

## Scientific and Clinical Advances Advisory Committee Paper

<b>Paper title</b>	<b>Reproductive immunology update</b>
<b>Paper number</b>	SCAAC(02/15)08
<b>Meeting date</b>	04 February 2015
<b>Agenda item</b>	<b>8</b>
<b>Author</b>	Sarah Testori (Scientific and Clinical Policy Manager)
<b>Information/decision</b>	Decision
<b>Resource implications</b>	None
<b>Implementation</b>	Update the patient information on the HFEA website
<b>Communication</b>	Update the HFEA website, to be referred to in responses to relevant patient queries
<b>Organisational risk</b>	Low
<b>Committee recommendation</b>	<p>Members are asked to:</p> <ul style="list-style-type: none"> <li>• Review the recent literature in this area and consider the safety and efficacy issues that may arise from such techniques.</li> <li>• Review the HFEA website text (Annex A) and provide comments to the Executive, relating to possible updates and changes including any studies they feel should be added to the website text as highlighted articles.</li> </ul>
<b>Evaluation</b>	None
<b>Annexes</b>	Annex A: Current website information

## **1. Introduction**

- 1.1. Reproductive immunology is an area of medicine that explores how the immune system and reproductive system interact with each other. In fertility treatment, it is based on the theory that there must be effective regulation of the maternal (and fetal) immune systems in order for a successful pregnancy.
- 1.2. Peripheral Natural Killer (NK) cells are part of the immune system and there has been much debate in the literature about their role in female reproductive performance. Uterine natural killer (uNK) cells are thought to play a significant role in the establishment and maintenance of early pregnancy.
- 1.3. Some clinicians believe that measuring levels of NK cells in the blood can give useful information about NK cell levels in the uterus and it is also thought by some, that high levels of NK cells in the uterus causes an abnormal immune response to sperm and/or embryos, which could cause infertility in many patients. Clinicians offering this service suggest that the chance of a successful pregnancy can be increased by using drugs and/or intravenous immunoglobulin (IVIg) to correct the immune response.

## **2. Background**

- 2.1. The HFEA publishes information for patients about reproductive immunology on its website (see Annex A). In October 2014 Professor Siobhan Quenby presented an update on reproductive immunology to the SCAAC to assist the committee in its review of this website information.
- 2.2. The Executive recommends an update to the website text where appropriate. This paper presents some relevant, recent literature and also incorporates some of the views expressed by Professor Quenby to SCAAC and at the Fertility 2015 ACE/BFS conference.
- 2.3. There are conflicting views about the value of NK cell assessment and immunosuppressive therapies, with some studies suggesting women suffering from recurrent miscarriage (RM) have a high number of peripheral NK cells which can be reduced by IVIg therapy, leading to an increase in live birth rates.
- 2.4. In the October 2014 SCAAC meeting the following research developments were presented:
  - 2.4.1. A recent study (Katano et al, 2013) aimed to identify the predictive value of preconceptional peripheral blood natural killer (pNK) cell activity in patients with recurrent pregnancy loss (RPL). A total of 552 patients with a history of two to six consecutive miscarriages were included in the study. The predictive value of preconceptional pNK cell activity for subsequent miscarriage was analysed. The study highlighted that the age and number of previous miscarriages, but not high pNK cell activity, were found to be independent risk factors for a subsequent miscarriage. Further to this, no effect of bed rest and previous live birth on the likelihood of live birth was observed. Elevated pNK cell activity was found to not be an independent risk factor for subsequent miscarriage. The study therefore suggested that clinicians should not

measure the plasma NK activity as a systematic recurrent pregnancy loss examination, because its clinical significance is yet to be established.

- 2.4.2. Clinical trials of immunotherapy in women with idiopathic recurrent miscarriage have, to date, failed to support efficacy in preventing miscarriage. Preconceptional uterine Natural Killer (uNK) cell density is higher in women with recurrent miscarriage and this has been treated with prednisolone (steroidal treatment) by some clinicians.
- 2.4.3. A recent study conducted in the UK (Tang et al, 2013), explored the feasibility of screening women with idiopathic recurrent miscarriage for high uterine natural killer cell density and randomising to prednisolone or placebo when pregnant. In a pilot randomised control trial, 160 eligible women were screened with an endometrial biopsy and those with high uNK cell density were invited to return when pregnant for randomisation to prednisolone or identical placebo tablets. The outcome measures were recruitment rate, women's perspectives, compliance, live birth and miscarriage rates, and pregnancy complications. There were no pregnancy complications or serious adverse fetal outcomes. This was a feasibility trial and therefore of insufficient size to assess efficacy or safety. The article discusses its limitations stating that inconsistency in the start date of the trial medication may have affected the outcome in the active treatment group. However, it demonstrated that it was feasible to recruit women with idiopathic recurrent miscarriage into a 'screen and treat' trial despite their desire for active medication.
- 2.4.4. A review article by Matthiesen et al (2014) discusses immunologic causes, and immune-regulatory therapies recommended for helping patients with a history of recurrent miscarriage, using evidence based approaches. The review highlights data that may support revalidation of heparin as a protective therapy (during early pregnancy) in such cases. The review also concludes that newly launched growth factors, GM-CSF, and potentially novel agents to suppress inflammatory rejection, including regulatory T cells, human chorionic gonadotropin, and M-CSF/IL-10, may work for couples with pregnancy losses. The review goes on to highlight that clinical studies on immune mediated pregnancy loss are difficult to further understand due to poor design, and that trials conducted on interventional therapy are restrained by small numbers, and a lack of appropriate controls therefore limiting the ability to draw accurate conclusions. The article concludes with highlighting that whilst development is difficult from a clinical trial perspective, the understanding of cell and molecular mechanisms at this level are developing apace and novel approaches may be developed.

### **3. Update**

- 3.1. In this section a number of studies identified since October 2014 are outlined.
- 3.2. A systematic review and meta-analysis of 22 studies aimed at evaluating the levels of NK cells in blood and endometrium in infertile versus fertile women, the association between NK cells and IVF outcome, and levels of NK cells in blood and

endometrium, in women with recurrent miscarriage (RM) was recently published (Seshadri and Sunkara 2013). In their meta-analysis, the authors found broadly that peripheral and uterine NK levels were not significantly different in fertile versus infertile women (although this was not the case if absolute cell levels rather than percentages were used as a measure), that patients with RM had significantly higher levels of peripheral NK cells than controls, and that there was no significant difference in live birth rates between patients with high versus low NK levels or activity of women undergoing IVF. The authors conclude that further research is needed before NK cell assessment can be recommended as a diagnostic tool in the context of female infertility or RM, and that on the basis of current evidence, NK cell analysis and immune therapy should be offered only in the context of clinical research.

- 3.3. In 2011, a systematic review of intravenous immunoglobulin for treatment of unexplained recurrent miscarriage was published (Ata et al, 2011). Six relevant RCTs were identified including 272 women with unexplained RM. The authors found that a beneficial effect of IVIg in treatment of RM was not observed, and concluded that, “given the absence of a proven mechanism of action, and the lack of a diagnostic algorithm to identify patients who are likely to benefit from such treatment, IVIg administration for treatment of recurrent miscarriage is not justified outside the context of properly designed RCTs.”
- 3.4. In the most recent Cochrane Library Review, Immunotherapy for recurrent miscarriage (Wong et al, 2014), evaluation of the effectiveness of IVIg from eight trials, with 303 women, found that this form of immunotherapy did not show significant differences between treatment and control groups in terms of subsequent live births. This was also found to be the case for paternal cell immunization (12 trials, 641 women), third-party donor cell immunization (three trials, 156 women), and trophoblast membrane infusion (one trial, 37 women).
- 3.5. Recent research has demonstrated that uNK cells are ‘activated’ rather than suppressed in normal pregnancy (Fu et al, 2013) and the evidence points to important physiological roles for uNK cells in healthy development of the placenta and to their dysfunction in pregnancy disorders, although the nature of this dysfunction is not currently known.
- 3.6. In a recent review (Moffett and Colucci 2014), the authors comment on the use of therapies in IVF designed to suppress NK cells: “Use of these treatments is based on a misunderstanding of the basic science (as the right degree of activation, rather than inhibition, of uNK cells is needed), and they could potentially have serious side effects.” The authors continue to say, “It is inappropriate to use therapies aimed at altering uNK cell function until more is known.”
- 3.7. It is important to recognise that the field of reproductive immunity is incredibly diverse and complex. This year alone, there have been papers:
  - addressing the role of immune cells known as T cells (specifically T<sub>helper</sub> (Th17) and T<sub>reg</sub> cells) and molecules involved in cell signalling called cytokines, in unexplained recurrent spontaneous abortions (Saifi et al, 2014);

- investigating the enrichment of uterine natural killer cells and other immune cells, called uterine macrophages, in the region where the outer cells of the embryo (the trophoblast) invade the lining of the uterus (the endometrium or decidua) (Helige et al, 2014);
  - reporting the discovery that the placenta is capable of producing asymmetric antibodies (of the IgG type) that can interact with other antibodies and certain immune cells, called leukocytes, to affect local immune reactions at the junction between two genetically distinct entities, such as mother and fetus (Gu et al, 2015);
- 3.8. In addition there have been a number of reviews tackling the role of the B cells (a type of immune cell) (Fettke et al, 2014); HLA-G proteins (cell surface proteins that are responsible for regulation of the immune system) (Nilsson et al, 2014), T cells (Nancy and Erlebacher 2014) and a cell signalling pathway called the endocannabinoid system (Bambang et al, 2012), in mediating healthy interactions between mother and fetus.
- 3.9. Dysfunction in any one of these strands of the immune system, not just in uNK cells, could impact on fertility. It is therefore possible that some of the immune therapies offered may be appropriate for some patients. It is the ability to correctly diagnose the cause of immunity-based infertility that is needed in order to prescribe the correct treatment. The blood tests currently offered, which tend to measure peripheral NK cell number or activity, do not provide information as to the health of the rest of the immune system (Moffett and Colucci 2014). The literature seems to show that the blood tests in use are not able to give that diagnosis.
- 3.10. By taking a biopsy of the endometrium at a the later stage of the menstrual cycle (called the luteal phase) and staining it, it is possible to determine whether the endometrium is as developed as should be expected given its age. This process, known as histological dating, was widely used in the past to evaluate whether the endometrium is functioning properly in patients with infertility and early pregnancy loss, but more recently has fallen out of favour (Fadare and Zheng 2005).
- 3.11. In a recent paper (Liu et al. 2014) carried out a retrospective study to determine the prognostic value of uNK cell count and histological dating in the mid-luteal phase of endometrial specimens of women with reproductive failure. The authors found that an endometrium that is less well developed than it should be given its age, is significantly associated with a higher miscarriage rate in women with reproductive failure, and that the prognostic value of uNK cell count is significantly increased when the result is combined with histological dating, primarily because histological dating is significantly correlated with pregnancy outcome.
- 3.12. In her plenary lecture at the Fertility 2015 ACE/BFS conference, Professor Quenby argued that endometrial defects may be the cause of much infertility. She argued that by diagnosing patients on the basis of sub-epithelial uNK cell density and histological dating, and only by carrying out properly designed and controlled RCTs will we be able to determine which treatments, (scratch, steroids, progesterone, etc.) are appropriate for which patients.

#### **4. Conclusions and recommendations**

- 4.1. The current literature does not provide sufficient data from well-designed RCTs and therefore the safety and efficacy questions surrounding the use of immune therapies in IVF remain unanswered. Therefore this update does not change the assessment made by SCAAC in 2014 that Professor Quenby and the Committee should review the website content regarding reproductive immunology and highlight the most important message to convey.
- 4.2. The aim of the patient information is to provide a fair, balanced and accurate picture on current progress regarding reproductive immunology to assist patients who are seeking to make decisions about fertility treatment. The current website contains information which appropriately states that most experts are sceptical about immune therapies for treatment in IVF, and strongly warns the patients about potential side effects and costs.
- 4.3. The Executive recommends that only a minor amendment, as suggested by the Committee in October 2014, to the patient information text on the HFEA website is required to update the stated position. The text should better address the following question: "Why did my fertility cycle fail?" This information should set out the circumstances needed for a successful pregnancy, both quality/euploid embryos and endometrial receptivity, before information on the available treatments is presented (See Annex A tracked changes). The Executive acknowledges that the Scientific and Clinical Advances Advisory Committee will continue to monitor this area as they have to date.
- 4.4. Members are asked to:
  - Review the recent literature in this area and consider the safety and efficacy issues that may arise from such techniques.
  - Review the draft information for patients about reproductive immunology (Annex A) and provide comments to the Executive, relating to possible updates and changes including any studies from this report or elsewhere, they feel should be added to the website text as highlighted articles.

#### **5. References**

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## Reproductive immunology

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### 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 [\(to February 2015\)](#)~~[\(to March 2010\)](#)~~. It does not reflect studies and views published after it was written.

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### [Why do pregnancies sometimes fail?](#)

[There are two key factors needed in order for a successful pregnancy:](#)

- [high quality embryos – During the production of egg and sperm cells mistakes can happen, usually while the precursor cells divide and sometimes when the DNA is being copied. This can lead to egg or sperm cells with too many or too few copies of sections of DNA or whole chromosomes. This is called aneuploidy. An egg or sperm with aneuploidy will give rise to an embryo with aneuploidy. Embryos can also become aneuploid when mistakes occur in the first few cell divisions of their development. Aneuploid embryos are almost always unable to develop to term, and this is the most common cause of an embryo failing to implant into the lining of the womb or miscarrying.](#)
- [endometrial receptivity – The lining of the womb is called the endometrium. Over the course of the menstrual cycle, the endometrium undergoes a process called decidualization which creates the necessary environment for an embryo to undergo implantation. If the endometrium does not go through the process of decidualization properly, or if it cannot respond correctly to a healthy embryo within the womb, implantation of the embryo will not be able to occur.](#)

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## 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 [and scientists](#) question this approach. It is 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.)

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## 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.

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### **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- $\alpha$  (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.

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## 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 (March 2010), 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.~~

~~The most recent Cochrane Library Review of Immunotherapy for recurrent miscarriage, evaluated data from eight randomised clinical trials, with 303 women. The authors did not find that there was no significant difference between treatment and control groups in terms of subsequent live birth rates.~~

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.

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

You can read more in the following sources:

1) For a review of the latest research please refer to the latest Cochrane Collaboration review of this field: [Wong, L. F., Porter, T. F. & Scott, J. R. Immunotherapy for recurrent miscarriage. \*Cochrane Database Syst. Rev.\* 10, \(2014\).](#)

~~Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev.* 2006; 19 (2): CD000~~

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) The Royal College of Obstetricians and Gynaecologists (RCOG) Scientific Advisory Committee have published an opinion paper (Immunological Testing and Interventions for Reproductive Failure. June 2008), which is available on their [website](#).

The opinion papers states that "measurement of peripheral blood NK (PBNK) cell numbers or activity as a surrogate marker of events at the maternal-fetal interface is inappropriate.... A recent large UK study reported PBNK cell levels in predicting IVF cycle outcome to be 'little better than tossing a coin'."

It concludes that "With the exception of aPL [anti-phospholipid antibodies] testing among women with recurrent miscarriage, there is little evidence to support any particular test or immunomodulatory treatment in the investigation and treatment of couples with reproductive failure. These tests and treatments should be restricted to those entered into formal research studies."

3) The British Fertility Society (BFS) have published a review of evidence for use of medical adjuncts (supplementary procedures) in IVF, which covers a range of immunological tests and treatments.: L Nardo et al. (2009) Medical adjuncts in IVF: evidence for clinical practice. *Human Fertility* 12(1):1 – 13.

4) Two papers reviewing the science of NK cells in pregnancy are freely available:  
Moffett A, Regan L, Braude P. Natural killer cells, miscarriage, and infertility. *BMJ.* 2004;329:1283-1285.

Rai R, Sacks G, Trew G. Natural killer cells and reproductive failure--theory, practice and prejudice. *Human Reproduction.* 2005; 20(5):1123-1126.

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

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**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, the RCOG opinion paper and the BFS review.

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.

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### **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?