

# Planning for a Healthy Baby: Screening for Cystic Fibrosis

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Perhaps the one and only benefit of infertility is that it gives you time to plan carefully for the pregnancy. With the explosion in genetic knowledge in the past couple of decades, heritable conditions have come to play an increasingly important role in pre-conception counseling. Gene identification, characterization of disease-causing changes (mutations), and advances in genetic technology have led to a number of tests for the diagnosis of genetic disorders. Physicians seeing infertile couples have a unique opportunity to screen for and prevent life-threatening conditions *before* conception occurs. Yet many doctors have been slow to incorporate genetic screening into their practices so the burden of inquiry often falls upon the patient. The common autosomal recessive diseases include cystic fibrosis, sickle cell anemia, Tay Sachs and the thalassemias each of which has maximal frequency in different racial and ethnic groups. The following discussion is designed to introduce you to the most common but also the most complex of these conditions – cystic fibrosis.

## What is an autosomal recessive (AR) disease?

AR conditions require that an individual with the disease inherits two deleterious mutations in the same gene, one from each genetic parent. Carriers have just one abnormal mutation and are not affected. Currently most people do not know whether or not they are carriers. Family genetic and medical history is of limited value in assessing the risk of AR diseases because the chance of a match between two carriers for CF is only 1 in 841. Therefore, screening for carriers of AR diseases is a clear example of how new technology can provide would-be parents with information which may influence their reproductive choices.

The inheritance of AR diseases follows the classic Mendelian patterns you may remember from your high school biology class. When both partners are carriers, 1 in 4 children inherit two defective genes and have the disease; half of the offspring inherit one defective gene and thus are unaffected carriers; 1 in 4 children inherit two normal genes. If only one partner is a carrier, half of the children are also carriers but none should have the disease.

## The clinical facts about cystic fibrosis (CF)

Cystic fibrosis (CF) is the most common AR disease in the Caucasian population. Most children with CF are born to couples who do not even know that they are at high risk, because mass pre-conception screening has not been widely utilized. Like other AR conditions, the carrier frequency varies in different ethnic groups. In whites of European extraction, the carrier frequency is 1/29 and the frequency of children with CF is 1/3,300. Close to 1,000 children with CF are born in the United States each year.

Cystic fibrosis is a multisystem disorder, affecting glands which produce sweat, mucus, tears, saliva and digestive juices. There is a remarkable variability in the severity of the disease. The most serious manifestation is recurrent pulmonary infections progressively

destroying the lung tissue. More than 95% of men with CF are infertile, because they are born with a “natural vasectomy” called congenital absence of the vas deferens (CAVD): sperm are produced in the testes but do not get into the ejaculate. Otherwise healthy infertile men with isolated CAVD have 2 mutations one of which is typically of a milder variety than those which cause full-blown CF. CF usually presents in early childhood, although approximately 4% of patients are diagnosed as adults. Currently, there is no cure and the average life span is about 30 years.

### **Screening for CF and its limitations**

It was only in October 2001 that the American College of Obstetricians and Gynecologists and the American College of Medical Genetics recommended that CF screening be offered to all “couples in whom one or both partners are Caucasian and are planning a pregnancy or seeking prenatal care” even in the absence of family history. Screening programs for CF carriers must take into account the varying frequency of different mutations in diverse ethnic groups as well as the limited detection rate with most tests. Over 900 different mutations have been described but the standard panel includes just the 25 commonest ones. Thus, even when a person tests negative for CF, there always remains a small risk that he or she is in fact a carrier for a rare mutation which was not included in the test.

The enclosed tables show the benefit of screening when both partners belong to one of several ethnic groups listed. Table 1 provides the risk of being a carrier before testing, the detection rate, and the residual risk of being a carrier after testing negative. Table 2 lists the risk of having a child with CF before and after negative testing of just one parent when both partners belong to the same ethnic group. With ever increasing ethnic diversity, the limited data available for many groups and the frequent intermarriages between members of different ethnic backgrounds, you can appreciate that difficulty may be encountered in quantifying the exact risks facing a given couple.

### **What to do if one partner is a CF carrier?**

First of all, the other partner should also be screened for CF, because it takes two carriers to have a child with CF. However, having a negative CF screening test, does not mean that the risk of having an affected child is zero. Since the standard test fails to detect some carriers, there is a residual risk of being a carrier despite a negative test. As you can see in the Table 1, this residual risk ranges from a low of 1/930 to high of 1/105. The corresponding risk of having an affected offspring when one genetic parent is a known carrier and the other tests negative on the standard test also varies widely from a low of 1/3,720 for Ashkenazi Jews to a high of 1/420 for Hispanic Americans. For sake of comparison, the risks of having a child with Down syndrome when the woman providing the eggs is 30, 35 and 40 years of age are 1/952, 1/385 and 1/106, respectively.

Only you can decide what odds are acceptable to you. Fortunately, a more extensive test for almost all the 900 known mutations in the CF gene has become available recently. While more expensive, in this test the entire gene is sequenced so it can provide reassurance to couples where one partner is a carrier.

## **How can two carriers build a healthy family?**

If both would-be genetic parents are carriers for CF, the likelihood of having an affected child is 1 in 4 which is unacceptably high for almost most couples. Such patients have three medical options:

1. They can use sperm or donor eggs from a donor who tests negative.
2. They can initiate a pregnancy and then abort the fetus if it is shown to be affected through amniocentesis or chorionic villus sampling.
3. They can turn to the high tech option of in vitro fertilization (IVF) in conjunction with pre-implantation genetic diagnosis (PGD) by embryo biopsy. Here the genetic testing and selection of healthy embryos for transfer take place before implantation and pregnancy have occurred. However, IVF with PGD has its drawbacks too. Since PGD tests just a single cell, it is less reliable than amniocentesis and errors have been reported. Obviously, the live birth rate from a single IVF cycle is far from 100% while the procedures are complex, invasive and expensive. The high tech PGD option is of most interest to infertile couples who already require IVF to conceive, such as couples where the man is infertile because of CAVD.

## **Screening egg and sperm donors for CF**

Few reproductive decisions are as carefully premeditated as the selection of an egg or sperm donor. Whereas genetic screening of sperm donors has been nearly universal for many years, a survey of donor egg programs published in 1999 revealed that 78% of ART programs did not screen egg donors for CF. The guidelines of the American Society for Reproductive Medicine (ASRM) have recommended testing for CF since 1993 but the adoption of screening by practitioners has lagged in part because of the unique complexity of CF tests.

The current 1998 ASRM guidelines not only recommend screening for the common AR diseases including CF, but also state that carriers need not automatically be excluded from donor pools. We have recently published an analysis of our initial experience with screening of donor egg applicants for CF at the Alta Bates IVF Program and the response of recipients to the inclusion of CF positive donors within the donor pool. While CF positive donors were about half as likely to be selected as non-carriers, some recipients did choose donors who were carriers for CF provided the recipient's partner tested negative. One of the donor applicants who turned out to be a carrier had previously donated in another California program without having ever been tested. Regardless of whether CF carriers are included in the donor pool, screening Caucasian egg donor applicants should be universal.

## **Making reproductive choices**

In contrast to screening for genetic disease in newborns and adults, screening for carriers has, as its main purpose, the identification of individuals who, while themselves healthy, are at risk for having children with a severe disease. Screening is appropriate in specific ethnic groups in which the carrier frequency is high enough to justify the cost. For cystic fibrosis that group comprises the entire Caucasian population. Although genetic testing for CF is not 100% reliable, the residual risk of having an affected child can be calculated

and discussed with the couple seeking conception. Assessment of risks by patients seldom coincides with expert opinion. However, the experts in the field of risk assessment wisely conclude that “in our democracy, people are final arbiters of how safe is safe enough”. Since the future child’s well-being must be the touchstone of policy and the would-be parents are the best guardians of their child’s welfare, the policy at Alta Bates has been to leave the decisions whether or not to test and what to do with the results of testing to fully informed consumers of our medical services.

**Table 1:** *The detection rate and the probability of being a carrier for cystic fibrosis before and after testing in different populations.*

<b>Ethnic Group</b>	<b>Risk of Being a CF Carrier</b>	<b>Detection Rate</b>	<b>Risk of being a CF carrier after negative testing</b>
Ashkenazi Jews	1/29	97%	1/930
Northern Europeans	1/29	90%	1/290
Southern Europeans	1/29	74%	1/111
Hispanics	1/46	57%	1/105

**Table 2:** *The probability of having a child with CF before testing and after one partner tests negative in different populations.*

<b>Ethnic Group</b>	<b>Risk of having a child with CF without testing</b>	<b>Risk of having a child with CF if one partner tests negative</b>
Ashkenazi Jews	1/ 3,364	1/ 101,880
Northern Europeans	1/ 3,364	1/ 33, 640
Southern Europeans	1/ 3,364	1/ 12, 876
Hispanics	1/ 8,464	1/ 19,320

**Additional Readings:**

The American College of Obstetricians and Gynecologists and American College of Medical Genetics. *Preconception and prenatal carrier screening for cystic fibrosis: Clinical and laboratory guidelines.* October 2001.

Ulrike Zenke and Richard Chetkowski. *Inclusion of heterozygotes for cystic fibrosis in the egg donor pool.* Fertility and Sterility September 2002; volume 73, pages 557-561.