Research adds insights into preeclampsia, a deadly pregnancy complication

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Preeclampsia is a dangerous complication during pregnancy that endangers both the mother and fetus, but clinicians still don't have an effective way of predicting who will develop it. New research has

uncovered a possible mechanism for how this potentially life-threatening condition occurs and the potential of the immunosuppressive drug hydroxychloroquine to treat it.

Researchers knew that in pregnancies complicated by preeclampsia, the development of the placenta is impaired, but they know little about how this happens. Furthermore, they knew that levels of placental DNA in the mother's blood, known as cell-free fetal DNA (cffDNA), are significantly higher in women who experience preeclampsia.

So, a team led by Vikki Abrahams, Ph.D., professor of obstetrics, gynecology & reproductive sciences, studied the interactions of cultured placental cells called trophoblasts with levels of cffDNA observed in preeclampsia, and they found that this significantly inhibited the movement of the trophoblasts. The team also found that treatment with hydroxychloroquine reversed the effects of cffDNA on the trophoblasts. They published their findings in the *Journal of Reproductive Immunology*.

"Our research is giving us insight into how high levels of cffDNA that we see in women with preeclampsia might be acting in a pathological way," says Abrahams, who was the paper's senior author. "It's informing us about how cell-free fetal DNA is negatively impacting trophoblast function and the process of placentation, as well as some insight into a potential therapeutic that could be used to at least stop that part of the disease."

Preeclampsia symptoms are linked to the placenta

Preeclampsia, in which women experience highly elevated blood pressure, is a condition that normally manifests in the late second, or third, trimester of pregnancy. If not adequately controlled, it can cause the mother to have seizures and also harm the developing fetus. The only

current remedy for the condition is to deliver the baby and placenta.

Scientists have made an intriguing observation that if a clinician delivers the baby but not the placenta, women will continue to experience symptoms of preeclampsia until the placenta is also delivered. "All of these pathological processes seemed to be coming from the placenta, but we didn't know how or why," says Abrahams.

While preeclampsia develops later during pregnancy, researchers believe that the origins of the disease may occur much earlier, during implantation and placental development. In women with preeclampsia, researchers have noticed abnormalities at the maternal-fetal interface—where the placenta and maternal endometrium [mucus membrane lining the uterus] meet.

During a normal pregnancy, trophoblasts migrate into the endometrium, an essential process for anchoring the placenta and allowing the placental cells to interact with maternal immune cells that is necessary. However, in cases of preeclampsia, there is insufficient migration of the trophoblasts, which impairs normal placental development. Furthermore, research has shown a strong inflammatory response at the maternal-fetal interface in cases of preeclampsia.

During a normal pregnancy, the placenta continuously sheds material, including cffDNA, from its surface. It enters the mother's blood stream and circulates throughout her body. Throughout the pregnancy, levels of cffDNA rise as the placenta grows and sheds more material, and after delivery, the levels completely drop off. In cases of preeclampsia, the levels of cffDNA rise significantly higher compared to a normal pregnancy. "We wondered if cffDNA was having a functional effect that was leading to the development of preeclampsia," says Abrahams. "So, we decided to examine this locally in terms of placentation."

Identifying potential mechanism for impaired placental development

In their latest study, Abrahams' team isolated cffDNA and added it to fresh cultures of trophoblast cells. Then, they measured the ability of the trophoblasts to spontaneously migrate in the presence and absence of the cffDNA. They found that cffDNA significantly inhibited the trophoblast's ability to migrate.

This finding uncovered clues about preeclampsia's mechanism. cffDNA, says Abrahams, is different from adult DNA. The differences in structure of cffDNA have similarities to bacterial DNA, and consequentially, it gets recognized as such by an innate immune receptor called Toll-like receptor 9 (TLR9).

Intrigued, the team added a synthetic TLR9 inhibitor to the culture and found that it reversed the inhibition of trophoblast migration. "We found that the inhibition of trophoblast migration by cffDNA is TLR9-mediated," says Abrahams. "Its interaction with cffDNA causes a downregulation of the ability of trophoblast cells to spontaneously migrate."

Hydroxychloroquine reverses pathological mechanism of preeclampsia

Next, the team examined whether various therapeutics may be useful in treating this pathological mechanism, including aspirin and hydroxychloroquine. Previous research suggested that aspirin, an anti-inflammatory drug, may be useful in preventing symptoms of preeclampsia in women at high risk. So, they added aspirin to the trophoblast cultures to see if it would reverse the effects of cffDNA on migration, but it had no effect.

The team then turned their attention to hydroxychloroquine, a drug that is often given to patients with autoimmune diseases such as lupus and is safe to use during pregnancy. It also is a TLR9 inhibitor. They found that this medication did indeed restore the trophoblasts' ability to migrate. "This not only underscores the role of TLR9 as the mechanism by which cffDNA is inhibiting trophoblast migration, but also gives us a potential therapeutic that could be useful in a targeted way if given early in pregnancy," says Abrahams.

Abrahams hopes her work will lead to finding better ways for treating women with preeclampsia. "Now that we have an idea of how this cffDNA might be functioning during pregnancy, I'm hoping we can turn it into more studies to help us gain a better understanding of cffDNA function at the maternal-fetal interface, so that we can figure out more ways to promote healthy pregnancies in women," she says.

More information: Daisy León-Martínez et al, Cell-free fetal DNA impairs trophoblast migration in a TLR9-dependent manner and can be reversed by hydroxychloroquine, *Journal of Reproductive Immunology* (2023). DOI: 10.1016/j.jri.2023.103945

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