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Risk factors for uterine fibroids: reduced risk associated with oral contraceptives

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Abstract

Risk factors for pathologically confirmed uterine leiomyomas (fibroids) were investigated using data from the Oxford Family Planning Association study, a long term follow up study of women using various methods of contraception. For each of 535 women who had had a fibroid an individual control was selected who matched the patient on age, date of entry into the cohort, and family planning clinic at recruitment and who was alive (and still being followed up) at the date the patient underwent surgery for fibroids. Case-control analysis showed that reproductive experiences were closely linked to development of fibroids. Risk of fibroids decreased consistently with increasing number of term pregnancies; women with five term pregnancies had only a quarter of the risk of women who had had none. Risk also decreased consistently with increasing duration of oral contraceptive use; the risk of fibroids was reduced by some 31% in women who had used oral contraceptives for 10 years.

Risk was strongly related to weight: women who weighed under 55 kg had a particularly low risk, and overall the risk rose roughly 21% for each 10 kg increase. Cigarette smoking was associated with a decreased risk of fibroids; smokers of 20 cigarettes a day had a risk roughly two thirds that of non-smokers.

These risk factors have all previously been identified as risk factors for endometrial cancer; this strongly suggests that the underlying risk factor is "unopposed" oestrogen.

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Introduction

Uterine leiomyomas are the most common pelvic neoplasms and may be the most common of all tumours in women[1,2]; they are benign tumours of smooth muscle, commonly referred to as fibroids. Despite the importance of these tumours, little is known about their epidemiology or aetiology.

Fibroids are most commonly diagnosed during reproductive life, usually in the fourth to fifth decade,[3] and they tend to shrink or fibrose after the menopause.[2] Fibroids have been consistently associated with infertility: in one review of several large series totalling 1698 patients, 464 (27%) had a history of infertility.[4] Case reports have suggested that oral contraceptives may play a part in the development or growth of the tumours,[5] but a study of the records relating to a small series of women who had undergone hysterectomy, with and without fibroids, suggested that an inverse relation may in fact exist.[6] Although it is generally thought that fibroids rapidly increase in size during pregnancy,[2] detailed studies have failed to confirm this.[7]

Although not well documented, it is widely accepted that fibroids are much more common in American black women than American white women[2]: one suggested explanation for this is that black women have a higher prevalence of pelvic infections than white women and that such infections cause myometrial irritation leading to abnormal uterine growth.[8] This hypothesis is untested, and we could find no useful data on this issue.

Using data from the Oxford Family Planning Association cohort study, we have tested some of these hypotheses and provide other relevant information.

Methods

The Oxford Family Planning Association study is a long term follow up study of white women who use different methods of contraception.[9] Between 1968 and 1974 17 032 women were recruited at 17 Family Planning Association clinics in England and Scotland. At the time of recruitment all women were married and aged 25-39 and were either using oral contraceptives and had done so for at least five months or were using the diaphragm or an intrauterine device (and had done so for at least five months) without previous use of oral contraceptives. At an admission interview the women were asked about their history of pregnancy, but no distinction was made between spontaneous and induced abortions; histories of oral contraceptive use were recorded in full, but histories of use of other contraceptive methods were restricted to the method they were using at the time of recruitment.

During follow up visits to the clinic women are questioned about reproductive events, interim contraceptive practices, and hospital visits as inpatients or outpatients. Women who stop attending the clinic are followed by mail, telephone, or, in some cases, a home visit. All women are contacted at least annually. Annual losses to follow up average 0·3%. Diagnoses on discharge from hospital are confirmed by obtaining copies of discharge letters or summaries.

As of July 1985, 538 women in this cohort had had pathologically confirmed fibroids (excluding women with pathologically confirmed fibroids before entry to the study). For each of these women we attempted to select an individual control matched on date of entry into the study (within same half year), age at entry (in two year age groups, 25-26, 27-28, and so on), and Family Planning Association clinic at recruitment. The control woman also had to have been followed and had to have had an intact uterus up to the date of surgical diagnosis of the case: when more than one woman was identified as a suitable control we chose one at random, subject to each control being used only once. The health history for both case and control groups was taken to end at the case's date of diagnosis. A control was successfully identified for 535 of the cases.

Age specific incidence of fibroids was calculated by standard methods: specifically, a woman's exposure was calculated from date of entry to the study to the date of last follow up, date of hysterectomy, or date of pathological diagnosis of fibroids, whichever was the earliest.

Statistical analysis of the case-control data was conducted with the use of multivariate logistic regression methods for individually matched case-control studies.[10] Relative risks were estimated by odds ratios. A case-control pair was excluded from any given analysis if the information for either the case or the control was not known for the relevant variables. All significant levels quoted (p values) are two sided.

Results

Table I shows the incidence for surgically (pathologically) confirmed fibroids by age at surgery. There was a steady increase in incidence with increasing age up to the age group 45-49; the condition was uncommon under 30 and was roughly three times commoner in women in their 40s than in women in their 30s. There was some indication of a decline in incidence beyond age 50.

TABLE I—*Age specific incidence of fibroids (pathologically confirmed cases only)*

Age (years)	Women with fibroids	Woman years at risk	Rate/1000 woman years
25-	7	22775	0·31
30-	48	50153	0·96
35-	169	63363	2·67
40-	201	43384	4·63
45-	103	16620	6·20
≥50	10	2358	4·24
Total	538	198653	2·71

The relative risk for fibroids was significantly decreased by increasing numbers of term pregnancies (live births and stillbirths) (table II). There was no reduction in risk associated with incomplete pregnancies but a slight, but not significant, increase in risk. Of all pregnancies among women with fibroids, 14·8% (184/1243) were incomplete compared with 11·3% (155/1367) among controls. The fibroid group had 64 pregnancies during follow up, of which 17 were spontaneous and 17 induced abortions; the comparable number of pregnancies for the control group was 92 (13 spontaneous and eight induced abortions). Eight of the incomplete pregnancies (four spontaneous and four induced abortions) in the fibroid group actually led to diagnosis of the fibroids.

The risk of fibroids was not related to age at first term pregnancy (see table II). The later the age at last term pregnancy, however, the lower the risk of fibroids (see table II).

Menopause was associated with an appreciably reduced risk of fibroids (table II): only three of the patients with fibroids were definitely postmenopausal (at least one year since last menstrual period at annual follow up) compared with 17 of the controls. This strongly supports the evidence in table I of a fall in incidence after the age of 50.

Of the women with fibroids, 283 (53%) had used oral contraceptives at some time compared with 315 (59%) of the controls, and there was a steady decrease in risk with increasing duration of oral contraceptive use (data not shown). Oral contraceptive use within the six months before pathological diagnosis of fibroids was particularly associated with a decreased risk, but there was little further change in risk as the time between last use of oral contraceptives and diagnosis increased (table III). This strongly suggested, and the detailed information we had on a proportion of patients confirmed, that in many cases the use of oral contraceptives had been abandoned between the initial clinical diagnosis of fibroids and the final pathological diagnosis. Accordingly, for the purposes of understanding aetiology, we restricted attention to oral contraceptive use up to six months before pathological diagnosis (table III). The risk clearly fell with increasing duration of use of oral contraceptives.

TABLE II—*Relative risks of fibroids by various possible aspects of term pregnancies and by menopausal state*

Factor	Women with fibroids	Controls	Matched relative risks	p (Two sided significance)
Term pregnancies				
0	57	32	1·00	0·00001*
1	88	55	0·87	
2	247	268	0·47	
3	105	120	0·43	
4	28	39	0·39	
5	10	21	0·24	
Age at first term pregnancy				
-19	28	32	1·00	0·47†‡
20-24	217	200	1·24	
25-29	124	161	0·86	
≥ 30	34	31	1·16	
Age at last term pregnancy				
-24	100	80	1·00	0·0007†§
25-29	235	235	0·79	
30-34	117	145	0·58	
≥ 35	26	43	0·42	
Menopausal state				
Premenopausal	532	518	1·00	0·001
Postmenopausal	3	17	0·18	

*For linear trend in logistic model; test for non-linearity, p=0·36.
†For linear trend in logistic model; statistics computed allowing for separate effect nulliparity.
‡Data not available for two family planning clinics.
§Test for non-linearity, p=0·96.

TABLE III—*Relative risks of fibroids by time since last use of oral contraceptives and by duration of use of oral contraceptives up to six months before pathological diagnosis*

Time (months)	Women with fibroids	Controls	Matched relative risks
Time since last use of oral contraceptives			
No use	252	220	1·00
0-6	98	128	0·64
7-24	38	36	0·90
25-48	51	52	0·85
≥49	96	99	0·85
Duration of use of oral contraceptives up to 6 months before diagnosis			
0	253	225	1·00*
1-	43	37	1·04
25-	52	56	0·80
49-	106	116	0·79
97-	67	80	0·73
≥145	14	21	0·54

*p=0·015 for linear trend in logistic model; test for non-linearity, p=0·96.

Table IV shows total oral contraceptive use up to six months before pathological diagnosis for each oral contraceptive formulation. It is difficult to know how to interpret these results, but data from the series of oral contraceptives all with 50 μg ethinyloestradiol and with varying amounts of norethisterone acetate suggested that the higher the dose of progestogen the more protective the oral contraceptive. This was most clearly seen when the few data on the oral contraceptive containing 2·5 mg norethisterone acetate were added to those on the 3·0 mg formulation. Moreover, results for the 30 μg ethinyloestradiol combined with either 0·25 mg or 0·15 mg brands also suggested this. None of the four oral contraceptive formulations with ethynodiol diacetate as progestogen was associated with a decreased risk of fibroids.

We did not have complete information on duration of use of other types of

contraception before entry into the study, but for women relying on intrauterine devices when recruited to the study we knew the duration of their current use (at entry) and subsequently obtained complete details: there was no relation between use of intrauterine devices and fibroids.

TABLE IV—*Total use of oral contraceptives up to six months before pathological diagnosis in women with fibroids and controls*

Oestrogen (μg)	Progestogen (mg)		Total months (No) Women with fibroids		Controls		Ratio of cases: controls (months)
Mestranol							
150	5·0	Lynestrol	85	(8)	108	(7)	0·79
100	2·5	Norethynodrel	400	(10)	323	(8)	1·24
100	2·0	Norethisterone	629	(20)	766	(30)	0·82
100	1·0	Ethynodiol diacetate	1648	(49)	1242	(57)	1·33
80	1·0	Norethisterone	160	(17)	186	(17)	0·86
75	2·5	Lynestrol	795	(39)	948	(53)	0·84
50	1·0	Norethisterone	4134	(128)	4361	(130)	0·95
Ethinyloestradiol							
100	2·0	Megestrol acetate	252	(20)	300	(27)	0·84
50	4·0	Norethisterone acetate	465	(24)	1105	(35)	0·42
50	3·0	Norethisterone acetate	2559	(75)	4155	(94)	0·62
50	2·5	Norethisterone acetate	212	(18)	453	(11)	0·47
50	1·0	Norethisterone acetate	2094	(74)	3079	(93)	0·68
50	4·0	Megestrol acetate	1120	(41)	873	(32)	1·28
50	1·0	Ethynodiol diacetate	1510	(47)	920	(29)	1·64
50	2·5	Lynestrol	1907	(70)	2129	(71)	0·90
50	0·25	Levonorgestrel*	269	(15)	455	(22)	0·59
50	0·5	Ethynodiol diacetate	144	(4)	84	(4)	1·71
30	0·25	Levonorgestrel*	488	(28)	964	(44)	0·51
30	0·15	Levonorgestrel*	455	(33)	440	(30)	1·03
	0·5	Ethynodiol diacetate	69	(2)	43	(4)	1·60
	0·35	Norethisterone	114	(11)	313	(20)	0·36
	0·0375	Levonorgestrel*	94	(7)	109	(8)	0·86

*Pills containing norgestrel have been converted to levonorgestrel equivalents to aid comparison between different pills.

Table V shows the relation between fibroids and weight on entry to the study. Risk increased steadily with increasing weight, so that women weighing 70 kg or more at entry had an almost threefold increased risk compared with women weighing less than 50 kg. The results were very similar when we considered Quetelet's index (weight in kg divided by height in m^2) rather than weight (table V).

TABLE V—*Relative risks of fibroids by weight and Quetelet's index on entry to study*

Factor	Women with fibroids	Controls	Matched relative risks	p (Two sided significance)
Weight (kg)				
-49·9	24	51	1·00	0·006*
50-	84	105	1·72	
55-	134	129	2·25	
60-	136	125	2·36	
65-	72	60	2·60	
≥70	85	65	2·82	
Quetelet's index				
-18·9	19	40	1·00	0·045†
19-	113	128	1·85	
21-	174	173	2·17	
23-	130	112	2·51	
25-	50	38	2·88	
≥27	49	44	2·47	

*For linear trend in logistic model; test for non-linearity, p=0·41.
†For linear trend in logistic model; test for non-linearity, p=0·32.

The data on hospital treatments showed that infections of the urinary tract were not associated with risk of fibroids (29 in the fibroid group and 31 in the control group); that the incidence of pelvic inflammatory disease was very low in this population (five cases and two controls); and that there was a slight (not significant) excess of cases with cervicitis (71 cases and 54 controls). The association between urinary tract infections and fibroids was further weakened after excluding six women with fibroids (0 controls) in whom cervicitis was diagnosed within one year of the diagnosis of fibroids.

Table VI shows that cigarette smokers had a decreased risk of fibroids, and this relation appeared to be dose dependent.

TABLE VI—*Relative risks of fibroids by number of cigarettes smoked per day at entry to study*

No of cigarettes/day	Women with fibroids	Controls	Matched relative risks	p (Two sided significance)
0	395	354	1·00	0·018*
1-	90	110	0·74	
≥15	50	71	0·65	

*For linear trend in logistic model; test for non-linearity, p=0·63.

When the factors (term births, age at last term birth, menopausal state, use of oral contraceptives, weight, and cigarette smoking) that were significant when considered as univariate variables were considered jointly all remained significant and, except for the obvious relation between number of term pregnancies and age at last term pregnancy, their effects were almost independent (table VII). There was no added effect of nulliparity per se over and above that of its effect described as a linear term with number of term pregnancies.

Discussion

The strong negative association between number of term pregnancies and the occurrence of fibroids is most likely to be due to the effects of two factors. Firstly, women who develop fibroids are relatively infertile compared with women who do not, and, secondly, term pregnancies per se reduce risk.

Relative infertility seems unlikely to be the total explanation. Among our subjects absolute infertility was uncommon—89% (478) of the women with fibroids had had at least one term pregnancy (possibly partly because all the women in the study were attending family planning clinics for contraceptive advice at recruitment). Furthermore, the total use of contraceptives after entry to the study of the women with fibroids was only slightly (and not significantly) less than the total used by the control group (average duration of contraceptive use of the women with fibroids was 69·4 months compared with 71·3 months for the control group). The interval from marriage to first birth also differed very little between the fibroid and control groups (relative risk of 1·20 for 10 or more years compared with less than two years).

Finally, the hypothesis that term pregnancies actually reduce risk is also supported by the finding that risk of fibroids is further reduced with each additional term pregnancy. The protective effect of term pregnancies is, however, not the complete explanation either. There is evidence that the presence of fibroids may prevent implantation or maintenance of the ovum in the uterus in a few women: 14 women with fibroids (*v* five controls) reported an infertility problem during follow up, and the pregnancies occurring in the women with fibroids ended in abortion considerably more often than the pregnancies occurring in the control women. This was true even for pregnancies occurring before entry to the study. Moreover, six of the 22 nulliparous women with fibroids achieved a term pregnancy after surgery for their fibroids.

The decrease in the risk of fibroids with increasing age at last term pregnancy (even after allowing for number of term births) suggests that a term birth indicates that the woman did not have a clinically important fibroid at that time. This complements the notion that fibroids can cause infertility.

This study provides the first real evidence that the risk of fibroids is reduced by use of oral contraceptives. There is roughly a 17% reduction in risk with each five years of oral contraceptive use.

We thought a priori that use of intrauterine devices might increase risk of fibroids, particularly since heavy menstrual flow is a common side effect of the use of intrauterine devices, and this symptom might lead to increased detection of fibroids. There was, however, no evidence of an association with use of intrauterine devices.

Risk of fibroids increased with increasing body weight: risk increased roughly 21% for each 10 kg increase. Cigarette smoking was associated with a significant decrease in risk of fibroids. We estimate that women who smoked 10 cigarettes a day had an 18% decreased risk in comparison with non-smokers.

TABLE VII—*Unadjusted and joint relative risks for term births, age at last term birth, menopausal state, use of oral contraceptives, and cigarette smoking**

Factor	Unit of change	Unadjusted risk (B)	Joint risk			
			B	Relative risk	t=B/SE(B)	p (Two sided significance)
Term births	1	−0·269	−0·220	0·80	−2·79	0·005
Age at last term birth	5 years	−0·283	−0·250	0·78	−2·74	0·006
Postmenopausal	Yes	−1·735	−1·733	0·18	−2·71	0·007
Use of oral contraceptives	5 years	−0·193	−0·184	0·83	−2·14	0·032
Weight	10 kg	0·185	0·190	1·21	2·66	0·008
Cigarette smoking	10/day	−0·211	−0·200	0·82	−2·10	0·036

*Parameters estimated from logistic regression model. Basic parameters (B) are such that relative risk=exp(B). SE(B)=standard error of B.

These factors modifying the risk of fibroids—protective effects of term births, use of oral contraceptives, cigarette smoking, and a harmful effect of increased body weight—are also the major factors associated with the risk of endometrial cancer. "Unopposed" oestrogen—that is, oestrogen exposure unaccompanied by a progestogen—has been clearly identified as the major cause of cancer of the endometrium, and all these risk factors can be interpreted in terms of the hypothesis of unopposed oestrogen.[11,12] This strongly suggests that unopposed oestrogen is also the underlying cause of fibroids.

After the menopause increased weight is associated with increased concentrations of circulating oestrogen, presumably because the major source of postmenopausal oestrogens is conversion of androstenedione to oestrogen in fat cells.[13] Before the menopause this oestrogen source is fairly unimportant in the face of ovarian production, but increasing weight is still closely associated with decreasing concentrations of sex hormone binding globulin and thus presumably with increasing concentrations of bioavailable oestradiol. Cigarette smoking has also been found to be associated with lower concentrations of urinary oestrogens.[14] If infertility is associated with a high risk of fibroids an oestrogen mechanism could also be proposed; this association could be due to high concentrations of unopposed oestrogen related to a high frequency of anovulatory cycles in such women. According to this hypothesis, the decreased risk associated with term pregnancies and use of oral contraceptives would be explained most readily by the oestrogen modifying effect of progestogens.

The data on the possibly increasing protective effect with increasing progestogen dose of oral contraceptives with the same ethinyloestradiol content (table IV) also provide some support for the unopposed oestrogen (protective effect of progestogens) hypothesis. The data on oral contraceptives containing ethynodiol diacetate are puzzling and need confirmation. Direct studies of the effect of different brands on the myometria may be informative.

Blood or urine concentrations of oestrogens in women with or without uterine fibroids appear not to have been measured. Alterations in oestrogen concentration and in oestrogen metabolism in leiomyomatous versus normal myometrium have been reported by some,[15] but not all investigators.[16] Further work may help explain why, unlike endometrial cancer, we have been unable to find any data linking oestrogen replacement therapy in postmenopausal women to an increased risk of fibroids; this apparently anomalous observation needs to be investigated closely. It would also be useful if future studies on women with endometrial cancer could report on the prevalence of fibroids in such women. We would, of course, expect women with endometrial cancer to have a raised risk of fibroids but we know of no data that address this issue.

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Corrections

Intramuscular loading dose of quinine for falciparum malaria: pharmacokinetics and toxicity

An error occurred in this paper by Dr Yupaporn Wattanagoon and others (5 July, p 11). The conversion of traditional to SI units is incorrect; the values for quinine should have been expressed in μmol/l, not mmol/l since, for quinine base, 1 mg/l is equivalent to 3 μmol/l.

Divided dose intramuscular regimen and single dose subcutaneous regimen for chloroquine: plasma concentrations and toxicity in patients with malaria

An error occurred in this paper by Dr R E Phillips and others (5 July, p 13). The conversion of traditional units to SI units is incorrect; for chloroquine base 1 mg/l is equivalent to 3 μmol/l. The values for chloroquine should have been in μmol/l, not mmol/l.