

Pregnancy in cystic fibrosis in the era of CFTR modulators: A case series

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ABSTRACT

Over the last 50 years, survival of people with cystic fibrosis (CF) has increased impressively. CF is no longer considered a pediatric disease since the majority of patients in Europe are now adults; and this change has inevitably led to concerns about parenthood among people with CF (PWCF). The number of pregnancies in women with CF has been increasing over time and many cases of unplanned pregnancies are reported after use of CFTR modulators. In the Adult CF Centre, G. Papanikolaou Hospital of Thessaloniki, Greece, nine pregnancies were carried by 7 women with CF. Two pregnancies took place under CFTR modulators and both women were not willing to take the risk of discontinuing the medication despite lack of data on its safety at that time. The final outcome was successful in all cases, and all women slowly regained their spirometric values within 6 months after delivery. Elexacaftor, tezacaftor, and ivacaftor demonstrated an increase in function of the F508del mutated CFTR protein at the cell surface, resulting in increased chloride ion transport. CFTR modulators are to be avoided during pregnancy due to lack of or limited data. However, no adverse impact of CFTR modulators on fetal chromosomes, organogenesis or survival is reported up to now. The decision to continue therapy during pregnancy is particularly challenging. Clinicians and patients should weigh the potential risk or clinical decline for fetus and mother, respectively.

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INTRODUCTION

Over the last 50 years, survival in people with cystic fibrosis (CF) has risen impressively. CF has been considered as a pediatric disease but the majority of patients in Europe are now adults¹; and this change has inevitably led to concerns about parenthood among people with CF (PWCF)². Although men with CF are almost without exception azoospermic, women with CF are generally capable of conceiving and carrying out a normal pregnancy. However, infertility or subfertility in women with CF is considered to be 15–30% higher than in general population³. An increase has been reported in the number of pregnancies in women with CF over time and many cases of unplanned pregnancies have been reported, after use of CFTR modulators, possibly because women considered themselves infertile. It is believed that CFTR modulators improve female fertility mainly by changing quality of cervical mucous secretions⁴.

CASE PRESENTATION

Over the last decade, nine pregnancies were carried by 7 women with CF, in the Adult CF Centre, G. Papanikolaou Hospital of Thessaloniki, Greece. All data were extracted after the women gave their informed consent. Two women had 2 pregnancies each and one had a twin pregnancy leading to 10 children overall. Women had a mean age of 33 years and a mean BMI of 21 and 20 (kg/m²) before

and after pregnancy, respectively. Five women had chronic infection with *Pseudomonas aeruginosa* and five needed hospitalization for exacerbation and intravenous antibiotics during pregnancy. Final outcome was successful in all cases with a mean of 36 weeks gestation. In Table 1, characteristics and pulmonary function are shown before and after delivery in all pregnant women. A mean decrease of about 200mL in FEV1 and 300mL in FVC were observed after delivery. The higher decrease was noted in case of twin pregnancy (Patient 6, Table 1). All women slowly regained their spirometric values within 6 months after delivery.

Two pregnancies took place under CFTR modulators. One woman was under lumacaftor/ivacaftor, and the other under elexacaftor/tezacaftor/ivacaftor (ETI). Both women decided to continue CFTR modulators. Interestingly, the second woman who had significantly improved after ETI initiation, was not willing to take the risk of discontinuing the medication despite the lack of data on its safety at that time. The woman was aged 41 years and had one F508del and one minimal function mutation. She also had diabetes mellitus under insulin therapy, pancreatic insufficiency and a chronic infection of *P. aeruginosa*. As shown in Table 2, her respiratory function improved during pregnancy in contrast to what was anticipated. She also continued insulin, formoterol, budesonide and vitamins, and she started LMWH in a prophylactic dose. No exacerbation was noted and the

Table 1. Characteristics and pulmonary function before and after delivery in seven pregnant women

Characteristics	Patient 1	Patient 1	Patient 2	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
CF genotype	ΔF508 / ΔF508	ΔF508 / ΔF508	E822X / 2789+5G>A	E822X / 2789+5G>A	ΔF508 / 164+1G>C	ΔF508 / c1617delTA	ΔF508 / W1282X	ΔF508 / 621+1G>T	ΔF 508 / 1717-1G->A
Age (years)	32	39	32	35	22	41	29	35	29
CFTR modulator	-	Lumacaftor/ ivacaftor	-	-	-	Elexacaftor/ tezacaftor/ ivacaftor	-	-	-
Pro BMI	22.8	22.3	20	21	16.6	24	19.5	19	20.7
Post BMI	19	21.67	19	20	16	25	20.3	19.5	23
Pro FVC (L)	2.8	3.08	-	3.87	2.14	2.37	2.33	2.7	3.39
Post FVC(L)	2.91	3.36	-	3.75	2.17	2.45	2.29	2.05	2.41
Pro FEV1(L)	1.88	1.87	-	2.89	1.15	1.34	2.05	1.5	2.22
Post FEV1(L)	2.09	1.98	-	2.84	1.21	1.38	1.94	1.04	1.57
GA at delivery	37	36	38	37	38	36	36	34	40
Delivery route	cesarean	cesarean	cesarean	vaginal	cesarean	cesarean	cesarean	cesarean	vaginal
Infant birth weight (g)	3000	2250	2770	2660	2760	3330	2210	1570/1870 twins	3330
Antenatal complications	2 exacerbations	1 exacerbation	1 exacerbation	0	0	0	6 months intravenous	3 exacerbations	hemoptysis

Table 2. Characteristics of Patient 4, showing respiratory function improvement during pregnancy

	FEV1 (L)	FEV1%	FVC (L)	FVC%
Before CFTR modulator	0.85	27.7	1.36	39.8
Before pregnancy	1.34	44	2.37	72
Week of pregnancy				
5th	1.46	51	2.42	73
16th	1.38	49	2.4	73
21st	1.41	50	2.55	77
28th	1.45	51	2.47	74
30th	1.51	53	2.45	74

improvement was retained after delivery. She delivered a full-term baby of 3.350 kg, which is the first baby born to a mother under ETI in Greece. The newborns' transaminases were normal and signs of cataract were not present.

DISCUSSION

ETI combination therapy exceeded the clinical benefit that previous CFTR modulators have shown. Ivacaftor functions as a potentiator of the CFTR protein for common gating mutations, allowing an increase in chloride ion flow⁵. Tezacaftor functions as a corrector to facilitate the folding and presentation of the mature CFTR protein to the cell surface, improving CFTR function for the F508del mutation⁶. Elexacaftor is a next-generation CFTR corrector that works at an alternate binding site than tezacaftor on the CFTR protein to further facilitate the functionality of the CFTR protein at the cell surface⁷. When they are used in combination, elexacaftor, tezacaftor, and ivacaftor indicate an increase in function of the F508del mutated CFTR protein at the cell surface resulting in increased chloride ion transport⁸. ETI is now indicated in people with CF with at least one F508del mutation⁹⁻¹¹.

During pregnancy, CFTR modulators are to be avoided due to a lack of or limited data⁵. However, data that have been collected from animal reproductive models suggest that the components of the new and very effective triple combination elexacaftor-tezacaftor-ivacaftor (ETI), do not cause teratogenicity at normal human doses. No adverse impact of CFTR modulators on fetal chromosomes, organogenesis or survival is reported up to now. Cataract has been reported to develop in children exposed to Ivacaftor³.

Continuing therapy during pregnancy is associated with unknown fetal impact, nevertheless the decision to discontinue therapy is related to the known risk of maternal health decline. In our center, both women on CFTR modulators were clearly in favor of continuing their medication despite the risk. The decision was easy to make and a successful result was the award.

Small number of case series of pregnancies under CFTR modulators have been published over the last few years. In the largest study to date on the effect of ETI on 45

pregnancies, the miscarriage rate was as expected in the general population. Complications possibly related to ETI use were noted in 2 mothers and 3 infants; 5 out of 6 women who discontinued the triple combination during pregnancy had to restart, because of clinical deterioration¹².

The ERS/TSANZ TASK force statement for pregnancy in women with airway diseases concluded that, despite limited, data CFTR modulators are of low risk and their use is probably safe during human pregnancy¹³. A prospective multi-center clinical trial called MAYFLOWERS is designed to enroll 285 pregnancies with or without CFTR modulators for a 35-month observation. This trial is expected to describe detailed outcomes in pregnancy and lactation in relation with CFTR modulators, but with, and also pre-existing, comorbid conditions¹⁴.

CONCLUSION

As a great number of CF people are now eligible for highly effective CFTR modulators, data from prospective trials are needed to provide evidence-based recommendations to women contemplating pregnancy. Until then, clinicians and patients should weigh the potential risk or clinical decline for fetus and mother, respectively.

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for disclosure of potential conflicts of interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. E. Papadaki and K. Manika report other financial or non-financial interests from Vertex Study Protocol. K. Manika also reports receiving Vertex honoraria for lectures.

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ETHICAL APPROVAL AND INFORMED CONSENT

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DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

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