

The European Network of Teratology Information Services, ENTIS: Position statement on acetaminophen (paracetamol) in pregnancy.

ENTIS holds the position that the evidence supporting an increased risk of untoward fetal effects and childhood neurodevelopment, including ASD & ADHD following in utero exposure to acetaminophen is weak, inconsistent and to a large extent fundamentally flawed. ENTIS holds the position that acetaminophen is the first-choice analgesic and antipyretic for pregnant women, but, as for any medication, should only be used when clearly indicated at the lowest dose and for the shortest possible duration.

On September 25th, 2021, Nature Reviews Endocrinology published a “Consensus Statement”: *Paracetamol during pregnancy – call for precautionary action.*¹ The 13 authors call for caution and suggest that there is now a growing body of evidence to support the hypothesis that in utero exposure to paracetamol (or acetaminophen, APAP) alters fetal development. The issue of APAP in pregnancy and risk of various untoward consequences to the fetus and childhood is a long-standing controversy. This is especially true for risk of childhood neurodevelopment and ASD/ADHD.

Considerations pertaining to this specific paper

- 1) It is unfortunate and misleading that this paper has been assigned “Consensus Statement” status. This usually signifies a broad collaborative effort on behalf of health authorities or medical specialty organizations to agree on a certain position with the ensuing authority and impact on clinical practice. While endorsed by 78 signatories, this paper reflects the views of the authors and is not endorsed by regulatory authorities or medical specialty organizations.
- 2) On face value, the conclusions by the authors can hardly be disagreed upon and could be used for any drug. These are, however, trivial: Nobody should use drugs without appropriate considerations on indication, efficacy & adverse reactions, and this even outside of pregnancy. Nobody should use drugs at higher doses or for longer duration of time than necessary. The authors seem to infer that pregnant women use APAP indiscriminately. Promoting their position and uncertainty on the safety of APAP will prevent its use in situations where it is clearly indicated.
- 3) These conclusions are preceded by seven pages in which the authors detail evidence they argue substantiate that APAP during pregnancy comes with non-trivial and disturbing risks to the fetus and long-term developmental risks. Some principal methodological points to consider in the portfolio of studies presented:
 - a. Drawing clinical conclusions using data from which causality cannot be effortlessly inferred.²
 - b. Use of unvalidated outcome measurements [i.e., parent or- teacher filled questionnaires on a Likert scale being transformed into continuous quantitative scales representing neurodevelopment].³ This applies to many of the underlying studies and these questionnaires are neither developed nor validated for the purpose and context in which they are used.
 - c. Not accounting for hereditary aspects of neurodevelopment, ASD and ADHD and the ensuing importance of this as confounder⁴
 - d. On urogenital development, the underlying studies are unconvincing and some of the data in the original studies does not appear to support the authors’ interpretation. A central study on APAP and cryptorchidism cited by the authors de facto reported an overall Null association between APAP exposure and risk of cryptorchidism (aOR 1.3, 95% CI 0.70-2.6).⁵ Likewise, in the pivotal study on

anogenital distance (AGD) and APAP exposure there was no difference in AGD between boys exposed to APAP and boys not exposed to APAP as per authors themselves "Maternal use of paracetamol was not significantly associated with AGD in boys after adjustment...".⁶ This null association has recently been confirmed.⁷

- e. Confirmation bias: Uncritical appraisal of studies supporting the narrative of the authors. One example: A recent study from the Boston Birth Cohort is assigned much weight by the authors to substantiate APAP exposure using umbilical cord plasma concentrations and correlating this to childhood ADHD, ASD and other neurodevelopmental diagnoses.⁸ This study has severe issues with external and internal validity. APAP or metabolites were detected in every single of the 996 umbilical cord samples. This does not compare well to our knowledge on the use of APAP during pregnancy. Among the 996 children, an unprecedented large proportion were diagnosed with ADHD/ASD (37%) and only 33% had no "developmental disability" diagnosis. Population prevalence estimates of ADHD is around 3-5%. The validity of the exposure construct "burden of APAP exposure" is undocumented and actual levels are not presented. Analytical methods are insufficiently accounted for including stability from up to 20 years of sample storage.
- f. Preclinical data may support some mechanistic aspects of a hypothesis. It cannot be summoned to support a clinical recommendation.

ENTIS acknowledges the authors right to hold their position. ENTIS does not share this position and believes the supporting evidence brought forward is weak, inconsistent and to a large extent fundamentally flawed.

The media headlines and social media reactions were predictable, and ENTIS believes that this paper and the ensuing reaction will promote unwarranted uncertainty, fear, and guilt among pregnant women. It will also likely result in use of less safe alternatives during pregnancy.

On behalf of the ENTIS Organization

For the Board: Orna-Diav Citrin (chair)

For the Scientific Committee: Per Damkier (chair)

References

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