Pregnancies and Outcome in Women with Cystic Fibrosis

Asher Barak MD1, Mordechai Dulitzki MD2, Ori Efrati MD1, Arie Augarten MD1, Amir Szeinberg MD1, Nira Reichert MD1, Dalit Modan MD1, Batia Weiss MD1, Mervin Miller MD1, Daniel Katzanelson MD1 and Yaakov Yahav MD1

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

Key words: cystic fibrosis, pregnancy, multidisciplinary approach, outcome

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 gestational age 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 FEV1 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.

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 (FEV1 >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 fears 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
<th>Age at pregnancy yrs</th>
<th>Pre/Post pregnancy FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Pre/Post** pregnancy BMI</th>
<th>Pancreatic disease***</th>
<th>Maternal and neonatal comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>19</td>
<td>32/32</td>
<td>–</td>
<td>PS</td>
<td>Preterm</td>
</tr>
<tr>
<td>2</td>
<td>W1282X/G85E</td>
<td>24</td>
<td>53/46</td>
<td>18/20</td>
<td>PI</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>AF508/AF508</td>
<td>19</td>
<td>35/22</td>
<td>22/21</td>
<td>PI</td>
<td>Respiratory deterioration; Preterm labor (30 wk)</td>
</tr>
<tr>
<td>4</td>
<td>G359, T360/G359, T360</td>
<td>21</td>
<td>84/78</td>
<td>21/21</td>
<td>PI</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>W1282X/G542X</td>
<td>23</td>
<td>77/65</td>
<td>21/21</td>
<td>PI, GD</td>
<td>Term twins</td>
</tr>
<tr>
<td>6</td>
<td>W1282X?</td>
<td>34</td>
<td>54/54</td>
<td>22/21</td>
<td>PI, GD</td>
<td>Lung-transplanted CF Esophageal atresia</td>
</tr>
<tr>
<td>7</td>
<td>AF508/AF508</td>
<td>29</td>
<td>51/44</td>
<td>17/17</td>
<td>PI</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>W1282X/G85E</td>
<td>29</td>
<td>73/1</td>
<td>20/20</td>
<td>PI, GD</td>
<td>CF-related liver disease</td>
</tr>
</tbody>
</table>

8 patients 24 ± 4.5 54 ± 22.49 ± 23 20 ± 2/20 ± 1 12 neonates

* Mean FEV<sub>1</sub> 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, and 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 AF508). 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: Premarital FEV<sub>1</sub> results varied significantly among patients (59 ± 23%), yet stayed stable throughout the pregnancy course in most (10/11). Initial FEV<sub>1</sub> results were <50% in 4 of the 11 pregnancies; pre-labor FEV<sub>1</sub> 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 patients was a severe deterioration of CF lung disease observed (from FEV<sub>1</sub> 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<sub>1</sub> 82%). In the 10th gestational week she was diagnosed with cytomegalovirus pneumonitis (on lung biopsies) and antiretroviral therapy was started with ganciclovir for the rest of the pregnancy.
- Exocrine pancreatic insufficiency: During 9 of the 11 pregnancies of the 8 CF women were pancreatic-insufficient, and only one patient (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 embroyotoxically. Various medications were used, including oral medications (ciprofloxacin, cephealexin, azithromycin, ursooxycholic acid, and pancreatic enzyme replacement therapy), inhaled (terbutaline or salbutamol, salmeterol or formoterol, budesonide or fluticasone, gentamicin or colistimiate, 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-conception stage with genetic consultation. This includes analysis of the spouses 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 pred gravid forced vital capacity <60% [19], FVC <50% [20], FEV1 <70% [21] and FEV1 <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 FEV1 <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 these 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 abotions, prematurity and low birth weight [10]. In our CF patient with lung transplant (patient 6), cytomegalovirus pneumonia 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
tenatogenicity and embrittoxicity. 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 FEV1 and FVC was
found to be similar to that in a comparable CF population [18] and
is considered remittable [19]. Only a few authors reported maternal
death in the year following pregnancy, mainly in women with severe
lung disease and pregestational FEV1 <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 patients 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
unit continuously discussed individual medical developments and
decisions regarding each CF mother, labor and fetal condition.
Treatments were adapted accordingly and results were commu-
nicated 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 multi-
disciplinary case management should be adopted to ensure the
immediate and long-term best maternal and neonatal outcome.

Acknowledgments. The authors thank the cystic fibrosis team for their
cooperation. D. Vilozni, O. Yona, B. Kochavi, K. Shalev, Y. Sofer, and
particularly A. Zelis.

References
2. Hilman BC, Altkein MI, Constantinescu M. Pregnancy in patients with
4. Willett MI, Ellis AG. Reproductive health in women with cystic fibrosis.
5. Odegaard I, Stray-Pedersen B, Halberg K, Haaneaas OC, Stormosten OT.
Johannesson M. Prevalence and outcome of pregnancies in Norwegian
and Swedish women with cystic fibrosis. *Acta Obstet Gynecol Scand*
6. Edenhorporugh FP. Women with cystic fibrosis and their potential for
8. Kent NE, Farquharson DF. Cystic fibrosis in pregnancy. *Can Med Assoc J*
Transplantation Pregnancy Registry: outcomes of pregnancies in lung
11. Michel SH, Mueller DH. Impact of lactation on women with cystic fibrosis
12. Edenhorporugh FP, Mackenzie WE, Stoborough DE. The outcome of 72
pregnancies in 55 women with cystic fibrosis in the United Kingdom
13. Odegaard I, Stray-Pedersen B, Halberg K, Haaneaas OC, Stormosten OT.
Johannesson M. Maternal and fetal morbidity in pregnancies of
Norwegian and Swedish women with cystic fibrosis. *Acta Obstet Gynecol
15. Gillet D, de Breukeler B, Bellis G, Durieu I. Cystic fibrosis and
170–4.
17. Goss CH, Rubenfeld GD, Otto K, Atiker ML. The effect of pregnancy on
18. Edenhorporugh FP, Stoborough DE, Mackenzie WE. Pregnancy in women
880–3.
22. Parry D, Hewat J, Robinson V, Banner N, Yacoub M. Pregnancy
1164–5.
23. Parry D, Hewat J, Banner N, Robinson V, Yacoub M. Pregnancy
24. Donaldson S, Novotny D, Paradowsky L, Atri R. Acute and chronic lung

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*