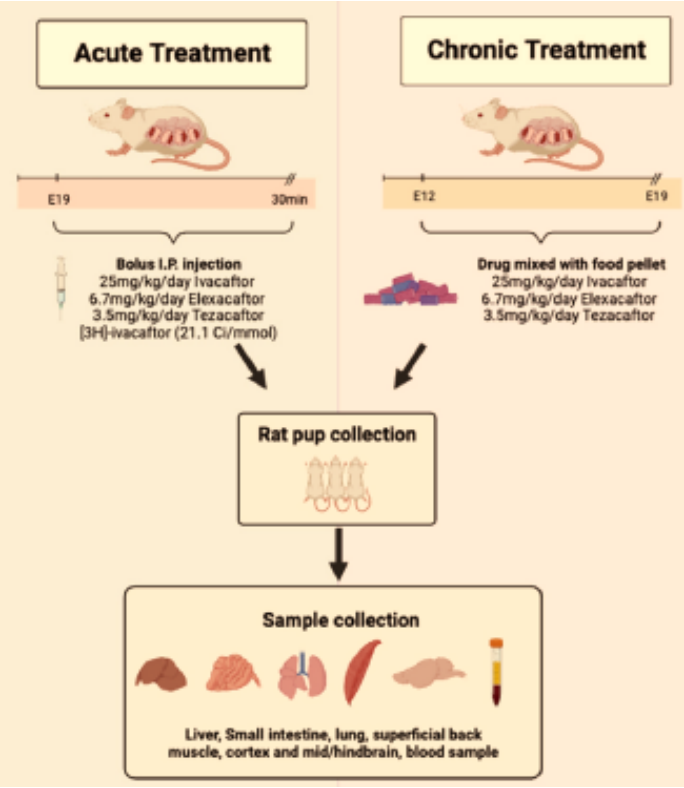
Contents lists available at ScienceDirect

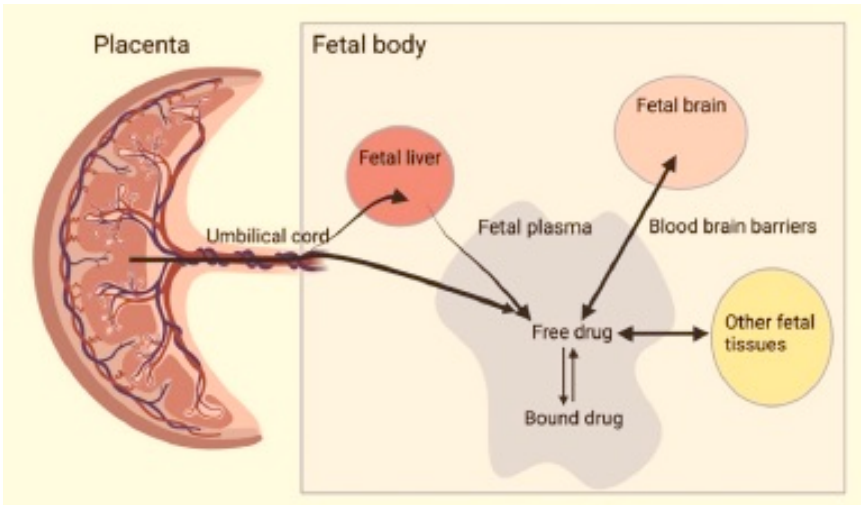
Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Fetal drug exposure after maternally administered CFTR modulators Elexacaftor/Tezacaftor/Ivacaftor in a rat model

Danni Li [a], Yimin Zhu [a], Martin Donnelley [b,c,d], David Parsons [b,c,d], Mark D. Habgood [a], Elena K. Schneider-Futschik [a,*]





Biomedicine & Pharmacotherapy 171 (2024) 116155

To investigate **fetal tissue distribution** of maternally administered ETI **by placenta transfer** in the rat fetus

Healthy rat model -non CF
- Fetal plasma concentration of ETI is variable
- Variable fetal exposure due to maternal physiological variability

Potential effect of ETI in pregnancy on prenatal development

Journal of Cystic Fibrosis 22 (2023) 680–682

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

The combination elexacaftor/tezacaftor/ivacaftor (ETI) modulates the *de novo* synthethic pathway of ceramides in a genotype-independent manner

Nara Liessi[a], Valeria Tomati[b], Valeria Capurro[b], Nicoletta Loberto[c], Mar Garcia-Aloy[d], Pietro Franceschi[d], Massimo Aureli[c], Nicoletta Pedemonte[b], Andrea Armirotti[a,*]

Journal of Cystic Fibrosis 22 (2023) 680–682

primary bronchial epithelial cells

modulation of dhCER associated with CF and to ETI
off target effect of ETI per se, independent of CFTR rescue
*genotype-independen*t CF (including non rescuable mutation) and non CF

increased dhCER blood levels reported for a DEGS1 genetic variant .. and DEGS1 mutations cause **neurological disordes … linked to neurodegeneration**

…further investigation

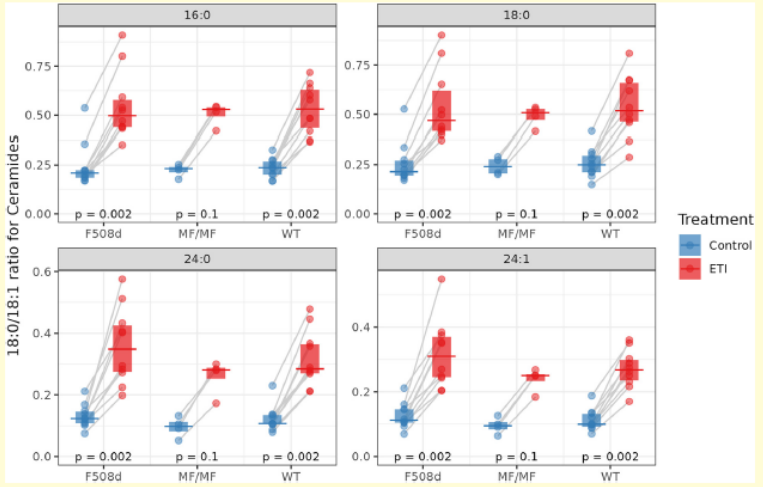


Fig. 1. d18:0/d18:1 abundance ratio for four ceramides (C16, C18, C24 and C24:1) observed in the BE for the three genotypes (10 WT, 10 F508del and 4 MF/MF subjects) upon 48 hours treatment with ETI or control DMSO. The reported significance values refer to a paired, non parametric Wilcoxon test.

Potential effect of ETI in pregnancy on prenatal development

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

Tezacaftor is a direct inhibitor of sphingolipid delta-4 desaturase enzyme (DEGS)

Dinu Zinovie Ciobanu [a], Nara Liessi [a], Valeria Tomati [b], Valeria Capurro [b], Sine Mandrup Bertozzi [a], Maria Summa [c], Rosalia Bertorelli [c], Nicoletta Loberto [d], Dorina Dobi [d], Massimo Aureli [d], Lucilla Nobbio [e], Tiziano Bandiera [f], Nicoletta Pedemonte [b], Rosaria Bassi [d], Andrea Armirotti [a,*]

Ciobanu DZ et al., 2024, J Cyst Fibros

DEGS dysfunction and *accumulation of dHCer in the brain* causes **impairment in the development of the neurvous system**, due to **derangement in *myelin* formation and maintenance**

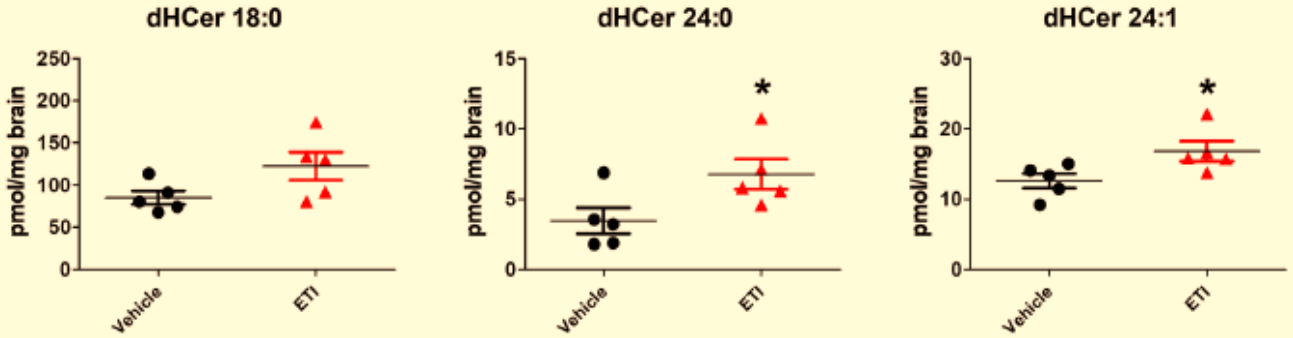


Fig. 5. dHCer levels of three abundant sphingolipid species observed in the brain of mice orally exposed to ETI for 4 days versus control animals treated with vehicle. *= $p < 0.05$ in an unpaired *t*-test Vs DMSO. Data refers to five animals per group.

NACFC 2025

110

Perinatal and postnatal elexacaftor/tezacaftor/ivacaftor concentrations in breastfeeding infants of mothers with CF: The MAYFLOWERS PK Sub-study

Journal of Cystic Fibrosis 24S2 (2025) S1–S530

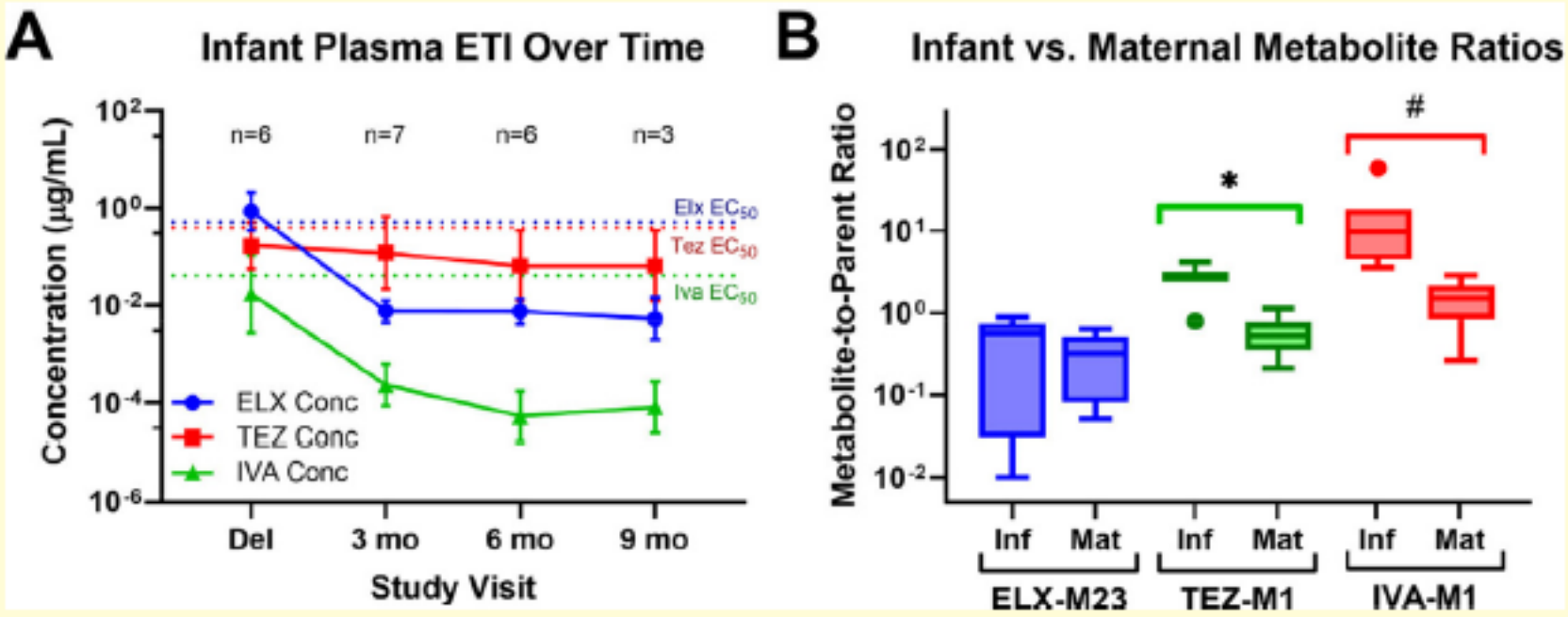


Figure 1 (abstract 110): A) Infant blood plasma ETI concentrations at delivery (Del) and 3, 6, and 9 month visits. Dotted lines represent published EC50 values; number of samples per visit is shown. B) Ratios of drug metabolite to parent drug in infants (Inf) and maternal (Mat) blood plasma at the 3 month study visit.

Potential effect of ETI in pregnancy on prenatal development

Ciobanu DZ et al., 2024, J Cyst Fibros

… Overall, the body of data available so far on the use of ETI in human would exclude short /midterm safety concern, but the story of this drug during pregnancy and in infancy is too short to derive reliable conclusions, particularly related to *mild alterations that mighy produce effects later in life.*

… and what about pregnancy in partner of in **MwCF treated with ETI**

Journal of Cystic Fibrosis 23 (2024) 412–416

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Short Communication

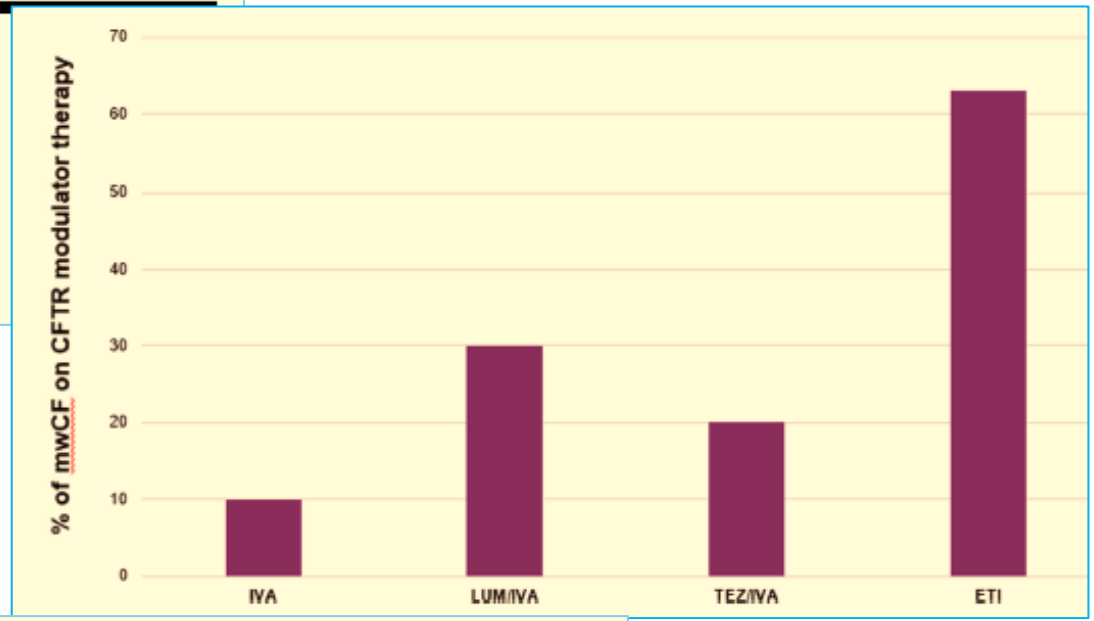
A provider survey assessing fetal impact of CFTR modulator use in males with CF during assisted and unassisted reproduction and partner pregnancy

Jennifer L. Taylor-Cousar [a,b,*], Rachel Janney [#,c], Peter G. Middleton [d], Raksha Jain [e], Julia Nightingale [f], Natalie E. West [g], Michal Shteinberg [h,i], Danielle Velez [j], Traci M. Kazmerski [k]

2021 - US, UK, Australia, Israel

35/42 on CFTRm during sperm retrieval (*stop 1 – 3 ms*)

40/42 ART



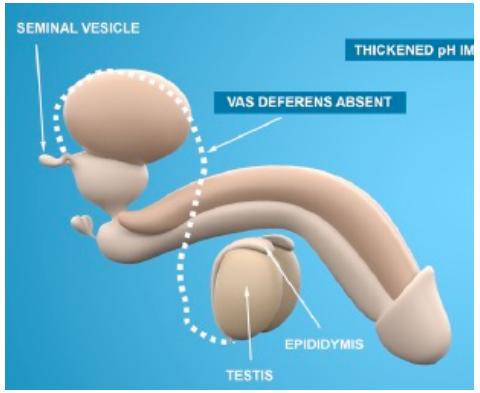
Results: We received 42 surveys for mwCF with partner pregnancies. Forty of 42 mwCF utilized ART; 35 continued modulators during sperm retrieval and 40/42 during partner pregnancy. One of four males who discontinued modulators experienced clinical deterioration. First trimester miscarriages occurred in 11.9 % of partner pregnancies. No congenital anomalies were reported.

Conclusions: Use of CFTR modulators during reproduction and partner pregnancy in mwCF did not result in a higher-than-expected miscarriage rate nor congenital anomalies.

Sexual and Reproductive Health (SRH) in Male wCF

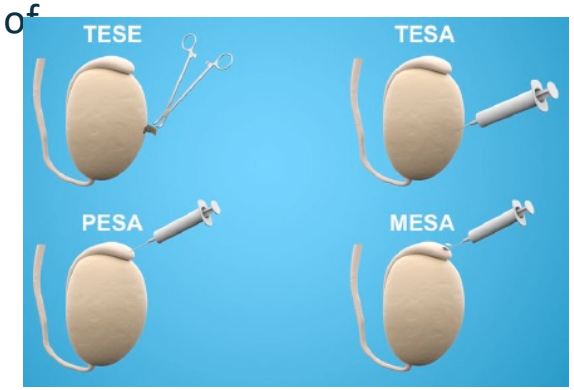
Men Fertility and CFTR

- 98% infertile because of surgically uncorrectable ostructive azospermia related to CBAVD
- 2% fertile
- Men with CF do produce sperm and testicular histology is normal



✓ Routine semen analysis recommended for all in late adolescence
(***low volume*** *acid ejaculate, azospermia*)

If man choose to pursue biologic parenthood -after confirmation of infertility- sperm extraction (possibility of semen cryopreservation), and subsequent ICSI and IVF (PMA).



. MESA/E or TESA/E with ICSI has been reported to result in **pregnancy rates of 30-35% per cycle**.

Hormonal ovarian stimulation and ovocytes retrievement needed in female partner
(risk for Ovarian Hyperstimulation Syndrome)

Success rate depends also on **maternal age** (<35 yrs success rate of a live birth 46-48%)

J Cystic Fibr 2019; 18:S105-S100
J Cystic Fibr 2022; 21: 657-661
Curr Opin Pulm Med 2020; 26:685-695

CFTR modulators and fertility in Male wCF

No reports of improved fertility in Male wCF with CFTR modulators

Case reports describe self resolving testicular pain in 7 pts after starting ETI therapy

Pediatr Pulmonol
2022; 57;S75-S88

J Cystic Fibr
2020;19; e39-e41

In G551D homozygous ferret exposed in utero throughout pregnancy to ivacaftor has been described rescue of the vas deferens and epididymis

The impact of modulators on fertility rescue has been described in a single case report

SCI Trans Med
2019; 11 eeau7531

Males who wish to completely avoid exposure of sperm to CFTR modulators must discontinue modulators for the life of an average sperm, approximately 80 days before semen extraction

Pediatr Pulmonol
2022; 57;S75-S88

SRH in Male wCF - CF providers attitude

Exploring provider attitudes and perspectives related to men's health in cystic fibrosis*

Journal of Cystic Fibrosis 21 (2022) 652–656

Key barriers affecting SRH discussion and provision by CF health care providers.

Barriers	Representative Quotes
Time	"[Time's] a big one [barrier], because we have so many things that we have to accomplish in each of the visits." (Adult provider)
Other CF topic prioritization	"I think part of it has always been and always will be just competing priorities for a complex, multisystem disease, and then it always gets, not intentionally always... pushed lower. ...It gets meant to be addressed, but then something happens." (Pediatric provider)
Lack of knowledge of non-fertility SRH subjects	"We don't have as much information as we should. A lot of the historical wisdom that we know... has... chang[ed], and pretty rapidly in the last couple of years." (Adult provider)
	"I would say among those that are pulmonologists, there is a lack of expertise in terms of impotence. About the actual sterility or infertility issues, I don't think there's a lack of knowledge... We are totally ignorant about...sexual activity... as it relates to CF." (Adult provider)
Provider discomfort	"One of the biggest barriers... is getting every member of the team to be comfortable talking about [SRH]." (Pediatric provider)
Patient/parent discomfort	"Patient refusal to be open to discussion [is a barrier]." (Adult provider)
	"[A barrier is] Conservative parents who do not want the subject raised, or who believe their child will be a virgin till they marry" (Pediatric provider)

SRH in Male-wCF – patients' perspective

Men's sexual and reproductive health in cystic fibrosis in the era of highly effective modulator therapies–A qualitative study

US 24 participants (mean age 33.7 ± 11.8 years, range 19–60)

Journal of Cystic Fibrosis 21 (2022) 657–661

suboptimal SRH care provision

infertility # sterility # *impotence*

earlier discussion (from adolescence), regular discussion

confidential, routinary, CF provider–initiated SRH discussion

safe sex behaviour discussion (sexually transmitted infections)
sexual functioning concerns (coughing, hemoptysis,dyspnea)
urinary stress incontinence

SRH in Male-wCF – patients' perspective

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Thorax 2005;**60**:326–330

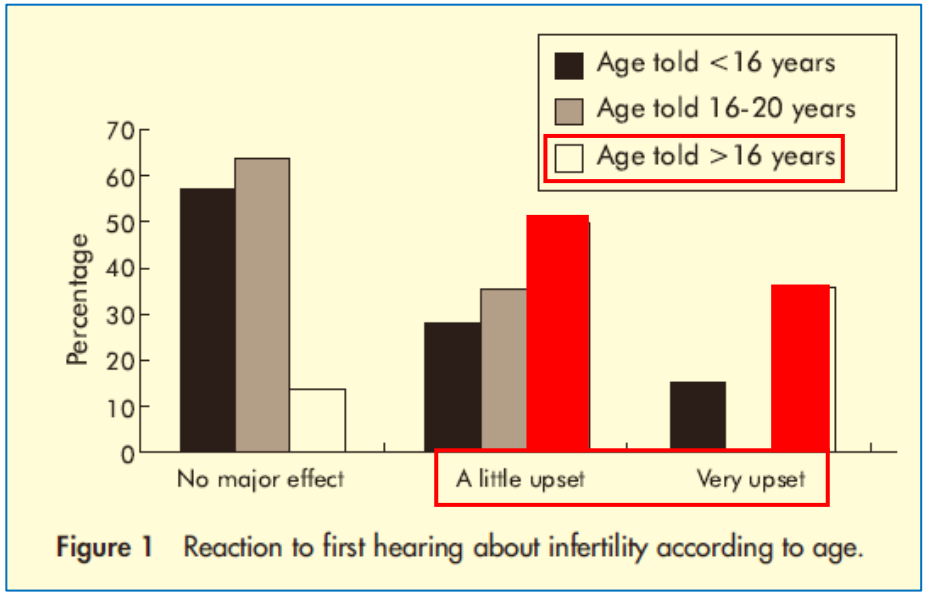


Figure 1 Reaction to first hearing about infertility according to age.

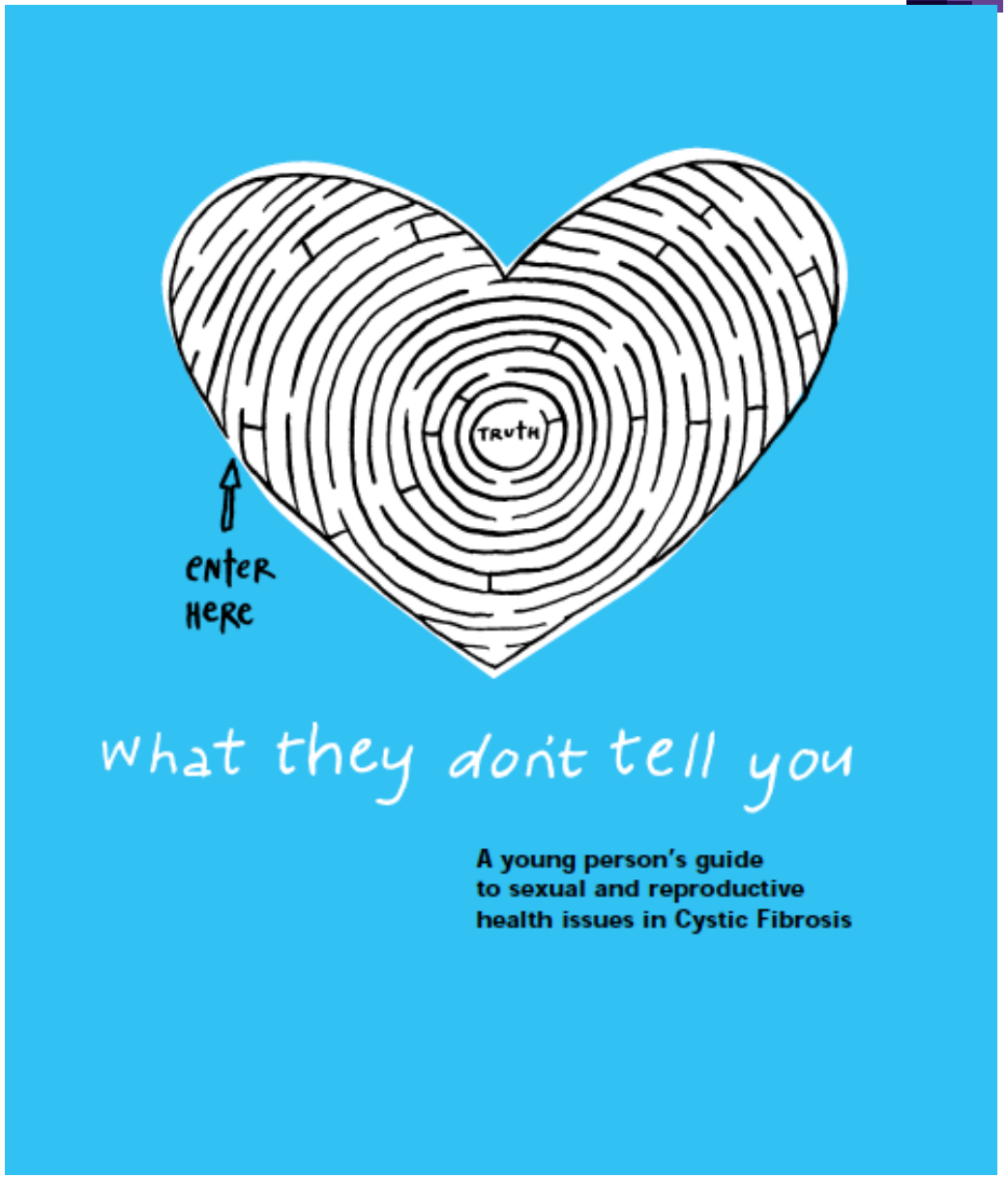
Male sexual and reproductive health in cystic fibrosis: A concept mapping study

Table 1
Participant-identified Patient-Centered Outcomes by Cluster.

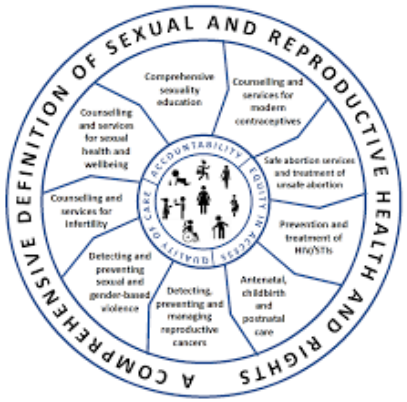
Overall

- SRH knowledge of MwCF, parents/partners of MwCF, and healthcare providers
- Ability of MwCF to make informed SRH decisions
- General decision making and communication outcomes (e.g., shared decision making, self-efficacy in patient-provider communication, trust)

1. **Family-building and fertility**
   - Success rates of ART in CF
   - Quantifying paths to parenthood
   - Family-building/fertility knowledge and education preferences
   - Access barriers to family-building/ART
   - Cost of ART for MwCF and families
   - Access to urology care
   - Semen analysis rates/outcomes/timing
   - Resources for ART/fertility
2. **Psychosocial aspects of SRH**
   - Mental health (depression, anxiety)
   - Body image
   - Eating disorder rates and treatments
   - Types and rates of use of gender affirming care and impacts in CF
   - Self confidence
   - Self esteem
3. **Being a parent or partner as a MwCF**
   - Impact of parenthood on physical health/mental health
   - Use of childcare support during times of illness for parents with CF
   - Strategies for dealing with concerns of childcare/risk of infection while parenting with CF
   - Receipt of resources for how/when to talk to your partner about infertility
   - Mental health impact of infertility discussions with partners
   - Rates of inclusion of partners/relationships in discussing impacts of CF in home/work life
4. **Sexual development, function, and treatments**
   - Receipt of SRH education in the pediatric setting in CF care
   - Rates of SRH discussions with parents of children with CF
   - Transition readiness related to SRH concerns in CF
   - Rates of inclusion of partners in CF appointments and discussions related to SRH care
5. **SRH education, communication, and awareness**
   - Patient and provider self-confidence in speaking about SRH
   - Rates of routine SRH discussions and care provision in CF care
   - Receipt of education related to safe sex practices
   - Perspectives of CF providers related to priority of SRH care
6. **SRH risks, comorbidities, and aging**
   - CF knowledge of SRH care specialists
   - Identification of common comorbidities more prevalent in MwCF



Australia, 2001



Thanks!

barbara.messore@gmail.com

February 12th