LETTER TO JMG

Prenatal detection of cystic fibrosis by ultrasonography: a retrospective study of more than 346 000 pregnancies

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Cystic fibrosis (CF) is the commonest severe autosomal recessive disease that affects children in white populations, with an incidence varying from 1/2500 to 1/5000 (carrier rate 1/25 to 1/35).¹ The disease, which is characterised by chronic pulmonary obstruction and infections, and by digestive disorders such as pancreatic insufficiency, is caused by mutations in a gene which encodes a protein called CFTR (cystic fibrosis transmembrane conductance regulator).

The cloning of the *CFTR* gene in 1989^{2–4} and the identification of more than 1000 mutations,⁵ with geographical and ethnic variations, have enabled prenatal testing for CF by direct detection of mutations. Initially, prenatal testing was only offered to families in which there was a previous history of CF. More recently, the medical assessment of pregnancy performed in some countries has allowed, through systematic ultrasound examinations, the prenatal diagnosis of bowel echogenicity, an abnormality suggestive of CF. The fetus can therefore become the proband in this disease.

Fetal echogenic bowel, defined as bowel with sonographic density greater than that of the surrounding bone, is diagnosed in 0.2–1.8% of fetuses during routine ultrasound examination in the second trimester of pregnancy.^{6–10} This intestinal echogenicity was initially described as a normal variant, which usually disappeared at 20 weeks of gestation.^{11, 12} More recently, it has also been associated with fetal abnormalities, such as chromosomal abnormalities,^{6, 8, 10, 13–17} congenital infections,^{18–20} intestinal obstruction,^{20–22} and CF. In this latter case, it is probably the result of the malfunctioning of the CFTR protein leading to the dehydration of mucus secretions, which become viscous, obstruct the bowel lumen, and cause meconium ileus.²³ The risk for CF in fetuses with echogenic bowel has been extensively studied^{6, 9, 10, 13, 16, 20, 21, 24–30} and is shown to vary from 0–33%. This wide range could be the result of differences in ascertainment, CF prevalence, and mutation detection rate.

The discovery of more than 1000 different mutations in the *CFTR* gene makes it impossible to detect all mutations by simple routine screening. Consequently, in general, prenatal testing consists of analysis of a limited number of known mutations, and the mutation detection rate varies according to the molecular technique used, the proportion of the gene screened, and the ethnic origin of the population tested.

In this study, we report 10 years of experience of prenatal testing for CF in pregnancies which showed an echogenic bowel in Brittany (France), a region with one of the highest incidences of CF in the world (incidence 1/2913, carrier rate 1/27)^{31–33} and where more than 99% of *CFTR* mutations have been identified.^{33, 34} We reviewed all consecutive cases of fetal echogenic bowel diagnosed in pregnant women referred for a prenatal test. We determined the frequency of echogenic bowel, the incidence of CF, the type and nature of *CFTR* mutations, and, using Bayesian calculations, the risk of CF in fetuses with echogenic bowel but with one or no *CFTR* mutations detected. Finally, we assessed the efficacy of ultrasonography as a screening tool for CF in utero and included infor-

mation about other diagnoses related to non-CF associated echogenic bowel.

METHODS

Study population

Over the 10 year period (1991–2000), 346 554 pregnancies had a routine ultrasonographic examination at 22 weeks in Brittany, a region of the western part of France, with 2.8 million inhabitants of mostly Celtic origin, and in which a CF neonatal screening programme has been implemented since 1989.^{33, 35} This number of pregnancies was obtained from the neonatal screening data. It corresponded to the number of neonates screened for CF at birth over this 10 year period (n=346 544), added to the number of therapeutic abortions performed for a diagnosis of CF over the same time (n=10). This calculation did not include spontaneous abortions or therapeutic abortions performed for other clinical reasons.

We retrospectively registered all the pregnant women in whom a fetal echogenic bowel was diagnosed, and who were referred for a prenatal molecular test for CF to one of the two genetic laboratories in Brittany (Brest or Rennes). A total of 142 cases were included in this study from 1 January 1991 (year of the first prenatal tests) to 31 December 2000.

This study fulfilled the bioethical rules applied in France. Informed consent was obtained before samples of blood and fetal tissue were taken.

Definition of echogenicity

In France, the medical follow up of pregnancy includes three obligatory ultrasound examinations around the 10th, 22nd, and 32nd weeks of gestation. An abnormality such as intestinal echogenicity can be detected during the examination in the second trimester. The bowel of a fetus is considered hyper-echogenic if its degree of echogenicity is similar to or greater than that of the surrounding bone.

Prenatal detection of cystic fibrosis in fetuses with an echogenic bowel

Couples whose fetus showed an echogenic bowel were referred for genetic counselling in order to explain the possibility of a prenatal test for CF and the methodology, which is shown in fig 1. They were also offered fetal karyotyping and dosage for infections including CMV, EBV, and toxoplasmosis.

Prenatal testing for CF consists of a search for the most common *CFTR* mutations in parental DNA samples. The initial molecular analysis relies on systematic amplification by polymerase chain reaction of three exons (7, 10, and 11), which contain 87% of the *CFTR* mutations in our population, followed by screening for mutations by denaturing gradient gel electrophoresis (DGGE)³⁴ or more recently by denaturing high performance liquid chromatography (DHPLC).³⁶

If both parents are found to be carriers of one *CFTR* mutation, prenatal diagnosis for CF is suggested to the couple. Their mutations are sought in chorionic villus samples or in

Figure 1 Strategy for testing for *CFTR* mutations following an ultrasound diagnosis of echogenic bowel. R^* =Residual risk of cystic fibrosis, assuming an incidence of 9.9% and a carrier rate of 7.7%.

amniotic fluid cells, depending on the term of pregnancy. The fetus is considered to be affected with CF when it carries mutations from both parents. In this case, parents are offered genetic counselling and the option of a termination of pregnancy. Data on the outcome of the pregnancies was obtained from the referring practitioners.

If the analysis of the parental samples identifies only one *CFTR* mutation, this mutation is sought in the fetal DNA sample. If the fetus also carries this mutation, another nine exons of the gene are analysed, in a predefined order according to the frequency of mutations in our population, as not all the mutations are systematically sought (exons 3, 4, 13, 14a, 14b, 17b, 19, 20, and finally 21). This extended analysis has a mutation detection rate of 98.5% (that is, a complementary rate of 11.5%). If this complementary analysis does not identify a second mutation in the fetus, genetic counselling is offered to parents to inform them about the residual risk of CF in their child.

Finally, if no *CFTR* mutation is detected in parental DNA samples, the molecular analysis is stopped and the parents are informed of the residual risk of CF.

The families in whom a CF affected or carrier fetus was identified were offered genetic counselling and cascade carrier screening. The pregnancies carried to term produced babies who were screened for CF at birth by the neonatal screening programme implemented in this region. The neonates in whom an echogenic bowel was prenatally diagnosed, and who were found to be carriers of one detectable *CFTR* mutation, were referred for a sweat test three months after birth.

Statistical analysis

Incidences of CF and of heterozygosity before a sonographic diagnosis of fetal echogenic bowel were calculated and compared to incidences in the general population. Mutations identified in affected fetuses and in heterozygotes were characterised.

The probability of finding CF in a fetus with echogenic bowel and either one or no *CFTR* mutations was determined using Bayesian calculations. These probabilities corresponded to the proportion of CF fetuses in which only one (or no) detectable mutation was identified among all fetuses with one (or no) detectable mutation. These risks allowed us to calculate the proportion of CF fetuses in which two, one, or no mutations would be detected by our strategy, and the proportion of non-CF fetuses carrying a single detectable mutation. They were calculated by the following formulae.

Residual risk of CF for fetus with echogenic bowel and one detectable mutation:

$$\text{Risk} = \frac{\text{Proportion of CF fetuses with one detectable mutation}}{\text{Proportion of fetuses with one detectable mutation}}$$

$$= \frac{P(1 \text{ mutation/CF}) * P(\text{CF})}{[P(1 \text{ mutation/CF}) * P(\text{CF})] + [P(1 \text{ mutation/non-CF}) * P(\text{non-CF})]}$$

Residual risk of CF for fetus with echogenic bowel and no detectable mutation:

$$\text{Risk} = \frac{\text{Proportion of CF fetuses with no detectable mutation}}{\text{Proportion of fetuses with one detectable mutation}}$$

$$= \frac{P(O \text{ mutation}/CF) * P(CF)}{[P(O \text{ mutation}/CF) * P(CF)] + [P(O \text{ mutation}/\text{non-CF}) * P(\text{non-CF})]}$$

where:

- P(CF): probability that the fetus has CF
- P(non-CF): probability that the fetus does not have CF
- P(1 mutation/CF): probability that the fetus has CF when one mutation is detected
- P(1 mutation/non-CF): probability that the fetus does not have CF when one mutation is detected.

Finally, we assessed the proportion of fetuses affected with CF that were diagnosed by ultrasonography over this period, and described the other diagnoses made in the non-CF fetuses.

RESULTS

Frequency of the diagnosis of echogenic bowel during pregnancy

Over this 10 year period, 346 554 pregnancies, which did not end with a spontaneous abortion, had an ultrasound examination. Echogenic bowel was diagnosed during the second trimester in 142 cases which were referred for a prenatal test for CF.

Incidence of cystic fibrosis among fetuses with echogenic bowel

We identified 14 fetuses which carried two *CFTR* mutations out of the 142 cases. This implies an incidence of CF in this population of approximately 1 in 10 (that is, 9.9%), a rate 294 times higher than the incidence of 1 in 2987 in the general population in Brittany, as calculated from the neonatal screening programme during the 10 years of study ($p < 0.001$).

Twelve of these 14 affected fetuses were tested prenatally, as described above. CF was diagnosed in 10 fetuses by the first step of the protocol (analysis of exons 7, 10, and 11) and in two fetuses after the complementary analysis. Nine of these pregnancies were terminated at the parents' request and three were carried to term (one because the diagnosis was only made at 34 weeks of gestation).

Prenatal testing gave a false negative result for two other cases despite the additional DNA analysis. These two fetuses carried, on one allele, the $\Delta F508$ mutation and, on the other, a rare mutation, which was not among the exons tested in our protocol (exons 6a and 17a). As the presence of fetal echogenic bowel together with one *CFTR* mutation is associated with an increased risk of CF, one of the two couples elected to terminate the pregnancy, whereas the other chose to carry it to term. The sweat test performed three months after birth in this last child was positive, and this led to an exhaustive screening of the gene, which identified the second mutation in exon 6a (Q220X). An extended screening of the gene was also performed in the couple who chose termination. This led to the detection of the mutation 3129del4 in exon 17a inherited from the other parent.

All the pregnancies carried to term among the 142 with echogenic bowel delivered babies who were screened for CF at birth by the neonatal screening programme implemented in our region. CF was not postnatally diagnosed in any of these children, except for the case in which the DNA testing was misleading, and for the affected pregnancy carried to term.

The *CFTR* mutations identified in the CF fetuses who showed an echogenic bowel were associated with pancreatic insufficiency and considered to be severe; they all belong to classes I or II of the classification proposed by Welsh and Smith.³⁷ All the fetuses carried the main mutation, $\Delta F508$, at least on one chromosome. Nine of them were homozygotes and five were compound heterozygotes, carrying on the other chromosome a severe mutation which is usually rare in our population: there were two nonsense mutations (Q220X,

W1282X), two splice mutations (4005+1 G→A, 1717-1 G→A), and one frameshift mutation (3129del4). The genotypes of the CF fetuses are shown in table 1.

Incidence of CF heterozygosity among fetuses with echogenic bowel

The fetus had a single *CFTR* mutation in 11 of the 142 cases (7.7% or 1 in 13). The analysis of nine other exons of the gene was continued in these fetuses but no other mutation was identified. The sweat tests performed in neonates with echogenic bowel and one *CFTR* mutation were all negative, except for the case in which the DNA test was misleading. The incidence of CF heterozygosity was significantly higher in fetuses with echogenic bowel than in the general population (rate estimated as 1 in 28, $p < 0.001$). The heterozygous fetuses carried a severe molecular abnormality ($\Delta F508$ ($n=9$) or G542X ($n=1$)), except one who carried a mild mutation (R347H).

Residual risk of cystic fibrosis for fetuses with echogenic bowel

The work presented here led us to calculate, using Bayesian calculations, the residual risk of CF in fetuses with echogenic bowel, and in which one or no *CFTR* mutation was identified. This risk depends heavily on the incidence of CF before a diagnosis of echogenic bowel (that is, the prior risk), on the carrier frequency, and on the mutation detection rate, which varies according to the test used, and between ethnic groups.^{23 28 38}

In our population, prenatal testing consists of the systematic analysis, in both parents, of three exons of the *CFTR* gene containing 87% of known mutations. This is followed by a complementary study in fetuses in which only one mutation is identified. This systematic analysis will identify two detectable mutations in 75.7% (0.87×0.87) of CF fetuses, one detectable mutation in 22.6% ($((0.87 \times 0.13) + (0.13 \times 0.87))$) of CF fetuses, and no detectable mutation in 1.7% (0.13×0.13) of CF fetuses. The complementary analysis performed when only one mutation is identified in a fetus detects 88.5% of the remaining mutations (that is, 11.5%/13%) and leads to an overall mutation detection rate of 98.5%. Therefore, the second mutation

Table 1 Incidence of cystic fibrosis and CF heterozygosity among fetuses with echogenic bowel in Brittany, France (1991–2000)

Fetuses with echogenic bowel	142
Affected fetuses	
Number	14
Incidence	1/10
Genotypes	
$\Delta F508/\Delta F508$	9
$\Delta F508/4005+1G \rightarrow A$	1
$\Delta F508/3129del4$	1
$\Delta F508/Q220X$	1
$\Delta F508/W1282X$	1
$\Delta F508/1717-1G \rightarrow A$	1
CF incidence in the general population during the present study	1/2987
Risk of CF: echogenic bowel fetuses/general population	294
Heterozygous fetuses	
Number	11
Incidence	1/13
Mutations	
$\Delta F508$	9
G542X	1
R347H	1
CF heterozygosity in the general population during the present study	1/28
Risk of CF heterozygosity: echogenic bowel fetuses/general population	2.2

Table 2 Ability of the ultrasound examination to detect cystic fibrosis

	Cystic fibrosis		Total
	Yes	No	
Ultrasound examination			
Abnormal	14	128	142
Normal	112	346 300	346 412
Total	126	346 428	346 554

will be identified in 88.5% of the 22.6% of fetuses for which the first analysis identified only one mutation (that is, in 20.0% of all CF fetuses). This second mutation will not be identified in 11.5% (1.5/13) of these fetuses (that is, in 2.6% of all CF fetuses).

This enables us to calculate the residual risk of CF by applying the formulae described in the methods section. The identification of a mutation in exons 7, 10, or 11 in a fetus with echogenic bowel increases the residual risk of being CF to 1 in 4.1 (24%) (assuming a prior risk of 9.9%, a mutation detection rate of 87%, and a carrier rate of 7.7%). The complementary analysis performed when a mutation is identified in one of these three exons enables us to reduce this risk from 1 in 4.1 to 1 in 28 (that is, 3.6%). Finally, when no mutation is identified in a fetus with echogenic bowel, the residual risk of CF is 1 in 500 in our population. The residual risk calculated in our population of fetuses with echogenic bowel in whom only one mutation was detected is in complete agreement with the theoretical risk value predicted by Bosco *et al.*²³

Frequency of CF fetuses diagnosed by ultrasonography over this 10 year period

Over this 10 year period, the neonatal screening programme identified 116 CF affected neonates among the 346 544 neonates screened (incidence 1/2987). A diagnosis of fetal echogenic bowel was made in four of these 116 children (the case in which the molecular analysis was misleading and the three cases in which the affected pregnancy was carried to term). Over the same period, 10 pregnancies, which showed an echogenic bowel, were terminated because of a diagnosis of CF. Consequently, among the 126 fetuses affected with CF over this period, 14 showed an echogenic bowel (table 2). The ultrasound examination had therefore enabled the identification of 11% of the CF fetuses.

Outcome of the non-CF fetuses

Among the 128 fetuses with echogenic bowel which did not have CF, six had a karyotypic abnormality (4.7%), including Down syndrome (n=3), Turner syndrome (n=2), and trisomy 18 (n=1). Four other fetuses had a congenital viral infection (3.1%), including cytomegalovirus infection (n=3) and toxoplasmosis (n=1). Finally, the following rare pathologies were diagnosed in two other fetuses: toxemia gravidis in one and tetralogy of Fallot in the other. We noted among these 128 pregnancies, eight terminations of pregnancy for medical reasons and nine deaths in utero.

DISCUSSION

Prenatal testing for CF was initially offered solely to families in which there was a previous history of CF. The medical follow up of pregnancy in some countries has allowed the diagnosis of bowel echogenicity, an abnormality suggestive of CF in which the fetus has become the proband of this disease.

In this study, we summarised 10 years of experience of prenatal detection of CF after an ultrasound diagnosis of echogenic bowel in a region with a homogeneous population (the inhabitants are mostly of Celtic origin) and where the

disease is frequent.^{31 32} Our results confirm that the ultrasound detection of fetal echogenic bowel is associated with an increased risk of CF in pregnancies otherwise at low risk for this disease (1/10 versus 1/2987). The rate is increased (9.9%) but remains within the range previously reported. It is close to the rate of CF neonates with meconium ileus (10-15%). The risk of CF following an ultrasound diagnosis of fetal echogenic bowel has been extensively studied and varies from 0% to 33.3%.^{6 9 10 13 16 20 21 24-30}

There are several possible explanations for this wide range. Firstly, the determination of bowel echogenicity remains relatively subjective, which can lead to variability in detection between operators and, therefore, variability in the incidence between studies.³⁹⁻⁴¹ This subjectivity is increased by the differences in the type of ultrasound equipment used (for example, transducer frequency, sonographer expertise)⁴² and by the multitude of sonographers included in studies. Some strategies can be used to increase the objectivity of this examination, such as comparison of the echogenicity of the bowel with that of other fetal tissues (for example, bone, liver) and grading of the degree of echogenicity. However, this definition remains imprecise and differs between authors. Indeed, according to Bromley *et al.*⁸ or to MacGregor *et al.*²⁵ echogenicity should be similar to the surrounding bone (criterion used in this study), whereas according to Nyberg *et al.*⁷ it should be similar to the liver. Hill *et al.*¹⁹ proposed the following grading of echogenicity: grade I when the echogenicity is greater than in the liver and grade II when it is greater than in the bone. The lack of standardisation in the definition of echogenic bowel could result in an increased number of false positive results and thus in an underestimation of the incidence. To illustrate this, Ferriman *et al.*⁴⁰ reported a 1.2% risk of CF in their fetuses with echogenic bowel without considering homogeneous criteria in the definition of echogenicity, whereas restricting this definition to a mass more echogenic than bone, the incidence was 6%.

Secondly, awareness of the high incidence of CF in some regions may lead practitioners to be more suspicious, therefore more ready to associate the diagnosis of echogenic bowel with CF, and to prescribe a prenatal test in case of doubt. This interventionist behaviour may also lead to variability in incidence.

Finally, in some regions, the diagnoses of echogenic bowel are sent, before molecular analysis, to a reference centre which confirms or refutes the diagnosis. In this situation, possible diagnoses can be refuted and the incidence of CF is therefore increased. This strategy is applied in our region and could explain the high incidence of CF we observed.

In previously published studies, prenatal testing relied on screening for a limited number of known mutations with a detection rate ranging from 75% to 90%.^{9 26-28} We adopted a different strategy in Brittany. We chose to study a larger part of the gene and, more particularly, scan routinely three entire exons known to contain more than 85% of the mutations present in our CF population (exons 7, 10, and 11). This approach allowed the detection of a larger spectrum of mutations and, notably, new mutations in this homogeneous population.

Our study also shows that the carrier rate among fetuses with echogenic bowel is significantly higher than the expected rate (1/13 versus 1/28). The finding of a high carrier rate is independent of the high mutation detection rate, since both identified mutations are routinely searched for. To our knowledge, this study is the first which reported a significant difference; Muller *et al.*²⁷ and Monaghan and Feldman²⁸ did not find a significantly increased rate. However, they based their comparison on an expected carrier rate in the general population which appears to be overestimated.¹

The *CFTR* mutations identified in fetuses with echogenic bowel that have been reported so far are associated with pancreatic insufficiency (for example, $\Delta F508$, G542X, G551D,

2183AA→G, ΔF311).^{9 13 27 43} To our knowledge, only one mutation associated with a mild phenotype (R117H)¹³ and one mild complex *CFTR* allele (D443Y-G576A-R668C)⁴⁴ have been identified in two of the CF affected fetuses.

In this series, fetal echogenic bowel is only associated with “severe” *CFTR* mutations. Besides the ΔF508 mutation, the five other mutations detected in affected fetuses are all “severe”. This was also observed in heterozygotes, excepted for one case (mutation R347H). The extensive screening of the gene performed when a sole mutation was identified did not lead to the identification of mild mutations or molecular abnormalities for which the pathogenicity was impossible to determine, which could have led to ambiguity in the prediction of the phenotype. Therefore, the spectrum of mutations identified in this fetal population is not representative of that identified in our CF population, in which we found a significant number of mild mutations or mutations for which the clinical consequences are not yet established (for example, G91R, R117H, R347L, R560K).^{34 35} These findings provide the foundation for further investigations towards understanding the pathogenesis of early bowel disease, but also why it results in manifestations in the bowel rather than in the lungs during the fetal period.

The probability of CF given echogenic bowel and one *CFTR* mutation varies according to the ethnic origin of the population, and the highest probability occurs in populations with the lowest detection rate and generally the lowest carrier frequency.^{23 28} Monaghan and Feldman²⁸ recently reported that the residual risk of CF in white fetuses of this type ranged from 14% to 50%, when considering a prior risk of 3.3% to 13.3% and a mutation detection rate of 90%. In the African-American population in which the detection rate is only 67%, the residual risk of CF varied from 61% to 90%.²⁸ Consequently, despite the high incidence of CF in Brittany, the residual risk remains relatively low (3.6%, that is, 1 in 28) because of the high mutation detection rate reached with the complementary DNA analysis. When no mutation is identified in fetuses with echogenic bowel, the residual risk is 1 in 500.

A similar rate of mutation detection to that reported in our population (about 87%) can easily be obtained with different kits available at this time, notably the OLA kit (PE-Biosystems) which identifies 31 mutations and leads to a detection rate of 80–90% in white populations.

We have recently validated a new technique, DHPLC,⁴⁵ for the scanning of the CF gene which can be performed in less than a week.³⁶ This scanning method will be very efficient in heterogeneous populations that are at low risk of CF and in which the mutation detection rate obtained by the available kits is very low.

This work highlights the importance of testing for *CFTR* mutation in cases of a prenatal diagnosis of echogenic bowel, as well as the importance of complementary efforts to search for a second mutation in apparently heterozygous fetuses, which greatly reduce the residual risk of CF. However, we should be aware that false negative results are still a possibility. Therefore, proper genetic counselling is much needed. Furthermore, these investigations generate anxiety in the families and can take time, because more than 1000 *CFTR* mutations have now been identified and the second mutation is often a rare one. An early diagnosis is crucial to allow the option of pregnancy termination, which, in some cases, cannot be offered because of the late discovery of fetal abnormalities combined with the difficulty of identifying rare mutations. It is very important to calculate the residual risk of CF in these couples, and to inform them of the limitations of the genetic testing, and particularly that a fetus with one *CFTR* mutation can carry an undetected mutation on the other allele and consequently have CF.

Our results show that ultrasound detection of fetal echogenic bowel is associated with an increased risk of CF. Therefore, CF testing, which is effective when based on our approach, should be included in the investigation when fetal echogenic bowel is

Key points

- Fetal echogenic bowel has been associated with an increased risk of cystic fibrosis (CF), but this risk varies according to studies.
- We report here a 10 year experience (1991–2000) of prenatal testing for CF performed in fetuses with echogenic bowel in Brittany (France), a region where the disease is frequent. Testing relied on an initial analysis of three exons of the *CFTR* gene (87% mutation detection rate) followed by an extended analysis of other exons when only one mutation was detected (98.5% detection rate).
- The incidence of CF in fetuses with echogenic bowel was 9.9%, a rate significantly higher than in the general population ($p < 0.001$). Only “severe” mutations were identified in these fetuses. The heterozygote rate was also significantly higher than expected (7.7%, $p < 0.001$). Based on this carrier rate, the residual risk for such fetuses of having CF was 1/28 when one mutation was detected by our protocol. Moreover, the ultrasound examination enabled us to diagnose 11% of CF fetuses over the period.
- Our results indicate that echogenic bowel is associated with an increased risk of CF, and that CF screening based on ultrasound examination is effective, particularly in populations where the disease is frequent. They also highlight the importance of efforts made to identify a second mutation in fetuses in which one mutation has already been detected. Finally, prenatal detection of CF by ultrasonography will modify the epidemiology of the disease as 11% of affected fetuses could be detected in utero.

detected by ultrasound. This should modify the epidemiology of the disease in populations of European extraction, as 11% of affected fetuses could be detected in utero.

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