Effect of introducing antenatal diagnosis on reproductive behaviour of families at risk for thalassaemia major

B MODELL, R H T WARD, D V I FAIRWEATHER

Summary and conclusions

Families who were at risk of producing a child with thalassaemia major were studied to determine the sequential effects on their reproductive behaviour of knowing the risk and, subsequently, of knowing that antenatal diagnosis was available. Knowing the risk caused them virtually to stop reproduction and to seek termination of 70% of pregnancies, most of which were accidental. The introduction of antenatal diagnosis in 1975 permitted the resumption of nearly normal reproduction by at-risk families, with fewer than 30% of pregnancies being terminated for thalassaemia major.

All couples at risk for thalassaemia major should be detected and counselled before they produce an affected child; responsibility for either choosing or refusing antenatal diagnosis should be theirs alone.

Introduction

As prevention of severe congenital disease by antenatal diagnosis and termination of affected pregnancies is becoming increasingly accepted in Western society, its effects on the at-risk family and community need to be documented. A clear-cut opportunity for measuring some of the social effects of this preventive approach for a severe disease with a high incidence in a defined population was provided by the introduction of antenatal diagnosis for thalassaemia major among the large Cypriot community of north-east London.

The wide distribution and great prevalence of β-thalassaemia major in the Middle and Far East make it the most common of all inherited human lethal conditions. It is transmitted as a Mendelian recessive; hence heterozygotes are symptomless but can be reliably detected by blood tests. When two heterozygotes marry the risk of producing an affected child is one in four in each pregnancy. Untreated, the patients usually die of anaemia between 2 and 6 years of age. Effective treatment consists of regular blood transfusions and intensive administration of the iron-chelating agent deferoxamine by subcutaneous infusion for eight to 12 hours nightly. Among Greek and Turkish Cypriots the prevalence of heterozygotes is about 15%, the prevalence of at-risk marriages 2%, and the birth rate of homozygous infants five per thousand.

In Britain there are about 300 patients with thalassaemia major, two-thirds of whom are of Cypriot origin and one-third of Indian or Pakistani origin. Each year about 15 children with the disease are born in Britain—that is, some 60 pregnancies are at risk yearly. During the past four years prevention of the disease by prospective genetic counselling and antenatal diagnosis of at-risk pregnancies has been offered to couples at risk. The feasibility of this approach depends on the accurate haematological diagnosis of couples of carriers even before they have had an affected child, the ability to diagnose homozygous fetuses by using micorsamples of fetal blood, and the development of obstetric methods of fetal blood sampling before the 20th week of gestation. The real usefulness of antenatal diagnosis to the population concerned, however, depends on other factors, such as the degree of awareness of the risk by health workers in the community, and by the community itself; the identification and accurate counselling of at-risk couples; and their response to even if accepting the risk, availability, and limitations of antenatal diagnosis.

We describe the effect in the first instance of knowing the risk, and subsequently of knowing that antenatal diagnosis is available, on the reproductive behaviour of at-risk couples in Britain.

Methods

From December 1974 to December 1979 we performed over 300 antenatal diagnoses for thalassaemia major and other haemoglobinopathies. This report is concerned with 77 of these that were done for 61 families resident in England who were available for complete follow-up, had open access to an antenatal diagnostic service, and shared the same environment as the native British.

COLLECTION OF INFORMATION ON COUNSELED AT-RISK COUPLES

We were kept aware of the number of pregnant at-risk couples detected and counselled, even when they were not referred for antenatal diagnosis, because even if an at-risk couple rejected antenatal diagnosis or were detected too late in pregnancy we were usually asked to provide a neonatal diagnosis from cord blood.

DETECTION OF AT-RISK COUPLES

The couples found themselves to be at risk (a) by producing an affected child; (b) as a result of maternal screening in the antenatal clinic (blood samples from heterozygotes show microcytosis and contain an increased proportion of haemoglobin A\textsubscript{i}; in such cases the husband is also tested); and (c) by premarital or intramarital testing before they undertook any pregnancies.

CONTENT OF COUNSELLING

Counselling was non-directive and entailed discussing with the couple the one-in-four chance of having an affected child in each pregnancy; the clinical manifestations and improving prognosis of thalassaemia major; the 7-10% risk of losing the pregnancy as a result of fetal blood sampling; and the method and risks of inducing midtrimester abortion by intra-amniotic injection of prostaglandin.

COLLECTION AND ANALYSIS OF DATA

The obstetric history taken included the date of marriage, year and outcome of each pregnancy, year when the couple found themselves at risk, and year and circumstances under which they discovered that antenatal diagnosis was available.

We divided each couple's married life into the number of whole married years passed in each of the following four phases, and recorded the number of pregnancies, terminations of pregnancy, and healthy children and children with thalassaemia born in each phase. Phase 1 (years when they did not know their risk) included the year of marriage to the year when they discovered their risk. Phase 2 (years when they knew their risk but antenatal diagnosis was not available) included the
year after they discovered their risk to the year before they discovered that antenatal diagnosis was available. Phase 3 (years when they knew both their risk and that antenatal diagnosis was available) included the year when they first heard of antenatal diagnosis to the end of 1979. Phase 4 (pregnancies started when they did not know the risk, but counselling given and antenatal diagnosis offered): 24 at-risk couples were discovered in the antenatal clinic, so the index pregnancy had been started in ignorance but had to be completed knowing the risk. Six couples had already had normal children in ignorance of their risk before antenatal diagnosis was available (phase 1). The year in which they were informed of their risk and decided what to do about the current pregnancy was counted as phase 4, and subsequent years as phase 3. Eighteen mothers were primigravidae who had married after antenatal diagnosis became generally available (1976). Their years from marriage to counselling were counted as phase 4, and subsequent years as phase 3.

All pregnancies started before November 1979 were included. Of 182 pregnancies, 12 (7%) ended in early spontaneous abortion; only the 170 continuing pregnancies were counted. All children not suffering from thalassaemia major are described as “healthy.” All parents were British nationals. Most were of Greek Cypriot or Turkish Cypriot ancestry and are grouped together as Cypriots; a smaller group either originated from or had ancestors originating from the north-western part of the Indian subcontinent (Indians, Pakistanis, and East African Asians) and are referred to as “Indians” in reference to their continental origin.

Results

The number of at-risk couples identified yearly rose from four in 1976 to 25 in 1979. Since the theoretical number of at-risk pregnancies yearly for the whole of Britain is 60, at least half the at-risk couples must be passing through antenatal clinics uncounseled.

CHOICES OF COUNSELLED AT-RISK COUPLES

Table I shows how the couples were identified and their choices after counselling. Ninety-four per cent of Cypriots and only 59% of Indians requested antenatal diagnosis (table II). The Cypriots are a uniform cultural group, but the Indian families fell into four groups (table III). The numbers are small, but interest appears to have been lowest among first-generation Indians of rural origin.

Indians in general experienced much more difficulty than Cypriots in deciding what to do. There was serious disagreement between the parents in three cases. One couple refused antenatal diagnosis in the first pregnancy but wanted it in the second, one couple requested it in the first pregnancy but not in the second, and one mother chose to continue her pregnancy despite a diagnosis of thalassaemia major. In the larger Cypriot group only one such change of mind occurred, one mother choosing antenatal diagnosis in her fourth pregnancy but not in her fifth, on religious grounds.

Table III—Choices of “Indian” couples in relation to social group

<table>
<thead>
<tr>
<th>No counselled</th>
<th>No choosing antenatal diagnosis</th>
<th>No (%) rejecting antenatal diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>East African Asians</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Rural Indians: First generation</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Second generation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

Table II—Ethnic origins and choices of counselled couples at risk of producing offspring with thalassaemia major

<table>
<thead>
<tr>
<th>Ethnic origin</th>
<th>No counselled</th>
<th>No (%) choosing antenatal diagnosis</th>
<th>No (%) rejecting antenatal diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypriot</td>
<td>50</td>
<td>47 (94)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Indian and Pakistani</td>
<td>22</td>
<td>13 (59)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Italian</td>
<td>3</td>
<td>1 (33)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>61 (81)</td>
<td>14 (19)</td>
</tr>
</tbody>
</table>

Discussion

Our results show an appreciable difference between Indians and Cypriots in the acceptability of genetic counselling and antenatal diagnosis for thalassaemia: there was an overwhelming demand for this service from the British Cypriot community and a resultant reduction in the number of normal pregnancies terminated. Unfortunately, it appears that antenatal diagnosis is being offered to under half the at-risk pregnant mothers who might wish to know it is available. One reason for this is a low index of suspicion for the heterozygotes, since doctors generally do not realise that while homozygotes for most inherited diseases are uncommon, heterozygotes may be very common: for instance, a north London GP may have 30 heterozygotes for thalassaemia...
Progress in demand (always staff, individuals from amniotic fluid the choose and is haemoglobin (see The of seven chance of became available United States,17 and Pregnancies available . counselled a preliminary routinely delivering are being among chance of delivering a child with thalassaemia major: she has a one in seven chance of being married to another heterozygote and if she is her chance of delivering a homozygous child is one in four. The risks among Indians are less well defined. Since in Britain haemoglobin is now usually measured by the Coulter S machine, which also routinely measures mean cell haemoglobin and mean cell volume, preliminary screening for microcytosis is extremely easy (see appendix) and costs nothing. It is well within the range of the GP, general obstetrician, hospital doctor, antenatal nursing staff, and indeed any health worker to identify individuals in need of definitive diagnosis by estimating the proportion of Hb A2, which must be done in a reliable laboratory.

Though sickle-cell anaemia may also be diagnosed reliably in heterozygotes and antenatally on fetal blood samples, the difference in demand for antenatal diagnosis for thalassaemia major (always a cause of great distress and affecting Cypriots and Indians) and sickle-cell anaemia (not always causing great distress and affecting Africans and West Indians) has been striking, the perceived risk of sickle-cell anaemia often being insufficient to offset the risk to the pregnancy of fetal blood sampling. The American experience is similar.16 Recent progress in diagnosing haemoglobinopathies by using DNA from amniotic fluid fibroblasts16 18 may reduce the risk of diagnosis to that of amniocentesis, so it is now also important to detect and counsel couples heterozygous for Hb S.

**TABLE V—Reproductive behaviour of couples choosing antenatal diagnosis for thalassaemia (25 couples passing through all phases 1-3)**

<table>
<thead>
<tr>
<th>No of couples</th>
<th>Total years married</th>
<th>Married years per pregnancy</th>
<th>% choosing antenatal diagnosis</th>
<th>% of pregnancies terminated</th>
<th>% of children healthy</th>
<th>Married years per healthy child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies started and completed not knowing risk</td>
<td>86</td>
<td>2-4</td>
<td>0</td>
<td>0</td>
<td>36</td>
<td>6-6</td>
</tr>
<tr>
<td>Pregnancies started knowing risk but antenatal diagnosis not available</td>
<td>93</td>
<td>4-9</td>
<td>0</td>
<td>34</td>
<td>96</td>
<td>4-6</td>
</tr>
<tr>
<td>Pregnancies started knowing risk and that antenatal diagnosis available</td>
<td>96</td>
<td>3-0</td>
<td>97</td>
<td>34</td>
<td>96</td>
<td>4-6</td>
</tr>
</tbody>
</table>

*Two of the 61 families choosing antenatal diagnosis were omitted as atypical: one was Italian and the other, having been infertile for 17 years, introduced a bias into the calculations.

**TABLE VI—Reproductive behaviour of couples choosing antenatal diagnosis for thalassaemia (24 couples without an affected child, detected during pregnancy)**

<table>
<thead>
<tr>
<th>No of couples</th>
<th>Total years married</th>
<th>Married years per pregnancy</th>
<th>% choosing antenatal diagnosis</th>
<th>% of pregnancies terminated</th>
<th>% of children healthy</th>
<th>Married years per healthy child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies started and completed not knowing risk</td>
<td>6</td>
<td>3-5</td>
<td>0</td>
<td>18</td>
<td>100</td>
<td>4-3</td>
</tr>
<tr>
<td>Pregnancies started knowing risk, but counselled and offered antenatal diagnosis</td>
<td>24</td>
<td>2-2</td>
<td>95</td>
<td>27</td>
<td>100</td>
<td>3-1</td>
</tr>
<tr>
<td>Pregnancies started knowing risk and that antenatal diagnosis available</td>
<td>12</td>
<td>1-9</td>
<td>100</td>
<td>30</td>
<td>100</td>
<td>2-7</td>
</tr>
</tbody>
</table>

**WHERE SHOULD SCREENING AND COUNSELLING BE DONE?**

Medical responsibility for the birth of children with avoidable congenital disease reaches its maximum in the antenatal clinic. If an affected child is born without the parents having been advised of their risk the responsibility is often thought to rest with the obstetrician. In women of the appropriate ethnic groups preliminary screening for thalassaemia trait should be done as early as possible in the antenatal clinic or preferably by the GP when pregnancy is diagnosed (or even before). Counselling at-risk couples about the one-in-four risk of having an affected child in each pregnancy is also simple, but specialist advice is needed about the nature of the disease and the problems inherent in midtrimester fetal blood sampling and termination of pregnancy.

Though screening must be done in the antenatal clinic, some couples may book too late to have the option of antenatal diagnosis, and in any case this is not the ideal way for young couples to learn that they might have a sick child, as they are called on to make hasty decisions in a state of shock. Where else should screening occur? On questioning, nearly all Cypriot couples said that people should know before they got married, in order to make their decisions about marriage and reproduction responsibly.

For a community with this attitude there are many possibilities for education and genetic counselling. Public education through newspapers and television has been successful in both England and Cyprus; parents' associations maintain a constant trickle of information: the genetics of thalassaemia is part of the biology curriculum in Cyprus and in some north London schools; information and the offer of screening through the school medical service at the time of BCG vaccination (13 years) has been considered (M Rossiter, personal communication); some
Orthodox churches are prepared to hand out leaflets advising blood tests to couples getting married; and many family planning doctors consider genetic counselling to be part of their role. In hospital and general practice all individuals of relevant racial groups may be incidentally screened for thalassaemic microcytosis when their blood is tested for any reason, and they should receive genetic counselling. It is as important for Cypriots to know that they are not heterozygotes as that they are. If information is available at all these points individuals become aware that they themselves might be a carrier and can request testing at the nodal point in their lives (courtship, marriage, or the start of a pregnancy) when they feel the need for it. As a corollary, there should be a high degree of awareness by all health workers in communities in which diagnosable inherited disease is common so that they can all, from the health visitor to the GP and hospital doctors, give simple, accurate counselling and ensure that individuals have access to blood testing and expert advice when they want it.

The needs of Indians differ from those of Cypriots. Their cultural patterns make it unlikely that any campaign of public education and premarital genetic counselling would be beneficial, and the best option may be highly confidential screening in the antenatal clinic. Even though a high rate of rejection of the proffered information is to be expected in some areas, such as Bradford and Leeds, the obstetrician should still share this information with his patients to achieve equitable distribution of responsibility.

We gratefully acknowledge the support given to us by Sheikh Faisal and Madame Nouha Al-Hegelan and the personal generosity of Prince Sultan bin Abdulaziz of Saudi Arabia, which made this work possible. We are appreciative of the help of the many colleagues who referred patients to us, especially Dr George Marsh, Miss Ruth Coles, Dr Elizabeth Letsky, and Dr Kay Hunt. This work was supported by grants from the Sir Halley Stewart Trust, the Wellcome Trust, the Medical Research Council, and the King Abdulaziz Research Fund.

Appendix
DETECTION OF THALASSAEMIA TRAIT

The table shows the haematological characteristics of β-thalassaemia trait. Typically, β-thalassaemia trait causes pronounced microcytosis in the absence of anaemia. Since most large hospitals now use the Coulter S machine, automated red-cell indices are routinely available and this front-line screen for thalassaemia trait costs nothing.

<table>
<thead>
<tr>
<th>Mean (± 1SD) haematological indices in β-thalassaemia trait*</th>
<th>Normal English man</th>
<th>Male Cypriots with β-thalassaemia trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>14.7 ± 1.01</td>
<td>13.5 ± 1.05</td>
</tr>
<tr>
<td>Mean cell haemoglobin (pg)</td>
<td>27.9 ± 1.47</td>
<td>21.0 ± 1.35</td>
</tr>
<tr>
<td>Mean cell volume (fl)</td>
<td>87.0 ± 4.7</td>
<td>65.0 ± 4.3</td>
</tr>
<tr>
<td>Mean cell haemoglobin concentration (%)</td>
<td>34.0 ± 1.04</td>
<td>32.8 ± 1.01</td>
</tr>
</tbody>
</table>

*Values from North Middlesex Hospital (by courtesy of Dr G Marsh).

β-Thalassaemia is definitively diagnosed by finding a raised fraction of Hb A2. This test is efficient if only those samples with a mean cell haemoglobin of less than 27 pg or a mean cell volume of less than 78 fl are analysed. Though values for Hb A2 differ between laboratories, normal individuals and those with β-thalassaemia trait may usually be clearly distinguished. For example, at the North Middlesex Hospital and this hospital the normal range is 1.8-3.2% for Hb A2 while in β-thalassaemia trait the value is above 4%. Results falling between 3 and 4% require further investigation.

Diagnostic problems may be created by existing severe iron deficiency (which may cause microcytosis and rarely reduces the proportion of Hb A3), α-thalassaemia trait, and unusual forms of thalassaemia such as δβ-thalassaemia trait (raised Hb F and normal Hb A2) or “silent” β-thalassaemia (microcytosis with a normal Hb A2 resembling α-thalassaemia; or near-normocytosis with a raised Hb A2). To deal with these problems the husbands of all women with appreciable microcytosis should have their blood tested, and if both partners have microcytosis they can be attributed simply to iron deficiency they should be referred, or blood sent, to a reliable reference centre for definitive diagnosis. Though this problem is most common among immigrants from the Mediterranean or Far East, it may also occur in one in 1000 people of traditional British stock.6 “Non-specific” microcytosis is common among children, especially those under 4 years old. The simplest approach to diagnostic difficulty in a child is to test the parents.

Booklets useful for genetic counselling of individuals who carry β-thalassaemia trait may be obtained from The United Kingdom Thalassaemia Society, 107 Nightingale Lane, London N8.

References

(Accepted 18 March 1980)

ONE HUNDRED YEARS AGO M Schwartz speaks in the Archiv für Gynäkologie of an extraordinary and shocking case, in which a midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which a midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which the midwife by inconceivable violence and shocking case, in which