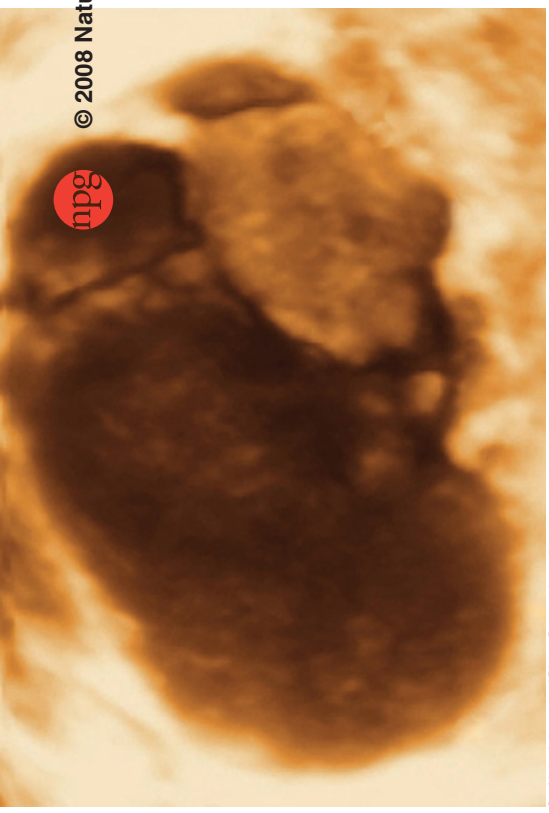
Common reproductive disorders may have immunological basis

Around the world, about 4 million women are affected each year by preeclampsia, a life-threatening increase in blood pressure during pregnancy, and an estimated 80 million suffer from endometriosis, a disorder involving the lining of the uterus. Theories abound to explain the onset and progression of these reproductive disorders, but one idea gaining traction is that these conditions are actually autoimmune diseases. If this proves true, it could lead to earlier diagnoses and much needed treatments.

In autoimmune disorders such as lupus and rheumatoid arthritis, the immune system produces 'autoantibodies'—renegade molecules that attack and destroy healthy tissue. Some researchers believe preeclampsia and endometriosis may fall into this category of diseases because women suffering from the disorders have been shown to have autoantibodies capable of driving up blood pressure and attacking the endometrium, respectively.

In endometriosis, the tissue that normally lines the uterus grows elsewhere and thickens, breaks down and bleeds as it would during the menstrual cycle. This trapped blood can irritate tissue and eventually cause cysts, scar tissue and the adhesion of organs, leading to pelvic pain and even infertility.



Dr. Najeeb Layyous / Photo Researchers, Inc

An unwanted development: Endometriosis

"A lot of evidence in scientific literature suggests there may be an immune abnormality associated with endometriosis," says Ninet Sinaii, an epidemiologist at the US National Institute of Child Health and Human Development in Bethesda, Maryland. "So it may be that endometriosis needs to be treated as an immune disorder, and that by treating the immune abnormalities we'll be able to treat the disease."

Women with endometriosis often suffer from well characterized autoimmune diseases. In a survey of nearly 3,700 women diagnosed with the condition, Sinaii and her colleagues found that 20% had more than one other chronic disease, and these subjects had higher than expected rates of autoimmune inflammatory diseases such as Sjögren's syndrome, a disorder in which the body attacks its own tear and saliva glands (*Hum. Reprod.* **17**, 2715–2724; 2002). In June, Indian researchers added to the growing number of studies conducted over the last two decades that have discovered increased production of autoantibodies against endometrial cells in women with endometriosis (*Reprod. Biomed. Online* **16**, 817–824; 2008).

Although Sinaii finds the evidence compelling, she says there are still many unanswered questions. "Is it because of immune abnormalities you get endometriosis? Or is it that endometriosis is the cause? There are so many factors we can't say yet what comes first." A better understanding of the immunological role could eventually lead to treatments, and measuring antiendometrial antibodies might provide a new diagnostic tool (diagnosis can currently take a decade or longer). Because endometriosis is considered an estrogen-dependent disease, it's usually treated with hormones and anti-inflammatory drugs to treat symptoms of pain. "Whether immunosuppressive therapy is more appropriate for endometriosis is an ongoing question and subject to much more research," Sinaii says.

Searching for answers

The picture may be clearer when considering preeclampsia, a leading cause of maternal and fetal morbidity and mortality globally, according to the World Health Organization. This condition, which affects about 5% of pregnancies, typically occurs in the last trimester and is characterized by high blood pressure, excess protein in the urine and edema. It also increases the risk of kidney disease in the mother and child later in life. Delivering the baby is the only cure.

Nearly a decade ago, German researchers found that blood from women with preeclampsia contained autoantibodies that activate the angiotensin AT1 receptor, which releases a chemical that causes blood vessels to narrow, driving up blood pressure (*J. Clin. Invest.* **103**, 945–952; 1999).

This summer, researchers at the University of Texas–Houston Medical School reported the first lab animal–based evidence that preeclampsia may be a pregnancy-induced autoimmune disease. They injected pregnant mice with the angiotensin receptor–activating autoantibody, taken from preeclamptic women. This induced several features of preeclampsia, including high blood pressure, proteinuria and placental abnormalities. The group also found they could prevent these effects by injecting mice with a seven–amino acid peptide that binds and neutralizes the antibodies (*Nat. Med.* **14**, 855–862; 2008).

"I think the idea that the disease might have an immunological basis is a little bit sounder after this paper," says Ananth Karumanchi, a kidney specialist at Beth Israel Deaconess Medical Center in Boston, who was not involved with the study. "It suggests to the field, to the skeptics like myself, that these antibodies are not epiphenomenon, that they're actually involved in the pathogenesis of the disease." The next steps, says Karumanchi, will be figuring out what triggers autoantibody production and whether they're involved in subtypes or all of the disease.

Yang Xia, who led the study, says that, if confirmed in human trials, the findings could one day lead to treatments.

Existing antihypertension drugs such as losartan block the angiotensin receptor but aren't an option for pregnant women, because they cause birth defects. And many immune suppressants are similarly dangerous. It may, however, be possible to block the AT1 receptor with peptides, as Xia's team did in the animal model. "But first we'll have to make sure this peptide can be stable in the blood circulation," she says. "Fifteen percent of premature babies are due to preeclampsia," says Xia. "Maybe targeting this autoantibody can prolong pregnancy."

How AT1 receptor signaling affects preeclampsia remains unclear, but some experts have already begun to speculate that the same receptor might have a role in endometriosis by being expressed in the uterine lining.

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