Cystic fibrosis carrier testing in early pregnancy by general practitioners

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Abstract

Objective—To assess the feasibility of genetic counselling in general practice by using cystic fibrosis carrier screening at the booking appointment as an integral part of routine antenatal care and as a paradigm for the wider participation of general practitioners in medical genetics.

Design—Maternal testing (male partner tested only if woman screens positive) and couple testing for cystic fibrosis carrier status in the antenatal population attending one general practice and, later, in a further six (outreach) practices also.

Setting—Two partner urban training practice (pilot practice) in south Manchester, and six north west practices (two inner city, three urban, one rural dispensing).

Subjects—Total practice population of 50 000 (pilot practice plus six outreach practices) with an estimated 500–800 pregnancies per year.

Main outcome measures—(a) Proportion of carriers of cystic fibrosis identified, counselled, and appropriately managed within the first trimester of pregnancy; (b) questionnaire and interview measures of patient satisfaction and stress.

Results—Eleven carriers of cystic fibrosis were detected including one carrier couple. This carrier couple, after extensive counselling, elected to have prenatal diagnosis by chorionic villus biopsy. The fetus was homozygous normal.

Conclusions—General practitioners can successfully integrate genetic counselling and cystic fibrosis carrier screening into the first antenatal booking appointment. When a carrier couple is identified clinical geneticists can help with the discussion of reproductive options, and prenatal diagnosis by chorionic villus biopsy can be completed within the first trimester. The results suggest that general practitioners will have an increasingly important role in medical genetics, subject to continuing evaluation of patient acceptability and stress.

Introduction

Effective genetic services require collaboration between clinical geneticists, other specialists, public health doctors, and general practitioners. All must be convinced that preventing genetic disease and congenital disability is acceptable only when patients are well informed and free to accept or reject screening and prenatal diagnosis. The need for this approach is particularly clear when introducing population screening in pregnancy for carriers of cystic fibrosis.

In 1989 the cystic fibrosis gene (cystic fibrosis transmembrane conductance regulator) was cloned and the major mutation in white people— $\Delta F508$ —characterised.¹ Since then over 230 cystic fibrosis mutations have been identified throughout the world (Cystic Fibrosis Genetic Analysis Consortium, personal

communications). This has made possible the detection of most of the carriers in the British population.

In a pilot study we evaluated cystic fibrosis carrier screening at the earliest practical time in pregnancy,² which showed that 96% of pregnancies booked in the pilot practice were of less than 14 weeks' gestation at the time of booking (average gestational age 8 weeks). This early opportunity for screening was lost by the time of the first hospital antenatal appointment four to six weeks later, taking many patients into the second trimester. We later extended the study by recruiting other practices not previously associated with a department of medical genetics.

Patients and methods

Outreach—Six additional practices in the north west were recruited, with a total practice population of about 50 000. Recruitment followed informal discussions when the organising general practitioner (HH) and a genetics associate visited each practice to meet all the partners and attached staff. The aims and methodology of the programme were explained in an illustrated talk and samples of all documentation were provided. It was emphasised that it was not intended that the cystic fibrosis programme should alter or impose standardised antenatal care within the recruited practices, but collaborating doctors were asked to follow the protocol. To simplify these procedures a single laboratory card for each sample was used to collect patient and partner data and obtain a brief genetic family history (fig 1). Evaluation of the project will be undertaken by genetics associates as for the pilot project (see below), except that only carriers will be followed up again at one year.

Booking appointment with general practitioner—Our study involved general practitioners themselves in counselling and testing for cystic fibrosis carrier status at the time of booking for antenatal care in general practice. Counselling took place within the context of a structured discussion of routine antenatal tests.

Information provided for patients—A general leaflet describing cystic fibrosis carrier screening emphasised that this was a research project entailing pregnancy carrier screening which was not routinely available. A more detailed leaflet was given to all antenatal patients, which emphasised that participation was voluntary. The implications of a positive carrier screening test result were explained, as was the residual risk of still being a carrier even when screening was negative. With their consent women were allocated alternately to maternal and couple testing groups. Women then provided a mouthwash sample and those allocated to couple testing given an explanatory leaflet and mouthwash kit to take home for their partner, returning the partner's sample to the practice next day.

Laboratory tests—Mouthwash samples were tested in the regional molecular genetics laboratory (St Mary's

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MATERNAL		PATERNAL	
Surname	Name of partner		
Forename	Address (if different)		
Date of birth	Postcode		
Address	Postcode		
Postcode	Postcode		
Telephone No	Postcode		
Date of last menstrual period	Postcode		
GP's name and address	Postcode		
Postcode	Postcode		
GP's signature	Postcode		
Date sample taken			
(Laboratory use only)			
Laboratory No	Date sample received	Date reported	Initial box when entered on computer ☐
Is there a history in the immediate family (parents, sibs, children) of:		Are two or more relatives (especially if unusually young) affected with:	
1) Cystic fibrosis 2) Down's syndrome 3) Spina bifida 4) Mental retardation 5) Any congenital abnormality 6) Any other inherited disease (please give details)		1) Ischaemic heart disease 2) Down's syndrome 3) Cancer 4) Diabetes 5) Any other common disease — for example, asthma, epilepsy, hypertension	
The above questions are a guide to the family history, which may indicate increased genetic risk to this pregnancy or future early morbidity			

FIG 1—Laboratory card for each sample used to collect patient and partner data

Hospital, Manchester) for four common cystic fibrosis mutations ($\Delta F508$, G551D, G542X, and $621+1G>T$) using a multiplex ARMS test developed by Cellmark Diagnostics.³ Within our local population these four mutations are predicted to detect 84.5% of carriers (A J Wallace, personal communication). Subjects were classified into four ethnic groups (fig 1) and carrier and pregnancy risks calculated taking account of disease prevalence and mutation detection rate within each ethnic group (detection rates were obtained from Cystic Fibrosis Genetic Analysis Consortium, personal communications). Pregnancies in Jewish parents were also tested for their high risk mutation, W1282X. Consanguinity between couples was recorded and pregnancy risks adjusted accordingly.

Reporting—With the prior agreement of general practitioners positive and negative results were sent by the laboratory direct to individual patients with a clear explanation of their carrier status and the risk to the pregnancy. The general practitioner, in addition to a copy of the patient's letter, received a laboratory report detailing the mutations tested for and the residual risk of cystic fibrosis to the pregnancy. Male partners not registered with the practice were also informed directly of their individual screening results but their general practitioners were sent modified results letters, with no reference to pregnancy, simply advising them that

their patient had taken part in a research project.

Evaluation of project—Evaluation included acceptability of the study and comprehension and retention of five essential facts about cystic fibrosis (table I). We gave particular attention to the possibility of severe stress induced by a positive carrier test result in a pregnant woman. Two genetics associates based in the department of medical genetics and not attached to the practices were responsible for following up all patients screened in the pilot study. Questionnaires with Spielberger state-trait anxiety index⁴ were sent to all patients after they had received their results. A home visit interview was conducted within the next two weeks. To detect possible late reactions all patients in the pilot project, both carriers and non-carriers, will also be followed up by questionnaire and interview at one year.

Results

In the combined pilot and outreach practices the average gestational age at booking was eight weeks, and 90% of patients booked before 14 weeks. A total of 244 pregnancies were screened, 127 women being allocated to the maternal testing group and 117 to the couple testing group. In the maternal testing group five carriers, all having the $\Delta F508$ mutation, were detected but their partners subsequently screened negative for the four mutations. With cooperation from the practices there was no significant delay in obtaining the paternal samples. In the couple testing group two women screened positive ($\Delta F508$) and four men screened positive (four with $\Delta F508$ and one with $621+1G>T$). All their partners screened negative. All the partners were tested simultaneously and there were no reporting delays. One carrier couple was detected (both partners $\Delta F508$, see below). Of the pregnancies not included in the study, 26 patients booked after 14 weeks and 11 declined screening. Seven men in the couple testing group failed to return their samples.

Prenatal diagnosis case—One $\Delta F508$ carrier couple was detected within the couple testing group. This couple, from a rural general practice, booked with the general practitioner at six weeks' gestation. It was the couple's second pregnancy. The first had resulted in a normal girl two years before. There was no family history of cystic fibrosis. The woman had a threatened miscarriage before carrier testing was completed and in the interval before prenatal diagnosis. Within three days of the booking appointment the laboratory reported that both partners carried $\Delta F508$ mutations. After prolonged counselling by clinical geneticists and genetics associates in collaboration with the general practitioner the couple opted for prenatal diagnosis by chorionic villus biopsy. After further counselling by the gynaecologist about the risk of biopsy, which was less than 3% in his personal series, chorionic villus biopsy was performed at nine and a half weeks' gestation and the fetus was shown to be homozygous normal (fig 2). The result was reported by the laboratory within 24 hours. The patient miscarried 10 days later. However, she subsequently stated her intention to request prenatal diagnosis in her next pregnancy.

Follow up and evaluation—Evaluation of patients in the outreach practices is continuing. Only the results of the pilot study are summarised here. Seventy patients were approached, 64 patients returned the questionnaire, and 57 patients were visited at home. Six patients were not sent questionnaires because they had miscarried or decided to terminate the pregnancy after their booking appointment. The results are summarised in tables II-IV. More than four out of five patients thought that they had had enough time after the consultation with their general practitioner to decide whether to take the test. More than two thirds

TABLE I—Results of questionnaire ascertaining efficacy of practice leaflet in helping patients understand cystic fibrosis and how it is inherited

Question (true answers in <i>italics</i>)			No of patients selecting each answer (n=64; some patients selected more than one)
Is cystic fibrosis	(1)	A disease causing kidney problems?	4
	(2)*	<i>A disease causing chest infections?</i>	47†
	(3)	A disease that makes muscles weak?	5
	(4)*	<i>A disease causing feeding difficulties?</i>	18
	(5)	Don't know	4
	(6)	Didn't answer	4
	(7)	A mild illness affecting children only?	4
	(8)	A severe illness affecting teenagers only?	1
	(9)	A severe illness affecting old people?	0
	(10)*	<i>A severe illness affecting babies, children, and young adults?</i>	49
	(11)	Don't know	8
	(12)	Didn't answer	3
How many people in Britain are carriers of cystic fibrosis gene?	(13)*	<i>One in every 20 people</i>	25
	(14)	One in every 10 people	1
	(15)	One in every 2000 people	22
	(16)	All women	0
	(17)	Don't know	15
	(18)	Didn't answer	2
How is cystic fibrosis inherited?	(19)	From one parent	12
	(20)	From neither parent	1
	(21)*	<i>From both parents</i>	42
	(22)	From child's father's family	0
	(23)	Don't know	7
	(24)	Didn't answer	3

*Items emphasised in practice information leaflet.

†Thirteen patients selected both answers 2 and 4.

thought that their general practitioner was the best person to discuss and offer the test and that the leaflet given at the time of booking contained enough information and was easy to understand. Only one patient said that she felt much more anxious while waiting for the test result, while two thirds felt no more anxious and two patients felt less anxious. More than four fifths correctly remembered their test result. Just under two thirds thought that they knew something about cystic fibrosis before seeing their general practitioner. About two thirds could correctly answer questions relating to the five key facts about cystic fibrosis included in the leaflet.

Discussion

Cystic fibrosis carrier screening offered by the general practitioner at the booking appointment ("first diagnosis of pregnancy") has important advantages.

FIG 2—Molecular genetic analysis of chorionic villous tissue from fetus identified at one in four risk. Samples were analysed by polymerase chain reaction amplification of exon 10 of the cystic fibrosis gene followed by polyacrylamide gel electrophoresis. Samples (genotypes in parentheses) were: (a) father (normal/ Δ F508); (b) and (c) chorionic villi (normal/normal); (d) mother (normal/ Δ F508); (e) mutation control (normal/ Δ F508); (f) negative control (no amplification).

TABLE II—Results of questionnaire follow up of patients in pilot study (expressed as numbers of patients answering selected questions)

Question	Yes	No	Don't know
Did you feel you needed more time to discuss the cystic fibrosis test with your doctor? (n=64)	8	55	1
Would you have liked more time to make up your mind between talking to your family doctor and having the test? (n=64)	4	57	3
Would you prefer to have had the first discussion about the cystic fibrosis test with a health worker other than your doctor? (n=51)	3	48	0
Did the leaflet on cystic fibrosis given to you at the booking appointment have enough information about the test? (n=64)	49	6	9

TABLE III—Questionnaire follow up of pilot study. Numbers of replies to question on knowledge about cystic fibrosis

Question	A lot	Quite a lot	A bit	Nothing	Don't know
Before you saw your family doctor how much did you think you knew about cystic fibrosis? (n=64)	0	9	28	26	1

TABLE IV—Questionnaire follow up of pilot study. Numbers of replies to question on how patients felt (compared with normal) while awaiting test

Subject of question	Less worried than usual	No more worried than usual	A little more worried than usual	Much more worried than usual	Don't know
How patients felt while waiting for test (n=64)	2	40	20	1	1

Foremost is the early window of opportunity for counselling and screening and for early prenatal diagnosis and abortion of affected fetuses if requested. This opportunity is usually lost if screening is delayed until the hospital antenatal clinic visit. General practitioner counselling and screening in very early pregnancy allows more relaxed consideration of options, and, when a carrier couple is detected, further genetic counselling and prenatal diagnosis can be completed within the first trimester. If the fetus is affected termination of pregnancy under anaesthetic can be offered close to the end of the first trimester, thus avoiding a much more psychologically and physically stressful induction of labour. If the couple opts to continue with the pregnancy prenatal diagnosis will allow very early treatment of the infant and thus remove the "delay in diagnosis" with its attendant anxieties for the family.

We now have extensive experience of counselling by general practitioners, and we are encouraged by the success of the continuing outreach project involving six varied north west general practices with a total practice population of 50 000. In one year we have screened 244 pregnancies and detected eight carrier women and five carrier men, including one carrier couple at six weeks'

gestation. The couple had several weeks to consider their options and elected to have prenatal diagnosis by chorionic villus biopsy, which showed the fetus to be homozygous normal at nine and a half weeks' gestation. This couple—the first identified in our programme from the general population and hence with no previous experience of cystic fibrosis—was counselled on several occasions both at home and in the department of medical genetics.

ETHICAL CONSIDERATIONS

We are further evaluating patient satisfaction and stress, and we are particularly concerned that the decision to accept cystic fibrosis carrier screening should be well informed and voluntary and that the busy general practitioner surgery environment does not lead to pressure on women to comply. Evaluation is carried out confidentially by genetics associates, not previously known to the patients and not associated with the practice. Although our evaluation is incomplete, and will be reported later, we are encouraged by the satisfaction expressed by women with the role adopted by the general practitioner as genetic counsellor. It is also striking that 110 of 117 women in the couple testing group successfully returned samples from their partners. Clearly well informed and motivated pregnant women can be effective counsellors. Only one patient (a nurse) would have liked the opportunity to discuss the test in more depth with a clinical geneticist.

We consider it essential to give each patient the result of the screening test as well as the risk to the pregnancy. Carrier status has continuing reproductive implications for the patient and for close relatives. General practitioners are equipped to retain lifetime records in the Lloyd George envelope or on computer, or both. Individual carrier risk leaves an opportunity for "cascade screening" of close relatives in the future and makes allowance for the transient nature of many partnerships. Children under 16 are not routinely offered screening in our laboratory.

WORKLOAD

Cystic fibrosis carrier screening at first booking in general practice is efficient and not excessively time consuming. Counselling and obtaining a mouthwash sample add around 10 minutes to the first antenatal consultation, or about six hours per annum for an average of 36 pregnancies per general practitioner. All positive and negative carrier test results are reported direct to the patients (copy to the doctor), who are invited to discuss this with the doctor. This does not create any appreciable workload. Our continuing evaluation compares testing the couple with initially testing only the woman. It is clearly cheaper and easier to test men only when the woman is found to be a carrier, because only one in 20-25 partners require cystic fibrosis screening and, working closely with an efficient laboratory, we find that there needs to be a delay of only a few days when the male partner subsequently requires screening. Although the five women so far involved in this way reported increased anxiety during the delay, their anxiety scores were within the normal range at the time of the home visit interview after a negative paternal test. However, counselling carrier couples in relation to prenatal diagnosis is demanding and requires cooperation between clinical geneticists and gynaecologists, although a great deal can be delegated to experienced genetics nurses or genetics associates.

COST

The cost of cystic fibrosis carrier screening is

difficult to calculate at present, as this project is funded as a research programme by the Wolfson Foundation. General costs in the United States and Britain have been estimated by Williamson⁵ as varying from \$100 to \$300 for commercial testing to marginal costs of about \$20 to \$25 in non-commercial laboratories with a high throughput.

COMPARISON WITH OTHER TRIALS

Williamson⁵ has recently reviewed community screening for carriers of cystic fibrosis, while the debate over carrier screening for this disorder has been fully recorded in the United States.⁶ The extent to which cystic fibrosis carrier screening will be used in future to facilitate prenatal diagnosis depends on the general perception of the severity of disease and the effectiveness of new forms of treatment.

This study uses cystic fibrosis carrier detection as a model for many genetic screening tests to come. These will probably include new genetic tests for predisposition to coronary artery disease, cancer, diabetes, and other common causes of death and disability. Thus this study was initiated because general practitioners will be exposed to new pressures from the applications of molecular technology which cannot be contained within existing departments of medical genetics. Although paediatricians, obstetricians, physicians, and other hospital specialists already include genetics in their work, they have few facilities for the continuing care of families with genetic problems. In contrast, general practice is ideally placed to evaluate the appropriateness of counselling and testing. There are 33 839 general practitioners in the United Kingdom (Royal College of General Practitioners, personal communication). They have detailed knowledge of families registered on their list and unique access to patients in early pregnancy. In this study we have shown that general practitioners and their patients can successfully adopt a basic family history, counselling, and genetic screening protocol if they are given adequate information and appropriate support, including access on request for counselling by clinical geneticists for couples found to be carriers. Given such support, general practitioners can greatly widen genetic health care and disease prevention. Indeed, band 3 health promotion now requires that a family history must be taken as part of the strategy for preventing coronary heart disease. We find that general practitioners have enthusiastically accepted cystic fibrosis carrier screening and genetic counselling as being more obviously valuable than some of the changes recently imposed on general practice.

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