

## **FDA has reviewed possible risks of pain medicine use during pregnancy**

### **Safety Announcement**

**[1-9-2015]** The U.S. Food and Drug Administration (FDA) is aware of and understands the concerns arising from recent reports questioning the safety of prescription and over-the-counter (OTC) pain medicines when used during pregnancy. As a result, we evaluated research studies published in the medical literature and determined they are too limited to make any recommendations based on these studies at this time. Because of this uncertainty, the use of pain medicines during pregnancy should be carefully considered. We urge pregnant women to always discuss all medicines with their health care professionals before using them.

Severe and persistent pain that is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure in the mother.<sup>1</sup> Medicines including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen can help treat severe and persistent pain. However, it is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines during pregnancy.

The published studies we reviewed reported on the potential risks associated with the following three types of pain medicines used during pregnancy (see Data Summary section for more information about these studies):

- Prescription NSAIDs and the risk of miscarriage in the first half of pregnancy.<sup>2-6</sup> Examples of prescription NSAIDs include ibuprofen, naproxen, diclofenac, and celecoxib.
- Opioids, which are available only by prescription, and the risk of birth defects of the brain, spine, or spinal cord in babies born to women who took these products during the first trimester of pregnancy.<sup>7, 8</sup> Examples of opioids include oxycodone, hydrocodone, hydromorphone, morphine, and codeine.
- Acetaminophen in both OTC and prescription products and the risk of attention deficit hyperactivity disorder (ADHD) in children born to women who took this medicine at any time during pregnancy.<sup>9</sup> Acetaminophen is a common pain reducer and fever reducer found in hundreds of medicines including those used for colds, flu, allergies, and sleep.

We found all of the studies we reviewed to have potential limitations in their designs; sometimes the accumulated studies on a topic contained conflicting results that prevented

us from drawing reliable conclusions. As a result, our recommendations on how pain medicines are used during pregnancy will remain the same at this time.

Pregnant women should always consult with their health care professional before taking any prescription or OTC medicine. Women taking pain medicines who are considering becoming pregnant should also consult with their health care professionals to discuss the risks and benefits of pain medicine use. Health care professionals should continue to follow the recommendations in the drug labels when prescribing pain medicines to pregnant patients.

We will continue to monitor and evaluate the use of pain medicines during pregnancy and will update the public as new safety information becomes available.

### **Facts about pain medicines during pregnancy**

- A variety of medicines are prescribed to treat pain, including severe and persistent pain in pregnant women. These include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen.
- NSAIDs are available by prescription and over-the-counter (OTC). They are used to relieve fever and pain, such as those associated with headaches, colds, flu, and arthritis. Examples of prescription NSAIDs include ibuprofen, naproxen, diclofenac, and celecoxib. Ibuprofen and naproxen are also available OTC at lower strengths.
  - Findings from two U.S. studies indicate that approximately 18-25 percent of pregnancies are exposed to OTC ibuprofen and 4 percent of pregnancies are exposed to OTC naproxen.<sup>10</sup>
- Opioids are a class of pain medicines available only by prescription. During each trimester of pregnancy, approximately six percent of pregnant women in the U.S. are exposed to opioids.<sup>11</sup> Examples of opioids include oxycodone, hydrocodone, hydromorphone, morphine, and codeine.
- Acetaminophen is used in prescription combination products to reduce pain and in OTC products to reduce pain and fever. Acetaminophen is found in hundreds of medicines including those used for colds, flu, allergies, and sleep.
  - Findings from two U.S. studies indicate that 65-70 percent of pregnant U.S. women reported using acetaminophen anytime during pregnancy.<sup>10</sup>

### **Additional Information for Pregnant Women**

- Always consult your health care professional about the use of all prescription and over-the-counter (OTC) medicines during pregnancy.
- Avoid using nonsteroidal anti-inflammatory drugs (NSAIDs) in the third trimester of pregnancy because these drugs may cause a blood vessel in the fetus to close prematurely.
- Do not stop taking any prescribed medicines without first talking to your health care professional.

- Talk to your health care professional if you have any questions or concerns about medicines you are taking.
- Report side effects from pain medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Additional Information for Health Care Professionals**

- As a result of recent reports raising concerns about the safety of prescription and over-the-counter (OTC) pain medicines used during pregnancy, FDA evaluated research studies published in the medical literature and determined they are too limited to make any recommendations at this time.
- Talk with each patient about the benefits and risks of analgesic use during pregnancy, which may differ among patients and by treatment indication.
- Continue to follow the existing recommendations in current drug labels regarding the use of analgesics during pregnancy.
- Current drug labels state that NSAIDs should not be used by pregnant women in their third trimester of pregnancy because of the risk of premature closure of the ductus arteriosus in the fetus.
- Report adverse events involving analgesics to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Data Summary**

#### Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and miscarriage

FDA reviewed five observational studies that evaluated the risk of the spontaneous loss of a pregnancy before the 20<sup>th</sup> week with NSAID use.<sup>2-6</sup> Miscarriage occurs in the general population at a frequency of about one in six pregnancies. Three retrospective case-control studies<sup>2-4</sup> which included over 100,000 subjects reported a positive association between prescription non-aspirin NSAID exposure and miscarriage (adjusted odds ratio [aOR]=7.0, 95% confidence interval [CI]=2.8-17.7; aOR=3.4, 95% CI=0.9-12.8; and aOR=2.4, 95% CI=2.1-2.8). These findings are difficult to interpret due to methodologic limitations in the studies' designs. For example, these studies did not identify the reason for NSAID use; women in these studies could have used NSAIDs for symptoms of miscarriage (i.e., cramping), so it could not be determined if NSAID use occurred before or after the onset of a miscarriage. In addition, these studies excluded potential NSAID users whose pregnancies ended in therapeutic (induced) abortion, possibly resulting in a finding of less NSAID use among controls compared to cases who experienced a miscarriage. Lastly, the studies did not consider the timing of study entry (i.e., the time during gestation when subjects were selected for the study). This is an important consideration given that the risk of miscarriage varies substantially by gestational age and, by definition, cannot occur after 20 weeks of gestation. In the absence of specific criteria, it cannot be determined whether the timing of study entry—and therefore risk of miscarriage at study entry—inherently differs with NSAID use.

Two other observational studies that included a total of 3,835 subjects were conducted in a prospective manner and were not subject to the same limitations in study design as the retrospective case-control studies above. However, these studies did not produce consistent results. One of the prospective cohort studies identified a positive association between prescription non-aspirin NSAID exposure and miscarriage, with an adjusted hazard ratio (aHR) of 1.8 (95% CI=1.0-3.2).<sup>5</sup> The other prospective study evaluated the association between over-the-counter non-aspirin NSAIDs and miscarriage, and did not identify an increased risk (aHR=0.9, 95% CI=0.7-1.1).<sup>6</sup>

Based on our evaluation of these observational studies, we believe that the weight of evidence is inconclusive regarding a possible connection between NSAID use and miscarriage.

#### Opioids and neural tube defects

We reviewed two retrospective case-control studies that reported on opioid exposure in early pregnancy and risk of neural tube defects.<sup>7,8</sup> The studies used interviews to gather information from over 28,000 women on maternal opioid use during pregnancy. Both studies found that mothers of infants with neural tube defects were more likely than mothers of infants without neural tube defects to report opioid use in early pregnancy (aOR=2.2, 95% CI=1.2-4.2; aOR=2.0, 95% CI=1.3-3.2). Although both studies were generally well-designed to assess the association between opioids and neural tube defects, both were susceptible to similar study limitations. In particular, use of maternal interviews could have affected the validity of these studies' findings. For example, mothers of neural tube defect-affected infants may have better recall of opioid exposure during their pregnancies than mothers of infants without birth defects. In addition, mothers of potentially exposed neural tube defect-affected infants may have higher rates of study participation.

Further investigation of this issue is needed before we can determine whether the weight of evidence supports the presence of an increased risk of neural tube defects related to opioid exposure in early pregnancy. The absolute risk of neural tube defects is low in the U.S. at about four to six per 10,000 live births.<sup>12,13</sup> Therefore, if true, a two-fold increased risk would represent a small increase in the absolute risk of neural tube defects.

#### Acetaminophen and attention deficit hyperactivity disorder (ADHD)

We evaluated a prospective cohort study that reported an increased association between acetaminophen use in pregnancy and ADHD in children.<sup>9</sup> Assessed outcomes included diagnosis of hyperkinetic disorder (HKD) and ADHD medication use beginning at age 5 and ADHD-like behaviors based on maternal interview of the child's behaviors at age 7. The study population included 64,322 pregnancies with information to assess HKD and ADHD medication use, and 40,916 pregnancies with information to assess child behavior.

In the study, mothers reporting any acetaminophen use during pregnancy reported more ADHD-like behavior in their children compared to unexposed mothers (adjusted risk ratio [aRR]=1.13, 95% CI=1.01-1.27). Women reporting any acetaminophen use in

pregnancy were also significantly more likely to have a child with an HKD diagnosis (aRR=1.37, 95% CI=1.19-1.59) or a child who used ADHD medications (aHR=1.29, 95% CI=1.15-1.44), compared to unexposed women. Associations for all outcomes were strongest for acetaminophen use in multiple trimesters and for more than 20 weeks during pregnancy.

This study had a number of methodologic limitations that make the findings difficult to interpret. The authors did not assess overall markers of health, including health care utilization and/or medication utilization in the year prior to and during the index pregnancy, which might make the observed associations incorrect. No information was provided on the acetaminophen strength and number of dosage units taken; therefore, no conclusions can be made regarding a dose-response relationship. The authors also did not assess clinical ADHD diagnoses. Findings from two other observational studies of neurodevelopment in children exposed to acetaminophen during gestation are conflicting; however, neither of these studies specifically assessed ADHD as an outcome.<sup>14, 15</sup>

Based on our evaluation of these studies, we believe that the weight of evidence is inconclusive regarding a possible connection between acetaminophen use in pregnancy and ADHD in children.

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