



Caution needed: paracetamol use in pregnancy

A new Consensus Statement calls for precautionary action around the use of paracetamol in pregnancy, through focused research efforts and by increasing awareness.

Paracetamol (*N*-acetyl-*para*-aminophenol (APAP), otherwise known as acetaminophen) is an important medication with an unclear mechanism of action that is widely used to reduce fever and relieve mild to moderate pain. A new Consensus Statement summarizes human epidemiological studies and experimental research in cells and animal models, which suggest that APAP exposure during pregnancy can alter fetal development and might increase the risk of certain neurodevelopmental, reproductive and urogenital disorders¹. The authors make several recommendations around minimizing exposure to APAP during pregnancy and increasing awareness, and present a call for focused research.

APAP is widely considered to be the safest option for relief of pain and fever in pregnancy. For example, the UK National Institute for Health and Care Excellence [factsheet on APAP](#) states that APAP use during pregnancy is not thought to be harmful. Similar to Bauer and colleagues¹, the [European Medicines Agency \(EMA\)](#) advises that APAP can be used in pregnancy but that it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency. Reports from both the [US FDA](#) and the [EMA](#) state that studies investigating a possible connection between APAP use in pregnancy and disorders in offspring were inconclusive. The authors of this Consensus Statement¹ call for medical regulatory agencies and for obstetrical and gynaecological associations to review the most recent research and reconsider their recommendations.

The management of chronic pain associated with pregnancy is understudied². Untreated severe and persistent pain can result in [adverse outcomes](#) in pregnant people. Furthermore, in utero exposure to severe fever can cause neural tube defects and cardiovascular problems later in life in the offspring¹. Other [opioid](#) or [non-steroidal anti-inflammatory-based](#) drugs have known risks to the fetus. A balance must be struck between potential harm to pregnant people and/or their fetuses from untreated pain and fever, and the increased risks of harm to the fetus from medications. As such, the recommendations by Bauer and colleagues¹ advise that pregnant people should only use APAP if medically indicated, that they should consult with their physician or pharmacist if they are uncertain about APAP use and that they should use the lowest effective APAP dose for the

shortest possible time. These recommendations might not substantially differ from current advice in some countries. However, the authors believe APAP-specific risk communication is needed between health professionals and pregnant people owing to prevalent APAP use and a widespread perception of negligible risk.

The human epidemiological studies summarized in Bauer et al.¹ suggest that prenatal APAP exposure might confer an increased risk of cryptorchidism and/or reduced anogenital distance in boys and neurodevelopmental disorders in girls and boys, primarily attention deficit hyperactivity disorder. These studies have limitations, including potential confounding and exposure or outcome misclassification. However, they are supported by experimental studies in animal and in vitro models¹. Owing to differences in size and physiology between humans and model systems, further human studies should be carried out before any firm conclusions can be drawn. As such, Bauer and colleagues make recommendations to aid the design of future robust studies in humans¹.

Of note, in both epidemiological and experimental studies, there seems to be a dose–response relationship, with the largest effect sizes being observed with long term use of APAP (>2 weeks in humans). In addition, the timing of APAP use in particular gestational windows might also be crucially important. These important issues should be further investigated. In addition, research should be undertaken to search for alternative safe pain medications for pregnant people. Finally, the issues discussed in this Editorial and the Consensus Statement¹ are relevant for all people who wish to become pregnant, including transgender individuals, non-binary people and intersex people. Future research should be more inclusive of these diverse groups of people.

Going forward, pregnant people should feel empowered to make their own informed choice as to the safest course of action for their situation. Although this Consensus Statement calls for caution, APAP is still the safest available drug to treat pain and fever in pregnant people.

1. Bauer, A. Z. Paracetamol use during pregnancy — a call for precautionary action. *Nat. Rev. Endocrinol.* <https://doi.org/10.1038/s41574-021-00553-7> (2021).
2. Ray-Griffith, S. L. et al. Chronic pain during pregnancy: a review of the literature. *Int. J. Womens Health* **10**, 153–164 (2018).

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