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.[2-4, 6] 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.

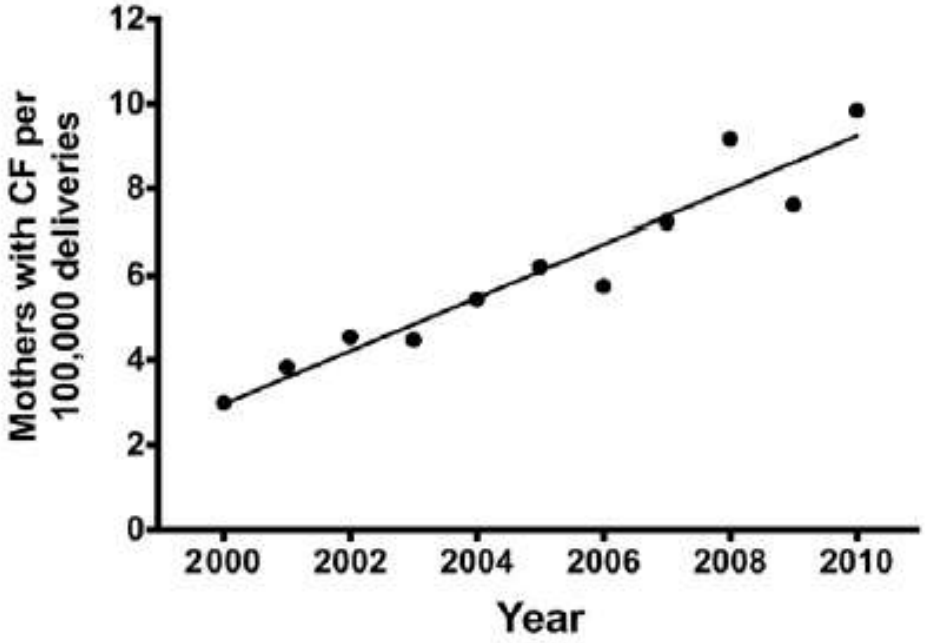
From the Albert Einstein Medical Center (Northern Div.), Philadelphia, Pa.

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

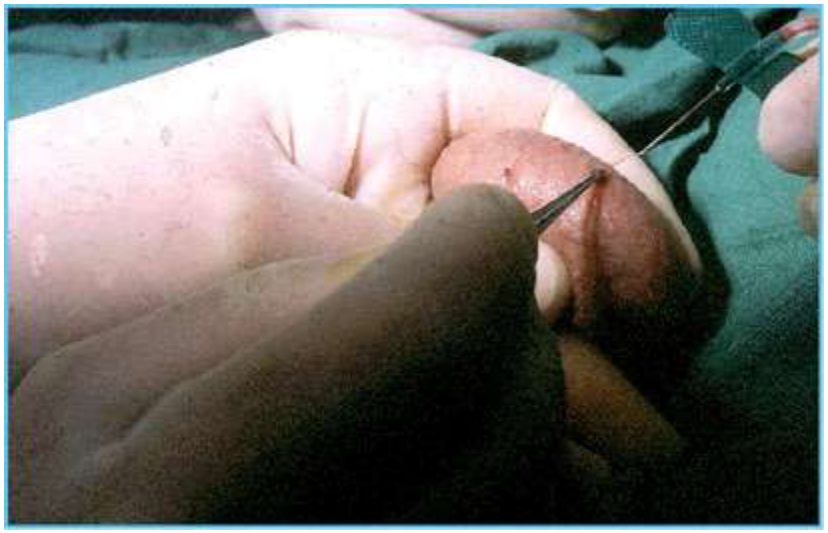
Outline

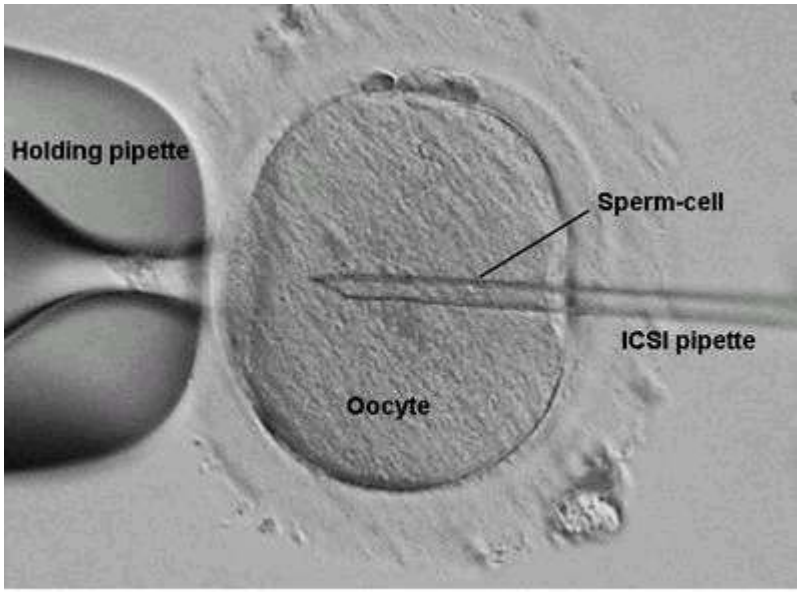
- Fertility in CF
  - Men
  - Women
- Pregnancy in CF
  - Physiologic changes in pregnancy
  - CF care during pregnancy:
    - Drug safety
    - Obstetric and Respiratory complications
- Delivery

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





ICSI

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
- FEV_1 60-65% pre-pregnancy

Infertility in Cystic Fibrosis

- Male CF infertility is (almost) universal and due to CBAVD[1]
- Reduced fertility has also been observed in women with CF[2]
- First report – 1973 - thick cervical mucus[3,4,5]
- CF patient successfully treated with intrauterine insemination (1986) [4,5]

1 - De Braekeleer M, et. al 1996 **Mutations in the cystic fibrosis gene in men with congenital bilateral absence of the vas deferens**. Mol Hum Reprod 2:669–677
2 Kopito LE et al., 1973 **Water and electrolytes in cervical mucus from patients with cystic fibrosis**. Fertil Steril 24:512–516
3 Oppenheimer EA et al., **Cervical mucus in cystic fibrosis: a possible cause of infertility**. Am J Obstet Gynecol. 1970 Oct 15;108(4):673-4.
4 Gervais R et al. **Hypofertility with thick cervical mucus: another mild form of cystic fibrosis?** JAMA. 1996 Nov 27;276(20):1638.

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]

1 -Chan LN et al., 2002 **Distribution and regulation of ENaC subunit and CFTR mRNA expression in murine female reproductive tract**. *J Membr Biol* 185:165–176
2 - Johannesson M et al., 1997; **Cystic fibrosis mRNA expression in rat brain: cerebral cortex and medial preoptic area.** *Neuroreport* 8:535–539
3. Schram CA et al., (2015) **Cystic fibrosis (cf) and ovarian reserve: A cross-sectional study examining serum anti-mullerian hormone (amh) in young women.**, *J. Cyst. Fibros.*, 14;3:398–402,

Sub/infertility among CF women

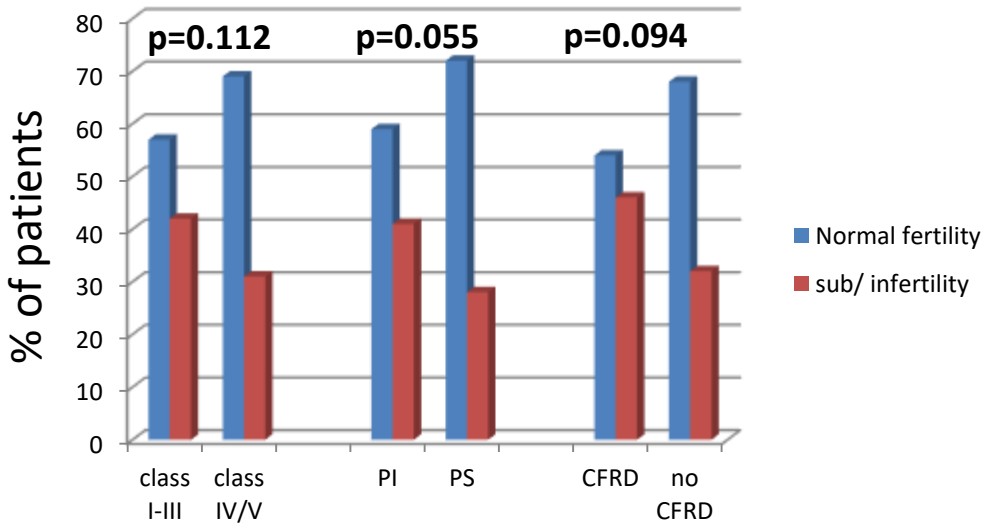
- Multicenter study (7 centers in Israel+ Lyon, Milan, Belfast)
- 524 adult women with CF
- Retrospective review of fertility and seeking assisted reproduction

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



Outline

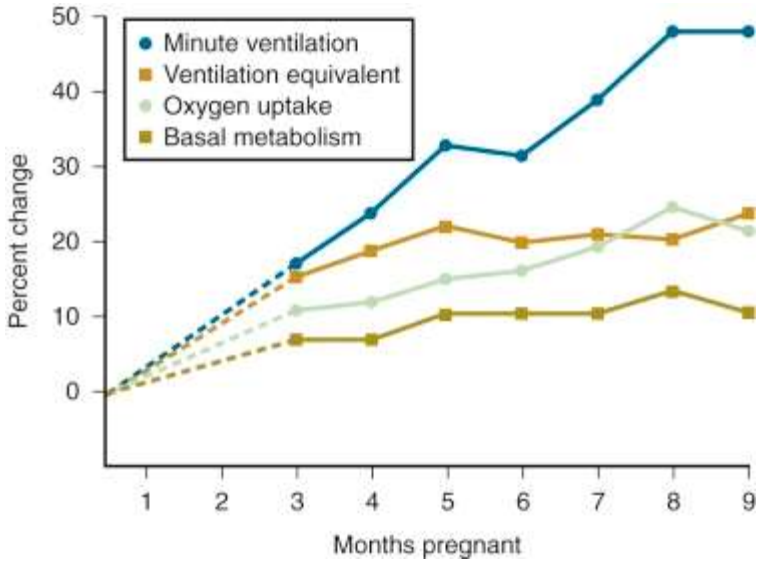
- Fertility in CF
  - Men
  - Women
- Pregnancy in CF
  - Physiologic changes in pregnancy
  - CF care during pregnancy:
    - Drug safety
    - Obstetric and Respiratory complications
- Delivery

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 (FEV_1= 55%)

Physiologic changes in pregnancy

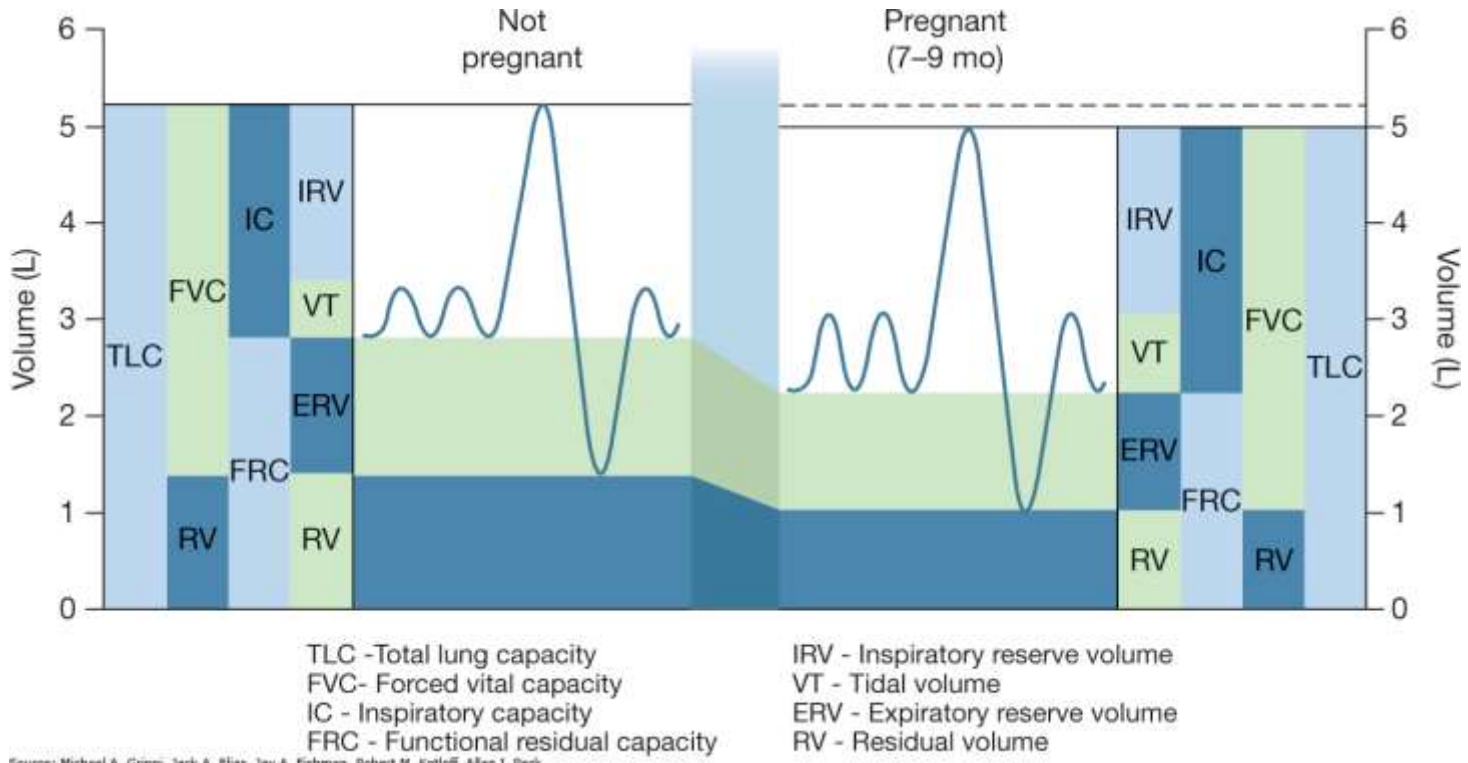
- Upper airway congestion, rhinitis- more common- up to 20% of gravid women
- Increase in minute ventilation (progesterone); often a sense of dyspnea



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_1 – no change
- Slowed intentinal transit
- Constipation- common (may aggravate DIOS)



Outline

- Fertility in CF
  - Men
  - Women
- Pregnancy in CF
  - Physiologic changes in pregnancy
  - CF care during pregnancy:
    - Drug safety
    - Obstetric and Respiratory complications
- Delivery

Review

Respiration

Respiration 2016;91:333–348
DOI: 10.1159/000444088

Received: June 8, 2015
Accepted after revision: January 13, 2016
Published online: March 5, 2016

Safety of Drugs during Pregnancy and Breastfeeding in Cystic Fibrosis Patients

Alice Panchaud[a] Ermindo R. Di Paolo[b] Angela Koutsokera[c]
Ursula Winterfeld[d] Etienne Weisskopf[a] David Baud[e] Alain Sauty[c]
Chantal Csajka[a]

[a]School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Geneva, [b]Service of Pharmacy, Department of Laboratory, [c]Service of Pneumology, Department of Medicine, [d]STIS and Division of Clinical Pharmacology, and [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.

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

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;)

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

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

SUPPLEMENT FACTS

Serving size: 1 softgel — Servings per container: 60

	Amount per softgel	%DV
Vitamin A (as 92% beta-carotene and 8% palmitate)	18167 IU	363%
Vitamin C (as sodium ascorbate)	75 mg	125%
Vitamin D (as cholecalciferol)	3000 IU	750%
Vitamin E (as d-alpha-tocopherol and d-alpha tocopheryl polyethylene glycol 1000 succinate)	150 IU	500%
Vitamin K (as phytonadione)	1000 mcg	1250%
Thiamin (Vitamin B1)	1.5 mg	100%
Riboflavin (Vitamin B2)	1.7 mg	100%
Niacin (as niacinamide)	10 mg	50%
Vitamin B6 (as pyridoxine hydrochloride)	1.9 mg	95%
Folic acid	200 mcg	50%
Vitamin B12 (as cyanocobalamin)	12 mcg	200%
Biotin	100 mcg	33%
Pantothenic Acid (as calcium d-pantothenate)	12 mg	120%
Zinc (as zinc sulfate)	10 mg	67%
Selenium (as selenium yeast)	75 mcg	107%
Coenzyme Q10	10 mg	*

*Daily value not established for these nutrients

Other ingredients: medium chain triglycerides (carrier), gelatin (outer shell), tocopherol rich extract (antioxidant), glycerin (plasticizer), sorbitol (humectant), water, natural caramel color, ethyl vanillin (flavor), titanium dioxide (colorant).

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

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

ELSEVIER

Journal of Cystic Fibrosis 15 (2016) 133–134

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Letter to the Editor

A successful uncomplicated CF pregnancy while remaining on Ivacaftor

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

[a] 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

Received 21 October 2015; revised 25 November 2015; accepted 25 November 2015
Available online 14 December 2015

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 FEV_1: 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.

Outline

- Fertility in CF
  - Men
  - Women
- Pregnancy in CF
  - Physiologic changes in pregnancy
  - CF care during pregnancy:
    - Drug safety
    - Obstetric and Respiratory complications
- Delivery

TABLE 1

Demographic data among pregnant women with CF at delivery

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

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

[a] Values are mean ± SD; [b] Values are median (quartile).

Patel. Cystic fibrosis in pregnancy. Am J Obstet Gynecol 2015.

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

Obstetric events present at time of delivery among women with CF

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

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

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

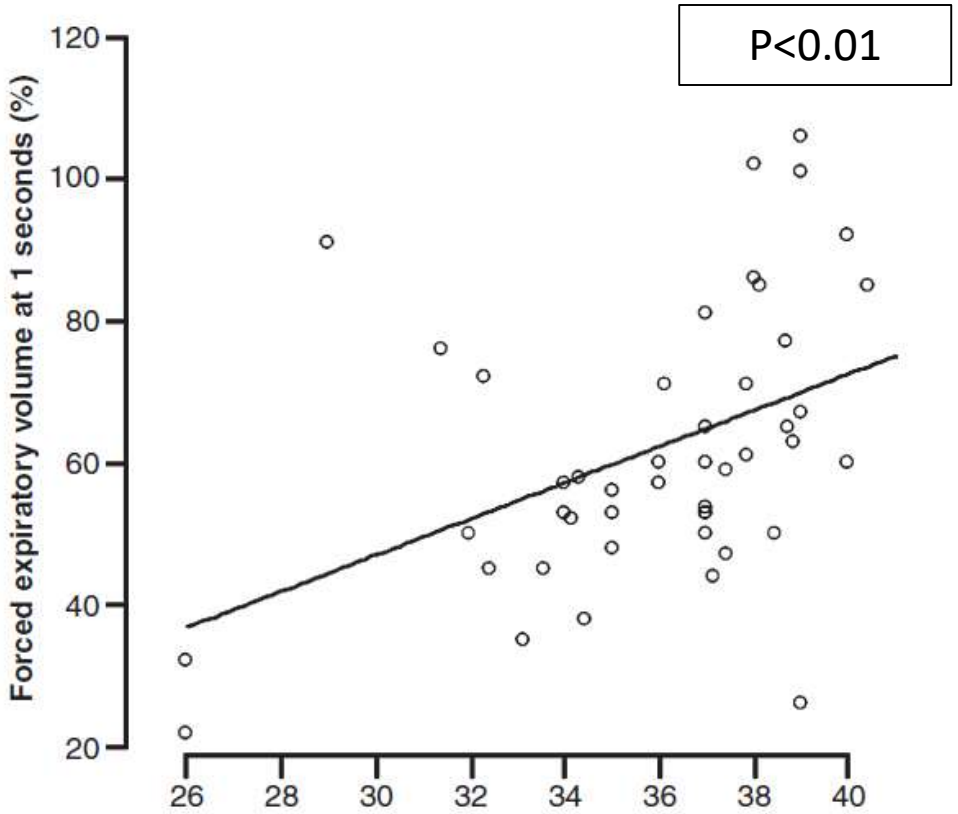
CF, cystic fibrosis; *CI*, confidence interval; *NIS*, Nationwide Inpatient Sample; *OR*, odds ratio.

[a] 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; [b] Composite CF outcome includes any of the following: death, mechanical ventilation, sepsis, pneumonia, acute respiratory failure, acute respiratory distress syndrome, or acute renal failure.

Patel. Cystic fibrosis in pregnancy. Am J Obstet Gynecol 2015.

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

Gestational age at delivery is correlated with lung function



JG Thorpe-Beeston et. al (2013) **The outcome of pregnancies in women with cystic fibrosis- single centre experience 1998-2011** BJOG: An International Journal of Obstetrics & Gynaecology 120:3; 354-361

Maternal long- term outcome

- 3/5 women with an FEV_1 <40% died within 18 months of delivery.
- 4/9 women with FEV_1 40–50% died between 2 and 8 years after delivery.
- Consistent with previous studies- FEV_1 most important contributor to outcomes[2]

1. JG Thorpe-Beeston et. al (2013) **The outcome of pregnancies in women with cystic fibrosis- single centre experience 1998-2011** BJOG120:3; 354-361
2. Edenborough, F. P et al.(2000), **The outcome of 72 pregnancies in 55 women with cystic fibrosis in the United Kingdom 1977–1996.** BJOG: 107: 254–261.

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.

Goss CH et al., **The effect of pregnancy on survival in women with cystic fibrosis**. Chest. 2003 Oct;124(4):1460-8.

Lung function post gestation

Single center, 15 pregnancies[1]:

Peripartum pulmonary function in CF (mean ± SD).

	Lung function			
	Baseline	Postpartum % changes		
		Delivery	6 months	12 months
FEV1 %pred	68.10 ± 16.5	−5.31 ± 13.3	−4.52 ± 10.2	−5.77 ± 6.8
FVC %pred	84.13 ± 19.8	−6.78 ± 11.9	−3.01 ± 13.2	2.37 ± 11.8
FEV1/FVC %pred	78.38 ± 8.8	−3.73 ± 7.9	−4.45 ± 7.5	−3.90 ± 14.7

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.

1. Renton, M et al. **Pregnancy Outcomes in Cystic Fibrosis: A 10-Year Experience from a UK Centre.** *Obstetric Medicine* 8.2 (2015): 99–101. *PMC*. Web. 4 Oct. 2017.
2. Schechter MS **Long-term effects of pregnancy and motherhood on disease outcomes of women with cystic fibrosis.** Ann Am Thorac Soc. 2013 Jun;10(3):213-9

Outline

- Fertility in CF
  - Men
  - Women
- Pregnancy in CF
  - Physiologic changes in pregnancy
  - CF care during pregnancy:
    - Drug safety
    - Obstetric and Respiratory complications
- Delivery

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.

Edenborough FP , **Guidelines for the management of pregnancy in women with cystic fibrosis.** J Cyst Fibros. 2008 Jan;7 Suppl 1:S2-32. Epub 2007 Nov 19.

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-?

Edenborough FP , **Guidelines for the management of pregnancy in women with cystic fibrosis.** J Cyst Fibros. 2008 Jan;7 Suppl 1:S2-32. Epub 2007 Nov 19.

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

Acknowledgements

Carmel CF Center:

- Dr. Galit Livnat- Levanon- Pediatric Pulmonology
- Dr. Michal Shteinberg- Adult Pulmonology
- Dr. Reut Lutzky- Gastroenterology
- Dr. Yigal Elenberg– Pediatric Gastroenterology
- Nona Purits- Nurse
- Orit Brazlavsky- Nurse
- Dr. Rachel Friedman- Social worker
- Ofra Tsuk- Physiotherapist
- Hila Alterovitz- Nutritionist
- Nursing and medical staff at Carmel pediatrics dept.

Technion- Israel Institute of Technology:

Prof. Zeev Blumenfeld

Carmel IVF Unit:

Prof. Martha Durenfeld

Dr. Shilrly Lahav- Baratz

Dr. Gil Peer