Pregnancy in lymphangioleiomyomatosis: clinical and lung function outcomes in two national cohorts

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ABSTRACT

Pregnancy in women with lymphangioleiomyomatosis (LAM) has been associated with increased complications and worsening lung function although objective data to advise patients are not available. We assessed lung function and CT scans before and after pregnancy in 16 women with LAM. During the pregnancy, pneumothorax was frequent and mean forced expiratory volume in 1 s (FEV_1) fell from 77%±19% prepregnancy to 64%±25% predicted and DL_{CO} from 66±26 to 57±26 (both p<0.01). After pregnancy, rates of FEV_1 decline were high and 10 patients required sirolimus. Women with LAM, especially with moderate or advanced disease should be counselled regarding adverse events and loss of lung function during the pregnancy.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare multisystem disease associated with cystic lung destruction, benign abdominal tumours and lymphatic involvement. LAM occurs sporadically or in association with tuberous sclerosis complex (TSC).[1] LAM is thought to be oestrogen dependent as it almost exclusively affects women, progresses more rapidly premenopause[2] and LAM cells are oestrogen receptor positive.[3] Retrospective reports suggest pregnancy is associated with increased LAM complications[4–6] and the safety of pregnancy is a major concern to patients; many of whom avoid or are discouraged from pregnancy despite little objective evidence.[7] To improve the evidence base for women with LAM considering pregnancy, we examined lung function and CT scans throughout pregnancy.

MATERIAL AND METHODS

The patient cohorts and analysis are described fully in the on line supplement. Subjects with pre and postpregnancy data were recruited from two national observational studies, the UK LAM Centre cohort and the LAM natural history and pathogenesis protocol at the National Institutes of Health (NIH) Clinical Research Center, USA. All participants provided written informed consent. Clinical course before and after pregnancy, serial lung function and pregnancy outcomes were obtained. Where prepregnancy and postpregnancy scans were available, the percentage of lung volume occupied by cysts was quantitated as described.[8]

To determine whether pregnancy affected lung function, only measurements taken while not taking an mTOR inhibitor were included. Analyses were adjusted for prepregnancy values of forced expiratory volume in 1 s (FEV_1), diffusion in the lung of carbon monoxide (DL_{CO}) and time of visit with timing of conception calculated from the fetal age at delivery using mixed effects models.[9] Generalised additive models with Kruskal-Wallis test were used to compare prepregnancy and postpregnancy FEV_1 and DL_{CO}. Pairwise comparisons were performed if the overall significance test was ≤0.05.

RESULTS

Nine UK and seven NIH patients with prepregnancy and postpregnancy data were identified. Mean age of diagnosis of LAM was 28.4±4.8 years. Ten presented with pneumothorax, three with dyspnoea, one due to TSC and two with renal angiomyolipoma. Age at pregnancy was 31.9±4.3 years and delivery 32.6±4.4 years. Mechanistic target of rapamycin (mTOR) inhibitors were withdrawn in three patients at or before pregnancy (table 1).

Pregnancy

During the pregnancy, five patients developed pneumothorax that was bilateral in four, two were treated by pleurodesis, one required a chest tube for 7 weeks until delivery, one developed pneumonia and empyema. Four deliveries were natural and 12 by caesarian section. Two patients developed pre-eclampsia. One baby was diagnosed with TSC and another developed respiratory distress but survived (table 1).

Postpregnancy outcomes

Following pregnancy, one patient had a single lung transplant 2 years after delivery and died 2 years later, another was considered for, but not transplanted. Ten of the 16 patients were started on sirolimus. At least one lung function measurement was available for 15 patients at 8.1±3.6 months before pregnancy and at 11.5±9.8 months after delivery. Pregnancy was associated with an absolute fall in FEV_1 from 77%±19% to 64%±25% predicted (difference −13, 95% CI −21 to −5.2, p<0.01), and DL_{CO} from 66±26 to 57±26 (difference −9.3, 95% CI −15.5 to −3.2, p<0.01). The mixed-effects models confirmed that percent predicted FEV_1 and DL_{CO} were lower after, than before pregnancy (both p<0.001). Two or more prepregnancy and postpregnancy FEV_1 and DL_{CO} measurements were available for 12 and 10 patients, respectively, measured over 2.5±0.5 years which were used to estimate rate of loss of lung function. Ten had greater rates of decline in FEV_1 and DL_{CO} after pregnancy compared with before although the mean (±SEM) difference for all subjects was not significant: before pregnancy versus after pregnancy: −120±46 vs −194±31 mL/year (difference

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Table 1 Clinical characteristics and outcomes

	Presentation			Pregnancy					Postpregnancy
Patient	Age	Feature	mTOR inhibitor treatment	Age	Gestation (weeks)	Delivery	Fetal outcome	Maternal complications	Treatment and outcome
1	22	TSC, PX	Sirolimus for 1 year stopped at pregnancy	24.6	28	C-section (FD)	Premature TSC	Bilateral pneumothorax, infected pleural space, oxygen dependent	Assessed for transplant, not performed. Sirolimus: 1-year PP
2	25	SOB		29.5	36	C-section (MH)	Healthy	Bilateral pneumothorax	Sirolimus: 0.8-year PP
3	30	PX		36.1	40	Natural	Healthy	None	Sirolimus: 0.7-year PP
4	31	PX	Everolimus stopped 3 years prior to pregnancy	35.0	37	C-section (MH)	Healthy	Pneumothorax, chest drain for 7 weeks, resolved post pregnancy. Pre-eclampsia.	
5	30	PX		31.8	40	Natural	Healthy	None	Sirolimus: 1.2 years PP
6	33	AML		35.4	39	C-section	Healthy	None	
7	29	SOB		30.9	34	C-section (MH)	Healthy	Bilateral pneumothorax, pleurodesis, deep vein thrombosis	Sirolimus: 0.4-year PP
8	24	AML, PX		26.2	38	C-section (MH)	Healthy	Bilateral pneumothorax and pleurodesis	Sirolimus: 0.8-year PP
9	35	AML		38.5	36	C-section (FD)	Fetal distress	None	
10	32	AML		34.4	36	Natural	Healthy	None	
11	36	PX		36.6	36	Natural	Healthy	Shortness of breath	Transplant, died
12	32	PX		37.6	36	C-section (OC)	Healthy twins	None	
13	31	PX		34.8	32	C-section (MH)	Healthy	Short of breath	Sirolimus: 5.4-year PP
14	19	TSC, PX		25.9	38	C-section (OC)	Healthy	Pre-eclampsia	Sirolimus: 1-year PP
15	23	PX	Sirolimus for 2.5 years stopped at pregnancy	29.8	40	C-section (MH)	Healthy	None	Sirolimus: 0.75-year PP
16	24	PX		34.4	40	C-section (MH)	Healthy	None	Sirolimus : 3.25 year PP

AML, angiomyolipoma; C-section, caesarean section; FD, fetal distress; MH, mental health; OC, obstetric concern; PP, postpregnancy; PX, pneumothorax; SOB, shortness of breath; TSC, tuberous sclerosis complex.

−73, 95% CI −189 to 44, p=0.06) and for DL_{CO}: −0.44±0.5 vs −1.2±0.2 mL/min/mm Hg/yr (difference −0.78, 95% CI −2.06 to 0.49, p=0.054), (table 2, figure 1 and online supplementary figure). Prepregnancy and postpregnancy CT scans were available for five subjects. Cyst scores increased in all cases, with a mean change from 11%±6% to 20%±12% (difference 9.6, 95% CI −0.65 to 19.8, p=0.06. figure 1). The impact of pregnancy was unpredictable with prepregnancy lung function unrelated to postpregnancy changes in FEV_1 (online supplementary figure).

DISCUSSION

For most women with LAM, pregnancy was associated with a fall in lung function and increased rates of loss of lung function. Although some had minimal or no change, rates of postpregnancy

Table 2 Yearly changes in FEV_1 and DL_{CO} before and after pregnancy

Subject	FEV_1 (% pred)	DL_{CO} (% pred)	ΔFEV_1 (mL/year)		ΔFEV_1 (%/year)		ΔDL_{CO} (mL/min/ mm Hg/year)		ΔDL_{CO} (%/year)	
Pregnancy	Before		Before	After	Before	After	Before	After	Before	After
2	1.6 (53)	13 (48)	−231	−198	−6.8	−5.99	−1.76	−1.55	−5.9	−3.9
3	2.6 (77)	20 (82)	−184	−284	−4.7	−7.9	−0.99	−0.93	−2.9	−2.6
4	2.8 (78)	18 (57)	−29	−173	−0.27	−4.2	−0.3	−0.71	−0.69	−2.0
5	2.5 (76)	18 (66)	−546	−315	−17.8	−10.2	−3.3	−2.59	−11.8	−9.3
8	3.4 (102)	17 (57)	−227	−420	−6.0	−11.9	–	–	–	–
9	2.8 (96)	19 (72)	−37	−66	−0.46	−1.5	0.78	−0.99	−3.29	3.3
10	3.3 (115)	29 (132)	50	−48	10.8	−0.87	3.7	-2	17.1	−8.6
12	2.8 (98)	19 (89)	−44	−95	−0.7	−2.6	−0.66	−0.78	−2.5	−3.2
13	3.4 (104)	–	21	−252	−0.9	−4.7	–	–		
14	2.1 (62)	15 (63)	−84	−151	−1.8	-4	−0.53	−0.81	−1.88	−3.0
15	1.7 (64)	11 (53)	−96	−165	−2.6	−5.6	−1.17	−0.96	−4.8	−4.2
16	2.0 (83)	17 (87)	−43	−157	−0.7	−6.0	−0.24	−0.98	−0.6	−4.3

Data shown only include measurements taken when not receiving an mTOR inhibitor. Subject numbers correspond to table 1 and the figure 1. ΔFEV_1 rate of change of FEV_1 (mL/year) and per cent predicted/year (%/year). ΔDL_{CO} rate of change of DL_{CO} (mL/min/mm Hg/year).
FEV_1, forced expiratory volume in 1 s.

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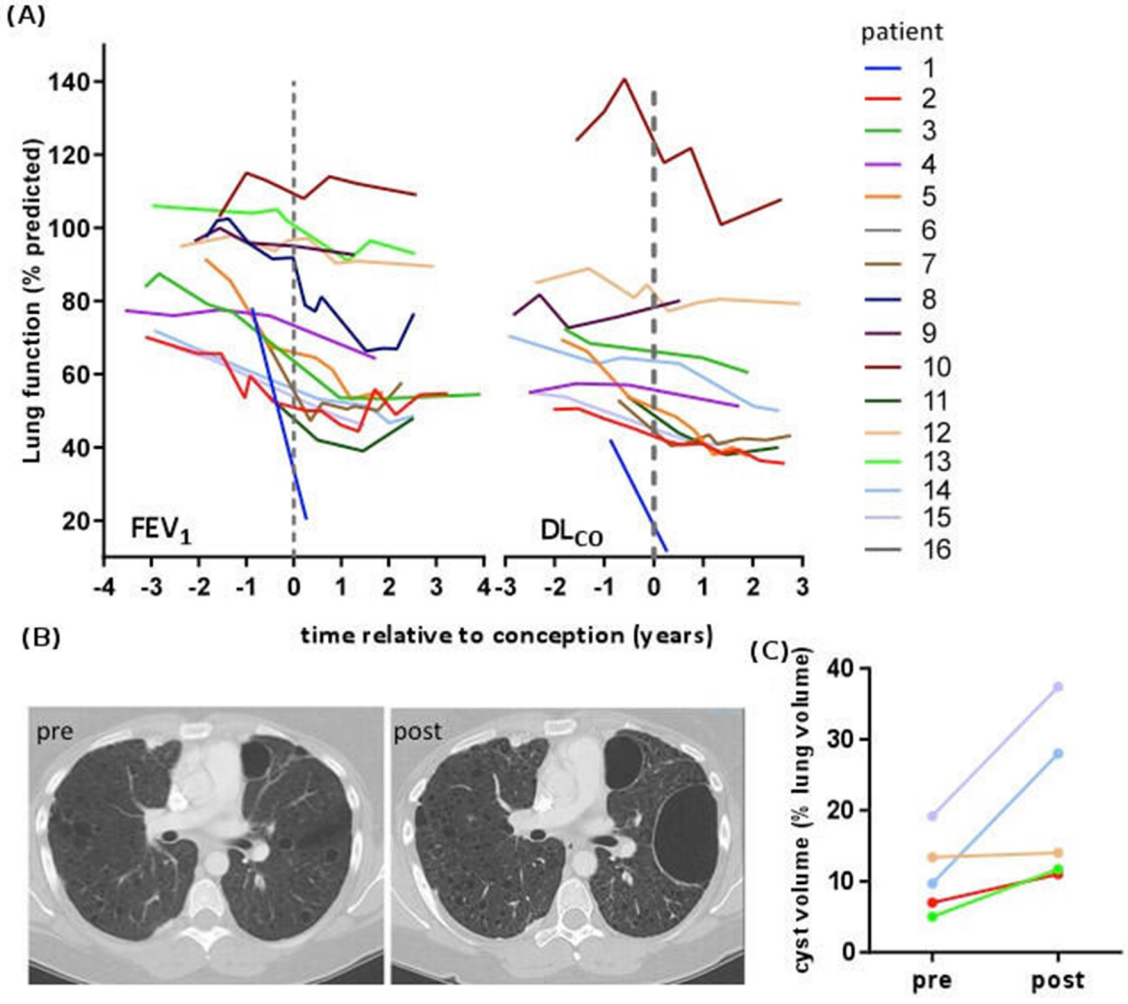

Figure 1 (A) Lung function trajectory in individual subjects before and after pregnancy for FEV_1 and DL_{CO}. The dashed line marks the start of pregnancy. Patient numbers correspond with tables 1 and 2 and (C). (B) CT scans of a LAM patient obtained 6 months before pregnancy (pre) and 6 months after delivery (post). Considerable progression of the cystic lung destruction was observed evidenced from an increase in cyst score from 9.8% to 28.8%. (C) Quantification of lung cyst scores as percentage of lung volume occupied by cysts for five subjects pre and post pregnancy. Two tail paired t-test p=0.06. FEV_1, forced expiratory volume in 1 s.

loss of FEV_1 and DL_{CO} were around twofold greater than reported in other cohorts of non-pregnant women with LAM.[3 9] Following pregnancy, 2 subjects were evaluated for lung transplant and 10 of 16 were treated with sirolimus.

Rates of pneumothorax, particularly bilateral pneumothorax, were high and while this may explain some changes in lung function: in most individuals rates of change in FEV_1 and DL_{CO} were greater after than before pregnancy with a mean increase of around 50%. There was also a trend towards increasing cyst scores after pregnancy. As LAM is a rare disease and lung function measurements variable, despite using two of the largest cohorts available, the small numbers of patients and variable timing of lung function measurements during pregnancy reduced study power and we could not definitively establish whether pregnancy was related to increased loss of lung function. Subjects here had a mean age of 28 at diagnosis, younger than many reported populations and loss of lung function greater than patients in other cohorts who were eventually treated with mTOR inhibitors.[10] Hence, another potential explanation for our findings is that the younger women undergoing pregnancy may have had more active disease before pregnancy than other premenopausal women with LAM. Larger prospective studies are required to definitively answer this question. Obstetric and fetal outcomes were reasonable; the high rate of caesarean sections observed were in many cases to prevent medical complications during labour rather than due to obstetric complications. Two babies with complications recovered and the remaining 14 were healthy.

Our study suggests that women with LAM may tolerate pregnancy and give birth to a healthy child. However, the risks of pneumothorax and loss of lung function should not be minimised even in those with near normal lung function. Those with moderate to severe lung disease should be warned of the potential of significantly reduced lung reserve after pregnancy.

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Patient consent for publication Not required.

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