What is reproductive immunology?

Reproductive immunology is a service offered by a few fertility clinics in the UK. It includes a range of tests and treatment to do with the patient’s immune system in pregnancy.

There is much debate about the role of the immune system in promoting or preventing a healthy pregnancy. This information outlines the latest findings and views of experts on the topic so far (to October 2008). It does not reflect studies and views published after it was written.

Why may I be offered tests and treatment on my immune system?

If you have had repeated miscarriages, some doctors think your immune system may be rejecting your pregnancy. Generally, your immune system fights off invading cells that have a different genetic pattern to yours. These invaders can include viruses or transplanted organs. A fetus in your womb also has a different genetic pattern, because it carries the father’s genes as well as yours. So, in a normal pregnancy, it is thought that your body does something to stop the fetus being rejected - in other words, to suppress the normal immune response. However, there is no convincing evidence that immune rejection of the fetus does actually ever happen in women with fertility problems.

Natural Killer (NK) cells are immune system cells that normally help the body fight infections. The idea has arisen that your NK cells may be attacking the fetus as an invader. The doctors may suggest testing your blood for high levels of NK cells and then using drugs to suppress the action of these cells.

However, many doctors question this approach. It’s not clear whether:

- the Natural Killer (NK) cells normally found in the blood ever do attack the fetus
- measuring and then suppressing the level of NK cells in the blood has any effect on the chances of a successful pregnancy.

What are Natural Killer (NK) cells?

NK cells are one type of lymphocyte - an immune cell - normally circulating in blood. The lining of the womb contains immune cells that resemble NK cells in many ways, so they are called uterine NK cells.

But there are two main differences:

- Uterine NK cells are not found in the blood. They occur only in the lining of the womb during early pregnancy, while the embryo is implanting itself there and the
placenta is developing. Therefore some doctors and scientists strongly doubt whether any meaningful information about uterine NK cells can be obtained from a blood sample.

- There is no evidence that uterine NK cells are destructive and attack placental or embryonic cells.

**What do uterine NK cells do?**

Uterine NK cells are present in large numbers in the wall of the womb at implantation and in the early months of pregnancy. They seem to help the placenta link up with your blood vessels and so set up a healthy supply line to the fetus. However, scientists don’t know exactly how they do it. (In mice that lack NK cells in the womb, development of the placenta is abnormal and the young are smaller than usual.)

**What tests are offered?**

Some clinics offer blood tests to measure the level of NK cells in your blood and how effectively they kill invader cells. But these blood tests will only measure blood NK cells and can’t measure or test uterine NK cells. There is no strong evidence that the number and activity of NK cells in the blood says anything about the number and activity of your uterine NK cells.

So these tests, and any treatment based on them, are in their early days and there is very little scientific evidence to show they are effective.

**What treatments are offered and what are their possible side effects?**

Treatments to "suppress NK cells" offered by some clinics include:

- high-dose steroids
- intravenous immunoglobulin (IVIg)
- tumour necrosis factor-a (TNF) blocking agents.

These treatments are not licensed for use in reproductive medicine. As with all medical interventions they carry risks and potential side effects. You should make sure you are told about all these. You should only receive treatment after giving fully informed consent.

Also, there is no widely accepted scientific explanation of any benefits these treatments may have in reproductive medicine.

**Steroids**

Corticosteroids are a type of drug (a synthetic hormone) that can suppress immune responses, and are routinely used in the treatment of arthritis, asthma and other autoimmune disorders.
However, there is no proven advantage in using steroids in the first three months of pregnancy, and the risks to you and your baby outweigh any possible benefits. The National Teratology Information Service recommends that pregnant women avoid all drugs at this stage unless they are likely to benefit your health.

The Committee on Safety of Medicines says that corticosteroids taken in pregnancy can carry a small risk of poor fetal growth, though there is little other risk to the fetus.

A clinical trial in Canada tested the effect of giving pregnant women, who had previously suffered two or more unexplained miscarriages, a corticosteroid (prednisone). The study found that prednisone didn’t prevent miscarriage, and increased the risk of high blood pressure, diabetes and premature birth.

**Intravenous immunoglobulin (IVIg)**

IVIg is made from antibodies extracted from the blood plasma of many different donors. It is mainly given by intravenous drip as a treatment for immune deficiencies and autoimmune diseases.

IVIg carries varied and sometimes unpredictable risks:

- Side effects can include headache, muscle pain, fever, chills, low back pain, thrombosis (blood clots), kidney failure and anaphylaxis (a bad reaction to the drug), though these effects are generally mild and occur in less than one in 20 patients.
- Because immunoglobulins come from donor blood, there is the possibility of introducing blood-borne infections, such as hepatitis, HIV or CJD.
- IVIg contains antibodies. During pregnancy, antibodies cross the placenta into the bloodstream of the fetus. Therefore, in theory, IVIg antibodies could enter the fetal bloodstream, where they might react against some of the baby’s cells. However, this has not been seen in practice.

A detailed review of the risks associated with IVIg states "the practitioner considering IVIG for an unproven use must seriously weigh the potential benefit versus potential harm because of its varying and sometimes unpredictable immunomodulatory effects".

**TNF-a blocking agents**

Tumour necrosis factor (TNF) is a chemical produced by immune system cells, such as NK cells, which promotes inflammation and allows the immune system to attack the source of infections. TNF-a blocking agents are drugs used to block the effect of TNF - stopping inflammation but making the attack on infection less effective - and are routinely used in the treatment of arthritis, asthma and other immune disorders.

Several clinics offer the use of TNF-a blocking agents (Enovel, Remicade and Humira). However, there are risks:
• The makers of Remicade (infliximab) warn that using it may increase the risk of septicaemia; chronic infections such as tuberculosis; cancer of the lymphatic system; liver problems; white blood cell disorders; and strong reactions to the drug.
• The British National Formulary says infliximab should not be used in pregnancy.
• Humira (adalimumab) is not licensed for use in implantation failure (when the embryo fails to embed itself in the lining of the womb). Its effects on reproduction and fetal development are unknown.

**What evidence is there to show these treatments work?**

These tests and treatments are very new. They are based on claims that women who have repeated miscarriages or failed IVF had raised levels of NK cells in the blood; and on studies of pregnancies in these women after being treated with IVIg. However, the research studies may not be valid because of the differences between blood NK and uterine NK cells. And because the sample of patients was small, there are doubts about the value of the research results.

Three additional trials have suggested that IVIg may help prevent miscarriage. But the results are not reliable as too few patients took part and their treatments varied.

To date (October 2008), there is little scientific proof that these treatments are effective in improving your chance of having a baby. The little evidence currently available is strongly questioned by other clinicians and experts.

Professional guidance suggests that you should only be offered these therapies as part of clinical trials that are prospective, randomised and controlled (in other words, trials where the method of analysis is decided beforehand; patients are assigned randomly to one of the treatments being compared; and the new treatment is being tested against at least one well-tried treatment). Also, doctors should assess the results from these trials before drawing reliable conclusions about their potential benefits.

**Where can I find out more about these treatments?**

You can read more in the following sources:


The Cochrane Collaboration is a group of over 11,500 volunteers in more than 90 countries who apply a rigorous, systematic process to review the effects of interventions tested in biomedical randomised controlled trials. Cochrane reviews are considered to be a reliable source of evidence in healthcare.

This review of immunotherapy for recurrent miscarriage concluded that:
"Neither immunization with paternal leukocytes nor treatment with intravenous immune globulin (IVIG) improve the live birth rate in women with unexplained recurrent miscarriage. Both are expensive and have potential serious side-effects. Moreover, women should be spared the pain and grief associated with false expectations that an ineffective treatment might work. These therapies should no longer be offered as treatment for unexplained recurrent pregnancy loss. Furthermore, immunological laboratory tests which have been previously advocated as justification for immunotherapies have no predictive value for pregnancy success and should be abandoned."

2) Two papers reviewing the science of NK cells in pregnancy are freely available:


New studies and views in this field are continually being published. The Cochrane Collaboration review and the RCOG opinion paper do not take into account studies that have gone to press since they were written.

**What is the HFEA’s view on these tests and treatments?**

Unlike IVF itself, immunological tests and treatments do not require a licence from the HFEA. The primary role of the HFEA is to license and monitor centres that provide IVF treatment, other assisted conception procedures and human embryo research.

But fertility clinics licensed by us do have to provide appropriate information about any proposed tests or treatment to make sure you understand any risks and side effects and are giving informed consent.

There is little scientific evidence to show that these treatments are beneficial. The best information we can give patients is that presented in the Cochrane Collaboration review and RCOG opinion paper.

We would advise anyone being offered such tests and treatment to discuss them fully with their GP and clinic and to question the reasons for and against having them.
**What should I ask my doctor?**

If you are recommended immunological treatments as part of your fertility treatment, we advise you to make sure you feel properly informed about the potential benefits and risks of the tests and treatment.

Your clinic should explain:

- why they think the tests and treatment may help you
- what the risks and side effects may be
- the costs you will incur.

Remember that treatments can only be properly assessed in the context of a randomised clinical trial. Stories about individual women who have achieved a successful pregnancy after receiving these treatments do not prove that the treatments were effective. Without a proper clinical trial there is no way to assess whether a particular treatment has had any benefit.

Before agreeing to any immunological treatment, it is important to talk through all these topics with your clinic as well as with your GP. You also need to have had an opportunity to weigh up all the issues, and you should feel happy with your decision.

Questions you may want to ask include:

- Why do you think I need this treatment - can you explain what you think is happening in my body?
- What data or evidence do you have to prove that this treatment will improve my chance of having a baby?
- What will the treatment involve for me?
- How much difference do you think having this treatment will make for me?
- What are the side effects and risks of the treatment?
- How much will the tests and treatment cost me?