FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid

NSAIDs may cause rare kidney problems in unborn babies

10-15-2020 FDA Drug Safety Communication

What safety concern is FDA announcing?

The U.S. Food and Drug Administration (FDA) is warning that use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications. NSAIDs are commonly used to relieve pain and reduce fevers. They include medicines such as aspirin, ibuprofen, naproxen, diclofenac, and celecoxib. After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid, so kidney problems can lead to low levels of this fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop.

Although this safety concern is well known among certain medical specialties, we wanted to communicate our recommendations more widely to educate other health care professionals and pregnant women. This issue affects all NSAIDs that are available by prescription and those that can be bought over-the-counter (OTC) without a prescription.

What is FDA doing?

For prescription NSAIDS, we are requiring changes to the prescribing information to describe the risk of kidney problems in unborn babies that result in low amniotic fluid. We are recommending avoiding NSAIDs in pregnant women at 20 weeks or later in pregnancy rather than the 30 weeks currently described in NSAID prescribing information. At around 30 weeks, NSAIDs can cause a problem that may result in heart issues in the unborn baby. If deemed necessary by a health care professional, use of NSAIDs between 20 and 30 weeks of pregnancy should be limited to the lowest effective dose for the shortest duration. The changes to the prescribing information also indicate that health care professionals should consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours.

We will also update the Drug Facts labels of OTC NSAIDs intended for use in adults. These labels already warn to avoid using NSAIDs during the last 3 months of pregnancy because the medicines may cause problems in the unborn child or complications during delivery. The Drug Facts labels already advise pregnant and breastfeeding women to ask a health care professional before using these medicines.

One exception to the above recommendations is the use of the low 81 mg dose of the NSAID aspirin for certain pregnancy-related conditions at any point in pregnancy under the direction of a health care professional.

What are NSAIDs and how can they help me?

NSAIDs have been widely used for decades to treat pain and fever from many different long- and short-term medical conditions such as arthritis, menstrual cramps, headaches, colds, and the

flu. NSAIDs work by blocking the production of certain chemicals in the body that cause inflammation.

NSAIDs are available alone and combined with other medicines to treat a wide variety of conditions, including pain, colds, coughs, flu, and insomnia. Examples of NSAIDs include aspirin, ibuprofen, naproxen, diclofenac, and celecoxib (see Table 1 for a list of NSAIDs).

What should pregnant women do?

Pregnant women should not use NSAIDs at 20 weeks or later unless specifically advised to do so by your health care professional because these medicines may cause problems in your unborn baby. Talk with your health care professional about the benefits and risks of these medicines during pregnancy before using them, especially at 20 weeks or later. Because many OTC medicines contain NSAIDs, it is important to read the Drug Facts labels to find out if the medicines contain NSAIDs. If you are unsure if a medicine contains NSAIDs, ask a pharmacist or health care professional for help.

Other medicines, such as acetaminophen, are available to treat pain and fever during pregnancy. Talk to your pharmacist or health care professional for help deciding which might be best.

What should health care professionals do?

We recommend that health care professionals should limit prescribing NSAIDs between 20 to 30 weeks of pregnancy and avoid prescribing them after 30 weeks of pregnancy. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found.

What did FDA find?

We reviewed the medical literature[1-27] and cases reported to FDA* for data about low amniotic fluid levels or kidney problems in unborn babies associated with NSAID use during pregnancy (See Data Summary).

Among the 35 cases of low amniotic fluid levels or kidney problems reported to FDA* through 2017, all were serious. This number includes only cases submitted to FDA, so there may be additional cases. Two newborns who died had kidney failure and confirmed low amniotic fluid when mothers took NSAIDs while pregnant; three other newborns who died had kidney failure without confirmed low amniotic fluid when mothers took NSAIDs while pregnant. The low amniotic fluid levels started as early as 20 weeks of pregnancy. In 11 cases where low amniotic fluid levels were detected during pregnancy, the fluid volume returned to normal after the NSAID was stopped. The information from the cases was similar to what was found in the medical literature. In these publications, low amniotic fluid levels were detected with use of NSAIDs for varying amounts of time, ranging from 48 hours to multiple weeks. In most cases, the condition was reversible within 3 to 6 days after stopping the NSAID. In many reports, the condition was reversed when the NSAID was stopped, and it reappeared when the same NSAID was started again.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS) database.

What is my risk?
All medicines have side effects even when used correctly as prescribed. It is important to know that people respond differently to all medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that pregnant women will experience these side effects when taking NSAIDs.

How do I report side effects from NSAIDs?
To help FDA track safety issues with medicines, we urge pregnant women, patients, consumers, and health care professionals to report side effects involving NSAIDs or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

How can I get new safety information on medicines I'm prescribing or taking?
You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Facts about NSAIDs

- NSAIDs are a class of medicines available by prescription and over-the-counter (OTC). They are some of the most commonly used medicines for pain and fever.
- NSAIDs are used to treat medical conditions such as arthritis, menstrual cramps, headaches, colds, and the flu.
- NSAIDs work by blocking the production of certain chemicals in the body that cause inflammation.
- NSAIDS are available alone and combined with other medicines. Examples of NSAIDs include aspirin, ibuprofen, naproxen, diclofenac, and celecoxib. See Table 1 for a list of NSAIDs.
- Common side effects of NSAIDs include stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Additional Information for Pregnant Women

- FDA is warning that using pain-relieving and fever-reducing nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks or later in pregnancy may cause kidney problems in the unborn baby, which can lead to low levels of amniotic fluid that surrounds the baby. This fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop. Complications can occur with low levels of this fluid.
- If you are pregnant, do not use NSAIDs at 20 weeks or later in pregnancy unless specifically advised to do so by your health care professional because these medicines may cause problems in your unborn baby.

- Many over-the-counter (OTC) medicines contain NSAIDs, including those used for pain, colds, flu, and insomnia, so it is important to read the Drug Facts labels to find out if the medicines contain NSAIDs.
- Talk to your health care professional or pharmacist if you have questions or concerns about NSAIDs or which medicines contain them.
- To help FDA track safety issues with medicines, report side effects from NSAIDs or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Additional Information for Health Care Professionals

- FDA is warning that use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.
- These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.
- Oligohydramnios is often, but not always, reversible with treatment discontinuation.
- Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
- If NSAID treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. As currently described in the NSAID labels, avoid prescribing NSAIDs at 30 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus.
- The above recommendations do not apply to low-dose 81 mg aspirin prescribed for certain conditions in pregnancy.
- Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs and follow up according to clinical practice.
- To help FDA track safety issues with medicines, report adverse events involving NSAIDs or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Data Summary

We searched the medical literature and the FDA Adverse Event Reporting System (FAERS) for cases of oligohydramnios or neonatal renal dysfunction associated with nonsteroidal anti-inflammatory drug (NSAID) use during pregnancy.

We reviewed the medical literature, including case reports, randomized controlled studies, and observational studies.[1-17] Most of the publications showed that oligohydramnios is mostly observed during the third trimester, but there are multiple reports suggesting an earlier onset, around 20 weeks of gestation. Low amniotic fluid levels were detected with use of NSAIDs for varying amounts of time, ranging from 48 hours to multiple weeks. In most cases, oligohydramnios was reversible within 72 hours to 6 days following the discontinuation of the NSAID. In many reports, oligohydramnios was reversed when the NSAID was discontinued, and the oligohydramnios reappeared after reinitiation of treatment with the same NSAID. In some reports, when a particular NSAID was discontinued and another one was started, oligohydramnios did not reoccur with the new NSAID.

We also identified case reports/case series in the medical literature describing the onset of renal failure in neonates exposed to NSAIDs in utero.[18-27] The duration of exposure ranged from 2 days to 11 weeks. The case reports and case series described 20 neonates exposed to NSAIDs in utero, who experienced neonatal renal dysfunction in the first days following birth. The severity of renal dysfunction varied greatly from normalization at 3 days to persistent anuria requiring dialysis and/or exchange transfusion. Out of 11 total deaths, eight neonates were reported to have died as a direct consequence of renal failure or due to complications from dialysis.

A search of FAERS through July 21, 2017, identified 35 cases of oligohydramnios or neonatal renal dysfunction associated with NSAID use during pregnancy. There were 32 cases of oligohydramnios, including eight cases of oligohydramnios and neonatal renal dysfunction, and three cases of neonatal renal dysfunction that did not report oligohydramnios. All cases reported a serious outcome. Five cases reported neonatal death, which in all cases were associated with neonatal renal failure. All cases reported a temporal association with an NSAID and oligohydramnios or neonatal renal dysfunction, with oligohydramnios occurring as early as 20 weeks gestation. In 11 cases, a positive dechallenge was reported where the amniotic fluid volume returned to normal after the NSAID was discontinued. In all 11 cases of neonatal renal dysfunction, the neonate was born preterm before 37 weeks gestation.

Table 1. List of nonsteroidal anti-inflammatory drugs (NSAIDs)

Generic name	Brand name(s)
aspirin*†	Aggrenox (combination with dipyridamole), Durlaza, Equagesic (combination with meprobamate), Excedrin Migraine, Fiorinal (combination with butalbital, caffeine), Fiorinal with codeine, Lanorinal (combination with butalbital, caffeine), Norgesic (combination with caffeine, orphenadrine), Percodan (combination with oxycodone), Synalgos-DC (combination with caffeine, dihydrocodeine), Yosprala (combination with omeprazole), Vazalore
celecoxib	Celebrex, Consensi (combination with amlodipine), Elyxyb

diclofenac	Cambia, Cataflam, Dyloject, Flector, Licart, Pennsaid, Solaraze, Voltaren, Voltaren-XR, Zipsor, Zorvolex, Arthrotec (combination with misoprostol)
diflunisal	No brand name currently marketed
etodolac	No brand name currently marketed
fenoprofen	Nalfon
flurbiprofen	No brand name currently marketed
ibuprofen*‡	Advil, Advil Dual Action, Caldolor, Ibu-Tab, Ibuprohm, Midol, Motrin IB, Motrin Migraine Pain, Profen, Tab-Profen, Duexis (combination with famotidine), Reprexain (combination with hydrocodone), Sine-Aid IB (combination with pseudoephedrine), Vicoprofen (combination with hydrocodone)
indomethacin	Indocin, Indocin SR, Tivorbex
ketoprofen	No brand name currently marketed
ketorolac	Sprix
meclofenamate	No brand name currently marketed
mefenamic acid	Ponstel
meloxicam	Anjeso, Mobic, Qmizz ODT, Vivlodex
nabumetone	No brand name currently marketed
naproxen*‡	Aleve, Aleve-24, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprosyn, Treximet (combination with sumatriptan), Vimovo (combination with esomeprazole)
oxaprozin	Daypro, Daypro Alta
piroxicam	Feldene
sulindac	No brand name currently marketed
tolmetin	No brand name currently marketed

*There are many over-the-counter (OTC) products that contain this medicine.
†One exception to these recommendations is the use of low-dose 81 mg aspirin at any point in pregnancy under the direction of a health care professional.
†These medicines are available by prescription and OTC.

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Related Information

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

OTC Drug Facts Label

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines