Violations of the international code of marketing of breast milk substitutes: prevalence in four countries

Anna Taylor

Abstract

Objective: To estimate the prevalence of violations of the international code of marketing of substitutes for breast milk in one city in each of Bangladesh, Poland, South Africa, and Thailand.

Design: Multistage random sampling was used to select pregnant women and mothers of infants ⩽6 months old to interview at health facilities. Women were asked whether they had received free samples of substitutes for breast milk (including infant formula designed to meet the nutritional needs of infants from birth to 4 to 6 months of age, follow on formula designed to replace infant formula at the age of 4 to 6 months, and complementary foods for infants aged ⩽6 months), bottles, or teats. The source of the free sample and when it had been given to the women was also determined. 3 health workers were interviewed at each facility to assess whether the facility had received free samples, to determine how they had been used, and to determine whether gifts had been given to health workers by companies that manufactured or distributed breast milk substitutes. Compliance with the marketing code for information given to health workers was evaluated using a checklist.

Setting: Health facilities in Dhaka, Bangladesh; Warsaw, Poland; Durban, South Africa; and Bangkok, Thailand.

Subjects: 1468 pregnant women, 1582 mothers of infants aged ⩽6 months, and 466 health workers at 165 health facilities.

Main outcome measures: Number of free samples received by pregnant women, mothers, and health workers; number of gifts given to health workers; and availability of information that violated the code in health facilities.

Results: 97 out of 370 (26%) mothers in Bangkok reported receiving free samples of breast milk substitutes, infant formula, bottles, or teats compared with only 1 out of 385 mothers in Dhaka. Across the four cities from 3 out of 40 (8%) to 20 out of 40 (50%) health facilities had received free samples which were not being used for research or professional evaluation; from 2 out of 123 (2%) to 21 out of 119 (18%) health workers had received gifts from companies involved in the manufacturing or distribution of breast milk substitutes. From 6 out of 40 (15%) to 22 out of 39 (56%) health facilities information that violated the code had been provided by companies and was available to staff.

Conclusion: Violations of the code were detected with a simple survey instrument in all of the four countries studied. Governmental and non-governmental agencies should monitor the prevalence of code violations using the simple methodology developed for this study.

Introduction

The World Health Organisation estimates that 1.5 million babies could be prevented from dying each year if women breast fed their infants (exclusively for about 6 months and until infants were 2 years old).[1] Where a mother uses an alternative to breast milk to feed her baby, it is important that she makes an informed decision and that she has not been pressured by commercial promotions to use a substitute. The international code of marketing of breast milk substitutes[2] was adopted by the World Health Assembly in 1981 to encourage breast feeding and to protect mothers from pressure to use substitutes for breast milk. At that time one member state (the United States) voted against the code and three abstained (Argentina, Japan, and Korea); by the 1996 World Health Assembly meeting all 191 member states had affirmed their support for the code, its implementation, and the implementation of relevant resolutions. By 1997, 17 countries had adopted all or substantially all of the code's provisions as legal requirements.[3] Adoption of the code represents the development of an international consensus.

Anecdotal evidence of violations of the code has been presented but no previous studies have used formal sampling techniques.[4] This study was designed to measure the prevalence of violations of the code using randomly sampled groups of women, health workers, and health facilities in four cities.

The study was overseen and supported financially or by other means by 27 churches, academic institutions, and international non-governmental organisations. Experts in infant feeding were contacted for advice. Accommodation was provided by Unicef United Kingdom. The organisations and people who chose to participate wanted to obtain unbiased information on violations of the marketing code. No funding, support, or advice was received from the manufacturers of breast milk substitutes or

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organisations forming part of the International Baby Food Action Network (Penang, Malaysia).

Subjects and methods

Sampling procedure

Since no studies of this kind had been done before a 10% prevalence of reported violations was assumed to be an important amount of violation. A sample of 800 women would give a 95% power to observe at least one reported violation if the true prevalence was 2%. If the prevalence was 10% the sample size would generate estimates of population prevalence with a standard error of 1%. Sample sizes for health workers and health facilities were constrained by practical considerations.

Selection of countries

Countries were grouped into three categories that reflected the status of requirements for compliance with the marketing code. In 63 countries compliance with the code was a legal requirement; in 36 countries compliance with the code was voluntary; and in 96 countries the code had another status, including no code, code awaiting government approval, or the status was unknown.[3] A small subset of countries where there were agencies already working in partnership with the Interagency Group on Breastfeeding Monitoring were selected in each category to participate in preliminary discussions on the feasibility of the study (3 of the 63 countries in which compliance was legally mandatory, 2 of the 36 in which compliance was voluntary, and 5 of the 96 classed as giving the code any other status). These countries had contrasting geographical and economic conditions. After discussions with partner agencies six countries were excluded from the study because government permission or personnel support could not be secured.

The final four countries selected were Bangladesh (where compliance with the code is a legal requirement), Poland (which has no code), South Africa (where compliance is voluntary), and Thailand (where compliance is voluntary).

Cities—The capital city was chosen for the study in each country; however, in South Africa, government authorities suggested that the study should be done in Durban because the University of Natal would be able to manage the study.

Districts—Seventeen districts in Warsaw and 23 in Bangkok in which there were at least four health facilities that served pregnant women and mothers of infants were identified and numbered serially; 10 districts were selected using random numbers. In Dhaka 17 districts which had a minimum of four health facilities and in which 20% of the people were living slums were selected to reflect the overall proportion of people living in slums in the city. Districts were numbered and 10 were selected using random numbers. In Durban there were 93 districts but there were not enough facilities in each district for the same selection procedure to be followed. To ensure a large enough sample of health facilities 23 districts were randomly selected.

Health facilities—To be considered eligible for sampling health facilities had to be large enough to see daily at least 10 pregnant women or mothers of infants who were ≤6 months old. Altogether 132 facilities met the inclusion criteria in Warsaw, and 159 met the criteria in Bangkok. All facilities that met the criteria in the 10 districts were numbered, and four were selected from each district using random numbers; thus, 40 health facilities were studied in each of these cities. In Dhaka 40 facilities met the inclusion criteria and in Durban 46 met the criteria; all of these facilities were included in the study. The coordinators in each country and the interviewers had had no prior contact with staff or mothers at the health facilities studied.

Definitions

All products marketed for infants younger than 6 months and all follow on formulas were considered to be breast milk substitutes. Infant formulas are those substitutes designed to be used from birth up to 4 to 6 months of age. Follow on formulas are designed to replace infant formulas at the age of 4 to 6 months. These definitions were based on World Health Assembly resolution 47.5 (1994) which clarified the code and recommended "fostering appropriate complementary feeding practices from the age of about six months." World Health Assembly resolutions passed after the code was adopted in 1981 have the same status as the code, which was adopted as part of World Health Assembly resolution 34.22. Article 2 of the code specifies the products covered by the code.

A gift was considered to be any item, except that which is defined as a product in the code, given to a health worker by a company that manufactures or distributes breast milk substitutes.

Extracts from the international code of marketing of breast milk substitutes[2]

Article 2 (products covered by the code)
The code applies to the marketing, and practices related thereto, of the following products: breast milk substitutes, including infant formula; other milk products; foods and beverages, including bottle fed complementary foods, when marketed or otherwise represented to be suitable, with or without modification, for use as a partial or total replacement of breast milk; feeding bottles; and teats. It also applies to their quality and availability, and to information concerning their use

Article 5.2 (provision of samples)
Manufacturers and distributors should not provide, directly or indirectly, to pregnant women, mothers, or members of their families, samples of products within the scope of this code.

Article 7.2 (provision of information to health workers)
Information provided by manufacturers and distributors to health professionals regarding products in the scope of this code should be restricted to scientific and factual matters and such information should not imply or create a belief that bottle feeding is equivalent or superior to breast feeding. It should also include the information specified in article 4.2.

Article 7.3 (provision of inducements to health workers)
No financial or material inducements to promote products within the scope of this code should be offered by manufacturers or distributors to health workers or members of their families.

Article 7.4 (provision of samples to health workers)
Samples of infant formula or other products within the scope of this code … should not be provided for health workers except when necessary for the purpose of professional evaluation or research at the institutional level. Health workers should not give samples of infant formula to pregnant women, mothers of infants and young children, or members of their families.

Subjects

Over two days 20 pregnant women or mothers of infants aged ≤6 months were selected from the appointment register at each facility and interviewed. Where no appointment register was available women were systematically sampled according to their position in the waiting room (for example, every fifth consecutive woman was selected). During the same two days, three health workers at each facility were interviewed. The selection of health workers depended on their availability for interview. Interviews with staff at different levels of seniority were sought. Wherever possible confidential interviews were carried out in a quiet designated area. A target sample size of 800 women and 120 health workers was set for each city, except Dhaka where there were problems with transportation because of the rainy season.

Interview procedure

The research coordinator (AT) trained 10 people in each country to interview pregnant women, mothers, and health workers using structured questionnaires; they were also trained to use a checklist to assess materials produced by companies that manufactured breast milk substitutes. (A copy of the checklist can be found on our website at www.bmj.com.) All data were collected within each country during one month between August and October 1996.

Country coordinators came from a variety of different backgrounds. In Dhaka the coordinator was a health visitor. In Durban the coordinator was an epidemiologist. In Bangkok the network director of a non-governmental organisation acted as coordinator and in Warsaw a doctor specialising in lactation management coordinated the study. Interviewers also came from a variety of backgrounds. In Dhaka interviewers had previous experience of similar work and were selected by interview. In Durban interviewers came from the university's faculty of medicine. In Bangkok professional market researchers collected the data, and in Warsaw postgraduate students from various disciplines collected the data.

As a result of a field test in Poland the format of the questionnaire was modified to make it easier to complete. In each country coded questionnaires were translated from English to the local language; in order to exclude linguistic errors they were then translated back by an independent translator. Interviews were confidential and responses anonymised. The number of people who declined to participate was recorded.

Pregnant women and mothers were asked if they had been given free samples of a breast milk substitute, feeding bottle, or teat. If they had, they were asked when and from whom it had been received. Health workers were asked whether they or the facility in which they worked had received any free samples and for what purpose they had been used. They were asked whether they had received any gifts from companies that manufactured products covered by the code and whether the gift had carried the brand name of a product.

Validation procedure—To confirm the validity of women's responses, 20% of the mothers in each city who had reported receiving free samples were asked about the samples and where they had received them. The details were recorded and then staff at the facility that had provided the sample were interviewed. Staff were asked about the availability of samples and their responses were compared with the woman's report.

Assessment of written information—Health workers were asked to show the interviewer the materials that had been provided for professional use by manufacturers. These materials were then assessed by the interviewer using a checklist based on the requirements of relevant articles of the code (4.2 and 7.2) (box).

Data management—The country coordinator was responsible for the quality of the data and supervision of the interviewers. In each country data were entered by a trained data clerk using EpiInfo software; data were analysed in London. Confidence intervals for proportions were estimated assuming a β binomial random effects model to take account of possible variation between clinics.[5]

Results

Health facilities and respondents

Forty health facilities were visited in Dhaka, 46 in Durban, 40 in Bangkok, and 39 in Warsaw (one facility was closed for a holiday). In Dhaka 704 women were approached for an interview and all agreed to participate. In Warsaw 794 women were approached and three declined to participate. In Durban 804 women were approached; five declined to participate. In Bangkok 748 women were approached; 52 declined to participate. In Dhaka 112 health workers were asked to participate; one declined. In Warsaw 119 were approached and four declined. In Durban 123 were approached and one declined. In Bangkok 112 were approached and eight declined.

Many factors may have affected the mix of women attending the facilities in the samples. Some facilities were privately run, some were run by the state, and some were run by non-governmental organisations. Criteria for registration at specific facilities varied from residence in specific catchment area (Warsaw) to personal preference for private facilities (Bangkok). In Dhaka facilities were often small outpatient clinics where the number of patients seen was just enough to qualify for inclusion in the study, though large hospitals were also included in the sample. In Durban, attendance at a particular facility was usually limited to specific ethnic groups. Ease of access for researchers also varied between and within cities. A police escort was needed to visit some facilities in Durban. In Dhaka it was necessary to wade through deep water to reach some clinics. Most facilities in Warsaw and Bangkok were easily accessible.

Free samples

In Bangkok 97 out of 370 (26%; 95% confidence interval 18% to 36%) mothers reported receiving free samples of a breast milk substitute, feeding bottle, or teat (table); many women received more than one sample. This was a greater proportion than that found in the other three cities. In Dhaka only one woman reported receiving a free sample. In all cities mothers were more likely than pregnant women to report having received free samples.

Health workers reported receiving free samples in as many as half of the facilities visited; none of the samples were being used for professional evaluation or

Free samples and gifts received by pregnant women, mothers of infants ⩽6 months old, and health workers by city, type of sample received, and source of sample; and number of health facilities that received information from manufacturers that violated the international code of marketing of substitutes for breast milk

Group or source	Dhaka	Warsaw	Durban	Bangkok
Pregnant women				
No (%) receiving free sample	0/319	6/364 (2)	3/407 (1)	13/378 (3)
Type of free sample (No)*:				
Infant formula	0	0	1	15F
Feeding bottle or teat	0	1	0	0
Other breast milk substitute†	0	4	2	1
Mothers of infants ⩽6 months old				
No (%) receiving free samples	1/385 (0.3)	34/430 (8)	13/397 (3)	97/370 (26)
Type of free sample (No)*:				
Infant formula	0	1	6	95
Feeding bottle or teat	0	7	4	55
Other breast milk substitute†	1	28	3	2
Source of free samples (No) provided to pregnant women and mothers				
Health facility	0	24	14	152
Direct mail or retail	1	6	0	17
Health workers				
No (%) reporting free samples received at health facility	3/40 (8)	8/39 (21)	9/46 (20)	20/40 (50)
Type of free sample (No)*:				
Infant formula	5	7	5	34
Feeding bottle or teat	0	0	1	0
Other breast milk substitute†	0	4	6	0
No (%) of health workers who reported receiving gifts	19/112(17)	21/119 (18)	2/123 (2)	9/112 (8)
No (%) of health facilities reported by health workers to have received information that violated the code	6/40 (15)	22/39 (56)	8/46 (17)	13/40 (33)

*Some women and health workers reported receiving more than one sample; in Warsaw one sample and in Bangkok two samples were of an unknown type and are not included in the table.
†Other breast milk substitutes include follow on formulas and complementary foods.

research at the institutional level as specified by article 7.4 of the code. The proportion of health facilities where staff reported receiving samples was highest in Bangkok (20/40) and lowest in Dhaka (3/40) (table).

The table shows that in each city except Dhaka the health service was the most common source of samples received by women. Only a small number were received by direct mail or from retail outlets. Of the samples that pregnant women and mothers reported receiving 118 out of 226 (52%) were infant formula and 67 out of 226 (30%) were bottles or teats (table). In Warsaw where other breast milk substitutes (complementary foods marketed for infants younger than 6 months and follow on formulas marketed for infants between 4 and 6 months old) contributed a greater proportion to the total number of samples received, 24 out of 32 (75%) of samples were received before the infant was 4 months old. Overall, health workers reported receiving samples of infant formula more frequently than other samples; other breast milk substitutes were also received in Warsaw and Durban.

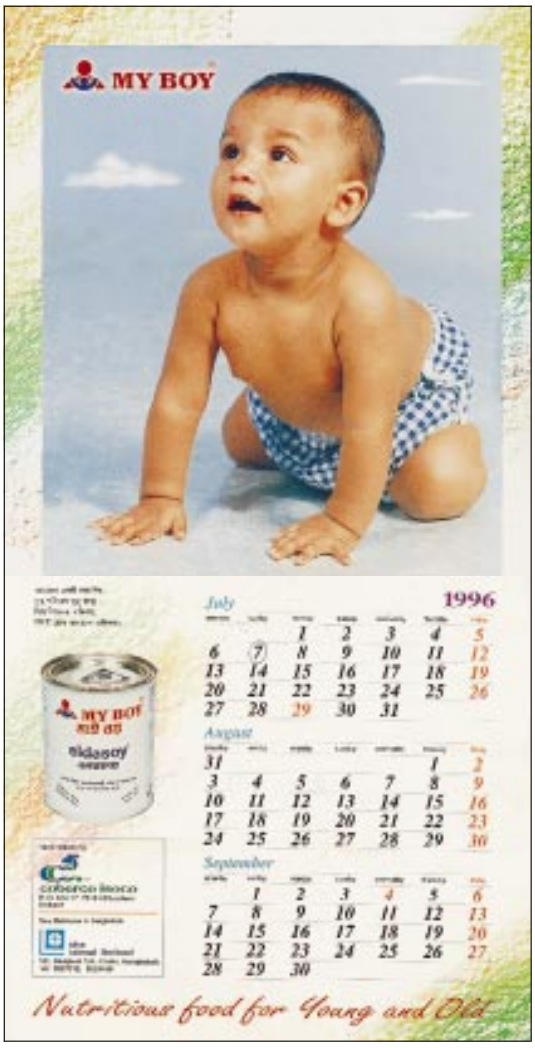
Validation

In Bangkok 97 out of 370 mothers reported receiving free samples. Eighteen of the 19 mothers in the validation subset described the samples they had received. The interviewer found that 12 samples were still available. One type of sample described was no longer available but the researcher was able to confirm that that type of sample had at previously been dispensed by the facility. No additional information could be obtained about the other five samples that mothers reported receiving. In Warsaw 34 mothers reported receiving free samples; some mothers received more than one sample. All seven mothers in the validation subset were contacted. Information was available about only three of the samples. In Dhaka the single reported free sample was not verified. Problems with transportation in Durban prevented us from verifying any of the 13 free samples reported.

Information and gifts provided to health workers

Health workers in 22 out of 39 (56%; 95% confidence interval 41% to 72%) health facilities in Warsaw received information from manufacturers which violated the code. This was higher than in the other three cities where prevalence ranged from 6 out of 40 (15%; 4% to 26%) health facilities in Dhaka to 13 out of 40 (33%; 18% to 47%) in Bangkok (figure).

Gifts donated by companies were received by 21 out of 119 (18%; 10% to 27%) health workers in Warsaw and 19 out of 112 (17%; 11% to 26%) health workers in Dhaka. Gifts were donated for personal use and included pens, notebooks, calendars, and tee shirts. Altogether 51 out of 70 (73%) gifts were reported to carry the brand name of a product.



Calendar given to a health worker in Dhaka, Bangladesh. The code states that no material inducement to promote a product should be offered by manufacturers of breast milk substitutes to health workers

Discussion

In this study pregnant women and mothers in four cities reported receiving free samples of infant formula, other breast milk substitutes, feeding bottles, or teats in contravention of articles 5.2 and 7.4 of the international code of marketing of substitutes for breast milk. None of the free samples were to be used for professional research purposes according to reports from health workers interviewed at the health facilities. The greater the number of facilities given samples in each city the greater the proportion of pregnant women and mothers who received samples. Most of the samples were reported to have come from a health facility; this suggests that samples given to facilities were passed on to mothers, whether or not that was the intention of the company donating the samples.

The effect of giving free samples of infant formula, bottles, and teats to women who are breast feeding has been examined in five studies.[6–10] Frank et al reported that women receiving a discharge pack that contained products consistent with the code (such as breast pads and pamphlets on breast feeding) were more likely to breast feed for longer than those receiving a commercial discharge pack (containing formula, bottles, or teats), were more likely to be breast feeding at 4 months post partum, and were more likely to delay feeding solid foods.[11] Two meta-analyses of the five studies confirmed that commercial discharge packs have a detrimental effect on breast feeding at one month after birth (odds ratios 1.45 (95% confidence interval 1.07 to 1.96)[12] and 1.4 (1.0 to 2.1)[13]).

Article 7.3 of the code outlines the responsibilities of both health professionals and manufacturers as they pertain to the donation and receipt of gifts, yet widespread violations were detected in the four cities surveyed. Although many of the gifts were of little value financially, health professionals working in underfunded healthcare systems, such as in Bangladesh, may find it difficult to resist accepting these inducements. The presence of brand name items in the health facility may constitute professional endorsement of a particular product to patients seen in the facility.

The code states that all information produced by companies that manufacture or distribute breast milk substitutes must include details on the benefits and superiority of breast feeding and the risks associated with bottle feeding (articles 4.2 and 7.2). Nevertheless, 15% to 56% of health workers interviewed stated that their facilities had received materials that contravened these articles.

It may not be possible to generalise these findings to other areas because conditions in rural districts could be different. Equally, the promotional activities of companies may vary from country to country and city to city. However, both the number and nature of code violations suggest that systematic contravention of the code exists; it would be reasonable to believe that similar violations are occurring at similar rates in other cities and countries. These findings are the consequences of the promotional activities of 21 companies, six of which were trying to sell their products in more than one of the countries studied.

Key messages

- A simple multistage random sampling procedure can be used to interview women and health professionals to assess whether violations of the international code of marketing of substitutes for breast milk are occurring
- 3050 women and 466 health professionals were interviewed at 165 health facilities in Bangladesh, Poland, South Africa, and Thailand
- 97 out of 370 mothers in Bangkok reported receiving free samples of breast milk substitutes, infant formula, bottles, or teats compared with only 1 out of 385 mothers in Dhaka. In Bangkok health workers reported that 20 out of 40 health facilities had also received free samples. Most free samples were distributed by health facilities
- In Warsaw 56% of facilities surveyed were found to have information available for health workers that had been provided by manufacturers or distributors of breast milk substitutes in contravention of the code; 18% of health workers in Warsaw had received free gifts from manufacturers

Importance of implementation and monitoring of the code

Bangladesh was the only country studied which had laws governing the marketing of breast milk substitutes; the smallest number of free samples were detected there. Warsaw had the highest number of health facilities in which information that violated the code was available to health professionals. Warsaw also had the highest proportion of health professionals who received free gifts; Poland has no legal or voluntary code governing any aspects of marketing discussed in this paper. South Africa and Thailand have voluntary codes. In Thailand the voluntary code was revised in 1995.

The frequency of the violations occurring in four major cities shows that 16 years after the World Health Assembly adopted the code, its requirements are still unmet. There is little to suggest that the situation would be different in many other countries; the code is not enforced in its entirety under current legislation in the United Kingdom and Europe.[14] There is little hope that breast feeding will be protected from commercial pressure as envisioned by the World Health Assembly unless there is a commitment to enforce and monitor the code nationally.

Monitoring is intermittently conducted at sentinel sites in many countries by the International Baby Food Action Network but this is the first study to measure the prevalence of violations in a random sample of women and health professionals. The results provide a baseline for continued surveillance. The protocol used in this study can be applied within a short time and with few resources, making it suitable for use by governments seeking to protect the health of mothers and young infants.

The Interagency Group on Breastfeeding Monitoring is a coalition of organisations and individuals established to monitor independently the marketing code.

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Contributors: Claire Grose, Dr Magdalena Gugulska, Christine Lucas, and Saree Aongsomwang acted as country coordinators. Alison Maclaine analysed the data. Caroline Leveaux provided managerial support. AT designed and implemented the study, wrote the paper, and is guarantor for the study.

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Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy

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Abstract

Objectives: To assess whether the levonorgestrel intrauterine system could provide a conservative alternative to hysterectomy in the treatment of excessive uterine bleeding.

Design: Open randomised multicentre study with two parallel groups: a levonorgestrel intrauterine system group and a control group.

Setting: Gynaecology departments of three hospitals in Finland.

Subjects: Fifty six women aged 33-49 years scheduled to undergo hysterectomy for treatment of excessive uterine bleeding.

Interventions: Women were randomised either to continue with their current medical treatment or to have a levonorgestrel intrauterine system inserted.

Main outcome measure: Proportion of women cancelling their decision to undergo hysterectomy.

Results: At 6 months, 64.3% (95% confidence interval 44.1 to 81.4%) of the women in the levonorgestrel intrauterine system group and 14.3% (4.0 to 32.7%) in the control group had cancelled their decision to undergo hysterectomy ($P < 0.001$).

Conclusions: The use of the levonorgestrel intrauterine system is a good conservative alternative to hysterectomy in the treatment of menorrhagia and should be considered before hysterectomy or other invasive treatments.

Introduction

Menorrhagia is a major reason for hysterectomy among fertile women.[1] Abnormal uterine bleeding is a common reason for consulting general practitioners.[2] Until recently, medical treatment has been disappointing,[3 4] and various surgical alternatives in the form of endometrial ablation have been developed.[5–7] The role of these surgical alternatives in the treatment of menorrhagia is not currently clear.[8]

The progestin levonorgestrel, released from an intrauterine system at a rate of 20 µg/24 hours, suppresses endometrial growth. The glands of the endometrium become atrophic and the epithelium inactive.[9] This system, originally developed for contraception,[10 11] has been shown to decrease the amount and duration of normal menstrual flow.[12] The results of a non-comparative study showed a reduction of menstrual blood loss of 86% in menorrhagic women in only 3 months and a further reduction to 97% 12 months after insertion of the device.[13] Comparison of the levonorgestrel intrauterine system with the non-steroidal anti-inflammatory drug flurbiprofen and tranexamic acid showed that the device decreased the measured volume of menstrual blood loss in comparison with control cycle measurements by 82% at 3 months and by 96% at 12 months, while the flurbiprofen and tranexamic acid treatments decreased menstrual blood loss by only 21% and 44%, respectively.[14]

Many women scheduled for hysterectomy as the final treatment for menorrhagia might still prefer a conservative alternative. We invited women who had already made a decision to undergo hysterectomy to participate in a randomised study comparing the levonorgestrel intrauterine system with their current medical treatment. Our primary aim was to assess after 6 months whether the device could provide a conservative alternative to hysterectomy in the treatment of excessive uterine bleeding or dysmenorrhoea, or both.

Patients and methods

Patients

From hospital waiting lists we recruited women who had spontaneous cycles and who were scheduled to undergo hysterectomy for treatment of excessive uterine bleeding with or without dysmenorrhoea. Women were excluded from the study if they had one fibroid larger than 3 cm in diameter or more than three uterine fibroids as assessed by ultrasonography, a history or current clinical evidence or suspicion of malignancy or active liver disease, adnexal tumours or cysts, or pelvic inflammatory disease within the previous 12 months. If the women were prepared to accept yet another conservative attempt at treatment they were enrolled into the study.

Study design and treatment

The study was an open phase III randomised multicentre study with two parallel groups: a levonorgestrel intrauterine system group and a control group. The study was conducted in three hospitals in Finland: the City Maternity Hospital and the University Hospital, Helsinki, and the Central Hospital of Middle Finland, Jyväskylä.

The study was conducted according to the principles of the Declaration of Helsinki. Copies of the protocol and the informed consent form were submitted to and approved by the ethics committees of the participating study centres before we started the study.

The women were randomly allocated to the levonorgestrel intrauterine system group or the control group by using a randomisation table, the randomisation being balanced in blocks of four. Concealment was secured by using sealed envelopes.

The levonorgestrel intrauterine system (Mirena) was inserted into the uterine cavity after menstruation according to the insertion instructions. The patients in the control group continued their existing medical treatment for excessive uterine bleeding or symptoms of dysmenorrhoea, or both. There was no wash out period of medication for bleeding or dysmenorrhoea at screening. Enrolment started on 15 November 1991 and finished at the end of 1993.

The primary measure of efficacy was the woman's decision at 6 months, at discontinuation, or when the hysterectomy became available as to whether she would prefer her current treatment or hysterectomy. If she chose to continue the current treatment she was asked again at 12 months. Finally, at the end of 1995 all the patients' records were checked to see how many women had undergone hysterectomy.

The degree of disturbance caused by their menstrual bleeding or pain, or both, on general well-being, work performance, physical activity, sexual activity, and general leisure time activity was assessed by using a visual analogue scale at screening, at 6 months, and at 12 months or at discontinuation. The visual analogue scale consisted of a horizontal line of 10 cm. The left end was indicated as "not disturbing," the right end as "very disturbing." The patients were asked to mark with a cross the point on the line that most closely indicated the effects of uterine bleeding or menstrual pain on normal life, without distinguishing between these two.[15]

The women were asked to mark in a menstrual diary their days of menstrual bleeding and spotting. The latter was defined as a bloody discharge not necessitating the use of pads or tampons. We calculated the distributions in centiles of the total number of days of bleeding and spotting in each month and each trimester using the menstrual diary analyser, a computer program developed for this purpose by JS.[16]

Statistical analysis

Power analysis was made before the study for the main measure of efficacy—that is, women preferring current treatment to hysterectomy at 6 months. We expected that 40% of patients in the levonorgestrel intrauterine system group and 10% in the control group would cancel the hysterectomy. The sample size required for the comparison of two binomial proportions of a two sided test at 5% level, when the power is 95, was 52 per group when $\pi_1 = 0.1$ and $\pi_2 = 0.4$. Taking into account the possibility of discontinuation, we planned to enrol 60 patients per group.

The study was started in two clinics. The rate of enrolment, however, was much slower than expected and a third clinic was therefore included. From the original recruitment time of 1 year the period was extended to 26 months. During that period the waiting time for hysterectomy shortened from over 12 months in each hospital to under 6 months in two hospitals. As the ethics committees had requested that women should be offered the operation once it became available, recruitment to a 6 month study became complicated. By this time, 28 patients were recruited per group, giving a power of 70%.

The main measure of efficacy—willingness to continue the current treatment instead of hysterectomy at 6 months—was analysed according to the principle of intention to treat by using the Mantel-Haenszel test. Comparison of visual analogue scale distributions between the groups at screening, differences between screening and 6 month results, and differences in the number of days of bleeding and spotting were analysed by using the Mann-Whitney U test. All statistical analyses were carried out with SAS software package version 6.08. A P value < 0.05 was considered significant. The tests were performed as two tailed tests.

Results

A total of 56 women were randomised, 28 to the levonorgestrel intrauterine system group and 28 to the control group. Three women cancelled participation before enrolment, two in the control group and one in the levonorgestrel group. The mean (SD) ages were 42.7 (3.4) and 41.7 (4.5) years in the levonorgestrel intrauterine system and control groups, respectively.

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Table 1 Reasons for discontinuation of use of levonorgestrel intrauterine device and histological diagnosis at hysterectomy

Case No	Month of discontinuation	Reason for dissatisfaction	Histological diagnosis
1	3	Weight gain, headache, operation offered from waiting list	Fibroids
2	6	Prolonged bleeding and spotting	Adenomyosis
3	6	Prolonged bleeding, pain	Fibroids, adenomyosis
4	6	Excessive bleeding	None
5	6	Wanted hysterectomy	Adenomyosis
6	6	Spotting, pain	Fibroids
7	6	Personal reasons	Adenomyosis
8	7	Pain	Adhesions
9	8	Spotting	None
10	9	Depression, acne	None
11	9	Prolonged bleeding, spotting	Several fibroids, adenomyosis
12	12	Prolonged	Chronic endometritis

Table 2 Menstrual disturbance scores by group. Figures are medians (Wilcoxon based 95% confidence intervals)

	At screening*		At 6 months†		
Variable	Control group	Levonorgestrel	Control group	Levonorgestrel	Levonorgestrel at 12 months
General wellbeing	87 (77 to 92)	90 (74 to 94)	79 (64 to 87)	24 (14 to 40)	10 (4 to 29)
Work performance	75 (61 to 80)	79 (62 to 89)	76 (54 to 87)	20 (5 to 35)	6 (3 to 11)
Physical activity	78 (64 to 92)	88 (64 to 95)	78 (55 to 88)	27 (9 to 38)	10 (3 to 28)
Sex life	66 (52 to 80)	68 (49 to 86)	66 (51 to 85)	36 (17 to 49)	8 (3 to 28)
Leisure time activty	74 (64 to 85)	76 (54 to 86)	74 (54 to 86)	11 (5 to 27)	6 (3 to 29)

*At screening there were no significant differences between groups. †At 6 months all differences between groups were significant (P=0.002 for sex life and P<0.001 for all other variables).

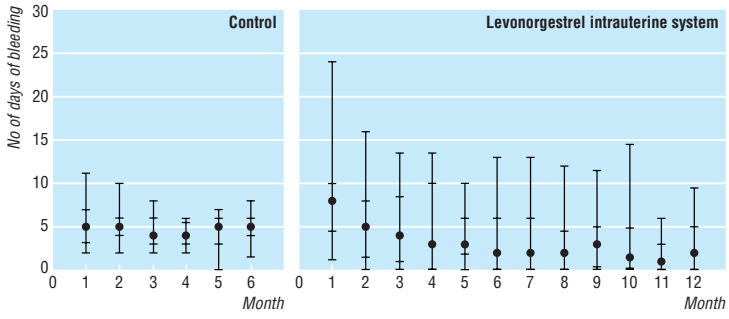

Fig 1 Number of days of bleeding per month in control group and in levonorgestrel intrauterine system group. Points are medians with 25th and 75th centiles and 5th and 95th centiles

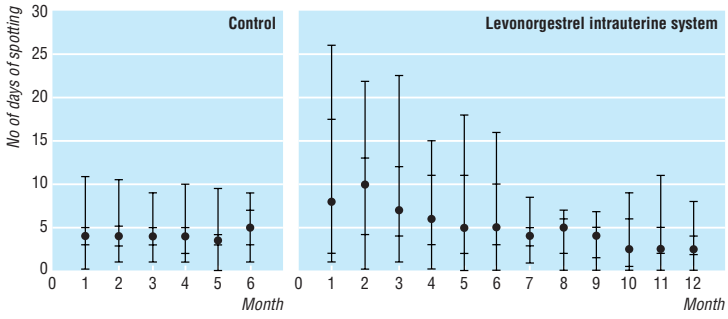

Fig 2 Number of days of spotting per month in control group and in levonorgestrel intrauterine system group. Points are medians with 25th and 75th centiles and 5th and 95th centiles

Eighteen out of 28 women (64.3%; 95% confidence interval 44.1% to 81.4%) in the levonorgestrel group and four out of 28 women (14.3%; 4.0% to 32.7%) in the control group cancelled hysterectomy at 6 months ($P<0.001$).

In the control group two women wished to continue their current drug treatment (prostaglandin synthesis inhibitors) and two decided to switch to the levonorgestrel intrauterine system. The proportion of women who decided to cancel hysterectomy was significantly higher in the levonorgestrel intrauterine system group ($P<0.001$) by 6 months.

At 12 months 12 women (57%) in the levonorgestrel group had discontinued the treatment. They all underwent hysterectomy. Table 1 gives the reasons for discontinuation and the histological diagnoses at hysterectomy.

By the end of 1995, 13 of 27 women (48%) continued using the levonorgestrel intrauterine system, with an average follow up time of 3 years (range 23-49 months).

Evaluation by visual analogue scale of the quality of life showed no difference between the groups at screening (table 2). Visual analogue scale scores had not changed at 6 months in the control group whereas they were significantly improved in each category in the study group ($P\leq0.002$). The beneficial effect was maintained in the levonorgestrel group at 12 months.

The distribution by centiles of the total number of days of bleeding during the first 6 months in the control group and during 12 months in the levonorgestrel group is presented in figure 1. The median number of days of bleeding remained at a constant level of 4-5 days per month in the control group, while in the levonorgestrel group it decreased from 7 in the first month to 3 in the sixth month and 2 in the 12th month. Differences in the number of days of bleeding between the groups did not reach significance.

The distribution of the number of days of spotting in both groups is presented in figure 2. In the control group the median number of days of spotting remained at a nearly constant level of about 4 days a month. In the levonorgestrel group the median number of days of spotting was at its highest level, 10 days a month, during the second month. Thereafter it declined to 5 in the sixth month and 2.5 in the 12th month. The number of days of spotting was significantly lower in the control group in the first 3 months ($P=0.001$) and also in the second 3 months ($P=0.016$). No serious adverse events were seen during the study.

Discussion

The levonorgestrel intrauterine system has been approved for contraception in several European countries and also for treatment of menorrhagia in most of these countries. We tested this new medical treatment as a final alternative in women who had already chosen hysterectomy. Our data suggest that the levonorgestrel intrauterine system gives good short term results. Two thirds of the patients with the levonorgestrel device cancelled their hysterectomy at the 6 month follow up. Only 14% in the control group cancelled hysterectomy. In addition, half of these women chose the levonorgestrel device as their future treatment.

Improvement in quality of life

The quality of life of women suffering from menorrhagia is impaired in many respects.[17] Excessive bleeding or pain, or both, may impose severe constraints on their professional, social, and family activities. There was no improvement in the menstrual disturbance score in the control group whereas it significantly improved in patients with the levonorgestrel intrauterine system in all aspects evaluated. This happened despite the fact that there was an initial increase in the number of days of spotting from a median of 8 days in the first month to a median of 10 days in the second month. An initial increase in the number of days of spotting for 3-6 months is well known when the levonorgestrel device is used for contraception.[16 18] Our results indicate that the improvement in the quality of life of levonorgestrel intrauterine system users is maintained as these improved scores were also seen at 12 months.

Because of the nature of the device it would be impossible to carry out a blind comparative study between it and other medical treatments. As this was an open study and the subjects were well aware of their treatment a possible placebo effect cannot be excluded. The levonorgestrel system has been on the market in Finland since 1990, and its reputation as regards reduction of menstrual bleeding has spread. The short term results with the current study design are also subject to bias because of the potential disappointment of the control group as regards continuing with their current treatment. This does not seem to have affected the overall conclusions, however, as only another three (11%) of the levonorgestrel users discontinued between 6 and 12 months. One woman reported lower back pain and depression. The other two women reported a poor response to the treatment, and one of the two experienced fibroid growth during the treatment. In long term follow up to a mean of 3 years 48% of the patients treated with the levonorgestrel system were still using it.

Effective conservative alternative

The insertion of a levonorgestrel intrauterine system is a simple procedure. Although it is slightly larger than many other intrauterine systems, insertion is usually easy for most parous women. Surgical methods of treatment for menorrhagia, including endometrial ablation, are effective but invasive operations; need operating theatre facilities; and can be associated with considerable morbidity.

The results of our study suggest an important clinical implication. A woman considering hysterectomy because of menorrhagia or dysmenorrhoea, or both, should be offered the levonorgestrel intrauterine system before she comes to a final decision on hysterectomy. Many menorrhagic women wish to retain their potential fertility. In addition, the levonorgestrel intrauterine system acts as a contraceptive in contrast with prostaglandin synthesis inhibitors and inhibitors of fibrinolysis or procedures used for endometrial ablation. A reduction in the number of annual hysterectomies, even by less than half, would be a considerable achievement. Even greater reductions in rates of hysterectomy could be achieved if medical treatment with intrauterine levonorgestrel could be started at an earlier stage.

Key messages

- Two thirds of women treated for menorrhagia with the levonorgestrel intrauterine system cancelled their decision to undergo hysterectomy
- The median number of days of bleeding decreased in the levonorgestrel group from 7 in the first month to 3 in the sixth month and 2 in the 12th month
- The variation between individual women in the number of days of bleeding and spotting is great in users of the levonorgestrel intrauterine system
- The treatment of menorrhagia with the levonorgestrel intrauterine system improved general well being and work performance and physical, sexual, and leisure time activity
- Treatment of menorrhagia with the levonorgestrel intrauterine system should be considered before hysterectomy is decided on

The levonorgestrel releasing intrauterine systems (Levonova/Mirena) were provided by Leiras Oy, Turku, Finland. Data analysis was also carried out by Leiras Oy. Dr Hannele Savonius is acknowledged for technical help during the study.

Contributors: PL initiated the study and participated in the design of the protocol, data analysis and interpretation and preparing the manuscript. MH contributed to the design of the protocol, supervised the clinical study, and participated in data interpretation and writing the manuscript. JP supervised the clinical study and participated in data interpretation and writing the manuscript. UR and SS participated in the clinical study, data collection, and writing the manuscript. JS participated in data analysis and interpretation, did the analysis of menstrual bleeding, and contributed to writing the paper. CGN contributed to the design of the protocol, the clinical study, and data collection and participated in data interpretation and writing the manuscript. HS participated in the clinical study. PL is guarantor for the study.

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Commentary: Promising results but wider recruitment needed

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Concern over rates of hysterectomy by both professional and lay people alike has resulted in great interest in alternative surgical and medical treatments for dysfunctional uterine bleeding. The late 1980s and early 1990s saw the widespread introduction of hysteroscopic procedures to ablate and resect the endometrium without the need to remove the uterus,[1] and their use has previously been discussed in this journal.[2] These procedures have become well established in medical practice and recent reports have established their effectiveness and safety in day to day practice.[3] Regrettably they have increased rather than reduced the surgical workload with an increase of 10 000 cases in the numbers of operative procedures undertaken in the United Kingdom between 1989 and 1993 for dysfunctional uterine bleeding. Attention has also turned to the effective use of medical treatments but comparison of established and effective treatments with transcervical resection has shown that women find the surgical approach more satisfactory and acceptable and in those requiring retreatment a considerably higher proportion would have further surgery.[4] There is thus a need for effective medical treatments that can compare favourably with the surgical approach to enhance patient choice.

This paper by Lähteenmäki et al looks at the use of the levonorgestrel releasing intrauterine device as a treatment that might provide an effective alternative. Previous work has shown that in excess of 80% of women offered this device while they are awaiting surgery for menorrhagia may be taken off the waiting list,[5] but the present work is, as far as I am aware, the first randomised trial looking at removal from surgical waiting lists as an end point. The study was well designed with an easily identified study population. It was, however, limited to those women awaiting hysterectomy, and thus we are unable to conclude that this may be an attractive alternative (from the patient's point of view) to all surgical approaches. As the threshold for surgical intervention may be lower when minimally invasive techniques are offered and used rather than hysterectomy this is an important deficiency in the current study and will have to be examined in the future. Had women awaiting minimally invasive procedures been included perhaps this study could have reached the numbers identified in the statistical analysis to give the study the required power.

One problem in conducting randomised trials of this nature is that it is difficult if not impossible to blind either subjects or investigators to the treatment used. It is not possible to use an inert intrauterine device as a placebo as they are recognised as being a cause of excessive menstrual loss. Alternative strategies to achieve amenorrhoea in both groups would entail expensive but effective treatments for menorrhagia but then would effectively exclude a true non-intervention control group of women awaiting hysterectomy. Possibly as a consequence of this lack of blinding two women in the control group elected to have a levonorgestrel device inserted. This then begs the question if alternative trial designs might be more appropriate. A recent report has shown that partially randomised patient preference trials may be a useful tool in the assessment of treatments for menorrhagia,[6] particularly when they compare medical versus surgical treaments when blinding would not be possible as in this trial. Another advantage of such an approach in this case might have been more rapid recruitment.

Despite its deficiencies the study by Lähteenmäki et al provides clear data to support the use of the levonorgestrel intrauterine device as an alternative treatment in menorrhagia. Anything that increases patient choice is to be welcomed, but further studies will be required to evaluate the long term clinical effectiveness of this strategy, the cost effectiveness of such an approach, and patient satisfaction. Until these further studies are available we will not be able clearly to evaluate the position of the levonorgestrel device in the treatment of menorrhagia, although these early data suggest that at last we have a potential long term effective alternative to surgery.

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Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study

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Abstract

Objectives: To investigate whether baseline serum cholestanol:cholesterol ratio, which is negatively related to cholesterol synthesis, could predict reduction of coronary events in the Scandinavian simvastatin survival study.
Design: Follow up of patients with coronary heart disease in whom baseline ratios were related to major coronary events.
Setting: Four universities in Finland.
Subjects: A subgroup of 868 patients with coronary heart disease selected from the Scandinavian simvastatin survival study.
Intervention: Treatment with simvastatin or placebo.
Main outcome measures: Serum concentrations of low density lipoprotein and high density lipoprotein cholesterol, total triglyceride concentration, and cholesterol:cholestanol ratio. Major coronary events.
Results: With increasing baseline quarter of cholestanol distribution the reduction in relative risk increased gradually from 0.623 (95% confidence interval 0.395 to 0.982) to 1.166 (0.791 to 1.72). The risk of recurrence of major coronary events increased 2.2-fold ($P < 0.01$) by multiple logistic regression analysis between the lowest and highest quarter of cholestanol. The ratio of cholestanol was related inversely to the body mass index and directly to high density lipoprotein cholesterol and triglyceride concentrations but their quarters of distribution were not related to risk reduction.
Conclusions: Measurement of serum cholestanol concentration revealed a subgroup of patients with coronary heart disease in whom coronary events were not reduced by simvastatin treatment. Thus, patients with high baseline synthesis of cholesterol seem to be responders whereas those with low synthesis of cholesterol are non-responders.

Introduction

The Scandinavian simvastatin survival study (4S) showed that simvastatin clearly decreases serum cholesterol concentration and considerably reduces mortality from all causes and coronary events and major coronary events in patients with coronary heart disease.[1] As the reduction in the relative risk of major coronary events was not associated with the baseline serum lipid concentrations in the survival study,[2] however, we considered that reduction in relative risk may be related to baseline intestinal absorption or to endogenous synthesis of cholesterol. From among the serum non-cholesterol sterols, the cholesterol precursor sterols—that is, lanosterol and other methyl sterols and demethylated cholestenol, desmosterol, and lathosterol—are directly related to cholesterol synthesis,[3–9] especially in the liver,[10] while cholestanol and plant sterols—that is, campesterol and sitosterol—are directly related to cholesterol absorption.[9 11] Accordingly, we would expect quantification of these sterols to reveal subgroups with high or low absorption or synthesis of cholesterol. To this end we examined whether measurement of baseline serum cholestanol concentration in the Finnish coronary subpopulation of the survival study predicts the extent to which simvastatin could reduce the risk of major coronary events.

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Patients and methods

The whole study population of the survival study and the methods used have been reported previously.[1 12] The present study population included the Finnish subgroup of 868 patients with coronary heart disease selected from 1374 candidates for the 4444 participants of the original study and were randomised to placebo (n = 434) or simvastatin 20-40 mg/day (n = 434) for 5 years and 3 months. Distributions of age, sex, and lipid concentrations were similar in the placebo and simvastatin subgroups and were comparable with those in the main study. The secondary end point of the survival study—major coronary events, including coronary deaths, non-fatal myocardial infarctions, and revascularisation procedures—was used for analytical purposes.

Concentrations of total and low and high density lipoprotein cholesterol and triglycerides were analysed at the central laboratory from serum obtained after an overnight fast.[12] Concentrations of cholesterol and non-cholesterol sterol were measured in two saponified baseline serum samples by gas-liquid chromatography on a 50 m long SE-30 capillary column (polydimethylsiloxane), with 5α-cholestane as an internal standard[13 14] by running the samples from a single patient in a single batch from frozen stored serum samples. The non-cholesterol sterols are transported in serum by lipoproteins, about 70% by low density lipoprotein, so that the decrease in concentration of low density lipoprotein cholesterol by simvastatin also changes the serum concentration of cholestanol and other non-cholesterol sterols. We have therefore expressed the values of these sterols in terms of mmol/mol of cholesterol—that is, as ratios to cholesterol. The values given are means of two baseline determinations.

Statistical analysis—The patients were ranked according to quarters of baseline distribution of body mass index (kg/m^2), serum concentrations of total and low density and high density lipoprotein cholesterol, total triglycerides, and cholestanol to cholesterol ratios. We counted major coronary events during the follow up of 5 years 3 months in the quarters of these variables and calculated relative risks (95% confidence intervals) between simvastatin and placebo groups.[15] Analysis of variance was used to compare means of

Table 1 Relative risk of major coronary events by simvastatin in patients defined by baseline quarters of total, low density lipoprotein and high density lipoprotein cholesterol and triglyceride concentrations, body mass index, and cholestanol proportion

	First quarter		Second quarter		Third quarter		Fourth quarter	
Variable	**Value**	**Relative risk (95% CI)**	**Value**	**Relative risk (95% CI)**	**Value**	**Relative risk (95% CI)**	**Value**	**Relative risk (95% CI)**
Cholesterol (mmol/l)	<6.0	0.795 (0.538 to 1.17)	6.0-6.6	0.652 (0.430 to 0.989)	6.7-7.1	0.953 (0.637 to 1.44)	>7.1	0.763 (0.482 to 1.21)
Low density lipoprotein cholesterol (mmol/l)	<4.2	0.683 (0.445 to 1.05)	4.2-4.6	0.823 (0.528 to 1.28)	4.7-5.1	0.704 (0.478 to 1.04)	>5.1	0.926 (0.604 to 1.42)
High density lipoprotein cholesterol (mmol/l)	<1.0	0.856 (0.609 to 1.20)	1.0-1.2	0.639 (0.425 to 0.961)	1.3-1.4	0.859 (0.550 to 1.34)	>1.4	0.738 (0.419 to 1.30)
Triglycerides (mmol/l)	<1.1	0.972 (0.674 to 1.40)	1.1-1.4	0.742 (0.457 to 1.20)	1.5-1.9	0.681 (0.457 to 1.01)	>1.9	0.702 (0.447 to 1.10)
Body mass index (kg/m^2)	<24.2	0.880 (0.589 to 1.32)	24.2-26.4	0.737 (0.485 to 1.12)	26.5-28.4	0.750 (0.493 to 1.14)	>28.4	0.791 (0.523 to 1.20)
Cholestanol (10^2 mmol/mol cholesterol)*	<107	0.623 (0.395 to 0.982)	107-126	0.657 (0.426 to 0.998)	127-148	0.753 (0.502 to 1.130)	>148	1.166 (0.791 to 1.720)

*In the four quarters, No (%) of events was 22 (21), 24 (23), 31 (26), and 38 (35) in simvastatin group and 37 (33), 39 (35), 36 (35), and 32 (30) in placebo group, respectively.

continuous variables in the quarters. Multiple logistic regression analysis was used to test the associations between different prognostic variables and the occurrence of major coronary events. The goodness of fit and consistency with logistic function were evaluated with Hosmer-Lemeshow and C C Brown tests, respectively. The statistical analyses were carried out with BMDP statistical software package.[16]

Results

In the Finnish subgroup the mean changes in lipid concentrations caused by simvastatin—that is, −28, −35, 8, and −15% for total, low density lipoprotein, and high density lipoprotein cholesterol and triglycerides, respectively—were similar to those seen in the main study population.[1]

The reduction in the risk of major coronary events in the whole subgroup studied (144 *v* 114 events in placebo *v* simvastatin group, respectively) was 21% (0.790; 95% confidence interval 0.642 to 0.971). When we analysed gradually increasing body mass index and serum lipid concentrations from the first to the fourth quarter only cholestanol:cholesterol ratio exhibited percentages of recurrent events, gradually increasing from 21% to 35% (values shown only for cholestanol) with the increasing baseline sterol quarters in the simvastatin but not in placebo group (footnote to table 1). The corresponding relative risk increased gradually from 0.623 (0.395 to 0.982) to 1.166 (0.791 to 1.720). Thus, the relative risk of major coronary events was increased by 16.6% (−20.9% to 72.0%) in the highest quarter of the cholestanol ratio and significantly reduced by 37.7% (−60.5% to −1.8%) in the lowest quarter. The concentrations of cholestanol showed inconsistent changes in the relative risk ratios. Age and the concentrations of total and low density lipoprotein cholesterol were similar in all the quarters separated according to the ratios of cholestanol (table 2). The serum concentrations of high density lipoprotein cholesterol increased whereas the serum concentrations of triglycerides and body mass index values decreased. The ratios of cholestanol to cholesterol were negatively related to those of cholesterol precursor sterols (cholestanol, desmosterol, and lathosterol) and strongly positively related to those of plant sterols (campesterol and sitosterol; data not shown).

As in stepwise logistic regression analysis the continuous cholestanol ratio was the only variable of table 1 significantly entered into the model (odds ratio 1.01; 1.00 to 1.02), the association between cholestanol and the occurrence of major coronary events was tested by using a fixed logistic model with three variables: treatment group, cholestanol as an ordinal scale variable based on quarters, and treatment group*cholestanol interaction. In this model both the goodness of fit (Hosmer-Lemeshow test, P value 0.983) and the consistency of logistic function (C C Brown test, P value 1.000) were good. For the treatment group the odds ratio was 3.29 (1.53 to 7.06) and the Wald's test value 3.05 ($P<0.001$). For cholestanol the odds ratio was 1.31 (1.07 to 1.61). The risk of recurrence of major coronary events increased 2.2-fold between the lowest and highest quarters of the distribution of cholestanol ratios by multiple logistic regression analysis ($P<0.01$; Wald's test value 2.63). For the interaction term the odds ratio was 0.73 (0.56 to 0.86) and Wald's test −2.29 ($P<0.02$).

Table 2 Mean (SD) baseline values for different variables defined by quarters of distribution of cholestanol at baseline (<107, 107-126, 127-148, >148)

	First quarter		Second quarter		Third quarter		Fourth quarter	
Variables	**Simvastatin (n=106)**	**Placebo (n=111)**	**Simvastatin (n=106)**	**Placebo (n=111)**	**Simvastatin (n=113)**	**Placebo (n=104)**	**Simvastatin (n=110)**	**Placebo (n=107)**
Age (years)	58.2 (6.9)	58.0 (5.8)	57.3 (6.9)	57.0 (7.4)	58.5 (6.3)	58.0 (6.4)	58.5 (6.4)	58.1 (6.2)
Body mass index (kg/m^2)	28.6 (3.7)	28.0 (3.9)	27.0 (3.5)	26.9 (3.6)	26.1 (2.6)	26.4 (3.1)	25.3 (3.1)*	25.0 (2.8)*
Cholesterol (mmol/l)	6.45 (0.75)	6.67 (0.72)	6.64 (0.71)	6.62 (0.85)	6.60 (0.75)	6.51 (0.75)	6.60 (0.85)	6.65 (0.73)
LDL cholesterol (mmol/l)†	4.50 (0.70)	4.71 (0.66)	4.70 (0.70)	4.70 (0.80)	4.68 (0.73)	4.58 (0.70)	4.68 (0.83)	4.71 (0.74)
HDL cholesterol (mmol/l)	1.18 (0.289	1.15 (0.25)	1.19 (0.31)	1.19 (0.34)	1.25 (0.34)	1.21 (0.32)	1.32 (0.33)*	1.33 (0.33)*
Triglycerides (mmol/l)	1.74 (0.69)	1.81 (0.66)	1.66 (0.63)	1.67 (0.66)	1.48 (0.59)	1.57 (0.64)	1.30 (0.52)*	1.31 (0.60)*
Cholestanol (10^2 mmol/mol cholesterol)‡	91 (13)	92 (12)	117 (6)	116 (6)	136 (6)	135 (6)	171 (19)	172 (26)

LDL=low density lipoprotein; HDL=high density lipoprotein.
*P<0.0001 by analysis of variance.
†Total and LDL cholesterol values differed in first quarter by pairwise comparison but by analysis of variance the two quartile lines were similar.
‡Lowest cholestanol values in fourth quarters were 148 for both groups.

Discussion

Multivariate logistic regression analysis indicated that the baseline lipid concentrations did not contribute to the results shown by the cholestanol ratio. The higher the quarter of the cholestanol ratio the greater was the risk of major coronary events. The risk of recurrence of major coronary events was 2.2-fold between the lowest and highest quarters of cholestanol, a finding not applicable to total, low density lipoprotein, or high density lipoprotein cholesterol. Thus, simvastatin treatment of patients with a low baseline cholestanol ratio predicts a clear reduction in risk of major coronary events, this improvement not being seen in patients with high baseline cholestanol ratio. Similar findings were also observed when the cholestanol ratios were used as continuous or dichotomised variables in statistical analysis. Thus, quantification of baseline cholestanol in patients with coronary heart disease would give important new information to clinicians or practitioners for evaluation of the future success of the statin treatment. The ability to predict the ineffectiveness of the relatively expensive statins in the treatment of coronary patients supports the use of such measurements. Today, automated instrumentation allows comparatively rapid gas liquid chromatographic measurements, each analysis measuring concentrations of cholesterol and several non-cholesterol sterols; the most predictive sterol for evaluation of treatment seems to be cholestanol.

Why resistance to statin treatment?

Why then are the coronary subjects with high cholestanol ratios resistant to reduction in recurrence of major coronary events? Cholestanol itself is hardly atherogenic, even though simvastatin increases the ratios of cholestanol and plant sterols,[17] phytosterolaemia is strongly atherogenic,[18] and high plant sterol concentrations may be atherogenic.[19] The incidence of major coronary events was, however, unrelated to the ratios of cholestanol (or plant sterols) in the placebo group. As already noted, the cholestanol ratios are positively related to absorption and negatively to synthesis of cholesterol,[9 11] measured either by the sterol balance technique or cholesterol precursor sterols in serum.[3–9 20 21] Thus, we suggest that patients with high baseline cholestanol ratios do not respond because of high baseline absorption and low synthesis of cholesterol. Preliminary studies showed lower responses induced by simvastatin in serum cholesterol concentrations of subjects with high rather than low baseline cholestanol ratios.

Suggested treatment

The present findings for the first time relate cholesterol metabolism to statin induced changes in the reduction of the risk of coronary events in secondary prevention. The discovery before treatment of a subgroup of patients who do not respond to statin treatment alone suggests that such patients should be treated by a combination of statin with hypolipidaemic agents increasing cholesterol synthesis—namely, bile acid binding resins or sitostanol ester induced cholesterol malabsorption.[22] The latter combination decreased low density lipoprotein cholesterol further by about 10%[23] and even more when it was combined with statins in patients with high baseline ratios of cholestanol and plant sterols.[24]

Key messages

- Recurrence of major coronary events is reduced by statin treatment in about one third of patients with coronary heart disease, to predict those who will not respond has not been possible from baseline lipid concentrations in the Scandinavian simvastatin survival.
- This study showed that increasing quarters of cholestanol:cholesterol ratio, reflecting decreasing synthesis of cholesterol, were related to recurrence of major coronary events during simvastatin treatment in a Finnish subgroup (n = 868) of the Scandinavian study.
- The subjects with lowest baseline quarters of cholestanol were associated with significantly reduced relative risk of major coronary events, while the risk in the highest quarter was unchanged and 2.2 times higher than in the lowest one.
- Cholestanol:cholesterol ratios were related inversely to the body mass index and directly to high density lipoprotein cholesterol and triglyceride concentrations, but their quarters were unrelated to risk reduction.
- The findings suggest that patients with coronary disease who have high absorption (high basal cholestanol:cholesterol) and low synthesis of cholesterol do not benefit from statin treatment alone and that they can be identified by measuring serum cholestanol concentration before treatment.

The results of this study were presented at the 11th international symposium on atherosclerosis in Paris, 1997. An abstract is published in *Atherosclerosis* 1997;134:48(150). The Finnish 4S investigators were TA Miettinen, H Vanhanen, TE Strandberg, K Hölttä, H Luomanmäki, T Pekuri, A Vuorinen (Helsinki University Hospital); A Pasternack, H Oksa, L Siitonen, R Rimpi (Tampere University Hospital); YA Kesäniemi, M Lilja, T Korhonen, A Rantala, M Rantala, M Savolainen, O Ukkola, L Laine, L Virkkala (Oulu University Hospital); K Pyörälä, S Lehto, A Rantala, H Miettinen, A Salokannel, R Räisänen (Kuopio University Hospital).

Contributors: TAM, the guarantor and a member of the steering committee of the survival study, initiated the research, formulated the hypothesis, monitored the analysis of serum sterols, and wrote the paper. HG participated in formulating the hypothesis, collecting and analysing data, and in writing and editing of the paper. TS participated in the preparation of the paper. SS performed the statistical analyses and participated in the preparation of the paper.

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Risk factors for coronary heart disease and infection with *Helicobacter pylori*: meta-analysis of 18 studies

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Abstract

Objective: To find out if chronic infection with *Helicobacter pylori* is correlated with risk factors for coronary heart disease.

Design: Meta-analysis of 18 epidemiological studies, involving a total of 10 000 patients, that measured serum antibody titres to *H pylori* and risk factors for coronary heart disease. Any study published in any language before 1998 was eligible for inclusion.

Results: Only small absolute differences in body mass index, blood pressure, or haematological risk factors were found between subjects who were seropositive and those who were seronegative. In those who were seropositive body mass index was slightly higher (0.37, SE 0.09) and concentrations of high density lipoprotein cholesterol were slightly lower (0.032 mmol/l, 0.008). None of the other differences were highly significant.

Conclusion: Previous claims of substantial correlations between *H pylori* seropositivity and certain vascular risk factors were largely or wholly due to chance or the preferential publication of positive results, or both.

Introduction

Epidemiological studies have shown that a weakly positive correlation exists between chronic gastric infection with *Helicobacter pylori* and coronary heart disease.[1] If this association is causal then infection with *H pylori* may increase the incidence of coronary heart disease by affecting other vascular risk factors. If there is a non-causal association between *H pylori* infection and coronary heart disease, then this association must be due to confounding factors. It would be useful to know if infection with *H pylori* is correlated with body mass index, blood pressure, or haematological factors such as blood lipids, particularly if these variables might also be correlated with coronary heart disease.

When examined individually, the findings of published reports of the possible correlates of *H pylori* infection seem to have been prone to the effects of chance, or the preferential publication of positive results (publication bias), or both; most studies have had small sample sizes, reported on several different factors, and omitted to perform systematic reviews of the findings of other studies. Systematic reviews of published evidence can increase the amount of data available for analysis; they can also reduce biases that may be introduced through the use of data from small studies that have not been supported by the results of other studies. Such reviews should be less liable to random error and bias than selective emphasis on particular publications would be. We reviewed published studies of the correlations between *H pylori* seropositivity and variables that might be risk factors for coronary heart disease.

Methods

Epidemiological and clinical studies in any language published before 1998 that reported on correlations between serum antibody concentrations of *H pylori* and specific vascular risk factors were identified by searching Medline, relevant reference lists, and gastroenterology and cardiology journals and by discussing studies with the authors of relevant reports. Risk factors examined were systolic blood pressure, diastolic blood pressure, body mass index, plasma viscosity,

white cell count, and concentrations of total cholesterol, high density lipoprotein cholesterol, triglycerides, fibrinogen, blood glucose, and C reactive protein. Combinations of key words used in the computer search included *Helicobacter pylori*, *Campylobacter pylori*, coronary heart disease, vascular disease, and the vascular risk factors described above. The difference between the mean values of the vascular risk factors in seropositive and seronegative subjects and an estimate of the standard error was obtained from the study or from one of the investigators. Two reports of white cell counts[2 3] and one of blood pressure[4] were excluded because they did not report measurements of *H pylori* serum antibody titres. Eighteen eligible studies were identified.[5–22] The following information was abstracted from each study: the number of people who were seropositive and the number who were seronegative, the difference in the value of the relevant risk factor between subjects who were seropositive and those who were seronegative, and the degree to which adjustments had been made for confounding variables. Studies were classed as having adjusted for age and sex only; for age, sex, and some of the risk factors; or for age, sex, some of the risk factors, and markers of social class. Most of the studies adjusted for more than just age and sex.

In general, studies reported on several vascular risk factors; results are presented for those characteristics that were, in the aggregate, studied in more than 500 subjects. The results from different studies were combined by calculating inverse variance weighted averages of the differences within each study. The variance of a comparison between individuals who were seropositive (n_1) and those who were seronegative (n_2) was calculated by multiplying $1/n_1 + 1/n_2$ by the square of the standard deviation of the relevant variable in the largest study that assessed that variable; for many of the variables this was the study of 2000 people by Murray et al.[10] χ^2 was used to test for heterogeneity.

Results

The numbers available for analysis varied from 600 (for C reactive protein) to 10 000 (for total cholesterol). Overall there were only small absolute differences between subjects who were seropositive and those who were not (table). Most of these differences were not significant. There were differences in plasma viscosity, blood glucose concentrations, body mass index, and concentrations of high density lipoprotein cholesterol. In those who were seropositive the body mass index kg/m^2 was slightly higher (0.37, SE 0.09) and concentrations of high density lipoproteins were slightly lower (0.032 mmol/l, 0.008); these were the only differences that were highly significant ($P < 0.0001$).

There was some evidence of heterogeneity between the six studies that measured white cell counts[5 12 13 18 19 21] ($\chi^2 = 18.3$, df = 5, $P < 0.01$), between the 13 studies in 10 reports that included measurements of diastolic blood pressure[6 7 9 10 12–16 20] ($\chi^2 = 25.3$, df = 12, $P = 0.01$), and between the 11 studies in 10 reports measuring fibrinogen concentrations [5 7 10 13–19] ($\chi^2 = 19.6$, df = 10, $P = 0.04$). There were no strong correlations overall between these three factors and *H pylori* seropositivity. Most of the heterogeneity was between studies that had first proposed the associations and larger subsequent studies that had failed to confirm the associations.

Correlation between seropositivity for *Helicobacter pylori* infection and various vascular risk factors in published studies of at least 500 people

Characteristic	No seropositive	No seronegative	Average (SE) difference between groups†	Z ratio‡
Total cholesterol (mmol/l)[5-16]	5106	5274	0.04 (0.02)	1.5
Systolic blood pressure (mm Hg)[6 7 9 10 12-16 20]	4502	4795	0.9 (0.4)	2.1*
Diastolic blood pressure (mm Hg)[6 7 9 10 12-16 20]	4502	4795	0.3 (0.3)	1.2
Body mass index (kg/m^2)[6-8 10 12-16 20]	4459	4739	0.37 (0.09)	4.2****
High density lipoprotein cholesterol (mmol/l)[5 6 8-12 15]	4109	4316	–0.032 (0.008)	4.3****
Triglyceride (mmol/l)[5-7 9 11-13 15 16]	3431	3851	0.02 (0.04)	0.6
Fibrinogen (g/l)[5 7 10 13-19]	2986	2228	–0.02 (0.03)	1.0
Plasma viscosity (mPa.s)[10 18]	1270	942	0.01 (0.004)	2.2*
White cell count (10^9/l)[5 12 13 18 19 21]	664	512	0.16 (0.11)	1.4
Blood glucose (mmol/l)[5 9 12]	570	492	0.14 (0.06)	2.4*
C reactive protein (mg/l)[19 22]	311	292	–0.2 (0.5)	0.4

†Inverse variance weighted average of differences within study (mean in seropositive group minus mean in seronegative group).
‡Ratio of average of differences to SE.
*P<0.05; ****P<0.0001.

Discussion

There have been several claims of strong and significant correlations between chronic *H pylori* infection and various possible vascular risk factors, such as fibrinogen concentration,[5 17] white cell count,[5] blood pressure,[23] body mass index,[23] blood lipid concentrations,[11] low alcohol consumption,[24] or concentrations of C reactive protein[22] (which, like the white cell count, may just be a non-specific marker of systemic inflammation). Our review of the published evidence provides results that are more reliable than any individual report. We found no significant correlations between infection with *H pylori* and blood pressure, white cell count, or concentrations of total cholesterol, fibrinogen, triglycerides, or C reactive protein. The differences in body mass index and high density lipoprotein cholesterol are both highly significant but, since the absolute differences between subjects who were seropositive and those who were seronegative are small and may have been exaggerated by publication bias, these variables are unlikely to be of much relevance to any association between infection with *H pylori* and coronary heart disease. The increases in plasma viscosity and blood glucose are only marginally significant; they may be largely or wholly due to chance or publication bias. More importantly, even if they are real, the absolute differences are too small to have a substantial effect on any epidemiological association between chronic infection and coronary heart disease.

Systematic reviews limit spurious associations that may arise from small sample sizes, multiple statistical comparisons, and a selective emphasis on extreme findings in particular studies. Despite our inclusion of studies reported as letters and as abstracts, and of data previously unavailable from published reports, some publication bias may remain; this reinforces our conclusion that correlations found in other studies

Key messages

- Epidemiological studies suggest that there is a weakly positive association between coronary heart disease and chronic infection with *Helicobacter pylori*
- A number of reports have also claimed that there are strong correlations between infection with *H pylori* and an increase in vascular risk factors, such as plasma fibrinogen concentrations
- Meta-analysis of 18 studies that involved 10 000 people found no strong correlations between *H pylori* seropositivity and vascular risk factors; previous findings of the existence of such correlations in small studies were largely or wholly due to chance or to the preferential publication of positive results

between *H pylori* seropositivity and these vascular risk factors are largely due to chance, or selective publication, or both. The clinical implication is that if there is any relation between chronic *H pylori* infection and coronary heart disease,[1] then it is not likely to be dependent on the risk factors described here.

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Contributors: JD initiated and performed the study, drafted the manuscript, and is guarantor for the study. RP helped interpret the data and draft the manuscript.

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Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study

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The influence of growth hormone on mortality in adults is well known in conditions such as growth hormone deficiency and acromegaly.[1 2] In both diseases the excess mortality is principally from cardiovascular disorders, but the occurrence of malignant disorders has also been reported in acromegaly.[2] To our knowledge the long term effect of physiological growth hormone on mortality in healthy adults has not been reported.

Subjects, methods and results

We studied 864 policemen aged 48 to 52 years who did not have cardiovascular disease, diabetes, or glucose intolerance and who had complete data in the Paris prospective study.[3] They were examined between 1967 and 1973 then followed for mortality until January 1989. The body mass index (weight(kg)/(height(m)^2)), ratio of iliac to thigh circumference (a marker of central fat distribution), heart rate, and both diastolic and systolic blood pressures were measured and smoking habits determined. Blood samples were taken at fasting to measure cholesterol and triglyceride concentrations and mean corpuscular volume, and both at fasting and 2 hours after a 75 g oral glucose tolerance test for concentrations of non-esterified fatty acids, glucose, insulin, and growth hormone with a technique described previously.[4]

Hazard ratios (95% confidence intervals) in Paris prospective study cohort (864 men, 48-52 years, 18 year follow up) of factors predictive of death from all causes, from cardiovascular disorders and from malignant disorders from a multivariate Cox model analysis. Variables are presented in order of entry into model using a forward method after adjustment for age

Factors in order of entry into model	Hazard ratios	P value
All causes		
Systolic blood pressure (mm Hg)	1.02 (1.01 to 1.02)	<0.0001
Smoking (cigarettes/day)	1.04 (1.03 to 1.06)	<0.0001
Fasting fatty acids (mg/l)*	2.45 (1.61 to 3.72)	<0.0001
2 hour growth hormone (μg/l)‡	2.54 (1.51 to 4.27)	0.002
Mean corpuscular volume (fl)†:		
Mean *v* mean+SD	1.21 (0.97 to 1.51)	0.07
Mean *v* mean–SD	0.95 (0.76 to 1.18)	
Fasting growth hormone (μg/l)‡	1.50 (1.12 to 2.02)	0.009
Cardiovascular disorders		
Diastolic blood pressure (mm Hg)	1.04 (1.02 to 1.05)	<0.0001
Mean corpuscular volume (fl)	1.06 (1.01 to 1.12)	0.02
Fasting growth hormone (μg/l)‡	1.79 (1.00 to 3.18)	0.05
Smoking (cigarettes/day)	1.03 (1.00 to 1.06)	0.06
Malignant disorders		
Smoking (cigarettes/day)	1.06 (1.04 to 1.08)	<0.0001
Fasting fatty acids (mg/l)*	2.88 (1.49 to 5.57)	0.002
Mean corpuscular volume (fl)	1.06 (1.01 to 1.10)	0.01
2 hour growth hormone (μg/l)‡	2.59 (1.17 to 5.73)	0.04

P values and hazard ratios are adjusted for variables already in the model.
*Log_{10} transformed.
†Non-linear relation (quadratic), hazard ratio, and P value were calculated for mean (98.7 fl) *v* mean+SD (98.7+5.7=104.4 fl) and for mean *v* mean–SD (93.0 fl).
‡Above *v* below the median at 0 hour (0.5 μg/l) and the 95th centile at 2 hours (1.1 μg/l).

We excluded from this analysis the three men for whom acromegaly was likely, using the criteria of fasting growth hormone concentration >10 μg/l and 2 hour growth hormone concentration >5 μg/l.

We studied deaths from all causes, from cardiovascular disorders, and from cancer. During the 18 years of follow up, 171 men died (64 deaths were due to malignant disorders, 49 to cardiovascular diseases).

Kaplan-Meier survival curves were estimated according to four classes of growth hormone (the limits corresponding to the limit of detection, the median, and the 95th centile) and compared by the Mantel-Cox test. The survival curves showed a significant difference for growth hormone concentration at 2 hours ($P=0.03$) and a trend at fasting ($P=0.11$), with a higher mortality above (*v* below) the median of 0.5 μg/l at fasting ($P=0.02$) and a higher mortality above (*v* below) the 95th centile of 1.1 μg/l at 2 hours ($P=0.004$). Growth hormone concentrations were therefore analysed in two classes, chosen after this exploratory data analysis.

Cox proportional hazards models were used to estimate hazard ratios for risk factors for death, after adjustment for age. Variables significant in univariate models were entered into stepwise multivariate analyses. The table shows the hazards ratios of factors that predict death from all causes, from cardiovascular disorders, and from malignant disorders.

Comment

The original finding of this 18 year prospective study is the independent predictive power of higher concentrations of fasting and 2 hour growth hormone for mortality.

We used an old fashioned technique to measure growth hormone concentration, which was the reference at that time.[4] A lack of assay precision would, however, have increased the variation of growth hormone within individuals, and the association between growth hormone concentration and mortality should be reduced and underestimated, not enhanced.

We could have excluded the 25 men (3%) who had a 2 hour growth hormone concentration >2 μg/l, another level accepted for the diagnosis of acromegaly; the trend remained unchanged for fasting growth hormone concentration when they were excluded.

Four other independent risk factors were associated with early mortality, in agreement with a previous analysis of the complete cohort.[3] For death from cardiovascular causes, fasting growth hormone—along with the two classic risk factors (arterial blood pressure and cigarette smoking)—seemed to be a risk factor. Indeed, a direct and causal relation between growth hormone and cardiovascular growth and function has previously been suggested.[2 5] We found a significant relation for 2 hour growth hormone concentrations with death from cancer. Growth hormone is also known to play a role in cancer.[2]

Since growth hormone treatment is being extended, these disturbing results merit an exploration in other studies of healthy populations.

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Endpiece

A problem often confronting editors

He draweth out the thread of his verbosity finer than the staple of his argument.

Shakespeare, *Love's Labours Lost*, V.i