OTC Painkillers Tied To Undescended Testes

BY JENNIE SMITH

FROM HUMAN REPRODUCTION

Women who take over-the-counter painkillers during pregnancy have an increased risk of having sons born with undescended testes, according to a study that also incorporates rat models to show why this might be.

Using data from a birth cohort study of singleton sons born to 1,463 women in Finland and 834 in Denmark, all of whom either completed written questionnaires or telephone interviews or both, the researchers, led by Henrik Leffers, Ph.D., of Rigshospitalet in Copenhagen, found the risk of cryptorchidism to increase sevenfold in boys born to women who used more then one of three over-the-counter painkillers – aspirin (acetylsalicylic acid), acetaminophen (paracetamol), or ibuprofen – simultaneously during their pregnancies.

Exact doses of the painkillers were not recorded.

The findings, published online Nov. 8 in the journal Human Reproduction (doi:10.1093/humrep/deq323), also showed that any of these painkillers that were used for any duration during the second trimester more than doubled the risk of cryptorchidism, although the association for acetaminophen did not reach statistical significance.

The highest risk was observed, Dr. Leffers and his colleagues reported, among women who used more than one compound simultaneously for more than 2 weeks in the second trimester (adjusted odds ratio, 21.7 [1.83-258]).

A possible mechanism for this effect, Dr. Leffers and his colleagues hypothesized, was demonstrated by some of the study's coauthors, who found in a linked investigation that intrauterine exposure to acetaminophen, at three times the recommended dose for humans, led to a reduction in anogenital distance among fetal rats, and also reduced testosterone production by about half in fetal rat testes.

Aspirin was also tested in rats, but the results were not conclusive.

"A particular strength of this study is the use of two complementary rat models to support the contention that the association between analgesic use and cryptorchidism seen in our cohort study may result from a reduction in androgen production," Dr. Leffers and his colleagues wrote.

Their study adds to findings published earlier this month (Epidemiology 2010;21:779-85) from a cohort of 47,000 boys born in Denmark, 980 of whom were identified in childhood as having cryptorchidism. That study, which also looked at acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy through telephone interviews and questionnaires with mothers, saw exposure to acetaminophen during both the first and second trimesters associated with increased cryptorchidism (hazard ratio, 1.33).

Acetaminophen exposure of more than 4 weeks between the 8th and 14th gestational weeks was associated with an HR of 1.38. However no association was found for either ibuprofen or aspirin.

Dr. Leffers and his colleagues' study found all but one of their statistically significant associations in the Danish part of their cohort, and speculated that differences in design of the Finnish and Danish cohort studies may have been partly responsible.

Although the Finnish questionnaire asked respondents to list only which medications were taken and when, the Danish telephone interviews asked the most pointed questions about over-the-counter and prescription pain medications, including which products were used in which weeks of pregnancy.

Although just more than a quarter (26%) of the Danish mothers who responded to the written questionnaire said that they had used mild analgesics, more than half (56%)of those interviewed by telephone said the same.

"These findings indicated that many mothers did not consider mild analgesics as medication and hence strongly underreported their use unless specifically asked. We therefore only included the data from the computer-assisted telephone interview from the Danish part of the study," the investigators wrote.

In a press release accompanying the study, Dr. Leffers said that a "single paracetamol tablet (500 mg) contains more endocrine disruptor potency than the combined exposure to the 10 most prevalent of the currently known environmental endocrine disruptors during the whole pregnancy."

Men who are born with cryptorchidism, the researchers noted, see an increased risk of having poor semen quality and testicular germ cell cancer.

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DRUGS, PREGNANCY, AND LACTATION

SSRI Use Late in Pregnancy

Selective serotonin reuptake inhibitors are currently used in an estimated 5%-7% of pregnant women, and it is now generally accepted that pregnancy is not protective with respect to new onset or relapse of depression.

Multiple studies indicate that if there is an increased risk for major congenital malformations associated with fetal exposure to antidepressants, the risk is particularly small, but other concerns about the safety of SSRI use across pregnancy prevail. Among the most prominent are the increased risk of poor neonatal adaptation associated with late trimester SSRI exposure and persistent pulmonary hypertension of the newborn (PPHN). While more recent results from studies suggest that risk for PPHN following SSRI use during pregnancy is far less than originally estimated, results in the literature consistently indicate that about 25%-30% of infants exposed to SSRIs late in pregnancy manifest symptoms of this transient jitteriness and "poor neonatal adaptation," with associated symptoms of restlessness, myoclonus, and tachypnea. Critically, these symptoms also have been consistently noted to be transient and not requiring particular intervention.

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Whether clinicians might do something that could attenuate risk for poor neonatal adaptation has been a lingering question over the past several years. Some clinicians have been vigilant about the use of SSRIs late in pregnancy and discontinue these drugs in their patients shortly before delivery. In fact, since 2004, the SSRI package inserts have suggested that tapering the drug in the third trimester be considered.

While taper of SSRI proximate to the end of pregnancy might appear to be intuitive, our group and others have questioned the wisdom of discontinuing an antidepressant shortly before delivery, when the risk of depressive relapse increases a woman's risk for postpartum worsening of mood.

A study published in June provides data that helps refine our understanding of the risks of antidepressant exposure during the latter stage of pregnancy on the health of newborns. Using a large administrative claims database, investigators in British Columbia linked maternal health and prenatal SSRI prescription claims data to more than 119,000 neonatal birth records between 1998 and 2001. To evaluate the impact of discontinuing SSRIs late in pregnancy, they compared infants exposed to SSRIs during the last 14 days of gestation to those exposed earlier in gestation, and controlled for possible confounding factors that could also affect obstetric and neonatal outcomes, such as maternal health characteristics (Acta Psychiatr. Scand. 2010;121:471-9).

Compared with the newborns exposed to SSRIs earlier in gestation, significantly more of the newborns exposed during the last 2 weeks had respiratory problems (36% vs. 30%) and convulsions (0.3% vs. 0%). However, the differences were no longer evident after investigators controlled for the severity of maternal illness in a subgroup of the cases, and the authors concluded that their results "showed that neonatal outcomes did not improve when SSRI medications were stopped before the last 2 weeks of gestation, even when accounting for measures of maternal illness severity."

This study represents the first effort to parse out the relative contributions of different factors to which women may be exposed on neonatal outcomes (including maternal depression during pregnancy) – and provides information that helps us to refine the risk-benefit decision. The findings of the study imply that women who are taking an SSRI during pregnancy may benefit from continuing with treatment across labor and delivery because exposure at this time does not appear to adversely affect neonatal outcome. This may be particularly true for women with a history of highly recurrent major depression who are at a significant risk for depressive relapse, even shortly after discontinuing antidepressant medication.

The study provides further pause for clinicians to perhaps reconsider tapering or discontinuing antidepressant proximate to delivery because that type of intervention puts a woman at risk for relapse of depression shortly before an "at risk" period such as the postpartum period.

Clearly, there is no perfect decision and no decision is risk free. Some women in collaboration with their physicians may choose to discontinue antidepressant therapy late in pregnancy and to reinstate treatment shortly after delivery. Nonetheless, women with serious histories, those with recurrent disease and evidence of a swift relapse when stopping or even lowering the antidepressant dose, can consider the results of this study to support a decision to continue the medicine across labor and delivery, to sustain euthymia and maternal wellness.

Considering the growing appreciation of what appear to be real effects of exposure to medicine *and* to the disorder, what we need now are large, *prospective* studies that provide more reliable data, comparing euthymic women on antidepressants with women who are not depressed and who are not on an antidepressant – a study that has not been conducted to date.

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