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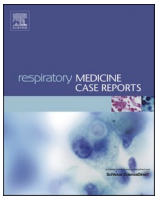

Case Report

# Experience to date with CFTR modulators during pregnancy and breastfeeding in the British Columbia Cystic Fibrosis clinic

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A B S T R A C T

The introduction and rapid uptake of CFTR modulator therapy, in addition to other treatments, has significantly increased life expectancy in CF and provided more women the opportunity to consider and successfully be managed throughout pregnancy. There is however limited evidence to guide patient management and enable informed decision making. Here we report the experience to date from a large multidisciplinary Cystic Fibrosis quaternary referral center in managing patients on CFTR modulators in the peri- and post-partum periods. While women in this case series were advised to discontinue CFTR modulators during pregnancy, they would likely receive a very different message today.

The introduction and rapid uptake of CFTR modulator therapy, in addition to other treatments, has significantly increased life expectancy in CF and provided more women the opportunity to consider and successfully be managed throughout pregnancy [1]. There is also limited data supporting the notion that CFTR modulator therapy improves fertility in women with CF [2]. There is however limited evidence to guide patient management and enable informed decision making, with phase III trials excluding pregnant women, and recent evidence showing that all 4 modulators can cross the placenta, and can be measured in infant plasma and cord blood [2].

The British Columbia Cystic Fibrosis (CF) program cares for over 250 patients with CF patients who are managed in multi-disciplinary clinics. Here we report our experience to date managing patients on CFTR modulators in the peri- and post-partum periods.

Patient 1 became pregnant with her first pregnancy whilst on Ivacaftor at age 33 in 2015. Her mutations are G551D and 1161 deletion c. She was diagnosed with CF at age ten months. She is and was at the time of her pregnancy considered to be a relatively healthy CF patient with an FEV1 in the 2–2.10L/(70–75%) range, physically active with a BMI of 25. She is known to be colonized with Pseudomonas, MSSA, Klebsiella Oxytoca and Herbaspirillium. The patient has a history of nasal polyps and sinusitis followed by ENT, asthma overlap with features of ABPA (never treated), pancreatic insufficiency, dysglycemia with a HbA1C of 4.9% and a previous cholecystectomy.

The patient was initiated on Ivacaftor (self-funded) in 2012. Since being on Ivacaftor the patient typically exacerbated once a year. She became pregnant spontaneously and intentionally after discontinuing her oral contraception four months prior in 2015. Her partner was not a CF carrier.

The patient presented to our CF clinic at approximately eight weeks gestation. She was advised to discontinue Ivacaftor at the time due to the unknown teratogenic potential but chose to continue regardless. Her lung function at her initial visit whilst pregnant was as follows: FEV1/FVC 2.35 (86%)/3.10 (99%). Sputum cultures consistently grew pseudomonas aeruginosa and staph aureus throughout pregnancy.

During pregnancy the patient experienced one pulmonary exacerbation in her second trimester and was treated with oral Keflex as well as nebulized cayston and inhaled pulmicort. Nebulized cayston was continued throughout the remainder of her pregnancy on

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alternating months.

An ultrasound done at 35 weeks 4 days gestation demonstrated no concerning pathology. Bpd was at 10th percentile, remainder of growth parameters were between 10th and 90th percentiles. Mild polyhydramnios was present with the single pocket measuring 9.6 cm.

The patient was ultimately admitted for induction of labour due to CF and mild polyhydramnios. She had an emergency cesarean section at 38 weeks 2 days for abnormal fetal heart rate with prolonged deceleration. A healthy male infant was delivered with normal apgars. Birth weight 3.2kg.

The patient was given prophylactic IV antibiotics in the form of piperacillin tazobactam and ceftazidime for 1 week post-partum. She was stable throughout delivery and into the post-partum period from a respiratory standpoint with an FEV1/FVC of 2.23 (82%)/ 3.16 (101%) 8 weeks post-partum.

The patient continued on ivacaftor throughout breastfeeding which ended when her infant was approximately 3.5 years with no issues. Today the child is physically normal and healthy. He had some speech delay assessed at age 2.5 by a speech therapist. He was thought to have full comprehension and had learned to communicate well via non-verbal means. He was not formally screened for cataracts.

Patient 2 is a 33 year old G3 T1 A1 L2 female DeltaF508 homozygous CF patient with an FEV1 in the 50% range who remained on Tricafta throughout pregnancy and into breastfeeding.

The patient was initiated on Tricafta in March 2020. She had previously been on Orkambi from 2017 to 2020. Her past medical history is otherwise significant for CF related diabetes managed with insulin, chronic rhinosinusitis, pancreatic insufficiency, asthma overlap, patellofemoral syndrome and cholelithiasis. Her sputum chronically grows Pseudomonas Aeruginosa, Staph Aureus, and E. Coli. She is a non-smoker. Her past surgical history is significant for a laparoscopic appendectomy (2008), insertion of a feeding tube (2012-subsequently removed), and Port-A-Cath placement in 2014 and again in 2016.

Obstetric and Gynaecologic history is significant for an uncomplicated vaginal delivery at 37 weeks gestation in June 2005. Her daughter is healthy. Subsequently the patient had a first trimester miscarriage managed with misoprostol in October 2020. Menstrual cycles had been regular at monthly intervals.

The patient's pregnancy was planned. Her partner is 35 years of age and was not a carrier on CF genetic screening. Prior to Tricafta the patient had frequent exacerbations and her FEV1 was 30% predicted. She had been actively listed for transplant. She had a high PRA. She was delisted following initiation of Tricafta in March 2020.

Baseline FEV1 prior to pregnancy was 1.53 L (53% predicted) and weight was 55.6 kg with a BMI of 23. The patient had had no recent admissions to hospital and had minimal issues with cough and dyspnea. HbA1C was 10% one month into the pregnancy.

The continuation of Tricafta was discussed with the patient. It was recommended to her that there was not enough data to ensure safety, however the patient elected to stay on the drug given the substantial clinic benefit she had experienced.

The patient was treated with a 14 day course of amox/clav at 31 weeks gestation for a pulmonary exacerbation. Otherwise her pregnancy was relatively unremarkable. Fetal echocardiogram was initially suggestive of possible coarctation of the aorta, however subsequent imaging and cardiology review ultimately deemed the patient low risk. The patient presented at 33 weeks gestation with preterm premature rupture of the membranes (PPROM). The patient completed a course of corticosteroids and antibiotics.

At 35 weeks the patient noted contractions and multiple complicated decelerations were noted when the patient was placed on a monitor. An emergency cesarean section was performed. The female infant weighed 3.1 kg at birth. APGAR scores were normal. The baby was admitted to the NICU for four days with neonatal hypoglycemia and jaundice. Mother and baby were discharged home subsequently. Both mother and daughter have been doing well since. Breastfeeding is ongoing and has continued for 6 months.

We report two cases of women successfully treated with CFTR modulators in the peri-and post-operative period and throughout breastfeeding. Recently, there has been growing literature supporting the continuation of CFTR modulators through pregnancy.

There have been a number of comprehensive reviews on medication considerations in pregnancy, with a recent focus on CFTR modulators [3]. These new agents have had profound effects on the health of the mother, decreasing disease severity and burden, and thus it has been hypothesized that the infant will receive indirect benefits during pregnancy. There have been previous case reports of rapid decline in pregnant women who abruptly discontinued CFTR modulators [4]. Data both from animal reproduction models, clinical case reports, case series such as this one, and expert recommendations support the ongoing use of CFTR modulators during pregnancy [2]. Rare cases of complications have been reported, however the direct contribution of the agents in question are unclear [5]. Another benefit of CFTR modulators has been an overall improvement in nutritional status and thus the caloric demands of pregnancy and breastfeeding may be less of a concern. Data related to the safety of CFTR modulators during breastfeeding are extremely limited, however both ivacaftor and lumacaftor have been shown to be extracted in breast milk [2]. As elevations in liver enzymes can be seen in patients on CFTR modulators, infant monitoring of liver enzymes can be considered. The two women in this case series breastfed for 6 and 42 months without complication. While both women in this case series were advised to discontinue CFTR modulators during pregnancy, they would likely receive a very different message today, with growing evidence supporting the continuation of CFTR modulators through pregnancy and in breastfeeding. We must however remain mindful that at present, there is a paucity of robust high quality data. Thus, continuation of CFTR modulators during pregnancy and lactation requires careful multi-disciplinary considerations and patient discussion regarding risk and benefit.

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