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Original Article

Pregnancy and neonatal outcome following in utero exposure to CFTR modulators: A multicentre prospective case series

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ABSTRACT

Background: Clinical data regarding in utero exposure to CFTR modulators (CFTRm) are limited. Our objective was to describe pregnancy outcomes, with particular attention to malformations, and neonatal adverse outcomes among prospective pregnancies exposed to CFTRm, using clinical data from the French Network of Pharmacovigilance Centres and the Teratology Information Service CRAT (Centre de Reference sur les Agents Tératogènes).

Methods: An observational multicentre study was performed on the reported CFTRm-exposed pregnancies with an expected delivery date between 2018 and 2023. We described prospective cases, defined as pregnancies for which the outcome was unknown and no adverse prenatal outcome was diagnosed at the time of first contact with the healthcare professional. Major congenital anomalies (MCA) were classified according to criteria of the European Registration of Congenital Anomalies and Twins.

Results: Fifty-eight pregnancies were included, mainly exposed to elezacaftor/tezacaftor/ivacaftor throughout pregnancy (87.9 %).There were 53 live births, four spontaneous abortions and one medical abortion (fetus with cystic fibrosis). One atrial septal defect and one acrania/anencephaly were observed, resulting in a MCA prevalence of 3.4 % (IC95 %: 0.4– 11.9). There were three neonatal adverse outcomes without a clearly identified cause: one sudden massive alveolar hemorrhage, one delayed respiratory distress and one delayed transient hypotonia. No cataract was found in children who had an ophthalmological examination ($n = 10$).

Conclusions: This prospective case series – the largest to date - does not suggest a high rate of MCA or neonatal adverse outcomes in CFTRm-exposed pregnancies. Further studies including long-term follow-up of *in utero* exposed children are needed to confirm these findings.

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1. Introduction

Over the past decade, advances in therapeutic approaches have dramatically changed the management of cystic fibrosis (CF) with the availability of a new class of drugs called cystic fibrosis transmembrane conductance regulator modulators (CFTRm) [1]. CFTRms are the first treatment to directly target the underlying defect in CF. The CFTRm combination elexacaftor/tezacaftor/ivacaftor (ETI) has significantly improved clinical outcomes and quality of life for people with CF, allowing more women to consider pregnancy. As a result and in parallel with improved fertility due to ETI, there has been an increase in the number of pregnancies in women with CF, as also observed in the USA, with more than a hundred pregnancies per year in France since 2021 [2, 3].

Animal data do not raise concerns regarding the potential teratogenicity of CFTRms [4,5]. In humans, the placental transfer of CFTRm has been demonstrated, with fetal concentrations at birth (measured in cord blood) equivalent to those of treated mothers [6–8]. Clinical safety data during pregnancy are limited, based on few case reports, two retrospective case series and one recent nationwide cohort study [9–11]. To date, these limited data are reassuring in terms of malformative effect or immediate neonatal adverse outcomes (where available). With this prospective case series of pregnancy exposed to CFTRm, our objective was to describe the pregnancy outcome with particular attention to malformations and neonatal adverse events, using the clinical data collected by the French Network of Pharmacovigilance Centres (FNPVC) and the Teratology Information Service Centre de Référence sur les Agents Tératogènes (CRAT).

2. Material and methods

2.1. Study design and settings

An observational multicentre study was conducted, using the clinical data from pregnancies exposed to CFTRm reported to the FNPVC, consisting of 30 regional centres [12] or the CRAT [13]. These national referral structures, accessible to healthcare professionals, provide expertise and advice on potential drug risks during pregnancy and breastfeeding and collect clinical data as part of the risk assessment process. Reported pregnancies are followed up at least until delivery to track adverse outcomes, congenital anomalies and neonatal manifestations.

2.2. Inclusion criteria

Inclusion criteria were prospective pregnancy among women treated with at least one of the following CFTRm (ivacaftor, lumacaftor, tezacaftor and elexacaftor) who continued their treatment during pregnancy (regardless of gestational age) with an expected date of delivery between 01/01/2018 and 12/31/2023 and a complete pregnancy follow-up. Prospective pregnancies were defined as pregnancies for which the outcome was unknown and no adverse prenatal event was diagnosed when the healthcare professional contacted one of the national referral structures [14]. Pregnancies with a known major teratogen or foetotoxic drug as concomitant treatment drug were also included.

2.3. Data sources

According to the CRAT and FNPVC procedures, at the first contact, healthcare professional provide informations on maternal characteristics (age, weight, obstetric history), medical history (e.g. cystic fibrosis, diabetes, arterial hypertension or other chronic conditions), details on the current pregnancy (conception date, ultrasound examinations, pregnancy disorders such as gestational diabetes or hypertension). Data on current treatments are also collected including gestational period of drug exposure, type of drug, dose, duration of exposure. Two months after the expected delivery date, a follow-up questionnaire is sent to the healthcare professional to collect informations (and relevant medical records) on the course and outcome of the pregnancy: type of outcome, preterm birth, gestational age, type of deliver, the newborn's health at birth (sex, weight, APGAR), feeding (breastfeeding or formula), the presence or absence of malformations or neonatal manifestations and whether neonatal transfer to intensive care unit was required.

2.4. Variables

Pregnancy outcomes were defined as : live births ; spontaneous abortions (SAB, corresponding to the loss of an embryo or fetus before 22 gestational weeks (GW) and fetal weight < 500 g), medical abortions (defined as the termination of a pregnancy for foetal and/or maternal health reasons), voluntary abortions (termination of a pregnancy at the woman's request for reasons other than for embryonic/fetal or maternal health) and stillbirths (in utero death of a fetus from 22 GW onwards, or weighing at least 500 g). Gestational age was calculated from the date of last menstrual period or first trimester ultrasound. Preterm births were defined as birth before <37 GW. Small for gestational age (SGA) was defined as a weight $<$ 10thpercentile for gestational age and sex, according to the French Audipog reference charts [15].

We defined congenital anomalies (CA) according to the World Health Organisation definition. An adjudication committee classified the major or minor characterisation of each CA using the European classification of malformations EUROCAT (European Registration of Congenital Anomalies and Twins) Guide 1.5 [16]. The analysis of major congenital anomalies (MCA) was performed among livebirths, stillbirths and elective terminations of pregnancy (medical or voluntary abortion) for which the information whether a congenital malformation was searched for was available. Neonatal and paediatric complications reported by healthcare professionals were also considered.

2.5. Data management

Data were reviewed to identify duplicate reports between FNPVC and CRAT as healthcare professionals may occasionally contact both referral structures to obtain multiple advices. Duplicates were identified on the basis of four parameters: maternal age, gestational age at birth, pregnancy outcome, and region where the delivery occurred. When duplicates were found, the earliest report (based on the reporting date) was retained.

2.6. Statistical analysis

Missing values were described but not replaced. Quantitative variables were described using mean and standard deviation (SD) or median and interquartile range (IQR), qualitative variables were described using frequencies and percentages. MCA prevalence was calculated with 95 % confidence interval (95 %CI). The denominator was based on live births, stillbirths, medical or spontaneous abortions for which the information whether a congenital malformation status was searched for was available in the database. A graphical representation of exposure periods and pregnancy outcomes for prospective cases was produced using R Statistical Software (v 4.3.2 ; R Core Team 2023).

2.7. Ethics and regulatory aspects

For FNPVC, all clinical data of pregnancy-drug exposure are registered in the French PharmacoVigilance Database (FPVD), which is approved by the Commission nationale de l'informatique et des libertés (CNIL) as ANSM n° 2014–302 and is deidentified to protect patient confidentiality. The CRAT database has been authorized by the CNIL on May 16, 1989, after the 89–41 deliberation process. This study complied with general protection data regulation (GPDR) and the French regulation while conforming to the reference methodology MR-004 (number

20,240,410,172,054 in the general treatment register of APHP).

3. Results

After exclusion of duplicate records ($n = 6$) and of pregnancy with unknown outcome ($n = 1$), 72 CFTRm-exposed pregnancies with known outcomes were reported (44 to the FNPVC and 28 to the CRAT) between 09/11/2018 (date of the first record) and 12/31/2023 (Fig. 1). Among those, 58 (80 %) were prospective cases.

Maternal characteristics are described in Table 1. The mean±SD age of the women included was 30 +- 5 years, and 21 (36.2 %) had pre-existing diabetes. All women had a CFTRm treatment at the time of conception, and 51 (87.9 %) were treated throughout pregnancy . The main exposure concerned the ETI combination (89.7 %). Among concomitant treatments, no women had teratogenic or fetotoxic drugs.

Among the 58 prospective cases, 53 (91.4 %) resulted in live born infants, four (6.9 %) in SAB and one medical abortion (1.7 %) due to a fetal CF, without reported MCA (Fig. 2).

Two cases of MCA were identified, all exposed during at least the first trimester of pregnancy: a fetus with acrania/anencephaly (absence of maternal diabetes and periconceptional folic acid supplementation; ending in SAB – case #1, Table 2) and a neonate with an atrial septal defect (context of maternal diabetes and family history with a sister with ASD – case #2, Table 2). Based on these two malformations, the prevalence of MCA was 3.4 % (IC95 %: 0.4 – 11.9). There was 3 minor CAs without a specific pattern (cases #3, #4, #5, Table 2). Neonatal adverse outcomes were reported in 22.6 % ($n = 12$) of newborns exposed in utero to CFTRm up to delivery, with 9 requiring transfer to the neonatal unit (Table 2). Respiratory distress was observed in 6 neonates (11.3 %) and hypotonia (2 transient and 1 persistent) in 3 neonates (5.6 %). Three neonatal adverse outcomes had no clearly identified cause: one severe alveolar haemorrhage (case #1′, Table 2, published [17], one hypotonia lasting 5 days (case #6′) and one respiratory distress associated with mild hypotonia, lasting 72 h (case #12′). These 3 neonatal complications occurred remotely from birth (H4, D3 and H24 respectively). Finally, in a child born without neonatal adverse outcome but with CF, the mother had reported some language delay and neurobehavioural disorders at 18 months, with suspicion of autism spectrum disorder (ASD) at 24 months (case #11′).

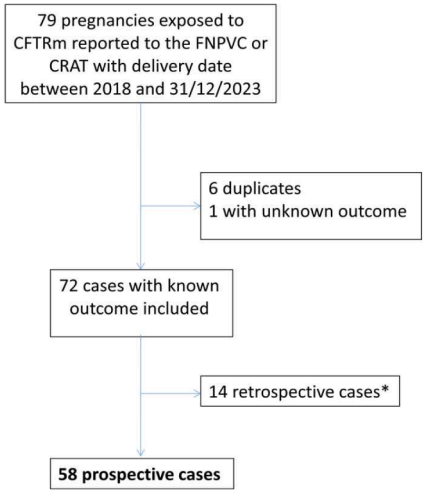

Fig. 1. Flow chart of the reported cases to the referral national structures.
*Retrospective cases are pregnancies for which the outcome was already known or an adverse prenatal disease outcome was diagnosed at the time of first contact of the healthcare professional to the referral national structure. Among those, there were four MCA (described in supplemental data, etable 2): one acrania, one atrial septal defect, one pelvic single kidney and one familial Mondini malformation; there was one neonatal death due to Benkiser hemorrhage.

Table 1
Maternal and neonatal characteristics; outcomes of pregnancies exposed to CFTRms.

	Prospective pregnancies n (%)
Number	58
French network of RPVC	35 (60.3)
TIS (CRAT)	23 (39.7)
Initial contact (year)	
2018	2 (3.5)
2019	0
2020	6 (10.4)
2021	12 (20.7)
2022	19 (32.7)
2023	19 (32.7)
Age (years), mean ± range (median)	30 ± 5.3 (29)
Age (years), category	1 unknown
15–20	1 (1.7)
21–25	11 (18.9)
26–30	24 (41.4)
31–35	13 (22.4)
36–40	8 (13.8)
41–45	0
Diabetes prior pregnancy /gestational diabetes	21 (36.2)
	3 (5.2)
CFTRm exposure	
LUM/IVA	5 (8.6)
IVA	1 (1.7)
IVA/TEZ	0
ETI	52 (89.7)
Trimester of exposure to CFTRm	
before conception	58 (100)
T1 only	6 (10.4)
T1-T2 only	1 (1.7)
T1,T2 and T3	51 (87.9)
Live birth	53 (91.4)
Spontaneous aborption	4 (6.9)
Medical abortion	1 (1.7)
Major congenital anomalies	2 (3.4)
Gestational weeks at birth; mean ± SD (median)	38±1.5; 38
Preterm birth (<37 GW)	3 (5.6)
Sex (F/M/UNK)	23/28/2
Weight (g); mean ± SD (median)	3171±453 (3193)
Low birthweight (<2500 g)	3 (5.6)
Small for Gestational Age	4 (7.5)
Apgar <7 at 5 min of life ($n = 47P / 6R$)	2 (3.7)
Transfert to neonatal care ($n = 50P/10R$)	9 (17)

Regarding neonatal and paediatric complications, no cases of cataract were identified among the 10 children with an ophthalmological examination.

4. Discussion

Our results do not suggest specific occurrence of adverse outcomes after in utero exposure to CFTRm, especially in terms of MCA or neonatal adverse events. More than 93 % of newborns had gestational age, birth weight and SGA within the normal range.

In our study, the prevalence of MCA in exposed pregnancies was 3.4 % (IC95 %: 0.4–11.9), which is similar to the baseline occurrence of congenital anomalies in the general population (around 3 %) [18]. In terms of malformation, atrial septal defect is a common malformation in the general population and there is a trend towards the occurrence of cardiac anomalies in infants of women with CF [4]. On the contrary, acrania – anencephaly is an uncommon malformation (anencephaly and similar: 4.11 (4.00 - 4. 23) per 10,000 live births [16]). There is currently no clear evidence from animal or clinical data, or similar published cases, to suggest a link between in utero exposure to a CFTRm and the occurrence of neural tube defect (NTD) anomalies, but CFTR expression has been demonstrated in the central nervous system during embryonic development [19]. Maternal diabetes and obesity increase the risk of NTD [20], but neither of the 2 women had these risk factors,

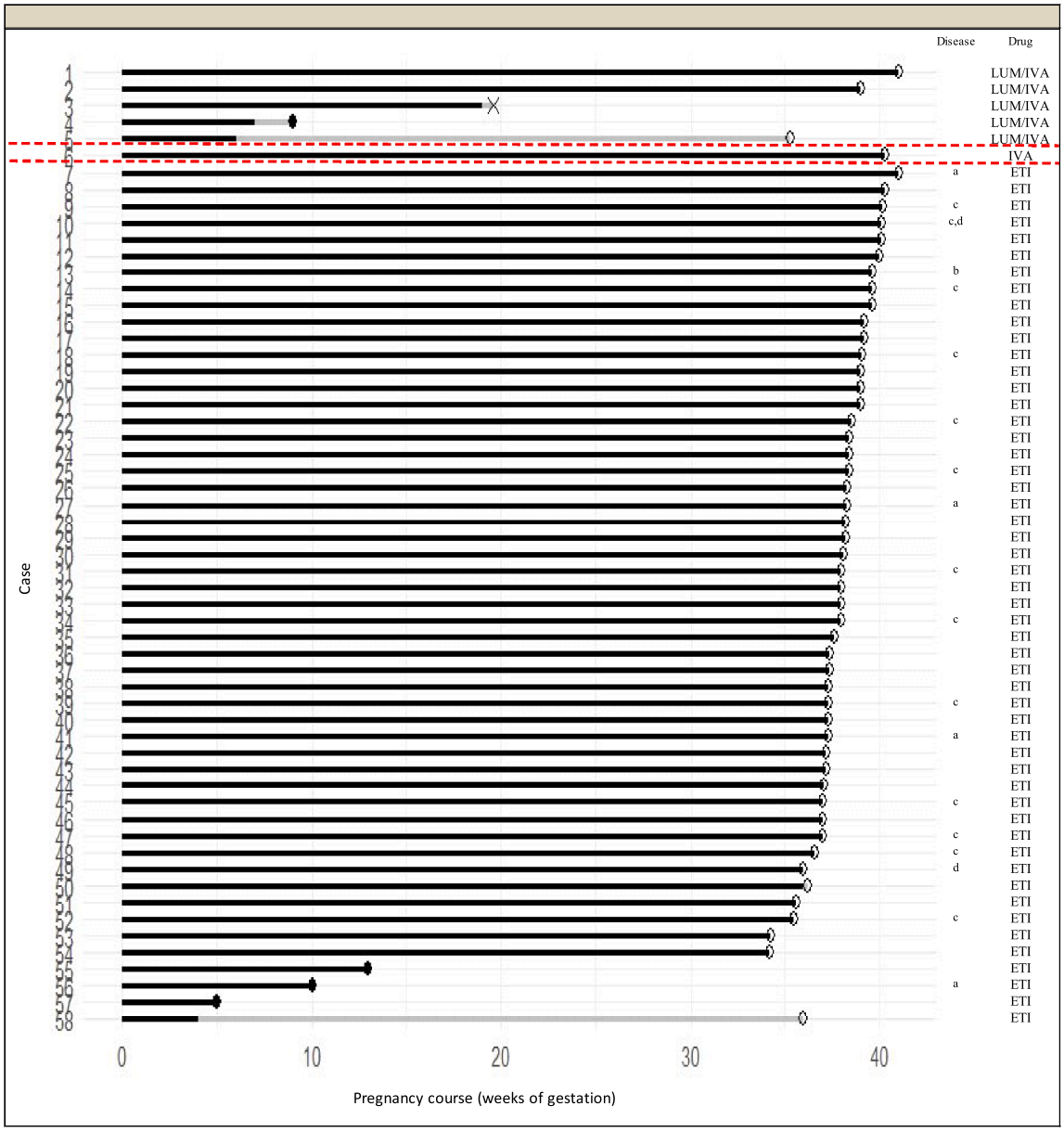

Fig. 2. Exposure pattern and outcomes of prospective pregnancies exposed to CFTR modulators . Each line symbolizes one pregnancy. Pregnancies are drawn according to type of CFTRm exposure and pregnancy term. (a) major malformation, (b) minor malformation (c) neonatal complication, (d) neurodeveloppemental complication. O = birth ; ● : spontaneous abortion (SAB) ; *X* = medical abortion for embryofetal anomalies. Legend: CFTRm : cystic fibrosis transmembrane conductance regulator modulators; ETI : elexacaftor/tezacaftor/ivacaftor; IVA : ivacaftor; LUM : lumacaftor.

and both had received folic acid supplementation, although their folate status was unknown.

Before the availability of CFTRm, pregnant women with CF have an increased risk of preterm delivery and SGA, depending on the pre-pregnancy lung function [21]. In our series, there was no signal on delivery or immediate neonatal adverse outcomes, as confirmed by 2 recent studies [4,11]. Respiratory distress, a common situation of neonatal care unit admission (about 1 % of births), occurred in six cases – four of which explained by prematurity or infection [22]. Nevertheless, the other two cases (one occurring 24 h after birth, and lasting 72 h, with associated mild hypotonia and the published case, with associated alveolar haemorrhage) had no clear cause. While there are no similar cases in the literature, few publications have reported that CFTRs play a role in fetal organ development and function, particularly in lungs, pancreas and kidneys [23]. In animals and in human lung cells, defective morphogenesis of pulmonary branches at the pseudo-glandular stage has been shown after CFTRm exposure [24,25]. These interferences with airway morphogenesis could perhaps explain potential neonatal pulmonary consequences and warrant further investigation.

One neonate experienced transient hypotonia for 5 days, unexplained by birth conditions, neonatal infection or genetics. As in the human fetus, CFTRs are abundantly present from the 13th GW in numerous nervous structures (notably in all cortical layers, motor neurons and in some migrating neurons in the developing cortex and cerebellum) [19], we cannot therefore rule out the hypothesis that CFTRms may interfere with these structures.

In our study, some neonatal effects appeared delayed after birth. A few cases of respiratory distress and pulmonary exacerbation had been considered to be as « withdrawal phenomenon » in adults or children with CF treated with ivacaftor for several months or years [26,27]. An abrupt cessation of CFTRm exposure at birth may disrupt chloride homeostasis and could be a plausible hypothesis to explain these observed

Table 2
Malformations, neonatal and paediatric complications observed after in utero CFTRm exposure. Legend: CFTRm : cystic fibrosis transmembrane conductance regulator modulators; ETI : elexacaftor/tezacaftor/ivacaftor; IVA : ivacaftor; LUM : lumacaftor.

Type of events	CFTRm exposure	Pregnancy outcome and gestationnel age (weeks)	Description of fœtal or infant clinical situation	Adjudication committee of events and comments (BC, BM, SG)
Malformations				
1	ETI throughout pregnancy	SAB 10	Acrania - anencephaly found à 7 GW, confirmed at 9 GW. Pregnancy spontaneously stopped at 10 GW. Anatomopathological examination: involutive intrauterine gestational process with no argument for a molar pregnancy. No maternal diabetes. Supplementation with folic acid.	Major malformation (EUROCAT).
2	ETI throughout pregnancy	Birth 37.3	Atrial septal defect, without clinical manifestations. Familial history (sister with ASD at birth; case #8′). Maternal diabetes, well balanced.	Major malformation (EUROCAT).
3	ETI throughout pregnancy	Birth 39.6	Left dacryocystocele of 8–10 mm seen antenatally and stable. Confirmation at birth.	Minor malformation (EUROCAT)
4	ETI throughout pregnancy	Birth 41	Congenital dysplasia of the hip. Braces for 4 months, resolved at 18 months of life.	Minor malformation (EUROCAT)
5	ETI throughout pregnancy	Birth 38.3	Congenital dysplasia of the hip. Familial history, instrumental vaginal delivery. Maternal diabetes. Resolved at 6 weeks of life.	Minor malformation (EUROCAT).
Neonatal complications				
1′	ETI all trimesters	Birth 36.6	Sudden respiratoy distress and severe pulmonary hemorrhage (published Nuytten et al., 2022). H4 after birth, no malformations, no other anomalies. Apgar 10/10/10. Maternal diabetes.	No etiology found. No phyisopathological explanation found for this event.
2′	ETI all trimesters	Birth 37	Transient neonatal axial hypotonia. Context of difficult delivery (pre-eclampsia and unbalanced type 1 diabetes). Apgar 2/6/8.	Context of polyhydramnios during pregnancy. Instrumental delivery (suction cups)
3′	ETI all trimesters	Birth 38	Minor retinal haemorrhage in the left eye at birth. Apgar 10/10/10. Unbalanced maternal diabetes.	Context of hydramnios, and reduced foetal movements at the end of pregnancy. Vaginal delivery.
4′	ETI all trimesters	Birth 39.6	Respiratory distress at birth. Transfert to neonatal care unit. Apgar 6/10/10. Abnormal pH (7.14) at birth.	Context of caesarean section during labour for abnormal foetal heart rate.
5′	ETI all trimesters	Birth 38.4	Respiratory distress at birth. Apgar 8/9/9	Context of twin pregnancy.
6′	ETI all trimesters	Birth 38.5	Axial hypotonia between D3 and D8, requiring hospitalization. Discharged with improved. Normal morphological assessment. Normal transthoracic, cardiac and abdominal ultrasound. Apgar 10/10/10. Search for Prader Willi negative. No more axial hypotonia at D10. Walking at M14. Normal growth at M21. Psychomotor development within normal limits. Monitoring of the fine motor development.	Context of caesarean section for abnormal foetal heart rate and unbalanced maternal diabetes.
7′	ETI all trimesters	Birth 39.1	Bacterial purulent conjunctivitis of the left eye at birth. Apgar 9/10/10. Maternal diabetes.	Confirmed bacterial infection.
8′	ETI all trimesters	Birth 40.1	Mild transient hypotonia 2 h after delivery. Neuropediatric consultation at one year of age: psychomotor developmental disorders, predominantly affecting gross motor skills, and associated with failure to thrive. Apgar 6/9/10	Identical history of the brother, without CFTRM exposure.
9′	ETI all trimesters	Birth 37.2	Hospitalization at the age of 1 month for acute E.Coli pyelonephritis. Renal ultrasound without abnormality. Breastfed infant. Apgar 10/10/10.	Confirmed renal infection without renal malformation.
10′	ETI all trimesters	Birth 37	Respiratory distress at birth. Transfert to neonatal care for 17 days. Bacterial infection. Apgar 10/10/10. maternal diabetes.	Confirmed pulmonary infection.
11′	ETI all trimesters	Birth 36	Normal neurobehavioural assessment at 6 and 12 months of age. Language delay at 18 months of age. Suspicion of autism spectrum disorders at 24 months of age. Apgar 10/10/10.	Infant with cystic fibrosis.
12′	ETI all trimesters	Birth 38	Respiratory distress at H24. Transfert to neonatal care. Lasted 72 h. Mild transient axial hypotonia associated. Apgar 10/10/10. Unbalanced maternal diabetes.	Context of meconial fluid at birth.
13′	ETI all trimesters	Birth 37.3	Respiratory distress at birth. Transfert to neonatal care. Resolved at D14. Apgar 10/10/10	Context of caesarean section for mild preclampsia.

delayed effects.

We did not observed any cataract in children who had an ophtalmological examination. This risk has been raised by animal data and a clinical publication on one newborn and two infants exposed in utero to ETI, which described small bilateral cataracts, without significant visual impairment and no worsening [28]. At this stage, the absence of extensive experience of CFTRm use during pregnancy justifies the recommendation of systematic ophthalmological monitoring of the child during the first year of life.

It is difficult to draw conclusions about the infant with suspected ASD. Some published data indicated that CFTRs are widely expressed in neurons of the human spinal cord [29] and CFTRms have been associated with neuropsychiatric toxicity in young children treated from the age of 2 [30]. Although these findings remain insufficient to draw any conclusions, they underscore the need for careful monitoring of the fetal brain developpement during pregnancy and of neurodevelopment outcomes in children following in utero CFTRm exposure.

Overall, these results are consistent with previously published data, which did not indentified specific malformative or severe neonatal signal regardless of the CFTRm prescribed. In most studies, exposure was continuous throughout pregnancy and our case series reflected this practice: CFTRm therapy was sustained until delivery in 87.9 % of pregnancies, and interruptions were limited to the oldest reports. Analysis of all the available data suggests that continuation of treatment is now commonplace, and after multidisciplinary discussion, including consideration of the documented risk of worsening maternal clinical status, it is no longer standard to interrupt treatment when pregnancy is detected [2].

5. Strengths

Our study is based on prospective pregnancies exposed to CFTRms reported to national referral structures. Given the nature and quality of these data, we provide significant added value to the previous state of the art for the assessment of teratogenic and neonatal risk to [13]. This multicentre study is not an exhaustive registry of pregnancies in France in women with CF treated with CFTRm as recruitment in our structures relies on spontaneous notification of cases. However, both CRAT and FNPVC are well established national referral structures (with 30 regional centres for the FNPVC). These structures are therefore readily consulted at the beginning of a pregnancy involving new drugs such as CFTRms. Hence, our national structures are able to accurately describe the whole pregnancy course, including precocious adverse pregnancy outcome (early miscarriage, severe malformations leading to pregnancy loss…). Besides, exposed children can be followed over a long period of time beyond pregnancy and the first few months after birth.

As women with CF are followed within the French Reference Network (47 CF regional centres), a close collaboration has been set up between this reference network and the FNPVC to enhance data collection and encouraging the reporting of CFTRm-exposed pregnancies. This effort proved effective: based on the findings of *Chouchana* et al. [11]. who identified 148 pregnancies in women with CF treated with CFTR modulators between 2018 and 2023 (the same period as our study) from the national medico-administrative database, CRAT and FNPVC were consulted for approximately 50 % of these cases (with a higher consultation during the first years). Among these, 58 pregnancies were reported prospectively (40 % of the total), thereby avoiding the risk of reporting bias associated with retrospective adverse outcome reporting. Based on the characteristics of the patients included in our study and those in the national cohort identified through medicoadministrative data (age, comorbidities and current treatments), we have no indication of under-representation in our data.

Another notable strength of our study is the use of clinical data, collected directly from healthcare professionals (physicians, pharmacists and midwives), which ensures detailed data, homogeneous medical interpretation of outcomes and reduces reporting errors associated with patient-reported data and recall bias.

6. Limitations

Our study lacked of a control group to assess the association between CFTRm exposure and pregnancy or neonatal outcome, although sample size would have limited the statistical power of such an analysis. In addition, follow-up duration was heterogeneous, from the neonatal period or longer, preventing for a clear assessment of long-term outcomes in children exposed in utero. Finally, we had very limited maternal information and were not able to describe the evolution of the maternal disease during pregnancy (respiratory function, respiratory exacerbation or patient-reporting outcome).

7. Conclusion

This prospective case series - the largest to date - does not suggest the occurrence of adverse outcomes in pregnancies exposed to CFTRm. The rate of MCA after first trimester exposure to CFTRm is close to the one expected in the general population. However, most of the available data relate only to the immediate neonatal period. Further studies are needed to confirm the absence of teratogenicity, including NTDs, or the risk of withdrawal syndrome, and to evaluate the mid- and long-term follow-up of children exposed in utero, with a particular attention to ophthalmological, pulmonary and neurodevelopmental systems.

Author contributions

SG, BC, BM and APJB : conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it, final approval of the version to be submitted ; MATB, LC, CA, JM, CG : acquisition of data, critical revision of the manuscript, final approval of the version to be submitted ; EE, PRB: critical revision of the manuscript, final approval of the version to be submitted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2025.06.001.

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