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

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Supplementary methods and results.

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Supplementary methods

Subjects and data collection.

Sixteen patients are the subject of this report. All had LAM as defined by current ATS/JRS criteria[1]. Nine patients participated in a UK country-wide study and were receiving clinical care at the UK LAM Centre. The remaining seven were enrolled at the NIH Clinical Research Center in a LAM natural history and pathogenesis protocol (NHLBI Protocol 95-H-0186). The studies were approved by East Midlands Research Ethics Committee (Reference 13/EM/0264) and the National Heart, Lung, and Blood Institute Institutional Review Board respectively. All subjects provided written informed consent.

Both cohorts prospectively recruited subjects to study the natural history of LAM. All clinical data and measurements were part of clinical care and taken according to individual medical need rather than at pre-determined intervals. All patients with clinical data prior to, and following pregnancy were selected for this study. Medical records of all patients were reviewed to establish time of gestation, date and method of delivery, fetal outcome, morbidity, complications during pregnancy, and clinical course before, during and following pregnancy. Pre and post-pregnancy pulmonary function data were available to evaluate changes in lung function. Of the 16 patients, 14 had at least one pre and post-pregnancy FEV_1 measurement, 12 had serial lung function data for FEV_1, and 10 for DL_{CO}. In the case of the NIH patients, in those with pre and post-pregnancy CT scans available, we measured cyst scores, by quantifying the percentage of lung volume occupied by cysts, as previously described[2].

Post bronchodilator lung function was performed either at the NIH Clinical Centre or lung function unit at Nottingham University Hospitals NHS Trust. As mTOR inhibitors reduce rate of loss of lung function, lung function measured when patients were taking an mTOR inhibitor was not included in the analysis. Rate of loss of lung function was calculated as the slope of a regression line through all measurements, calculated using Microsoft Excel as previously described[3].

Statistical analysis.

To determine whether pregnancy affected lung function, changes in lung function were examined using mixed effects models[4]. The primary endpoint was the comparison of rate of

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loss of lung function before and after pregnancy. Analyses were adjusted for pre-pregnancy values of FEV_1, DL_{CO} and time of visit with timing of conception calculated from the foetal age at delivery. Generalized Additive Models with Kruskal-Wallis test were used to compare pre and post-pregnancy FEV_1 and DL_{CO}. Pairwise comparisons were performed if the overall significance test was ≤0.05.

Because our dataset contained a small number of subjects, the unstructured covariance matrix was thought to be the most flexible since it imposes no pattern on the covariances. However, the mixed effects modelling could not derive a variance matrix of covariance parameter estimates for DL_{CO} with the assumption of unstructured covariance matrix. We therefore used both the compound symmetry and the Toeplitz covariance matrix assumptions. We compared these covariance structures by using the same model but specifying a different covariance structure for each, comparing the two model fit statistics using AICC. Toeplitz performed better than the compound symmetry. Of note, when using FEV_1 as the outcome, Toeplitz performed as well as the unstructured covariance matrix. We therefore assumed Toeplitz as the correlation structure for all the analyses.

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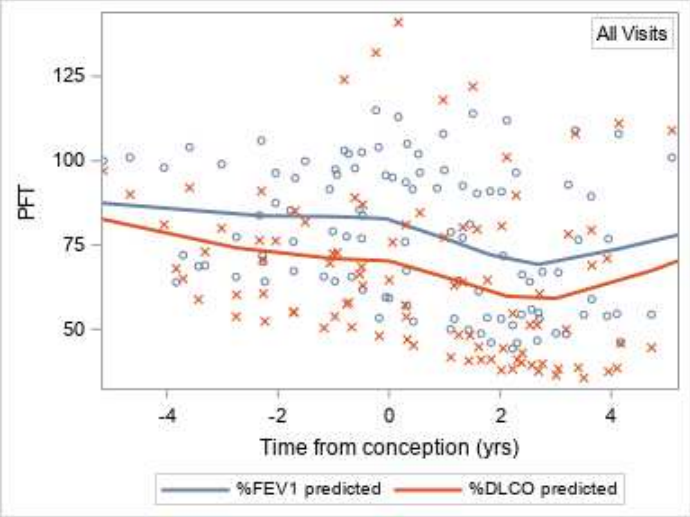
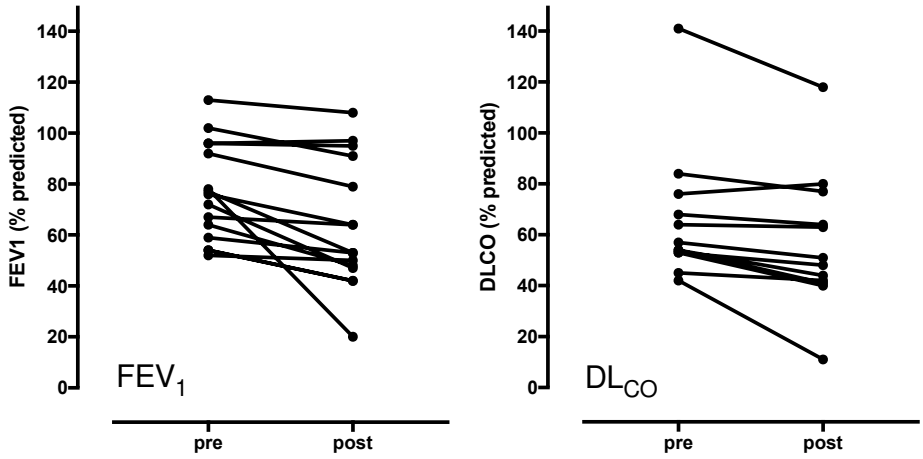
Supplementary results

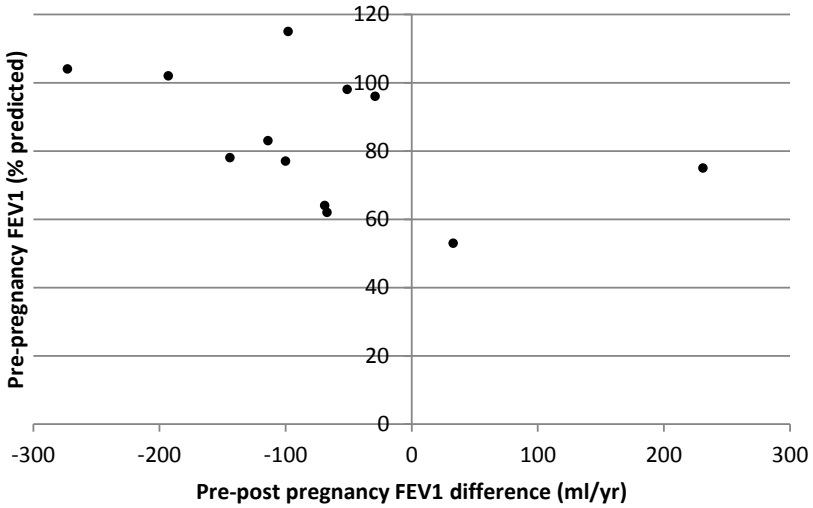
Supplementary figure 1. Combined pulmonary function tests for all visits. Taken within 5 years of before or after conception, from all subjects. Depicted lines are based on a non-parametric (Loess) estimate of the relationship of PFT and time from conception. Negative time indicates years before conception.



Supplementary figure 2. Lung function before and after pregnancy. Values shown are FEV_1 (n=14) and DL_{CO} (n=12) closest before conception and closest following delivery for all subjects where data were available (both p<0.01 by paired t-test).



Supplementary figure 3. Pre-pregnancy lung function and pregnancy associated lung function change are unrelated. Figure shows the difference in pre- and post-pregnancy annual change in FEV_1 according to percent predicted FEV_1 prior to pregnancy. There was no significant association between pre-pregnancy lung function and change following pregnancy.



Supplementary References

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