Papers

Risk of testicular cancer in cohort of boys with cryptorchidism

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Abstract

Objective: To determine the risk of testicular cancer in relation to undescended testis and its treatment based on recorded details of the maldescent, treatment, and biopsy from case notes.
Design: Cohort study.
Setting: Hospital for Sick Children, Great Ormond Street, London.
Subjects: 1075 boys with cryptorchidism treated by orchidopexy or hormones at the hospital during 1951-64.
Main outcome measures: Relative risk of testicular cancer in the cohort compared with men in the general population.
Results: 12 testicular cancers occurred in 11 of the patients during follow up to mid-1990 (relative risk of cancer in males with cryptorchidism = 7.5 (95% confidence interval 3.9 to 12.8)). The relative risk fell significantly beyond 15 years after orchidopexy but did not decrease with younger age at orchidopexy. Risk was significantly raised in testes that had had biopsy samples removed during orchidopexy (relative risk = 66.7 (23.9 to 143.3) compared with a testis in a man in the general population) and was significantly greater in these testes than in undescended testes that had not had biopsy samples taken at orchidopexy (6.7 (2.7 to 13.5)). No reasons for biopsy or distinguishing clinical aspects of the testes that had had biopsy samples taken and later developed malignancies were evident in the case notes. No histological abnormalities were evident at initial biopsy except in one testis that had features of dysgenesis.
Conclusions: Biopsy seems to be a stronger risk factor for testicular cancer than any factor previously identified. The trauma of open biopsy may contribute substantially to risk of malignancy or the testes may have been selected for biopsy on the basis of clinical factors predictive of malignancy but not mentioned in the case notes.

Introduction

Cryptorchidism is the most common congenital genitourinary abnormality in males and is important because of its associations with infertility and malignancy. Patients usually receive orchidopexy or hormonal treatment to bring the testis into the scrotum in the belief that this reduces these risks. As evidence has mounted that substantial risks of infertility and malignancy remain in boys who have had orchidopexy late in childhood,[1] there has been a move towards early operation because adverse histological changes begin in the second year of life if the testis remains undescended.[2] The effect of age of orchidopexy on the risk of malignancy remains unclear, however,[3-7] as do the risks of malignancy in different types of cryptorchidism—for instance, unilateral and bilateral.

Most studies of risk of testicular cancer in relation to cryptorchidism have been of case-control design,[3 5 6 8] with considerable potential for misclassification and bias [6] in ascertaining maldescent. It is impossible to assess the effect of type of operation or of operative complications on risk in studies dependent on patients' or parents' recall. Cohort studies following up patients with undescended testis can overcome these problems, but those conducted have not been large and have not analysed risks in relation to type and number of operations and whether biopsy was performed.[7 9-11]

The Hospital for Sick Children, Great Ormond Street, London, has retained the case notes of its patients for the past 45 years. We followed up cancer incidence and mortality in patients who had orchidopexy at the hospital.

Subjects and methods

We identified all boys with a discharge diagnosis of cryptorchidism during 1951-64 by searching discharge lists. The case notes of each of these patients were examined, and patients were included in the study if they had had orchidopexy or hormonal treatment during the study period and did not have any major congenital malformations or any syndromes of which cryptorchidism formed a minor part. We included patients whose first orchidopexy was before 1951 but who had a subsequent orchidopexy during the study period; their follow up was counted only from the orchidopexy within the study period. For each subject we used a standardised abstraction schedule to obtain data from hospital notes on demographic details, type of maldescent and its treatment, other diseases, and biopsies and other investigations.

To obtain follow up information we sent identifying data for the cohort members to the NHS Central Register. The register includes records of virtually all British residents of England and Wales, and the register staff extracted information on mortality, cancer

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registrations since 1971, and emigrations. We also used the register to find, where possible, the patients' current general practitioners. The general practitioners were sent a questionnaire asking if the patient had had further operations since he was last seen at the Hospital for Sick Children and whether testicular cancer had occurred. We sent two repeat mailings if there was no response.

We used the EPICURE computer program[12] to compare observed numbers of deaths and cancers in the cohort with expected numbers. These expected numbers were calculated by applying the person years at risk in the cohort according to age and calendar year to the corresponding mortality and cancer registration rates for males in England and Wales. Confidence intervals and significance tests for these relative risks were obtained by likelihood based inference. All P values cited are two sided.

To enable analysis of risk in relation to variables that can have different values for the two testes in an individual—for instance, the age at which the testis was brought into the scrotum or whether biopsy had been done on the testis—we conducted most analyses of risk of testicular cancer per testis rather than per person. We stratified these analyses by side of the testis (that is, we calculated observed and expected numbers separately for left and right testes) to prevent negative confounding by side: there is a tendency for testicular cancer at the study ages to be right sided[13 14] and probably for cryptorchidism to be left sided,[10 15] which would reduce the apparent risk of ipsilateral malignancy. Since national data on testicular cancer have not been collected by side we estimated the expected incidence rates for each side by multiplying the age specific incidence rates of testicular cancer in England and Wales by the age specific proportions of tumours that were left and right sided in data from the South Thames region, 1958-77.[14]

Follow up for death was to 30 September 1994 or to emigration if earlier. For cancer incidence, follow up was to 30 June 1990 or to death or emigration if earlier. National mortality data were not available for 1991 onwards and therefore 1990 data were used as the comparison for 1990-94. Similarly, cancer registration data for 1988-90 were not available and 1987 data were used as the comparison for these years.

Results

A total of 1182 boys without major malformations had treatment for cryptorchidism at the hospital during 1951-64. Twenty eight (2.4%) could not be traced at the NHS Central Register, and a further 30 (2.5%), although traced, had no record that they had ever been registered with a general practitioner. The remaining 1124 patients who were traced and had follow up information from the register formed the study cohort. We received questionnaire replies from general practitioners for 792 (70%) of these subjects.

During follow up to 30 September 1994, 28 of these subjects died, 62 emigrated, 14 entered the armed forces, and 21 were lost to follow up because the NHS register had inactivated their records when they left their general practitioner and did not reregister elsewhere (they are likely to have emigrated). Total follow up was for 39 055 person years. The relative risk of death overall was 0.6 (95% confidence interval 0.4 to 0.8), and of non-cancer death 0.6 (0.4 to 0.9). Seven deaths from cancer occurred: one each from oesophageal, pancreatic, and lung cancers, Hodgkin's disease, and myeloid leukaemia, and two from testicular cancer. The relative risk of death from cancer was 0.8 (0.3 to 1.5), from testicular cancer was 5.0 (0.8 to 15.4), and from other cancers 0.6 (0.2 to 1.4).

Analyses of cancer incidence were conducted only from 1 January 1971 onward because the NHS Central Register does not contain data on cancers incident before then. Of the 1124 patients in the cohort, 49 were not included in the analysis of cancer incidence because they had died, emigrated, or otherwise been lost to follow up before 1971. Of the remaining 1075 men, 865 had had orchidopexy(s) only, 85 hormonal treatment only, and 125 both treatments.

Seventeen cancers were registered during 26 389 person years of follow up of the cohort. There were 12 testicular cancers (nine teratomas, two seminomas, and one mixed teratoma-seminoma), two non-melanoma skin cancers, one pancreatic cancer, one lung cancer, and one myeloid leukaemia. Two of the testicular cancers were incident on opposite sides, at different dates, in the same man. One registered case of testicular cancer led to death. The other death from testicular cancer occurred before 1971, in a man whose bilateral ectopic testes had been brought into the scrotum by orchidopexy at age 11 years without biopsy.

Compared with the general population, the relative risk of cancer in the cohort was 1.4 (0.8 to 2.2), of testicular cancer 7.5 (3.9 to 12.8), and of cancers other than testicular 0.5 (0.2 to 1.2). The analyses below are in terms of relative risks per testis not per person. They are based on 1405 undescended testes and 718 testes that were opposite an undescended testes and were themselves either descended (693) or not stated to be undescended (25) in the 1075 men. Twenty seven testes were not entered in the analysis because they had been excised before 1971.

The overall risk of malignancy in an undescended testis compared with a testis in a man in the general population was 11.3 (5.9 to 19.4) (table 1). One testicular cancer occurred in a descended testis opposite a maldescended testis (relative risk = 2.1). All of the analyses below relate to malignancy in undescended testes. The risk of malignancy was greater, but not significantly so, for a maldescended testis opposite a maldescended testis (relative risk = 14.3) than for a unilaterally maldescended testis (8.5). All testicular cancers occurred in testes with either inguinal (10.9 (5.0 to 20.4)) or ectopic (12.4 (3.1 to 32.1)) maldescent.

Table 1 Relative risk of testicular cancer in a testis by position of that testis and opposite testis before treatment

Position of testes	No of testes	Observed/ expected No of cancers	Relative risk (95% CI)
Descended opposite maldescended†	718	1/0.48	2.1 (0.1 to 9.2)
Unilaterally maldescended	697	4/0.47	8.5 (2.6 to 19.8)*
Maldescended opposite maldescended	708	7/0.49	14.4 (6.2 to 27.8)**
Abdominal maldescended‡	199	0/0.13	0 (0 to 28.4)
Non-abdominal maldescended‡	1206	11/0.84	13.0 (6.8 to 22.3)**
Maldescended‡	1405	11/0.97	11.3 (5.9 to 19.4)**

*P<0.01, **P<0.001.
†Includes 21 descended testes for which the contralateral maldescended testis had been excised before the follow up period.
‡Regardless of position of other testis.

The relative risk of malignancy was not significantly greater in testes described as small or atrophic at surgery (12.3 (2.0 to 38.0)) than in those not so described (11.1 (5.3 to 20.0)).

Ten of the cancers occurred after orchidopexy alone (relative risk = 13.7) and one (a teratoma) after hormonal treatment alone (relative risk = 9.5) (table 2). The relative risk of testicular cancer tended to be lower at older ages (P for trend = 0.06) but was not related to age at descent of the testis (P = 0.43). Risk was not related to whether herniorrhaphy had been performed on that side (relative risk = 11.4 for herniorrhaphy, 11.2 for no herniorrhaphy). Most of the herniorrhaphies were done at the same time as an orchidopexy. There was no significant trend of risk with number of orchidopexies on the testis. Risk of malignancy after orchidopexy decreased significantly with duration since orchidopexy (table 2); effectively, however, this analysis was for categories of duration 10-14 years and greater, because the unavailability of cancer incidence data before 1971 meant that there were few person years (and no cancers) in the analysis for the period less than 10 years after orchidopexy. The most common methods of orchidopexy were the Dennis Browne, after which five testicular cancers occurred (relative risk = 16.2 (5.8 to 34.9)), and the Torek, after which no malignancies occurred (0.12 expected). Thirty four of the orchidopexies were followed by haematoma and 19 by wound infection, but in none of these did malignancy follow.

The largest risk of testicular cancer was in relation to biopsy (table 3). Five testicular cancers occurred in testes that had had biopsy samples removed, giving a relative risk of malignancy in such testes of 66.7 compared with 6.7 for testes that had not had biopsy samples taken (difference in risk between groups, $P < 0.001$). Two testes in which biopsy was followed by malignancy were in the same man, but the risk of malignancy after biopsy was still highly significant if only one testis from this man was included in the analysis. The large risk relating to biopsy was present both for a maldescended testis in a patient with bilateral maldescent and for a unilaterally maldescended testis (table 3), and in each instance the risk was significantly greater than for a corresponding testis that had not had a biopsy sample removed.

The operation notes for the five cases in which testicular cancer had occurred after biopsy revealed no features in common other than the biopsy. Two of the testes were ectopic and three inguinal. In two an inguinal hernia was also present and in one hypospadias. In three orchidopexy had been done once; two had required repeat operations, in one instance with repeat biopsy. In no case were any operative or postoperative complications mentioned. Three of the testes were described as of normal size, one as smallish, and one as two thirds the size of the contralateral testis. No reason was stated for biopsy in any case.

On histological examination biopsy material from the four cases where biopsy was done at ages 10 years or younger showed tubules containing immature Sertoli cells and occasional spermatogonia but no Leydig cells (M C Parkinson, personal communication). This was the pattern seen in most biopsy specimens taken at these ages from cryptorchid testes in which cancer had not subsequently occurred.[16] In the fifth case, where the biopsy was at age 14, and in one case in which biopsy was repeated at age 15 there were mature Sertoli cells, occasional spermatogonia, and Leydig cells—again a usual pattern in maldescent at these ages (M C Parkinson, personal communication). One of the biopsy specimens, taken at age 7, showed features of dysgenesis. Carcinoma in situ was found in a repeat biopsy specimen from a testis taken at age 15 but was not seen in the first biopsy at age 9. Further details of this case have been reported.[16] None of the biopsy specimens showed atrophy. Judging from the shapes of the pathological specimens and the dates of the biopsies, all had been obtained by open, not needle, biopsy.

Table 2 Relative risk of testicular cancer in maldescended testis by treatment of that testis, age at descent of testis, number of orchidopexies, and time since first orchidopexy

Risk factor	No of testes (n=1405)	Observed/ expected No of cancers	Relative risk (95% CI)
Treatment on that side:			
None	26	0/0.02	0 (0 to 184.4)
Hormones only	145	1/0.11	9.5 (0.5 to 41.8)
Orchidopexy plus hormones	170	0/0.12	0 (0 to 30.7)
Orchidopexy only	1064	10/0.73	13.7 (6.9 to 24.0)**
Age at descent (years):			
0-4	110	1/0.07	14.6 (0.8 to 64.4)
5-9	473	6/0.33	18.1 (7.2 to 36.6)**
10-18	597	4/0.42	9.5 (2.9 to 22.0)*
Never descended	225	0/0.15	0 (0 to 24.6)
			Trend χ^2 =0.64, df=1; P=0.43†
No of orchidopexies on that side:			
0	171	1/0.12	8.2 (0.5 to 36.1)
1	1096	8/0.76	10.6 (4.8 to 19.6)**
2	130‡	1/0.09	11.5 (0.7 to 50.7)
≥3	9‡	1/0.01	181.1 (10.3 to 797.6)*
			Trend χ^2=1.86, df=1; P=0.17
Time since first orchidopexy on that side (years):			
≤14§	¶	2/0.06	33.1 (5.5 to 102.3)*
15-19		3/0.17	17.5 (4.3 to 45.2)**
20-24		4/0.26	15.5 (4.8 to 36.0)**
≥25		1/0.36	2.8 (0.2 to 12.2)
			Trend χ^2=4.63, df=1; P=0.03

*P<0.01, **P<0.001.
†Test of trend restricted to subjects with eventual descent.
‡Includes one testis that contributed to both categories during follow up.
§Both of the malignancies and almost all of the expectation in this category were at 10-14 years after orchidopexy.
¶Numbers of testes are not presented because most testes contributed to several categories of this time dependent variable.

Table 3 Relative risk of testicular cancer in maldescended testis according to whether biopsy sample was taken from it and whether maldescent was unilateral or bilateral

	No of testes	Observed/ expected No of cancers	Relative risk (95% CI)
No biopsy:			
Unilateral maldescent	625	2/0.44	4.6 (0.8 to 14.1)
Bilateral maldescent	660	4/0.46	8.7 (2.7 to 20.2)*
Total	1285	6/0.90	6.7 (2.7 to 13.5)**
Biopsy:			
Unilateral maldescent	72	2/0.05	43.0 (7.1 to 132.6)**
Bilateral maldescent	48	3/0.03	105.6 (26.3 to 273.9)**
Total	120	5/0.08	66.7 (23.9 to 143.3)**

*P<0.01, **P<0.001.

Discussion

The raised risk of testicular cancer in men with cryptorchidism has been known for 140 years or

more.[17] The overall relative risk we found is similar to that reported in most case-control studies (relative risks 5-10),[3 5 6 8 18] and in previous cohort studies, which with the exception of a study with only two cases of malignancy,[10] have found relative risks of 5 to 7.[7 9 11] The relative risks in cohort studies (including ours) that used general population rates to generate expectations are about 10% underestimates of the results if comparison could have been made with rates in men without cryptorchidism because the general population rates include malignancies in men with undescended testes in the general population. Nevertheless, adding 10% to our result would still leave it compatible with the ranges above.

Our analyses of cancer incidence omitted the years before 1971 because national cancer incidence follow up was not then available. The person years lost were mainly under age 20; this reduced the power of our study at these ages, when testicular cancer is uncommon, but did not in itself bias it since both person years and cancers in the period were omitted. A bias could have occurred if the effect of cryptorchidism was to create a small pool of susceptible testes, in many of which testicular cancer occurred before 1971 leading to withdrawal from follow up. Only one death from testicular cancer occurred before 1971, however, despite a relatively high fatality from the malignancy at that time, and no cases before 1971 were reported in the questionnaire responses from general practitioners.

Compared with expectations from the general population the relative risks of developing and dying from cancers other than testicular were reduced but not significantly lower in the cohort, and the risk of non-cancer deaths was significantly decreased. This raises the possibility of incomplete follow up. Flagging of deaths by the NHS Central Register is highly complete,[19] so the mortality deficit is unlikely to be due to underascertainment. Furthermore, if there had been appreciable underascertainment of deaths we might have expected to have received questionnaire responses from general practitioners explaining that their patients had died. No such responses were received (we did not mail general practitioners of patients known to have died). Notification of cancer incidence is less complete than for mortality,[19] which is why we also contacted general practitioners for cancer information. This revealed one testicular cancer (which since it had been registered with a cancer registry we included in the analysis) and one brain tumour, not notified by the NHS Central Register. The low death rate might reflect socioeconomic selection of patients treated for cryptorchidism at the hospital or might have been due to chance. Whatever the reason, it could not plausibly explain the findings for testicular cancer.

Risk factors for testicular cancer

The risks of testicular cancer in relation to different types of cryptorchidism and its treatment are not well established. It would be expected that the risk would be greater in a man with bilateral maldescent than one with unilateral maldescent, simply because he has twice as many high risk (maldescended) testes. Our results, however, suggest that maldescended testes in bilateral cases carry a greater risk than those in unilateral cases, and the limited previous data support this suggestion.[6 9] If our results were not explicable by confounding variables (and they were not by the most obvious potential confounder, position of the testis (table 3)) this would support the theory that susceptibility to malignancy is determined by prenatal factors that both cause cryptorchidism and raise the risk of malignancy rather than by the position of the undescended testis.[20]

The risk of testicular cancer in relation to age at orchidopexy has implications for aetiological theories,[20] as well as being clinically important. We found no benefit from surgery at younger age, and previous studies have been inconclusive.[3-7 11] Adverse histological changes start to appear in the maldescended testis at age 2 years,[2] so it might be that only orchidopexy done at a very young age can reduce risk. We had relatively few subjects operated on at ages under 5, and previous studies have had few[4 6 11] or no[3 5 7] data on risk after orchidopexy at these ages. It remains uncertain whether surgery at a sufficiently young age can be prophylactic.

Association with biopsy

Much the largest risk found was in relation to biopsy. We can find no previous studies of this, and the risk needs further study. The result was highly significant and did not seem to be due to artefact. One explanation would be that biopsy had been conducted selectively on testes with clinical characteristics that were risk factors for malignancy. The operation notes describing the biopsies did not mention any consistent clinical abnormalities or any justification for the selection of the testes for biopsy. Two possibilities—the position and the size of the testis—carried a much lower relative risk of malignancy than biopsy. The histology found at first biopsy of the testes was not abnormal, except in one instance where features of dysgenesis were seen. In another instance the testis was normal at first biopsy, but carcinoma in situ was found at second biopsy several years later; it is possible, however, that this could have been the result of the first operation. The surgeons may have selected the testes for biopsy on the basis of subtle risk factors not recorded in the notes—for instance, the consistency of the testis. If so, these factors need to be identified as they must be far stronger long term predictors of future malignancy than any yet found (other than, perhaps, rare genetic abnormalities with large, as yet unquantified, risks).[21]

The raised risk of malignancy could also be partly related to the damage caused to the testis by the biopsy. Biopsy has been shown to cause considerable widespread damage to the testis in the bull,[22] rhesus monkey,[23] and rat.[24 25] In humans, biopsy can cause granuloma formation (M C Parkinson, personal communication) and, especially when conducted in childhood, can lead to atrophy.[15] At postpubertal ages the operation can cause a significant decrease in sperm count[26 27] and formation of antisperm antibodies.[28] There are many instances in organs other than the testis where trauma appears to lead to cancer, perhaps because of increased mitotic activity in response to, and for repair of, the damage.[29] Data on risk of testicular cancer in relation to external testicular trauma—for example, from sporting activities—have shown raised risk in some instances but are difficult to interpret because of potential recall bias.[30] Further epidemiological and laboratory investigation should be con-

Key messages

- The reasons for increased risk of testicular cancer in cryptorchidism are unclear
- Risk of testicular cancer was determined in follow up of 1075 boys with cryptorchidism treated during 1951-64
- The relative risk of testicular cancer in the cohort compared with men in the general population was 7.5 and did not decrease with younger age at orchidopexy
- Risk was much greater in undescended testes from which a biopsy sample had been taken during orchidopexy than in those with no biopsy
- Biopsy was a stronger risk factor for testicular cancer than any factor previously identified

ducted into the possibility that biopsy causes malignancy. It is also worth considering whether biopsy of other organs could be carcinogenic.

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Words to the wise

Learning from the past

Recent discussion of using cannabis in the symptomatic treatment of AIDS, cancer and chronic pain (*BMJ,* 1 March, p 626) reminds me that A H Douthwaite, who also led a successful campaign in the defence of heroin for the treatment of intractable pain, strongly recommended Extractum cannabis (BPC) for duodenal ulcer. As the tincture has such an unpleasant taste and the resin is precipitated by water, Douthwaite had cannabis made up in capsules, and recommended giving over one gram a day. But the drug was never smoked, and that is where the Americans have made a fundamental error—no-one likes doctors prescribing a smoking product.

In 1948 when I was a house physician at Pembury—a Guy's sector hospital—we prescribed this extract of cannabis indica. I can well remember the patients on intra-gastric milk drips sitting in bed like well drilled troops; but unlike troops they all appeared quite euphoric. As far as I can remember they mostly did pretty well and at out-patient follow-up none had withdrawal symptoms, for Douthwaite did not allow cannabis to be given outside the hospital. In those days patients were not told the nature of the drugs prescribed so were blissfully ignorant of the potential addictive qualities of cannabis.

In a lecture given to the Brighton Medico-Chirurgical Society in 1947 Douthwaite[1] gave no indication as to the number of patients he had treated with cannabis nor the results of such treatment; neither controlled trials nor outcome indices entered our vocabulary in those far off days. But he did claim that cannabis "lends enchantment to the dietary"—no mean feat in the rationed days of 1947. It was used mainly if phenobarbitone failed to induce the required "langorous state and sense of well-being" and was rarely needed for more than two weeks.

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1 Douthwaite A H. Choice of drugs in the treatment of duodenal ulcer. *BMJ* 1947;2:43-47.

Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus

Klas Malmberg for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group

See editorial by Nattrass

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Abstract

Objectives: To test the hypothesis that intensive metabolic treatment with insulin-glucose infusion followed by multidose insulin treatment in patients with diabetes mellitus and acute myocardial infarction improves the prognosis.
Design: Patients with diabetes mellitus and acute myocardial infarction were randomly allocated standard treatment plus insulin-glucose infusion for at least 24 hours followed by multidose insulin treatment or standard treatment (controls).
Subjects: 620 patients were recruited, of whom 306 received intensive insulin treatment and 314 served as controls.
Main outcome measure: Long term all cause mortality.
Results: The mean (range) follow up was 3.4 (1.6-5.6) years. There were 102 (33%) deaths in the treatment group compared with 138 (44%) deaths in the control group (relative risk (95% confidence interval) 0.72 (0.55 to 0.92); P = 0.011).The effect was most pronounced among the predefined group that included 272 patients without previous insulin treatment and at a low cardiovascular risk (0.49 (0.30 to 0.80); P = 0.004).
Conclusion: Insulin-glucose infusion followed by intensive subcutaneous insulin in diabetic patients with acute myocardial infarction improves long term survival, and the effect seen at one year continues for at least 3.5 years, with an absolute reduction in mortality of 11%. This means that one life was saved for nine treated patients. The effect was most apparent in patients who had not previously received insulin treatment and who were at a low cardiovascular risk.

Introduction

It is well established that patients with diabetes mellitus are more likely than patients without diabetes to die after an acute myocardial infarction. The increased mortality is seen both in the acute phase and during one year of follow up.[1-3] Studies that followed up patients for more than one year all showed a continued increased mortality among patients with diabetes.[4-9] The unfavourable prognosis of diabetic patients has mainly been attributed to more pronounced left ventricular dysfunction[7 10-12] and a high likelihood of reinfarction, many of which are fatal.[1 4 13] Many factors may contribute to this unfavourable outcome, such as severe and diffuse coronary artery disease, diabetic cardiomyopathy, disturbed autonomic tone, and abnormal fibrinolytic and platelet function, as well as purely metabolic factors causing more oxygen consuming use of free fatty acids during acute myocardial ischaemia.[14]

We previously showed that the one year mortality in diabetic patients with acute myocardial infarction can be reduced by 30% with acute administration of insulin and glucose followed by intensive treatment with multidose subcutaneous insulin.[15-17]

This report describes the long term effect on overall mortality of intensive insulin treatment in diabetic patients after an acute myocardial infarction.

Subjects and methods

Study design

A detailed description of the diabetes mellitus, insulin glucose infusion in acute myocardial infarction (DIGAMI) study, including design, definitions, and methods, has been given elsewhere.[15 16] All patients admitted to the coronary care units of 19 Swedish hospitals were considered for inclusion if they had had an acute myocardial infarction within the preceding 24 hours combined with previously known diabetes mellitus and a blood glucose concentration > 11 mmol/l or a similar blood glucose concentration without known diabetes mellitus. Patients who could not participate for reasons of health, refused to participate, lived outside the hospital catchment area, were enrolled in other studies, or had participated previously in DIGAMI were excluded. Remaining subjects were randomised blindly to one of two groups: insulin and glucose or control. The randomisation was performed as soon as possible after hospital admission (mean (SD) 13 (7) hours after onset of symptoms). Besides standard treatment in a coronary care unit, patients in the insulin-glucose group received an insulin-glucose infusion according to a predefined protocol for at least 24 hours. This was followed by subcutaneous insulin four times daily for at least three months. Control patients were treated according to standard practice. These patients did not receive any insulin unless clinically indicated.

Before randomisation the patients were classified as being at high risk if they fulfilled two or more of the following criteria: age > 70 years; previous myocardial infarction; history of congestive heart failure; and current treatment with digitalis. Before randomisation the patients were stratified into one of four groups according to risk (high; low) and to previous antidiabetic treatment (insulin; no insulin). Predefined groups were: no insulin-low risk (n = 272); no insulin-high risk (n = 129); insulin-low risk (n = 119); and insulin-high risk (n = 100).

Concomitant drug treatment was managed according to strict, predefined guidelines to achieve a uniform treatment in the two groups, apart from the use of

Table 1 Characteristics of patients before admission for myocardial infarction. Values are numbers (percentages) of patients in each group unless stated otherwise

Variable	Control group (n=314)	Infusion group (n=306)	P value
Mean (SD) age (years)	68 (9)	67 (9)	0.4
Sex:			
Male	197 (63)	191 (62)	0.9
Female	117 (37)	115 (38)	0.9
Mean (SD) body mass index (kg/m^2)	27 (4)	27 (4)	0.5
Previous diseases:			
Myocardial infarction	117 (37)	121 (40)	0.6
Angina	164 (52)	176 (58)	0.2
Hypertension	154 (49)	143 (47)	0.6
Congestive heart failure	70 (22)	69 (23)	0.9
Type of diabetes mellitus:			
Non-insulin dependent	265 (84)	251 (82)	0.5
Insulin dependent	49 (16)	55 (18)	0.5
Previously unknown	47 (15)	31 (10)	0.2
Median (range) duration of diabetes (years)	8 (0-67)	8 (0-68)	0.9
Antidiabetic treatment:			
None	47 (15)	31 (10)	0.1
Diet	39 (12)	33 (11)	0.1
Tablets	115 (37)	140 (46)	0.1
Insulin	113 (36)	102 (33)	0.1
Mean (SD) blood concentrations:			
Glucose at randomisation (mmol/l)	15.7 (4.2)	15.4 (4.1)	0.4
Haemoglobin A_{1c} at randomisation (%)	8.0 (2.0)	8.2 (1.9)	0.2
Glucose 24 h after randomisation (mmol/l)	11.7 (4.1)	9.6 (3.3)	<0.0001
Glucose at hospital discharge (mmol/l)	9.0 (3.0)	8.2 (3.1)	<0.01

insulin. If there were no contraindications thrombolysis and treatment with β blockers and aspirin were initiated as soon as possible.

The DIGAMI protocol was approved by the ethics committees at the Karolinska Institute and the Universities of Gothenburg, Linkoping, Lund, and Uppsala.

Details of patients

Altogether 1240 diabetic patients with suspected acute myocardial infarction were admitted during January 1990 to December 1993. Half of them were excluded because of the exclusion criteria, leaving 620 patients. A detailed report of exclusion criteria and characteristics of excluded patients has been given elsewhere.[16] Of the 620 study patients, 314 were allocated to the control group and 306 to the infusion group. Table 1 gives details of the patients allocated to the two groups and shows that the groups were balanced.

All patients were followed up prospectively for one year, with scheduled visits at three and 12 months after randomisation, when specific case record forms were completed. These included information on mortality and morbidity. After one year the patients were followed up by their physician by regular visits according to the patient's need. On 31 July 1995 the vital status of all patients was checked and verified by the physician responsible for the study in each participating centre. No patient was lost to follow up.

Statistics

Standard statistical methods were used. Values are presented as means (SD). The significance of the differences between the two groups was tested by Student's *t* test and Fisher's exact test. Differences within groups were tested by a paired test. For survival data the log rank test was used. The effect and its confidence interval was estimated by the relative hazards rate in a Cox analysis.[18] Cumulative mortality curves were estimated by the Kaplan-Meier method. All these data were handled according to the intention to treat principle. The Cox model was used to adjust simultaneously for other factors. A two tailed P value less than 0.05 was considered significant.

Results

The mean (range) follow up time was 3.4 (1.6-5.6) years, and no patients were lost to follow up as regards mortality.

Treatment

During the period in hospital almost half of the patients were given thrombolysis. At the time of hospital discharge 496 (80%) patients were taking aspirin and 434 (70%) β blockers. Angiotensin converting enzyme inhibitors were given to 192 (31%) patients. Besides antidiabetic treatment, including insulin, there were no significant differences between the two groups in the treatment in hospital or during follow up. During the first year of follow up 13 patients in the infusion group and 16 in the control group had a percutaneous transluminal coronary angioplasty, and bypass surgery was performed in 33 patients in the infusion group compared with 35 in the control group. At discharge from hospital 266 (87%) patients in the infusion group were taking insulin treatment compared with 135 (43%) in the control group ($P<0.0001$). The corresponding numbers were 245 (80%) and 141 (45%) ($P<0.0001$) after three months and 220 (72%) and 141 (49%) after one year ($P<0.0001$).

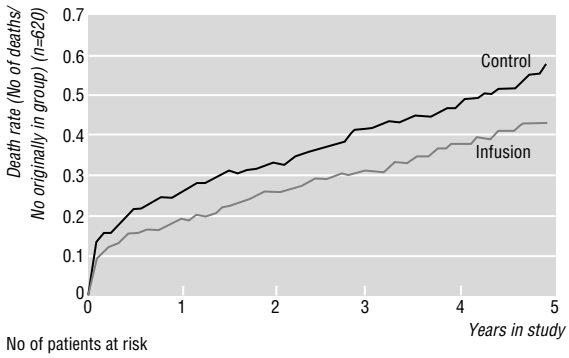
Metabolic control

At randomisation the two groups did not differ in concentration of glycated haemoglobin (A_{1c}, table 1). Haemoglobin A_{1c} decreased significantly in both groups during follow up. The reduction was greater in the infusion group both at three (1.1 (SD 1.6%) *v* 0.4 (1.5%); $P<0.0001$) and 12 months (0.9 (1.9%) *v* 0.4 (1.8%); $P<0.01$). Fasting blood glucose one year after randomisation did not differ between the two groups.

In the low risk-no insulin group the corresponding haemoglobin A_{1c} value at three months was (1.3 (1.8%) *v* 0.6 (1.5%); $P<0.001$) and at 12 months was (1.3 (1.9%) *v* 0.5 (1.5%); $P<0.001$).

Mortality

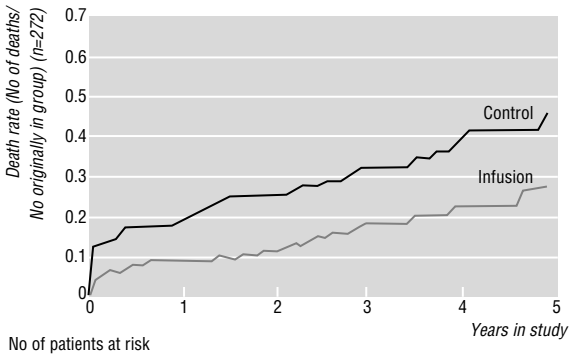
During the initial year of follow up, including deaths in hospital, 82 (26%) patients died in the control group compared with 58 (19%) in the insulin group. This corresponds to a relative reduction in mortality of 30% ($P=0.027$). Most of the reduction occurred after discharge from hospital. Only in patients without previous insulin treatment and at low cardiovascular risk (44% of all patients) was this reduction already significant during the hospital phase (from 12% in the control group to 5% in the infusion group; relative reduction 58%; $P<0.05$).



No of patients at risk

Control	314	232	187	116	58	14
Infusion	306	248	202	128	50	13

Fig 1 Actuarial mortality curves during long term follow up in patients receiving insulin-glucose infusion and in control group among total DIGAMI cohort. Absolute reduction in risk was 11%; relative risk 0.72 (0.55 to 0.92); P=0.011



No of patients at risk

Control	133	109	91	53	28	11
Infusion	139	127	113	72	30	9

Fig 2 Actuarial mortality curves during long term follow up in patients receiving insulin-glucose infusion and among control group of patients at low risk who were not taking insulin before randomisation. Absolute reduction was 15%; relative risk 0.49 (0.30 to 0.81); P=0.004

During the continued follow up there were 138 (44%) deaths in the control group compared with 102 (33%) in the infusion group. Figure 1 presents the mortality curves for all patients. After one year there was a separation between the curves, which tended to increase with time. The relative reduction in mortality at the end of follow up (mean (range) 3.4 (1.6-5.6) years) was 28% by the Cox model (95% confidence interval 8% to 45%; P = 0.011).

Table 2 presents the long term mortality within the prestratified risk groups. The most apparent effect was achieved in the low risk group not taking insulin, with an absolute reduction in mortality of 15%, from 33% in the control group to 18% in the infusion group. This corresponds to a relative reduction of 51% (19% to 70%; P = 0.004) by the Cox model. Figure 2 gives the mortality curves for this group.

Discussion

Diabetes mellitus is an independent marker of morbidity and mortality after acute myocardial infarction.[1 8] The DIGAMI study has previously shown that the one year mortality in diabetic patients after an acute myocardial infarction could be reduced by 30% with intensive insulin treatment and that this treatment tended to influence all cardiovascular causes of death favourably.[16 17] This report shows that this effect is sustained for more than three years and further supports the theory that metabolic control is of utmost importance in macrovascular death.

Study limitations

One limitation of this study is that exact information about insulin treatment during long term follow up is not available. However, 220 (72%) in the infusion group and 154 (49%) in the control group were taking insulin at one year. Our experience is that withdrawal of insulin treatment after more than one year is uncommon. There was a gradual increase in insulin treatment among control patients, presumably reflecting the natural course of non-insulin dependent diabetes.

Importance of metabolic control

As previously reported the reduction in mortality increased during the first year of follow up.[16] After one year the curves were still separate, and this impression increased during late follow up. It was clearly evident in low risk patients without previous insulin treatment. This suggest that long term metabolic control by means of intensified insulin treatment contributed to the beneficial result in the infusion group. In the no insulin-low risk group, however, mortality was already significantly reduced by half during the time in hospital, indicating dual effects of the complete regimen. Several recent studies have reported that metabolic control measured as fasting blood glucose or haemoglobin A_{1c} concentration is a major determinant of future development of coronary heart disease among patients with non-insulin dependent diabetes mellitus.[19-22] Cardiovascular events decreased by 40% after intense treatment of patients with insulin dependent diabetes in the diabetes control and complications trial.[23] In the current study 97% of all deaths during the first year of follow up had cardiovascular causes, and there was a trend in reduction of all types of cardiovascular deaths including fatal reinfarctions in the intervention group.[17] During the first year

Table 2 Long term mortality according to insulin treatment and risk of death. Values are numbers (percentages) patients unless otherwise stated

Detail	No insulin–low risk (n=272 (44%))	No insulin–high risk (n=129 (21%))	Insulin–low risk (n=119 (19%))	Insulin–high risk (n=100 (16%))
Mean (range) follow up time (years)	3.4 (1.7-5.6)	3.3 (1.6-5.5)	3.4 (1.6-5.6)	3.5 (1.7-5.6)
Total mortality	69 (25)	69 (53)	42 (35)	60 (60)
Mortality by group				
Control	44 (33)	35 (53)	26 (40)	33 (66)
Insulin	25 (18)	34 (54)	16 (30)	27 (54)
P value	0.004	>0.2	>0.2	>0.2

Key messages

- Diabetes mellitus is common among patients with acute myocardial infarction
- Diabetic patients with myocardial infarction have a poor short and long term prognosis
- Poor metabolic control is common among diabetic patients with myocardial infarction
- Improved metabolic control by means of acute insulin-glucose infusion followed by long term intensive insulin treatment improves long term prognosis among these patients

haemoglobin A_{1c} concentration decreased in both groups but significantly more in the infusion group, suggesting that long term metabolic control is important in the prevention of macrovascular death in patients with diabetes mellitus.

Possible mechanisms

The varying effects in different risk groups are interesting. They show that patients who had not previously been treated with insulin and who had a comparatively low risk profile benefited the most. This is in agreement with Rogers *et al*, who found the best treatment effect of glucose-insulin-potassium infusion in non-diabetic patients with a low Killip class and an overall low mortality.[24] The effect in the no insulin-low risk group may be related to reduced ischaemic injury during the acute phase, protecting against subsequent development of myocardial dysfunction. This may be further enhanced by continued subcutaneous insulin treatment with subsequent improved metabolic control. Intense insulin treatment may restore impaired platelet function,[26] correct the disturbed lipoprotein pattern,[25] and decrease plasma activity of plasminogen activator inhibitor, which is high in diabetic patients.[27] The extended insulin treatment, with its beneficial secondary metabolic effects, is one possible mechanism for the reduced long term mortality in the infusion group. Another possible explanation, in view of the open study design, is that the institution of insulin was paralleled by an improvement in general patient care. If this is the case, however, it should not be seen as a bias but rather as part of a comprehensive care programme for diabetic patients with myocardial infarction. The similarity in concomitant treatment (including revascularisation procedures) between the two groups makes this factor less likely as a major contributor. Future studies should be designed to elucidate whether an acute or a long term metabolic effect is responsible for the net result. They should also focus on specific pathophysiological mechanisms behind the beneficial effects we have seen.

In summary, insulin-glucose infusion followed by intensive subcutaneous insulin treatment in diabetic patients with acute myocardial infarction improves long term survival by nearly a third, and the effect seems to last for at least 3.5 years. Even more important the absolute reduction in mortality was 11%, implying one saved life for nine patients treated according to the DIGAMI protocol. The reduction in mortality is most apparent in patients without previous insulin treatment and at a low cardiovascular risk.

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Conflict of interest: None.

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Case-control study of sudden infant death syndrome in Scotland, 1992-5

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Abstract

Objective: To investigate the relation between routine infant care practices and the sudden infant death syndrome in Scotland.
Methods: National study of 201 infants dying of the sudden infant death syndrome (cases) and 276 controls by means of home interviews comparing methods of infant care and socioeconomic factors.
Results: Sleeping prone (odds ratio 6.96 (95% confidence interval 1.51 to 31.97)) and drug treatment in the previous week (odds ratio 2.33 (1.10 to 4.94)) were more common in the cases than controls on multivariate analysis. Smoking was confirmed as a significant risk factor (odds ratio for mother and father both smoking 5.19 (2.26 to 11.91)). The risk increased with the number of parents smoking ($P < 0.0001$), with the number of cigarettes smoked by mother or father ($P = 0.0001$), and with bed sharing ($P < 0.005$). A new finding was an increased risk of dying of the syndrome for infants who slept at night on a mattress previously used by another infant or adult (odds ratio 2.51 (1.39 to 4.52)). However, this increased risk was not established for mattresses totally covered by polyvinyl chloride.
Conclusions: Sleeping prone and parental smoking are confirmed as modifiable risk factors for the sudden infant death syndrome. Sleeping on an old mattress may be important but needs confirmation before recommendations can be made.

Introduction

There has been considerable interest in recent years about the role of infant care practices and environment in the sudden infant death syndrome. Previous studies showed the risk associated with sleeping prone,[1 2] and modification of this practice has been associated with a major reduction in the syndrome worldwide.[3] This improvement prompted our search for other modifiable risk factors. We report a four year case-control investigation of risk factors for the sudden infant death syndrome in Scotland from 1992 to 1995, when the rate of deaths from the syndrome fell from 1.1 to 0.7 per 1000 live births.

Methods

Population

The registrar general for Scotland reported to us all infant deaths occurring after the seventh day of life to the end of the first year. The computerised maternity record for each infant was provided by the information and statistics division of the Common Services Agency. In the case of deaths from the sudden infant death syndrome our office was also notified directly by the pathologist responsible for the necropsy. We defined the sudden infant death syndrome according to Beckwith as the sudden death of any infant or young child which is unexpected from the history and in which a thorough postmortem examination fails to show an adequate cause for death.[4]

Consistency in classification was sought by the use of a standard necropsy protocol with agreed diagnostic criteria.[5] In addition, all death certificates of infants aged 1 week to 1 year were scrutinised for possible misclassification of explained deaths. Overall, 201 out of 798 postperinatal infant deaths were diagnosed as the sudden infant death syndrome. Six other sudden deaths may have been misdiagnosed as bronchopneumonia and were not included in the study.

We identified two controls for each case of the syndrome—the births immediately before and after the index case in the same maternity unit. In this way controls were matched for age, season, and maternity unit. After permission had been obtained from the general practitioner a fieldworker employed by the study contacted the mother by letter, asking for her cooperation in completing a questionnaire during a home visit. All home visits were made within 21 days of the index case's death to minimise differences in age related circumstances between cases and controls. Questionnaires were completed on 147 cases out of a total of 201 reported and on 276 controls. The failure to acquire data on the remaining 54 cases was largely due to delay in notification by the pathologist or parents not being at home on at least two occasions, making a visit within 21 days of the death impossible. For 108 cases there were two controls, for 27 cases there was one control, and for 12 cases there were no controls. For 29 controls there was no case interview. The characteristics of the cases without an interview were compared with the characteristics of those with an interview and were similar in terms of maternal age, social class, and deprivation category.[6] There was a small difference in age at death of cases (the mean age of cases whose parent was interviewed was 15 weeks and that of those who were not was 18 weeks; $P = 0.04$).

Data collection

The questionnaire provided core medical and social data about the infant, as well as details of infant care practices in the home. Data were collected on routine childcare practices for cases and controls and on practice on the night of death for cases only.

The questionnaire was divided into six main categories: social and prenatal factors, feeding regimen, sleeping habits, sleeping environment, exposure to smoking, and illnesses.

Socioeconomic status was assessed by two methods. The first was assessment of deprivation on the basis of postal code in seven categories in ascending order of deprivation.[6] These categories take cognisance of overcrowding, male unemployment, low socioeconomic status, and a lack of a car. The second was the registrar general's social class from standard occupational classification.

The tog value (warmth rating) of both clothing and bedding was calculated with the scoring system supplied by the Shirley Institute, Manchester.[7] We used the average of day and night tog values in analyses. We took special note of the extra thermal implications of swaddling and how much of the body was swaddled.

Exposure to smoking was assessed in two ways. The first used the following ordinal scale: neither parent smoked, father only smoked, mother only smoked, mother and father both smoked. The second calculated a dose response by determining the total number of cigarettes (0, 1-9, 10-19, ≥20) smoked daily by mother, father, or other household member.

Exposure to old mattresses was assessed by asking parents if their infant routinely slept at night on a new mattress or on one previously used by another infant or an adult.

Data analysis

The primary analyses focused on routine childcare practices (see table 1), but routine practice and practice on the night of death were compared for cases (see table 2). The baseline comparison group always had the opposite definition—for example, maternal age <27 was compared with maternal age ≥27—unless otherwise stated in the footnotes to table 1.

Univariate analysis

Binary and categorical factors were analysed by conditional logistic regression analyses, which were fitted using the PROC PHREG program in SAS. This method allows for the matched nature of the data but is unable to use information on the unmatched cases and controls. Quantitative factors were analysed in random effects models fitted by the PROC MIXED program in SAS. Matched set was fitted as a random effect to allow for any correlations in the data due to matching. This method has the advantage that it uses information from unmatched cases and controls.

Over 100 factors were analysed, and about half of these were significant. However, many of the significant factors became non-significant when adjusted for obvious confounding factors or for socioeconomic factors. Results for the factors that remained significant after these adjustments are presented in table 1. Quantitative factors were categorised in this table so that all factors could be directly compared by odds ratios. Cut off points correspond to values expected to be most relevant on the basis of previous knowledge or as defined within other studies. All results in table 1 are based on comparisons between routine sleeping practices of cases and controls.

Table 1 Summary of risk factors for sudden infant death syndrome

Risk factor	Proportion (%) of: Cases	Controls	Univariate analysis odds ratio (95% CI)	P value	Multivariate analysis odds ratio (95% CI)*	P value
Exposure to smoking:						
Mother and father smoke	83/146 (57)	48/275 (17)	7.92 (4.32 to 14.55)		5.19 (2.26 to 11.91)	
Mother only smokes	32/146 (22)	45/275 (16)	5.26 (2.31 to 11.98)		5.05 (1.85 to 13.77)	
Father only smokes	11/146 (8)	45/275 (16)	1.72 (0.94 to 3.13)		2.12 (0.99 to 4.55)	
Neither parent smokes	20/146 (14)	137/275 (50)	1.00 (reference)	0.0001†	1.00 (reference)	0.0001†
Does not regularly change position during sleep	93/146 (64)	148/274 (54)	1.88 (1.01 to 2.50)	0.05	2.67 (1.42 to 4.99)	0.002
Old mattress used at night	91/145 (63)	108/274 (39)	2.50 (1.61 to 3.85)	0.0001	2.51 (1.39 to 4.52)	0.002
Maternal age <27	125/201 (62)	109/276 (39)	2.87 (1.85 to 4.45)	0.0001	2.37 (1.23 to 4.58)	0.01
Deprivation score of 7	46/195 (24)	25/266 (9)	9.59 (3.32 to 27.68)	0.0001	2.56 (1.20 to 5.49)	0.02
Drug treatment in previous week	49/131 (37)	43/186 (23)	1.99 (1.22 to 3.26)	0.02	2.33 (1.10 to 4.94)	0.03
Routine position put down to sleep[2]:						
Prone	13/146 (9)	5/275 (2)	5.37 (1.70 to 16.95)		6.96 (1.51 to 31.97)	
Side	75/146 (51)	104/275 (38)	1.58 (1.01 to 2.46)		1.51 (0.76 to 2.98)	
Variable	13/146 (9)	19/275 (7)	1.56 (0.71 to 3.42)		1.68 (0.52 to 5.42)	
Supine	45/146 (31)	147/275 (53)	1.00 (reference)	0.0001†	1.00 (reference)	0.04†
Has moved under bedclothes	35/146 (24)	35/274 (13)	2.48 (1.42 to 4.34)	0.001	2.18 (1.03 to 4.64)	0.04
Unmarried mother‡	130/200 (65)	87/276 (32)	4.22 (2.90 to 6.13)	0.0001	1.87 (1.00 to 3.48)	0.05
Social class IV or V§	88/201 (44)	53/276 (19)	2.55 (1.66 to 3.93)	0.0001	1.84 (0.99 to 3.43)	0.05
Male sex	138/201 (69)	138/275 (50)	1.84 (1.22 to 2.77)	0.004	1.76 (0.97 to 3.20)	0.06
Cot bumper not used routinely	104/146 (71)	154/274 (56)	2.00 (1.23 to 3.22)	0.005	1.74 (0.94 to 3.21)	0.08
Routinely sleeps with parents	11/146 (8)	6/275 (2)	3.92 (1.35 to 11.37)	0.01	2.90 (0.75 to 11.26)	>0.1
Any symptoms in previous week	113/147 (77)	162/275 (59)	2.16 (1.32 to 3.52)	0.002	1.58 (0.83 to 3.01)	>0.1
Gestation ≤36 weeks	44/196 (22)	17/276 (6)	4.49 (2.25 to 8.17)	0.0001	2.47 (0.67 to 9.12)	>0.1
Was usually swaddled in previous week	55/146 (38)	71/275 (26)	1.71 (1.06 to 2.76)	0.03	1.60 (0.77 to 3.33)	>0.1
Other infant death in family	21/146 (14)	14/276 (5)	2.76 (1.30 to 5.84)	0.008	2.45 (0.32 to 18.76)	>0.1
Usually sweaty on waking	68/146 (47)	77/275 (28)	1.93 (1.26 to 2.96)	0.003	1.27 (0.68 to 2.34)	>0.1
Tog value ≥10¶	45/147 (31)	50/275 (18)	1.98 (1.17 to 3.34)	0.01	1.10 (0.50 to 2.42)	>0.1
Mother left school aged ≤16	124/144 (86)	168/276 (61)	4.28 (2.41 to 7.62)	0.0001	1.07 (0.48 to 2.38)	>0.1
Not currently breast fed	137/147 (93)	209/275 (76)	4.35 (2.13 to 9.09)	0.0001	1.01 (0.39 to 2.71)	>0.1
Two or more previous live births	78/197 (40)	64/276 (23)	2.28 (1.46 to 3.56)	0.0003	0.99 (0.50 to 1.96)	>0.1
Birth weight <2.5 kg	42/197 (21)	19/276 (7)	3.79 (2.05 to 6.99)	0.0001	0.99 (0.29 to 3.38)	>0.1

*Odds ratios are adjusted for all other factors listed in table.
†For linear trend.
‡Includes mothers who were single, divorced, or cohabiting.
§Obtained from father's occupation or from mother's occupation if father's was unknown; includes 60 subjects for whom neither parent had an occupation to prevent their deletion in the multivariate model.
¶Average of day and night total tog values.

Multivariate analysis

A multivariate analysis was carried out to determine which factors were independently significant when adjusted for all other factors found to be important in the study. This was carried out using a conditional logistic regression model that included all of the factors listed in table 1.

Interactions

Interactions with factors of particular interest were tested in conditional logistic regression models.

Results

Frequencies, odds ratios, and P values for factors that remained significant after adjusting for obvious confounding factors and for socioeconomic factors are presented in table 1.

Nearly all of the people who smoked did so during and after pregnancy. Overall, 79% of mothers of cases (115/146) smoked compared with 34% of control mothers (93/275; univariate odds ratio 5.91 (95% confidence interval 3.61 to 9.68)). There was a dose relation, with the risk of the sudden infant death syndrome increasing with the number of cigarettes smoked by the mother ($P=0.0001$), father ($P=0.0001$), and other people in the household ($P=0.001$); each factor was analysed separately. The risk also increased significantly with exposure (table 1). The risk caused by maternal smoking increased when the infant shared a bed ($P<0.005$). Given that smoking is causal, the population attributable risk of smoking during and after pregnancy was 62%.

Sleeping prone remained a significant risk factor, although few infants in the control population were routinely placed prone (2%(5/275)); 9% of the index mothers (13/146) opted for this position routinely, resulting in an increased risk for their infants (table 1). At death 50 of the 147 infants were found prone (34%), though only 19 (13%) had been placed prone (table 2).

Sleeping on the side was also a significant risk factor on univariate analysis (odds ratio 1.58 (1.01 to 2.46)). 51% of the index mothers (75/146) placed their babies on their sides, compared with 38% of controls (104/275). Sleeping on the side was the most labile sleeping position, but cases and controls routinely tended to move from sleeping on their side to sleeping supine if they moved at all rather than to sleeping prone. We noted that routinely only 44% (33/75) of index babies placed on their sides were found in a different position on wakening, compared with 68% (70/104) of controls (odds ratio 0.37 (0.20 to 0.68). Indeed, regardless of the position in which they were put down or found, controls were more likely than cases to change position regularly during sleep (odds ratio 0.53 (0.40 to 0.99)).

Mattresses used previously by at least one other infant or an adult seemed to place an infant at increased risk of the sudden infant death syndrome. The risk from routinely being on an old mattress at night also increased for infants who had undercovers with a lower tog value ($P=0.05$), who had colds ($P=0.02$), and who were off their feeds ($P=0.02$). No significant interactions occurred with smoking, sleeping place—for example, cot or pram—sleeping position, and birth order, so we could not draw any firm conclusions on the influence of these factors. There was no detectable increase in risk with old mattresses completely covered by polyvinyl chloride (table 3). The increase in risk was associated with both the so called combination mattresses, in which the bottom two thirds of the mattress is covered by polyvinyl chloride and the top third consists of ventilated foam covered by netting, and with cloth covered mattresses. We had insufficient data to investigate interaction of old mattresses with routine bed sharing. However, 34% of the index cases (48/142; table 2) were sleeping with parents at death—30% (42/142) in an adult bed and therefore on mattresses used by others.

We asked parents whether they had ever found that their baby had moved under the bedclothes. Overall, 24% of parents of cases (35/146) said that they had compared with 13% of controls (35/274), and this difference was significant on multivariate analysis (odds ratio 2.18 (1.03 to 4.64)) (table 1). On the day or night of death 13% (19/146) of the index cases were found under bedcovers.

Receiving any drug treatment in the week before death emerged as a strong risk factor in the multivariate analysis (table 1). After adjustment for symptoms in the previous week, consultation with a general practitioner, prematurity, and low birth weight, no individual drug was significant. We noted that the index cases were more likely to have had one or more of a range of symptoms and to have been seen by their general practitioner because of illness during the previous week. The symptoms with the highest odds ratios on univariate analysis were unusual sleepiness (odds ratio 2.61 (1.26 to 5.51)), snuffles (1.61 (1.07 to 2.44)), and sickness (1.69 (0.92 to 3.10)). The only symptom more common in controls was increased irritability.

Poverty was confirmed as a significant risk factor for the syndrome, the rate increasing with deprivation score, as shown in table 4. Low socioeconomic status (classes

Table 2 Sleep practices routinely at night and at death in 147 babies who died of sudden infant death syndrome. Values are numbers of cases

	Routinely	At death
Placed prone	13	19
Found prone	16	50
Placed on side	75	78
Found on side	43	44
Placed variably	13	0
Found variably	21	0
Placed supine	45	47
Found supine	65	51
Total tog ⩾10	45	40
Shared bed with parent	11	48
Duvet used	31	50
Pillow used	20	35
Swaddled	55	43

Table 3 Old mattress, type of cover, and risk of sudden infant death syndrome (excluding routine bed sharers)

Type of cover	Proportion (%) of: Cases	Controls	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)*
All mattresses	78/130 (60)	101/264 (38)	2.27 (1.46 to 3.52)	2.46 (1.34 to 4.52)
Polyvinyl chloride throughout	24/36 (67)	30/50 (60)	0.92 (0.22 to 3.77)	0.44 (0.09 to 2.05)
Other	53/93 (57)	70/213 (33)	2.27 (1.29 to 4.00)	4.07 (1.90 to 8.68)

*Adjusted for all factors in table 1. Odds ratios remained virtually identical when infants bed sharing at death were excluded.

Table 4 Association between deprivation score and sudden infant death syndrome

	No (%) of:	
Deprivation score	Cases (n=195)	Controls (n=266)
1	6 (3)	22 (8)
2	10 (5)	26 (10)
3	27 (14)	70 (26)
4	48 (25)	56 (21)
5	39 (20)	35 (13)
6	19 (10)	32 (12)
7	46 (24)	25 (9)

P<0.0001 for trend.

IV and V) was also significant even when adjusted for deprivation score in the multivariate model.

Factors significant on univariate but not on multivariate analysis were being male, sleeping on the side, non-routine use of cot bumper, routine sleeping with parent(s), any symptoms in previous week, gestation ≤36 weeks, usually being swaddled in previous week, previous infant death in family (sibling, half sibling, or first cousin), usually being sweaty on wakening, tog value of bedding and clothing ≥10, mother leaving school at ≤16, bottle feeding at time of death, two or more previous live births, birth weight <2500 g. However, their significance on univariate analysis makes them noteworthy. In particular, the finding of a high thermal score of bedding plus clothing is consistent with other published data.[8] A high thermal score seemed to be more risky for boys than for girls (P=0.03).

Examples of factors that were not significant on univariate analysis included the time between the last two pregnancies, twin birth, non-European mother, complementary feeding (combined breast and bottle feeding), age at introduction of solids, sleeping room, sleeping place (other than parents' bed), use of pillow, use of duvet, type of mattress covering, use of sheepskin, swaddling, heated sleeping room, and admission to hospital in week before death. Significantly more babies died on a Saturday or Sunday than would be expected by chance (42% (84/201), P<0.01); 11% (17/158) of deaths occurred when the infants were away from their usual place of residence.

The decrease in the rate of the sudden infant death syndrome over the four years was 0.4 per 1000 live births. We assessed whether attributable risks were likely to have changed during the study by testing whether factors had changed during the study in the control group. The following factors changed significantly: the number of parents who smoked was reduced (P=0.02), more infants were placed supine (P=0.01), and mothers were older (P=0.008). Thus, assuming constant relative risks, population attributable risks had decreased for parents' smoking, use of prone and side sleep positions, and younger mothers.

Discussion

Smoking

Parental smoking during and after pregnancy is a major, potentially modifiable, risk factor found in many other studies.[9,10] If only the father smoked the risk was almost significant. The finding of a dose response with the number of people smoking in the household adds weight to the possibility of smoking being causally related to the sudden infant death syndrome, as does the increased risk related to the number of cigarettes smoked. If smoking is causal two thirds of the cases of the syndrome might be avoided if mothers did not smoke during and after pregnancy. Health promotion initiatives to discourage young girls from starting to smoke and to help smokers reduce their habit are urgently required.[11,12]

Sleeping position and place

Although sleeping prone remains a strong risk factor, its low prevalence in the infant population in Scotland indicates that only a small percentage of deaths from the syndrome can now be attributed to this. Sleeping on the side was more risky than sleeping supine and since 38% of control infants were routinely placed this way, a significant number of deaths may be attributed to this sleep position. Sleeping on the back is the safest, so parents should be advised to use this position wherever possible.

The significance of failure to change position during sleep (table 1) supports observations by Schechtman *et al* that infants considered at increased risk of the syndrome show fewer spontaneous arousals from sleep and fewer movements during sleep than do control infants.[13]

The New Zealand cot death study found an increased risk for infants sleeping with a parent only if the mother smoked.[14] A subsequent report from California failed to confirm this risk,[15] but our data are consistent with the New Zealand findings. In addition, the greatly increased incidence of bed sharing in cases at death concerns us. We accept that routine bed sharing may be underreported, but it is difficult to believe that it could account for an increase from 8% routinely to 34% at death.

In Scotland most infants routinely share a room with their parent(s) at night—78% of index cases and 75% of controls. As nearly all the mothers in the study were European, the high prevalence of room sharing was not associated with an ethnic minority group, as noted in some studies.[16,17] In our study it was not a significant factor (odds ratio 1.20 (0.69 to 2.09) on univariate analysis. This differs from the data of Scragg *et al*, who found it to be protective.[18] We recognise that our data, in contrast to those of the New Zealand study,[14] were collected when the incidence of the syndrome and the rate of prone sleeping (2%) were low and the rate of room sharing was high (75%) in controls, making comparison difficult. On the basis of our results, however, we believe that advice on room sharing is not at present indicated in Scotland.

Mattresses and other factors

The results from the mattress analysis were unexpected. There is an increased risk of some kind, regardless of parity and social deprivation, for infants sleeping on mattresses previously used by others, although the risk was not established for mattresses completely covered by polyvinyl chloride. Our findings therefore lend no support to the hypothesis that household fungi interact with fire retardant chemicals in the plastic covering of cot mattresses and release toxic gases, which in turn cause sudden infant death.[19] The failure to establish risk with mattresses completely covered with polyvinyl chloride may be because they can be kept clean, regardless of age, while others cannot.

Key messages

- Parental smoking is currently the most important modifiable risk factor in the sudden infant death syndrome
- In this study sleeping prone and, to a lesser extent, sleeping on the side increased the risk of the syndrome, so babies should be put down to sleep only on their back
- Bed sharing with an infant should be discouraged if the mother smokes
- Sleeping on an old mattress may carry an increased risk

Although drug treatment was an independent risk factor for the sudden infant death syndrome no one drug was significant after adjustment. However, these tests lacked statistical power owing to the small numbers of infants taking each drug. Drug treatment may be a surrogate for some other risk factor(s) that we have not identified.

Young maternal age has historically been associated with an increased risk of the sudden infant death syndrome,[3] and our study confirmed this. There was a shift in the mean maternal age nationally at delivery for the four years of our study compared with the mean age during a previous Scottish study.[20] Mothers were, on average, older during the later study (72% ≥25 in 1992-5 *v* 30% in 1981-2.) We estimate that this swing accounts for about 9% of the decrease in the rate of the syndrome between the two studies.

Pillows and duvets were more commonly used on the night of death than routinely. On further examination the use of a duvet proved to be a surrogate for sharing the parental bed, whereas use of a pillow was not; therefore pillows may pose an increased risk.

The higher incidence of cases at weekends confirms previous findings.[21]

We have considered the possibility that some of the associations are the result of recall bias. The design of our study, requiring the home interview to take place within 21 days of death for cases, was aimed at limiting recall bias. Any drugs given may have been more easily remembered by parents of cases. For other findings—for example, smoking—recall bias would be more likely to lead to an underestimation by parents of cases compared with parents of controls as a self protective mechanism to allay guilt.

Our study confirms that smoking and sleeping prone are significant modifiable risk factors for the sudden infant death syndrome. It also supports suggestions that bed sharing when the mother smokes carries increased risk. Sleeping on an old mattress may be a new modifiable risk factor but merits further investigation.

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One hundred years ago

Are athletes healthy?

A question which has lately been much discussed in the daily papers, namely, "Are athletes healthy?" is one of considerable importance. Not that athletes are themselves particularly interesting people. Training of muscle, displays of bodily strength, and violent competitions for prizes and applause certainly do not tend to the development of the highest type of man, any more than do the moral surroundings of the average athlete. But the glory and notoriety which attend success in athletic sports have tickled the vanity of our youth, who see therein a short cut to fame. Fashion also drifts in the same direction; a cult has arisen, and thus it happens that both schools and colleges are now often chosen for the athletic rather than for the academic possibilities which they offer. Sports have, in fact taken so large a place in the thoughts and ambitions of the rising generation that it becomes and anxious matter to determine whether the life of the athlete is conducive to health. We do not here refer to people who merely "go in" for exercise and games, but to men who "train." We have very little hesitation in answering this question in the negative.
(*BMJ* 1897;ii:730.)

Reproductive pattern, perinatal mortality, and sex preference in rural Tamil Nadu, South India: community based, cross sectional study

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Abstract

Objectives: To study reproductive pattern and perinatal mortality in rural Tamil Nadu, South India.
Design: Community based, cross sectional questionnaire study of 30 randomly selected areas served by health subcentres.
Setting: Rural parts of Salem District, Tamil Nadu, South India.
Subjects: 1321 women and their offspring delivered in the 6 months before the interview.
Main outcome measures: Number of pregnancies, pregnancy outcome, spacing of pregnancies, sex of offspring, perinatal and neonatal mortality rates.
Results: 41% of the women (535) were primiparous; 7 women (0.5%) were grand multiparous (>6 births). The women had a mean age of 22 years and a mean of 2.3 pregnancies and 1.8 live children. The sex ratio at birth of the index children was 107 boys per 100 girls. The stillbirth rate was 13.5/1000 births, the neonatal mortality rate was 35.3/1000, and the perinatal mortality rate was 42.0/1000. Girls had an excess neonatal mortality (rate ratio 3.42; 95% confidence interval 1.68 to 6.98; this was most pronounced among girls born to multiparous women with no living sons (rate ratio 15.48 (2.04 to 177.73) *v* 1.87 (0.63 to 5.58) in multiparous women with at least one son alive).
Conclusions: In this rural part of Tamil Nadu, women had a controlled reproductive pattern. The excess neonatal mortality among girls constitutes about one third of the perinatal mortality rate. It seems to be linked to a preference for sons and should therefore be addressed through a holistic societal approach rather than through specific healthcare measures.

Introduction

During the past three decades, death and birth rates in India have declined considerably.[1 2] This decline is more pronounced in Tamil Nadu than in many of the other Indian states.[3] The decline in fecundity is in line with India's current policy of two children per family. Depending on reproductive failure (spontaneous abortion, stillbirth or infant death), women go through varying numbers of pregnancies to achieve the desired number of surviving children. In India, most couples desire at least one son, and many couples may thus go beyond the recommended or desired family size.[4]

Considering the decline in birth rate in India, it is uncertain how many pregnancies a woman has to go through to achieve the desired number and sex of children. Few community based studies describe the reproductive pattern in relation to perinatal mortality and sex preference among rural women in a developing country. This paper presents such data for a rural population in Tamil Nadu, South India.

Subjects and methods

The field study was carried out in the rural parts of Salem district in Tamil Nadu, South India; its main objective was to investigate aspects of antenatal care among women in rural Tamil Nadu. At the time of the study Salem district had a total population of 3 896 382 (1991 census), of which 24% was urban and 76% rural (R Balasubramaniam, personal communication). In rural areas, the government provides primary health care through 35 community health centres, 117 primary health centres, and 666 health subcentres. A health subcentre serves an average population of 5000. In the rural areas of Salem district, most people earn their living from agriculture or from smallscale industry.

To obtain a representative sample of the rural population in Salem district, a sample of 30 health subcentres was selected from a list of 615 (excluding those in semiurban and tribal areas) using a list of random numbers. The sampled centres served an estimated population of about 156 000.

We developed a questionnaire containing questions about reproductive history, antenatal care, delivery care, health status of the woman after the birth, health status of the youngest child, nutritional practices during pregnancy and postpartum, breast feeding, family planning, and socioeconomic status. The questionnaire was field tested by 50 women outside the study population who had just given birth; this resulted in a series of modifications. The final questionnaire was translated into Tamil. Three different people translated it back to English to ensure that the Tamil translation was in line with the original English version. A detailed set of guidelines to the questionnaire (including an inclusion guide) was developed and translated into Tamil.

Data were collected between 18 August and 27 September 1995. Through a meticulous house-to-house survey, 15 specially selected and trained local female interviewers identified and interviewed all eligible women in the catchment area of the 30 health subcentres. The interviewers were under close supervision of two experienced field leaders. Women were included in the study if they had delivered within the preceding six months; spoke Tamil; had stayed in the uptake area for more than two days; and were not mentally retarded. All questionnaires were reviewed daily by the two field leaders, and forms with missing information or visible inconsistencies were returned. If an eligible woman was not at home or if the time was not convenient for her to be interviewed, the interviewer came back later the same day or on the following day. In total,

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Table 1 Characteristics of 1320 newly delivered women in rural Tamil Nadu, 1995

Characteristic	No (%)
Age (years)*	
≤18	182 (13.8)
19-24	789 (59.8)
25-29	275 (20.8)
30-34	55 (4.2)
≥35	18 (1.4)
Parity	
1	535 (40.5)
2	439 (33.3)
3	215 (16.3)
4	81 (6.1)
5	31 (2.3)
6	12 (0.9)
7-10	7 (0.5)
Women with one or more dead children	
1	23 (4)
2	62 (14)
3	79 (36)
4	56 (69)
5	23 (74)
6	11 (92)
7-10	7 (100)
Level of education	
None	508 (39)
1-5 Years	349 (26)
6-10 Years	367 (28)
11-12 Years	61 (5)
>12 Years	35 (3)
Land ownership (acres)*	
None	748 (57)
<1	229 (17)
1-4	257 (20)
>4	85 (6)
Type of house*†	
Hut	382 (29)
Kutcha	216 (16)
Semipucca	522 (40)
Pucca	150 (11)
Mansion	49 (4)
Family type	
Nuclear	674 (51)
Joint	646 (49)

*Information missing for one woman.† Hut=one room, mud walls with thatched roof; kutcha house=more than one room, mud walls and thatched roof; semipucca=house with cement or mortar used for plastering wall or floor or with tiled roof; pucca=built with foundation, using stone or bricks with mortar and cement and having concrete or stone laid roof or tiled roof; mansion=large house containing more than five rooms.

1396 eligible women were identified, 1321 (95%) were interviewed, 68 (5%) were not at home on either of the two visits, 4 (0.3%) chose not to be interviewed, 3 (0.2%) had died, and data on socioeconomic factors and obstetric history were missing for one woman (0.1%).

To estimate interobserver and intraobserver reliability, double data collection was made in 11% of the cases selected randomly. In 69 (5%) of the cases the interviewer went back to the same informant twice to present the same questionnaire, and in 72 (6%) of the cases the interviewer presented the same questionnaire to women formerly interviewed by another field worker. Six key variables were chosen from the questionnaire; κ measures between 0.72 and 1.0 were found for interobserver reliability and between 0.76 and 1 for intraobserver reliability. Double data entry was made. The data were processed with EpiInfo 6.03.

Bivariate analysis of categorical data was based on the χ^2 test. Mean (SD) values are presented. For comparison of mean values of continuous data, a two sample *t* test was used. Rate ratios were used to compare mortality for boys and girls. Confidence intervals for rate ratios were computed as described by Rothman.[5] Statistical significance was defined as $P<0.05$, and for rate ratios 95% confidence intervals are presented.

Results

Table 1 shows maternal and socioeconomic characteristics of the 1320 women with valid information on these matters. Of these, 261 women (20%) had experienced the death of one or more children. The women were aged between 14 and 54 years (mean 22 years). Primiparous women had a mean age of 20.2 (SD 3.3) years and multiparous women had a mean age of 23.9 (3.9) years. All women were married.

The women had had an average of 2.3 pregnancies and had 1.8 living children, based on a reported total of 2618 live born babies, 68 stillborn babies, 275 postnatal deaths, 280 spontaneous abortions, and 60 induced abortions. The rate of stillbirth was 13.5 per 1000 births, the perinatal mortality rate was 42.0/1000, the early neonatal mortality rate was 28.9/1000, and the late neonatal mortality rate was 6.6/1000.

Of the 1321 index pregnancies, 1309 (99%) were singleton pregnancies and 12 (1%) were multiple. Overall, 690 (51.7%) infants were boys and 644 (48.3%) were girls (107:100; $P=0.68$ for comparison to expected value). In total, 1291 (98.6%) singletons were liveborn and 18 (1.4%) stillborn. Of the liveborn singleton infants, 53 (4.0%) died postnatally: 34 (64%) in the early neonatal period (before 7 days), 7 (13%) in the late neonatal period (8-28 days), and 12 (23%) one month or more after birth. The multiple pregnancies (11 twins and one set of quadruplets) were all live births. The quadruplets all died in the early neonatal period; one twin died in the late neonatal period and one died later.

More boys than girls were born (table 2). Stillbirths and postneonatal deaths were equally distributed with regard to sex but a higher proportion of neonatal deaths occurred among girls (rate ratio 3.42; 95% confidence interval 1.68 to 6.98). The proportion of girls who died in the late neonatal period was non-significantly higher (6.62; 0.80 to 54.99) but the proportion of girls who died in the early neonatal period was significantly higher (3.07; 1.43 to 6.57).

Daughters of multiparous women had a relative risk of neonatal death of 4.36 (1.78 to 10.71) compared with sons, but daughters of primiparous women had no excess mortality (2.04; 0.61 to 6.78) (table 3). This association was stronger for neonatal mortality in daughters of multiparous women who did not have living sons (15.48; 2.04 to 177.73) in comparison to multiparous women with at least one living son (1.87; 0.63 to 5.58) (table 4).

The mean age of living children born before the index child was 2.80 (SD 1.70) years for the 312 sons and 2.87 (1.68) years for the 367 daughters ($P=0.80$).

Discussion

This study showed that women in this area of southern India have a controlled reproductive pattern. They give

birth to their first child relatively late and have a limited number of children. Female infants have an increased risk of early neonatal death in families who already have daughters but no living sons.

As the sampling frame included only women who had just given birth, trends in birth and death rates as well as measures of infertility cannot be described. As well, the average number of pregnancies and children per woman applies only to a population of women who just gave birth. Due to the sampling frame, abortion rates may be underestimated.

Sources of possible bias

Women who had a dead child may be more reluctant to be interviewed than women with a living child. This tendency may be even more pronounced among women who had a dead girl because of the current focus in the Indian media and among government officials on missing girls. But the refusal rate was low (0.3%), and the field workers and their supervisors were thorough in identifying and including all women who had just given birth, so we estimated that only a minimum of bias existed here.

Some of the eligible women (5%) were not found at home even after two visits. Some of those women may have had a dead child. Usually women who have just given birth stay indoors for several months with their infant because they fear of meeting an evil spirit, with fatal consequences for their child. Missing eligible women may thus introduce some bias and lead to an underestimation of actual mortality.

Demographic factors

In this study, few mothers were adolescents. In Tamil Nadu, the legal age of marriage—that is, of the onset of sexual activity—is 18 years. In all India, and in neighbouring countries like China and Sri Lanka, an increasing trend in age at the time of marriage has been observed.[6-11] The results of this study are consistent with findings from other studies that age at marriage and thus age at first birth have increased in the past few decades.

We found a perinatal mortality rate of 42.0/1000. This is not statistically different from the official local rate of 47.5 (0.67 to 1.15).

Other studies have found that in countries with a high preference for sons, spacing of pregnancies is related to the sex and vital status of the previous children [12]; after the birth of a girl there is a shorter interval before the next birth. This was not found in our study.

The sex ratio at birth was as expected in a country with absence of social and behavioural interference in the sex of offspring,[13 14] indicating that these women did not practise sex selective abortion or underreport the birth of daughters. In China, which also has a strong preference for sons, the proportion of boys born is higher than expected[13-15]; in 1990 it was 111.75.[15]

Neonatal mortality

Girls had a significantly higher risk of neonatal mortality than boys, and this was even more pronounced among girls born to multiparous women without living sons. Without this excess mortality the perinatal mortality rate would be reduced by one third and would then reflect the distribution of stillbirths and early neonatal deaths which is seen in other countries—that is, half of the perinatal deaths occuring in utero and half occuring after birth.

In developing countries, neonatal mortality is largely due to birth asphyxia, pneumonia, tetanus, congenital anomalies, birth injuries, and prematurity. It is difficult to assess the contribution of hypothermia and delayed onset of breast feeding to early neonatal death.[16] Boys generally have a higher risk of neonatal mortality, possibly because of a complex combination of genetic and environmental factors.[17 18] Postneonatal deaths, on the other hand, are often caused by infectious diseases, the incidence and severity of which are affected by immunisation, health care, and other factors such as nutritional status. A difference in allocation of food and health care to boys and girls will thus change the usual pattern of postneonatal mortality. An excess of deaths among girls has been found in countries with a strong preference for sons and is most evident at ages 1-5 years, when a child's health and survival depend heavily on parental care.[19 20] These behavioural patterns may be a result of economic and cultural forces, as economic pressure forces parents to distribute limited resources such as food and medical care to offspring selectively.[15 21-25]

The substantially increased risk of neonatal death among girls born to multiparous women without living sons indicates that other causes of death than those mentioned earlier should be considered. Some communities in India and also elsewhere have practised infanticide for many years.[16-28] However, primary data on this are scarce.

Table 2 Sex distribution of liveborn and dead children (singleton pregnancies), Tamil Nadu, 1995. Values are numbers (percentages) unless specified otherwise

	Total (n=1309)	Boys (n=682)	Girls (n=627)	Rate ratio (95% CI)
Liveborn infants	1291	673 (52)	618 (48)	1.00
Stillborn infants	18	9 (50)	9 (50)	1.09 (0.43 to 2.72)*
Infants who died:	53	17 (32)	36 (68)	2.31 (1.30 to 4.11)
Neonatal (1-28 days)	41	10 (24)	31 (76)	3.42 (1.68 to 6.98)
Early (1-7 days)	34	9 (26)	25 (74)	3.07 (1.43 to 6.57)
Late (8-28 days)	7	1 (14)	6 (86)	6.62 (0.80 to 54.99)
Postneonatal (>28 days)	12	7 (58)	5 (42)	0.77 (0.24 to 2.43)

*Computed as a risk ratio.

Table 3 Sex distribution of liveborn singleton children who died within one month born to primiparous and multiparous women, Tamil Nadu, 1995 (singleton pregnancies)

	No (%) of boys	No (%) of girls	Rate ratio (95% CI)
Primiparous women:			
Liveborn infants (n=522)	266 (51)	256 (49)	1.00
Neonatal deaths (n=12)	4 (33)	8 (67)	2.04 (0.61 to 6.78)
Multiparous women:			
Liveborn infants (n=768)	407 (53)	361 (47)	1.00
Neonatal deaths (n=29)	6 (21)	23 (79)	4.36 (1.78 to 10.71)

Information missing for one woman.

Table 4 Sex distribution of liveborn children and children who died within one month born to multiparous women with and without living sons, Tamil Nadu, 1995 (singleton pregnancies)

	No (%) of boys	No (%) of girls	Rate ratio (95% CI)
Multiparous women with live sons:			
Live births (n=372)	189 (51)	183 (49)	1.00
Neonatal deaths (n=14)	5 (36)	9 (64)	1.87 (0.63 to 5.58)
Multiparous women without live sons:			
Live births (n=396)	218 (55)	178 (45)	1.00
Neonatal deaths (n=15)	1 (7)	14 (93)	15.48 (2.04 to 117.73)

Key messages

- In this area of Tamil Nadu, women have a controlled reproductive pattern, with an average of 2.3 pregnancies and 1.8 living children; the average age at the birth of the first child is 20
- The sex ratio at birth is 107 boys to 100 girls
- Girls have a substantial excess neonatal mortality, which is most pronounced among girls born to multiparous women with no living sons
- This excess neonatal mortality among girls seems to be linked to a preference for sons and must be addressed through a holistic societal approach

The significantly higher risk of neonatal mortality among girls born to multiparous women without living sons indicates that a preventive healthcare system that reflects a biomedical approach to improving perinatal mortality rates among girls would have a limited effect, as such a system is unlikely to focus on factors causing the excess mortality among girls. If perinatal mortality is to decline further, a holistic approach is required to change the complex interplay between available resources and the value of girl children.

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Eye disease associated with handling pet tarantulas: three case reports

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Tarantulas are becoming increasingly popular as pets. They are widely available, easily maintained, and considered harmless as many are non-venomous. Unfortunately the popular American varieties that are less venomous have evolved highly urticarious hairs to leave on their webs and flick at predators. We describe three cases of ocular injury from urticarious hairs of tarantulas.

Case reports

All three patients presented with complaints of itchy, gritty, red eyes. Two patients associated the onset of symptoms with the handling of a tarantula, and the third case was recognised only by astute history taking. Initially a similar clinical picture was seen in the three patients. The main findings were of multiple fine intracorneal hairs with an associated keratoconjunctivitis. In all three patients the right eye was more affected than the left; all the patients were right handed. One case settled quickly with topical steroid treatment, and at follow up at 36 months the patient had a normal eye. The two other patients had developed a progressive pan-uveitis still clinically active at follow up at 24 months and 72 months.

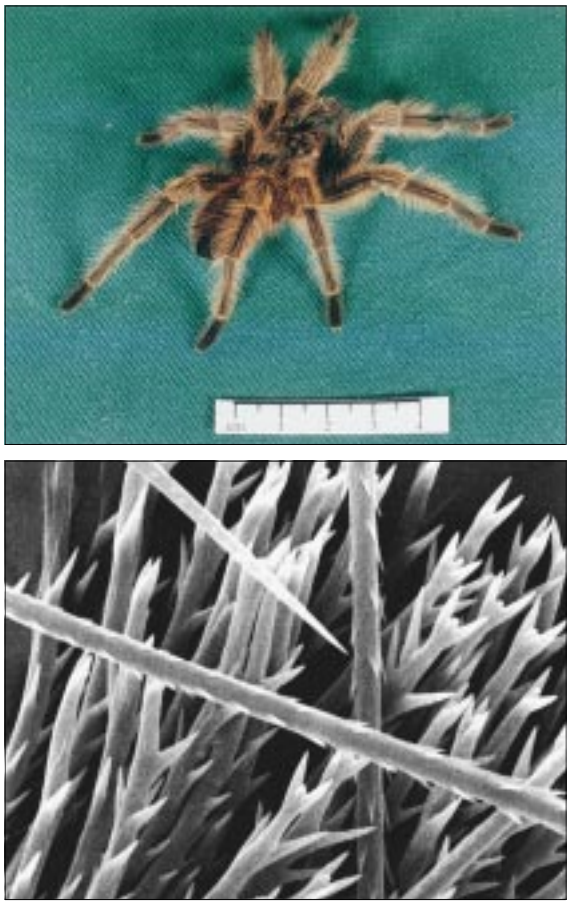

Fig 1 Scanning electron micrograph showing urticarious hairs (with point and barbs) from a Chilean Rose tarantula; hairs were collected after provocation

In the patients with the pan-uveitis the hairs seemed to be migrating relentlessly through the media of the eye. This has led to multiple foci of inflammation at all levels within the globe, causing corneal granulomas, iritis, peripheral anterior synechiae, cataract, vitritis, and chorioretinitis. One patient developed reduced visual acuity (6/18 N10 corrected) and raised intraocular pressure (mid-20s). At 24 months since presentation this patient is currently being treated with systemic steroids and topical antiglaucomatous drugs and is being considered for vitrectomy and extraction of a cataract.

The chronic complicated cases were associated with handling of a Chilean Rose (*Grammastola cala*) tarantula (fig 1 (top)), whereas the short uncomplicated case occurred after the handling of a Thailand Black (*Haplopelma minax*) tarantula.

Comment

Ophthalmia nodosa secondary to tarantula hairs is rare, and previous reports, where stated, have involved Mexican Red Knee (*Brachypelma smithi*) tarantulas with a short lasting, anterior segment dominated, inflammatory condition with no long term sequelae.[1-3] This condition is similar to the case involving the Thailand Black spider. The clinicopathology seen in the two other cases is, however, more chronic and serious than previous reports and more consistent with cases of ophthalmia nodosa secondary to caterpillar hairs of the Lymantriidae family.[4]

We studied the morphology of urticarious hairs from a Chilean Rose tarantula with a scanning electron microscope (fig 1 (bottom)). The morphology of the hairs seemed almost identical to that of caterpillar hairs and noticeably different from the phylogenetically much more closely related Mexican Red Knee spider.[5] This gives credence to the suggestion that hair morphology dictates the clinical outcome.

The urticarious hairs of tarantulas are poorly recognised as potential ocular irritants. Interestingly and alarmingly, Chilean Rose tarantulas are the most popular and widely available spiders on the market because of their hardiness, docility, and apparently harmless, non-venomous nature. They are often bought for children.

Our clinical experience suggests that the transfer from spider to hand to eye of urticarious hairs form the Chilean Rose tarantula may result in devastating ocular inflammation. We recommend not handling tarantulas routinely. If people must handle tarantulas then we suggest that they wear gloves, avoid rubbing the eyes during handling, and thoroughly wash their hands after handling to minimise the transfer of hairs. Raising awareness of this issue among those selling tarantulas and owners will hopefully prevent further cases.

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