Pregnancies and Outcome in Women with Cystic Fibrosis

Asher Barak MD[1], Mordechai Dulitzki MD[2], Ori Efrati MD[1], Arie Augarten MD[1], Amir Szeinberg MD[1], Nira Reichert MD[1], Dalit Modan MD[1], Batia Weiss MD[1], Mervin Miller MD[1], Daniel Katzanelson MD[1] and Yaacov Yahav MD[1]

[1]National Cystic Fibrosis Center, Safra Children's Hospital, and [2]High Risk Pregnancy Unit, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Abstract

Background: Along with the increased life expectancy in cystic fibrosis and the remarkable progress in its management and therapy, issues of female fertility and pregnancy are frequently raised. These include infertility, severity of lung disease, pancreatic insufficiency, poor nutritional status, glucose intolerance and diabetes, drug safety, and long-term maternal and neonatal outcome.

Objective: To describe the experience of our CF center in the management of CF pregnant woman from 1977 to 2004.

Methods: We analyzed 27 years of records (1977–2004) of the national CF registry of all CF women who wished to conceive and became pregnant.

Results: Eight CF women (mean age 24 ± 4.5 years) who wished to conceive had 11 pregnancies and delivered 12 neonates. The pregestational results of forced expiratory volume per 1 second varied significantly among patients (59 ± 23%), yet most (10/11) stayed stable throughout the pregnancy course. Maternal deterioration in CF condition occurred in only one mother, necessitating cesarean section. In 9 of the 11 pregnancies the women were pancreatic-insufficient. Of the 11 pregnancies, 2 CF women had diabetes mellitus and 3 developed gestational diabetes. One pregnancy occurred in a mother with a transplanted lung. Of the 12 neonates, 3 were preterm and one was born with esophageal atresia. No miscarriages, terminations or neonatal mortalities occurred. Although most of the CF mothers had FEV_1 below 55% before pregnancy, the maternal and neonatal outcome was favorable and lung function tests generally remained stable.

Conclusions: We conclude that pregnancy in CF is feasible with a positive maternal and neonatal outcome. Early participation of the CF physician in the wish of the CF woman to reproduce is required. The integration of an intensive multidisciplinary approach during pregnancy, which includes close follow-up of maternal and fetal condition by the various specialists, should ensure an optimal outcome.

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The life expectancy of patients with cystic fibrosis has doubled in the last 20 years, with a current average age of nearly 33 years and more than one-third of the total CF population being over the age of 16. More CF women having reached their reproductive period wish to conceive and seek information regarding pregnancy [1–7]. In the past, all pregnancies in CF women were considered risky [8], however more recent data suggest that pregnancy risk correlates with disease severity, and reproductive issues are currently managed as part of the routine work in medical CF centers [1–3,5].

CF = cystic fibrosis
FEV_1 = forced expiratory volume per 1 sec

Cystic fibrosis affects many organs, all of which may in turn affect pregnancy, but it is pulmonary deterioration and complications that play a major role in the morbidity and mortality of the CF pregnant woman. Limited lung disease (FEV_1 >50%) is associated with favorable outcome [6]. Acute deterioration of pulmonary function may be associated with higher morbidity and mortality for both mother and fetus, thus routine and thorough evaluations of the CF pregnant mother with repeated lung function tests should be performed on a monthly basis, with aggressive management of pulmonary infections when needed [3].

Many other clinical problems may affect maternal and neonatal outcome, including infertility issues, physiologic adaptations to pregnancy, pancreatic and nutritional status, diabetes and glucose tolerance, and CF-related liver disease [6]. Other issues influencing pregnancy in CF still need to be studied, such as ethical and psychological issues (e.g., maternal and emotional fear and stress), tolerance and risk of physiotherapy in the pregnant CF woman, medical aspects in the organ-transplanted CF woman [9,10], and possible long-term effects on the infants [6].

The complex management of CF pregnancy has shown that a multidisciplinary approach is required [3,6]. This multidisciplinary approach includes pre-conception screening, close surveillance, aggressive management, and a well-interconnected team approach in order to achieve the best pregnancy outcome. We describe our experience with the management of CF women during their pregnancies and labors, focusing on maternal medical and obstetric status and neonatal outcome following the delivery; and discuss the feasibility of pregnancy in CF women and the importance of the multidisciplinary approach.

Materials and Methods

We performed a retrospective survey of CF pregnancies during 1977–2004 in our CF center. All women were previously diagnosed with CF according to evolving CF symptoms, positive sweat tests and mutation analysis. Patient 1 was diagnosed as having CF by means of clinical symptoms (bronchiectatic lung disease) and positive sweat test results [Table 1]. CF women who wished to reproduce and became pregnant were assessed. General and clinical data during pregnancy and following labor were noted, including CF genotype, body weight and nutritional condition, severity of lung disease with variations in pulmonary function (specifically sputum cultures), exocrine and endocrine pancreatic function, liver disease, diabetes, complications during pregnancy

Table 1. Characteristics of CF disease, pregnancies and neonatal outcome

Patient	Mutation	Age at pregnancy (yrs)	Pre/Post* pregnancy FEV_1	Pre/Post** pregnancy BMI	Pancreatic disease***	Maternal and neonatal comments
1	–	19	32/32	–	PS	Preterm
		21	31/33	–	PS	Preterm (32 wk)
2	W1282X/G85E	24	53/46	18/20	PI	–
		28	32/27	18/18	PI, DM	–
3	ΔF508/ΔF508	19	35/22	22/21	PI	Respiratory deterioration; Preterm labor (30 wk)
4	Q359, T360/Q359, T360	21	84/78	21/21	PI	–
		23	77/65	21/21	PI, GD	Term twins
5	W1282X/G542X	34	54/54	22/21	PI, GD	–
6	W1282X/?	25	88/90	17/18	PI, DM	Lung-transplanted CF Esophageal atresia
7	ΔF508/ΔF508	29	51/44	17/17	PI	–
8	W1282X/G85E	29	73/	20/20	PI, GD	CF-related liver disease
8 patients		24 ± 4.5	54 ± 22/49 ± 23	20 ± 2/20 ± 1		12 neonates

* Mean FEV_1 results pre/post-pregnancy

** Mean BMI results pre/post-pregnancy

*** Exocrine pancreatic disease (PS, PI) and endocrine disease (DM, GD)

BMI = body mass index, PS = pancreatic sufficient, PI = pancreatic insufficient, DM = diabetes mellitus, GD = gestational diabetes.

(bleeding, toxemia), labor modality, and maternal and neonatal long-term outcome. Body mass index and forced expiratory volume per one second were regularly evaluated prior to pregnancy and during pregnancy on a monthly basis from the first month of pregnancy until 9 months after delivery. Long-term outcomes were retrieved from patients' data. Average and standard deviation values pre-pregnancy and 9 months after delivery were used to assess patients. The results of various evaluations and case management coordinated by the CF physician were noted, and reports of the bi-monthly multidisciplinary follow-up by the CF team were analyzed.

Results

The national CF center followed and evaluated eight CF women (age 24 ± 4.5 years) who wished to conceive; all became pregnant. Complete data were retrieved from all 11 pregnancies, resulting in the delivery of 12 neonates (including twins). Nine of the 12 were full-term neonates and 3 were premature (gestational age 30–32 weeks) [Table 1].

Genetic analysis

Genetic analysis for CF mutations was performed in the pre-marriage or pre-conceptive period. Six of the eight CF mothers carried severe CF mutations (W1282X or ΔF508). All eight spouses were tested and found to be negative. A genetic consultation was held with the parents and isolated genetic risks for the child and all genetic issues were discussed. None of the neonates were affected with CF.

Spontaneous pregnancies versus assisted reproductive techniques

All pregnancies were conceived spontaneously. Two of the eight women (patient 4, second pregnancy, and patient 8) deliberately opted for intrauterine insemination to facilitate immediate gestation; in one of them, twins were conceived.

Disease characteristics of CF mothers

- *Lung disease:* Pregestational FEV_1 results varied significantly among patients (59 ± 23%), yet stayed stable throughout the pregnancy course in most (10/11). Initial FEV_1 results were <50% in 4 of the 11 pregnancies; pre-labor FEV_1 results were below 50% in 6 but long-term follow-up showed improvement and re-stabilization in 5 of these 6 pregnancies. Only in one of the six (patient 3) was a severe deterioration of CF lung disease observed (from FEV_1 34% to 22%) with respiratory infections and hypoxia. This patient required hospitalization and oxygen supplement from the beginning of the second-trimester until preterm labor. Cesarean section was performed at 30 weeks gestational age. This patient underwent lung transplantation 15 months post-delivery.
- Sputum cultures of all patients were colonized with *Pseudomonas aeruginosa*; 2/11 had Aspergillus sp, but without evidence of active infection. None of the CF women had *Burkholderia cepacia*.
- One woman (patient 6) conceived 2 years after receiving a lung transplant and exhibited good lung function during pregnancy (FEV_1 82%). In the 10th gestational week she was diagnosed with cytomegalovirus pneumonitis (on lung biopsies) and antigemia and was treated with ganciclovir for the rest of the pregnancy.
- *Exocrine pancreatic insufficiency:* During 9 of the 11 pregnancies 7 of the 8 CF women were pancreatic-insufficient, and only one (patient 1 with two pregnancies) was pancreatic-sufficient.
- *Gestational diabetes and diabetes mellitus:* Two of the 11 pregnancies were in CF women who had diabetes mellitus prior to pregnancy. In another three women, gestational diabetes developed and

was controlled by diet only, but after delivery these women became normoglycemic.

- *Liver disease:* One CF woman had CF-related liver disease prior to the pregnancy (patient 8). Liver enzymes remained mildly elevated throughout the pregnancy course. Liver enzymes were tested and found normal throughout all the other pregnancies.

Obstetric data

The overall pregnancy course was good, with no obstetric complications such as vaginal bleeding, placental rupture, hypertension, preeclampsia, toxemia, maternal vulvovaginitis, miscarriages or stillbirths. There were no maternal or neonatal mortalities documented.

Vaginal delivery vs. cesarean section

Eight of the 11 pregnancies resulted in normal spontaneous vaginal deliveries, while 3 ended in cesarean section: one was elective (patient 6), one had twins at breach presentation (patient 4), and one was due to fetal distress with evolving maternal respiratory failure because of severe lung disease (patient 3).

Neonatal outcome

Eleven of the 12 neonates were born healthy. One child, born to the lung-transplanted CF mother (patient 6), had esophageal atresia, which was successfully corrected on the second day of life.

Drug safety during conception, pregnancy and lactation

Medications were administered to all CF women based on drug and drug-interaction safety directives and adapted to the accumulated knowledge of drug teratogenicity and embryotoxicity. Various medications were used, including oral medications (ciprofloxacim, cephalexin, azithromycin, ursodeoxycholic acid, and pancreatic enzyme replacement therapy), inhaled (terbutaline or salbutamol, salmeterol or formeterol, budesonide or fluticasone, gentamicin or colistimitate, rhDNase), and systemic (ceftazidime, meropenem, insulin). No drug complications were noted in CF mothers or their neonates.

Discussion

The management of CF pregnancies engages a variety of medical disciplines. The integration and coordination of all these disciplines is crucial and starts at the pre-conceptive stage with genetic consultation. This includes analysis of the spouse's CF carrier state, the heredity pattern, and elaborate antenatal diagnosis. Genetic consultation was previously advocated to assure the best neonatal outcome and to prevent and prepare for the possible birth of a CF infant [2,5,6,11–13]. Still, several births of CF neonates to CF mothers have been reported [14,15].

Along with the wish to conceive, CF parents and physicians confront major ethical issues regarding abortion, premature termination of pregnancy, and possible arrangements in the event of morbidity or maternal mortality [2,6] – all of which should be discussed prior to pregnancy.

Currently, fertility issues in CF women are not considered an obstacle in their wish to conceive. Spontaneous pregnancies are feasible, yet delayed contraception may occur due to viscid secretions in the uterine cervix [6]. Once the woman is pregnant, a protocol of high risk management should be performed by a specialized high risk obstetrician.

CF is characterized by various disease factors, including deterioration of lung disease, diabetes mellitus, poor nutritional status, and pancreatic insufficiency among others, all affecting the general pregnancy course. The severity of CF lung disease is believed to be the most significant factor influencing maternal and neonatal outcome, and is sometimes suggested to contraindicate pregnancy [6]. Although there are no absolute guidelines, several parameters were suggested as indicative for poor maternal outcome, such as pregravid forced vital capacity <60% [19], FVC <50% [20], FEV_1 <70% [21] and FEV_1 <50% [6]. However, despite these findings, several cases of good maternal outcome have been reported. In our experience 8 of the 11 pregnancies with low initial FEV_1 < 55% (patients 1,2,3,5, and 7) were still compatible with good maternal outcome. Repeated visits to the CF unit – which included room air saturation tests, extended lung function tests (lung volumes and spirometry), sputum cultures, adjusting appropriate oral/inhaled and/or systemic antibiotic therapy, chest physiotherapy or even oxygen therapy – were intensively used to treat and stabilize pregnant CF women.

There are a few reports of pregnancies in lung-transplanted recipients [22–24], but scarce reports of pregnancies in lung-transplanted CF women [9,10]. Results of those studies demonstrate higher pregnancy and rejection risks when compared with other solid organ transplant recipients. Maternal risks include shortness of breath, lung infection and lung rejection (up to 38%). Fetal/neonatal risks include therapeutic or spontaneous abortions, prematurity and low birth weight [10]. In our CF patient with lung transplant (patient 6), cytomegalovirus pneumonitis occurred during the pregnancy and was treated with ganciclovir from the second trimester until delivery, with good neonatal outcome.

Initial reports of CF pregnancies were mostly in pancreatic-sufficient women. Pancreatic insufficiency, poor pre-pregnant body weight, and poor maternal weight gain were initially considered markers of CF disease severity and were associated with poor pregnancy outcome. However, due to improved nutritional status, more pancreatic-insufficient CF patients are reported to have successful pregnancies [6,14]. Most of the pregnancies in our study (9/11) were in pancreatic-insufficient women with stable body mass index [Table 1] and resulted in a good outcome. In CF patients with diabetes mellitus and gestational diabetes, both the mother and the infant had a significant adverse outcome, as in non-CF pregnancies [6,25].

Drug safety during conception, pregnancy and lactation plays an important role in the assessment of possible fetal and maternal risk. All medications and drug interactions should be evaluated by the CF physician and clinical pharmacist to assure both maternal and neonatal safety. The medication chosen should be adopted according to accumulated data and drug safety guidelines regarding

FVC = forced vital capacity

teratogenicity and embryotoxicity. In all cases drug safety should always be weighed against maternal benefits.

Preterm delivery is considered the most common neonatal complication (up to 24%) in patients with severe CF disease and complications such as severe lung disease, diabetes and liver disease [13,15]. Of the 12 infants in our study, 3 (25%) were preterm (<32 weeks) born to two mothers with severe lung disease.

Our study of CF pregnancy and long-term maternal outcome demonstrates that pregnancy does not affect overall disease severity and/or maternal survival, as compared to the entire adult female CF population [16,17]. The decline in FEV_1 and FVC was found to be similar to that in a comparable CF population [14] and is considered retainable [18]. Only a few authors reported maternal death in the year following pregnancy, mainly in women with severe lung disease and pregestational FEV_1 <50% [8].

In order to optimize maternal and neonatal outcome in pregnant CF women, intensive individual multidisciplinary case management, as described briefly here and mentioned in other studies [6,11], is recommended. Our multidisciplinary team followed each pregnant CF patient and coordinated all decisions with a variety of specialists. Each CF pregnant woman visited the CF Unit, supported by the high risk pregnancy unit, on a bi-monthly basis for evaluation and treatment. Team work was coordinated by a CF physician who managed the patient's treatment and follow-up plan. Our team included a genetic consultant, high risk obstetrician, clinical pharmacist, endocrinologist, gastroenterologist, medical dietician, physiotherapist, psychologist and social worker. The multidisciplinary team continuously discussed individual medical developments and decisions regarding each CF mother, labor and fetal condition. Treatments were adapted accordingly and results were communicated among specialists and documented.

In summary, our experience shows that pregnancy in CF females is feasible with a positive maternal and neonatal outcome. For CF women wishing to reproduce and who have a variety of medical problems affecting many organs, an intensive individual multidisciplinary case management should be adopted to ensure the immediate and long-term best maternal and neonatal outcome.

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Correspondence: Dr. A. Barak, Pediatric Pulmonary Unit, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 52625, Israel.
Phone: (972-3) 530-2884/218
Fax: (972-3) 534-5914
email: ashbar@netvision.net.il

I live in that solitude which is painful in youth, but delicious in the years of maturity

Albert Einstein