

# Pregnancy outcomes in cystic fibrosis: a 10-year experience from a UK centre

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## Abstract

**Background:** Cystic fibrosis manifests as a multisystem disease, despite this female fertility is relatively preserved with levels approaching that of the non-cystic fibrosis population. We reviewed pregnancies in cystic fibrosis patients over a 10-year period from a UK adult cystic fibrosis centre by considering maternal and fetal outcomes.

**Methods:** We conducted a retrospective case-note review of pregnancies during 2003–2013 using respiratory and obstetric records.

**Results:** We observed moderate falls in lung function immediately after delivery, which persisted at 12 months postpartum. We found that a decline in lung function at delivery was a marker for further decline in function during the subsequent postpartum period. We found baseline lung function was predictive of gestational age at delivery. We observed a high incidence of haemoptysis.

**Conclusion:** Consistent with current guidance we found pregnancy is feasible and well tolerated in the majority of patients with cystic fibrosis. There was a high incidence of haemoptysis, which warrants further study.

## Keywords

High-risk pregnancy, maternal-fetal medicine, thoracic medicine, complications, perinatal medicine

## Introduction

Cystic fibrosis (CF) is the most common genetic condition in the Caucasian population. CF occurs due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR ion channel facilitates sodium, chloride and bicarbonate transport, and functions as a regulator of surface liquid.<sup>1</sup> CF manifests as a multi-system disease involving the exocrine glands and epithelial tissues of the pancreas, sweat glands and mucous glands of the respiratory, digestive and reproductive tracts.<sup>2</sup>

Advancements in understanding and clinical management of CF have led to a progressive increase in life expectancy, with a predicted mean survival of greater than 50 years for CF patients born in the 21st century.<sup>3,4</sup> Despite the multisystem effects of CF, female fertility is relatively preserved with levels approaching that of the non-CF population.<sup>5,6</sup> As a result pregnancy in CF patients is becoming increasingly relevant, with annual rates increasing dramatically.<sup>3,5,7</sup> In general, outcomes reported in the setting of mild CF disease appear to be successful, and without long-term implications on maternal health or survival.<sup>8,9</sup> Whilst pregnancy can be well-tolerated in CF patients, the additional physiological demands of pregnancy can however lead to deterioration in maternal condition with deleterious effects on maternal and fetal health.<sup>10</sup>

Guidelines advocate optimising preconception respiratory, cardiovascular and metabolic parameters.<sup>8</sup> Poor lung function is commonly cited as the most significant single predictor of maternal morbidity, prematurity and fetal complications.<sup>11–20</sup> Pregnancy is not recommended in significant lung disease (forced expiratory volume in one second (FEV1) <50% predicted) with a low body mass index (BMI), whilst cor pulmonale and pulmonary hypertension are considered absolute contraindications.<sup>6,8,11</sup> Current understanding and antenatal counseling is limited by a paucity of published series. The aim of the current study is to review pregnancies in CF patients over a 10-year period from a UK adult CF centre by considering maternal and fetal outcomes.

## Methods

We performed a clinical database search for all pregnancies occurring in patients with CF at Oxford University Hospitals NHS Trust, UK.

This facilitated a retrospective case-note review of all the pregnancies during the period 2003–2013 at this centre, using both respiratory and obstetric records.

Initial demographics considered were maternal age, BMI, pancreatic status, CF-related diabetes, *Pseudomonas aeruginosa* colonization, pulmonary function using FEV1 and forced vital capacity (FVC) during 6 months prior to pregnancy.

Longitudinal parameters and outcome measures were recorded for outcome of pregnancy, mode of delivery, gestational age at delivery, birth weight, obstetric cholestasis, gestational diabetes, haemoptysis, postnatal depression and pulmonary function at delivery, 6 and 12 months postpartum. All spirometry measures were best-recorded values. Haemoptysis was characterised as fresh bleeding outside the context of exacerbations, occurring during or after (<12 months) pregnancy.

Statistical analysis: descriptive statistics were analysed using SPSS Statistical Packages Social Sciences version 21. The FEV1 and FVC were calculated as percentage predicted values. Pearson's two-tailed correlations were performed, with a p value of <0.05 considered statistically significant.

## Results

Our clinical database search identified 15 singleton pregnancies in eight women. The descriptive statistics are summarized in Table 1. Prior to pregnancy, all women were offered usual adult CF care including at least 3-monthly review by a multidisciplinary team at the CF Centre; women attended for regular CF medical appointments preconception in 11 out of the 15 pregnancy cases. The combined oral contraceptive pill was used prior to pregnancy by six out of eight women; information on prior contraception in the remaining two women was not

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**Table 1.** Descriptive statistics.

Baseline	Mean $\pm$ SD	Range	Median
Age	26.9 $\pm$ 7.1	17.0–38.0	27.0
BMI	24.0 $\pm$ 4.8	13.8–29.9	24.0
FEV <sub>1</sub> %pred	68.10 $\pm$ 16.5	37.0–98.0	70.0
FVC %pred	84.13 $\pm$ 19.8	51.0–124.0	81.9
FEV <sub>1</sub> /FVC	0.78 $\pm$ 0.08	0.64–0.93	0.76
Pancreatic insufficiency			11/15 (73.3%)
CF-related diabetes			2/15 (13.3%)
<i>Pseudomonas aeruginosa</i> colonization			13/15 (86.7%)

BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume; FVC: forced vital capacity.

available. All of the women conceived naturally with no requirement for assisted conception. Patients' vitamin A supplements were modified based on measurement of blood vitamin A levels, in line with UK guidelines on pregnancy in CF.<sup>8</sup> Baseline pulmonary function data were available for 11 out of 15 pregnancies. From this group, eight women had a baseline FEV<sub>1</sub> >60%.

## Baseline cohort characteristics

### Outcome measures

**Obstetric.** Live births accounted for 13/15 of the pregnancy outcomes, with 1/15 stillbirth and 1/15 therapeutic termination. Vaginal deliveries occurred in 7/13 of the cases, with the remaining 6/13 deliveries by caesarean section. Deliveries were classified as preterm (<37 weeks gestational age) for 8/15, with a mean gestational age of 36.0 weeks ( $\pm$ 3.78 range 24–40). Birth weight mean was 2624.6 g ( $\pm$ 940.3 range 964–3842).

**Maternal health complications.** Obstetric cholestasis was reported in 1/15 pregnancy. Three out of 15 pregnancies were associated with the development of gestational diabetes, with further two pregnancies occurring in women with underlying CF-related diabetes (Table 1); all cases of diabetes were managed with insulin therapy and ongoing high-calorie dietary intake, in keeping with UK guidelines.<sup>8</sup> Haemoptysis was recorded in 6/15 (40%) pregnancies (5/8 women 62.5%). The haemoptysis developed during the pregnancy or follow-up (<12 months), with the exception of one patient with pre-existing intermittent haemoptysis, which worsened during pregnancy.

One maternal death occurred from complications of CF, at 9 months following a therapeutic termination at 18-weeks gestation, for the indications of maternal pulmonary hypertension and excessive risk to the mother in continuing the pregnancy; this patient's BMI was 13.8 prepartum. Postnatal depression was observed in 3/8 women.

### Longitudinal pulmonary function

Longitudinal pulmonary function was available for nine out of 15 pregnancies (Table 2). Pulmonary function was reduced at delivery and 6 months postpartum. FVC returned to above baseline values at 12 months follow-up, but a reduction in FEV<sub>1</sub> of 5.77% persisted at 12 months postpartum.

### Correlations

Pearson's correlation identified significant positive correlations between baseline FEV<sub>1</sub> and FVC with gestational age at delivery

**Table 2.** Peripartum pulmonary function in CF (mean  $\pm$  SD).

	Lung function			
	Baseline	Postpartum % changes		
		Delivery	6 months	12 months
FEV <sub>1</sub> %pred	68.10 $\pm$ 16.5	-5.31 $\pm$ 13.3	-4.52 $\pm$ 10.2	-5.77 $\pm$ 6.8
FVC %pred	84.13 $\pm$ 19.8	-6.78 $\pm$ 11.9	-3.01 $\pm$ 13.2	2.37 $\pm$ 11.8
FEV <sub>1</sub> /FVC %pred	78.38 $\pm$ 8.8	-3.73 $\pm$ 7.9	-4.45 $\pm$ 7.5	-3.90 $\pm$ 14.7

FEV<sub>1</sub> pred: predicted forced expiratory volume in one second; FVC pred: predicted forced vital capacity.

( $r=746$ ,  $p=013$  and  $r=859$ ,  $p=003$ , respectively), demonstrating that higher baseline pulmonary function was significantly associated with a longer gestation period. Gestational age at delivery was found to be associated with FEV<sub>1</sub>/FVC at 12 months ( $r=950$ ,  $p=004$ ): the longer the gestation period, the more preserved the FEV<sub>1</sub>/FVC at 12 months postpartum.

Reductions at delivery of both FEV<sub>1</sub> and FVC were associated with greater reductions in FEV<sub>1</sub> at 6 months postpartum ( $r=765$ ,  $p=017$  and  $r=669$ ,  $p=049$ , respectively). FVC reductions at 6 months were correlated with greater reductions in FEV<sub>1</sub> and FVC at 12 months ( $r=844$ ,  $p=035$ ,  $r=825$ ,  $p=043$ ).

## Discussion

Here we report a single-centre retrospective study of pregnancy outcomes in CF. Consistent with current guidance we found pregnancy to be feasible and well-tolerated in the majority of patients with CF. In keeping with other recent studies,<sup>14,16,21</sup> we observed that pregnancy is occurring at an older age (mean 26.9 years) with lower lung function (mean FEV<sub>1</sub> 68.1%) than noted in older studies.<sup>11</sup> Indeed, pregnancy most commonly occurs in relatively mild CF, with recent UK data showing that 58.1% CF pregnancies occurred with FEV<sub>1</sub> >60%.<sup>3</sup> We did however observe moderate falls in FEV<sub>1</sub> immediately after delivery, which persisted at 12 months postpartum (Table 2). In comparison, annual declines in FEV<sub>1</sub> of 0.65–1.65% have been reported in another UK Centre for comparable (non-pregnant) birth cohorts albeit at an earlier age (18–22 years).<sup>22</sup> Although the lack of matching to our pregnant cases precludes definitive conclusions, it is likely that our observed rate of FEV<sub>1</sub> decline postpartum is significantly greater than expected in non-pregnant patients. Not unexpectedly, we found that a decline in lung function at delivery was a marker for further decline in function during the subsequent postpartum period.

We found baseline FEV<sub>1</sub> and FVC measures to be significantly associated with gestational age at delivery. Recent UK data also found FEV<sub>1</sub> to be significantly associated with gestational age at delivery.<sup>21</sup> We reported high rates of preterm (46.7%) and CS (46.15%) deliveries. This is in keeping with data from most other studies,<sup>11,12</sup> although differs from a recent report from Burden et al.<sup>21</sup> of 100% vaginal deliveries, reflecting the multifactorial indications for CS.

The frequent finding of haemoptysis (in five out of eight women) outside the usual setting of pulmonary exacerbations is noteworthy and has not been reported in previous studies. This may simply be a chance finding reflecting the relatively small size of our cohort, although it warrants further investigation in a larger population sample. Pregnancy-related haemoptysis has previously been described as a distinct entity.<sup>23</sup> There are suggestions that the associated increased cardiac output and pregnancy-related hormonal changes may trigger abnormal bronchial vessel development, expansion of pulmonary arteriovenous malformations and recanalisation of vessels.<sup>23–25</sup>

In addition to the physiological impact of pregnancy in CF, the psychosocial implications must also be considered. Although estimates

vary, clinical prevalence of postnatal depression is reported as 13%.<sup>26</sup> In our cohort we reported that 37.5% of our patients suffered with postnatal depression, reflecting the need for maximum support from a multidisciplinary CF team beyond management of physical disease.

Despite reports of successful pregnancies in women with FEV1 <60% in the setting of CF,<sup>27</sup> current guidelines do not recommend pregnancy with an FEV1 <60%.<sup>8</sup> Despite this, 19.7% pregnancies occur with FEV1 <40%, and 22.2% with FEV1 40–60%.<sup>3</sup> Pregnancy in one of our patients with severe disease and very low BMI resulted in therapeutic termination and subsequent maternal death 9 months later. This case is similar to a report from the recent French CF literature.<sup>28</sup> It remains challenging to reliably predict adverse outcomes based on available maternal factors. There is an urgent need for data on women with more advanced disease to enable appropriate antenatal care and risk prediction.

Even with good outcomes, pregnancy in CF is associated with higher rates of exacerbation and hospitalization.<sup>29</sup> The success of pregnancy is reliant on integrated care from a multidisciplinary team of CF specialists, obstetricians, geneticists, obstetric anaesthetists, dietitians and fetal medicine experts. With the continuing improvement in survival rates, pregnancy management in CF will increasingly become a routine part of care for many patients. Large, prospective studies of maternal and fetal outcomes are needed in order to inform optimal management of pregnancy in this patient group.

### Declaration of conflicting interests

The authors declare there is no conflict of interest.

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### Ethical approval

This study comprises a retrospective assessment of clinical course and outcome of anonymised patients who had received usual clinical care, without randomisation or experimental intervention, and hence did not require ethical approval or patient consent.

### Guarantor

SJ Chapman.

### Contributorship

MR and SJC conceived and designed the study. MR and LP performed data collection. MR performed data analysis. MR and SJC drafted the manuscript. All authors read and commented on the final manuscript.

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