Investigating the link between a type of antibody and miscarriage

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Miscarriage affects an estimated 15% of pregnancies, but in about half of cases the cause is unclear. At Yale, reproductive immunologist Vikki Abrahams and reproductive biologist Mancy Tong are interested in

shining a light on one of these causes.

In a study published in the journal *Arthritis & Rheumatology*, Abrahams, professor of obstetrics, gynecology, and reproductive sciences at Yale School of Medicine and director of the Division of Reproductive Sciences, and Tong, an associate research scientist in the Abrahams lab who will start her own lab at Yale in September, combined their expertise to investigate how a certain type of autoantibody known to be a risk factor for miscarriage affects the uterus.

They found that the antibodies alter the uterine environment in way that puts pregnancy at risk and assessed a drug that may be able to help.

They sat down with Yale News to discuss their findings. This interview has been edited and condensed.

How would you describe your research?

Vikki Abrahams: I'm a reproductive immunologist. I study the role of the immune system and immunological processes in the context of normal pregnancy and in pregnancy complications like preterm birth and preeclampsia.

The immunology of pregnancy is interesting because it's a paradox. On one hand, the mother's immune system has to tolerate the fetus and the placenta that are genetically from both the mother and father. So there are foreign elements from the father in the placenta and baby that the mother's immune system should reject, but it doesn't. At the same time there has to be immunological protection against threats like infection. My interest is in the role that the placenta plays in protecting the pregnancy against threats such as infection, but also non-infectious insults that might come from the mother. Moreover, I am interested in what happens if the placenta responds to these threats in a way that

might harm the pregnancy.

Mancy Tong: I'm a placental biologist by training and I'm very interested in how the fetal placenta and maternal uterus communicate with each other throughout pregnancy. I'm currently funded by the NIH [National Institutes of Health] to study endometrial function—the function of the uterine lining that supports pregnancy. As I'm starting to think about my own lab, I'm excited to explore the roles of extracellular vesicles, which are secreted by all sorts of cells to communicate with other cell types, as a potential method of crosstalk between the placenta and endometrium in both normal and diseased pregnancies. My ultimate goal is to try to understand how miscommunication between the endometrium and placenta during early implantation phases could affect pregnancy success and set the stage for later pregnancy complications such as preeclampsia or other obstetric complications.

Your new study focuses on antiphospholipid antibodies—what are they?

Abrahams: Antiphospholipid antibodies are really one of the strongest predictors of miscarriage. Antiphospholipid syndrome is an autoimmune disease where people have high levels of these antiphospholipid antibodies (aPLs), which attack your own tissues. In women, these autoantibodies can cause miscarriage, but also preeclampsia, preterm birth, stillbirth, and intrauterine growth restriction.

And you looked at the effect they have on endometrial stromal cells—why are these cells important?

Tong: Endometrial stromal cells form the bulk of the endometrial tissue. And every month throughout the menstrual cycle changes in estrogen and progesterone levels cause endometrial stromal cells to first

proliferate and then to differentiate through a process called decidualization. This process is key to preparing the uterus for pregnancy, creating an endometrium that is receptive to support embryo growth.

What did you find?

Tong: We demonstrated that aPLs cause endometrial stromal cells to upregulate a very specific group of factors that are pro-inflammatory and can attract certain immune cells that may be detrimental to pregnancy.

We also found that aPL exposure can increase decidualization. You would think that increased decidualization maybe is a good thing, but there's a phenomenon called "super-fertility" where the endometrium is overly receptive and actually becomes less selective, supporting embryos that may have genetic abnormalities that normally would have been lost before the pregnancy is even detected. Our working hypothesis is that perhaps this is what aPLs cause but we're still studying this.

Also, during decidualization, there is a differentiation of the stromal cells to become decidual cells or senescent cells [prematurely aged]. A balance of both of these cell types is important for pregnancy. Here we saw that aPLs hugely increased the number of senescent cells. We posit that this is probably bad for pregnancy because we know that in other organ systems an initiating senescent population can cause neighboring cells to also become senescent and then you have a spread of inflammation and dysfunctional cells.

Is there any way to prevent these effects?

Abrahams: Antiphospholipid syndrome is classically a pro-thrombotic

disease. People are at high risk for thrombotic events—blood clots, stroke, cardiovascular problems. And so heparin [an anticoagulant] is often used as a therapy to prevent this. Obstetric antiphospholipid syndrome is not a thrombotic problem. It's a proinflammatory disease predominantly. But we know that heparin has different properties, including some anti-inflammatory, which may account for why some studies have shown that heparin can improve pregnancies in women with these autoantibodies. It's really the only go-to therapy we have. And so we chose to study it here.

Tong: In the study, we saw that heparin reduced aPL's ability to increase the stromal cell inflammatory and decidualization responses. It's good that now we can provide a potential justification for how heparin may be acting to help improve pregnancy for these patients, but antiphospholipid syndrome is such a complicated disease that's highly variable patient to patient so more work must be done in this area.

In this study, we uncovered the pathways that aPLs activated to cause the effects that we observed. This offers up opportunities for potential targeted therapeutics in the future.

More information: Mancy Tong et al, Antiphospholipid Antibodies Increase Endometrial Stromal Cell Decidualization, Senescence, and Inflammation via Toll-like Receptor 4, Reactive Oxygen Species, and p38 MAPK Signaling, *Arthritis & Rheumatology* (2022). DOI: 10.1002/art.42068