

Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study

S Collins, M G Law, A Fletcher, A Boyd, J Kaldor, C L Masters

Summary

Background Apart from the small number of iatrogenic and familial cases, the cause of most cases of Creutzfeldt-Jakob disease (CJD) is not known. We aimed to identify risk factors for sporadic CJD.

Methods In a case-control study, we compared the medical history and selected demographic characteristics of 241 definite (neuropathologically confirmed) and probable (clinically likely) patients with CJD, ascertained from the Australian National Creutzfeldt-Jakob Disease Registry between Jan 1, 1970, and October 31, 1997, and of 784 controls, recruited from the community by random telephone interview in August, 1997. Standard logistic regression was used for the comparisons.

Findings Surgical procedures were significantly associated with the development of sporadic CJD. This risk progressively increased with the number of surgical treatments to a maximum for three procedures (odds ratio 2.13 [95% CI 1.34–3.41], $p=0.002$). There was also a significant association between risk of CJD and residence or employment on a farm ($p<0.001$) or market garden ($p=0.002$) for longer than 10 years. We found no significant risk associated with a history of blood transfusion, organ transplantation, major dental work, or occupation.

Interpretation Our findings accord with the hypothesis that a range of surgical treatments may serve as unrecognised contamination events and account for a proportion of cases of sporadic CJD. Possible biases in different methods and times for the acquisition of data on cases and controls suggest our findings need to be replicated in independent studies with community controls.

Lancet 1999; **353**: 693–97

Australian National Creutzfeldt-Jakob Disease Registry, Department of Pathology, The University of Melbourne, Parkville, Victoria, 3052 Australia (S Collins FRACP, A Fletcher BSc, A Boyd RN, Prof C L Masters FRCPA); and The National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, St Vincent's Hospital Medical Centre, Sydney, NSW (M G Law MSc, Prof J Kaldor PhD)

Correspondence to: Dr S Collins
(e-mail: s.collins@pathology.unimelb.edu.au)

Introduction

By contrast with iatrogenic and familial cases of Creutzfeldt-Jakob disease (CJD), the aetiology of the most common form, sporadic CJD, which constitutes 85–90% of all cases,^{1,2} is unknown. One hypothesis is that sporadic disease is caused by a rare (one in a million) spontaneous somatic mutation within the cerebral neuronal pool of the prion protein (PrP).³ An alternative is low-level contamination events.⁴ The excess of homozygosity at codon 129 in iatrogenic disease⁵ has also been found in sporadic CJD, and may increase the chance of normal PrP (PrP^C) converting to the abnormal, disease-associated isoform (PrP^{Sc}) when the normal and abnormal conformers interact, as could occur after a contamination event.

Previous case-control studies have investigated possible causes or risk factors for sporadic CJD, without identifying any consistent or major influences.^{7–14} In our case-control study of risk factors for sporadic CJD, we used the Australian National Creutzfeldt-Jakob Disease Registry to ascertain cases. Controls were recruited from the general community by random telephone survey, unlike most previous studies that used hospital-based controls.^{9–14}

Methods

Cases

The Australian National Creutzfeldt-Jakob Disease Registry¹⁵ collected cases retrospectively to Jan 1, 1970, and prospectively from Oct 1, 1993. 241 patients with sporadic CJD (122 men, mean age 63.1 years, 119 women, mean age 66.6 years; combined age range 25–84 years) represented all Australian cases of sporadic CJD that occurred up to Oct 31, 1997. The diagnostic subclassifications of this cohort were 151 definite (neuropathologically confirmed) and 90 probable (clinically likely) cases of CJD, according to previously published criteria.¹ For probable cases, clinical investigation excluded the possibility of an alternative explanation and triphasic periodic complexes on the electroencephalogram, the presence of 14-3-3 protein in the cerebrospinal fluid, or both were usually present. In all cases, a history of potential iatrogenic transmission in the form of dura mater and corneal grafts or exposure to human cadaveric pituitary hormones was sought and excluded.

The ascertainment methods were approved by an Ethics Committee of the University of Melbourne. The main sources of case reporting provided about 91% of the total cases and were: neurologists (32%) and neuropathologists (20%); death certificates (25%); searches of separation codes at university-affiliated hospitals with ICD-9 CM 046.1 (specific for CJD) and 290.1 (for presenile dementia), or the equivalent codes from earlier versions of the International Classification of Diseases when appropriate (12%); and similar systematic reviews of the Health Information Morbidity Data for each

	Cases (n=241)	Controls (n=784)	Odds ratio (95% CI)	p
Country of birth				
Australia	155	598	1.0	
UK	32	86	1.44 (0.92–2.23)	0.109
Other European	36	48	2.89 (1.81–4.62)	<0.001
Asia	3	19	0.61 (0.18–2.08)	0.430
Other	6	33	0.70 (0.29–1.70)	0.434
Not known	9	0	—	
Any surgery				
No	38	233	1.0	
Yes	153	550	1.71 (1.16–2.51)	0.007
Not known	50	1	—	
Any dialysis, chemotherapy, radiotherapy, or arterial embolisation				
No	171	758	1.0	
Yes	4	24	0.69 (0.23–2.01)	0.494
Not known	66	2	—	
Ever lived or worked on a farm or market garden or employed in an abattoir or as a butcher				
No	77	523	1.0	
Yes	94	261	2.61 (1.84–3.71)	<0.001
Not known	70	0	—	
Blood transfusion				
No	118	616	1.0	
Yes	27	158	0.89 (0.57–1.40)	0.621
Not known	96	10	—	
Relative with dementia				
No	156	632	1.0	
Yes	7	148	0.20 (0.09–0.43)	<0.001
Not known	78	4	—	
Close personal contact with non-relative with dementia				
No	133	695	1.0	
Yes	26	85	1.60 (0.99–2.59)	0.055
Not known	82	4	—	
Major dental work				
No	89	403	1.0	
Yes	62	375	0.75 (0.53–1.07)	0.115
Not known	90	6	—	
Transplant recipient				
No	165	780	1.0	
Yes	2	3	2.67 (0.44–16.3)	0.288
Not known	74	1	—	
Travel abroad >1 month*				
No	48	406	1.0	
Yes	29	377	0.70 (0.43–1.15)	0.157
Not known	36	1	—	
Lived in UK >1 month in 1980s*				
No	97	718	1.0	
Yes	4	65	0.46 (0.16–1.30)	0.132
Not known	12	1	—	

All factors adjusted for age, sex, and urban or rural residence. *Cases (n=113) since 1990 only.

Table 1: **Risk of CJD by medical and demographic variables**

State and Territory (2%). The medical histories of all cases, detected through the death certificate and hospital separation coding, were reviewed and validated on-site by a field researcher. Registry staff compiled a medical and demographic profile of each case of sporadic CJD with a standard comprehensive questionnaire (72% of cases) that was completed by the spouse or a first-degree relative (92%) and occasionally in consultation with the patient's general practitioner. Questionnaires were routinely posted to the appropriate relative or spouse for completion at his or her leisure, without time constraints; a few case questionnaires were completed by telephone interview.

The retrospective retrieval of information was more difficult the longer the time since death; the datasets least likely to be complete were for cases from the 1970s.

Controls

Controls were recruited and interviewed through a random dialling telephone survey. All interviews were in English and took place over 3 days at the end of August, 1997. We developed an abridged questionnaire for controls to find out:

	Cases (n=241)	Controls (n=784)	Odds ratio (95% CI)	p
Total number of surgical procedures				
0	38	233	1.0	
1	55	241	1.36 (0.86–2.14)	0.185
2	43	154	1.67 (1.03–2.71)	0.037
≥3	55	155	2.13 (1.34–3.41)	0.002
Not known	50	1	—	
Type of surgery				
No surgery	38	233	1.0	
Skin lesions	27	141	1.17 (0.69–2.01)	0.557
Appendix	25	115	1.33 (0.77–2.31)	0.307
Tonsils	9	93	0.59 (0.28–1.28)	0.181
Heart	11	19	3.55 (1.57–8.04)	0.002
Hip/knee	5	41	0.75 (0.28–2.01)	0.565
Hysterectomy	28	58	2.96 (1.68–5.21)	<0.001
Thyroid	4	9	2.73 (0.80–9.29)	0.109
Haemorrhoids	8	11	4.46 (1.69–11.8)	0.003
Gall bladder	18	51	2.16 (1.14–4.09)	0.018
Hernia	18	46	2.40 (1.26–4.57)	0.008
Cataract/eye	24	24	6.13 (3.16–11.9)	<0.001
Ear	3	5	3.68 (0.84–16.0)	0.083
Varicose veins	10	15	4.09 (1.71–9.76)	0.002
Carpal tunnel	6	4	9.20 (2.48–34.1)	0.001
Prostate	4	16	1.53 (0.49–4.83)	0.466
Other	89	203	2.69 (1.76–4.11)	<0.001

Factors adjusted for age, sex, urban or rural residence, except reasons for surgery or treatment.

Table 2: **Risk of CJD by surgical procedures**

surgical procedures; specific selected non-surgical hospital treatments (controls were asked about dialysis, chemotherapy, radiotherapy, and arterial embolisation); temporally separate episodes of blood transfusion; recipient of organ transplantation; major dental work (beyond fillings and dental hygiene); travel outside Australia for longer than 1 month (including specifically to the UK); residence or employment on a farm (of any type including a market garden); work in an abattoir or as a butcher; relative with dementia; and close personal contact with a person with dementia who was not a relative. This abridged questionnaire was specifically based on that used for cases, with the retained questions selected because of their a priori relevance to transmission of CJD. However, telephone interviews necessitate more direct questions, and the responses captured, if possible, through a restricted series of options rather than through an open-ended approach.

We intended to interview 750 controls (about three for each case of CJD), matched to the cases by age (in 5-year age groups), sex, and urban or rural residence (as defined by the Australian Bureau of Statistics¹⁶) and in proportion to the resident population of each State and Territory. Listed telephone numbers were called randomly and on answer we asked for the oldest man in the household to give his verbal consent to the interview. If the relevant male age stratum was already completed, or if no man was available in the household, the oldest woman was asked to give her consent. In each case, we sought the oldest person in the household because of the age distribution of CJD cases.⁵ A person in an incomplete age and sex stratum who gave his or her consent was directly questioned. We did not seek independent corroboration of the volunteered information, nor verify data provided by respondents from independent sources such as general practitioners.

Statistical analysis

Cases and controls were compared by standard logistic regression techniques. All analyses were adjusted for age, sex, and urban or rural residence. Because of the incompleteness of datasets in the cases from the 1970s, we did statistical analyses for the 128 sporadic CJD cases that occurred after 1987, and all 241 cases from 1970. In view of the similar results, we mostly present findings for the entire group. However, analyses of travel abroad and residence in the UK in the 1980s were based on cases of CJD diagnosed after 1989.

	Cases (n=241)	Controls (n=784)	Odds ratio (95% CI)	p
Residence or employment				
Farm	73	205	2.59 (1.78-3.76)	<0.001
Market garden	10	21	3.43 (1.54-7.64)	0.002
Abattoir	6	23	1.87 (0.73-4.80)	0.198
Butcher	5	9	3.97 (1.28-12.3)	0.017
Not known	0	8	—	
Duration (years) lived or worked on farm or market garden				
None	77	523	1.0	
<10	12	64	1.33 (0.68-2.59)	0.404
10-19	17	46	2.71 (1.47-5.02)	0.001
≥20	24	65	2.78 (1.60-4.81)	<0.001
Not known	20	30	—	

All factors adjusted for age, sex, and urban or rural residence.

Table 3: **Risk of CJD by residence and occupation**

Results

784 controls completed the telephone interview. 12 387 telephone calls were made, 2577 (21%) of which were number unobtainable, engaged, or no reply, and in 22 (0.2%) calls an appointment was made to ring back. In 1308 (11%) of the calls, permission for the interview was refused, and in 7349 (60%), the relevant age, sex, and urban or rural residence quota was full. Of the 1131 calls in which interviews began, 347 calls were halted—the respondent did not want to continue in 63 (6%), there were language or hearing difficulties in 158 (14%), or for other reasons in 126 (11%) calls. In 784 (69%) calls the interviews were completed.

Controls and cases were well matched for age, sex, State or Territory of residence, and urban or rural residence (data not shown). However, there was some deficit of controls from non-English speaking European countries, probably because our interviews were conducted in English.

Table 1 shows each medical and demographic variable by risk of CJD. Of the variables analysed, surgical procedures were the factor most significantly associated with risk of CJD (table 2). The risk of CJD progressively increased with the number of surgical procedures. Mean time from first surgery to death was 29 (SD=17.4) years. Assessment of separate surgical procedures indicated that the risk of CJD increased over a range of operations and was not associated with a specific anatomical site or complexity. There was no association between the risk of CJD and non-surgical hospital treatments (dialysis, chemotherapy, radiotherapy, and arterial embolisation).

Residence or employment on a farm or market garden (presence of livestock not specified), was associated with a risk for CJD, which increased with longer duration of residence or employment (table 3).

Blood transfusion was not associated with subsequent risk of developing CJD, irrespective of the total number of infusion episodes, reason for transfusion, or date of the first procedure (table 4). Other non-predisposing factors are shown in table 1 and include: major dental work; organ transplantation; close physical contact with an unrelated person with dementia and travel to the UK in the 1980s. A relative with dementia was associated with a decreased risk of CJD (table 1).

Discussion

In this case-control study, we found a range of surgical treatments were associated with an increased risk of sporadic CJD. Two previous case-control studies, also with community controls, found the risk of CJD was

	Cases (n=241)	Controls (n=784)	Odds ratio (95% CI)	p
Number of transfusions				
0	118	616	1.0	
1	20	105	0.94 (0.56-1.58)	0.804
2	4	28	0.70 (0.24-2.03)	0.506
≥3	3	25	0.58 (0.17-1.96)	0.382
Not known	96	10	—	
Reason for transfusion				
No transfusion	118	616	1.0	
Accident	0	14	—	
Illness	1	20	0.26 (0.03-1.96)	0.192
Operation	17	109	0.81 (0.47-1.41)	0.462
Childbirth	2	15	0.70 (0.16-3.08)	0.633
Not specified	9	19	—	
Year of first transfusion				
No transfusion	118	616	1.0	
1979	11	70	0.80 (0.41-1.56)	0.510
>1980	13	74	0.81 (0.43-1.52)	0.510
Not known	3	14	—	

All factors adjusted for age, sex, and urban or rural residence.

Table 4: **Risk of CJD by blood transfusion**

associated with hospital-related therapy,^{8,9} but this significance was lost when the data were pooled as part of a meta-analysis.¹³ The absence of this finding in a third study¹² may reflect methodological differences, since the controls were selected only from hospital populations and not from the community. One possibility is that our finding of an association between surgery and increased risk of CJD may be due to the more complete ascertainment of surgical histories in cases than controls as a result of different data-acquisition methods. The design of this study differs fundamentally from all previous case-control series.⁷⁻¹⁴

In accord with the report by Kondo and Kuroiwa,⁸ we found that increased risk of CJD was significantly associated with various surgical procedures, but there was no consensus with regard to anatomical site, complexity, or postoperative length of stay in hospital. We also assessed progressive risk of CJD from multiple operations and found it to be cumulative, independent of the type of surgery. The mean of 29 years between first surgery and eventual death from CJD differs from the results of Kondo and Kuroiwa⁸ who reported a significant association for operations performed within 5 years of symptom onset. The explanation for this difference is unknown, but our results fall within the range of reported incubation periods for iatrogenic transmission events.¹⁷ The exception in our study was surgery involving tissue transplants, which may reflect the high level of precaution and screening in relation to graft donors. There were, however, few transplants performed among the study population.

Davanipour and colleagues⁹ also reported a positive association, although the discerned surgical risk was less pervasive. The only significant associations were for procedures involving the head, face, and neck. However, hospital controls constituted about half of those recruited, and selection bias may have contributed to these more restricted findings. The possibility of similar recruitment bias was also acknowledged in the largest case-control study by van Duijn and colleagues¹⁴ who did not find that risk of CJD was related to medical history, including the limited range of surgical procedures assessed. However, after they excluded neurological inpatient controls, the previous inverse relation for surgery of the vertebral column and other invasive investigations was lost, which lends support to

concerns about the selection of controls.¹⁴ Differences in study design may contribute to the conflicting findings of this and previous case-control studies, particularly with regard to risk of CJD and surgical treatments.

Given the absence of any form of transmissible spongiform encephalopathy in Australian domesticated livestock,¹⁸ the apparent association between risk of CJD and long-term agricultural residence and work is difficult to reconcile. However, the increasing risk associated with longer duration of residence or employment does lend some support to this result. Nevertheless, this finding contrasts with the more understandable absence of clear-cut risk seen for domestic butchers and abattoir workers, and the generally negative findings for various agricultural exposures, assessed by van Duijn and colleagues¹⁴ in Europe. Our finding may stem from matching ages of controls at interview (in 1997) with ages of cases at death (1970–97). Any trends over this period toward fewer Australians living and working on farms could create an association with the risk of CJD. However, our analysis restricted to cases since 1987 gave similar results (if anything larger odds ratios). Furthermore, the persistence of increased risk of CJD in market gardeners, among whom exposure to commercial farm animals would seem to be kept to a minimum, indicates that more generic explanations may account for the increased risk with farm domicile and employment, as Cousens and co-workers¹⁹ suggested for the increased rates for CJD in dairy farmers from countries with negligible endemic bovine spongiform encephalopathy. Given the potential for specious associations when many risk factors are analysed, circumspection is required when dealing with implausible or non-intuitive findings.

Despite anecdotal claims to the contrary,²⁰ the absence of detectable increased risk of CJD from blood transfusion accords with previous case-control studies.^{8,9,12–14} This lack of association was maintained despite a detailed analysis that included total number of transfusion episodes, reason for the resuscitation, and date of the first infusion. Other pertinent findings were the lack of association with major dental work and contact with people with dementia. Although there was no association between risk of CJD and travel to the UK in the 1980s, there were probably too few cases to assess this risk reliably. However, to date, cases of variant CJD have not been detected in Australia.¹⁸

The apparent “protective” effect of a family history of dementia conflicts with previous findings.^{12–14} This apparent effect probably arises from our careful exclusion of cases with any familial forms of CJD. Since classification of familial CJD is based largely on family history, the exclusion of all familial cases could have also removed some cases with a relative with some other form of dementia; the control population was not selected on this basis.

The retrospective nature of information retrieval for most of the cases led to predictable limitations of data completeness, which generally, but not exclusively, increased with the length of time since the patient's death. However, our analysis of cases after 1987, and separately of all patients, did not qualitatively affect the findings, which suggests any lack of information probably arose unsystematically. The possibility of recall bias by surrogate respondents (spouses and close relatives) who completed the medical demographic

questionnaires relating to patients is unavoidable.

Other possible biases may have resulted from the way we selected and interviewed controls, as suggested by the deficiency of non-English speaking Europeans in the controls. Since controls were selected from listed telephone numbers, they may not represent an entirely random sample of the Australian population. Controls were interviewed in person which raises the possibility of different recall bias compared with cases for whom a surrogate supplied information. A similar study¹⁴ discounted methodological discrepancies in interviewees for control data, but did not assess the potential for systematic bias relevant to our study since we used different data acquisition methods. Another potential bias is that data were ascertained in August, 1997, for controls and from 1970 to 1997 for cases, so any time trends over this period could bias results. Although the concordance of our results with previous studies in terms of absence of risk from blood transfusion^{8,12–14} and dental work^{8,10–14} suggest that large or pervasive biases were not introduced, our results need to be replicated in independent studies with community-based controls.

We believe our findings should reinforce the heightened vigilance about infection control at all levels of care in hospital settings, particularly given the emergence of the probable zoonotic forms of variant CJD.

Contributors

S Collins and A Boyd reviewed all cases. A Fletcher managed all data entry and manipulation. Statistical analyses were done by M Law and J Kaldor. The project design, including development of the control questionnaire, was done by S Collins, M Law, J Kaldor, and C Mastos.

Acknowledgments

This study was partly funded by grants from the Australian Commonwealth Department of Health and Family Services. We thank the referring physicians and ethics committees of tertiary hospitals for their cooperation.

References

- 1 Masters C, Harris J, Gajdusek D, Gibbs C, Bernoulli C, Asher D. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Ann Neurol* 1979; **5**: 177–88.
- 2 Brown P, Gibbs C, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Ann Neurol* 1994; **35**: 513–29.
- 3 Prusiner SB. Prion diseases and the BSE crisis. *Science* 1997; **278**: 245–51.
- 4 Bruce ME, Will RG, Ironside JW, et al. Transmissions to mice indicate that ‘new variant’ CJD is caused by the BSE agent. *Nature* 1997; **389**: 498–501.
- 5 Collinge J, Palmer M, Dryden A. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* 1991; **337**: 1441–42.
- 6 Palmer M, Dryden A, Hughes J, Collinge J. Homozygous prion protein genotype predisposes to sporadic Creutzfeldt-Jakob disease. *Nature* 1991; **352**: 340–42.
- 7 Bobowick A, Brody J, Matthews M, Ross R, Gajdusek D. Creutzfeldt-Jakob disease: a case-control study. *Am J Epidemiol* 1973; **98**: 381–94.
- 8 Kondo K, Kuroiwa Y. A case control study of Creutzfeldt-Jakob disease: association with physical injuries. *Ann Neurol* 1982; **11**: 377–81.
- 9 Davanipour Z, Alter M, Sobel E, Asher D, Gajdusek D. Creutzfeldt-Jakob disease: possible medical risk factors. *Neurology* 1985; **35**: 1483–86.
- 10 Davanipour Z, Alter M, Sobel E, Asher D, Gajdusek D. A case-control study of Creutzfeldt-Jakob disease: dietary risk factors. *Am J Epidemiol* 1985; **122**: 443–51.
- 11 Davanipour Z, Alter M, Sobel E, Asher D, Gajdusek D. Transmissible virus dementia: evaluation of a zoonotic hypothesis. *Neuroepidemiology* 1986; **5**: 194–206.
- 12 Harries-Jones R, Knight R, Will R, Cousens S, Smith P, Matthews W. Creutzfeldt-Jakob disease in England and Wales, 1980–1984: a case-control study of potential risk factors. *J Neurol Neurosurg Psychiatry* 1988; **51**: 113–19.

- 13 Wientjens D, Davanipour Z, Hofman A, et al. Risk factors for Creutzfeldt-Jakob disease: a reanalysis of case-control studies. *Neurology* 1996; **46**: 1287-91.
- 14 van Duijn C, Delasnerie-Lauprêtre N, Masullo C, et al. Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. *Lancet* 1998; **351**: 1081-85.
- 15 Collins S, Fletcher A, De Luise T, Boyd A, Masters C. Creutzfeldt-Jakob disease in Australia. In: Court L, Dodet B, eds. Transmissible subacute spongiform encephalopathies: prion diseases. Paris: Elsevier, 1996: 405-15.
- 16 Australian Bureau of Statistics. Statistical geography, vol 1. Canberra: Australian Government Printing Services, 1996: ABS catalogue no 1216.
- 17 Brown P, Preece M, Will R. "Friendly fire" in medicine: hormones, homografts, and Creutzfeldt-Jakob disease. *Lancet* 1992; **340**: 24-27.
- 18 Collins S, Masters C. Iatrogenic and zoonotic Creutzfeldt-Jakob disease: the Australian perspective. *Med J Aust* 1996; **164**: 598-602.
- 19 Cousens S, Zeidler M, Esmonde T, et al. Sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of epidemiological surveillance data for 1970-96. *BMJ* 1997; **315**: 389-95.
- 20 Klein R, Dumble L. Transmission of Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 1993; **341**: 768.
- 21 Defebvre L, Destée A, Caron J, Ruchoux M, Wurtz A, Remy J. Creutzfeldt-Jakob disease after an embolization of intercostal arteries with cadaveric dura mater suggesting a systemic transmission of the prion agent. *Neurology* 1997; **48**: 1470-71.
- 22 Antoine J, Michel D, Bertholon P, et al. Creutzfeldt-Jakob disease after extracranial dura mater embolization for a nasopharyngeal angiofibroma. *Neurology* 1997; **48**: 1451-53.

Comparison of three single doses of mifepristone as emergency contraception: a randomised trial

*Task Force on Postovulatory Methods of Fertility Regulation**

Summary

Background Mifepristone is a highly effective and well-tolerated emergency contraceptive when given in a dose of 600 mg within 72 h of unprotected coitus. We assessed whether the same effectiveness can be achieved with lower doses of mifepristone (50 mg and 10 mg) and a longer postcoital treatment period (120 h).

Methods We undertook a multicentre, single-masked, randomised trial in 11 family-planning clinics in Australia, China, Finland, Georgia, the UK, and the USA. 1717 healthy women with regular menstrual cycles who requested emergency contraception within 120 h of unprotected coitus were randomly assigned to three treatment groups.

Findings 32 women were lost to follow-up and one was pregnant before treatment. The 600 mg, 50 mg, and 10 mg groups did not differ in the proportions of pregnancies (seven [1.3%] of 559, six [1.1%] of 560, and seven [1.2%] of 565). Two pregnancies (both in the 50 mg group) were tubal. Among women without further acts of intercourse, treatment delay did not appear to influence the effectiveness. No major side-effects occurred, except a delay in the onset of next menses, significantly ($p < 0.01$) related to the mifepristone dose.

Interpretation Lowering the dose of mifepristone sixty-fold did not decrease its effectiveness as an emergency contraceptive under typical use, though a study of this size cannot exclude differences in effectiveness up to almost three-fold. Lower doses of mifepristone were associated with less disturbance of the menstrual cycle. Thus, a dose as low as 10 mg seems preferable to the 600 mg dose.

Lancet 1999; **353**: 697-702

*Members and study organisation given at end of paper

Correspondence to: Dr Helena von Hertzen/Dr Paul F A Van Look, Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland (e-mail: vonhertzenh@who.ch or vanlookp@who.ch)

Introduction

Two UK randomised controlled trials of emergency contraception compared a single dose of 600 mg mifepristone with the Yuzpe regimen of oral contraceptives (ethinylestradiol 100 µg plus levonorgestrel 500 µg, repeated after 12 h) given within 72 h of unprotected coitus.^{1,2} Mifepristone seemed to be a better option—three pregnancies were reported among 597 women who received mifepristone, compared with nine pregnancies among 589 women who received the Yuzpe regimen. The difference in proportions of pregnancies was not significant, but women who received mifepristone had significantly less nausea and vomiting, which are major drawbacks of the Yuzpe regimen. Women who received mifepristone were, however, more likely to have a delay in the onset of the next menses, presumably because antiprogesterone administered in the preovulatory phase of the menstrual cycle delays or blocks ovulation.³ Such delay can worry women already fearful of an unintended pregnancy. In addition, delayed ovulation means a conception risk later in the prolonged cycle if no contraception is used. In one of the UK trials,² the three pregnant women were reported to have conceived 10-15 days after mifepristone treatment.

Research on the effects of mifepristone on ovarian and endometrial functions suggests that doses lower than 600 mg may confer protection against pregnancy when used for emergency contraception.⁴⁻⁶ Lower doses would reduce the cost and are consistent with the principle that the lowest effective dose of a drug should be used.

This randomised controlled trial aimed to compare the effectiveness and side-effects, including the timing of the subsequent menstrual period, of single doses of 600 mg, 50 mg, and 10 mg mifepristone when the treatment was given within 120 h (5 days) of unprotected coitus.

Methods

Protocol

This trial was carried out in 11 family planning clinics in six countries on four continents. We obtained approval for the