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JOURNAL CLUB

ISSN #1555-0117 (online)

BRINGING CLINICIANS TOGETHER TO DISCUSS CURRENT DRUG THERAPY

September 2023
Checklist

BEFORE THE MEETING

- ☐ Print your copy of *Pharmacist's Letter Journal Club* LEADER NOTES, which will be emailed to you from *Pharmacist's Letter*
- ☐ Provide the LEADER NOTES to the *Pharmacist's Letter Journal Club* discussion leader
- ☐ Instruct your *Pharmacist's Letter Journal Club* participants to go to PharmacistsLetter.com to print their PARTICIPANT NOTES. Instruct them to look for "Journal Club" under the "Browse" heading. Be sure to tell them which month of *Pharmacist's Letter Journal Club* you intend to use
- ☐ Provide instructions to your PARTICIPANTS and LEADERS about how to obtain PDFs of original articles from your local medical library (Adhere to institution's copyright policy)

DURING THE MEETING

- ☐ Pass out any needed *Pharmacist's Letter Journal Club* PARTICIPANT NOTES
- ☐ Use your *Pharmacist's Letter Journal Club* LEADER NOTES to facilitate the discussion

AFTER THE MEETING

Go to PharmacistsLetter.com to learn about other topics in this month's issue, including charts, algorithms, toolboxes, etc, and listen to panelists and experts discuss our recommendations in *Emerging Recommendations Panel*

Pharmacist's Letter Journal Club. We do the digging, you do the discussing.

LEADER NOTES

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PREGNANCY

Patients are seeing headlines questioning whether acetaminophen is safe during pregnancy.

The debate is being stirred up by a recent "expert consensus statement" calling for limited use of acetaminophen in pregnancy.

It's due to studies linking perinatal acetaminophen exposure to a very small risk of problems in offspring...such as ADHD, autism, and early puberty.

Keep in mind, consensus statements are usually based on the opinion of a small group of experts...when evidence isn't robust. The idea is to help clinicians with decision-making.

But reassure expectant moms that this statement isn't based on new evidence. In fact, it confirms current practice...to use acetaminophen at the lowest dose and duration if needed in pregnancy.

Point out limitations. For example, studies are in animals at high doses...or are observational, so they can't determine cause and effect.

Emphasize that there's NO PROOF acetaminophen exposure is risky.

Even the consensus statement says acetaminophen is still the safest option if an analgesic is needed during pregnancy.

That's because NSAIDs are linked to miscarriage, fetal kidney problems, and premature ductus arteriosus closure. Topical NSAIDs might still be risky in pregnancy...despite lower absorption.

For aches and pains, continue to recommend starting with nondrug measures...hot or cold packs, physical therapy, stretching, etc.

It's also okay to suggest OTC topicals with menthol (*Vanishing Scent Bengay Gel*, etc) or lidocaine (*Icy Hot Lidocaine Cream*, etc).

But check labels closely...and avoid topical salicylates (*Ultra Strength Bengay Cream*, etc) or NSAIDs (*Voltaren Arthritis Pain* gel, etc).

Continue to recommend acetaminophen if needed for mild or moderate pain or a fever during pregnancy. Educate that a fever over 102°F can be risky to the fetus.

See our chart, *Analgesics in Pregnancy and Lactation*, for a deeper dive into the evidence...and options for severe pain.

(For more on this topic, see Clinical Resource #371105 at PharmacistsLetter.com.)

Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy – a call for precautionary action. Nat Rev Endocrinol 2021 Sep 23. doi: 10.1038/s41574-021-00553-7. Online ahead of print.

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DISCUSSION QUESTIONS

OVERVIEW OF CURRENT THERAPY

1. **What is known about the safety of acetaminophen during pregnancy? How does this compare to other options for mild to moderate pain in expectant moms?**

- The FDA and European Medicines Agency (EMA) have long considered acetaminophen to have minimal risk during pregnancy when used at appropriate doses.
- However, high-dose animal studies suggest that acetaminophen may have the potential to affect neurodevelopmental or reproductive development.
- And observational studies of acetaminophen use for several weeks or longer in expectant moms suggest a very small risk of genital malformations (e.g., cryptorchidism), early puberty, decreased IQ, and neurodevelopmental concerns (e.g., ADHD, autism). However, short-term use for mild to moderate pain or fever is not linked to problems in the baby.
- Overall, whether acetaminophen exposure during pregnancy has adverse consequences in offspring is a long-standing controversy.
- In contrast, NSAID use before week 20 is possibly linked to miscarriage. In addition, analgesic doses of NSAIDs used around 20 weeks or later may cause perinatal renal impairment and/or oligohydramnios and its complications. And third trimester use increases the risk of premature closure of ductus arteriosus and inhibition of labor.
- There's no proof that topical NSAIDs are safer than systemic agents in pregnancy.

ANALYSIS OF NEW EXPERT CONSENSUS STATEMENT

2. **What is an "expert consensus statement" and how is it different than a clinical practice guideline? What are the criteria for development of a consensus statement?**

- Expert consensus statements are recommendations based on the opinions of a panel of experts in a given therapeutic area. They generally aim to help clinicians with decision-making when evidence isn't robust.
- However, there are no criteria for development or evaluation of a consensus statement.
- In contrast, recommendations of clinical practice guidelines are generally based on the results of a systematic literature review.
- Several agencies or professional organizations have developed criteria for guideline development or evaluation. These criteria generally address factors such as transparency with regard to composition of the guideline development group, conflicts of interest, evidence review and rating of evidence, peer review, and financial support.
- Such guidance is available from the National Academy of Medicine (formerly the Institute of Medicine, IOM) and Council of Medical Specialty Societies (CMSS). The Users' Guides to the medical literature also provide guidance on how to evaluate and use clinical practice guidelines. Finally, tools such as G-TRUST (Guideline Trustworthiness,

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Relevance, and Utility Scoring Tool) are available to evaluate whether a guideline is useful.

3. **Is the consensus statement evidence based? Is evidence linked to recommendations with a strength of recommendation grading system?**

- The expert consensus statement appears to be at least somewhat evidence based. Two of the authors conducted a comprehensive literature review with appropriate search terms. However, the approach to the literature review is not well defined within the consensus statement.
- Evidence to support the effects of acetaminophen exposure during pregnancy is summarized separately for each possible impact (e.g., urogenital and reproductive effects, neurodevelopmental effects). But no system (e.g., GRADE) was used to evaluate the strength of the evidence. This is an important consideration, as the evidence to support risk with acetaminophen exposure during pregnancy is weak (e.g., animal studies, observational studies).
- In addition, when individual studies were reviewed in the supplementary material, results were inconsistent.

4. **Is the consensus statement unbiased and representative of a wide range of clinicians?**

- It is difficult to determine if the consensus statement is unbiased.
- Competing interests, which is another way to say "conflicts of interest" were given after the reference list. Only 1 author had a competing interest.
- The statement was developed by 13 clinicians. Authors were specialists (neurologists, OBGYNs, pediatricians), epidemiologists, and scientists (e.g., toxicologists, reproductive medicine experts). However, there were no pharmacists or primary care providers included in the expert group.
- The statement was developed independently of any specific society or college and has not been endorsed by any organization, despite endorsement by 78 international specialists. In fact, other organizations (e.g., European Network of Teratology Information Services) have developed position statements that are not in support of this expert consensus or question its validity.

5. **Is the consensus statement based on outcomes important to patients?**

- In general, yes. Parents are concerned about birth defects such as genital malformations, neurodevelopmental effects such as ADHD or autism, and early puberty in children.
- However, the supportive evidence is weak and results are inconsistent among studies.
- In addition, the risk of untreated fever during pregnancy was not considered.

6. **Are the interventions proposed in the consensus statement feasible in all practice settings?**

- Yes, mostly. Some of its recommendations simply reinforce current practice, such as to use acetaminophen at the lowest dose for the shortest time during pregnancy.
- Other recommendations aren't applicable to day-to-day practice. For example, several recommendations are targeted toward government agencies (e.g., FDA, EMA) or professional organizations to update labeled warnings or guidelines.

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7. Has the consensus statement been prospectively validated?

- No, this statement hasn't been prospectively validated, and plans for validation are not defined within the publication.
- In order to prospectively validate guidance, it has to be applied to a population of patients and be shown to improve outcomes.
- However, prospective evaluation of this consensus statement would be difficult. A randomized, controlled study evaluating the impact of acetaminophen exposure during pregnancy is not feasible. A prospective, observational study would be appropriate to evaluate the impact of acetaminophen exposure on offspring, but would need to be a very large study with many years of follow-up. In addition, as the authors note, future studies should control for confounders (e.g., indication for use, genetic factors) and capture dosage and duration of exposure.

8. What are the major recommendations of the consensus statement?

- Future studies of acetaminophen exposure in pregnancy should be designed to control for confounding, accurately capture exposure and outcomes, and evaluate the impact of dosing and duration of exposure.
- In general, pregnant women should use acetaminophen at the lowest possible dose and duration. Healthcare providers should counsel expectant moms to avoid using acetaminophen unless it is necessary and consult with a physician or pharmacist before using it long-term.
- Government agencies (e.g., FDA, EMA) should issue or update drug safety recommendations, and obstetric and gynecological organizations should update their guidance.
- Medications with acetaminophen should include recommendations and warning labels about use during pregnancy. If possible, acetaminophen should only be sold by pharmacies.

9. Are the recommendations in the consensus statement expressed in terms we care about and can use?

- Mostly. The recommendations are mostly based on outcomes that parents care about (e.g., genital malformations, neurodevelopmental effects, early puberty)

HOW SHOULD THE NEW FINDINGS CHANGE CURRENT THERAPY?

10. Does the consensus statement change your practice? How?

- No. The recommendations that are geared toward clinicians simply confirm current practice to use acetaminophen at the lowest dose and duration if needed in pregnancy.
- This consensus is not based on new evidence. Whether acetaminophen exposure during pregnancy leads to problems in offspring is controversial despite some animal and observational studies suggesting a small risk. But there is still no proof acetaminophen is risky during pregnancy.

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APPLY THE NEW FINDINGS TO THE FOLLOWING CASE

MW is a 28-year-old female G1P0 who is 25 weeks pregnant and seeing you for her routine OB visit. During the course of the visit, she complains of having low back pain intermittently and asks if she can take ibuprofen or acetaminophen for pain control. She's seen recent news headlines stating that acetaminophen may be risky for her baby.

11. How do you counsel MW regarding the safety of OTC pain medications during pregnancy?

- In general, advise MW to avoid NSAIDs at any time during pregnancy.
- NSAID use during the first trimester of pregnancy is linked with an increase in miscarriage rates.
- NSAID use 20 weeks or later has been associated with kidney problems in the fetus, resulting in low amniotic fluid levels, renal dysfunction, or even death.
- In the 3rd trimester, at 30 weeks or later, NSAID use may result in premature ductus arteriosus closure.
- The recent "expert consensus statement" that recommends limiting the use of acetaminophen during pregnancy is due to studies linking perinatal acetaminophen exposure with a small risk of problems in offspring, including autism, ADHD, genital malformations, and early puberty.
- Explain to MW that this consensus statement is based on the opinion of a small group of experts rather than new data from well-designed studies. Remind MW that the studies were done in animals, using high doses of acetaminophen, or were observational, which can't determine cause and effect. Currently there is no proof that acetaminophen exposure during pregnancy is risky.
- Initially, suggest that MW try OTC topicals with menthol or lidocaine such as *Vanishing Scent Bengay* or *Icy Hot Lidocaine Cream*. However, if needed, remind MW that low dose acetaminophen may be safely used for a short duration of time for pain or fever. In fact, even the consensus statement indicates that acetaminophen is the safest analgesic option in pregnancy.
- Remind MW that it's important to treat a fever during pregnancy as a fever over 102° F can be harmful for the fetus. Acetaminophen would be indicated for fever reduction.

MW takes your advice and uses conservative measures to combat her low back pain. She returns about 2 weeks later stating she's tried OTC remedies including acetaminophen, but continues to experience the back pain, which has worsened in intensity since the last visit. She wonders if she needs a stronger pain medication, noting that oxycodone worked well for her in the past.

12. What alternate methods do you advise MW to consider to better control her musculoskeletal back pain? How do you counsel her on the use of opioids in pregnancy?

- Advise MW that nondrug methods such as heat or ice application, physical or massage therapy, and stretching are best for management of typical musculoskeletal aches

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and pains associated with pregnancy. Consider referring MW to physical and/or massage therapy.

- Counsel MW on risks of opioid use in pregnancy. These include neural tube defects and withdrawal issues in the newborn. Opioid withdrawal also increases the risk of fetal distress and premature labor.
- Remind MW that other agents such as tramadol, benzodiazepines, gabapentin, SSRI drugs, and marijuana can also lead to withdrawal symptoms in the newborn and are not recommended.
- Save opioid use for severe pain when other measures are not effective. If absolutely necessary to use, use a short-acting agent at the lowest dose for the shortest duration possible.

MW agrees to try physical and massage therapy, along with a home stretching regimen and intermittent acetaminophen use for her low back pain. You also encourage her on regular gentle exercise, such as walking to help mitigate the pain.

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Additional Pharmacist's Letter Resources available at PharmacistsLetter.com

Chart, Analgesics in Pregnancy and Lactation. Pharmacist's Letter/Prescriber's Letter. November 2021.
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