Mini-commentary on: BJOG-20-1967.R2: Use of non-steroidal anti-inflammatory drugs in early pregnancy and preterm birth: Is the jury still out?

Lara S. Lemon[1,2]

1 Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine, University of Pittsburgh

2 Department of Clinical Analytics, University of Pittsburgh Medical Centers

Correspondence: Lara S. Lemon, PhD, PharmD
Department of Clinical Analytics
UPMC
Suite 9030
Forbes Tower
3600 Forbes Avenue at Meyran Avenue
Pittsburgh, PA 15213
lemonl@upmc.edu
412-802-6910 (voice)

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When an analgesic or antipyretic is needed in pregnancy, nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated at 20 weeks' gestation (WG) or later[1]. Nevertheless, NSAIDs are thought to be used commonly prior to 20WG, though exact utilization is difficult to quantify because of over-the-counter use. With continued use and lack of early pregnancy guidance, the findings of this large, French study conducted by Quantin et al.[2] are noteworthy, but conclusions should not be overstated.

Using a powerful database of over 1.5 million deliveries, 130,815 exposed to a NSAID prior to 22WG, authors demonstrated an 8% increased risk of preterm birth associated with early NSAID exposure; risk increased with the degree of prematurity (aOR=1.76 [1.54-2.00] for 22-27 WG). Results identify 5 specific NSAIDs driving that risk, of which ibuprofen was not one.

Quantin et al. did an admirable job studying this challenging topic. Investigators overcame inherent weaknesses shared with large, retrospective datasets and simultaneously capitalized on its strengths. Owing to cohort size, they were able to evaluate both grades of prematurity and individual anti-inflammatory drug. Authors strengthened findings by limiting exposure to prior to 22WG and livebirths post-22WG thereby cleverly decreasing immortal time. Additionally, they conducted numerous sensitivity analyses including: 1. No adjustment for preeclampsia nor placental abruption, 2. Chronic versus episodic use of NSAIDs, 3. Stratified by autoimmune disease status, and 4. Excluding women with a history of hypertension or diabetes.

Unfortunately, despite pairing a comprehensive cohort with thoughtful methods, it is this reader's opinion that there is still an "elephant in the room": unmeasured confounding. As certain indications for NSAIDs are themselves associated with preterm delivery (e.g., autoimmune diseases), the question becomes: is the risk attributable the NSAID or the condition

being treated? Moreover, should these findings invoke change in clinical practice? As the potential for confounding by indication remains, conclusions must be tempered.

Investigators had no markers of indication severity and certain findings suggest a stronger association in those with more advanced disease. For example, risk of preterm birth was highest in pregnancies exposed to both NSAIDs and biologics (aOR=3.16[1.37-7.28]) and those exposed to indomethacin (aOR=1.92[1.37-2.70])— these treatments are often indicative of more severe, recalcitrant disease. Additionally, there was no association between NSAID use and preterm birth in women *with* autoimmune diseases. Finally, not included in the results, there was no dose-response relationship (aOR=1.00 [0.99-1.01]). Demonstration of dose-response would support the risk being attributable to the NSAID itself, not the condition nor other medications more frequently taken by NSAID users.

It is critical that clinicians communicate the appropriate message from these findings to their patients. These results, although compelling and perhaps even foreboding, are justification for further research that quantifies the impact of indication and severity, better captures exposure (frequency, dose, duration), and evaluates the risk-benefit ratio of early NSAID use. For instance, is a fever itself more dangerous to a pregnancy or a single dose of ibuprofen? Questions like this remain unanswered, though these authors provide the necessary motivation for fellow researchers to take a deeper dive.

References

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2. Quantin C, Yamdjieu Ngadeu C, Cottenet J, et al. Early exposure of pregnant women to non-steroidal anti-inflammatory drugs delivered outside hospitals and preterm birth risk: nationwide cohort study. *BJOG*. 2021. Epub ahead of print.