

LAM ACTION

Supporting women with
Lymphangiomyomatosis



Lymphangiomyomatosis

LAM

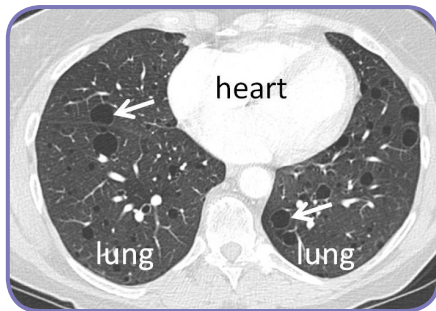
Fact Sheet

Lymphangiomyomatosis or LAM is a rare lung disease that occurs almost exclusively in women. For every million women approximately 7 will have LAM. We are aware of approximately 240 women in the United Kingdom who have LAM and around 10 new cases are diagnosed each year. It appears to occur worldwide and to be equally rare in other countries.

The average age of onset of LAM in patients in the United Kingdom is 34 years. It nearly always starts before the menopause and when, rarely, it has been diagnosed after the menopause, it has usually been in women who were taking hormone replacement therapy.

WHAT IS LAM?

LAM mainly affects the lungs, where an abnormal type of cell (called a LAM cell) builds up. This build up of LAM cells occurs around the airways (breathing tubes) and also around the blood vessels and the lymph vessels (lymph vessels drain excess fluid from the lungs). The LAM cells lead to cysts developing in the lung and these may be seen on a chest x-ray and are shown very clearly on a CT lung scan. The main effects of LAM are in the lung but around half of patients also have tumours in the kidneys; they are not malignant but can cause bleeding. Lymph nodes may also be enlarged, usually in the chest or abdomen but they only cause problems occasionally.



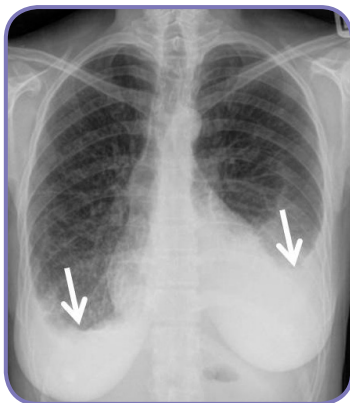
CT Scan of the lungs from a patient with LAM

Black, air filled lung cysts, shown by arrows, are seen within normal lung tissue which appears grey in the scan.

The name lymphangiomyomatosis reflects the different components of the disease. *Lymph* and *angio* refer to the lymph and blood vessels that are involved and *leiomyo* refers to smooth muscle which LAM cells resemble. LAM that occurs on its own is sometimes called sporadic LAM to distinguish it from LAM that occurs in patients who also have tuberous sclerosis (see page 5).

WHAT HAPPENS WHEN YOU HAVE LAM?

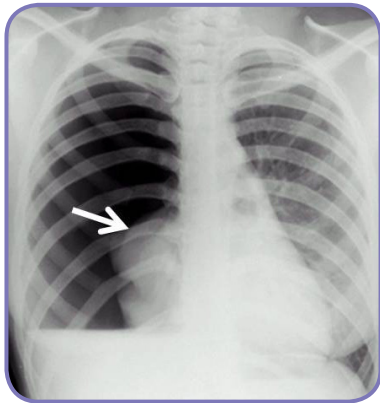
LAM affects different women in different ways. The main problem usually is breathlessness, particularly when a woman exerts herself. This is due to the effect of the cells on the airways and also to the cysts which take up space in the lungs. Some people are breathless due to the development of fluid around the lung (known as a pleural effusion). The fluid is usually milky (chylous) and occurs when the lymph vessels are blocked. Occasionally some lymph is coughed up as sticky whitish phlegm. Similarly, because LAM can affect the blood vessels in the lung, some women cough up blood from time to time.



Chest X-ray showing chylous effusions

The white areas at the bottom of both lungs (arrows) are a build up of chylous fluid around the lungs. This restricts the lung's capacity to inflate and causes breathlessness.

For many women with LAM the first sign of the disorder is when they develop a collapsed lung, known as a pneumothorax. This occurs when one of the cysts bursts and air leaks into the space around the lung. A pneumothorax usually causes sudden breathlessness, often with a sharp pain, and it requires treatment in hospital (see below). If the pneumothorax recurs an operation is usually needed; this will prevent a further pneumothorax though some women continue to be aware of occasional gurgling in their chest after the operation.



Chest X-ray showing a pneumothorax

The x-ray shows the right lung (left of the picture) has collapsed (arrow). The remainder of the right lung is filled with air which looks darker than the normal, inflated, left lung on the x-ray.

WHAT IS THE CAUSE OF LAM?

The cause of sporadic LAM is at present unknown. We know that it is not inherited and it is not passed on to children. We also know that one of two proteins (called tuberin and hamartin) are abnormal in LAM tissue. This is due to mutations in the genes responsible for these proteins. The proteins act as a brake on the growth of LAM cells and when they are abnormal there is excessive growth of these cells. Why this should happen is not clear, however, but stopping the growth of these cells is the main focus of research (see below).

EFFECT OF HORMONE CHANGES ON LAM

LAM usually progresses over time although the rate at which it progresses varies considerably between individuals. Since LAM occurs almost exclusively in women and generally occurs before the menopause it is thought to be influenced by female hormones such as oestrogen which may accelerate the disease. The effect of events such as pregnancy that cause hormone levels to change and the effect of hormones in 'the pill' and in hormone replacement therapy (HRT) are not well established but the best evidence to date suggests the following:

- **Pregnancy** Some women with LAM have been pregnant without any problems whilst in others the progress of the disease appears to have accelerated. Complications such as pneumothorax and pleural effusion appear to occur more often during pregnancy.
- **Hormone replacement therapy (HRT)** HRT contains oestrogens and there is some evidence to suggest that it may make LAM worse.
- **Menopause** The rate at which LAM progresses may slow down after the menopause, although this is not always the case.
- **The contraceptive pill** Most contraceptive pills contain oestrogen and progesterone and although the evidence that the contraceptive pill makes LAM worse is limited, a progesterone only contraceptive pill may be safer. Alternative means of contraception which do not use hormones could also be used.
- **Fertility treatment** If oestrogen makes LAM worse it is likely that fertility treatment will do the same.

Women with LAM who wish to consider becoming pregnant or who are taking or wish to take the contraceptive pill, hormone replacement therapy or fertility treatment should discuss this with their physician before making changes.

HOW IS LAM DIAGNOSED?

Many symptoms of LAM are similar to those of more common lung diseases such as asthma and for this reason women may have symptoms for some time before LAM is diagnosed. Symptoms, X-rays and breathing (lung function) tests may suggest LAM but the diagnosis is usually confirmed by a CT scan (a detailed X-ray

scan] of the lungs and sometimes with a lung biopsy. In a woman with LAM the CT scan usually shows typical cysts throughout the lungs. In around one third of cases a lung biopsy is performed to ensure that the diagnosis is correct. This is usually carried out through a fairly small incision in the chest under a general anaesthetic. In LAM the biopsy will show the typical cysts and LAM cells. The kidney tumours are also seen best on a CT scan although they can also be seen with ultrasound. If a patient has kidney tumours or tuberous sclerosis in addition to the characteristic changes on the lung CT scan a diagnosis of LAM can usually be made without the need for a lung biopsy. Recently a raised blood level of a LAM related protein, called VEGF-D, has also been used as a diagnostic pointer for LAM. All of these features should therefore be looked for before deciding to perform a lung biopsy.

HOW DOES LAM PROGRESS?

As the LAM cells build up and lung cysts form there is a deterioration in lung function, but the rate at which this occurs varies markedly between patients. A few women still have moderately well preserved lung function 20 years after being diagnosed with LAM, whilst others are less fortunate and deteriorate quite rapidly. Most patients are between these extremes. Looking at change in lung function over a period of time gives a good indication of the rate at which the disease is progressing in an individual.

IS THERE ANY TREATMENT FOR LAM?

Unfortunately there is no cure for LAM as yet. However there is now evidence to show that one drug (sirolimus or Rapamycin) can slow the rate of decline in lung function and reduce the size of the kidney tumours. Other treatment may be given to deal with particular symptoms or complications (supportive treatment).

TREATMENT TO PREVENT LAM PROGRESSING

Recently, a number of studies have shown that the drug Rapamycin (sirolimus) can slow the rate of loss of lung function and shrink kidney tumours in women with LAM. However, use of Rapamycin and similar drugs for LAM is still new and a number of important questions remain, including what is the safest effective dose, when should we start treatment and what is the best way to monitor treatment? Rapamycin commonly causes side effects and needs careful monitoring and it is not appropriate for all patients. At present Rapamycin is mainly prescribed for women with more severe LAM and those with chylous pleural effusions.

In the past, various hormone treatments have been tried for LAM but because LAM is rare they have not been studied in the normal way i.e. by comparing treatment with a dummy treatment (placebo) in a controlled trial. These treatments, such as progesterone, tamoxifen and hormones that reduce the release of oestrogen, are used less often now since the evidence available does not suggest that they are useful.

New experimental approaches to treating LAM are under investigation including combinations of hormone blocking treatments and Rapamycin, and clinical trials are starting in various countries. New treatments have to be assessed carefully as the drugs are not without risk. LAMPost and the LAM Action website www.lamaction.org will keep you up to date on developments.

SUPPORTIVE TREATMENT

- 1. For breathlessness.** Treatment for breathlessness depends on the cause of the breathlessness. For example, if there is a pneumothorax or a pleural effusion treating these should help the breathlessness. Some patients benefit from the β -agonist inhalers used for asthma such as Ventolin and Bricanyl. For breathlessness due to panic attacks - see below.
- 2. Fluid on the chest (pleural effusion).** If this is large it may help to remove the fluid, though in the long term it is better to prevent it accumulating. This may be helped by Rapamycin, or if that isn't possible by a low fat diet. If it continues to build up an operation may be needed to stick the outside of the lung to the inside of the ribcage. This is known as a pleurodesis and is usually carried out with a general anaesthetic.
- 3. Pneumothorax.** This is usually treated initially by sucking the air out of the space around the lung with a needle or tube inserted under a local anaesthetic. If it recurs it may also be treated by a pleurodesis so that the lung can't collapse again.

- 4. Oxygen.** When breathlessness becomes more troublesome breathing additional oxygen may help. Oxygen can be given from oxygen cylinders or from a machine called a concentrator which extracts oxygen from air. Having a concentrator is more convenient if you need oxygen for several hours a day and means you don't need to keep replacing oxygen cylinders which may only last for 6 hours. Portable oxygen systems are also available. There are no hard and fast rules as to when oxygen should be started but patients who have to stop after walking 100 to 200 yards are likely to benefit.
- 5. Lung transplant.** Lung transplantation is a possibility for patients with severe LAM. More than 100 women with LAM have had a lung transplant worldwide and overall the outcome in patients with LAM appears to be at least as good as the outcome in patients who have had a lung transplant for other conditions. A lung transplant is a major undertaking, however, and the results are not yet as good as those for a kidney transplant. It is only considered therefore when LAM has become very severe.

GENERAL

- 1. Smoking.** It is clearly not sensible to smoke if you have LAM since the damage to your lungs from smoking will only add to that of LAM.
- 2. 'Flu jab.** As with all people with a significant lung condition it is sensible to have a 'flu jab each winter. It may also be worth having a pneumococcal vaccination to reduce the risk of pneumonia. This should be discussed with your doctor.
- 3. Chest infections.** These occur more often in women with LAM and can be more protracted. Prompt treatment with antibiotics is usually appropriate.
- 4. Keeping fit.** There is good evidence from other types of lung diseases that there are benefits from keeping fit, and keeping weight under reasonable control. When LAM becomes more severe a pulmonary rehabilitation course may provide an extra stimulus but the main thing is to walk as much as you can. Exercise often helps to promote a feeling of well-being in addition to helping fitness.
- 5. Emotional Support.** Being given a diagnosis of LAM is frightening and upsetting and women may need a lot of emotional support at this time from family and friends. Further help can be obtained from other women through LAM Action (see below), and professional help should be sought if necessary.
- 6. Panic attacks.** As with other chronic illnesses, women with LAM may suffer from bouts of anxiety and depression, and people with respiratory problems, such as LAM, often suffer from panic attacks. These attacks exacerbate symptoms of breathlessness and may suggest that LAM is more advanced than it is. Help for panic attacks should be sought through LAM Action or from a doctor. Learning good breathing techniques from a physiotherapist can help.

TREATMENT OF KIDNEY TUMOURS

Some women with LAM have one or more benign tumours in the kidney (called an angiomyolipoma). Most kidney tumours in LAM are small, do not cause symptoms and do not need treatment as they are benign. Women with LAM should have a kidney scan to see if angiomyolipomas are present, and if they are present, they should be monitored to ensure they are not growing. Occasionally larger tumours cause pain or bleeding and may need to be treated. This is done either by removing the tumour with an operation or blocking its blood supply (embolisation) which causes it to shrink. Embolisation is done through a catheter inserted into the artery to the kidney and it does not normally need a general anaesthetic. Patients recover more quickly from embolisation. It is not possible to treat all tumours in this way however and the procedure is not performed in all hospitals. The aim of treatment is to preserve as much normal kidney as possible, and avoid removing a kidney unless there is no alternative.

LAM AND TUBEROUS SCLEROSIS

Both the lung condition and the kidney tumours seen in LAM can occur in people with a disease called tuberous sclerosis. Tuberous sclerosis is generally associated with unusual skin changes, tumours in other organs and sometimes epilepsy (fits), learning and behavioural problems. There is a very important difference between tuberous sclerosis and sporadic LAM which is that tuberous sclerosis is inherited whereas sporadic LAM is

not inherited. Most women presenting with LAM do not have tuberous sclerosis and when tuberous sclerosis is present it is usually obvious from childhood. Very occasionally people with tuberous sclerosis have a limited form of the disease and few medical problems, so the diagnosis may be overlooked for a time. For these reasons some women with LAM may need more tests to ensure they do not have a mild form of tuberous sclerosis in association with LAM.

UK NATIONAL CENTRE FOR LAM

The National Centre for LAM is in Nottingham. It delivers specialist clinical care for women with LAM and suspected LAM. The service can be accessed by all those with LAM in England and Scotland and elsewhere by arrangement. It is designed to help ensure timely diagnosis and best management, and it has links to colleagues in Birmingham for management of kidney problems, and at the Freeman hospital in Newcastle for issues relating to lung transplantation. More information is available at:

[https://www.nuh.nhs.uk/our-services/all-services/national-centre-for-lymphangiomyomatosis-\(lam\)/](https://www.nuh.nhs.uk/our-services/all-services/national-centre-for-lymphangiomyomatosis-(lam)/)
or by e-mail at: LAMcentre@nuh.nhs.uk

AIR TRAVEL

Those with LAM often wish to travel by air and the question is whether it is safe to do so. The simple answer is not completely, although the risk is small. It depends to some extent on the type and severity of the lung disease and recent treatment. If in doubt discuss this with your doctor.

Problems with air travel may occur for different reasons, all due to the fall in air pressure in the cabin as the plane gains height. The first is a general problem. Anyone who is breathless on modest exertion, for whatever reason, is likely to be more breathless in an aeroplane because oxygen levels are lower as a result of the lower air pressure. Low oxygen levels may also make flying more tiring. Breathlessness is unlikely if you are reasonably active but it could be a problem if life is now fairly restricted by LAM. In general people who can walk 100 yards or climb ten steps without being breathless should have no problems. Oxygen saturation levels are probably a better guide (normal values 98%). If resting values are above 92% oxygen should not be needed. The cut off point should be slightly higher, around 95%, for patients at particular risk for a pneumothorax, for example, or those who had one within the last year.

The other problems relate specifically to LAM. Women with a small pneumothorax prior to flying will find that this becomes larger and breathlessness will worsen. There is also a very small risk of a cyst expanding and causing a new pneumothorax during air flight. Neither problem should occur in patients whose lung has been stuck down (pleurodesis). Cysts could in theory enlarge without bursting but we have no evidence to show that this occurs. Flying should be postponed for six weeks after a pneumothorax, uncomplicated thoracic surgery or a significant chest infection.

So how big is the risk? In a survey in the US one in 20 women with LAM had had a problem when flying; we don't know exactly what the problems were but most were not serious. The risk appears to be fairly small in women with reasonable lung function and no new symptoms prior to flying to suggest that they have developed a small pneumothorax (e.g. an increase in breathlessness or chest pain). Women with symptoms before flying may need a chest X-ray to determine whether or not a pneumothorax is present. The risks otherwise depend on individual factors including lung function and whether the lung has been stuck down.

Practical tips. It is possible to get oxygen for a flight although the system varies with different airlines (some charge whilst others don't). It must always be ordered in advance. You can't take your own cylinder or concentrator. For more detailed information contact LAM Action or go to the LAM Action website. Some women with LAM have found it difficult to obtain insurance for holidays abroad whilst others have not. If you are having difficulty LAM Action may be able to advise. Finally, air travel is tiring for the hale and hearty so consider ways of reducing the hassle e.g. asking in advance for a wheel chair at the airports.

LAM REGISTER

A confidential register of UK women with LAM is held in Nottingham by Professor Simon Johnson of the University of Nottingham. This is used to help with research. We encourage all women with LAM in the UK to sign up to the register. To do so please contact Jill Pateman for a registration form.

WHAT IS HAPPENING IN OTHER COUNTRIES?

In the United States the LAM Foundation, started in 1995, has been very successful in bringing LAM to the attention of important national bodies and in raising money for research, in addition to providing support for women with LAM. The National Institutes of Health in the United States (NIH) has a register of women with LAM and assesses patients on a regular basis.

Many countries around the world now have support groups and/or LAM registers. Because LAM is rare it is particularly important that knowledge, discussion of best practice and research ideas are shared. This is widely recognised by both women with LAM and scientists with regular international meetings and communication between groups.

One consequence of this collaboration was the development of the European Respiratory Society Guidelines for the diagnosis and management of LAM in 2010. This document covers all aspects of LAM and used the most up to date evidence to determine the best way that LAM should be diagnosed and how patients with different complications should be managed.

WHAT RESEARCH IS TAKING PLACE?

Since 1995 both laboratory and clinical research into LAM has increased dramatically. In particular the US LAM Foundation has successfully involved a number of centres in basic laboratory work to try to find the cause of LAM. Data on women with LAM are being collected in several countries, including the UK.

Research in Nottingham (supported by LAM Action) involves both clinical and laboratory research. Clinical research, including several surveys of women with LAM, has provided a clearer picture of how lung function (breathing) tests change over time, the role of early life events in women with LAM and more details of the long term progress in individuals. These figures and the LAM register help us to plan studies of treatment. In the laboratory research is focusing on how changes in the two proteins that are abnormal in LAM, tuberin and hamartin, lead to the increased growth of LAM cells. Knowledge of the cellular events involved in LAM led to the suggestion that one treatment (Rapamycin) might be helpful in LAM, and subsequent confirmation in clinical trials.

These approaches provide hope that more effective and safer treatments can be found. Substantial progress has already been made and we expect to have more treatment options within the next five to ten years.

THE FUTURE - A THREE-PRONGED APPROACH

1. The best solution for those with LAM is to find out how to counteract the effects of the abnormal proteins in LAM cells so that the disease can be prevented or at least halted. This is the purpose of basic laboratory research.
2. Clinical studies are needed to find out more about LAM and to test potential new treatments as they become available. To do this properly requires well designed clinical trials comparing one treatment with another or with a dummy. Because LAM is rare this is difficult but with international collaboration it should be possible to find enough women who would be willing to take part in a treatment trial for maybe one or two years.
3. To provide help and support for those with LAM. People with a rare disease suffer from isolation and LAM Action has enabled women to meet others with LAM, to communicate by phone, email or other social media, and learn more about LAM through the website and LAMPost. The annual meeting in Nottingham has grown steadily and all those with LAM and their families and friends are welcome.

LAM ACTION

Those with LAM are unlikely to know anyone who has heard of LAM or who has the condition and this may lead to feelings of isolation. The UK LAM Trust was set up in 1997 following a meeting of 21 women with LAM in Nottingham. In 2003 the name was changed to LAM Action when the association became an independent charity (registered charity number 1167610). LAM Action is primarily a support group, providing information and encouragement to those with LAM and their families. It has a very active email support group together

with a network of women willing to talk and provide support to others. There is also a lively, informative and entertaining newsletter for members of LAM Action called LAMPost, which is published 3 times a year, and a comprehensive website www.lamaction.org. LAM Action has strong links with the medical profession and other LAM organisations and groups around the world.

The other primary function of LAM Action is to advance research into LAM. It also raises money to fund its primary activities.

For further information about LAM Action, contact

Jill Pateman
LAM Action Coordinator
LAM Action
Nottingham Voluntary Action Centre
7 Mansfield Road
Nottingham NG1 3FB
Telephone: 07710 527636

E mail: jill.pateman@office.lamaction.org

Or visit www.lamaction.org



FEEDBACK

This fact sheet was prepared by Simon Johnson and Anne Tattersfield from Nottingham, and LAM Action's Executive Committee. Comments on the format and content are welcome.

Professor Simon Johnson
Professor of Respiratory Medicine,
Division of Respiratory Medicine,
University Hospital,
Nottingham,
NG7 2UH

simon.johnson@nottingham.ac.uk

Professor Anne Tattersfield

anne.tattersfield@nottingham.ac.uk



LAM Action members making their way home from the Annual Meeting