HELP FOR POLYCYSTIC OVARY SYNDROME

Small pill for common hormone disorder

Millions of women suffer from polycystic ovary syndrome (PCOS), a condition that causes them to develop male body characteristics and become overweight. Bayer researchers are now developing a novel treatment to combat one of the most common female hormone disorders worldwide.

Attractive culprit: the male sex hormone testosterone, shown here heavily magnified in crystalline form, is also found in the female body. Women who produce too much of the male hormone are frequently affected by hirsutism (i.e. excessive hairiness in women similar to male hair patterns), infertility and arteriosclerosis.
When their hormones play up like this, it often feels to women like a massive assault on their femininity: their hair falls out, and stubble grows on the chin, upper lip, cheeks, chest and around the belly button. Their skin becomes oily and breaks out in spots. Their menstrual cycle is irregular. Ovulation and periods are repeatedly missed and some affected women are infertile. Their metabolism also changes, with an above-average likelihood of becoming overweight or obese and developing arteriosclerosis (hardening of blood vessels). In addition to the physical discomfort, the symptoms often also have a severe impact on patients’ minds, leaving many feeling stigmatized.

In most cases, these women have a metabolic disorder known as polycystic ovary syndrome or PCOS for short. This condition affects five to ten percent of all women of childbearing age and is usually first diagnosed in a woman’s late teens, although the initial signs appear even earlier.

A key factor in PCOS is an excess of male sex hormones, known as androgens, in the woman’s bloodstream, explains Dr. Thomas Zollner, head of the Gynecological Therapies Research Department at Bayer. The condition gets its name from the cysts that most affected women have on their ovaries. These do not directly cause any symptoms but may lead to infertility.

“At gynecological conferences, you very often hear about the pressing need for therapeutic options,” says biologist Dr. Martin Fritsch, Senior Scientist in Bayer’s Pharmaceuticals Division in Berlin. “In the United States, there is no approved treatment for this condition, a disorder that is associated with elevated mortality.” He and his team are developing an active substance for a new treatment that could bring marked relief to millions of affected women. The treatment blocks the nuclear receptors for androgens and has already been successfully tested in preclinical experiments. In a next step, the team plans to test the active substance in an initial clinical study in women.

Not only is it a challenge to find the right treatment, it is usually not easy for doctors to make the diagnosis either. This is because the degree to which the typical signs and symptoms are present varies significantly from woman to woman. Doctors still know very little about what causes PCOS, and their therapeutic options are limited. The current standard of care is generally aimed at relieving the patient’s individual symptoms. This means, for instance, prescribing treatments for acne and diabetes, or oral contraceptives to regulate the menstrual cycle. In experimental trials, certain potent anti-androgens which are primarily used in the treatment of prostate cancer have been employed in severe cases of PCOS.

Significant side effects, however, exclude these substances from broader use in this indication. “So far there is no specific treatment approved for PCOS that allows doctors to gain overall control of the condition,” explains Fritsch.

Bayer’s researchers want to address this medical need with a new active ingredient. Their approach targets the androgen receptor which mediates the majority of androgenic effects in men. Interestingly, the androgen receptor is present in a great many cells in women’s bodies too. It can be found, for instance, in both male and female fatty tissue, where it controls the tissue’s metabolic activity. When male sex hormones such as testosterone or dihydrotestosterone dock with the androgen receptor, various genes are activated that are responsible for the expression of male characteristics. “Our active substance binds to the androgen receptor without activating it, and consequently prevents androgens like testosterone from exerting their effect,” says Zollner, explaining the mechanism of the androgen receptor antagonist.

The therapeutic aim is not just to suppress outwardly visible masculinization, however. The substance could also...
Signs of masculinization

In patients with PCOS, the hormone balance is disrupted. The disease can manifest itself to very different degrees; some sufferers notice almost no external symptoms, while others are aware how much their bodies are changing and becoming increasingly masculine. This is also a psychological burden for these women.

Acne is a symptom which is also caused by increased androgens and occurs frequently in PCOS.

A receding hairline and male-pattern hair loss are seen in many PCOS patients and are also caused by an excess of androgens.

The androgens frequently lead to a heavy body and facial hair growth.

Cysts in the ovaries (the right ovary in this case) give the syndrome its name. They are found in 80 percent of PCOS patients.

In many cases, the body cells of the affected patients become insulin-resistant. Consequently, insulin produced in the pancreas (highlighted here in yellow) does not exert its physiological function, which can ultimately lead to type 2 diabetes.

Common symptoms of PCOS directly related to ovarian cysts are menstrual cycle irregularities and reduced fertility.

Obesity is one of the most common consequences of PCOS and further aggravates the disease.

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Research into women’s health care

Many typical women’s complaints are due to hormone disorders. Bayer scientists are exploring numerous ways of improving women’s health and quality of life. They are developing modern hormonal contraceptives and new therapeutic approaches, for example to treat menstrual problems and gynecological disorders such as uterine fibroids and endometriosis. In endometriosis, for example, tissue from the lining of the womb migrates around the body and settles in certain areas of the abdomen where it can cause severe pain, subfertility and adhesion of abdominal organs.
Breaking down taboos

This woman suffers from the metabolic disorder known as polycystic ovary syndrome or PCOS for short. But Harnaam Kaur from southern England is fighting the challenge by being very open about her condition. Her prolific beard and hair growth started back when she reached puberty – the photo on the left shows her aged 13, while the photo on the right shows her today. Women with this disorder can also suffer from a host of other symptoms such as infertility and obesity.

“The researchers therefore set up new test systems in cells, but also in animals to investigate whether their candidate actually had appropriate activity against PCOS. “We were able to get weight gain under control, restore the animals’ menstrual cycle and overcome insulin resistance,” says Fritsch.

Optimization of a potential new treatment is like walking a tightrope, however. “The desired effect needs to be attainable even at low doses of the substance. In addition, you also need to ensure that neither the substance itself nor its breakdown products cause unacceptable side effects,” says Zollner. The substance therefore underwent comprehensive testing to this end.

Researchers want to better understand the mechanisms behind PCOS

“If things continue to go this well, we hope to advance this drug into Phase I clinical development soon,” says Zollner. New drug candidates have to undergo three phases of clinical testing before they can be approved to be available commercially for patients’ use.

In addition to the promising results to date, Fritsch and Zollner also want to gain a better understanding of the mechanisms underlying the condition. Doctors already know that there is increased secretion of luteinizing hormone from the pituitary gland and that insulin resistance, as occurs in type 2 diabetes, tends to exacerbate the condition. But why the patients’ levels of testosterone, in particular, are elevated is still unclear. In their own experiments, Bayer’s researchers now aim to discover, for example, how testosterone forms in the fatty tissue of PCOS patients and how it controls the tissue’s activity.

The results might be helpful in the search for other active substance candidates as well. With their blockade of the androgen receptor, Bayer’s scientists already have one key mechanism underlying PCOS in their sights. “But we also want to find other ways of treating PCOS,” says Fritsch.