

Confidential inquiry into families with two siblings with cystic fibrosis

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Abstract

Objective—To audit the care that had been provided to couples before the birth of a child with cystic fibrosis where a sibling had been previously diagnosed.

Design—Retrospective review of case notes.

Sample—Families where at least one affected child had been born between 1 January 1991 and 30 June 1995 and the diagnosis in the first child was made before the second affected pregnancy reached 20 weeks. The combination of information on these families with data from the prenatal diagnosis register allowed the reconstruction of a cohort of pregnancies in women with a previous affected child.

Main results—Forty six eligible families with a second affected child were identified. Details from the paediatrician who had diagnosed the first affected child were obtained in 43 cases: all 43 couples were offered genetic counselling, but where provided by a paediatrician this was difficult to assess as no couple was sent a summary letter. Details were obtained from the obstetrician in the subsequent affected pregnancy in 42 cases: prenatal diagnosis was not offered in 10 (24%), offered and declined in 24 (57%), offered and accepted but termination declined in eight (19%). In the overall cohort of at risk pregnancies, the estimated rate of prenatal diagnosis offer was 97%, prenatal diagnosis uptake 86%, false negative prenatal diagnosis rate 0%, and uptake of termination 95%.

Conclusions—(1) Parental choice was an important determinant of second affected births. (2) Despite widespread availability, prenatal diagnosis was not offered in an estimated 3% of at risk pregnancies. (3) There were shortcomings in counselling documentation, in particular failure to send a summary letter to counselled couples.

(*Arch Dis Child* 1997;77:501-503)

Keywords: cystic fibrosis; genetic counselling; prenatal diagnosis

Cystic fibrosis is the commonest life threatening autosomal recessive disorder in the UK, with an incidence of 1/2486 live births for the period 1978-85.^{1,2} Prenatal diagnosis can affect the distribution of live births and terminated pregnancies. Avoiding further affected

children in families at risk of serious genetic disorders may be seen as an important public health goal. However a free society insists that a primary concern is to provide accurate and timely information to couples so that they can choose whether or not to seek prenatal diagnosis in their next pregnancy. For this to be achieved, a heavy responsibility falls on professionals—usually paediatricians—to diagnose cystic fibrosis as early as possible in the first affected child both to allow early treatment and to transmit genetic information to parents and their general practitioner (GP) with timely counselling including advice on the availability of prenatal diagnosis for subsequent pregnancies.

Our study identified the birth of children with cystic fibrosis into 46 families where a sibling had been previously diagnosed. Our objective was to audit the care provided against the following standards:

(1) After diagnosis, the parents should be made aware of the possibility of recurrence in a future pregnancy and of the opportunity for prenatal diagnosis. A letter should be sent to the parents and copied to the GP, summarising locally available genetic counselling;

(2) Mutation analysis, central to prenatal diagnosis for a future pregnancy, should be undertaken in the affected older sibling;

(3) In subsequent pregnancies the referral letter from the GP must alert the obstetric team to the history of cystic fibrosis in the older sibling;

(4) A family history should always be taken by the obstetric team at the first hospital antenatal clinic visit;

(5) The availability of prenatal diagnosis should be made clear to women with a previous history of a child affected with cystic fibrosis.

Methods

Initially all 510 paediatricians throughout the UK known to have cystic fibrosis patients under their care were contacted through the UK Cystic Fibrosis Survey.¹ Paediatricians were sent general information about the study and asked to complete a reply slip indicating the number of families in their care with two or more affected children where at least one affected child was born between 1 January 1991 and 30 June 1995.

Clinicians involved in the care of an eligible family (paediatrician, GP, obstetrician) completed questionnaires based on information contained in case notes. In cases where families were undergoing shared care at both a regional cystic fibrosis clinic and a local hospital, details

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Accepted 18 July 1997

were obtained from the regional clinic. Copies of the following documentation were requested: details of counselling after the first diagnosis of cystic fibrosis including any summary letter sent to the woman/couple, letter sent to the GP by the paediatrician making the first diagnosis, letter sent by the GP to the obstetrician dealing with the subsequent affected pregnancy. Documentation regarding counselling was also requested from any clinical geneticist involved. At the time of publication, all patient, professional, and hospital identifying details will be destroyed.

Results

CASE ASCERTAINMENT

Altogether 488 (96%) paediatricians responded. Forty six families were identified in which the diagnosis in the first child was made before the second affected pregnancy reached 20 weeks. One case was excluded from analysis as the family had moved overseas and no details were available, leaving 45. In 10 cases, the family was living in Northern Ireland during the subsequent affected pregnancy. Where relevant, data for Northern Ireland are given separately because the Abortion Act does not apply there and this may affect uptake of prenatal counselling.

ASSESSMENT AGAINST STANDARDS OF CARE

Table 1 indicates whether defined standards of care were met.

Details requested from the paediatrician diagnosing the first affected child were obtained in 43/45 (98%) cases. All 43 couples were offered counselling, but seven (17%) declined. A paediatrician counselled 18 (43%) cases but further assessment was incomplete as no couple was sent a summary letter and other documentation was limited. Counselling was given by a genetic team to 17 (40%) couples, of whom seven were sent a summary letter. In one case information on who provided counselling was not given.

We reviewed 42 letters sent by the paediatrician to the GP after first diagnosis of cystic fibrosis in the family. One letter had been lost. All 42 letters reviewed referred to the diagnosis of cystic fibrosis and 41 to details of treatment. Seventeen (40%) of letters referred to the genetic aspects of the disorder, but antenatal diagnosis in future pregnancies was specifically referred to in only four (10%).

Details requested from the obstetrician for the subsequent affected pregnancy were ob-

tained in 42/45 (93%) cases. Prenatal diagnosis was not offered to 10 couples. The reason given by the obstetrician was late booking in three cases (gestational age = 18, 20, 29), and 'Northern Ireland' in two. No reason was documented in five cases (gestational age = 12, 12, 14, 15, 16 respectively), although it was noted that in one case, the pregnancy resulted from in vitro fertilisation. In one case results of previous mutation analysis in the older sibling were heterozygous $\Delta F508$ and unknown mutation, and in another case although the family history of cystic fibrosis was noted at hospital booking, the father of the current pregnancy was not the same as for the previous child and there was no documentation that he had been offered carrier screening.

EXPERIENCE OF PRENATAL DIAGNOSIS

We have used information regarding live births derived from this study and the data accumulated by the UK cystic fibrosis prenatal diagnosis register, under the direction of Dr Maurice Super, in an attempt to reconstruct the cohort of pregnancies from 1 January 1991 to 30 June 1995 in women with a previous diagnosed affected child. For ease of interpretation, data from Northern Ireland have been excluded.

The data for England, Scotland, and Wales from this confidential inquiry covering 33 live births during the above period are: not offered prenatal diagnosis, five; declined prenatal diagnosis, 22; positive prenatal diagnosis, declined termination of pregnancy (TOP), six.

The two live births in England where no details were available have been ignored in these calculations.

Fifteen centres (Edinburgh, Royal Manchester Children's Hospital, Cardiff, Great Ormond Street, Guy's Hospital, St Mary's Hospital (London), Wessex, Oxford, Sheffield, St Mary's Hospital (Manchester), Cambridge, Newcastle, Nottingham, Birmingham, Bristol) contributed to the cystic fibrosis prenatal diagnosis register for the period 1 January 1991 to 30 June 1995 as follows: negative prenatal diagnosis, 293; positive prenatal diagnosis, TOP, 65; positive prenatal diagnosis, outcome of pregnancy unknown, 12.

Four women (five chorionic villus biopsies, two positive, two TOP) did not have a previous affected child so the numbers are reduced as follows: negative prenatal diagnosis, 290; positive prenatal diagnosis, TOP, 63; positive prenatal diagnosis, outcome of pregnancy unknown, 12. In three of these 12 cases, the maternal date of birth and date of prenatal diagnosis matched cases in the inquiry, so we assume the remaining nine were terminated giving the following data: negative prenatal diagnosis, 290; positive prenatal diagnosis, TOP, 72; positive prenatal diagnosis, live birth, three.

Seven centres (Glasgow, Liverpool, Leeds, Stoke-on-Trent, Brompton, King's (London), Lewisham) did not contribute to the register between 1 January 1991 and 30 June 1995. With no further information on these centres, the numbers are estimated to be 7/15 of the numbers from the 15 centres providing data for

Table 1 Number (%) meeting defined standard of care

Standard	No (%) of cases where standard met
Details from paediatrician diagnosing first affected child	
Counselling offered after diagnosis	43/43 (100)
Mutation analysis undertaken	36/43 (84)
Details from obstetrician for subsequent affected pregnancy	
GP referral letter provided: letter alerted obstetric team to family history of cystic fibrosis	27/32 (84)
Failsafe mechanism when no reference to cystic fibrosis in GP referral letter: family history taken by obstetric team revealed family history of cystic fibrosis	5/5 (100)
Prenatal diagnosis offered (country born)	
England, Wales, or Scotland	28/33 (85)
Northern Ireland	4/9 (44)

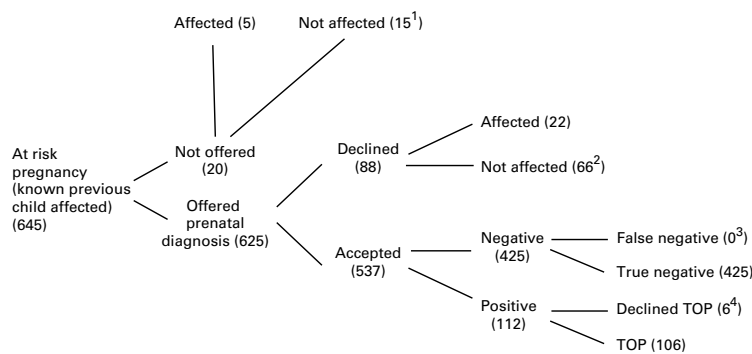


Figure 1 Cohort flow diagram; 1 = estimated (3×5); 2 = estimated (3×22); 3 = none found in inquiry; 4 = based on data from inquiry, estimates suggested four cases. It has been assumed there were no false positives.

the period. Results from the 22 centres were assumed to be as follows: negative prenatal diagnosis, 425; positive prenatal diagnosis, TOP, 106; positive prenatal diagnosis, live birth, four (although calculations suggest four, six cases were known to the inquiry).

The cohort of at risk pregnancies as shown in fig 1 has been reconstructed and provide estimates of rates as follows: per cent offered prenatal diagnosis, $625/645 = 97\%$; uptake of prenatal diagnosis, $537/625 = 86\%$; false negative prenatal diagnosis rate, $0/112 = 0\%$; uptake of termination, $106/112 = 95\%$.

LATE DIAGNOSIS

Although this inquiry did not review cases where the first diagnosis of cystic fibrosis in the family was made after a second affected child was born, we include this information to provide an overall picture. The inquiry identified 68 families with two or more affected children from separate pregnancies. Information on the antecedent circumstances surrounding the birth of a subsequently affected child was available for 64. There were 28 (51%) children in England, Wales, and Scotland and four (44%) in Northern Ireland whose birth appears to have followed the parents' decision to decline prenatal diagnosis or termination of pregnancy. However other factors associated with the birth of subsequently affected children were late diagnosis of cystic fibrosis in the first born child (22 (40%) in England, Wales, and Scotland and none in Northern Ireland) and failure to offer prenatal diagnosis (five (9%) in England, Wales, and Scotland and five (56%) in Northern Ireland).

Discussion

Our findings suggest parental choice is the most important determinant of the birth of a child with cystic fibrosis into a family where a sibling had been previously diagnosed. However clinicians and/or clinical geneticists did not offer prenatal diagnosis to a significant proportion of the couples, 15% of the cases in England, Wales, and Scotland and 56% of those in Northern Ireland for whom details are known. The response to our requests for information was high, discounting the risk of bias.

Key messages

- At the time of diagnosis of an affected child, the paediatrician should provide general education literature for the parents to inform them about cystic fibrosis symptom management, recurrence risk, prenatal diagnosis options, and the need for early booking in a subsequent pregnancy
- Prompt counselling and prenatal diagnosis should be offered in the first trimester of an at risk pregnancy whenever possible
- Parental choice was an important determinant of second affected cystic fibrosis births within families where a previous child had been diagnosed

Although the number of births reviewed is small, this audit identifies and suggests remedies for deficiencies in the management of pregnancies at high risk of the birth of children with serious genetic disorders.

Recommendations

- (1) Early and accurate information regarding the diagnosis should be made available to the GP and the couple including advice to the couple to preserve the test results and other information to show to their GP and obstetrician as soon as any subsequent pregnancy is confirmed.
- (2) DNA mutation analysis should always be undertaken on the affected child and parents, to facilitate prenatal diagnosis in a subsequent pregnancy.
- (3) Prompt counselling and prenatal diagnosis should be offered in the first trimester of an at risk pregnancy whenever possible.
- (4) General educational literature for parents should be available, to inform them about cystic fibrosis symptoms management, the recurrence risk, prenatal diagnosis options and the need for early booking in a subsequent pregnancy. This should be provided initially by the paediatrician at the time of diagnosis of an affected infant/child.
- (5) Educational literature for primary care teams should be available, specifically about cystic fibrosis but also as part of the general process of education about genetics.

The inquiry team is grateful to the paediatricians, obstetricians, GPs, their teams and secretaries for their cooperation. We would like to thank Mrs Sue Morison, UK Cystic Fibrosis Survey, for liaising with paediatricians to facilitate case ascertainment.

The UK Cystic Fibrosis Prenatal Diagnosis Register was funded by the UK Cystic Fibrosis Trust.

A copy of the full report to the Department of Health is available from the Royal College of Physicians of London.³

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