

## DRUGS, PREGNANCY, AND LACTATION

# Opioids and Birth Defects

Because opioid analgesics are widely used among women of reproductive age for pain, any potential detrimental effects of these drugs during pregnancy clearly are important to a large population of women.

To date, therapeutic doses of opioid analgesics have not been linked to an increased risk of major congenital malformations. But the data in pregnant women are limited, with few comparative studies on the risk of opioid exposure in the first trimester.

For these reasons, a recently published study using data from the National Birth Defects Prevention Study of infants born in 10 U.S. states between October 1997 and December 2005 raised considerable interest. The study reported a significant association between the therapeutic use of opioid analgesics early in pregnancy and several different birth defects. Among the 17,449 mothers who had a baby with a malformation, 2.6% reported use of opioids during pregnancy, compared with 2% of the 6,701 women in the control group, whose babies had no malformations. Treatment with an opioid analgesic between 1 month before and 3 months after conceiving was associated with a significantly increased risk of the following malformations in their infants: conoventricular septal defects (odds ratio, 2.7), atrioventricular septal defects (2.0), hypoplastic left heart syndrome (2.4), spina bifida (2.0), and gastroschisis (1.8).



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Codeine and hydrocodone were the most common opioids women reported using (34.5% each), followed by oxycodone (14.4%) and meperidine (12.9%).

The authors considered a biologically plausible mechanism for their findings, and noted that their results were consistent with earlier studies, concluding that “it is critical that health care providers weigh the benefits of these medications along with their potential risks when discussing analgesic treatment options with patients who are or may become pregnant.” The study, conducted by researchers at the Centers for Disease Control and Prevention (CDC), was published

online in February (*Am. J. Obstet. Gyn.* 2011 [doi:10.1016/j.acog.2010.12.]). Despite the study’s large sample size, in my view, the small effects detected were most likely due to recall bias as will be explained here. Importantly, the increased risk for the malformations suggested in the study has not been detected in numerous studies among large numbers of women who abuse and/or are addicted to opioids such as heroin, methadone, and oxycodone during pregnancy, and are exposed to far higher doses than women who are treated with therapeutic doses.

The recommendation made by the authors to consider the association when making treatment decisions implies that they proved causation. But this type of study can never prove causation. Women whose babies had a malformation were

interviewed an average of 11 months after their estimated delivery date. There is a large body of research that has demonstrated marked differences in how women who have babies born with malformations recall what happened during their pregnancy compared with those with unaffected babies. Women who have babies with malformations are more likely to remember events and treatments they encountered during pregnancy, because they have a reason to go back and figure out what may have contributed to the outcome.

The only method to correct for this different memory pattern is to recruit a control group of mothers who have had a baby with other malformations that are not the focus of the study. As an example, a Motherisk study published in 1997 addressed whether Möbius syndrome (facial nerve and limb abnormalities) is caused by in utero exposure to the prostaglandin analogue misoprostol in Brazil, where the drug is misused by women in attempts to terminate pregnancy. To control for the recall bias of participating mothers, the study included a control group of women who had a baby born with spina bifida, and found that these control mothers, despite having children with a malformation, did not recall taking misoprostol, whereas the majority of women with Möbius anomaly remembered taking misoprostol (*N. Engl. J. Med.* 1998;338:1881-5). Prospective controlled studies are needed to determine whether the association identified in the CDC study is genuine. A controlled study of a large group of

women who abuse opioids as part of an addiction pattern, who are exposed to much higher opioid doses, would also be helpful in addressing this question.

Many of the calls we receive at Motherisk are from women who are in the first trimester and are concerned that they took an opioid before they knew they were pregnant. We counsel them that the analysis of the available data does not suggest they are at an increased risk of having a baby with a malformation. If a woman calls us and is planning a pregnancy or is in early pregnancy and, for example, is taking methadone to manage addiction, we recommend that she continue methadone because staying off illicit opioids is far more important.

For a woman who is in early pregnancy and needs a strong analgesic after surgery, we recommend using an opiate. We are now enrolling women who call us about having taken an opioid analgesic before they know the outcome of pregnancy in a prospective study. ■

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## Pregnancy After Liver Transplant Raises Risk of Graft Loss

BY MITCHEL L. ZOLER

FROM THE AMERICAN TRANSPLANT CONGRESS

PHILADELPHIA – Women who become pregnant after receiving a transplanted liver face an elevated risk of graft rejection, especially during or immediately following the pregnancy, based on a review of 161 U.S. cases.

“The data suggest poorer outcomes for both mothers and their newborns in female liver recipients with risk factors for graft loss within 5 years post pregnancy,” Dr. Carlo B. Ramirez said at the meeting.

“The findings highlight the high-risk nature of this group, warranting closer follow-up of both mother and child,” said Dr. Ramirez, a transplant surgeon at Thomas Jefferson University, Philadelphia.

Of the 161 women who became pregnant following a liver transplant and were enrolled in the National Transplantation Pregnancy Registry (in place since 1991), 16 (10%) lost their graft within 5 years following their first posttransplant pregnancy. The pregnancy and the 3 months following pregnancy posed a particular risk, with half of the women who eventually lost their graft experiencing rejection during that time. In a multivariate model that took into account baseline risk factors, women with a liver transplant faced a 14-fold increased risk for graft loss during the pregnancy, Dr. Ramirez said.

“A lot of patients who have a stable equilibrium with

their graft may destabilize under stress. It is possible that there is low-grade, clinically insignificant rejection in some of these patients prior to pregnancy” that then becomes exacerbated by the stress of pregnancy, commented Dr. Jean C. Emond, professor of surgery and director of transplantation at Columbia University in New York. Dr. Emond suggested that a liver biopsy prior to pregnancy might be warranted to assess the stability of the transplant.

Other risk factors for graft loss included younger age of the mother and low gestational age at the time of delivery. In the multivariate analysis, the risk for graft loss fell by a statistically significant 26% for each additional year of age for the mother. Graft loss fell by a statistically significant 5% for each additional week of gestational age when delivery occurred.

Among the 16 women who lost their graft during pregnancy or the following 5 years, their average age when they conceived was 22 years old, compared with an average age of 28 years among the 145 women who did not lose their graft. Average gestational age at delivery was 33 weeks among the women who lost their graft, and 37 weeks among the women who did not lose their graft.

The average age of the women at the time they received their liver transplant was 18 years among those who later lost their grafts, and 23 years among those who retained their grafts. However, the average time between transplantation and conception was an identical 4.3 years in both groups.

The only other risk factor for graft loss that approached statistical significance in the multivariate model was viral hepatitis as the etiologic agent for the

liver failure that led to the transplants. Viral hepatitis was the cause of liver failure for six (38%) of the women who lost their grafts following pregnancy, and for 23 (16%) of the women who did not lose their grafts. In the multivariate model, viral hepatitis as the cause of liver failure was linked with a nearly fourfold in-

creased risk for women losing their graft during or after pregnancy, but this relationship failed to meet the standard criterion for statistical significance, Dr. Ramirez said.

The congress was sponsored by the American Society of Transplant Surgeons. Dr. Ramirez said he had no disclosures. The National Transplantation Pregnancy Registry has been supported by grants from Novartis, Astellas, Genentech, Pfizer, Teva, and Sandoz. ■

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