Novel autoantibodies implicated in pregnancy disorders

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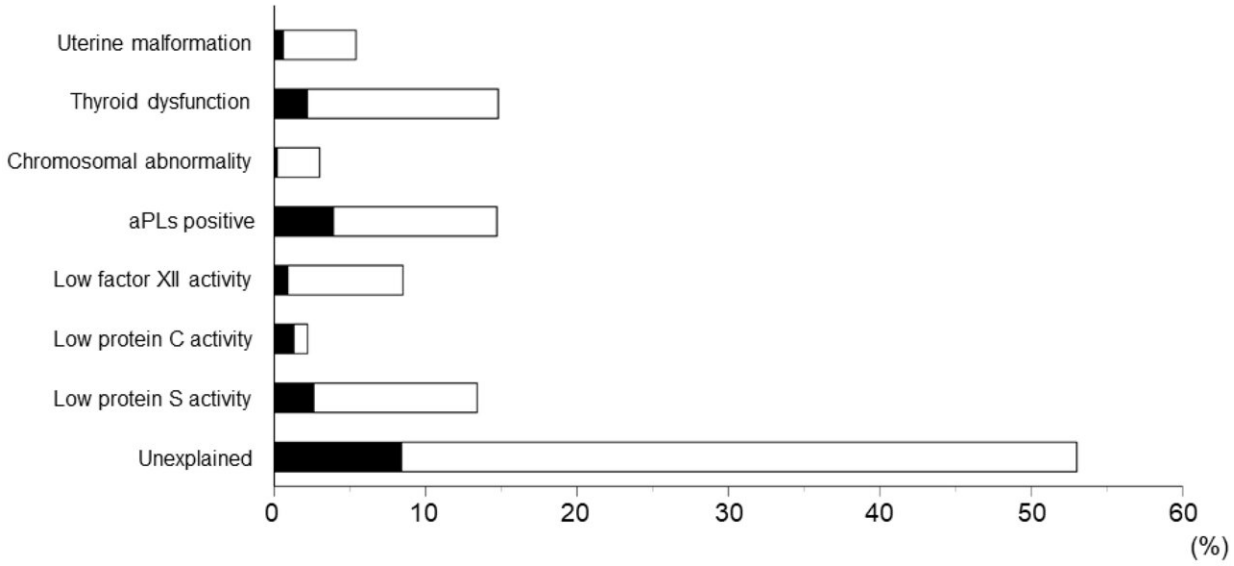

Risk factors for recurrent pregnancy loss (RPL) among 462 women with RPL. Black bars indicate the frequencies of women with RPL who tested positive for anti-β2GPI/HLA-DR antibody (n = 78). Abbreviations: aPLs, antiphospholipid antibodies; β2GPI, β2-glycoprotein I; HLA, human leukocyte antigen. Credit: *International Journal of Molecular Sciences* (2023). DOI: 10.3390/ijms241310958

A research group has found that novel autoantibodies that had been found to cause thrombosis and other conditions in joint research conducted by Kobe and Osaka universities in 2015, are also implicated

in pregnancy disorders, including hypertensive disorders of pregnancy and fetal growth restriction.

The team was led by Associate Professor Tanimura Kenji from the Department of Obstetrics and Gynecology at Kobe University Graduate School of Medicine, Professor Yamada Hideto, Director of the Center for Recurrent Pregnancy Loss at Teine Keijinkai Hospital, and Professor Arase Hisashi from the Osaka University Research Institute for Microbial Diseases.

This result could illuminate the mechanisms underlying hypertensive disorders of pregnancy, fetal growth restriction, recurrent pregnancy loss, and infertility, the causes of which are not fully understood, as well as contribute to the development of drugs to treat these conditions.

These findings were published in the *International Journal of Molecular Sciences* on June 30.

Hypertensive disorders of pregnancy involve high blood pressure, along with damage to vital organs such as the brain, liver, and the kidneys, and can endanger the life of the pregnant mother or the baby. In fetal growth restriction, unborn babies weigh much less than normal for their gestational age, and in the worst case, may die in the womb or soon after birth.

Women who successfully become pregnant may run the risk of having to undergo a cesarean section at an early stage of pregnancy to protect their own life when diagnosed with hypertensive disorders of pregnancy or fetal growth restriction, losing their baby or having a surviving child with severe disabilities. This exacerbates the issues posed by Japan's declining birthrate. Currently, however, almost nothing is understood about the mechanisms underlying these disorders of pregnancy (adverse obstetric outcomes), and there are no effective methods of treatment.

Research undertaken jointly by Hisashi and Kenji revealed novel autoantibodies that cause a condition called antiphospholipid antibody syndrome, which can trigger disorders such as cerebral infarction and other forms of thrombosis as well as miscarriage and hypertensive disorders of pregnancy, etc. A paper describing the results of that project was published in 2015.

Subsequently, a multicenter research project led by Kobe University that involved five university hospitals found that about a quarter of 227 women suffering from recurrent pregnancy loss who had repeated miscarriages after becoming pregnant and were unable to carry a healthy baby to term tested positive for these autoantibodies. This suggested that the autoantibodies could be a leading cause of recurrent pregnancy loss, a result reported in a paper published in 2020. A recently published multicenter study involving Teine Keijinkai Hospital, Yamanashi University, and Kobe University found that the autoantibodies are also associated with infertility, endometriosis-associated infertility, and repeated implantation failure.

Although this association of autoantibodies with infertility and recurrent pregnancy loss has become increasingly clear, their relationship with adverse obstetric outcomes such as hypertensive disorders of pregnancy, fetal growth restriction, and preterm delivery has not previously been addressed. In this new study, joint research conducted in five hospitals (Teine Keijinkai Hospital and four university hospitals including Kobe University) was the first in the world to investigate whether there is any association between adverse obstetric outcomes and autoantibodies.

Research findings

Autoantibodies were measured in the blood collected from (1) women who had suffered recurrent pregnancy loss, (2) women with past or present hypertensive disorders of pregnancy, fetal growth restriction, or

preterm delivery, and (3) postpartum women with no pre-existing conditions or obstetric abnormalities in previous pregnancies who had given birth to full-term infants of normal weight after an uncomplicated pregnancy (women who experienced normal delivery), who were inpatients or outpatients at one of the five Japanese participating hospitals and who had consented to take part in the study. The team used statistical analysis to compare the autoantibody positivity rates of these three groups and investigate their association with recurrent pregnancy loss, hypertensive disorders of pregnancy, fetal growth restriction, and preterm delivery.

The autoantibodies were measured by a technique devised and patented by the team members. This involves creating cells that express a complex comprising a protein called β2-glycoprotein I (believed to be the target of the antibodies that cause antiphospholipid antibody syndrome) and an HLA Class II antigen (the HLA type that is more susceptible to antiphospholipid antibody syndrome) on the cell surface. These cells react with the patient's blood to detect antibodies that bind to the complex on the cell surface.

The results showed that the positivity rates for autoantibodies were 78/462 women (16.9%) with recurrent pregnancy loss, 24/138 women (17.4%) with past or present hypertensive disorders of pregnancy, 19/124 women (15.3%) with past or present fetal growth restriction, 8/71 women (11.3%) with past or present preterm delivery, and 27/488 women (5.5%) who experienced normal delivery.

Statistical analysis of the strength of the associations between the autoantibodies and the various adverse obstetric outcomes, taking account of other factors that can affect hypertensive disorders of pregnancy and fetal growth restriction such as the women's age, body mass index (BMI, an indicator of obesity), and smoking, showed that the autoantibodies were strongly associated with recurrent pregnancy loss,

hypertensive disorders of pregnancy, and fetal growth restriction.

Table. Association between neoself antibody and adverse obstetric outcomes

	Adjusted odds ratio *2	
Recurrent pregnancy loss	3.3	↑
Hypertensive disorders of pregnancy	2.7	↑
Fetal growth restriction	2.7	↑

Credit: Kenji Tanimura (CC BY)

Research on autoantibodies may help to illuminate the mechanisms of the onset of recurrent pregnancy loss, hypertensive disorders of pregnancy, and fetal growth restriction, and decrease the number of couples, pregnant women, and children suffering from these conditions and handicaps caused by them. The team might even venture to say that they could be key to resolving the issue of Japan's low birthrate.

Future prospects

This study has shown that the novel autoantibodies the team discovered are associated not only with recurrent pregnancy loss and infertility, as previously reported, but also with other adverse obstetric outcomes such as hypertensive disorders of pregnancy and fetal growth restriction.

In the future, the group aims to develop drugs that suppress the production of these autoantibodies or block their action, leading to potential treatments for recurrent pregnancy loss, infertility, hypertensive disorders of pregnancy and fetal growth restriction. Similar autoantibodies might also be present in common autoimmune diseases such as rheumatoid arthritis, and this discovery could bring about revolutionary progress in immunology.

More information: Kenji Tanimura et al, Anti-β2-glycoprotein I/HLA-DR Antibody and Adverse Obstetric Outcomes, *International Journal of Molecular Sciences* (2023). DOI: 10.3390/ijms241310958

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