Acid reflux drug is a surprising candidate to curb preterm birth

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Lansoprazole, an over-the-counter acid reflux drug that is often taken by pregnant women, may be a promising therapy to reduce preterm birth, according to a computational drug repurposing study that also tested

several of the drugs in mice.

The study also identified 12 other FDA-approved drugs that are deemed safe in pregnancy. While the drugs encompass a variety of modalities, the scientists said they all appear to act on biological pathways that affect the immune response, which is implicated in preterm birth.

"Inflammation clearly plays a role in initiating labor and preterm birth," said Marina Sirota, Ph.D., assistant professor of pediatrics, a member of the Bakar Computational Health Sciences Institute at UCSF, and the senior author of the study, published Feb. 13, 2020, in *JCI Insight*. "Immune pathways are very significantly dysregulated in women who end up delivering preterm, and they're also dysregulated in babies who are born early. However, we have seen from our previous work that there is an interaction between the maternal and fetal immune systems and a breakdown in maternal-fetal tolerance."

To identify candidate drugs that might be effective in preventing preterm birth, the scientists first looked at which genes were up- or down-regulated in the blood cells of women who experienced spontaneous preterm birth to identify a gene expression "signature." Then they looked for the opposite signature in cells that had been exposed to 1,309 different drugs, reasoning that if a drug could correct the effects that preterm birth had on the women's blood cells, the drugs might also prevent preterm birth itself.

The scientists identified 83 drug candidates, but when they excluded those found to have pregnancy risks in animal or human studies, they wound up with 13 drugs, ranked according to their "reversal score," a measure of the extent to which they were able to reverse the gene expression signature of preterm birth.

The other drugs identified by the computational screen included

progesterone, which is already used to treat recurrent spontaneous preterm birth, folic acid, which is given to women during pregnancy to prevent birth defects, three antibiotics, an antifungal, an antidepressant, an anti-diabetic, and a blood pressure medication.

The fact that predictable drugs like progesterone came up in the screen gave the scientists confidence that the drugs they identified may turn out to be effective once they are tested in pregnant women. Three of the other drugs that came up in the screen—folic acid, clotrimazole and metformin—have also been shown in previous studies to be effective against preterm birth.

"Finding progesterone on the list was a promising validating step," said Brian Le, Ph.D., a postdoctoral scholar in the UCSF Department of Pediatrics and the Bakar Computational Health Sciences Institute, and the first author of the study. "Four of the drugs on our list have seen effectiveness in past studies that were either experimental or retrospective. This leads us to believe in the biology behind the identification of these drugs."

The scientists chose lansoprazole for further testing because, in addition to its high reversal score, it is available over the counter, and they know from their previous work that it affects a stress-response protein, heme oxygenase-1, that has been linked with pregnancy disorders. Lansoprazole, which is a proton-pump inhibitor marketed as Prevacid, had the second-highest reversal score of the 13 drugs identified as being safe and effective. Progesterone was further down the list.

The scientists tested lansoprazole in pregnant mice that had been given a bacterial component to induce inflammation, which causes some fetuses to die in utero, where they are reabsorbed. When these mice were given lansoprazole, they had more viable fetuses. Lansoprazole also worked better in these mice than progesterone.

Although it is a good measure of how inflammation affects pregnancy in mice, the scientists said the fetal resorption mouse model is not an adequate model of human preterm birth. They said more work, including studies in people, would need to be done before lansoprazole or any of the dozen other drugs they identified could be proven effective in pregnant women at risk for preterm birth. But the computational study provides leads for a condition that currently has few treatment options.

"This, basically, is a proof of concept that this drug has anti-inflammatory properties, which are not the properties the drug was designed for," said David K. Stevenson, MD, a professor of pediatrics at Stanford University and an author of the study. "This is a short way to get to new therapeutics for known diseases."

More information: *JCI Insight*, doi.org/10.1172/jci.insight.133761DS1

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