Cystic fibrosis in pregnancy

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Objective: To review the outcomes of pregnancies in women with cystic fibrosis (CF) and to address issues pertinent to the obstetric care of such women.
Data sources: English-language case reports and case series published from 1960 to 1991 identified through a search of MEDLINE and *Index Medicus*. The terms of reference were "cystic fibrosis" and "pregnancy." Not all the reports reviewed addressed all the outcomes under consideration.
Study selection: A total of 20 reports citing cases of pregnancy in women with CF.
Data extraction: Outcomes included the number of spontaneous abortions, pregnancies continued beyond 20 weeks, preterm deliveries, maternal deaths at 6 months and 2 years after delivery and perinatal deaths. Breast-feeding was addressed. Measures to assess the severity of maternal disease included the mean age at diagnosis of CF, weight gain during pregnancy, pulmonary function studies if available and the need for pancreatic enzyme replacement therapy.
Data synthesis: Of 217 pregnancies in 162 women spontaneous abortion occurred in 10 (4.6%). Pregnancy progressed beyond 20 weeks in 81.6% of cases; 24.3% of the deliveries were preterm. The maternal death rate did not exceed that among age-related women with CF who were not pregnant. The rate of perinatal death was 7.9%. Breast milk was not hypernatremic. Poor outcomes were associated with a weight gain of less than 4.5 kg and a forced vital capacity of less than 50% of the predicted value.
Conclusions: Premature labour and delivery remain a significant risk for pregnant women with CF, contributing to a high rate of perinatal death. Maternal illness and death result from deteriorating pulmonary function. Breast-feeding is not contraindicated. Attention to energy intake and pulmonary function is important.

Objectif : Examiner l'issue de la grossesse chez les femmes atteintes de fibrose kystique (FK) et traiter des questions pertinentes aux soins obstétricaux de ces femmes.
Sources des données : Exposés et recueils de cas publiés en anglais de 1960 à 1991 et identifiés au moyen d'une recherche dans MEDLINE et l'*Index Medicus*. Les mots clés étaient «fibrose kystique» et «grossesse». Les exposés examinés ne traitent pas tous de l'ensemble des issues à l'étude.
Sélection d'études : Un total de 20 exposés mentionnant des cas de grossesse chez des femmes atteintes de FK.
Extraction de données : Les issues comprenaient le nombre d'avortements spontanés, les grossesses qui ont dépassé 20 semaines, les accouchements prématurés, les décès maternels 6 mois et 2 ans après l'accouchement et la mort périnatale. On a traité de l'allaitement maternel. Les mesures pour évaluer la gravité de la maladie chez la mère comprenaient l'âge moyen au moment du diagnostic de FK, le gain de poids pendant la grossesse, les études fonctionnelles respiratoires le cas échéant et la nécessité du traitement de substitution des enzymes pancréatiques.

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Synthèse des données : Sur 217 grossesses chez 162 femmes, un avortement spontané est survenu dans 10 (4,6 %) cas. La grossesse a dépassé 20 semaines dans 81,6 % des cas; 24,3 % des accouchements étaient prématurés. Le taux de mortalité maternelle n'a pas dépassé celui des femmes du même âge atteintes de FK qui n'étaient pas enceintes. Le taux de mortalité périnatale était de 7,9 %. Le lait maternel n'était pas hypernatrémique. Les issues défavorables étaient liées à un gain de poids de moins 4,5 kg et à une capacité vitale forcée de moins de 50 % de la valeur prévue.

Conclusions : Le travail et l'accouchement prématurés demeurent un risque significatif chez les femmes enceintes atteintes de FK, ce qui contribue à un taux élevé de mort périnatale. La maladie et le décès de la mère sont attribuables à une détérioration de la fonction respiratoire. L'allaitement maternel n'est pas contre-indiqué. Il est important de prêter attention à l'apport énergétique et à la fonction pulmonaire.

Cystic fibrosis (CF) is an autosomal recessive disease of exocrine glands. It causes the production of excess secretions and of secretions with abnormal electrolyte concentrations and, ultimately, the obstruction of the ducts of glands. Major manifestations include obstructive pulmonary disease, malabsorption, diabetes mellitus, liver and biliary disease and interference with fertility. Pulmonary hypertension and cor pulmonale can result.

Advances in both the detection and management of CF over the last 30 years have increased the median age at death, from infancy to the mid-30s or 40s.[1] Pregnancy in women with CF is no longer rare. The recent presentation at our hospital of two pregnant young women with this condition prompted a review of the outcomes.

We reviewed English-language articles on CF and pregnancy published from 1960 to 1991. Individual case reports and case series were identified through a search of MEDLINE and *Index Medicus* with "cystic fibrosis" and "pregnancy" as the terms of reference. Outcomes of interest included the number of pregnancies completed beyond 20 weeks, the incidence of spontaneous abortion, the proportion of women giving birth preterm (i.e., before 37 weeks' gestation), the maternal rate of death at 6 months and 2 years after delivery and the perinatal death rate. Breast-feeding in women with CF has not been identified as important, by and large, but we did review the small number of articles addressing this issue. Not all the individual case reports included information on all the outcomes of interest.

CF and pregnancy

The literature on CF and pregnancy dates back to a case report in 1960.[2] Since then, 20 reports of individual cases or reviews of case series have been published. The outcomes of interest have varied; however, all the case series addressed the spontaneous abortion rate, preterm delivery rate, maternal death rate at 6 months and 2 years and perinatal death rate.

The two largest case series to date are those by Cohen, di Sant'Agnese and Friedlander,[3] in 1980, and Canny and associates,[4] in 1991. The former was a survey of CF clinics in North America from 1975 to 1976; 129 pregnancies in 100 women were reviewed. The latter looked at 38 pregnancies in 25 women at a single centre from 1963 to 1990. The remaining articles were much smaller in scope, ranging from single case reports[2,5–12] to a series of 14 pregnancies.[13] Given the small numbers overall and the variation in outcomes reported, the results are limited. However, there is consensus on some outcomes of interest.

Unfortunately, there were no consistent criteria for the severity of the CF, which made comparisons difficult. In many reports the mean age at diagnosis of CF was provided. This was used to gauge the severity of the underlying disease, since as a general rule the earlier the age at diagnosis the more severe the CF. The mean age at diagnosis ranged from 5 months to 19 years. Pulmonary status was also a measure of severity. A number of articles stated the results of pulmonary function studies.[4–6,8,9,11,13,14] Maternal weight gain and the need for pancreatic enzyme replacement were also considered markers of the severity of the disease.[3,4,10,13,14]

A summary of the review of the literature appears in Table 1. There were 215 pregnancies reported in 160 women. To this we have added our two recent cases.

The overall rate of spontaneous abortion was 4.6%, ranging from 0% to 21.4%. Not all the pregnancies terminating voluntarily or involuntarily were reported.

In 81.6% of the cases the pregnancy progressed beyond 20 completed weeks; in 24.3% of these the delivery was preterm. Five preterm deliveries were because of maternal complications secondary to CF; however, in the remainder (88.4%) there was spontaneous preterm labour and delivery. One of the possible causes proposed for this high preterm labour rate included the potential effect of chronic hypoxia on the fetus, especially in women with poor pulmonary status. In a smaller series involving eight women Palmer and collaborators[13] addressed this by dividing their patients into two groups on the basis of pregravid pulmonary status. All cases of preterm labour and delivery and of maternal death occurred in the three women with the poorest pulmonary function before pregnancy. Pittard, Sorensen and Schnatz[16] found that out of four women the two cases of maternal death and the one case of preterm labour and delivery occurred in the two women with the worst lung function. The results of specific pulmonary function

studies are not stated in this review. The association between pulmonary status and poor outcome was also reflected in the initial case series, published in 1966,[15] in which 50% of the women had a deterioration in lung function during or shortly after their pregnancy. The preterm labour rate was also 50%. (Again, maternal death was related to progressive pulmonary dysfunction.) Many of these early reported cases occurred in women whose CF had been diagnosed late in their life or even during the index pregnancy.

In the largest series to date, the highest rate of preterm labour and delivery occurred in women who died of deteriorating lung function within 2 years after their delivery.[3] Perinatal death in this review was almost always the result of prematurity and, hence, highest in the offspring of the same group of women.

Preterm labour and delivery may also be related to poor maternal nutrition and pancreatic insufficiency, which would lead to malabsorption. Cohen and colleagues[3] noted a relation between preterm delivery, perinatal death and a weight gain of less than 4.5 kg throughout the pregnancy. Two studies reported the use of total parenteral nutrition to maintain energy intake sufficient to bring the pregnancy close to term before induction.[10,11]

Three studies reported on the need for pancreatic enzyme replacement therapy in 49 pregnancies in 32 women.[4,13,14] Pancreatic insufficiency was associated with a worse outcome in the series by Corkey and coworkers.[14] They demonstrated that the two women who required enzyme replacement therapy had a greater deterioration in lung function than the five who did not require enzymes. There were no cases of preterm labour or maternal death in their small series. It may be that the sample comprised women with less severe disease, since the mean age at diagnosis in this group was 15 years. In the larger series reported by Canny and associates[4] from the same unit, 50% of the 25 women required pancreatic enzyme replacement therapy; yet, there was no difference in outcome based on pancreatic insufficiency. The preterm delivery rate was only 5.9%, and there were no cases of perinatal death. Again, their sample may have included women with milder disease, because the mean weight gain was 10.4 kg and the mean prepregnancy forced vital capacity (FVC) was 80% of the predicted value. The mean age at diagnosis in this study was 12 years. Palmer and collaborators[13] found an equal number of women requiring pancreatic enzymes among those with marginal lung function and among those with good pulmonary function.

With regard to the maternal death rate, 7.9% of the women died within 6 months after delivery, and 13.6% were dead within 2 years. Maternal death was directly related to maternal pulmonary status. In the review by Cohen and colleagues[3] the 10 women who died within 6 months after delivery all had moderately severe pulmonary disease before pregnancy and exacerbations of their disease during the pregnancy. However, "moderately severe" was not defined. The maternal death rate in the sample was found to be similar to the death rate over the same period in nonpregnant women of similar ages with CF.

In 1972 Larson[8] reviewed the limited published reports to that point and felt that a prepregnancy FVC of less than 50% of the predicted value or the presence of cor pulmonale constituted a basis for a recommendation to terminate the pregnancy. The evidence for this recommendation was not well founded, since no measures of

Table 1: Outcomes of pregnancy in women with cystic fibrosis

Study	No. of pregnancies (and women)	No. (and %) of completed pregnancies*	No. (and %) of spontaneous abortions	No. (and %†) of preterm deliveries‡	No. (and %†) of maternal deaths		No. (and %†) of perinatal deaths
					< 6 mo after delivery	< 2 yr after delivery	
Case reports, 1960–79[2,5–8,15]	15 (12)	15 (100.0)	–	6 (40.0)	2 (13.3)	4 (26.7)	2 (13.3)
Cohen et al, 1980[3]	129 (100)	97 (75.2)	6 (4.7)	26 (26.8)	10 (10.3)	15 (15.5)	11 (11.3)
Corkey et al, 1981[14]	11 (7)	10 (90.9)	0	0	0	0	0
Palmer et al, 1983[13]	14 (8)	11 (78.6)	3 (21.4)	3 (27.3)	1 (9.1)	2 (18.2)	0
Pittard et al, 1987[16]	4 (4)	4 (100.0)	–	1 (25.0)	1 (25.0)	2 (50.0)	–
Case reports, 1980–87[9–12]	4 (4)	4 (100.0)	–	3 (75.0)	–	–	–
Canney et al, 1991[4]	38 (25)	34 (89.5)	1 (2.6)	2 (5.9)	0	1 (2.9)	1 (2.9)
Present report	2 (2)	2 (100.0)	0	2 (100.0)	–	–	0
Total	217 (162)	177 (81.6)	10 (4.6)	43 (24.3)	14 (7.9)	24 (13.6)	14 (7.9)

*At least 20 weeks' gestation.
†Proportion of completed pregnancies.
‡Rate of spontaneous preterm labour is 88.4% (38/43).

pulmonary status had been done in the small number of cases.

Most recently, Canny and associates[4] reported on two women with a prepregnancy FVC of less than 50% of the predicted value. The women elected to continue their pregnancies, and both pregnancies went to term. It was noted that the pulmonary status of the two women had been stable before they became pregnant. This was felt to be a more significant prognostic factor than the actual FVC.

Perinatal death occurred in 14 cases, for a rate of 7.9%. In 12 of these, death was largely the result of prematurity. In general, the infants were not small for gestational age at birth. There was no instance of congenital anomaly, despite the widespread use of antibiotics. There was one reported case of CF in an infant, a much lower rate than the 2.5% predicted from a carrier rate for the CF gene of 1:20 in the Caucasian population when the carrier status of the male partner is unknown. All the surviving offspring are obligate carriers of the gene.

Breast-feeding in women with CF

This issue has been sporadically addressed in the literature. The first analysis of breast milk from a mother with CF was reported in 1977.[17] A single sample obtained by manual expression early in the postpartum course was found to be hypernatremic. This led to a widespread belief that breast milk from mothers with CF was always hypernatremic. Subsequent reports disagreed with this conclusion.[18–20]

The level of sodium in colostrum is high, normal values being up to 60 mmol/L or more. It drops progressively to 10 mmol/L by day 20 (mature milk) because of an increase in the active reabsorption of sodium in the mammary gland by day 11. A nonlactating gland has a sodium content in the collecting ducts similar to that of plasma, because of stasis. The high sodium level found in the initial report[17] could be explained by these factors.

The first reported analysis of the breast milk of a mother with CF who breast-fed for 15 weeks showed the sodium concentration to be similar to that of control subjects without the condition.[18] The investigators also found an increase in the protein concentration and a decrease in the levels of total lipids. In 1983, Alpert and Cormier[19] confirmed that the sodium level in breast milk from two mothers with CF was normal, as was the protein concentration. A further report in 1989 confirmed this and showed that the total fat levels were in the low-normal range.[20] Bitman and associates[21] analysed the specific lipid content of milk from six women with CF. The mean total lipid levels were slightly less than those of normal controls, but in all cases they supplied the energy needs of the nursing infants. There have been no reports of infections developing in infants secondary to breast-feeding, despite the colonization of these mothers with *Staphylococcus aureus* and *Pseudomonas* species. Hypernatremic breast milk as a cause of hypernatremia in infants has been reported,[22] but none of the mothers had CF.

The two cases in our hospital illustrate the problems that can be encountered in pregnant women with CF. One case involved an 18-year-old primiparous woman with a prepregnancy FVC of 53% of the predicted value and a total weight gain during the pregnancy of 2 kg. She went into spontaneous preterm labour at 28 weeks' gestation and had a live male infant. During her pregnancy she had required a 2-week admission for intensive physiotherapy and intravenous antibiotic therapy at 14 weeks' gestation. The second case involved a 26-year-old primiparous patient who had been admitted three times during her pregnancy, at 8, 18 and 27 weeks' gestation, for the same reasons. She was also being followed for insulin-dependent diabetes mellitus, diagnosed 3 years before the pregnancy. The patient was admitted at 30 weeks' gestation with increasing abdominal pain secondary to poor bowel function and known intra-abdominal adhesions. Her prepregnancy FVC had been 90% of the predicted value and she had a weight gain of 10.5 kg. By 35 weeks of gestation she was requiring increasing doses of morphine for worsening bowel pain, and labour was induced. She had a live male infant. In both cases the maternal CF was diagnosed shortly after birth. The infants' birth weights were appropriate for gestational age. The second infant was breast-fed for 3 weeks after birth until maternal weight loss made it difficult to continue. The first was not breast-fed at all because of the mother's concerns about her ability to maintain an adequate energy intake.

Conclusions

Women with CF can have a successful pregnancy. Because of increased nutritional and cardiovascular demands the important concerns in the care of these women include careful management of lung function and adequate energy intake. Preterm labour and delivery constitute a significant obstetric risk. Patients should be educated about the symptoms and signs of preterm labour, such as increased vaginal discharge, vaginal bleeding, the onset of regular contractions and an increased pressure sensation. Routine examination of the cervix should be considered. The maternal death rate is similar to that among nonpregnant women of similar ages with CF, and death occurs predominantly as a result of pulmonary complications. Patients with a prepregnancy FVC of 50% or less of the expected value or evidence of cor pulmonale may be discouraged from becoming pregnant because they may be at greatest risk. However, that in itself is not grounds to consider termination of a pregnancy if the degree of lung function has been stable for some time. Perinatal death rates are higher among infants of women with CF, largely as a result of increased preterm deliveries. There appears to be

no great increase in risk to the fetus, aside from prematurity and the risk of inheriting the disease. Breast-feeding is not contraindicated, provided adequate energy intake can be maintained.

As the mean age of survival in patients with CF continues to rise, the number of women with this condition who become pregnant will continue to grow. Hence, we can look forward to meeting the challenges that these pregnancies present more often in the years to come.

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Oct. 3–6, 1993: American Nuclear Society Executive Conference on Engineering Excellence — Engineering's Role in Providing Technically Excellent Products in a Cost-Efficient Manner
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Jerome H. Goldberg, general chairman, American Nuclear Society Executive Conference, 555 N Kensington, La Grange Park, IL 60525; tel (708) 352-6611, fax (708) 352-6464

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Du 6 au 8 oct. 1993 : Conférence canadienne sur la gestion des déchets — Solutions innovatrices en matière de gestion des déchets : Perspectives d'avenir
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Oct. 9–13, 1993: Medical Oncology Board Review Course
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