Pregnancy in Cystic Fibrosis*

Fetal and Maternal Outcome

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Objective: **To assess the effect of pregnancy on pulmonary function and survival in women with cystic fibrosis (CF) and to assess the fetal outcome.**
Design: **Cohort study. The data analyzed were collected from the Toronto CF database, chart review, and patient questionnaire.**
Setting: **Tertiary-care center.**
Patients: **All women with CF who, at the time of diagnosis or pregnancy, attended the Toronto Cystic Fibrosis Clinics between 1961 and 1998.**
Results: **From 1963 to 1998, there were 92 pregnancies in 54 women. There were 11 miscarriages and 7 therapeutic abortions. Forty-nine women gave birth to 74 children. The mean follow-up time was 11 ± 8 years. One patient was lost to follow-up shortly after delivery, and one was lost after 12 years. The overall mortality rate was 19% (9 of 48 patients). Absence of *Burkholderia cepacia* ($p < 0.001$), pancreatic sufficiency ($p = 0.01$), and prepregnancy $FEV_1 > 50\%$ predicted ($p = 0.03$) were associated with better survival rates. When adjusted for the same parameters, pregnancy did not affect survival compared to the entire adult female CF population. The decline in FEV_1 was comparable to that in the total CF population. Three women had diabetes mellitus, and seven developed gestational diabetes. There were six preterm infants and one neonatal death. CF was diagnosed in two children.**
Conclusions: **The maternal and fetal outcome is good for most women with CF. Risk factors for mortality are similar to those for the nonpregnant CF population. Pregnancies should be planned so that there is opportunity for counseling and optimization of the medical condition. Good communication between the CF team and the obstetrician is important.**

(CHEST 2000; 118:85–91)

Key words: cystic fibrosis; diabetes mellitus; fertility; outcome; pregnancy

Abbreviations: BMI = body mass index; CF = cystic fibrosis; PI = pancreatic insufficiency; PS = pancreatic sufficiency

The survival of patients with cystic fibrosis (CF) has improved remarkably over the last few decades. In an increasing adult population, issues such as fertility, family planning, and pregnancy have become important for CF patients and their caregivers. Early reports of pregnancy in patients with CF were discouraging,[1,2] but studies have attested to the safety of pregnancy in women with good lung function.[3–6] An increased risk of premature delivery has been reported.[7] Pulmonary function impairment has been suggested as the most important predictor of maternal and fetal outcome.[3,6] Other factors that may affect long-term survival are nutritional status, the existence of diabetes mellitus, the presence of *Burkholderia cepacia*, and frequent infectious exacerbations.[5,7]

In our two previous reports on pregnancy in patients with CF,[8,9] 71% and 48%, respectively, of the patients had pancreatic sufficiency (PS) vs 21% in the entire adult CF population,[10] suggesting a milder form of CF in pregnant women. Since our last report,[9] we have encountered an increasing number of women with CF who have pancreatic insufficiency (PI) and have completed a successful pregnancy.

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Supported in part by the Canadian Cystic Fibrosis Foundation (M.G.).
Manuscript received August 30, 1999; revision accepted March 23, 2000.
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Therefore, we sought to review all pregnancies and to study the effect of pregnancy on pulmonary function, nutritional status, and survival. We also analyzed the role of prepregnancy pulmonary function, body mass index (BMI), pancreatic function, and the presence of *B cepacia* in long-term survival.

Materials and Methods

All women with CF who attended the CF program from 1960 to 1998 at the Hospital for Sick Children or at St. Michael's/Wellesley Hospital (from 1992) were eligible for the study. Demographic and clinical follow-up data were abstracted from the patient database. In general, patients were seen one to four times per year, and the following pertinent data were recorded: height; weight; pancreatic function; and pulmonary function, as assessed by spirometry.[11] Information on gestational age, birth weight, and gender of the child also was available from the database. Additional data that were not available in the database (*eg*, obstetric data such as mode of delivery and obstetric complications) and information on breast feeding habits were retrieved from chart review and patient interviews for 29 of the 39 women who were still alive. Most patients have been followed-up primarily by their obstetrician during pregnancy but with regular visits to the CF clinic.

Statistical Analysis

Pregnancies with gestational lengths of > 26 weeks were included in the statistical analysis.

Data were presented as mean ± SD or median with range, as appropriate. Paired data (pre- and postpregnancy) were analyzed using a two-tailed *t* test. Subgroups were compared using a two-tailed *t* test or the Mann-Whitney test. The significance level was set at $p \leq 0.05$.

Kaplan-Meier estimates of survival were computed, using data from the first completed pregnancy for each woman. Survival was determined from the woman's age at conception to December 31, 1998, the censored time. The log-rank test was used to compare survival in women categorized by pancreatic function, FEV_1, BMI, diagnosis date, and *B cepacia*.

The Cox proportional hazards model was used to assess the effects of pregnancy, clinical variables, age, and pulmonary function on survival, using all women with CF in our clinic population during the same time period.

Computer software (SAS, version 6.12; SAS Institute; Cary, NC or StatView, version 5.0; Abacus Concepts; Berkeley, CA) was used for all analysis.

Results

Outcomes of Pregnancies

For prepregnancy characteristics see Table 1.

From 1963 to 1998, there were 92 pregnancies in 54 women, with 74 births in 49 women (range, 1 to 3 births [no multiple births]). There were 11 miscarriages and 7 medical terminations. Terminations were for psychosocial reasons in three patients and poor health in four patients (PS, 1 patient; PI, 3 patients). In the latter group, one patient carried a pregnancy to term 4 years later, but she deteriorated during and after the pregnancy and died 4 years after delivery.[9] One woman who deeply regretted the abortion had four early miscarriages then carried two pregnancies to term and is alive 18 years after the first completed pregnancy. One patient died 2 years after a therapeutic abortion, and one patient had a double lung transplant 4 years later.

Obstetric History and Outcome in Infants

The mean gestational age (40 ± 2 weeks) and birth weight (3.2 ± 0.6 kg) were normal,[12] with no difference between women with $FEV_1 < 50\%$ or $> 50\%$ predicted. A mean weight gain of 8 ± 5 kg was reported for 50 pregnancies with available data (24 pregnancies in 12 women with PS and 26 pregnancies in 21 women with PI). Six infants were

Table 1—*Prepregnancy Characteristics (First Completed Pregnancy) in 49 Women With CF

Characteristics	All women (n = 49)	FEV_1		
		> 50% Predicted (n = 37)†	< 50% Predicted (n = 5)	Unknown (n = 7)‡
Age, yr	25 ± 5(16–35)	24 ± 5(16–35)	26 ± 3(23–30)	26 ± 5(16–30)
CF diagnosed after first pregnancy	8 (16)	6 (16)	0 (0)	2 (29)
PS	20 (41)	15 (40)	0 (0)	5 (71)
Genotype				
FF	13 (27)	11	2	0
FO	20 (41)	14	2	4
OO	10 (20)	9	0	1
NA	6 (12)	3	1	2
B cepacia	13	8	4	1

* Values given as mean ± SD (range) or No. (%). FF = ΔF508 homozygous; FO = ΔF508 and one other mutation; OO = two other mutations; NA = not available.

† Prepregnancy FEV_1 was missing for 16 women but was estimated to be $> 50\%$ of predicted based on an $FEV_1 > 50\%$ postpregnancy for 10 women.

‡ Postpregnancy $FEV_1 < 50\%$ of predicted, and prepregnancy data were unavailable.

preterm (< 37 weeks gestation), four infants were small for the gestational age, and three had a low birth weight (< 2.5 kg).[13] There were no stillbirths, but one infant, delivered at 31 weeks' gestation to a diabetic mother with moderately severe lung disease, died 18 days after delivery due to sepsis.[9] Of infants born to mothers with prepregnancy diabetes, two of three were preterm with low birth weight. One child of a mother with gestational diabetes was small for the gestational age. The only malformation recorded was one infant with cleft soft palate. CF was diagnosed in one infant. Prepregnancy genetic counseling had been given, and screening of the father for the most common CF mutations was negative (performed elsewhere). CF was diagnosed in a second offspring on screening at age 23 years, after CF was diagnosed in her mother.

In the 40 pregnancies completed since 1991 and not previously reported,[9] cesarean section was performed in five deliveries. The reasons for performing a cesarean section were breech presentation, cord around neck, poor progression despite induction at full term, and narrow birth channel. In the latter case, a repeat cesarean section was needed 4 years later. Seven deliveries in five patients were induced. The reasons for induction were the following: pulmonary infection and poor fetal growth in five women; diabetes, elevated BP, and cholecystitis in one woman; and social reasons in one woman. During pregnancy, six women were hospitalized because of pulmonary infections, hemoptysis, and poor weight gain. Three women did not seek medical advice or refused antibiotics because of a fear of possible harm to the fetus. All three patients required hospitalization to receive IV antibiotics after delivery. One woman had a severe uterine hemorrhage and, therefore, underwent a hysterectomy 1 month after delivery, and another patient was hospitalized because of infectious complications after cesarean section. Five infants had immediate but not serious medical problems, two requiring an incubator, one who was small for gestational age, one with transient respiratory problems, and one with hypoglycemia.

Long-term Outcome (Completed Pregnancies)

The mean follow-up time was 11 ± 8 years. One patient was lost to follow-up shortly after delivery, and one after 12 years. A double lung transplantation was carried out in 3 patients at 6, 10, and 13 years after the first completed pregnancy. Five years after delivery, 26 women (90%) were alive and 3 women (10%) had died; 10 years after delivery, 19 women (79%) were still alive (Tables 2, 3). Death occurred in nine women at a median of 8 years (range, 3 to 30 years) after the first completed pregnancy. The causes of death were respiratory insufficiency and cepacia syndrome.

Factors Associated With Survival

Figure 1, *left*, *a*, shows the survival curve for all women following their first completed pregnancy. Figure 1, *right*, *b*, compares women who are chronically infected with *B cepacia* with those who do not have this organism. As of December 31, 1998, 9 of 49 women had died, with a cumulative survival rate of 87% 10 years after pregnancy. All subsequent results are reported for 10-year survival following pregnancy. Based on the nutritional status before pregnancy, there was no difference in survival between women with BMIs < 20 (n = 16) or BMIs ≥ 20 (n = 19) (79% vs 81%, respectively; p = 0.78). Better outcomes were seen for those who were negative for *B cepacia* (n = 36) than for those who were positive for *B cepacia* (n = 13) (95% vs 67%, respectively; p < 0.001). Similarly, women who had PS (n = 20) had better chances of survival than women who had PI (n = 29) (94% vs 80%, respectively; p = 0.01). Patients with good pulmonary function

Table 2—*Most Recent Data in 39 Women With CF, Alive 1 to 28 Years After First Completed Pregnancy

Follow-up, yr	N	Age at Pregnancy, yr	PS	FF	Diagnosed After First Pregnancy, No.	*B cepacia*	BMI*	FEV_1, % Predicted
0.6–5	13	28 ± 5	1	6	0	1	20 ± 3†	65 ± 18†
6–10	7	24 ± 5	2	1	0	2	22 ± 4†	57 ± 30
11–15	11	23 ± 5	5	3	2	2	22 ± 4‡§	69 ± 25‡§
16–20	4	25 ± 2	4	0	1	1	24 ± 3	60 ± 25
21–28	4	24 ± 6	4	0	3	0	27 ± 5	77 ± 26

* Values given as mean ± SD, unless otherwise indicated. See Table 1 for other abbreviation.

† Data unavailable in one patient.

‡ Data unavailable in two patients.

§ Double lung transplantation in one patient 10 years after delivery.

Table 3—*Prepregnancy Characteristics for the First Completed Pregnancy in Nine Women With CF Who Died 3 to 30 Years After Delivery

Patient No.	Age at Diagnosis, yr	Age at Gestation, yr	Death Postpregnancy, yr	FEV_1 % Predicted Prepregnancy	BMI Prepregnancy	Genotype	Pancreatic Function	*B cepacia*
1	0.5	32	3†	90	25	F/?	PI	+
2‡	1.9	30	4	24	15	F/G551D	PI	−
3	7.5	19	5	63	NA	NA	PI	+
4§	2.7	25	6†	27	21	F/N1303K	PI	+
5‖	9.7	21	8	65	18	NA	PS	−
6§‖	12	29	13†	53	23	F/F	PI	+
7	8.4	21	14	95	19	F/F	PI	+
8†	24	22	25	34	NA	?/?	PS	−
9	57	28	30	NA	NA	?/?	PS	−

F = ΔF508; ? = unidentified mutation; + = positive, − = negative; NA = not available.

† Cepacia syndrome.

‡ Medical termination of pregnancy. 3 years previously because of poor lung functions.

§ Lung transplantation later.

‖ Another full-term pregnancy.

before pregnancy (FEV_1, $\geq 50\%$ of predicted; n = 37) had better survival rates than women with more impaired lung function (FEV_1, $< 50\%$ of predicted; n = 5) (89% vs 50%, respectively; p = 0.03). Prepregnancy FEV_1 measurements were not available for 17 women but were estimated to be $> 50\%$ of predicted for 10 women, based on a postpregnancy FEV_1 of $> 50\%$ of predicted.

The Cox proportional hazards model showed that pregnancy did not affect survival in the whole female CF population when adjusted for age, pancreatic status, *B cepacia* status, and pulmonary function.

Pulmonary function and BMI both before and after pregnancy were available for 41 and 42 pregnancies in 32 women (Table 4). There was a significant decrease in FEV_1 from a mean of 68% of predicted before pregnancy to 65% of predicted after delivery. The calculated yearly rate of decline in FEV_1 was 1.6% predicted per year, which is comparable to the rate of decline in the whole CF population attending the Toronto clinics.[14,15] The average BMI before pregnancy was 21 ± 2.6, which was not different from the average BMI after pregnancy. Prior to pregnancy, three women had diabetes mellitus requiring insulin, and seven women developed gestational diabetes, with five requiring insulin.

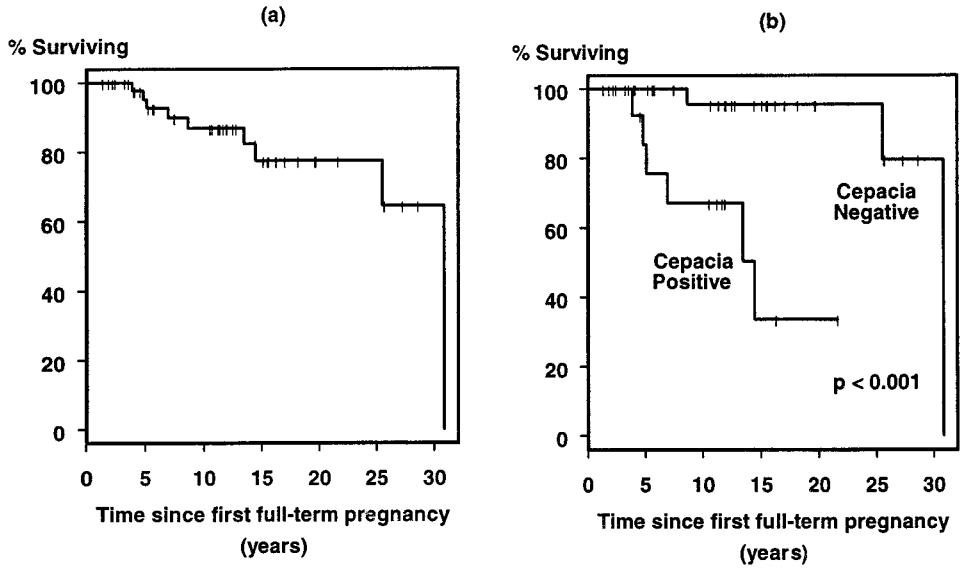

FIGURE 1. Kaplan-Meier survival curves for 49 women with CF after their first completed pregnancy. Overall survival (*left*, *a*) and survival (*right*, *b*) for *B cepacia*-negative vs *B cepacia*-positive women ($p < 0.001$ [log-rank test]). Vertical lines indicate censored observations (*ie*, those patients still alive on December 31, 1998).

Table 4—*Pulmonary Function and BMI Before and After Pregnancy in 40 Women With CF

Characteristics	N	Before Pregnancy	After Pregnancy	Change
Age, yr†	41	25 ± 5	27 ± 5	1.8 ± 1.0
FEV_1† % predicted				
All	41	68 ± 21	65 ± 21	−3.1 ± 7.3‡
PS	12	71 ± 18	72 ± 18	1.1 ± 5.6
PI	29	67 ± 22	62 ± 21	−4.7 ± 7.3§
BMI	42	21 ± 2.6	21 ± 2.6	0

* Values given as mean ± SD, unless otherwise indicated. The calculated yearly decline in FEV_1 % predicted was 2.58% for the PI and 1.67% for the whole group. No decline was seen in the PS group.
† Age = age at the time of spirometry.
‡ $p = 0.01$.
§ $p < 0.01$.

Fertility and Breast Feeding

Thirteen of 29 women (45%) reported that it took > 2 years to conceive. Four of these women had no difficulties conceiving in a subsequent pregnancy, while three women were unable to conceive a second time. Four women received hormonal treatment and insemination with the husband's sperm.

Breast-feeding information was available for 43 pregnancies in 29 women. Fifteen women never breast-fed, while 14 breast-fed one or all of their children. Ten children were breast-fed for 1 to 3 months, and 8 were breast-fed for > 4 months. Several patients were discouraged from breast feeding because of a concern for maternal health or possible harm to the infant from medications. A few preterm infants did not take to the breast, and a number of patients never considered breast feeding as it was not common at the time or for economic reasons.

Discussion

The fetal outcome was good for this population, with a mean gestational age and birth weight comparable to data for Ontario from 1973 to 1993.[12] A higher percentage of pregnancies resulting in live births in women < 25 years of age was seen compared with the whole Ontario population (42% vs 32%, respectively).[12] The number of infants who were small for gestational age did not substantially differ from the numbers reported for Canada.[16] Hilman et al[7] reported a higher percentage of preterm infants (35%), compared to that in our population (9%; 1 case).

The early reports of pregnancy in patients with CF described a high percentage of premature delivery, progressive pulmonary disease, and even maternal and fetal death.[1,2,17] In the United States/Canada survey of 1975, poor maternal and fetal outcome was associated with severe pulmonary disease and the exacerbation of pulmonary infection during pregnancy.[18] It was suggested that pregnancy should be avoided if the Taussig or Schwachman score was < 80.

In several reports, prepregnancy FEV_1 was found to be the most useful factor for outcome and counseling, as when FEV_1 is > 50 to 60% of predicted the outcome is usually good.[3,4,6] Despite having few individuals with an $FEV_1 < 50\%$ of predicted in our study, we found a poorer outcome in these women. However, in our population, one patient with a prepregnancy FEV_1 of 35% of predicted is well and maintains the same pulmonary function 9 years later, and another woman lived 25 years after delivery with a prepregnancy FEV_1 of 35% of predicted. Thus, it is difficult to use definitive values of FEV_1 as a cutoff level when advising a patient on the termination of a pregnancy. However, pulmonary hypertension occurs at a late stage in CF, and most would agree that it is an indication for therapeutic abortion. Pregnancy does not appear to have a detrimental effect on maternal health. Some women experienced their best health during pregnancy, while others described the onset of deteriorating health. This reflects the variable nature of CF, with stability over years in some patients and acute deterioration in others. The rate of decline in FEV_1 was comparable to the whole Toronto CF population. The failure to demonstrate any effect of pregnancy in the rate of decline in pulmonary function has been described by others.[5,19]

In a previous report by Canny et al,[9] 48% of the women had PS, while 9 years later the profile of women with CF who become pregnant is more representative of the overall CF population. In pregnancies since 1990, 29% had PS vs 21% in the entire adult CF population.[10] A low percentage of women were homozygous for the ΔF508 mutation (27%), compared to 44% in the Toronto adult CF population,[10] also indicates milder disease in the majority of women carrying pregnancies to term. The same risk factors for early death apply to this group of pregnant women as to the entire CF population.[20,21] Repeated pulmonary infections, poor nutritional status, and the existence of *B cepacia* in sputum are factors consistent with a worse prognosis. Six of seven women who died within 15 years after delivery had PI and had either an FEV_1 of < 40% of predicted at the time of pregnancy or were positive for *B cepacia*. The importance of *B cepacia* for outcome in pregnant CF women has been recognized by others.[5,22]

The subgroup of patients with diabetes was too small for a statistical analysis of the outcome of

pregnancy, but two of the three women with preexisting diabetes had infectious problems during pregnancy. This may reflect more severe disease overall, since both patients had PI with moderately severe lung disease. The prevalence of gestational diabetes was 14% (7 of 49 patients), which is higher than in the general population[23,24] and is consistent with the high prevalence of diabetes mellitus in the adult CF population.[25,26] Screening for diabetes is recommended at 20 weeks' gestation.[27]

There were no pregnancies after lung transplantation, and the worldwide experience of pregnancy after lung or heart-lung transplantation is limited, with a suggested worse outcome compared to other solid organ transplantation.[28–30]

The anatomic and physiologic changes during pregnancy are well-described.[31] The altered hormonal balance causes estrogen-related capillary congestion and mucous hypersecretion, and progesterone-induced hyperventilation. Cardiac output, metabolic rate, and oxygen consumption are increased. The functional residual capacity is decreased from the second trimester, while the vital capacity and FEV_1 are well-maintained throughout the pregnancy in healthy women. Gastric and esophageal pressures are increased. Airway closure may occur above functional residual capacity in late pregnancy and may, in part, explain ventilation-perfusion mismatch and hypoxemia. These changes are well tolerated in the healthy individual, but may cause severe problems in patients with CF. There is a risk for atelectasis and impaired clearance of mucus with subsequent pulmonary infections. This, in turn, will aggravate ventilation-perfusion mismatch.

Some women seemed to underestimate their health problems during pregnancy, when interview results were compared to clinical data. Whether this was caused by a strong wish to be healthy, to avoid medication, and to deny the severity of the disease or by a true feeling of well-being during pregnancy, despite chest infections and falls in FEV_1, is unclear. On the other hand, some women with normal lung function described severe pulmonary infections requiring hospitalization, IV antibiotics, and even oxygen. A few of these women had not received a diagnosis of CF, but investigation of the pulmonary complications during pregnancy led to the diagnosis. There is good evidence for the safety of the use of many antibiotics during pregnancy and breast-feeding, although a careful assessment has to be made in each case. Gestational age is important for the choice of antibiotics, and dosages may need to be adjusted for a changed volume of distribution during pregnancy.[7,32] For women with pulmonary tuberculosis, the infection is considered a greater risk for the fetus than the possible adverse effects from medications.[33] Pregnant women with asthma are advised to continue their inhaled steroids and bronchodilators.[34] The same approach should be used for CF.

Advice on breast-feeding should be given based on the overall health, social situation, and the mother's personal wish. Possible side effects of medications were one common reason in women's decisions not to breast-feed. Most medications needed for the treatment of CF are safe to take during breast-feeding. However, a woman who needs antibiotics because of a chest infection would probably benefit from the calories gained by discontinuing breast-feeding. The breast milk of mothers with CF has a normal electrolyte content but a slightly lower fat content than normal, specifically for essential fatty acids, although it has enough to nourish the child.[35]

Since 1991, genetic counseling with testing for the most common CF mutations has been offered to all presumptive fathers at our center. One expectant father was found to be a carrier for the R117H mutation, a mild mutation associated with PS.[36] The couple decided to continue the pregnancy and declined further prenatal investigation of the fetus. The child did not inherit the mutation. One infant had CF diagnosed, despite having no mutations found on a previous genetic screening of the father that had been performed elsewhere. One female offspring of a mother with CF received a diagnosis of CF as an adult; she had normal lung function and was healthy when diagnosed at 23 years of age, exemplifying the varying severity of this disease.

Because of abnormalities of the cervical mucus and anovulatory cycles, fertility may be reduced for some women who have CF.[37,38] Our study focused on completed pregnancies, and, consequently, we do not have complete data on infertility in our female CF population. It is clear that even women with advanced disease may become pregnant. Our impression is that most young women are aware of the possibility of becoming pregnant but that there are still some for whom this fact is a surprise. Education on fertility and the importance of pregnancy planning should be given during the teenage years and repeated after transition to the adult clinic. Questions, such as who should raise the child in the case of maternal death, also must be addressed.

The Toronto Cystic Fibrosis Clinics provide care for patients from southern Ontario, but some patients travel $>1{,}000$ km to the clinic. This is an important factor in the organization of the follow-up for these patients, since frequent visits to the CF clinic are not always possible. Good communication between the CF team and the obstetrician and with the local internist, respirologist, or general practitioner is necessary in order to provide adequate care.

Conclusion

Pregnancy was well-tolerated in our population of CF women. Most patients carrying a pregnancy to term had mild to moderate disease. The risk factors for deteriorating health and early death after pregnancy are the same as for the whole adult female CF population, with the presence of *B cepacia* being the most important risk factor for early death. Pregnancy did not affect the rate of yearly decline in FEV_1. Follow-up studies of pregnant women with poor lung function and of women with diabetes mellitus will help to assess the safety of pregnancy in these groups. Pregnancy in women with CF preferably should be planned, and teamwork between the obstetrician and the CF team is necessary.

ACKNOWLEDGMENT: The authors thank Anna Tsang and Sandi Peroff for their assistance in contacting patients, and the Ottawa CF clinics for follow-up information.

References

1 Siegel B, Siegel S. Pregnancy and delivery in a patient with cystic fibrosis of the pancreas. Obstet Gynecol 1960; 16:438–440
2 Grand R, Talamo R, di Sant'Agnese P, et al. Pregnancy in cystic fibrosis of the pancreas. JAMA 1966; 195:117–124
3 Edenborough FP, Stableforth DE, Webb AK, et al. Outcome of pregnancy in women with cystic fibrosis. Thorax 1995; 50:170–174
4 Kent NE, Farquaharson DF. Cystic fibrosis in pregnancy. Can Med Assoc J 1993; 149:809–813
5 Frangolias DD, Nakielna EM, Wilcox PG. Pregnancy and cystic fibrosis. Chest 1997; 111:963–969
6 Jankelson D, Robinson M, Parsons S, et al. Cystic fibrosis and pregnancy. Aust N Z J Obstet Gynaecol 1998; 38:180–184
7 Hilman BC, Aitken ML, Constantinescu M. Pregnancy in patients with cystic fibrosis. Clin Obstet Gynecol 1996; 39:70–86
8 Corkey CWB, Newth CJL, Corey M, et al. Pregnancy in cystic fibrosis: a better prognosis in patients with pancreatic function? Am J Obstet Gynecol 1981; 140:737–742
9 Canny GJ, Corey M, Livingstone RA, et al. Pregnancy and cystic fibrosis. Obstet Gynecol 1991; 77:850–853
10 Gilljam M, Corey M, Tullis D. Diagnosis of cystic fibrosis: epidemiological data from Toronto 1992–1997 [abstract]. Am J Respir Crit Care Med 1999:159:A684
11 Knudson R, Lebowitz M, Holberg C. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983; 127:725–734
12 Wadhera S, Millar W. Reproductive health, pregnancies and rates, Canada, 1974–1993. Ottawa, Canada: Statistics Canada, 1996
13 Kliegman R. Fetal and neonatal medicine. In: Behrman REKR, ed. Nelson essentials of pediatrics. New York, NY: WB Saunders, 1998; 167–225
14 Nolan G, McIvor P, Levison H, et al. Antibiotic prophylaxis in cystic fibrosis: inhaled cephaloridine as an adjunct to oral cloxacillin. J Pediatr 1982; 101:626–630
15 Reisman J, Rivington-Law B, Corey M, et al. The role of conventional physiotherapy in cystic fibrosis: a three year study. J Pediatr 1988; 113:632–636
16 Canadian Institute of Health. The health of Canada's children: a statistical profile. 2nd ed. Ottawa, Canada: Canadian Institute of Health, 1994; 224–414
17 Larsen J. Cystic fibrosis and pregnancy. Obstet Gynecol 1972; 39:880–883
18 Cohen LF, di Sant'Agnese P, Friedlander J. Cystic fibrosis and pregnancy. Lancet 1980; 2:842–844
19 Fiel S. Pulmonary function during pregnancy in cystic fibrosis: implications for counseling. Curr Opin Pulm Med 1996; 2:462–465
20 Kerem E, Reisman J, Corey M, et al. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992; 326:1187–1191
21 Corey M, Farewell V. Determinants of mortality from cystic fibrosis in Canada, 1979–1989. Am J Epidemiol 1995; 143: 1007–1017
22 Tanser S, Hodson M, Geddes D. *Pseudomonas cepacia* and poor outcome in cystic fibrosis pregnancy [abstract]. Am J Respir Crit Care Med 1999; 159:A681
23 Pasui K, McFarland KF. Management of diabetes in pregnancy. Am Fam Physician 1997; 55:2731–2738
24 Coustan D. Screening and testing for gestational diabetes. Obstet Gynecol Clin North Am 1996; 23:125–136
25 Lanng S, Hansen A, Thorsteinsson B, et al. Glucose tolerance in patients with cystic fibrosis: five year prospective study. BMJ 1995; 311:655–659
26 Moran A, Doherty L, Wang X, et al. Abnormal glucose metabolism in cystic fibrosis. J Pediatr 1998; 133:10–17
27 Moran A, Hardin D, Rodman D, et al. Diagnosis, screening, and management of cystic fibrosis-related diabetes mellitus: a consensus conference report. Diabetes Res Clin Pract 1999; 45:61–73
28 Haugen G, Aass H, Ihlen H, et al. Pregnancy in heart and heart-lung transplant recipients. Acta Obstet Gynecol Scand 1998; 77:574–581
29 Armenti VT, Gertner GS, Eisenberg JA, et al. National transplantation pregnancy registry: outcomes of pregnancies in lung recipients. Transplant Proc 1998; 30:1528–1530
30 Troche' V, Ville Y, Fernandez H. Pregnancy after heart or heart-lung transplantation: a series of 10 pregnancies. Br J Obstet Gynaecol 1998; 105:454–458
31 Elkus R, Popovich J. Respiratory physiology in pregnancy. Clin Chest Med 1992; 13:555–565
32 Hedstrom S, Martens MG. Antibiotics in pregnancy. Clin Obstet Gynecol 1993; 36:886–892
33 Davidson P. Managing tuberculosis during pregnancy. Lancet 1995; 346:199–200
34 Luskin A. An overview of the recommendations of the Working Group on Asthma and Pregnancy. J Allergy Clin Immunol 1999; 103(suppl):S350–S353
35 Bitman J, Hamosh M, Wood DL, et al. Lipid composition of milk from mothers with cystic fibrosis. Pediatrics 1987; 80:927–932
36 Rosenstein B, Cutting G. The diagnosis of cystic fibrosis: a consensus statement. J Pediatr 1998; 132:589–595
37 Sawyer SM. Reproductive health in young people with cystic fibrosis. Curr Opin Pediatr 1995; 7:376–380
38 Johannesson M, Landgren B-M, Csemiczky C, et al. Female patients with cystic fibrosis suffer from reproductive endocrinological disorders despite good clinical status. Hum Reprod 1998; 13:2092–2097