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Painkiller may disrupt sex hormones, placing unborn babies at risk

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Use of the painkiller acetaminophen during pregnancy may cause harmful sex hormone abnormalities, according to a study led by San Diego researchers.

The study adds to concerns about the drug, sold under the brand name Tylenol. Previous studies have found potential for harming offspring exposed to acetaminophen during pregnancy.

In this study, researchers found an association with use of the drug and lower levels of "sulfated" forms of sex hormones in men and women. Also called neurosteroids, many of these hormones are active in the brain. One of these hormones, DHEA-S, is well known to be important for placental health.

The lowered levels roughly equated to the natural effect of 35 years of aging in adults, potentially affecting their health. But the greatest risk appears to be to the developing fetus. Acetaminophen may reduce the placenta's ability to regulate hormone levels, the study said.

The study was published last week in the journal *EBioMedicine*. It builds on previous research in mice and human tissue on prenatal exposure to acetaminophen, also called paracetamol.

A 2017 study found that exposure is associated with male urogenital malformation and altered male brain masculinization, which controls gender-linked behavior in mice, such as the frequency of intercourse and

aggression toward rival males.

A 2015 study found evidence that prenatal exposure to acetaminophen may reduce the ability of the male fetus to produce testosterone. Testosterone production was reduced in human fetal testicular tissue that had been transplanted into castrated mice given acetaminophen for a week.

This new study referenced those previous findings as a reason to more fully explore the effects of acetaminophen.

Research published last month has linked Tylenol use during pregnancy to language delays in baby girls. That research was published too recently to be included in this study.

Acetaminophen's newfound ability to affect both placental health and the nervous system through reduction in neurosteroid production may explain these findings, said study leader Isaac Cohen of Human Longevity in La Jolla. Established by genomic researcher J. Craig Venter, Human Longevity sells comprehensive health assessments.

The research also indicates a possible new path toward developing new drugs.

No drugs have been approved to specifically target neurosteroid metabolism, said Cohen, who is also a doctorate of pharmacy candidate at the University of California, San Diego. Drugs that do so could potentially help relieve chronic pain and depression.

The study was observational, not a randomized clinical trial designed to definitively determine cause and effect. Cohen said the study was designed that way for safety—nobody was intentionally exposed to acetaminophen to test for possible harm.

Still, the study results are strong enough that further research into acetaminophen's effects is warranted, Cohen said.

The linkage was originally found in data from people who had undergone health assessments at Human Longevity. The data is aggregated and used anonymously for research.

"We have all this data from Human Longevity, and what we do is we look back at all the data that we already have, instead of putting new people at risk," Cohen said.

Researchers looked at data from thousands of subjects. This includes their genetic profiles and the presence of metabolites, which are biomolecules produced during metabolism. In particular, they identified biomarkers characteristic of acetaminophen use.

The data came from multiple sets of subjects with varying ethnic backgrounds. By using multiple unrelated groups, researchers gained confidence that the findings were real and not a one-time coincidence.

The correlation was first established in data from 455 people over 18 examined at Human Longevity. To validate the early findings, researchers then examined data from two additional groups.

They included 1,880 twins of European ancestry from the TwinsUK study; and 1,235 individuals of African American and Hispanic ancestry from the Insulin Resistance Atherosclerosis Study.

In addition to Human Longevity, the study included authors from J. Craig Venter Institute and UC San Diego in La Jolla; along with Metabolon, Durham in North Carolina; and King's College London in the United Kingdom.

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