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Relation of pulmonary lymphangioleiomyomatosis to use of the oral contraceptive pill and fertility in the UK: a national case control study

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Abstract

Background **– Pulmonary lymphangioleiomyomatosis is a rare progressive disease of unknown aetiology affecting premenopausal women. Since the oral contraceptive pill has been implicated in its pathogenesis, a case control study was carried out to determine whether women with the disease were more likely to have taken the oral contraceptive pill, and whether the disease was associated with other conditions related to sex hormones including pregnancy, parity, and fibroids.**

Methods **– All chest physicians in the UK were asked for details of all live patients with pulmonary lymphangioleiomyomatosis; the patient's family doctor was then asked for four age and sex matched control subjects from their patient register. Details of lifetime use of the oral contraceptive pill, pregnancy, parity, history of fibroids, and smoking were obtained from cases and controls. Relative odds of exposure to potential risk factors were estimated by conditional logistic regression.**

Results **– Medical details were obtained from all 23 cases of lymphangioleiomyomatosis identified; questionnaires were completed by 21 cases (one by proxy) and by 46 matched controls of mean (SD) age 43 (10) and 44 (11) years, respectively. The patients had a mean age of 34 (9) years at onset of symptoms and a median (range) time of 2 (0–29) years from onset of symptoms to diagnosis. Compared with control subjects, cases did not differ in the use of the oral contraceptive pill (odds ratio (OR) 0·39, 95% CI 0·09 to 1·68), diagnosis of fibroids (OR 3·12; 95% CI 0·52 to 18·7), age of menarche, menstrual history, or lifetime smoking. They were, however, less likely to have been pregnant (OR 0·14, 95% CI 0·03 to 0·71) or to have had children (OR 0·13, 95% CI 0·03 to 0·67). More pregnancies had ended in spontaneous abortion (28% *v* 8%) but the proportion of women undergoing spontaneous abortion was similar in cases and controls (OR 2·13, 95% CI 0·47 to 9·3).**

Conclusions **– This study does not support the hypothesis that use of the oral contraceptive pill is causally associated with the development of pulmonary lymphangioleiomyomatosis. Sex hormones may be involved, however, since patients were less likely to have been pregnant or to have had children, and tended to have had more spontaneous abortions and an increased incidence of fibroids.**

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Pulmonary lymphangioleiomyomatosis is a rare disease which affects premenopausal women. It is characterised pathologically by extensive peribronchial, perivascular, and perilymphatic smooth muscle proliferation which results in airways obstruction, alveolar disruption, and the development of cysts in the lungs.[1 2] Patients present with dyspnoea, recurrent pneumothoraces, haemoptysis, and chylous pleural effusions. The disease usually progresses to cause death from respiratory failure.

The aetiology of pulmonary lymphangioleiomyomatosis is unknown, but sex hormones have been assumed to be important since the disease develops exclusively in women and almost invariably women of reproductive age.[1 3–6] Treatment has usually invoved antioestrogen measures in the form of oophorectomy[3 4 7] or treatment with tamoxifen,[8–10] medroxyprogesterone,[8 11–13] and luteinising hormone releasing hormone analogues.[14] None of these treatments has been assessed in a controlled trial and their value is uncertain.[15] Reports of the disease occurring in women on the oral contraceptive pill[2 11 16–18] and of exacerbations of the disease during pregnancy[8] have added to the suspicion that sex hormones are involved. We have therefore conducted a case control study to determine whether pulmonary lymphangioleiomyomatosis is associated with the use of the oral contraceptive pill or other conditions associated with sex hormones such as pregnancy, parity, and fibroids.

Methods

CASES AND CONTROLS

Chest physicians in the UK on the British Thoracic Society register were sent an explanation of the study and asked for details of all known live patients with pulmonary lymphangioleiomyomatosis. The physicians were asked to forward to such patients a written request asking them to participate in the study, plus a questionnaire and consent form which

asked the patient to allow us to approach their family doctor to obtain further information about their treatment.

The family doctor was then sent an explanation of the study and asked to provide details of the patient's previous drug treatment and to identify four control women from their age/sex register who were within five years in age to the case. Each control subject identified by the family doctor was then sent the same questionnaire and consent form as the cases. Letters to the cases, family doctor, and control subjects were followed up with a telephone reminder when necessary.

The study was approved by the Nottingham City Hospital ethics committee.

QUESTIONNAIRES

The questionnaire sent to consultants asked for details of the date of diagnosis, method used to reach the diagnosis, and treatment the patient had received after the diagnosis. The general practitioner's questionnaire asked for details about medical and surgical treatment history before and after the diagnosis was made. The questionnaire sent to patients and control subjects asked about children, pregnancies, menstruation, smoking history, use of the oral contraceptive pill, hormone therapy, history of fibroids, oophorectomy, and hysterectomy.

DATA ANALYSIS

Odds ratios and their 95% confidence intervals were determined for lifetime use of the oral contraceptive pill, children, parity, smoking, uterine fibroids, and the proportion of women who had been pregnant and had had a spontaneous abortion in relation to disease status using conditional logistic regression of matched data in the programme EGRET (SERC, Seattle, USA). The proportion of pregnancies that ended in spontaneous abortion were compared by the χ^2 test, and the pregnancy rate before the development of symptoms was compared in cases and controls by a Normal approximation for comparison of two Poisson rates.

Results

Of the 400 consultant chest physicians approached 358 (89·5%) responded to our inquiry and 23 patients with pulmonary lymphangioleiomyomatosis were identified. Medical details were obtained from the consultants for all 23 patients. One patient did not wish to take part in the study and consultants asked us not to contact a further two although the consultant provided details for one. The family doctors sent details on 62 matched control subjects with at least one control subject for each patient. One control subject did not wish to take part in the study and a further 15 did not respond despite reminder letters. Thus details were obtained on 21 patients and 46 matched control subjects.

PATIENT DETAILS

The diagnosis had been made by open lung biopsy in 18 of the 23 patients and by transbronchial biopsy in three. In two patients the diagnosis was based on compatible features on a chest radiograph and computed tomographic scan.

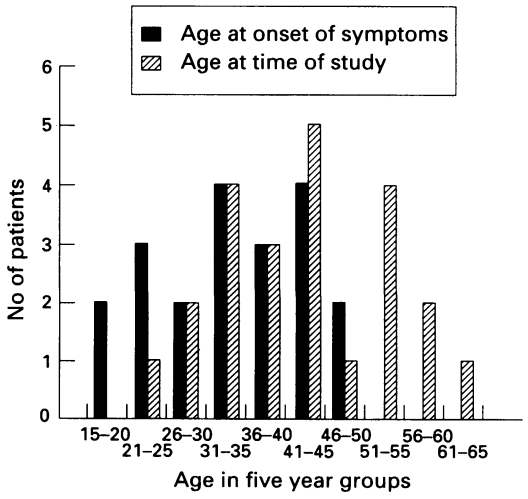
The mean (SD) age at the onset of symptoms was 34 (9) years and the median (range) time from onset of symptoms to time of diagnosis was 2 (0–29) years. The age distribution of patients is illustrated in the figure. One patient had cutaneous and neurological features of tuberous sclerosis. The median interval since the onset of symptoms was six years, with eight patients having survived for more than 10 years since the onset of symptoms.

Pregnancy

Eleven of the 21 patients had been pregnant (table 1). Of the 32 pregnancies nine ended in spontaneous abortion, including five from one patient. Seven of these nine pregnancies occurred before the onset of chest symptoms. Three pregnancies ended with an induced abortion and are assumed to have been normal for the analysis. Of the normal pregnancies six women had all their pregnancies (17 in total) before the onset of chest symptoms, two women had all their five pregnancies after the onset of chest symptoms, and three women had some pregnancies before and some after the onset of symptoms of the disease (five before and five after). Ten patients had never been pregnant of whom one was advised against pregnancy after the disease was diagnosed, three failed to become pregnant despite attempts to do so, two did not specify reasons, and four chose not to become pregnant.

Treatment of lymphangioleiomyomatosis

At the time of the questionnaire eight patients were taking no treatment, 12 were receiving medroxyprogesterone (one with prednisolone, four with tamoxifen), and one was taking



Distribution of age of patients and age at the onset of chest symptoms in patients with pulmonary lymphangioleiomyomatosis.

Table 1 Details of menarche, menstruation, pregnancies, and spontaneous abortions in patients with lymphangioleiomyomatosis and control subjects

	Cases	Controls	p value
No. of subjects	21	46	
Age at onset of menarche (years)			
Mean	13	13	
Range	11–16	10–16	
No. (%) of patients currently menstruating	10 of 21 (48%)	27 of 46 (59%)	NS
Duration of bleeding (days)			
Mean	4·4	4·7	
Range	3–7	3–6	
Description of menstrual blood loss			
Heavy	4	3	
Normal	6	19	
Light	0	4	
No. of subjects becoming pregnant	11	41	
No. of pregnancies (spontaneous abortions)			
Total	32 (9)*	126 (10)	<0·01
Before symptoms	22 (7)	103 (8)†	<0·01
After symptoms	10 (2)	23 (2)	<0·01
No. of patients having one or more spontaneous abortion	4	8	NS

* Figures in parentheses refer to number of spontaneous abortions.
† Number of pregnancies (abortions) in controls below the age at which their matched case noticed symptoms.

tamoxifen alone. One patient had had bilateral oophorectomy for pulmonary lymphangioleiomyomatosis and one had had a hysterectomy and bilateral oophorectomy for an ovarian mass which showed features of lymphangioleiomyomatosis on histological examination. The two patients with the longest disease duration (31 and 16 years) had both had a hysterectomy and oophorectomy 10 years previously; at the time of the study one was on medroxyprogesterone and tamoxifen and the other was on no treatment. Two patients had had a heart-lung transplant.

COMPARISON OF CASES AND CONTROLS (tables 1 and 2)

The mean (SD) ages of the patients and control subjects were closely matched (43 (10) years and 44 (11) years). There was no difference in age of menarche or menstrual history between the two groups and the mean (SD) age at first pregnancy was similar (24 (4·7) and 24 (4·3) years).

Patients were less likely to have ever taken the oral contraceptive pill (13 of 21) than control subjects (32 of 44 subjects) although this was not statistically significant (odds ratio 0·39, 95% CI 0·09 to 1·68; p=0·2). Patients were significantly less likely to have been pregnant (11 of 21 patients) than control subjects (41 of 46 subjects) giving an odds ratio of 0·14 (95% CI 0·03 to 0·71; p<0·01) and the total number of pregnancies per woman was less (1·52 *v* 2·74; p<0·01). The number of pregnancies per case and control that occurred below the age at which the case first noticed symptoms (1·01 *v* 2·24) was also significantly different (p<0·01). Cases were also significantly less likely to have had children (10 of 21 patients) than control subjects (41 of 46 subjects), giving an odds ratio of 0·13 (95% CI 0·03 to 0·97; p<0·01). Amongst the cases nine of 32 pregnancies ended in spontaneous abortion compared with 10 of 126 pregnancies in the control subjects ($\chi^2=9·13$; p<0·01), although the proportion of cases and controls who had been pregnant and had had a spontaneous abortion did not differ significantly (four of 11 *v* eight of 41; odds ratio 2·13, 95% CI 0·4 to 9·3).

More cases (five of 21) had had uterine fibroids than control subjects (four of 46) although this was not statistically significant (odds ratio 3·12, 95% CI 0·52 to 18·7; p=0·2). There was no difference in the number of cigarette smokers between patients (eight of 21) and control subjects (22 of 46), (odds ratio 0·58; 95% CI 0·20 to 1·71; p=0·3).

Table 2 Matched odds ratio with 95% confidence intervals (95% CI) and p values for suspected risk factors in patients with pulmonary lymphangioleiomyomatosis compared with control subjects

Factor	Odds ratio	95% CI	p value
Use of the oral contraceptive pill	0·39	0·09 to 1·68	NS
Children	0·13	0·03 to 0·67	<0·01
Parity	0·14	0·03 to 0·71	<0·01
Smoking (past and present)	0·58	0·20 to 1·71	NS
Known fibroids	3·12	0·52 to 18·7	NS
Spontaneous abortion amongst women who had been pregnant	2·13	0·47 to 9·3	NS

Discussion

This study compares patients with lymphangioleiomyomatosis with age-matched control subjects to try to determine whether the disease is associated with the use of the oral contraceptive pill or other factors related to sex hormones.

Because pulmonary lymphangioleiomyomatosis is rare it is difficult to obtain hard data on risk factors or to determine the effectiveness of treatment. In the largest retrospective clinical review of 32 cases of pulmonary lymphangioleiomyomatosis from a tertiary referral centre the authors found it difficult to draw firm conclusions on the relation of the disease to pregnancy and use of the contraceptive pill or the effectiveness of treatment because of the variable nature of the disease and because many patients had had more than one form of treatment.[19] Our study is the first controlled study to try to determine risk factors in patients with pulmonary lymphangioleiomyomatosis. The response rate from chest physicians was high, so our 21 patients probably include most of the cases available in the UK. Nevertheless, the number of subjects even at a national level is small, so our findings are relatively susceptible to a type I error. Our patients are likely to be more representative of patients with the disease in the general population than studies based on tertiary referral, although the findings will be biased towards patients who survive longer.

Female sex hormones have been assumed to play an important part in the pathogenesis of pulmonary lymphangioleiomyomatosis for several reasons. The disease develops in premenopausal women and there are several reports of the disease occurring in patients on the contraceptive pill,[2 11 16–18] of exacerbation of the disease during pregnancy,[8] of prolonged survival following the menopause,[20 21] and of an association with uterine fibroids (five of the 11 who had died in one review had fibroids[1]).

We found no association between oral contraceptive pill use and the development of

lymphangioleiomyomatosis; in fact, our observation of a low odds ratio suggests that oral contraceptive use might even protect against the disease. Cases did not differ from control subjects in age of menarche or menstrual history but they were significantly less likely to have been pregnant and to have had children. This was also true when we looked at the number of pregnancies per case and control that occurred before the date at which the case first noticed symptoms. Only one patient said she had not had children because of the disease. Spontaneous abortion occurred more often in cases than control subjects, but this was largely due to one patient in whom all five pregnancies before the onset of symptoms ended in spontaneous abortion; if this patient is excluded from the analysis the finding is not statistically significant. The proportion of women having a spontaneous abortion did not differ significantly between cases and controls. Seven of the nine spontaneous abortions occurred before the development of chest symptoms. Since the reduction in pregnancies and increase in spontaneous abortions was seen before patients developed symptoms, the association with lymphangioleiomyomatosis is unlikely to be due to symptoms of lung disease or knowledge of the diagnosis; it could be due to an effect of the disease on reproductive capacity or, alternatively, an imbalance in oestrogen and progesterone causing problems with fertility and predisposing to lymphangioleiomyomatosis. It is also possible that our results are influenced by survivor bias, patients who had been on the oral contraceptive pill or who had been pregnant having a worse prognosis.

A relative deficiency of progesterone is supported anecdotally by the response to treatment with medroxyprogesterone and would fit with our finding that oral contraceptive use was less common amongst cases than the age matched control subjects, albeit not statistically significant. McCarty *et al*[12] first described improvement in a patient with pulmonary lymphangioleiomyomatosis with a chylous effusion following treatment with medroxyprogesterone, and there have been subsequent reports of benefit, mostly in patients with a chylous effusion or chylous ascites.[8 11 17] When reviewing their 32 patients Taylor *et al*[19] found more evidence in favour of medroxyprogesterone than anti-oestrogen measures. None of the 16 patients undergoing an oophorectomy or nine given tamoxifen had shown benefit, whereas two of the 19 patients given medroxyprogesterone for at least six months had improved and six had remained stable for an average of 32 months. The two who improved deteriorated when the dose was reduced. Some studies have found abnormal expression of oestrogen and progesterone receptors on proliferating smooth muscle cells in lymphangioleiomyomatosis[17 22] but others have not[23 24] and Taylor *et al*[19] were unable to find any correlation between oestrogen and progesterone receptor status and the response to hormone therapy when reviewing the literature.[8 12 17 25] How progesterone might be effective is uncertain, but it may reduce the responsiveness of oestrogen and progesterone receptors in the lung. Alternatively progestins might have a direct inhibitory effect on myocytes in pulmonary lymphangioleiomyomatosis. One report suggested that pregnancy might exacerbate the disease.[8] An observational study such as this does not allow conclusions to be drawn on the effects of pregnancy or the oral contraceptive pill on lymphangioleiomyomatosis once the disease is established.

In conclusion, patients with pulmonary lymphangioleiomyomatosis were no more likely than individually matched control subjects to have taken the oral contraceptive pill, and although not significant, the odds ratio of 0·39 suggests that the use of the contraceptive pill is, if anything, associated with a lower risk of disease. There is some evidence for a role for hormonal factors. Although there was no difference in age of menarche, menstrual history, or the proportion of pregnant women undergoing spontaneous abortion, patients were significantly less likely to have been pregnant and to have had children, and the number of spontaneous abortions was higher. The findings argue against the use of oral contraceptives as a risk factor, but are consistent with the disease or hormonal factors associated with the disease affecting parity.

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1 Corrin B, Liebow AA, Friedman PJ. Pulmonary lymphangioleiomyomatosis: a review. *Am J Pathol* 1975;**79**:348–82.
2 Carrington CB, Cugell DW, Gaensler EA, Marks A, Redding RA, Schaaf JT, *et al*. Lymphangioleiomyomatosis: physiologic–pathologic–radiologic correlations. *Am Rev Respir Dis* 1977;**116**:977–89.
3 Silverstein EF, Ellis K, Wolff M, Jaretzki A III. Pulmonary lymphangiomyomatosis. *AJR* 1974;**120**:832–50.
4 Bush JK, McLean RL, Sieker HO. Diffuse lung disease due to lymphangiomyoma. *Am J Med* 1969;**46**:645–54.
5 Wolff M. Lymphangiomyoma: clinicopathologic study and ultrastructural confirmation of its histogenesis. *Cancer* 1973;**31**:988–1007.
6 Basset F, Soler P, Marsac J, Corrin B. Pulmonary lymphangiomyomatosis. *Cancer* 11976;**38**:2357–66.
7 Shuman RL, Elgelman R, Kittle CF. Pulmonary lymphangiomyomatosis. *Ann Thorac Surg* 1979;**27**:70–5.
8 Hughes E, Hodder RV. Pulmonary lymphangiomyomatosis complicating pregnancy, a case report. *J Reprod Med* 1987; **32**:553–7.
9 Tomasian A, Greenberg MS, Rumerman H. Tamoxifen for lymphangioleiomyomatosis. *N Engl J Med* 1982;**306**: 745–6.
10 Shen A, Iseman MD, Waldron JA, King TE. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous oestrogens. *Chest* 1987;**91**:782–5.
11 Adamson D, Heinrichs WL, Raybin DM, Raffin TA. Successful treatment of pulmonary lympangioleiomyomatosis with oophorectomy and progesterone. *Am Rev Respir Dis* 1985;**132**:916–21.
12 McCarty KS Jr, Mossler JA, McLelland R, Sieker HO. Pulmonary lymphangiomyomatosis responsive to progesterone. *N Engl J Med* 1980;**303**:1461–5.
13 Sawicka EH, Morris AJ. A report of two long-surviving cases of pulmonary lymphangioleiomyomatosis and the response to progesterone therapy. *Br J Dis Chest* 1985;**79**: 400–6.
14 Ross GA, Balbi B, Oddera S, Lantero S, Ravazzoni C. Response to treatment with an analogue of the luteinizing-hormone-releasing homone in a patient with pulmonary lymphangioleiomyomatosis. *Am Rev Respir Dis* 1991;**143**: 174–6.
15 Eliasson AH, Phillips YY. Treatment of lymphangioleiomyomatosis. *N Engl J Med* 1990;**325**:63.
16 Stovin PG, Lum LC, Flower CD, Darke CS, Beeley M. The lungs in lymphangiomyomatosis and in tuberous sclerosis. *Thorax* 1975;**30**:497–509.
17 Svendson TL, Viskum K, Hansborg N, Thorpe SM, Nielsen

NC. Pulmonary lymphangioleiomyomatosis: a case of progesterone receptor positive lymphangioleiomyomatosis treated with medroxyprogesterone, oophorectomy and tamoxifen. *Br J Dis Chest* 1984;**78**:264–71.
18 Banner AS, Carrington CB, Emory WB, Kittle F, Leonard G, Ringus J, *et al.* Efficacy of oophorectomy in lymphangioleiomyomatosis and benign metastasizing leiomyoma. *N Engl J Med* 1981;**305**:204–9.
19 Taylor JR, Ryu J, Colby TV, Raffin TA. Lymphangioleiomyomatosis, clinical course in 32 patients. *N Engl J Med* 1990;**323**:1254–60.
20 Sinclair W, Wright JL, Churg A. Lymphangioleiomyomatosis presenting in a postmenopausal woman. *Thorax* 1985;**40**: 475–6.
21 Baldi S, Papotti M, Valente ML, Rapellino M, Scappaticci E, Corrin B. Pulmonary lymphangioleiomyomatosis in postmenopausal women: report of two cases and review of the literature. *Eur Respir J* 1994;**7**:1013–6.
22 Colley MH, Geppert E, Franklin WA. Immunohistochemical detection of steroid receptors in a case of pulmonary lymphangioleiomyomatosis. *Am J Surg Pathol* 1989;**13**:803–7.
23 Hauck RW, Konig G, Permanetter W, Weiss M, Wockel W, Fruhmann G. Tuberous sclerosis with pulmonary involvement. *Respiration* 1990;**57**:289–92.
24 Popper HH, Gamperl R, Pongratz MG, Kullnig P, Juttner-Smolle F-M, Pfragner R. Chromosome typing in lymphangioleiomyomatosis of the lung with and without tuberous sclerosis. *Eur Respir J* 1993;**6**:753–9.
25 Brentani MM, Carvalho CR, Saldiva PH, Pacheco MM, Oshima CT. Steroid receptors in pulmonary lymphangiomyomatosis. *Chest* 1984;**85**:96–9.