

CYSTIC FIBROSIS CARRIER TESTING IN PREGNANCY IN CANADA

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Abstract

Objective: To assess the role of cystic fibrosis (CF) testing within the Canadian health care environment.

Methods: The Genetics and Maternal Fetal Medicine Committees of the Society of Obstetricians and Gynaecologists of Canada (SOGC) reviewed *Preconception and Prenatal Carrier Screening for Cystic Fibrosis Clinical and Laboratory Guidelines* produced by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) and other educational material from ACOG and ACMG.

Results: Background information related to cystic fibrosis, genetic mutation analysis, and one large clinical cystic fibrosis screening trial are reviewed.

Evidence: The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the report of the Canadian Task Force on the Periodic Health Exam.

Recommendations:

1. CF testing in pregnancy is indicated for individuals who may be at increased risk for CF due to considerations of family history or clinical manifestations. (II-2A)

Key Words

Cystic fibrosis, pregnancy, screening, prenatal diagnosis, molecular carrier testing

2. Before CF screening could be undertaken, each province/territory would have to review the ethnic diversity of its reproductive population to ensure that CF screening would be appropriate. (III-C)
3. Screening of all women during pregnancy for CF carrier status cannot be recommended at this time. (III-C)

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BACKGROUND

A large amount of obstetric and genetic screening is undertaken once a woman is identified as being pregnant. Of the considerable amount of "routine blood work" done in pregnancy, little has been evaluated for evidence-based outcomes. More recently, screening technology such as maternal serum screening and ultrasound has resulted in debate about the advantages and disadvantages of these screening technologies for routine use in pregnancy. Four areas that must be considered with regard to any form of screening in the pregnant (as well as the non-pregnant) population include: (1) opportunity for counselling of the

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patient prior to the screening, to assure informed choice, (2) timing of the screening, (3) laboratory technology, and (4) opportunity for diagnosis to occur to allow the option of termination of pregnancy.

Cystic fibrosis (CF) is inherited in an autosomal recessive fashion. If both biological parents of the fetus are carriers of a CF mutation, there is a 25% risk that the fetus would inherit the mutation gene from both parents and develop CF. Recent studies have identified more than 900 mutations within the CF gene.¹ Many of these mutations are rare, making complete carrier screening and reassurance difficult. The first CF mutation identified was $\Delta F508$,² which accounts for 70% of the CF mutations in Caucasians of Northern European descent³ but only 30% of CF mutations in individuals of Ashkenazi Jewish descent.⁴ A different mutation, W1282X, is more common in the Ashkenazi Jews.⁵ For Caucasians of Northern European descent the next most common 15–20 mutations account for less than half of the remaining detectable CF alleles.⁶ Table 1 reviews the incidence and carrier risk for CF based on race and ethnicity.⁷

Two screening strategies that have been considered are *couple-based screening*, in which both parents are tested simultaneously, and *sequential screening*, in which one parent is tested and, if identified as a carrier, his or her partner is then tested.

Counselling before screening requires a significant amount of time and must include discussion of many factors: the purpose of screening, the voluntary nature of the testing, the range of symptoms and severity of CF, the treatment of the disease and life expectancy, the genetics of CF and the population-estimated carrier risks in the parents' ethnic or racial group, factors to consider in deciding whether or not to have screening, and results. Most importantly, the implications of positive and, particularly, negative test results need to be carefully explained. If the patient/couple are found to be carriers of CF (true positive) this will cause anxiety and stress related to increased fetal risks and decisions regarding prenatal diagnosis and pregnancy outcome. Negative test results are usually true negatives but a false negative carrier test could result in an unexpectedly affected newborn/child. The mutation analysis has a very low rate of false positive or negative results.⁸

The timing of carrier screening is very important, and if

this type of program were to be introduced, a strong emphasis should be placed on preconception screening. Screening at the time of pregnancy adds significant stress to the process because of the specific time limits for prenatal diagnosis and termination of pregnancy.

METHODS

The Genetics and Maternal Fetal Medicine committees of the Society of Obstetricians and Gynaecologists of Canada reviewed the joint recommendations on preconception and prenatal carrier screening for cystic fibrosis produced in 2001 by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG), in their document *Preconception and Prenatal Carrier Screening for Cystic Fibrosis*.⁷ The colleges' patient information pamphlets *Cystic Fibrosis Carrier Testing: The Decision Is Yours* and *Cystic Fibrosis Testing: What Happens if Both My Partner and I Are Carriers?* were also reviewed. The major question addressed was how the recommendations from ACOG and ACMG relate to the Canadian obstetrical/genetic health care system.

The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table 2).⁹

DISCUSSION

The more than 900 cystic fibrosis trans-membrane conductance regulator (CFTR) mutations,¹ the ethnic diversity of Canadians, and the varied frequency of specific mutations in different ethnic groups present a major challenge for the laboratories involved in CF screening. The American College of Medical Genetics' statement on CF screening recommends testing a group of 25 mutations.⁸ For quality assurance, testing would need to be performed in laboratories familiar with molecular genetics technology and staffed with individuals with human genetics expertise who were able to provide interpretation of both positive and negative results, including residual risk. Current funding and human resources available for molecular genetic services in Canada would be unable to take on the additional workload generated by a population-wide CFTR screening program.

Prenatal diagnosis techniques such as chorionic villus sampling (CVS) or amniocentesis are available for the diagnosis of CF. The advantages, disadvantages, and risks of these techniques are well known¹⁰ but must be related to the patient as part of her prescreening education. The risk of pregnancy loss following these prenatal procedures would be estimated at 0.5% to 1.0% for amniocentesis and 1% to 2% for CVS.^{10,11}

At time of writing, the largest clinical experiment with CF prenatal screening took place with 27,000 women in a large California HMO.¹² This program offered prenatal screening

TABLE 1

INCIDENCE AND CARRIER RISK FOR CYSTIC FIBROSIS BASED ON RACE OR ETHNICITY⁷

Racial or Ethnic Group	Incidence of CF	Carrier Risk
Caucasians	1/3,300	1/29
Hispanics	1/8,000–9,000	1/46
African Americans	1/15,300	1/62
Asian Americans	1/32,100	1/90

TABLE 2 QUALITY OF EVIDENCE ASSESSMENT ⁹	CLASSIFICATION OF RECOMMENDATIONS
<p>The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.</p> <p>I: Evidence obtained from at least one properly randomized controlled trial.</p> <p>II-1: Evidence from well-designed controlled trials without randomization.</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</p> <p>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.</p> <p>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</p> <p>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</p> <p>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</p>

in a sequential format. The acceptance of testing was high and their carrier identification rate was appropriate for their population at 1 in 28. Screening was done by a panel of 37 CFTR mutations and the poly T variant.¹² Questions that continue to be asked regarding this type of program are related to cost effectiveness, the population request versus industry/medical/legal interest, and the larger issue of the ethics of screening during an already stressful time such as pregnancy.

The cost estimation of screening all pregnancies for cystic fibrosis by molecular techniques in Canada is not available. An estimate of the cost of screening for the Province of British Columbia can be calculated to give some perspective to the

laboratory cost but cannot estimate the additional costs of counselling, ultrasound, amniocentesis, and obstetrical management. The cost per person is \$160.00 (CDN), with approximately 4% of pregnant patients being positive, thus incurring subsequent testing of their partners. It is expected that 80% of women would give consent to prenatal maternal CF screening. Using an estimate of 40,000 deliveries, the cost is represented in Table 3.

RECOMMENDATIONS

1. CF testing in pregnancy is indicated for individuals who may be at increased risk for CF due to considerations of family history or clinical manifestations. (II-2A)
2. Before CF screening could be undertaken, each province/territory would have to review the ethnic diversity of its reproductive population to ensure that CF screening would be appropriate. (III-C)
3. Screening of all women during pregnancy for CF carrier status cannot be recommended at this time. (III-C)

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TABLE 3 ESTIMATED ANNUAL COST OF CF TESTING IN BRITISH COLUMBIA BASED ON 40,000 DELIVERIES		
N Tested		Cost of test (\$160 CDN)
Pregnant women (% of total pregnancies)	32,000 (80)	\$5,120,000
Partners after women tested positive (% of pregnancies tested)	1280 (4)	\$204,800
TOTAL	33,280	\$5,324,800
Source: Personal communication, S. Langlois, Molecular Geneticist, Canadian College of Medical Genetics.		

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