

A person wearing a beige, textured robe is sitting on a bed with white linens. They are holding a clear glass of water in their right hand and a small pile of white, round pills in their left hand. The scene is softly lit, creating a calm and intimate atmosphere.

# Immunotherapy

# Treatment options for immunological fertility disorders

Approximately 10% of patients at assisted reproduction centres have some form of immune disorder that may be causing their inability to conceive and/or deliver a child. We can medically treat a number of these immune disorders and thus increase the chance of pregnancy and its favourable outcome.

Medical immunointervention must be supported by the patient's medical history, clinical picture and test results. Prescribing immunological treatment blindly or with a 'what else could we try' approach is never recommended. On the other hand — it's the people being treated, not laboratory results — so it's equally wrong to start immunointervention treatment on the basis of a single laboratory deviation when nothing else indicates an immune disorder.

Here is a brief summary of the treatment methods that we offer for immunological causes of fertility disorders.



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# Corticosteroids

These are still some of the most effective and most frequently used immunomodulators. Corticosteroids allow us to influence the number of white blood cells (leukocytes and lymphocytes), the production of pro-inflammatory agents (cytokines), the function of a number of enzymes and the permeability of blood vessels for important players in the inflammatory process, and to suppress the production of wrong antibodies.

## **In reproductive immunology, we especially use corticosteroid tablets or injections in the following cases**

- ✓ when an incorrect and/or excessive amount of leukocytes is detected in the blood and/or in the endometrium, which can make the sperm meeting with the egg, implantation and the life of the embryo in the uterus difficult;
- ✓ in the case of unwanted inflammation;
- ✓ when the formation of incorrect auto/antibodies needs to be suppressed.

The dose, form and duration of treatment are always determined by an immunologist with knowledge of the nature of the immune disorder and with regard to its intensity and course.

Administration of corticosteroids can be problematic in women with diabetes, high blood pressure, a high degree of obesity, inflammatory stomach diseases, severe blood clotting disorders, difficult-to-treat intraocular pressure disorders, or severe depression.

Doses of corticosteroids used in reproductive immunology are usually small

or moderate, so the treatment is associated with a very low risk of adverse reactions.

Side effects that may occur include increased susceptibility to infections, mood swings, headaches, or swelling related to poor management of sodium and water.

The doctor may prescribe medicines along with the corticosteroids to protect the stomach from irritation, vitamin D and calcium to protect the bones and teeth, or tablets with potassium and magnesium.

## Intralipids

These are sterile fat emulsions containing soybean oil and lecithin. The blend of various unsaturated fats affects the immune system very quickly, especially the functions of white blood cells.

In reproductive immunology, we primarily use intralipids in cases where we need to quickly and forcefully suppress the unwanted reactions of NK (natural killer) cells and T-lymphocytes. It is an extemporaneous preparation prescribed by a doctor directly for a specific patient and made immediately before administration. This is one of the reasons why we use intralipids for precisely timed conception, i.e. especially in embryo transfers. The immunomodulating effect of intralipids is related to their dose and concentration, and the first infusion should

be given before progesterone levels begin to rise. This is why we also use proven dosing regimens for intralipid therapy, which usually include the administration of the first infusion ahead of time before the embryo transfer. They can be administered during pregnancy at one to three-week intervals, with a reduction in amount in the second trimester.

Intralipids are given by intravenous infusion, which takes about 1.5 hours. The treatment is very safe and well tolerated. Intralipids cannot be administered to people with allergies to soy, eggs and peanuts, and administration may be problematic in women with severe fat metabolism disorders or severe liver disease.

## Immunoglobulins

These are medicinal products made from the plasma of many thousands of blood donors. They contain diverse IgG class antibodies against a wide range of harmful substances, which is why they are called polyspecific. Their effect on the functioning of immunity is multifaceted; in reproductive immunology we mostly use them for the maturation and increase in the number of regulatory T lymphocytes (Treg), which are the primary immunological guarantor of the induction of foetal tolerance by the mother's immunity. These are blood derivatives, so treatment is very expensive, and they also have relatively strict prescription restrictions.

This means that treatment with them is only covered by public health insurance for a few diagnoses. In reproductive immunology, their administration can be considered in women with repeated miscarriages or after repeated embryo implantation failure if a cellular immunity disorder is proven. The second group includes women with insufficient production of their own important immune factors (e.g. antibodies).

Polyspecific immunoglobulins are administered in intramuscular injections, subcutaneous infusions or intravenous infusions.

## Phosphodiesterase inhibitors

These are medications that inhibit the formation of embryotoxic agents in white blood cells. In reproductive immunology, we use them in cases where we cannot or must not use corticosteroids for a cellular immunity disorder, or when their effect is insufficient. Pentoxifylline is most commonly used, and it is very well tolerated. Side effects include a decrease in blood pressure with associated mild problems, such as headaches.



## Hydroxychloroquine

This drug can be used in the treatment of immunologically related fertility disorders, especially in women who have an autoimmune disease or an increased risk of immunological complications in pregnancy. In women with autoimmune diseases such as lupus or antiphospholipid syndrome, hydroxychloroquine may help reduce the risk of complications during pregnancy, including miscarriage or preeclampsia. Some studies suggest that hydroxychloroquine may improve outcomes in women undergoing assisted reproduction by reducing immunological responses that can prevent embryo implantation. In women with chronic inflammation, hydroxychloroquine can help reduce inflammatory activity and improve the uterine environment for a successful pregnancy.

Hydroxychloroquine takes several weeks to take effect, but it is a very safe drug and is usually very well tolerated with no serious side effects.



## Other medications

### Low-molecular-weight heparin

Low-molecular-weight heparin can be used to modulate the immune response in cooperation with a haematologist. These are injections that affect blood clotting. If they are used in prophylactic doses, i.e. as protection against the formation of a blood clot, they can have an additional immunomodulating effect – they favourably influence the complement cascade. Heparin treatment is used in patients with autoimmune disease and positivity of antiphospholipid antibodies; its administration can reduce the number of early pregnancy losses and the incidence of preeclampsia.

### Acetylsalicylic acid

The anti-inflammatory effects of this acid have been known for a long time. It positively affects the balance of local enzymes and hormones, thereby protecting the blood vessels supplying the foetus from clots and inflammation. It is used in women with antiphospholipid syndrome and is effective in preventing preeclampsia in women at high or moderate risk of this disease if treatment is started before the 16th week of pregnancy.



### Vitamin D

Vitamin D is classified as a fat-soluble vitamin, but the latest findings show that it is a hormone with a multifaceted effect that plays an important role in regulating immunity. A sufficient amount is required at the site of embryo implantation for the correct balance of components of immunity, which protect the embryo from adverse environmental influences. Vitamin D is also important for the proper development of the blood vessels of the placenta – their disorder may only become apparent in advanced pregnancy and lead to preeclampsia and other pregnancy complications.

### Metformin

This drug is used in the treatment of type 2 diabetes, but it is also used as an auxiliary drug for ovulation disorders caused by polycystic ovary syndrome (PCOS). Especially in women with PCOS who are overweight, doctors use metformin for its anti-inflammatory effect. Obesity is a pro-inflammatory condition, and inflammation is one factor affecting fertility in obese women. However, we do not use metformin separately as an immunomodulator.

We currently do NOT use certain medications for fertility disorders that our patients may have become interested in based on a recommendation by other (often foreign) workplaces, or medications they learn about in online consultations and discussions.

- **Therapeutic monoclonal antibodies:** biological drugs: this is mainly due to the disproportion between the high risk of side effects and the possible benefit of this treatment. However, if biological treatment is used due to a chronic autoimmune disease (idiopathic intestinal inflammation, multiple sclerosis, rheumatoid arthritis, etc.), we follow the recommendations of the relevant specialist. There is already strong and clear evidence of the safety of many biological treatments in both the conception process and in pregnancy.
- **Growth factors:** again, the reason is the lack of sufficient evidence for their use and the risk of side effects.
- **Tacrolimus:** for the same reasons as the two above medications.
- **Immunisation with the partner's white blood cells:** this method has been abandoned worldwide a while ago due to ineffectiveness and the risk of hypersensitivity.
- **Azathioprine:** this is a very effective drug for the treatment of a number of immune disorders, and it is also safe to use during pregnancy, as it does not enter the bloodstream of the foetus. However, it only begins to work after a few months, so we do not use it to influence the immunological factor of infertility. But if a woman is using azathioprine long-term to treat an autoimmune disease (e.g. Crohn's disease) or after a transplant, we let her continue to take it.



## Are you ready to take the first step?

If you're ready, book your first appointment at our clinic. Our coordinators can offer you a meeting in person, over the telephone or a video meeting. We are available during normal business hours, or at other times that suit your preferences.

## Book a consultation with one of our fertility specialists



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**If you have any questions,  
ask us.**



You dream. We care.