

Antenatal screening for cystic fibrosis: a trial of the couple model

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Abstract

Objective—To assess the delivery and acceptability of antenatal couple screening for cystic fibrosis. Carrier status was notified only when both members of a partnership had cystic fibrosis alleles and therefore a one in four risk of having an affected child.

Design—Mouthwash samples were tested when both partners participated. Results were returned only to positive couples.

Setting—Two large maternity hospitals in Edinburgh.

Subjects—Screening was offered to all couples who booked at one of the two hospitals.

Main outcome measures—(a) The take up of screening, carriers and carrier couples identified, take up of prenatal diagnosis, and numbers of affected fetuses detected; (b) questionnaire measures of patient satisfaction and stress.

Results—Screening was offered to 8536 couples. 714 (8.4%) were regarded as ineligible, usually because of late booking or absence of a partner. 1900 (24.3%) of the remainder declined screening. Among the 5922 screened couples, four tested positive—that is, both partners were cystic fibrosis heterozygotes. All four elected to have prenatal diagnosis. There were three terminations of pregnancy because of an affected fetus, one couple having two successive pregnancies with affected fetuses. The participation rate was 76% for eligible couples (5922/7822) and 69% for all couples (5922/8536). Only 89 screened couples (1.5%) requested information on individual carrier status. No anxiety was detected among a cohort of the screened population, and 99% of questioned participants expressed satisfaction with the concept of couple screening.

Conclusions—Antenatal couple screening is a satisfactory and acceptable way of screening for cystic fibrosis and has been adopted as routine in the two trial hospitals.

Introduction

Over the past three years we have carried out a pilot trial of cystic fibrosis heterozygote screening in the antenatal clinics of a large Edinburgh maternity hospital.¹ We used a “two step” mode of testing. Firstly, women were screened for six mutant alleles, representing about 85% of cystic fibrosis chromosomes. If they were negative for these alleles no further action was taken. If they were positive, then their male partners were also tested. When both members of the partnership tested positive the couple was referred to a consultant obstetrician for discussion of possible prenatal diagnosis.

The participation rate in the trial was high and there seemed to be no long term adverse psychological consequences among identified carriers of the dis-

order.¹⁻³ However, one in 26 women carried a mutant cystic fibrosis allele and needed counselling. Though most were reassured when their partner was found to be negative, anxiety levels were high as they awaited their partner's test result. It was necessary to have a trained genetics nurse in attendance at all times.

An alternative method of screening for recessively inherited disorders was proposed by Wald.⁴ He suggested that the couple should be considered as the screened unit and be regarded as positive only when each partner carried a cystic fibrosis allele. When one partner tested positive and the other did not they would be treated as “couple negative” and be given the same residual risk of an affected child as couples in whom only the woman had been tested and found to be negative (fig 1). In this scheme only about one in 676 couples would need counselling and further investigation.

We have carried out trials of couple screening for cystic fibrosis in the antenatal clinics of two maternity hospitals.

Patients and methods

RECRUITMENT

When the booking clinic appointment was sent out the letter included a leaflet explaining the main

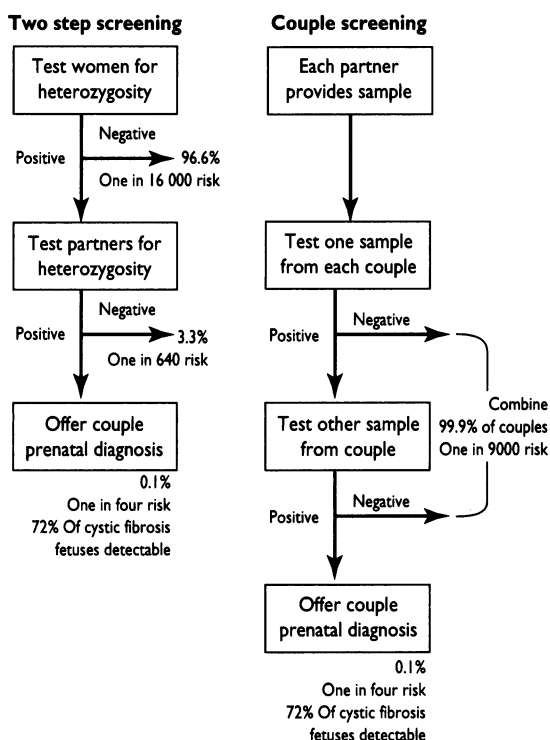


FIG 1—Two step and couple screening. Percentages and risks are based on detection of six (about 85%) of mutant alleles and birth incidence of cystic fibrosis of one in 2500

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BMJ 1994;308:1459-62

features of cystic fibrosis and the nature of the trial and inviting participation.⁵ Two universal containers were enclosed. Couples were told that they would be tested only if both members agreed to take part and that the return of a mouthwash sample from each (together with signed consent forms) indicated their willingness to be screened. The leaflet stated that if they had heard nothing from the trial coordinator 10 days after giving samples they were not a high risk couple. It was emphasised that screening would reduce but not abolish the chance of a child with cystic fibrosis.

The average booking time at both hospitals was 12 weeks, giving most couples about three weeks to consider the invitation. At the clinic samples and consent forms were collected by a midwife. If a woman was not accompanied by her partner and had forgotten to bring his mouthwash sample she was asked to take the containers home so that they could be sent to the laboratory by post. No testing was done unless a sample from each partner was available.

COUNSELLING AND REPORTING OF RESULTS

Additional information on the screening trial was provided on request by midwives or a genetics nurse in the clinic. Couples were not encouraged to ask for individual results, but if they did these were freely available. When both partners tested positive they were notified by telephone and referred to their consultant for counselling and possible prenatal diagnosis.

PSYCHOLOGICAL STUDIES

All couples entering the trial were asked to complete a 12 item general health questionnaire⁶ before testing (GHQ0), 10 days after being tested (GHQ1), six weeks after being tested (GHQ2), and six weeks after their baby was born (GHQ3). This study was discontinued when 300 completed sets of replies were received from each sex. In a separate study participants as well as non-participants were asked a set of simple questions on their attitude to couple screening. This was discontinued after 100 replies were received from non-participants.

LABORATORY ANALYSES

We used our own assay⁷ and the Cellmark system,⁸ which together detect the $\Delta F508$, G551D, G542X, R553X, $\Delta I507$, and 621+1G-T mutations, making up 85% of mutant alleles in our population.⁹ Analyses were first carried out on the female sample, and only if it was positive (or in the event of sample failure) was the male sample tested. Results were obtained on all samples within the specified 10 days.

Results

Couple screening was introduced into the Eastern General Hospital, Edinburgh, in March 1992 and replaced two step screening in the Simpson Memorial Maternity Pavilion in January 1993. As no significant differences in the two hospitals were seen table I gives the combined results to January 1994.

Screening was not offered to 370 couples in whom the woman had tested negative in a previous pregnancy. It was offered but the couple was considered ineligible when booking was after 18 weeks' gestation (470) or when only one sample was provided (234). No containment facilities were available for samples from 10 subjects who were HIV positive. In the Eastern, 26% of eligible couples declined testing, and in the Simpson 21% declined. Screening was done on 76% of eligible couples (5922/7822) and 69% of those (5922/8536) to whom the offer was originally made. In 10% of screened couples the samples were sent in by post.

There were 238 heterozygotes among the women

TABLE I—Results of screening trial (8536 women offered screening)

	No (% of subtotal) [% of all 8536 women]
<i>Women ineligible for screening</i>	
Late gestation	470 (65.8) [5.5]
No partner	234 (32.8) [2.7]
HIV positive	10 (1.4) [0.1]
Total ineligible	714 (100.0) [8.4]
<i>Women eligible for screening</i>	
Declined screening	1900 (24.4) [22.3]
Screened	5922 (75.7) [69.4]
Total eligible	7822 (100.0) [91.6]
<i>Outcome in screened women</i>	
Carriers detected	238 (4.0)
Heterozygous couples	4 (0.07)
Affected fetuses	3 (0.05)*
All screened women	5922 (100.0)

*One couple had two successive affected pregnancies.

screened, made up of 208 with $\Delta F508$, 16 with G542X, 11 with G551D, two with 621+1G-T, and one with R553X. Four women with $\Delta F508$ mutations had heterozygous partners, each also being $\Delta F508$. The four couples opted for prenatal diagnosis and two were found to be carrying affected fetuses (homozygous $\Delta F508$). Both pregnancies were terminated. One couple embarked on another pregnancy during the trial; that fetus also was affected and the pregnancy terminated. All three diagnoses were confirmed in abortus material.

Eighty nine of the 5922 (1.5%) screened couples requested information on individual carrier status. In this group were two carrier women.

PSYCHOLOGICAL STUDIES

Results for the first 300 couples who completed the general health questionnaire at all four points are shown in figure 2. There was no indication of an increase in respondents with positive scores (3 or more) after testing and during the pregnancy (GHQ1 and GHQ2), though anxiety levels rose when parents returned home (GHQ3). The data were very similar to those reported for non-carriers in the two step trial.^{1,2}

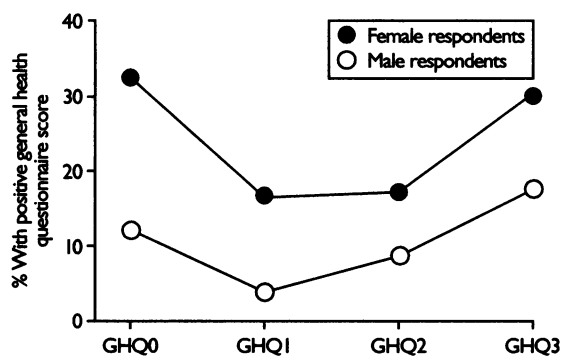


FIG 2—Percentages of female (●) and male (○) respondents in first cohort of 300 with positive general health questionnaire scores. Points of inquiry are defined in text

Answers to the question on the preferred time of screening are shown in table II. This study was stopped and the responses analysed after 100 had been received from non-participants.

TABLE II—Preferred time for being screened

	No (% of participants)	No (% of non-participants)
During pregnancy	716 (54.0)	45 (39.5)
Before pregnancy but with partner	592 (44.7)	57 (50.0)
Before meeting partner	17 (1.3)	12 (10.5)
Total	1325 (100.0)	114 (100.0)

Discussion

Two studies have shown that the extent of voluntary participation in cystic fibrosis heterozygote screening trials depends on the way in which the programme is presented. Watson *et al* reported that when the offer of screening was made by a personal approach at either general practice surgeries or family planning clinics take up was between 76% and 87% but that when it was made by a standard invitation letter take up was only 10%.¹⁰ This was confirmed by Bekker *et al*, who found that the direct suggestion by a research worker that a person should immediately be screened was the only effective approach.¹¹ The participation rate was 70%. Other forms of recruitment had very low take up.

In the completed two step antenatal screening trial in the Simpson the take up rate was 83% among eligible women and 71% among all women.¹ However, as we had found that nearly half the women agreeing to screening did so without reference to their partners,¹² we assumed that couple screening, needing a joint decision between partners, might have a low response rate. This was not the case. The take up rates of 76% for eligible women and 69% for all women were closely comparable to those of two step screening. In the Simpson the changeover from two step to couple screening has led to no decline in the participation rate. If the take up rate continues at or near 70% it should be possible to reach 50% of at risk couples ($0.7 \times 0.85 \times 0.85$). It is noteworthy that all four heterozygous couples in this trial and all six in the two step trial² opted for prenatal diagnosis.

ANXIETY AND TIMING OF SCREENING

As measured by the general health questionnaire, couple screening appeared to cause little anxiety in participants. In the two step trial¹² and in other studies in pregnancy¹³ a fairly high proportion of women presenting to booking clinics had positive general health questionnaire scores before any procedures were carried out (GHQ0). This proportion declined at the two other measurement points during pregnancy (GHQ1 and GHQ2) but rose again, presumably because of the stress of taking a new baby home (GHQ3). The positive responses among both women and men (fig 2) were almost identical with the proportions seen among non-carriers and male controls in the two step trial.² However, the sharp peak in anxiety affecting over half of the carrier women awaiting their partner's results in two step screening was conspicuously absent in this trial.

There were initial worries that not giving any results at all to most participants might have generated some anxiety. However, only 1.5% of couples asked for information on their individual carrier status. Two identified carriers in this group were satisfied when they learnt that their partners' results were negative.

A substantial proportion of a cohort of women who entered the trial, as well as those who chose not to enter, said that screening during pregnancy was their preferred option. Very similar numbers of women suggested that screening before pregnancy was desirable, provided that it was done with their partner. We found little support for the idea of individual carrier testing (table II). This is powerful support for the concept of the couple as the screening unit. Several respondents asked to write comments on the timing of screening remarked that discovering their cystic fibrosis carrier status before forming a relationship might have inhibited partner bonding or prevented marriage. This aspect of screening in primary care has not been fully investigated.^{10 11}

ETHICS

An aspect of couple screening that may be worrying is whether it is ethical to set the programme up in such

Clinical implications

- The participation rate in an antenatal couple screening trial for cystic fibrosis is about 69%
- Some 24% of couples may decline the offer of screening
- All positive couples may be expected to accept the offer of prenatal diagnosis
- Around 1.5% of couples may request information on individual carrier status
- In this series no anxiety was detected among a representative cohort of the screened population

a way that people are usually unaware of their carrier status. Our prime reason for doing this was to avoid causing anxiety in couples in whom one partner is shown to be a carrier while the other is test negative. Such couples have a residual chance of an affected child of one in 640. There are currently no practical steps which can be taken to reduce this risk.

In the two step trial these positive-negative couples usually needed two counselling sessions with a trained genetics nurse, and many remarked that they would prefer to have been screened simultaneously and to have been informed only if their risk was one in four.¹⁴ Theoretically, prepregnancy screening permits some reproductive choice in that couples could decide not to have children, to resort to artificial insemination by a screened donor, or even to change partners. In practice, experience from other screening programmes shows that these options are seldom pursued.^{15 16} That so few couples in our trial sought information on their individual status supports this observation.

MacIntyre and Sooman raised the question of the impact of illegitimacy on prenatal carrier screening.¹⁷ In a review of reports they cited possible non-paternity rates of 1.4% to 30%. However, they included data from several unreferenced sources which preceded the precision of DNA based systems. Two studies using molecular genetic techniques have shown non-paternity rates of 1.1% (Scotland)¹⁸ and 2.8% (France).¹⁹ Both have been criticised on the ground that they were based on families attending genetic counselling clinics for estimation of recurrence risks, where any doubts about paternity might have led to self exclusion. This objection cannot be levelled at our broadly based antenatal carrier screening trials, in which information leaflets have exhorted couples with doubts about the identity of the father not to take part. The proportions of couples citing this as the reason for non-participation were 1.4% in the two step trial² and 2.7% in this trial.

A possible difficulty with couple screening is that it reduces the opportunity for heterozygote testing in the immediate families of identified carriers. In the two step trial about 10% of carriers referred first degree relatives to the genetic counselling clinic for testing.¹ Super *et al* have been enthusiastic advocates of this type of "cascade" testing, pointing out that in terms of the ratio of carriers detected to tests performed it is very efficient.²⁰ This is plainly true, but cascade testing is an addition to and not a substitute for population screening.²¹ In order to reach all those at risk in an equitable way—an accepted criterion of screening²²—it is necessary to find convenient points through which a substantial proportion of the relevant population passes. We suggest that antenatal clinics are suitable turnstiles and that couple screening is an efficient form of delivery.

We thank the medical and nursing staff of the Eastern General Hospital and the Simpson Memorial Maternity

Pavilion, Edinburgh, for making this trial possible. The study was funded by grants from the Medical Research Council and the Cystic Fibrosis Trust. We are grateful to Cellmark Diagnostics for reagent kits and to Professor N J Wald for helpful discussion.

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(Accepted 22 March 1994)

Active cascade testing for carriers of cystic fibrosis gene

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Abstract

Objective—To examine the acceptability, practicability, efficiency, and application of active screening for carriers of the cystic fibrosis gene in the extended families of those in whom the disease is present (cascade screening).

Design—Paediatricians and physicians provide details of their affected patients, pedigrees are drawn up, and relatives offered tests after initial contact by the affected nuclear families. Affected patients are genotyped in a laboratory with a special interest in the genetics of cystic fibrosis.

Setting—North Western health region.

Subjects—Relatives and partners of 607 people with cystic fibrosis.

Interventions—Genetic counselling by letter for people found to be carriers; formal genetic counselling and when indicated arrangements for prenatal diagnosis for couples discovered to be carriers.

Main outcome measures—Number of carrier couples detected; action in pregnancy of detected carrier couples; extent of the uptake of screening by relatives.

Results—Of 1563 relatives or partners tested, 15 carrier couples were detected; of nine pregnancies undertaken by these 15, eight had prenatal tests and three terminated pregnancies. An average of 16 people per family have come forward for testing so far.

Conclusions—Cascade screening for carriers of cystic fibrosis is well accepted by relatives, especially on the mother's side of the family; it is 10 times more efficient in detecting carrier couples than unfocused screening. Detected carrier couples make practical use of the information in pregnancy. Active cascade screening for carriers is effective in cystic fibrosis and widespread application is recommended. These principles could be applied to other recessive disorders.

Introduction

As long as cystic fibrosis remains a disorder with considerable morbidity and reduced lifespan there will

be those who will want to avoid having affected offspring. Carrier screening allows the discovery of couples at one in four risk of having children affected by this autosomal recessive disorder. Since 1989 when the gene and its major mutation, $\Delta F508$, were discovered¹ testing capable of detecting 80% to 90% of carriers has been feasible, especially in countries such as Britain, where $\Delta F508$ accounts for a high proportion of all cystic fibrosis mutations.²

There is more to introducing screening than simply tests capable of detecting carriers. As soon as the gene was discovered it was generally agreed that carrier testing should be offered to those with a family history of cystic fibrosis, whereas general or unfocused population screening required careful study to determine whether and how it might be introduced.³ Several official and quasiofficial bodies took no set position about whether screening should be offered to the general population but did recommend screening for those with a family history.^{4,5} After the publication of results of pilot studies of general population screening on pregnant and non-pregnant populations⁶⁻⁸ doubts still remain about whether the time is now ripe for general screening.⁹ Some added stress was noted, at least in the short term, in women or couples offered screening in pregnancy, though participation was fairly high.¹⁰ Screening offered in general practice to a non-pregnant population had a poor uptake unless the tests were taken on the day of the visit to the general practitioner by a keen research worker.⁷

Some profession led general screening programmes^{6,10,11} currently exist, being aimed at women or couples with pregnancies under way. The idea is to use the "turnstile" of pregnancy as the way to detect couples at risk. Thus with relatively high uptake in a group of people who would find it more difficult to refuse a test once offered than would people who were not pregnant, the hope is to identify a great number of carrier couples and to offer them prenatal diagnosis and selective abortion. In two programmes a way of dealing with the stress of testing in pregnancy has been to inform only those couples in which both people had positive results and therefore were at one in four risk of having affected offspring.^{6,10} It is accepted that were

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BMJ 1994;308:1462-8