Pregnancy experiences among women with lymphangioleiomyomatosis

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Summary
Lymphangioleiomyomatosis (LAM) is a rare lung disease affecting women. Following case reports that pregnancy exacerbates LAM, patients are frequently advised to avoid pregnancy. Our objective was to determine pregnancy and health outcomes in LAM to provide better evidence with which to counsel patients contemplating pregnancy.

We surveyed 328 women with LAM regarding pregnancy outcomes, pulmonary function, subjective and psychological functioning, quality of life, dyspnoea and fatigue.

Amongst childless women the main reason not to attempt pregnancy was based on concerns about potential effects of pregnancy on LAM. Almost two thirds of patients had been pregnant, the majority before LAM was diagnosed, in whom pregnancy outcome was generally favourable. Women diagnosed with LAM (n = 15) during pregnancy had high rates of pneumothorax (67%), miscarriage (7%) and premature birth (47%). The group diagnosed with LAM before or during pregnancy (n = 12) had lower mean FEV1, FVC and DLCO after pregnancy compared with those diagnosed following pregnancy or never pregnant. There were no differences in subjective or psychological functioning, quality of life, dyspnoea or fatigue scores between groups. In newly diagnosed LAM patients there was a high incidence of premature birth and pneumothorax. These adverse outcomes may be a marker of aggressive LAM.

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Introduction
Lymphangioleiomyomatosis (LAM) is a rare disease of women which affects the lungs and lymphatics. Clinical symptoms include shortness of breath with exertion, pneumothorax, and fatigue leading to debilitating respiratory impairment in many cases. 1,2 Angiomyolipoma, a benign kidney tumour, is also present in up to 50% of patients with LAM. 3 LAM is rare
in the general population (sporadic LAM) but is common in women with tuberous sclerosis complex (TSC-LAM). Both TSC and LAM are linked to mutations in the TSC1 and TSC2.4,5 The disease is generally progressive resulting in increasing airflow obstruction and impairment of gas transfer although clinical progression and rate of decline of lung function vary markedly between patients.6–8 Although no prospective data are available, retrospective 10-year survival from the onset of symptoms is between 71 and 91%.9,10 There is no proven treatment for LAM and patients generally receive supportive care including bronchodilators, supplemental oxygen and lung transplantation as appropriate.

Since LAM almost exclusively affects women and can be exacerbated by exogenous oestrogen it has been assumed that oestrogen is associated with disease progression and that increased oestrogen levels during pregnancy might exacerbate the disease. A number of case reports have described LAM presenting or worsening during pregnancy.11–13 A small series has shown that although some women have uncomplicated pregnancies, overall, pregnancy in LAM is associated with an increased incidence of pneumothorax.14 Although there is no firm evidence about the relationship between LAM and pregnancy, women with LAM are frequently advised to avoid pregnancy as it may exacerbate the disease. It is therefore important to know both the effect of pregnancy on LAM progression and the effect of LAM on pregnancy so that women with LAM considering pregnancy can make informed decisions.

To address these questions we used two international registries of LAM patients to survey women with LAM about their pregnancy experiences. The following questions guided the research: Did the diagnosis of LAM affect a woman’s decision to attempt pregnancy? Does LAM affect pregnancy outcome? And does pregnancy have an impact on the natural progression of LAM?

Methods

After the University of Toronto and the Trent multi-centre research ethics committees granted institutional research ethics board approval we mailed a questionnaire to women registered with the U.S. LAM Foundation (n = 448) and U.K. LAM Action (n = 59). Informed consent was assumed by return of the completed questionnaire. Non-respondents were mailed a second survey, followed 3 months later by a postcard reminder.

The survey included questions on date of birth, date of diagnosis with LAM, age of first LAM symptoms, and whether the respondent had a diagnosis of tuberous sclerosis complex (TSC). We gathered further information pertaining to LAM symptoms and complications, obtained a pregnancy history and collected health outcome data as detailed below.

- **Pulmonary function**: LAM Foundation participants were asked to send copies of their most recent pulmonary function tests (PFTs), including spirometry, lung volumes and diffusing capacity where available.
- **Activities of daily living**: The Functional Performance Inventory (FPI) is a reliable indicator of functional performance status and is validated in patients whose activity is limited by chronic lung disease.15 The FPI assesses several domains including physical exercise, ability to maintain the household, and body care scores are from 1 to 4, where 1 = ’no difficulty’ and 4 = ’don’t do because of health’.
- **Psychological functioning**: The Psychological General Well-Being Schedule (GWB) measures overall sense of well-being and has six subscales: anxiety, depression, vitality, self-control, general health, and positive well-being over the previous month.16 Higher scores represent better psychological health (less distress). Two questions pertaining to ‘general health’ were omitted because they did not apply to women with LAM.
- **Overall quality of life (QOL)** was measured by using a Visual Analogue Scale. Participants were asked to indicate their QOL over the preceding 4 weeks by placing a mark on a 10-cm line at the point that best depicts their rating. This measure has been used in prior health outcomes research to evaluate subjective QOL.17
- **Dyspnoea** was assessed by asking respondents about their frequency of shortness of breath (never, almost never, a little of the time, some of the time, a good bit of the time, most of the time and all of the time, scored 1—7).18
- **Fatigue** was assessed by the use of a 10 cm visual analogue scale (1 = most fatigued/tired, 10 = least fatigued/tired).

**Statistical analysis**

To assess the effect of LAM on pregnancy, we compared the pregnancy outcomes (full term or premature birth, miscarriage or therapeutic abortion) of the first three pregnancies for respondents who had ever been pregnant. These were categorised into three groups: women diagnosed prior to pregnancy, diagnosed during pregnancy, or diagnosed after pregnancy. We also determined the percentage of women in each group who had symptoms suggestive of LAM, namely, pneumothorax, chylothorax or breathlessness during a pregnancy.

To assess the effect of pregnancy on LAM, we compared longer term health outcomes for four groups: women diagnosed prior to pregnancy, women diagnosed during pregnancy, women diagnosed after pregnancy and women who had never been pregnant. These comparisons included continuous variables: the mean values for GWB, depression and anxiety subscales, dyspnoea and fatigue scores, QOL and FPI. Other comparisons included the percentage ever on a waiting list for lung transplant, ever had a lung transplant, pneumothorax, chylothorax or use of supplementary oxygen. To ascertain whether differences in pregnancy outcomes could be explained by other confounders, we determined the patients’ age at the time of pregnancy and socioeconomic status. Since only one woman was a current smoker, we did not compare smoking status.

Due to small numbers of pulmonary function test results, we combined the mean values between women diagnosed prior to or during pregnancy vs. those diagnosed after...
pregnancy or never pregnant. Chi-squared test, ANOVA (controlling for age and history of pneumothorax) were used to test for statistical significance using SAS version 8.0.

Results

We received 338 questions, of which 10 were incomplete leaving 328 usable questionnaires (overall response rate 70.5%). Most respondents were from the US (63.7%), 14.9% were from the UK, 6.7% were from Canada and 14.6% from other countries. Of the respondents, 51 (16.0%) had been diagnosed with TSC. Thirty women had been on a waiting list for transplant and 10 were post transplant.

Never pregnant group

One hundred and twenty three women (37.3%) had never been pregnant. Of these, 22% had no partner, 31% did not want children or did not want children yet. A further 8.2% had not become pregnant despite trying to conceive (Table 1). In total, 55% of the women without children avoided pregnancy because of concerns about the potential impact of a pregnancy on LAM: either because a health care professional had advised them against pregnancy (25%) or because they were concerned that a pregnancy would worsen their LAM symptoms (30%). A further 3% avoided pregnancy because they were worried about passing tuberous sclerosis on to their child.

Pregnancy group

Two hundred and five (62.6%) had been pregnant at least once (mean 1.8 pregnancies, range 1–8). Twenty-three women (12.4%) wanted additional children, but only three (1.6%) actually planned on having more children. Two hundred and four women provided information about their first five pregnancies (n = 373 pregnancies); all except two had three pregnancies or fewer. Most women (n = 178, n = 346 pregnancies) were diagnosed with LAM more than a year after completing their pregnancies. Fifteen women were diagnosed with LAM during a pregnancy (n = 15 pregnancies) and 12 women embarked on 15 pregnancies after they were diagnosed with LAM.

Effects of LAM on pregnancy

Pregnancy outcomes are listed in Table 2. Overall patients diagnosed with LAM during pregnancy had a worse pregnancy outcome, with significantly more premature births and miscarriages (53%, n = 8) than those diagnosed before pregnancy (20%, n = 3) or after pregnancy (15%, n = 50). More women with an existing or emerging diagnosis of LAM during pregnancy had their pregnancies terminated (17%, n = 5) compared with women diagnosed after pregnancy (7%, n = 24).

A diagnosis of LAM during pregnancy was associated not only with a worse obstetric outcome, but also with increased maternal respiratory complications: significantly more of the women whose LAM was diagnosed during pregnancy suffered breathlessness, pneumothorax or chylothorax than those whose LAM was diagnosed before or after pregnancy (Table 2). Of note, 5% of women who were diagnosed with LAM more than a year after their last pregnancy had a pneumothorax during a pregnancy implying that they may have already had LAM but the diagnosis was delayed.

Participants who were diagnosed with LAM after pregnancy were on average older than the other women at time of the survey (p < 0.0001) but were significantly younger (24.9 vs. 28.7–29.6 years) at the time of their first pregnancy (p < 0.0001).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Reasons for not having a pregnancy (n = 123).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason</td>
<td>N</td>
</tr>
<tr>
<td>No partner</td>
<td>27</td>
</tr>
<tr>
<td>Does not want children/not ready to have children</td>
<td>38</td>
</tr>
<tr>
<td>Unable to have children despite trying</td>
<td>10</td>
</tr>
<tr>
<td>Unable to have children due to sterilisation</td>
<td>12</td>
</tr>
<tr>
<td>Afraid to have children due to LAM</td>
<td>37</td>
</tr>
<tr>
<td>Advised by health care professional not to get pregnant</td>
<td>31</td>
</tr>
<tr>
<td>Concerned about inheritance of TSC</td>
<td>4</td>
</tr>
</tbody>
</table>

| a | Percentages do not add to 100% as multiple responses were allowed. |
The time since diagnosis did not vary between groups at the time of analysis ($p = 0.69$). There were no significant differences in socioeconomic status between women who were diagnosed prior to pregnancy, during pregnancy, after pregnancy or with no pregnancy. Women who had never been pregnant were less likely to be married ($p < 0.0006$).

Effect of pregnancy on LAM

Given the hypothesis that LAM is a hormone-dependent condition we investigated whether pregnancies affected the natural history of LAM (Table 3). There were no differences between the four groups for the FPI subscales body care, household maintenance or exercise, mean dyspnoea score, GWB total score, depression, anxiety or mean fatigue scores. Mean QOL scores were 7.2, 7.3, 7.3 and 7.4 for the four groups ($p = 0.92$).

The differences in proportions of women in the four groups who had ever been on a waiting list for transplant were not statistically significant. There were also no differences in the percentage of women who ever had a pneumothorax, chylothorax or were currently using supplemental oxygen. More women who were diagnosed during pregnancy were subsequently treated with progesterone ($p = 0.002$) than women in the other groups.

Pulmonary function tests

PFT results were received from 117 (36%) of women (Table 4). Not all women had test results for all PFT parameters. Compared to women who had been diagnosed after pregnancy, women who had been diagnosed before or during pregnancy had poorer lung function, with lower FEV$_1$, FVC and DLCO. There were also borderline differences in FEV$_1$/FVC ($p = 0.06$) and RV/TLC ($p = 0.08$).

Lung function in women who had never been pregnant was similar to lung function in women who were diagnosed with LAM after pregnancy on all parameters except the never pregnant group had a higher FEV$_1$/FVC ratio ($p = 0.003$).

Discussion

In this retrospective study of pregnancy and LAM over a third of women did not have children, compared to 15% in the general population. The majority of women based

| Diagnosis before pregnancy | Diagnosis during pregnancy | Diagnosis after pregnancy | Never pregnant | P-value$^a$ | P-value$^b$
|---------------------------|---------------------------|---------------------------|----------------|-----------|-----------
| $n = 12$ | $n = 15$ | $n = 177$ | $n = 123$ |
| Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Age at time of survey (years) | 37.1 (7.6) | 39.0 (4.5) | 48.7 (9.7) | 44.5 | 0.0001 |
| Age at first pregnancy (years) | 31.4 (7.3) | 28.9 (4.7) | 25.1 (5.3) | NA | NA |
| Time since diagnosis (years) | 6.6 (4.6) | 7.4 (3.7) | 6.6 (5.9) | 6.1 (5.3) | 0.77 |
| GWB total score | 71.6 (11) | 64.7 (14) | 70.0 (13) | 70.9 (13) | 0.37 |
| Anxiety (range 0–28, low = more anxious) | 17.3 (2.4) | 17.0 (2.5) | 17.4 (2.4) | 17.3 (2.6) | 0.96 |
| Depression (range 0–22, low = more depressed) | 16.3 (3.5) | 13.5 (4.2) | 15.3 (4.1) | 15.4 (3.7) | 0.25 |
| Dyspnoea score (1 = low, 7 = high) | 3.8 (1.5) | 4.3 (1.4) | 4.3 (1.4) | 4.2 (1.5) | 0.96 |
| Fatigue score (1 = low, 10 = high) | 4.6 (2.6) | 3.4 (2.0) | 4.2 (2.4) | 4.4 (2.6) | 0.44 |
| FPI body (1 = low, 4 = high) | 1.33 (0.49) | 1.27 (0.45) | 1.36 (0.54) | 1.40 (0.57) | 0.81 |
| FPI household (1 = low, 4 = high) | 1.73 (0.52) | 1.77 (0.59) | 1.80 (0.69) | 1.79 (0.75) | 0.99 |
| FPI exercise (1 = low, 4 = high) | 1.88 (0.55) | 1.93 (0.67) | 2.19 (0.78) | 2.10 (0.81) | 0.36 |
| Quality of life (1 = low 10 = high) | 7.22 (2.0) | 7.23 (1.5) | 7.35 (2.2) | 7.34 (2.2) | 0.92 |

NA: not applicable; FPI: Functional Performance Inventory; GWB: General Well-being Score.

$^a$ ANOVA: between three pregnancy groups.

$^b$ ANOVA: between four groups.

$^c$ Chi-square or Fisher’s exact test three groups.

$^d$ Chi-square or Fisher’s exact test four groups.
their decision not to have children on their disease, either out of concern that pregnancy would worsen LAM, because they were concerned about passing on TSC to their offspring, or because they had been advised by a health care professional not to get pregnant because of LAM. Ten percent of women had undergone sterilisation. Abortion rates were higher in women who were diagnosed with LAM prior to or during pregnancy than in women who became pregnant before they were diagnosed with LAM; suggesting that the extra abortions may have been performed on the account of LAM, possibly due to concerns about maternal health or pregnancy outcome.

In addition to the women who decided to remain childless, a further 8% of women were unable to conceive despite trying (compared to 4% in the general population). This is in keeping with previously published data, which demonstrated that women with LAM were less fertile and had fewer children. The reason for the lower fertility is not known, but chronic ill health may hinder conception and specific to LAM, progesterone treatment is contraceptive.

Sixty two percent of women studied had been pregnant at least once. Most of these pregnancies (88%) occurred at least 1 year before the diagnosis of LAM. Pregnancy outcomes in this group were good, with only 5% of pregnancies ending in miscarriage or still birth and only 5% delivering prematurely, even though a proportion of these women probably did have LAM at the time of their pregnancy (almost 5% of these pregnancies were complicated by development of a pneumothorax but LAM was not formally diagnosed until at least 1 year later).

Women who were diagnosed during pregnancy had the worst outcomes, with almost half of the pregnancies ending in premature delivery. It is not known whether these premature births were spontaneous or whether delivery was initiated by the obstetricians because of concerns about the foetus’ well-being or deteriorating health of the mother.

These findings are in keeping with early reports that describe the dramatic onset of LAM-associated symptoms during pregnancy. For example, Brunelli et al. describe a 26 year old woman in the 35th week of pregnancy presenting with massive bilateral chylothorax leading to an emergency caesarean section. Urban et al. reviewed 69 LAM patients, 75% of whom had at least one pregnancy. The onset of pulmonary symptoms occurred in 20% of these pregnancies, and marked exacerbation of existing LAM was observed in two patients during pregnancy. Johnson and Tattersfield evaluated 50 LAM patients of whom 28 had been pregnant and 27 had children. There was a higher rate of pneumothorax and chylous effusions during pregnancy than at other times and seven patients (14%) developed their first symptoms of LAM during, or immediately after a pregnancy. A study by Mitchell et al. examined 25 women with TSC and LAM who had 61 pregnancies; 4.9% had a pneumothorax during a pregnancy (all in the third trimester). In a comprehensive review article, Sullivan notes that “it is not clear whether pregnancy caused the acute progression of LAM or whether the haemodynamic and ventilatory perturbations associated with pregnancy simply brought out the symptoms of LAM that would otherwise not have been noticed until the disease progressed further”. It is also possible that LAM diagnosed during pregnancy may be a marker of more aggressive disease, as radiological and invasive procedures would probably have been delayed until after delivery for milder symptoms. On the other hand pregnancy may trigger a LAM flare in some women, although it is not known what predisposes to such an adverse response. One possible explanation is the variable expression of oestrogen and progesterone receptors in LAM tissue which could account for some women being more sensitive to hormonal changes than others.

Women who were diagnosed with LAM prior to pregnancy were at intermediate risk both for obstetric and respiratory complications compared to those women who were diagnosed whilst they were pregnant or those who completed their pregnancies prior to being diagnosed. The more favourable outcome compared to those with new active disease during pregnancy may be a reflection of disease severity. It is conceivable that women with milder disease are more likely to contemplate pregnancy, be more fertile and have a more favourable course during pregnancy whereas women with a more severe disease who may have poor pregnancy outcomes either avoid pregnancy or are less fertile.

Table 4 Most recent pulmonary function tests at time of survey by pregnancy status and timing of diagnosis of LAM.

<table>
<thead>
<tr>
<th>PFT</th>
<th>Diagnosis before or during pregnancy</th>
<th>Diagnosis after pregnancy</th>
<th>P-value**</th>
<th>Never pregnant</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 12</td>
<td>n = 65</td>
<td></td>
<td>n = 40</td>
<td></td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>Mean (SD)</td>
<td>49.9 (19.7)</td>
<td>0.006</td>
<td>68.6 (28)</td>
<td>0.12</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>Mean (SD)</td>
<td>75.8 (15.6)</td>
<td>0.038</td>
<td>78.5 (22)</td>
<td>0.44</td>
</tr>
<tr>
<td>FEV/FVC %</td>
<td>Mean (SD)</td>
<td>53.6 (18)</td>
<td>0.06</td>
<td>67.1 (16)</td>
<td>0.003</td>
</tr>
<tr>
<td>TLC % predicted</td>
<td>Mean (SD)</td>
<td>98.6 (12.1)</td>
<td>0.51</td>
<td>92.8 (15)</td>
<td>0.37</td>
</tr>
<tr>
<td>RV % predicted</td>
<td>Mean (SD)</td>
<td>139.5 (77)</td>
<td>0.22</td>
<td>110.1 (20)</td>
<td>0.08</td>
</tr>
<tr>
<td>FVC/TLC %</td>
<td>Mean (SD)</td>
<td>45.1 (15)</td>
<td>0.08</td>
<td>40.8 (11)</td>
<td>0.17</td>
</tr>
<tr>
<td>DLCO sb % predicted</td>
<td>Mean (SD)</td>
<td>41.2 (23)</td>
<td>0.004</td>
<td>64.4 (23)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

* ANOVA controlling for age and history of pneumothorax (diagnosis before or during pregnancy vs. diagnosis after pregnancy).
** ANOVA controlling for age and history of pneumothorax (diagnosis after pregnancy vs. never pregnant).
However it appears to be true for both groups that an established or emergent diagnosis of LAM during pregnancy may have a long lasting effect. On average, women with existing or emerging LAM who embarked on pregnancy had significantly poorer lung function (lower FEV₁, FVC and DLCO) than women who had children earlier and developed LAM later in life. Women who developed a pneumothorax during pregnancy but were not diagnosed formally with LAM (n = 18) had similar health outcomes, including lung function, as those who were diagnosed during pregnancy (data not shown). On the other hand women who were pregnant before a diagnosis of LAM had similar lung function to those women who had never been pregnant. These observations remained valid after correction for age, disease duration and history of pneumothorax. Our findings, although based on small numbers, support the perception that pregnancy adversely affects the natural history of LAM. Consistent with this, a previous study of 57 patients found that patients who had been pregnant reached MRC grade 3 dyspnoea sooner than those who had never been pregnant.⁷⁵

Women diagnosed before or around the time of pregnancy were on average 5 years older during their first pregnancy than those diagnosed more than 2 years after the birth of their child. A possible explanation for this observation may be that women who did not develop symptoms when faced with the hormonal challenge of pregnancy have a milder or less reactive disease phenotype and that the observed difference in respiratory function cannot solely be attributed to pregnancy.

In addition to counselling women with LAM about the possible effect pregnancy may have on their respiratory health, their emotional well-being should also be taken into account. Studies of women with fertility problems have shown high rates of depression, anxiety and difficulties with their partners.²⁵,²⁶ However, in our study there was no difference in the measures of quality of life, general well-being, depression or anxiety between women with or without children.

Although this is the largest study to address pregnancy in LAM our findings are still based on a relatively small number of patients. Given this caveat, our data suggests that if LAM remains stable during pregnancy, miscarriage rates are not increased and premature births are comparable to those in the general population. However, whilst women with LAM can have uncomplicated pregnancies (60% of pregnancies in women with existing LAM went to term): respiratory complications and adverse pregnancy outcomes are more common in patients who flare during pregnancy or in those who are first diagnosed during pregnancy, which may be a sign of a more aggressive disease. Furthermore pregnancy may adversely effect lung function long term although this does not appear to translate into worse dyspnoea or quality of life.

Conflict of interest

None of the authors has any competing interests to declare.

References