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# Audit of prenatal diagnosis for haemoglobin disorders in the United Kingdom: the first 20 years

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## Abstract

**Objectives:** To audit services for prenatal diagnosis for haemoglobin disorders in the United Kingdom.
**Design:** Comparison of the annual number of cases recorded in a United Kingdom register of prenatal diagnoses for haemoglobin disorders, with the annual number of pregnancies at risk of these disorders, by ethnic group and regional health authority. The number of pregnancies at risk was estimated using data on ethnic group from the 1991 census and data from the United Kingdom thalassaemia register, which records the number of babies born with thalassaemia.
**Setting:** The three national prenatal diagnosis centres for haemoglobin disorders.
**Subjects:** 2068 cases of prenatal diagnosis for haemoglobin disorders in the United Kingdom from 1974 to 1994.
**Main outcome measures:** Utilisation of prenatal diagnosis by risk, ethnic group, and regional health authority. Proportion of referrals in the first trimester and before the birth of any affected child.
**Results:** National utilisation of prenatal diagnosis for haemoglobin disorders was around 20%. During the past 10 years it has remained steady at about 50% for thalassaemias and risen from 7% to 13% for sickle cell disorders. Utilisation for sickle cell disorders varies regionally from 2% to 20%. Utilisation for thalassaemias varies by ethnic group. It is almost 90% for Cypriots and ranges regionally for British Pakistanis from 0% to over 60%. About 60% of first prenatal diagnoses are done for couples without an affected child. Less than 50% of first referrals are in the first trimester.
**Conclusions:** National utilisation of prenatal diagnosis for haemoglobin disorders is far lower than expected, and there are wide regional variations. A high proportion of referrals are still in the second trimester and after the birth of an affected child. The findings point to serious shortcomings in present antenatal screening practice and in local screening policies and to inadequate counselling resources, especially for British Pakistanis.

## Introduction

Population screening for haemoglobin disorders has been practised for over 20 years and now provides the most extensive available experience of screening for inherited disease.[1] Carriers are reliably detected by a screen that includes measurement of red cell indices (a mean cell haemoglobin concentration $<27$ pg suggests a thalassaemia) and electrophoresis for abnormal haemoglobins, followed by definitive diagnostic tests.[2] Therefore, in principle, all couples at risk of having

*See p 784*

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children with a haemoglobin disorder can be identified before they have an affected child—that is, prospectively—and offered first trimester prenatal diagnosis. By contrast, couples at risk of other inherited disorders are usually identified retrospectively, after diagnosis in an affected child. In the United Kingdom it is recommended practice to offer screening for haemoglobin disorders to all pregnant women who are not of northern European origin. When a carrier is identified her partner is offered testing. Carrier couples are referred for expert risk assessment and counselling, including the offer of prenatal diagnosis.[3 4]

Prenatal diagnosis of haemoglobin disorders at 18-23 weeks of pregnancy (by fetal blood sampling and globin biosynthesis) was introduced in 1974,[5-7] and routine antenatal screening for carriers was started in north London in 1977.[8] First trimester diagnosis by chorionic villus sampling was introduced in 1982.[9 10] This depends on DNA analysis, which was feasible from the outset by Southern blotting for couples at risk of $\alpha^0$ thalassaemia or sickle cell anaemia and for many couples at risk of β thalassaemia. Since 1990 first trimester diagnosis by a mutation specific polymerase chain reaction has been possible for all couples at risk.[11] There is no contraindication to chorionic villus sampling because the mid-trimester alternative, fetal blood sampling, carries a similar obstetric risk (1-2%).[12] Diagnostic accuracy, which was 98.3% with globin biosynthesis and 98.8% on Southern blotting, has risen to 99.7% with increasing experience and the use of the mutation specific polymerase chain reaction (J M Old et al, unpublished data).

The objective of carrier screening is informed choice.[3 4 14] Therefore the choices that counselled couples make in practice are a useful guide in developing services to meet the community's needs.[2] The obstetric risk and the 25% risk of having to decide whether to abort a wanted pregnancy naturally lead to a strong preference for early diagnosis. When second trimester diagnosis is the only available option, uptake is high for the (predictably severe) thalassaemias among Mediterranean, Indian, and South East Asian couples.[8 15] Uptake for the less predictable sickle cell disorders is highly sensitive to gestation at counselling: 80% of referred couples counselled in the first trimester request prenatal diagnosis compared with only 40% counselled later (M Layton, unpublished data).[16] Uptake for thalassaemia by British Pakistanis is equally sensitive to early counselling.[17 18] We believe that all couples have a right to be informed and to choose for or against prenatal diagnosis at a stage when first trimester diagnosis is available.

Chorionic villus sampling is widely available in the United Kingdom, but DNA diagnosis for haemoglobin disorders is concentrated at our three centres. We conducted a national audit on the basis of a British register of prenatal diagnoses for haemoglobin disorders and with the support of the Department of Health. In this paper we describe the evolution of the service in relation to time, risk, regional health authority, diagnostic method, and ethnic group. We also examine service utilisation (the percentage of at risk pregnancies coming to prenatal diagnosis) in the past 10 years and two indicators of service quality—namely, the proportion of tests performed for couples detected prospectively and the proportion carried out in the first trimester.

## Subjects and methods

The three British centres for prenatal diagnosis of haemoglobin disorders are in north London (University College Hospital Obstetric Unit), south London (King's College Hospital), and Oxford (National Haemoglobinopathy Reference Centre). Laboratory records at the three centres are complete. Clinical records are complete at University College Hospital from the outset and at King's College Hospital from 1989, but many samples are sent to Oxford with minimal clinical information. The haematology department of the University College Hospitals provided information on a further 46 diagnoses by globin biosynthesis. No other British laboratory is known to have ever provided this service.

A computerised patient record was created by one of us (SG) using the Microsoft Access database. All records were reviewed and the following core data for all prenatal diagnoses for British residents to the end of December 1994 entered retrospectively: mother's identifier, parents' ethnic group, district health authority and regional health authority of residence, risk, number of fetuses, date(s) and type of obstetric procedure(s), diagnostic method, fetal diagnosis, and diagnostic errors. The register is numerically almost complete: any missing cases reflect loss of laboratory records, a rare event.

The data were analysed by year, risk, regional health authority of patients' residence, and result. We excluded four cases in which an unnecessary procedure was performed for couples who were not at risk. Diagnostic accuracy and 23 misdiagnoses will be reported elsewhere. Data from University College Hospital were analysed separately for retrospective and prospective detection of couples at risk and for gestation at diagnosis.

The utilisation of prenatal diagnosis (the number of prenatal diagnoses as the percentage of pregnancies at risk) was calculated for the most recent five years (1990-4). The denominator, the annual number of pregnancies at risk, was derived in two ways. For all cases it was calculated using 1991 census data on ethnic group for infants aged 0-4 years.[4] Figures for black Africans and black Caribbeans, the groups mainly at risk of sickle cell disorders, were combined because their respective contribution to the census categories "black, other" and "other, other" cannot be separated.[18] Estimation of the number of expected pregnancies at risk is also complicated because numbers, birth rate, and rate of marriage outside ethnic group (which reduces the number of at risk pregnancies[19]) change constantly in ethnic minority groups. In this paper we use recent, verified, and adjusted estimates (M Hickman et al, unpublished data).[20] A register of patients, the United Kingdom thalassaemia register) exists for β thalassaemias, so hard data on annual conceptions can be obtained as the sum of the number of thalassaemia major pregnancies diagnosed and terminated and the number of live births reported to the register.

**Table 1** Numbers of prenatal diagnoses for haemoglobin disorders in United Kingdom, 1974-94

| Year | $\alpha^0$ Thalassaemia (hydrops fetalis) | β Thalassaemias | Sickle cell disorders | Total | No (%) of fetuses homozygous for disease |
|---|---|---|---|---|---|
| 1974 | | 2 | | 2 | 0 |
| 1975 | | 2 | | 2 | 0 |
| 1976 | | 10 | | 10 | 3 (30) |
| 1977 | | 24 | | 24 | 6 (25) |
| 1978 | | 24 | | 24 | 10 (42) |
| 1979 | | 30 | 3 | 33 | 9 (27) |
| 1980 | 1 | 45 | 5 | 51 | 8 (16) |
| 1981 | | 61 | 8 | 69 | 12 (17) |
| 1982 | 1 | 53 | 13 | 67 | 16 (24) |
| 1983 | 4 | 71 | 10 | 85 | 27 (32) |
| 1984 | 6 | 81 | 33 | 120 | 26 (22) |
| 1985 | 1 | 79 | 33 | 113 | 34 (30) |
| 1986 | 6 | 86 | 39 | 131 | 36 (27) |
| 1987 | 3 | 99 | 66 | 168 | 42 (25) |
| 1988 | 6 | 80 | 54 | 140 | 48 (34) |
| 1989 | 3 | 91 | 57 | 151 | 41 (27) |
| 1990 | 5 | 92 | 73 | 170 | 41 (24) |
| 1991 | 2 | 62 | 48 | 112 | 23 (21) |
| 1992 | 8 | 72 | 96 | 176 | 38 (22) |
| 1993 | 7 | 72 | 119 | 198 | 61 (31) |
| 1994 | 8 | 82 | 132 | 222 | 50 (23) |
| Total | 61 | 1218 | 789 | 2068 | 531 (26) |

## Results

By the end of December 1994, 2068 prenatal diagnoses had been carried out in 2035 pregnancies (table 1). There were 33 sets of twins, each fetus being counted separately. A total of 531 fetuses were diagnosed as being homozygous for a haemoglobin disorder.

Annual prenatal diagnoses for β thalassaemias increased rapidly from 1974, settling around 1984 at about 80 per year. Of 1218 such prenatal diagnoses, 1188 were for homozygous β thalassaemia, 16 for haemoglobin E-β thalassaemia, and 15 for rare indications such as haemoglobin Lepore-β thalassaemia or haemoglobin O Arab-β thalassaemia. A total of 305 fetuses were diagnosed as being homozygous, and 296 of these pregnancies were terminated. There were 7-8 prenatal diagnoses per year for α thalassaemia hydrops fetalis. Twenty fetuses had homozygous disease, and 19 of these pregnancies were terminated.

Prenatal diagnosis started almost 10 years later for sickle cell disorders than for thalassaemias, but the numbers of diagnoses exceeded those for thalassaemias around 1992. Of 789 such prenatal diagnoses, 671 were for sickle cell anaemia, 68 for sickle cell-haemoglobin C disease, 33 for sickle cell-β thalassaemia, and 17 for fetuses with a 50% risk of disease because one parent had a sickle cell disorder and one was a carrier. One couple were at risk of sickle cell-haemoglobin D disease. A total of 206 fetuses were diagnosed as being homozygous for sickle cell disease (26%).

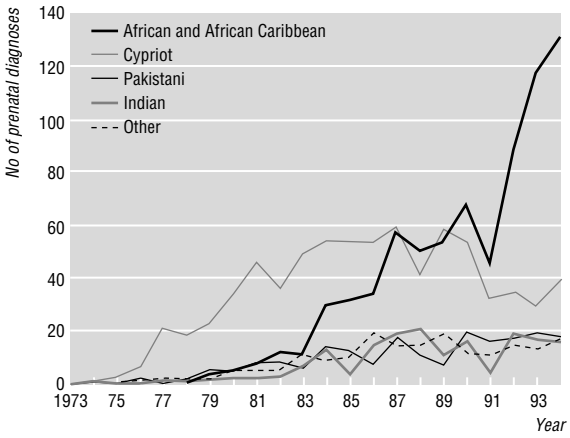


**Fig 1** Numbers of prenatal diagnoses for haemoglobin disorders for residents of United Kingdom according to ethnic group in 1991 census

Figure 1 shows a rapid recent increase in prenatal diagnoses for couples of African origin and a fall for Cypriots. The rapid rise reflects increasing numbers of couples at risk, as well as increasing utilisation of prenatal diagnosis for sickle cell disorders; the fall reflects an increase in the number of marriages outside the Cypriot community, which reduces the risk.[20] There are far fewer diagnoses for British Indians and Pakistanis. Table 2 shows utilisation of prenatal diagnosis in the two most recent five year periods by ethnic group. Utilisation for thalassaemias was steady at around 55% (900/1653) but ranged from 89% (461/517) among Cypriots and others (Italians, Chinese, Middle East, mixed race) to around 28% (147/522) among Pakistanis and 10% (17/168) among Bangladeshis. Utilisation by Indians rose from 42% (59/142) to over 60% (92/142). Utilisation by Africans and African Caribbeans, mainly for sickle cell disorders, rose from around 7% (229/3163) to 13% (457/3565).

Figure 2 shows utilisation of prenatal diagnosis by regional health authority. For thalassaemias it ranges

**Table 2** Utilisation of prenatal diagnosis for haemoglobin disorders by disorder and ethnic group, 1985-94

| | Sickle cell diseases | Ethnic group | | | | | | Thalassaemias and sickle cell diseases |
|---|---|---|---|---|---|---|---|---|
| | | Cypriot | Indian | Pakistani | Bangladeshi | Other | Thalassaemias | |
| **1985-9** | | | | | | | | |
| No of pregnancies at risk | 3163 | 296 | 142 | 261 | 84 | 71 | 855 | 4018 |
| No of prenatal diagnoses | 229 | 296 | 59 | 78 | 7 | 62 | 475 | 704 |
| Utilisation of prenatal diagnosis (% of pregnancies at risk) | 7 | 100 | 41 | 30 | 8 | 88 | 56 | 18 |
| **1990-4** | | | | | | | | |
| No of pregnancies at risk | 3565 | 222 | 142 | 261 | 84 | 71 | 780 | 4355 |
| No of prenatal diagnoses | 457 | 192 | 92 | *69* | 8 | 64 | 425 | 882 |
| Utilisation of prenatal diagnosis (% of pregnancies at risk) | 13 | 87 | 65 | 26 | 9 | 91 | 54 | 20 |

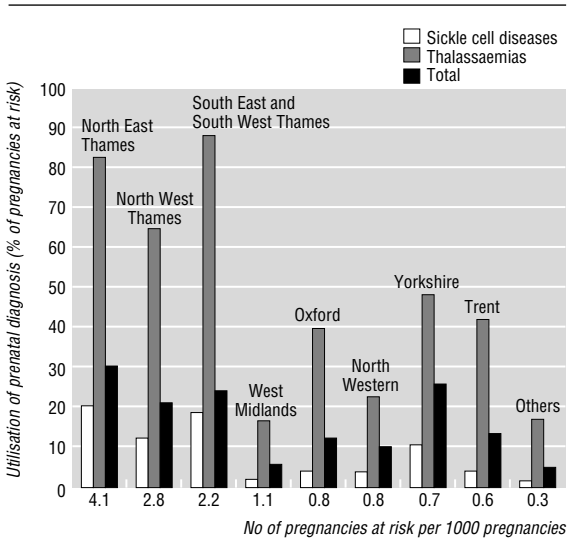


**Fig 2** Utilisation of prenatal diagnosis for thalassaemias and sickle cell disorders in United Kingdom, 1985-94, by regional health authority in 1991 (others refers to Scotland, Wales, and East Anglia, Mersey, Northern, South Western, and Wessex regional health authorities)

from 16% (17/105) to 89% (73/82) and for sickle cell disorders from 2% (5/309) to 20% (180/910), utilisation for the two groups varying together. Utilisation was only loosely related to prevalence of at risk pregnancies: it was highest in south east England, but in Yorkshire (0.66 pregnancies at risk per 1000 pregnancies) utilisation was 26% (42/164), while in the west Midlands, where prevalence was almost twice as high, utilisation was 5% (22/414) ($\chi^2 = 49.14$, df = 1, $P < 0.01$).

Table 3 shows observed major β thalassaemia conceptions and prenatal diagnoses by ethnic group and region. It shows that ethnic differences do not fully account for regional differences.

Analysis of data from University College Hospital for the past 10 years showed that in north London the proportion of first diagnoses done prospectively (before the birth of any affected child) was around 33% (6/18) for $\alpha^0$ thalassaemia, 70% (162/232) for β thalassaemia, and 60% (115/191) for sickle cell disorders. Table 4 shows that during 1990-4 around 50% of couples with an affected pregnancy detected by antenatal screening were referred in the first trimester, but in subsequent pregnancies around 90% referred themselves in the first trimester.

## Discussion

Our results show that antenatal screening as currently practised identifies risk too late to provide a satisfactory service to over half the population at risk.

**Service utilisation does not reflect service provision**

Antenatal screening and genetic counselling for haemoglobin disorders has become standard practice in the United Kingdom in the past 20 years. There is now a national network of 32 sickle cell and thalassaemia counselling centres,[21] and a multiprofessional UK Forum on Haemoglobin Disorders was established in the United Kingdom in 1995. Nevertheless, national utilisation of prenatal diagnosis for thalassaemias is around 50%, contrasting with over 95% in Cyprus[22] and Sardinia[23] and 75% in mainland Italy and Greece.[2] Utilisation for sickle cell disorders, at 13%, is also lower than expected from reports of 50% uptake in community based studies in London and the United States (M Layton, unpublished data).[24 25] Utilisation is highest in south east England, where prevalence is highest. Wide regional and ethnic differences and parallel variations for thalassaemias and sickle cell disorders raise important questions about the adequacy of service provision.

**Possible reasons for low utilisation**

There are probably several contributing factors. Firstly, no health professional has clear responsibility for delivering genetic population screening, making it difficult to integrate this service for haemoglobin disorders into routine medical services. The Department of Health therefore advises district health authorities to form multidisciplinary teams to develop local policy, key members being a haematologist interested in red cell disorders and a haemoglobinopathy counsellor.[3] To what extent does service utilisation reflect the existence of such teams?

Secondly, couples have a strong preference for early prenatal diagnosis. Does low service utilisation reflect the fact that antenatal screening usually identifies risk in the second trimester? As recently as 1990-4 over 50% of first prenatal diagnoses were

**Table 3** Utilisation of prenatal diagnosis for β thalassaemia by region and ethnic group, 1983-92*

| | Cypriot | | Indian | | Pakistani | | Other | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| Region | No of affected conceptions† | No (%) diagnosed prenatally | No of affected conceptions† | No (%) diagnosed prenatally | No of affected conceptions† | No (%) diagnosed prenatally | No of affected conceptions† | No (%) diagnosed prenatally | No of affected conceptions† | No (%) diagnosed prenatally |
| South East England | 137 | 121 (88) | 48 | 28 (58) | 40 | 26 (65) | 49 | 25 (51) | 274 | 200 (73) |
| North East Thames | 88 | 80 (91) | 13 | 8 (62) | 15 | 9 (60) | 19 | 4 (21) | 135 | 101 (75) |
| North West Thames | 18 | 16 (89) | 24 | 12 (50) | 16 | 11 (69) | 15 | 11 (73) | 73 | 50 (68) |
| South East and South West Thames | 31 | 24 (77) | 11 | 8 (73) | 9 | 6 (67) | 15 | 10 (67) | 66 | 48 (73) |
| Rest of United Kingdom | 8 | 6 (75) | 40 | 9 (23) | 85 | 15 (18) | 19 | 4 (21) | 152 | 33 (22) |
| West Midlands | 1 | 0 | 12 | 2 (17) | 22 | 0 | 5 | 0 | 40 | 3 (8) |
| Yorkshire | | | 6 | 3 (50) | 28 | 10 (36) | 1 | 0 | 35 | 13 (37) |
| North Western | 2 | 0 | 3 | 0 | 18 | 2 (11) | 5 | 1 (20) | 28 | 5 (18) |
| Other | 5 | 3 (60) | 19 | 4 (21) | 17 | 3 (18) | 8 | 3 (38) | 49 | 13 (27) |
| Total | 145 | 126 (87) | 88 | 37 (42) | 125 | 41 (33) | 68 | 29 (43) | 426 | 234 (55) |

*Data are incomplete after 1992.
†Sum of prenatal diagnoses of and terminations for thalassaemia major in the United Kingdom prenatal diagnosis register and number of babies born with the disease reported to the United Kingdom thalassaemia register.

performed in the second trimester and 40% were retrospective, after the birth of an affected child. Indeed, six such couples are known to have sued their obstetrician for negligence. Participants at the meeting on antenatal screening of the UK Forum on Haemoglobin Disorders in the United Kingdom in October 1996 agreed unanimously that this is a key problem. Many couples, especially Muslims and those at risk of sickle cell disorders, decline prenatal diagnosis when pregnancy is advanced,[15 26] and many have an affected child. Unless couples are put in touch with a specialist centre, delays often recur in subsequent pregnancies.[26] Couples who once attend a specialist centre can make contact directly in subsequent pregnancies, and the fact that over 90% do so in time for first trimester diagnosis suggests this as the ideal for the service.

Thirdly, religious and social reservations are particularly important for Muslim couples, most of whom are unaware that prenatal diagnosis is available in Pakistan and Iran.[27] The register includes 190 prenatal diagnoses for British Pakistanis, utilisation being 65% in London and 18% elsewhere. Do these differences reflect availablility of counselling by a trained person in the clients' language, preferably at home, as recommended for this group by the Royal College of Physicians?[4 28]

**Can access to the service be improved?**

The extent to which service utilisation reflects parents' informed choice is currently being investigated for β thalassaemia in the Royal College of Physicians' national confidential inquiry into genetic counselling.[29] This examines the records of counselling associated with live births of babies with thalassaemia and terminations of pregnancy for the disease since 1990.[2] A separate study of antenatal screening for sickle cell disorders points to late identification of risk as the key problem.[26]

Service standards are needed, including a clear screening policy and line of responsibility in each district health authority,[3 4] carrier screening in early pregnancy with rapid referral of couples at risk for expert counselling, and counselling in the client's own language when necessary. The feasibility of increasing the involvement of primary care teams in carrier screening and counselling should be investigated.

**Key messages**

- This audit for the United Kingdom found that utilisation of prenatal diagnosis for thalassaemias is about half that expected and for sickle cell disorders one third that expected
- Differences in prevalence of couples at risk or in ethnic group did not account for the wide regional differences observed
- First trimester prenatal diagnosis is feasible for all couples at risk of haemoglobin disorders, but less than half of those having prenatal diagnosis are first referred in the first trimester
- To achieve the objective of the service—informed choice for couples at risk—each district health authority needs a policy promoting screening for carriers early in pregnancy and before pregnancy, immediate expert counselling in couples' own language when appropriate, and fast track referral

**Table 4** Occurrence of prenatal diagnosis in first trimester in relation to parents' experience (University College Hospital, 1990-4)

| | First prenatal diagnosis | | Second or later prenatal diagnosis | |
|---|---|---|---|---|
| | No | No (%) in first trimester | No | No (%) in first trimester |
| $\alpha^0$ Thalassaemia | 7 | 2 (29) | 8 | 7 (88) |
| β Thalassaemia | 75 | 41 (55) | 113 | 102 (90) |
| Sickle cell disorders | 128 | 58 (45) | 33 | 30 (91) |
| Total | 210 | 101 (48) | 154 | 140 (91) |

The difference between proportion in the first trimester in index and subsequent pregnancies is highly significant: $\chi^2$=56.53, df=2, P=<0.001.

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# Audit of process of antenatal screening for sickle cell disorders at a north London hospital

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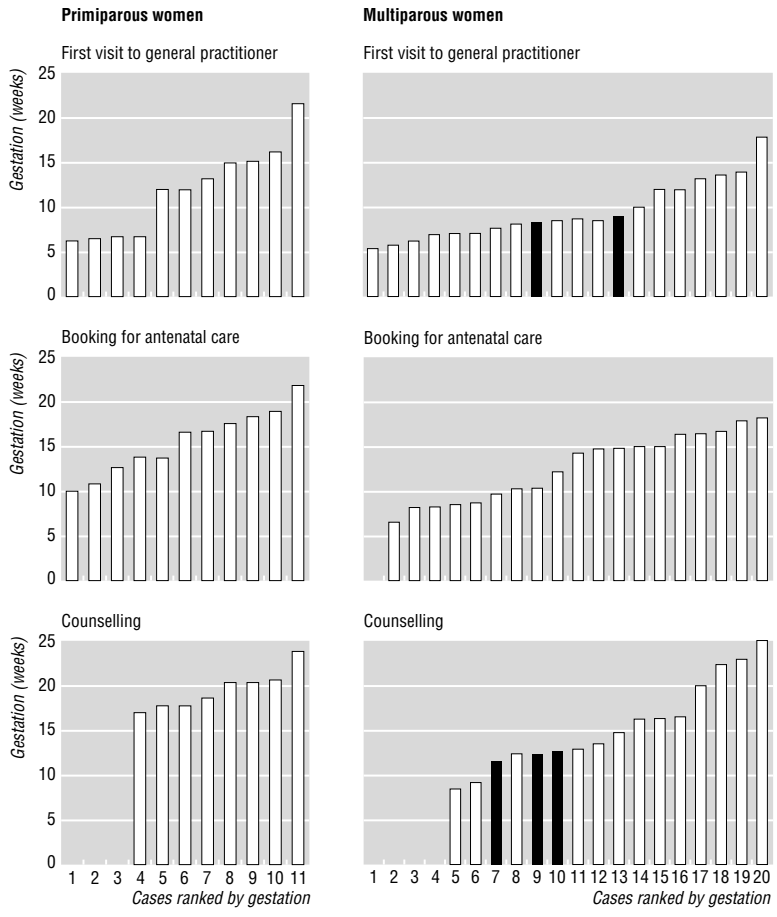
*See p 779*

Antenatal screening for haemoglobin disorders (sickle cell disorders and thalassaemias) is now routine.[1] Couples who are at risk have a strong preference for prenatal diagnosis during the first trimester,[2] but most are identified too late for this in the presenting pregnancy.[3] We studied the process of antenatal screening and counselling for sickle cell disorders at this hospital, where 40% of births are in groups at risk. The hospital has a policy of universal antenatal and neonatal screening for haemoglobin disorders. Two community based haemoglobinopathy counsellors are notified when a pregnant carrier is identified and invite the couple within two days to attend for testing of the partner and counselling. About 80% of couples attend. Couples who are interested in prenatal diagnosis are referred to a specialist centre.




Gestation (weeks) at three points in antenatal screening for haemoglobin disorders—first visit to the general practitioner, booking for antenatal care, and counselling—in 31 women at risk of having children with sickle cell disorder. Black bars denote those who had prenatal testing

## Subjects, methods, and results

Thirty one women at risk were identified among those booking for antenatal care between 1 January and 31 December 1994: 29 from laboratory records and two after the birth of an affected child. Since couples at risk have a 1 in 4 chance of having an affected child, this suggests that about six additional couples were not identified. The number of couples at risk was probably about 37. Obstetric notes were reviewed. Six women were of African Caribbean descent and 25 of African descent. Eleven were primiparous (most of whom were unaware of their risk before this pregnancy) and 20 were multiparous (most of whom had been screened and informed of their risk in a previous pregnancy). Gestation at the time of the first visit to the general practitioner, booking for antenatal care, and counselling are shown in the figure.

In the 11 primiparous women the mean gestation at the first visit to the general practitioner was 11.9 weeks, at booking 15.7 weeks, at partner's blood test result 19.2 weeks, and at counselling 19.5 weeks. Three couples did not attend counselling. All declined prenatal testing; one attended the specialist centre for counselling at 16 weeks' gestation. Seven out of 11 liveborn children had a sickle cell disorder.

In the 20 multiparous women the mean gestation at the first visit to the general practitioner was 9.2 weeks. Two of the 20 women were referred directly to the prenatal diagnosis centre for counselling and had early prenatal testing. One affected fetus was aborted. Mean gestation at booking in the remaining 19 cases