Reproductive Headache? Investigating Acetaminophen as a Potential Endocrine Disruptor

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The presumed safety profile of acetaminophen has made it a popular choice of painkiller among pregnant women. In fact, acetaminophen, also known as paracetamol, is the only analgesic that the U.S. Food and Drug Administration (FDA) considers safe, when used as recommended, to take throughout pregnancy. However, researchers have found evidence that acetaminophen—although still considered the safest pain reliever for pregnant women—may interfere with the action of some key hormones in utero.

“There’s a perceived notion that because a medicine is over-the-counter [OTC], its use has been well studied in pregnancy,” says Christina Chambers, a reproductive and perinatal epidemiologist at the University of California, San Diego. But that is not necessarily the case. In reality, she explains, only limited pregnancy safety data are available for most OTC products, and safety recommendations are often based on assumptions rather than on rigorous evidence.

The FDA gives acetaminophen a “B” rating for pregnancy risk in all three trimesters, meaning that animal studies have shown no risk of congenital birth defects but that effects in pregnant women have been either not studied or not confirmed. This lack of research means that acetaminophen is being used with what some experts say is an unclear prenatal safety profile.

At the same time, “Acetaminophen certainly is no thalidomide,” says Danish biologist David Kristensen, an assistant professor at the University of Copenhagen, referencing the notorious drug for morning sickness that caused severe birth defects in the 1950s and 1960s. The associations noted in studies to date—most commonly between acetaminophen exposure and abnormalities in the male reproductive tract—are quite subtle, Kristensen says.

He adds, however, that one must consider how many women use the drug in pregnancy. “When millions of pregnant women are using acetaminophen worldwide, even a low [potential] risk becomes concerning,” he says.

In one 2005 analysis of data from two large U.S. case–control studies, roughly two-thirds of the pregnant women surveyed reported taking acetaminophen at some point during their pregnancy. Nearly 60% of these women had taken it during the first trimester, a period of rapid fetal development. Other studies have also reported common use of acetaminophen during pregnancy.

Women may use mild analgesics for many reasons during pregnancy: headache, fever, chronic joint pain, or an acute injury such as a sprain. “Any time that illness or pain impacts the underlying general health of the mother, there’s reason to take measures to alleviate that pain,” says family physician Lynn Lillie.

Image: © andriano.cz/Shutterstock.
Women may use mild analgesics for many reasons during pregnancy: headache, fever, chronic joint pain, or acute injury such as a sprain. Although complementary or alternative treatments, including acupuncture, massage, and relaxation techniques, can help soothe some ailments, other conditions may call for medication use, says Lynne Lillie, a family physician in Rochester, Minnesota, and member of the board of directors for the American Academy of Family Physicians.

“Any time that illness or pain impacts the underlying general health of the mother, there’s reason to take measures to alleviate that pain,” Lillie says. For example, a high fever could increase the risk of pregnancy complications, a toothache could prevent adequate nutrition, or a sore back could reduce mobility, she explains.

The story of research on acetaminophen and fetal outcomes actually began with another chemical family: phthalates. There is evidence that certain phthalates used as plasticizers and solvents in numerous consumer products may contribute to male genital abnormalities in humans and laboratory animals. Some of the abnormalities reported include undescended testicles (or cryptorchidism) and a reduction in the distance between the anus and the base of the penis, a measure known as anogenital distance (AGD).

Approximately two decades ago, researchers in Denmark proposed that abnormal gonadal development in fetal life may contribute to multiple adult reproductive disorders, including cryptorchidism, hypospadias, testicular germ cell cancer, and poor semen quality—a cluster of symptoms they called testicular dysgenesis syndrome. A few years later, Kristensen noticed a striking similarity between the chemical structures of some of the environmental chemicals suspected of disrupting male development—notably phthalates—and the mild analgesics most Danes kept in their medicine cabinets. “We wondered, ‘could these mild analgesics themselves be endocrine disruptors?’” remembers Kristensen.

Finding Fetal Impacts

In a paper published in 2010, Kristensen and colleagues provided evidence that mild analgesics may indeed act as antiandrogens in the fetal environment, although the findings were inconsistent. The researchers asked 491 Danish women and 1,463 Finnish women in their third trimester of pregnancy with boys about their use of OTC analgesics, including acetaminophen, aspirin, and ibuprofen. Approximately 9% of the Danish boys and 2% of the Finnish boys were born with undescended testicles. The mothers of the Danish cryptorchid boys were an estimated 43% more likely to have reported using one or more mild analgesics during pregnancy than mothers of boys with normal testicles. However, in the Finnish cohort, mothers of cryptorchid sons were an estimated 26% less likely to have taken analgesics during pregnancy.

That study also included an experimental component in which the researchers fed pregnant rats doses of acetaminophen adjusted for their body weight. Male rat pups whose mothers were fed acetaminophen had a significantly shorter AGD than those with no prenatal acetaminophen exposure, suggesting a potential antiandrogenic effect.

Kristensen’s experiments coincided with a larger study of 47,000 Danish mothers and sons that took place at the same time.
However, positive associations were reported only for mothers who said they had used acetaminophen in both the first and second trimesters and for those who used acetaminophen for at least 4 weeks specifically during gestational weeks 8 through 14. These weeks are thought to be a critical window of development for testicular descent. The authors noted that they found no dose–response associations, possibly a result of imprecise dose measurements.

In human pregnancy cohorts, use of acetaminophen specifically and of mild analgesics overall has been associated with shortened AGD in some research. Four pregnancy studies—three in Denmark8,15,16 and one in the United Kingdom17—found associations between maternal analgesic use and genital abnormalities in sons. However, studies of Finnish and French cohorts reported weaker or no such associations.15,18

All said, the subject is far from settled, stated the authors of a recent review of prenatal acetaminophen exposures and male reproductive effects. “It cannot be concluded that exposure to paracetamol is a direct cause of male reproductive disorders,” they wrote, “nor that analgesics should simply be avoided during pregnancy.”19

Compared with what is known about effects on males, even less is known about potential impacts on the developing female reproductive tract. One mouse study published in 2016 showed that female pups exposed throughout pregnancy to doses of acetaminophen commonly measured in pregnant women in the United States and Europe were born with fewer ovarian follicles.20 From middle age onward, the adult female mice born with fewer follicles had trouble breeding and experienced premature ovarian insufficiency. They were completely infertile by 10 months, an age when female lab mice typically just begin to experience waning fertility.

In addition to studies on the reproductive organs, researchers have investigated prenatal acetaminophen exposure with respect to development of the brain and the immune system. Carl-Gustaf Bornehag, an epidemiologist at Karlstad University in Sweden, heads up the Swedish Environmental Longitudinal Mother and Child Asthma and Allergy (SELMA) study, a pregnancy cohort of more than 2,000 mothers and their children.21 He has analyzed the breakdown products of acetaminophen in women’s urine obtained during pregnancy. In preliminary findings among a small subset of 48 girls and 63 boys, the researchers found that girls whose mothers had higher levels of acetaminophen in their urine during pregnancy were more likely to experience language delays at 30 months of age than girls whose mothers had lower levels. Nonsignificant inverse associations were seen in boys.22

Studies in Denmark, Norway, Spain, and the United Kingdom have estimated positive associations between maternal use of acetaminophen in pregnancy and behavioral problems, symptoms of attention deficit/hyperactivity disorder, and diagnosis with an autism spectrum disorder.23,24,25,26 Studies of immune function also found associations between prenatal exposure to the medication and asthma in childhood.27

However, as with reproductive effects, the limitations of studies to date preclude the ability to draw firm conclusions.28 Joseph Wax, chairman of the American Congress of Obstetricians and Gynecologists Committee on Obstetrics Practice, adds that it is unclear whether the findings from many of the epidemiological studies are clinically significant. “In the human studies, you see very mild, very modest [associations] that could easily be explained by confounding variables,” he says.

Multiple pregnancy studies have reported associations between maternal analgesic use and genital abnormalities in sons, although others reported weaker or no such associations. Less is known about potential effects in girls. Image: © Pikul Noorod/Shutterstock.
Next Steps for Research
It is becoming apparent that study limitations must be addressed in future research. “In these studies, you run into issues with confounding by indication for use,” says Shanna Swan, a reproductive health scientist at Icahn School of Medicine at Mount Sinai who has worked with Bornehag. In other words, it is possible that an adverse developmental outcome may be caused not by the medication but by the health complaint that caused the mother to take it in the first place.

There is another common pitfall in studies that rely on participants to remember how much medicine they took and when: this is known as recall bias. People may not remember accurately, or they may not even know whether they used a particular medication, explains Kristensen. The latter is quite likely in the case of acetaminophen: A search for “acetaminophen” on the National Library of Medicine’s Pillbox database turns up nearly 2,600 OTC and prescription products that contain the drug.

Kristensen and colleagues learned about this the hard way in their initial study in 2010, when they asked women to report the amount of acetaminophen they used during pregnancy. Roughly 26% reported using the compound. But when the women were asked about specific acetaminophen-containing medications by brand name, that number jumped to 57%.

One way to solve problems with recall bias is to use biomarkers, says Bornehag. Biomarkers are measurable substances in blood or urine that indicate an individual has been exposed to a given compound. Acetaminophen has a plasma half-life of 1.5–2.5 hours and is almost completely excreted within 24 hours, so biomarkers may only be useful to identify chronic users or those who happened to take acetaminophen recently.

It is impossible to prove cause and effect based on the evidence to date, points out Bornehag. “We’re identifying potential bad actors and raising hypotheses that other scientists in experimental toxicology can then test for causality in the laboratory animal and cell models,” he says.

Mechanistic studies that get at the how and why of acetaminophen’s potential effects are an essential piece of future research in this area, according to investigators. This type of research can help scientists to understand whether developmental outcomes across different domains—reproduction and neurodevelopment, for example—are related to disruption of the same hormonal processes during pregnancy. These types of studies could also show whether acetaminophen might work through the same cellular pathways as other environmental agents, such as phthalates. If this were the case, it would raise concerns about additive effects, says Bornehag.

The prenatal period is important in setting up reproductive development, but exposures at other points in the life course must be studied too, researchers say. Studies that look for associations between the use of mild analgesics in adulthood and hormonal disruption may provide a new perspective on reproductive outcomes, says Melissa Smarr, an epidemiologist at the Eunice Kennedy Shriver National Institute of Child Health and Human Health.

Last year, Smarr and colleagues conducted a preliminary study of the relationship between concentrations of acetaminophen in urine and time to pregnancy in 501 U.S. couples who were trying to conceive. Spot urine samples showed that nearly all study participants had measurable levels of the chemical or its breakdown products in their urine. Roughly 70% of couples achieved pregnancy during the study, and most of these pregnancies occurred in multiple surveys, large percentages of women have reported taking acetaminophen at some point during pregnancy. But because acetaminophen is found in hundreds of products, prospective mothers may not realize they have even taken it. Image: © mandritoiu/Shutterstock.
within six menstrual cycles. However, couples in which the men had the highest concentration of acetaminophen in his urine took slightly longer to get pregnant than those in which the men had the lowest levels. The researchers found no association between the female partner’s urinary acetaminophen levels and time to pregnancy.

Soon, Smarr hopes to compare urinary levels of acetaminophen in men with known reproductive problems, such as poor sperm quality, to those in men with no known reproductive abnormalities. This information could prove useful in understanding the relative importance and consequences of adult exposures, says Smarr. “I think researchers are beginning to recognize that acetaminophen is an [endocrine-disrupting chemical],” she says. “But we have miles to go before we can come up with a conclusive statement about what those exposures mean for human health and whether they are cause for medical concern.”

In addition to acetaminophen exposure in utero, exposures at other points in life should be assessed for potential reproductive effects. One preliminary study suggested that a couple’s time to pregnancy could be affected by the male partner’s exposure to acetaminophen. Image: © RuslanDashinsky/iStockphoto.

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