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Commentary

Commentary: Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms

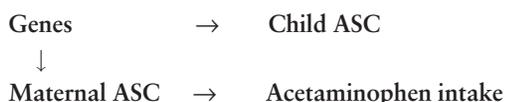
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Proper use of medicine is important for public health as well as clinical medicine. Clinicians need to treat diseases well and public health epidemiologists should take an interest in potential side effects of the drugs. Often both the clinical and public health epidemiologists share interests in these prognostic and aetiological factors. Due to concerns of ‘confounding by indication’, the clinical epidemiologist will prefer evidence from a randomized control trial (RCT) if possible. Observational studies on side effects that are not related to the treated disease, and therefore not necessarily subject to confounding by indication, can often provide valid results, given these studies can sufficiently control for other sources of bias and confounding.

The main concern in Avella-Garcia’s study¹ perhaps is not confounding by indication but confounding by genetic factors. If genes causing autism spectrum conditions (ASC) also lead to frequent use of medication, including a common painkiller like acetaminophen, a non-causal back-door path is open. The confounding structure is illustrated in this directed acyclic graph (DAG):



The graph links maternal acetaminophen intake with child ASC via the non-causal back door; Child ASC ← Genes → Maternal ASC → Acetaminophen intake. This path can be closed by adjusting for genes (if recorded and known) or partly by adjusting for maternal symptoms of ASC, which is what is done in most studies. Using a sibling-comparison

design may also to some extent address this genetic confounding. In the study,¹ the authors adjusted for diseases/symptoms that are treatable by acetaminophen, but not for ASC status in mothers (or fathers), leaving the possible genetic confounding open.

Drug use in pregnancy is usually not backed up by RCTs for ethical reasons. If the drug passed the placenta barrier—most drugs do—they will expose the developing fetus, and potential health problems are quite unpredictable. Most research interest in this setting has been given to congenital abnormalities probably related to the thalidomide disaster in the 1960s,² but we should keep in mind that many other side effects are possible. If the drug passes the fetal blood-brain barrier, mental problems should also be addressed. It is strange that acetaminophen has not been well studied concerning the potential transgenerational side effects. Most people buying a drug over the counter or even in a supermarket, will consider this drug to be safe even for their unborn child if taken during pregnancy.

A number of recent research findings indicated this may not be true, perhaps related to a potential hormonal disruptive effect;³ but whatever the possible mechanism could be, these findings give reasons for concern, also for regulatory bodies. We have seen prenatal exposure to acetaminophen being related to cryptorchidism,⁴ asthma⁵ and now also functional effects especially—but not limited to—hyperactivity^{6,7}. How much more evidence is needed before the regulatory bodies need to act? The answer may not be straightforward, due to the complexity related to this type of research. We have to rely on self-reported data for

acetaminophen use (only a very small part is based on prescription in many countries). The drug is commonly used and therefore leaves no long-term memory tracks, making self-reported historical data unreliable. Furthermore, the outcomes we study are not very well defined. Some may argue we all have ‘more or less’ ADHD or ASC. We have no measurements that live up to the G. Rasch’s standards for ‘specific objectivity’⁸ on these diseases.

In addition, other causes of these traits or behaviours are not well known and there are no simple ways to deconfound the analyses, although sibling comparison designs are strongly supported by many to address genetic factors. Sibling designs are, however, vulnerable to bias due to limited sample sizes, diagnostic ‘carry-over’ effect from one sibling to the other, potential sex and birth order effects, non-shared confounding within sibling-pairs and potential oversampling of measurement errors.⁹ Further, sample sizes need to be very large to generate sufficient information. Sibling comparison is susceptible to systematic change of underlying factors for siblings, such as that maternal behaviour changed systematically from one ‘poor’ pregnancy (i.e. adverse birth outcomes, ASC or ADHD) to other pregnancies, or other pregnancy behaviour changes associated with birth order, maternal age or occupation; and thus the characteristics for non-fixed confounders may be systematically different in the affected children and their control sibling. In a regular analysis, we can still find children born to other mothers with similar characteristics for comparisons but, within siblings, we may not be able to address these because the comparison is limited to the sibling.⁹ Furthermore, siblings only share 50% of their gene variants, leaving room for genetic confounding. These and other sources of error can go in both directions. We may see spurious findings and we may grossly underestimate effects.

What then should we do? Maybe more research is not needed before the FDA or EMA act, but more research is needed for the rest of us. Fortunately, data are available in many of the established pregnancy cohorts as demonstrated by Avella-Garcia’s study, and many more research groups have data that will allow us to see if the findings in Avella-Garcia’s paper are transportable¹⁰ or reproducible in other datasets collected using different designs from different populations. We also need to see results based on clinically diagnosed outcomes (ADHD and ASC) and with longer follow-up. The used Spanish cohorts have a strong

emphasis on measuring behavioural problems early in life, perhaps a bit too early. More predictable traits may require measures over a longer age range, but the study stresses that studies on potential ‘fetal programming’ of adult diseases are not only about nutrition and cardiovascular diseases. These studies should also address infections, environmental exposure, the microbiome and social conditions, and microchimerism may also play a role. Pregnancy/birth cohorts are necessary research tools for many of these studies, and fortunately they exist and many of these cohorts are open for use. The pregnant women with fever and headache are waiting for answers. In the meantime, mothers-to-be should be advised to use these drugs only when needed.

Conflict of interest: The authors declare to have no conflicts of interest.

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