Patients becoming parents-
Fertility and pregnancy in CF

Michal Shteinberg
Pulmonology Institute and CF Center
Carmel Medical Center
Technion- Israel Institute of Technology,
the B. Rappaport Faculty of Medicine
The story of Ibrahim and Ines

• Brother and sister with CF (N1303K/N1303K). Both- PA colonization. Ibrahim- also CFRD; past ABPA
• Ages- 28, 26
• Ibrahim- father of healthy 10 month old boy
• Ines- mother of 12 month girl with CF (N1303K/5T)
Outline

• Fertility in CF
  – Men
  – Women

• Pregnancy in CF
  – Physiologic changes in pregnancy
  – CF care during pregnancy:
    • Drug safety
    • Obstetric and Respiratory complications

• Delivery
Pregnancy and Delivery in a Patient with Cystic Fibrosis of the Pancreas

Report of a case

BERNARD SIEGEL, M.D., and SEYMOUR SIEGEL, M.D.

In recent years there has been a marked increase in medical writing on cystic fibrosis of the pancreas in young adults. This condition was originally considered to be uniformly fatal in the early years of life, but it is now known that many afflicted patients live well beyond this period. Milder degrees of involvement undoubtedly account for some long survivals; also responsible are modern antibiotics, better understanding of the pathology, and early diagnosis.

Even so, survival to adulthood is still uncommon. Beyond this, for conception to occur in the afflicted young adult, and for the pregnancy to be carried to term and delivery must be rare indeed, for we have found no previously reported case.

The disease was first described in 1936 by Fanconi in Switzerland. It is a hereditary disease due to dysfunction of the exocrine glands characterized by chronic pulmonary disease, pancreatic deficiency, abnormally high sweat electrolytes, and sometimes cirrhosis of the liver. A marked impetus was given to interest in the disease with the appearance of the sweat test in the early 1950's as a simple, reliable, diagnostic tool. Symptoms are primarily those resulting from involvement of the respiratory tract and gastrointestinal tract, but different degrees of involvement of each may produce vastly different clinical pictures. Fatalities seem to result primarily from extensive pulmonary involvement. Our case seemed to have less severe involvement confined to the respiratory system.

CASE REPORT

The patient was a 20-year-old white female who first developed a persistent cough following an attack of measles at age 12. Prior to this she had been perfectly well with no marked gastrointestinal or respiratory symptoms. The cough at first was not severe, with slight expectoration of mucus. At age 15 she had an attack of pneumonia which was followed by an increase in her cough and expectoration, which persisted and grew worse. In 1955 she was hospitalized for 1 month as a tuberculosis suspect because of the appearance of the chest X-ray. Studies at that time, including bronchoscopy, revealed no malignancy or acid-fast bacilli. Bronchograms showed diffuse cylindrical bronchiectasis.

The cough persisted and was intermittently productive of large amounts of mucoid material, but the patient was otherwise clinically well with good appetite and normal physical and sexual development. She married at age 19 and shortly thereafter became pregnant. Physical examination prior to pregnancy revealed a thin, fairly well-developed, young white female in no acute distress, with blood pressure, 100/70; T, 98.6°. The chest was somewhat emphysematous with "sticky" rales present throughout. Respiration was effortless with slight prolongation of expiration, but with no use of the accessory muscles. The heart showed a normal sinus rhythm, no murmurs, and P 2 greater than A 2. The abdomen was negative, and there was
Trend in the number of pregnant women with cystic fibrosis per 100,000 deliveries

Patel, EM. et al. (2015), Medical and obstetric complications among pregnant women with cystic fibrosis American Journal of Obstetrics & Gynecology, 212 :1; 98.e1 - 98.e9
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The story of Ibrahim and Ines

- Ibrahim- underwent TESE in Oct 2015
- (TEsticular Sperm Extraction)
- Requires general anesthesia
- IVF; usually ICSI
- due to small amount of sperm retrieved
The story of Ibrahim and Ines

- Ines underwent 2 years of fertility treatments
- Partner found to be carrier of IVS95T
- Couple consulted and decided not to undergo PGD
- 2/2016- pregnancy with IVF
- FEV₁ 60-65% pre-pregnancy
Infertility in Cystic Fibrosis

• Male CF infertility is (almost) universal and due to CBAVD¹
• Reduced fertility has also been observed in women with CF²
• First report – 1973 - thick cervical mucus³,⁴,⁵
• CF patient successfully treated with intrauterine insemination (1986) ⁴,⁵

2 Kopito LE et al., 1973 Water and electrolytes in cervical mucus from patients with cystic fibrosis. Fertil Steril 24:512–516
CF and the female reproductive system

• Expression of CFTR in multiple female reproductive tissues as well as the hypothalamic-pituitary-gonadal axis \(^1\)

• Endocrine disorders found in CF women with infertility \(^2\) - lower AMH \(^3\)

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2. Johannesson M et al., 1997; *Cystic fibrosis mRNA expression in rat brain: cerebral cortex and medial preoptic area. Neuroreport* 8:535–539
Sub/infertility among CF women

• Multicenter study (7 centers in Israel+ Lyon, Milan, Belfast)
• 524 adult women with CF
• Retrospective review of fertility and seeking assisted reproduction
Sub/infertility among CF women

- Women attempting pregnancy- 195
- Sub/infertility- 68 (35%); normal- 127
- 2 hr OGTT significantly higher among sub/infertile (108 vs 62 mg%, $P=0.019$)
- Lung function, PA, Exacerbations- no correlation
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The story of Ibrahim and Ines-Pregnancy

- 4/2016 stopped physiotherapy after IVF
- 2 exacerbations 1 month apart-treated with ceftazidime
- Gained 4 kgs during pregnancy
- Constipation in the last trimester-managed with stool softener
- 1 year post delivery- not gained back lung function ($\text{FEV}_1 = 55\%$)
Physiologic changes in pregnancy

- Upper airway congestion, rhinitis - more common - up to 20% of gravid women
- Increase in minute ventilation (progesterone); often a sense of dyspnea

From: Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. Anesthesiology 26:381, 1965
Physiologic changes in pregnancy

- Change in lung volumes- TLC, FRC, RV decreased
- Decrease in FVC- 18%, or 300-500 ml; FEV\textsubscript{1} – no change
- Slowed intestinal transit
- Constipation- common (may aggravate DIOS)
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Safety of Drugs during Pregnancy and Breastfeeding in Cystic Fibrosis Patients

Alice Panchaud\textsuperscript{a}  Ermindo R. Di Paolo\textsuperscript{b}  Angela Koutskokera\textsuperscript{c}
Ursula Winterfeld\textsuperscript{d}  Etienne Weisskopf\textsuperscript{a}  David Baud\textsuperscript{e}  Alain Sauty\textsuperscript{c}
Chantal Csajka\textsuperscript{a}

\textsuperscript{a}School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Geneva, \textsuperscript{b}Service of Pharmacy, Department of Laboratory, \textsuperscript{c}Service of Pneumology, Department of Medicine, \textsuperscript{d}STIS and Division of Clinical Pharmacology, and \textsuperscript{e}Materno-Fetal and Obstetrics Research Unit, Department of Gynecology and Obstetrics, University Hospital of Lausanne, Lausanne, Switzerland
Drug safety

• Inhaled agents- minimal absorption, recommend to continue

• Systemic antimicrobials:
  – Penicillins, cephalosporins and macrolides are first-line treatments during pregnancy
  – Clindamycin, sulfonamides, trimethoprim, and co-trimoxazole- second choice
  – Aminoglycosides- small risk of fetal oto- and nephrotoxicity; reserved for life threatening infections. OK to use inh. Tobramycin
  – Quinolones have been associated with irreversible damage of joint cartilages in young animals treated directly (i.e. none resulting from in utero exposure); recommended to use well documented Ciprofloxacin
  – Antifungals- high doses of Azoles- teratogenic (animal studies); itraconazole, fluconazole- first choice.

Drug safety

- SABA, LABA - reports associated with fetal malformation - possibly effect of asthma. Probably safe - use most established (salbutamol/albuterol for SABA; salmeterol or formoterol for LABA;)

Drug safety

• UDCA- No malformations reported, but scarce data do not allow a proper risk assessment. Thus, this drug should be avoided during the first trimester of pregnancy.

• Vit A- A teratogenic effect similar to retinoids has been associated with high doses of vitamin A (>25,000 UI). A daily dose of <10,000 UI is considered safe

Drug safety

• **Cyclosporine** is one of the best-studied immunosuppressants during pregnancy. While **tacrolimus** is also compatible with pregnancy, **mycophenolate** should be avoided.

Panchaud A et. al., *Safety of Drugs during Pregnancy and Breastfeeding in Cystic Fibrosis Patients.* Respiration 2016;91:333-348
Letter to the Editor

A successful uncomplicated CF pregnancy while remaining on Ivacaftor

Rachel Kaminski a,b,*, Dilip Nazareth a,b

* Bristol Adult Cystic Fibrosis Centre, University Hospitals Bristol NHS Foundation Trust, Upper Maudlin Street, Bristol BS2 8HW, United Kingdom
b University of Bristol, United Kingdom

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Keywords: Cystic fibrosis; Pregnancy; Ivacaftor

Sir,

The survival of patients with Cystic fibrosis (CF) has improved dramatically. As more children become adults, issues such as fertility and pregnancy become more important in adult CF care. It is now, not uncommon, for a woman with CF to complete a successful natural delivery.

More recently selective potentiators of the CFTR protein have changed the spectrum of CF management and have significantly benefitted those patients with specific genetic mutations such as G551D. One such drug, Ivacaftor (Kalydeco®), licensed in the treatment of appropriate CF patients has been shown to significantly increase lung function and reduce the burden of CF related co-morbidities [1].

Ivacaftor during pregnancy and during breastfeeding. Subsequently, she made an informed decision to continue the drug during her pregnancy, due to gains in her lung function and quality of life while on the drug. She did not experience any side effects during her pregnancy, her lung function remained stable (average FEV1: 95%) and she required 2 courses of oral antibiotics during her pregnancy.

At 39 weeks, she was delivered of a baby girl (7 lb 8 oz) by a normal uncomplicated spontaneous vaginal delivery. Both mother and baby did well following their hospital stay of <24 h and the mother has chosen to remain on Ivacaftor. She had previously chosen not to breastfeed for personal reasons, the evidence for Ivacaftor in breastfeeding, not contributing to her decision.
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### TABLE 1
Demographic data among pregnant women with CF at delivery

<table>
<thead>
<tr>
<th>Description</th>
<th>CF  n = 1119</th>
<th>No CF n = 12,627,627</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race/Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>794 (70.9)</td>
<td>5,570,518 (44.1)</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>African American</td>
<td>45 (4.0)</td>
<td>1,511,168 (12.0)</td>
<td>0.2 (0.2–0.3)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>70 (6.3)</td>
<td>2,426,137 (19.2)</td>
<td>0.2 (0.2–0.3)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>10 (0.9)</td>
<td>559,837 (4.4)</td>
<td>0.1 (0.1–0.2)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Other</td>
<td>30 (2.7)</td>
<td>603,467 (4.8)</td>
<td>0.3 (0.2–0.5)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Missing</td>
<td>170 (15.2)</td>
<td>1,956,499 (15.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>26.5 ± 13.5</td>
<td>27.6 ± 13.7</td>
<td>—</td>
<td>.006</td>
</tr>
<tr>
<td><strong>LOS, d</strong></td>
<td>3 (2, 4)</td>
<td>2 (2, 3)</td>
<td>—</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Total charges, $</strong></td>
<td>13,727 (8471, 26,494)</td>
<td>10,002 (6785, 15,096)</td>
<td>—</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

*CF*, cystic fibrosis; *CI*, confidence interval; *LOS*, length of stay; *OR*, odds ratio; *SD*, standard deviation.

* Values are mean ± SD; *b* Values are median (quartile).

### Obstetric events present at time of delivery among women with CF

<table>
<thead>
<tr>
<th>Condition</th>
<th>CF n = 1119</th>
<th>No CF n = 12,627,627</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean delivery</td>
<td>351 (31.4%)</td>
<td>4,041,005 (32.0%)</td>
<td>1.0 (0.9–1.1)</td>
<td>.67</td>
</tr>
<tr>
<td>Operative vaginal delivery</td>
<td>100 (8.9%)</td>
<td>792,143 (6.3%)</td>
<td>1.5 (1.2–1.8)</td>
<td>.0002</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>39 (3.5%)</td>
<td>267,193 (2.1%)</td>
<td>1.7 (1.2–2.3)</td>
<td>.0013</td>
</tr>
<tr>
<td>GDM</td>
<td>148 (13.2%)</td>
<td>714,940 (5.7%)</td>
<td>2.5 (2.1–3.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Preeclampsia, eclampsia, gest HTN</td>
<td>76 (6.8%)</td>
<td>931,154 (7.4%)</td>
<td>0.9 (0.7–1.1)</td>
<td>.48</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>209 (18.7%)</td>
<td>1,051,494 (8.3%)</td>
<td>2.5 (2.2–2.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Abruption</td>
<td>16 (1.4%)</td>
<td>136,053 (1.1%)</td>
<td>1.3 (0.8–2.2)</td>
<td>.22</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>29 (2.6%)</td>
<td>271,882 (2.2%)</td>
<td>1.2 (0.8–1.8)</td>
<td>.26</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>15 (1.3%)</td>
<td>321,959 (2.5%)</td>
<td>0.5 (0.3–0.9)</td>
<td>.012</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>36 (3.2%)</td>
<td>323,531 (2.6%)</td>
<td>1.3 (0.9–1.8)</td>
<td>.17</td>
</tr>
</tbody>
</table>

Patel, EM. et al. (2015), Medical and obstetric complications among pregnant women with cystic fibrosis American Journal of Obstetrics & Gynecology, 212:1; 98.e1 - 98.e9
## Medical events present at time of delivery among women with CF

<table>
<thead>
<tr>
<th>Condition, n (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CF n = 1119</th>
<th>No CF n = 12,627,627</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>11 (1.0)</td>
<td>921 (0.007)</td>
<td>125 (67–233)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>25 (2.2)</td>
<td>9003 (0.07)</td>
<td>31.9 (21.4–47.5)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Transfusion</td>
<td>20 (1.8)</td>
<td>131,684 (1.0)</td>
<td>1.7 (1.1–2.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>75 (6.7)</td>
<td>13,150 (0.1)</td>
<td>68.7 (54.3–86.9)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>14 (1.2)</td>
<td>5450 (0.04)</td>
<td>29.6 (16.7–48.0)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>11 (1.0)</td>
<td>7075 (0.06)</td>
<td>16.4 (8.9–30.4)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Composite CF outcome&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>95 (8.5)</td>
<td>33,275 (0.26)</td>
<td>35.3 (28.6–43.5)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

*CF, cystic fibrosis; CI, confidence interval; NIS, Nationwide Inpatient Sample; OR, odds ratio.*

<sup>a</sup> The NIS does not allow reporting the number of cases when the cell frequency is less than or equal to 10. There were 10 or fewer cases of myocardial infarction, cardiac arrest, acute heart failure, pulmonary edema, acute respiratory distress syndrome, pulmonary embolism, deep vein thrombosis, stroke/cerebral vascular accident, sepsis, pyelonephritis and influenza among women with CF; <sup>b</sup> Composite CF outcome includes any of the following: death, mechanical ventilation, sepsis, pneumonia, acute respiratory failure, acute respiratory distress syndrome, or acute renal failure.

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Gestational age at delivery is correlated with lung function

Maternal long-term outcome

• 3/5 women with an $\text{FEV}_1 < 40\%$ died within 18 months of delivery.
• 4/9 women with $\text{FEV}_1 40–50\%$ died between 2 and 8 years after delivery.
• Consistent with previous studies- $\text{FEV}_1$ most important contributor to outcomes\(^2\)

Maternal long-term outcome

- Comparing 680 CF women who were pregnant to >3000 matched women who were never pregnant
- After adjustment for the initial severity of illness, women who became pregnant did not have a significantly shortened survival.

Lung function post gestation

Single center, 15 pregnancies:\(^1\):

<table>
<thead>
<tr>
<th>Lung function</th>
<th>Baseline</th>
<th>Postpartum % changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delivery</td>
<td>6 months</td>
</tr>
<tr>
<td>FEV1 %pred</td>
<td>68.10 ± 16.5</td>
<td>-5.31 ± 13.3</td>
</tr>
<tr>
<td>FVC %pred</td>
<td>84.13 ± 19.8</td>
<td>-6.78 ± 11.9</td>
</tr>
<tr>
<td>FEV1/FVC %pred</td>
<td>78.38 ± 8.8</td>
<td>-3.73 ± 7.9</td>
</tr>
</tbody>
</table>

FEV1 pred: predicted forced expiratory volume in one second; FVC pred: predicted forced vital capacity.

The finding of decreased lung function after pregnancy was not confirmed by other studies.

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Delivery

• Vaginal or operation?
• Most deliveries of CF women are vaginal
• The foetal indications are no different to those in non-CF women but
• Shorten the second stage of labour in women with severe CF to prevent prolonged Valsalva maneuvers.

What do guidelines say?

• Contraindications for pregnancy?
• Absolute- cor pulmonale and PHT
• Relative- ??
  – FEV1 <60%? 70%?
  – FVC<50%?
  – Poor nutritional status (BMI<18)?
  – *Burkholderia cepacia* colonization-?

Summary

- Parenthood more common in CF d/t better health
- Infertility is overcome by assisted reproduction
- Pregnancy in CF
  - Physiologic changes in pregnancy may resemble pulmonary exacerbations
  - CF care during pregnancy:
    - Drug safety- most drugs may be continued
    - Obstetric and Respiratory complications common for severe patients
- Delivery- no different except for severe patients
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• Nona Purits- Nurse
• Orit Brazlavsky- Nurse
• Dr. Rachel Friedman- Social worker
• Ofra Tsuk- Physiotherapist
• Hila Alterovitz- Nutritionist
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