correspondence column, which acts as a safety valve in newspapers and journals.

Getting the balance right

Surely it is up to the television authorities to show that the balance is in their favour, or at least equal. Doctors know that some programmes have done harm: can the producers show that there have been programmes that have done an equal amount of good? (Some might mention the *Horizon* feature as having reduced the number of inductions done, but it might equally well be argued that the *BMJ* paper from the Cardiff obstetricians¹ giving the facts unemotionally had had more effect on the profession than any television programme.) Producers obviously fear that balance tends to lead to dullness, yet surely it is possible to achieve it more often than at present. For the other great danger is the effect of superficial programmes on our legislators. Mr Christopher Price, MP, is quoted as saying "I think it (ECT) is so dangerous that, in the long term, I would like to get rid of it completely." Scrutiny of Mr Price's *Who's Who* entry does not suggest that he is an expert on ECT, and hence to show a one-sided programme to a potentially important decision-maker such as he could have serious implications for official policy.

I believe that the present arrangements for vetting medical television programmes are inadequate, and that to give the public a more balanced view there must be more scrutiny. This is not to advocate avoiding the difficult issues, giving all sides,

or to recommend censorship, or to imply that the orthodox medical view must prevail, but merely to suggest adding the checks and balances that apply to most serious scientific work, such as the refereeing system. The need for this is particularly urgent in those programmes that have no formal advisory service at all—which includes *Panorama* and the News services—but some sort of reviewing committee is, I believe, a necessity for all programmes. The Scottish Division of the BBC has a joint committee with some doctors among its members; it meets monthly and gives doctors the opportunity of suggesting subjects that the BBC could tackle as well as the BBC of sounding doctors out on its medical projects.

Despite their stated constant preoccupation with the effect of programmes on audiences, many of the less experienced producers would benefit from more humility, not assuming that eight weeks' saturation in a subject gives them a depth of knowledge and judgment that would not be claimed by experts who have spent 30 years studying it. Perhaps the producers should hang up Cromwell's words over their desks "I beseech you, in the bowels of Christ, think it possible you may be mistaken."

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Contemporary Themes

Antenatal diagnosis of thalassaemia major

D V I FAIRWEATHER, B MODELL, V BERDOUKAS, BLANCHE P ALTER, D G NATHAN, D LOUKOPOULOS, W WOOD, J B CLEGG, D J WEATHERALL

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Summary and conclusions

Haemoglobin synthesis was studied in fetal blood samples obtained at 17 to 20 weeks' gestation in 22 women at risk

Departments of Obstetrics and Paediatrics, University College Hospital, London WC1

D V I FAIRWEATHER, MD, FRCOG, professor of obstetrics
B MODELL, PHD, MB, lecturer in paediatrics
V BERDOUKAS, MB, BS, research fellow in paediatrics

Haematology Department, The Children's Hospital Medical Centre, Boston, Massachusetts

BLANCHE P ALTER, MD, assistant professor of paediatrics
D G NATHAN, MD, director, professor of paediatrics

First Department of Internal Medicine, University of Athens, Vassilevs Pavlos Hospital, Athens 609

D LOUKOPOULOS, MD, assistant professor of medicine

Nuffield Department of Clinical Medicine, Oxford

W WOOD, PHD, university lecturer
J B CLEGG, PHD, university lecturer
D J WEATHERALL, FRCP, FRS, professor

of carrying a fetus with homozygous β -thalassaemia. A presumptive diagnosis of homozygous β -thalassaemia was made in four cases, and the pregnancy was terminated. An inconclusive answer was obtained in one case, and the patient also chose to have her pregnancy terminated. Two fetuses were lost as a result of the procedure. Of the remaining 15 pregnancies, 13 proceeded to term and two to 36 weeks; in each case a normal infant or one heterozygous for β -thalassaemia was delivered.

Current efforts should be directed towards improving the blood sampling technology so that fetal blood sampling can be used widely in those countries where thalassaemia is a major problem.

Introduction

The β -thalassaemias are the commonest genetic disorders of haemoglobin synthesis and occur with great prevalence throughout the Mediterranean and the Middle and Far East.¹ In Britain they occur mainly in immigrants from Cyprus, north-west India, and Pakistan.² Because of the severity of the homozygous state many couples in Britain who have had an affected child refrain from further pregnancies and seek abortion for accidental

pregnancies. Furthermore, since heterozygotes can be diagnosed with certainty and the immigrant communities are becoming increasingly aware of the nature of the disease, many couples who find that they are both carriers are seeking advice about the advisability of pregnancy.

The β -thalassaemias result from inherited defects in the synthesis of the β -chains of adult haemoglobin (HbA, $\alpha_2\beta_2$).¹ The main haemoglobin of intrauterine life is haemoglobin F (Hb F, $\alpha_2\gamma_2$) and the switchover to HbA production—that is, β - to γ -chain synthesis—occurs just before birth. Hence it was thought until recently that β -thalassaemia could not be diagnosed in the fetus. There have been several reports of finding HbA in the blood of young fetuses,³⁻⁴ however, and more recent studies of haemoglobin synthesis in fetal life indicate that β -chain synthesis is activated at a low level as early as eight weeks' gestation.⁵⁻⁶ Furthermore, the β -thalassaemia defect is expressed during early fetal life⁷⁻⁹ and hence it has been possible to diagnose β -thalassaemia in utero.

We describe our experiences in the prenatal diagnosis of β -thalassaemia in 25 women who were at risk of carrying a fetus homozygous for the condition.

Patients and methods

PATIENT SELECTION

Twenty-five pregnant women at risk of carrying an infant homozygous for β -thalassaemia were referred for prenatal diagnosis, 11 from Greece and the remainder from England. Standard techniques established the presence of a β -thalassaemia gene in the women and their husbands. Most had become pregnant accidentally and were prepared to consider terminating the pregnancy if prenatal diagnosis was not available. Twenty-one already had one or more affected children. The couples were interviewed and the experimental nature of the technique was explained, in some cases with the help of an interpreter. The couples were advised to consider early termination seriously and were given a week to reach a final decision. Three couples elected for termination.

Once a decision was made to attempt prenatal diagnosis the gestational age was checked by ultrasound measurement at about 15 weeks' gestation. Prenatal diagnosis was carried out at 17 to 18 weeks' gestation. About seven to 10 days before this the patient was admitted overnight for blood transfusion to raise the haemoglobin level to about 14 g/dl. Repeat ultrasound checks for placental location were performed immediately before fetal blood sampling.

OBSTETRIC TECHNIQUES

The objective was to obtain a small, relatively pure sample of fetal cells from a vessel on the chorionic plate of the placenta. The site and extent of the latter and the depth of the chorionic plate from the anterior abdominal wall were determined by ultrasound. One hour before the procedure the patient was sedated, and a blood sample was taken for assessing the relative rates of α - and β -chain synthesis and for α -fetoprotein levels. In those cases with an anterior placenta a blind needling technique similar to that used in amniocentesis was used. A fetal vessel was punctured and leaked into the surrounding amniotic fluid, and 0.2 to 0.5 ml of bloodstained fluid was withdrawn into a heparinised syringe. With posterior placentas a needlescope or fetoscope (Dyonics model 400) was used; under direct vision a relatively pure fetal blood sample (more than 0.1 ml) was withdrawn from a fetal vessel.¹⁰ In the earlier cases up to 20 small samples of blood-stained fluid or fetal blood were taken from up to three resittings of the needle, and the relative numbers of fetal cells were determined by the acid-elution technique.¹¹ Later in the series a Coulter particle-size analyser was brought into the labour ward so that the size of the red cells in the sample could be assessed immediately.¹² In this way it was possible to distinguish rapidly fetal from maternal red cells by their volume and so ascertain whether a satisfactory sample had been obtained.

One to three hours after the procedure a second sample of maternal blood was obtained for repeat α -fetoprotein estimation and for an acid-elution test to estimate the extent of fetomaternal bleeding.

These obstetric techniques and the equipment used will be described in greater detail elsewhere.

HAEMOGLOBIN SYNTHESIS IN FETAL BLOOD SAMPLES

The relative rates of synthesis in the α -, β -, and γ -chains in the fetal blood samples were determined by incubating them with ³H-leucine, washing and lysing the cells, precipitating the globin, and separating the globin chains by carboxymethylcellulose chromatography in an 8 M urea/mercaptoethanol/phosphate buffer system, pH 6.7.^{13,14} After determining the total radioactivity incorporated into each chain the β : γ -chain production ratio was calculated to determine the relative amounts of β -chain synthesis. In samples where adequate numbers of fetal cells were present this procedure was sufficient to provide this information. Where there was heavy contamination with maternal blood, however, or where the incorporated radioactivity was relatively low, a correction had to be made for β -chain synthesis in contaminating maternal reticulocytes, even though hypertransfusion of the mother had kept the latter to a minimum. In all cases maternal blood was incubated under identical conditions with those of the fetal sample so that a correction could be made for contamination of the fetal sample with radioactive maternal β -chain.^{9,12} When the sample contained less than 10% of fetal cells, two dilutions of the "fetal" sample into maternal blood were made to allow correction by the extrapolation method of Cividalli *et al.*¹⁵

Results

The percentage of fetal cells in the sample in which the diagnosis was made ranged from 0.6 to 100%. Adequate globin chain synthesis (fig 1) was achieved in 21 of the 22 cases. The β : γ -chain synthesis ratios fell into two groups (fig 2). In four cases there was virtually no detectable β -chain synthesis and these were presumed to be β -thalassaemia homozygotes, and the pregnancies were terminated. In three out of these four cases further globin chain synthesis analyses were carried out on blood obtained from the fetus, and the absence of β -chain synthesis was confirmed. In the remaining cases the β : γ -chain production ratio ranged from 0.049 to 0.130. Although the ratios

FIG 1—Elution patterns of globin chains from fetal blood samples. Above: Sample containing 4% of fetal cells (case 14) shows β : γ -ratio of 0.102, result within normal range. Counts due to maternal β -chain synthesis were virtually absent since mother had been transfused with four units of blood 10 days previously, so her reticulocyte production was suppressed. Below: Sample containing 100% fetal cells (case 18) shows nearly no β -chain synthesis, suggesting homozygous β -thalassaemia. Fetus was aborted, and repeat study confirmed absence of β -chain synthesis.

tended to segregate into two groups with means of about 0.10 and 0.07 respectively, there was considerable overlap, and it was not possible to distinguish between normal and heterozygous infants by this technique. All the infants with detectable β -chain synthesis were allowed to go to term, although two were delivered prematurely: all had an appreciable amount of HbA present in the cord blood and this was confirmed by biosynthesis in most cases (table I). All the babies are now more than 6 months old, and clinical follow-up studies have confirmed that none of them has homozygous β -thalassaemia. In one case where the laboratory data were considered equivocal the patient refused further attempts at fetal blood sampling and elected for termination of pregnancy.

The relevant obstetric data are summarised in table II. Eleven patients needed more than one attempt at fetal blood sampling because of failure to obtain an adequate sample. The procedure was repeated later the same day if the sample contained less than 5% fetal cells. Six repeat samplings were needed owing to technical difficulties in handling the sample in the laboratory. Eleven patients had only one sampling procedure, and it is significant that these include six of the last eight cases when the particle-size analyser and needlescope were both in use.

There were two intrauterine deaths. In the first the placenta was anterior and sampling was repeated on the same day because no fetal cells were present in the first 13 samples; 11 out of 15 samples at the second attempt contained more than 5% fetal cells. Three days later the mother noticed slackening of her breasts and diminution of uterine

FIG 2—Scatter diagram of β : γ -ratios obtained on fetal blood samples and on cord blood at birth. Note difference in scales. There is clear difference between fetuses making very little or no β -chain, diagnosed as thalassaemia major, and those that are normal or have β thalassaemia trait, although these two cannot be distinguished with certainty. Follow-up on cord blood was obtained for 13 of 20 fetuses on which firm diagnosis was made: four were aborted as having thalassaemia major, two died in utero as a result of the procedure, and one delivered in Cyprus, where biosynthetic follow-up could not be obtained, though cord blood electrophoresis showed presence of 13% HbA.

TABLE I—Patients with detectable β -chain synthesis who were allowed to go to term

Case No	% Fetal cells in sample	β : γ ratio	Outcome of pregnancy	Cord blood β : γ -ratio
1	10		FTND	0.91
2	45	0.079	FTND	0.47
3	100	0.096	FTND	1.09
4	41	0.130	FTND	0.95
5	65	0.072*	Terminated	No follow-up
6	30	0.109	FTND	0.89
7	15	0.044	FTND	0.92
8	74	0.080	IUD	No follow-up
9	0.6	0.096	FTND	0.53
10	100	0.064	FTND	0.84
11	1.6	0.081	FTND	1.02
12	50	0.060	FTND	0.28
13	26	0.100	IUD	No follow-up
14	20	0.102	FTND	0.65
15	100	0.115	Premature (36/52)	2.03 at 3 months
16	20	0.09	FTND	0.19
17	6	0.075	FTND	13% HbA on electrophoresis (Absent β -chain confirmed)
18	100	No β	Terminated	No follow-up
19	6	No β	Terminated	0.25
20	8	0.104	Premature (36/52)	(Absent β -chain confirmed)
21	90	No β	Terminated	(Absent β -chain confirmed)
22	100	No β	Terminated	(Absent β -chain confirmed)

*Some doubt about identity of β -peak, which failed to align with β -protein. Patient elected to terminate rather than repeat procedure.
FTND = Full-term normal delivery. IUD = Intrauterine death.
Cases 1-5 were reported by Alter *et al*.¹⁶

size. Ultrasound examination showed no fetal heart beat, and abortion was induced by intravenous prostaglandins. At delivery two puncture marks were seen in a large placental vessel close to the insertion of the cord.

The second fetus died at the third sampling attempt. The first attempt was successful but because of technical difficulties in the laboratory it had to be repeated. The second produced no suitable samples, and at the third attempt 10 out of 18 samples contained more than 5% fetal cells. After abortion a puncture mark was found in a large vessel near the insertion of the cord. In two further cases leakage of bloodstained amniotic fluid by the vagina was noted the day after the procedure. In the first case this ceased after a short period of bed rest, and the pregnancy continued normally; a normal infant was delivered at term. In the second case there was intermittent leakage of fluid for two weeks, and the 42-year-old mother delivered prematurely at 36 weeks.

Discussion

After it was shown that it might be feasible to diagnose the β -chain haemoglobinopathies in utero,⁷⁻⁹ two groups described their experiences with the prenatal diagnosis of β -thalassaemia. Alter and her colleagues¹⁶ described 11 attempts; one pregnancy

TABLE II—Obstetrical data on 22 patients

Case No	Placental site	No of attempts	Gestational age (weeks)	Samples		Remarks
				Total No	No >4%	
1	Anterior	3	16, 17	23	9	Analytical methods too insensitive for diagnosis Maternal transfusion introduced
2	Anterior	3	17, 19	26	4	
3	Anterior	2	17, 19	25	10	
4	Fundal	1	17	8	4	
5	Anterior	1	17	19	3	Intrauterine death
6	Anterior	1	17	12	7	
7	Posterior/lateral	1	19	13	2	
8	Anterior	2	17	28	11	
9	Fundal	2	15, 17	26	3	Intrauterine death Needlescope failed. Amniotic fluid leak by vagina
10	Anterior/lateral	1	18	15	2	
11	Fundal/posterior	3	16, 17	38	3	
12	Lateral	4	17, 19	77	14	
13	Lateral	3	17, 21	47	14	Particle-size analyser introduced Needlescope
14	Posterior	3	16, 17	46	4	
15	Anterior	1	21	18	5	
16	Anterior	1	18	15	2	
17	Posterior	1	17	18	4	Amniotic fluid leak by vagina Needlescope
18	Anterior	1	19	15	3	
19	Anterior	2	16, 17	43	4	
20	Anterior	3	16, 17	42	2	
21	Posterior	1	18	9	9	
22	Anterior	1	18	6	5	

ended in premature labour with loss of the fetus. Homozygous β -thalassaemia was diagnosed in two cases in which the pregnancies were terminated and was suspected in a further case but the pregnancy went to term and the infant was found to have β -thalassaemia trait. Seven predictions that infants would not have homozygous disease were confirmed. Kan and his colleagues¹² attempted prenatal diagnosis of thalassaemia in 22 cases. In two, fetal blood samples were not obtained, and there were three fetal deaths. Of the remainder, four pregnancies with presumed homozygous β -thalassaemia were terminated, and the remainder went to term; there were no misdiagnoses.

Our results support the view that prenatal diagnosis of homozygous β -thalassaemia is feasible without risk to the mother, although the risk of fetal loss attributable to the procedure is still considerable. There was a clear segregation of β : γ -chain synthesis ratios in the fetal blood samples, and adequate globin chain synthesis analysis could be done with as little as 1% fetal cells in the "fetal blood sample." Although the absence of β -chain synthesis in the fetus is highly suggestive that it has homozygous β -thalassaemia, this cannot be proved without allowing the fetus to go to term and seeing whether it develops the disorder after delivery. Clearly this is not justified. None of the infants who were allowed to go to term and delivered, however, had homozygous β -thalassaemia. Furthermore, by combining the results of the present study with the two previous series there have been 51 attempts at prenatal diagnosis in mothers at risk of carrying homozygous fetuses. So far there have been 35 normal or heterozygous infants allowed to go to term, and homozygous β -thalassaemia has been diagnosed 10 times. It would have been predicted that one in four of the infants would be homozygotes, a figure close to that observed. As the results of larger numbers of prenatal diagnoses become available it should be possible to see if this relationship holds.

There are two major types of β -thalassaemia: β^0 -thalassaemia in which there is no β -chain synthesis, and β^+ -thalassaemia in which there is some β -chain production but at a greatly reduced rate.¹ There was no genetic evidence in any of the families studied here to distinguish which type of β -thalassaemia gene was segregating, although since most of the families were Greek or Greek Cypriots it seemed likely that most cases would be β^+ -thalassaemia.¹ The fact that these infants had virtually no detectable chain synthesis in utero is encouraging and suggests that it is possible to diagnose both β^0 - and β^+ -thalassaemia in utero.

At the moment the major difficulty with the prenatal diagnosis of β -thalassaemia is obtaining an adequate fetal blood sample, and the present rate of fetal loss after the procedure is unacceptable. We encountered more difficulty with fundal or lateral placentas than anterior or posterior ones. The stage of gestation at the time of sampling was also important. When the procedure was carried out before 16 weeks' gestation it was less likely to be successful; seven out of 10 unsuccessful attempts were made before 16 weeks as compared with only six out of 31 at 17 weeks or over.

The needlescope is of particular value where the placenta is posterior, and in these cases a sample can be taken under direct vision, avoiding the danger of damage to the cord. Technical modifications are being introduced that should permit the use of the needlescope in all patients, but the development of a flexible fetoscope would be particularly helpful in approaching anterior, lateral, and fundal placentas. The routine use of the particle-size analyser for cell sizing^{9,12} is invaluable since needling of the placenta can be stopped as soon as an adequate sample is obtained. Transfusion of the mother is also useful since it reduces the amount of haemoglobin synthesis in contaminating maternal blood, and this is particularly valuable where the samples are heavily contaminated with maternal cells. This manoeuvre permitted an accurate diagnosis on samples of blood that contained as few as 0.6% fetal cells. Kan and his colleagues have attempted to enrich the number of fetal cells in mixtures of fetal and maternal cells by using the anti-i antibody to

agglutinate differentially with the fetal cells.¹⁷ This method is applicable only in samples containing more than 5% fetal cells. With the improving techniques of fetoscopy it should be possible to obtain samples richer in fetal cells and therefore to obviate the need for maternal transfusion or for separating cell populations.

Once samples containing 100% fetal cells can be reliably obtained, it should be possible to simplify the laboratory techniques for haemoglobin analysis, and a rapid electrophoretic study of the blood sample should suffice. Until then the more complicated haemoglobin synthesis studies will be needed to make an accurate diagnosis. Therefore current efforts should be directed to improving the fetal blood sampling technology since this would enable the technique to be used widely in those countries where thalassaemia is a major public health problem. Thalassaemia is a complicated heterogeneous disorder, and it will be necessary to use prenatal diagnosis in combination with careful evaluation of the type of thalassaemia in both parents, together with expert genetic counselling. Furthermore, we should take care to observe the social effects of applying prenatal diagnosis to such an extremely common genetic disorder.

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The local schools have asbestos blankets for wrapping up children in case of fire. Does the possibility of inhaling asbestos fibres make them dangerous?

Asbestos blankets used in schools and the fire service contain only white asbestos, which should not constitute a hazard. In any case, there is no effective alternative available. Such blankets remain stable for long periods, but sensible precautions should be taken in their use. New blankets may give off considerable quantities of dust and should be gently shaken downwind before being replaced in their container. They should then remain in the container until needed in an emergency, when they will be easy to remove by pulling on the strap. Fire drill should be carried out with ordinary blankets.