Use of paracetamol during pregnancy and child neurological development

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PUBLICATION DATA
Accepted for publication 3rd February 2015.
Published online

ABBREVIATIONS

BDNF	Brain-derived neurotrophic factor
EMA	European Medicines Agency
HED	Human equivalent dose
HKD	Hyperkinetic disorder
MoBa	Norwegian Mother and Child Cohort study
SDQ	Strength and Difficulties Questionnaire

Paracetamol (acetaminophen) remains the first line for the treatment of pain and fever in pregnancy. Recently published epidemiological studies suggested a possible association between paracetamol exposure in utero and attention-deficit–hyperactivity disorder/hyperkinetic disorder (ADHD/HKD) or adverse development issues in children. However, the effects observed are in the weak to moderate range, and limitations in the studies' design prevent inference on a causal association with ADHD/HKD or child neurological development. In parallel, recent animal data showed that cognition and behaviour may be altered following exposure to therapeutic doses of paracetamol during early development. These effects may be mediated by interference of paracetamol with brain-derived neurotrophic factor, neurotransmitter systems (including serotonergic, dopaminergic, adrenergic, as well as the endogenous endocannabinoid systems), or cyclooxygenase-2. However, no firm conclusion can be made on the relevance of these observations to humans. We conclude that additional well-designed cohort studies are necessary to confirm or disprove the association. In the context of current knowledge, paracetamol is still to be considered safe in pregnancy and should remain the first-line treatment for pain and fever.

Information on safety of the fetus exposed to drugs during pregnancy is generally limited.[1] Among 172 medications approved in the USA between 2000 and 2010, 73% had no data on the safety in pregnancy and 98% had insufficient data to evaluate teratogenic risk.[2] In the European Union (EU), 68% of marketed product via the EU centralized procedure, and published on the European Medicines Agency (EMA) website, indicate in their Summary of Product Characteristics that there is no clinical experience during pregnancy.[3] Pregnant females are typically excluded from clinical trials, thus, there is often an absence of evidence-based information in this group of patients at the time of marketing authorization. The EMA recently conducted an analysis of data sources on drug exposure during pregnancy and has noted several issues in obtaining high quality data.[4] However, use of medication during pregnancy is extremely common. Over-the-counter drugs, in particular, are the most common medications used[5] with about 67% of females reporting the use of over-the-counter medication during pregnancy in Europe.[6] Figures are probably more variable in developing countries. A recent pharmacovigilance study conducted on 994 pregnant females using the platform of the Rufiji Health and Demographic Surveillance System in Tanzania, found that more than 98% of these females reported taking at least one medication during pregnancy.[7] Analgesics were among the most frequently reported medications (24%).

Paracetamol (acetaminophen) is a widely used analgesic and antipyretic. It is also an active substance in a series of readily available over-the-counter medicines. Taken during pregnancy, paracetamol is generally considered safe and effective when used at the recommended dosage. Approximately 51% of western EU females and 61% of northern EU females reported the use of paracetamol during pregnancy.[6]

The placental barrier is known to be permeable to paracetamol. Thus, paracetamol and its metabolites could be detected in the infant's urine after the mother had taken the drug a few hours before delivery.[8] Data from epidemiological and animal studies are reassuring regarding the risk of malformations and, although lately a link was suggested between paracetamol exposure in utero and cryptorchidism or asthma, available data show no conclusive association.[9]

Very little, however, is known about the long-term effects of paracetamol in utero exposure on child neurological development. Recently, the results of three cohort studies have cast some doubts on the reassuring picture of

neurodevelopmental safety associated with paracetamol use during pregnancy. Two studies reported an association between in utero exposure to paracetamol with attention-deficit–hyperactivity disorder (ADHD)/hyperkinetic disorders (HKD) disorders,[10,11] and a third with detrimental effects on several neurodevelopmental outcome measures.[12] It is essential to ensure that health providers can make proportionate risk-benefit decisions supported by sufficient and valid evidence-based data regarding the use of medication during pregnancy. Here, we critically review the evidence for a potential deleterious neurological effect of paracetamol in utero exposure and the non-clinical data on the possible underlying mechanism.

PHARMACOEPIDEMIOLOGICAL STUDIES

Before 2013 only one study (Streissguth et al.[13]) had evaluated the impact of acetysalicylic acid (aspirin) and paracetamol taken during pregnancy on the child's IQ and attention skills in a selected cohort of 421 infants examined at 4 years of age. In this group, the authors concluded that maternal paracetamol use during the first half of the pregnancy was not significantly related to IQ or attention decrement.

In 2014, Liew et al.[10] published a prospective cohort study evaluating the risk of developing ADHD-like behavioural problems or HKD in children following prenatal exposure to paracetamol. The study is based on the Danish National Birth Cohort, a cohort of pregnant females and children with long-duration follow-up (about 11y). Over half of all mothers reported paracetamol use during pregnancy (56%). Danish registries were used to identify, among the cohort of 64 322 children aged 5 years or more, those who received a hospital diagnosis of HKD or who were using ADHD medications. To assess ADHD-like behaviours, the cohort was further restricted to children whose caregiver responded to a self-administered online/mail questionnaire when the child turned 7 (40 916 children). Parental reports based on the standardized Strength and Difficulties Questionnaire (SDQ) were used for assessing the 7-year-old child's ADHD-like behaviours. Paracetamol use during pregnancy was associated with significantly higher scores for the following items: ADHD-like behaviours (risk ratio 1.13; 95% CI 1.01–1.27); diagnoses of HKD (hazard ratio 1.37; 95% CI 1.19–1.59); and prescriptions of ADHD medications (hazard ratio 1.29; 95% CI 1.15–1.44).

The major strengths of this study are the large sample size, allowing the detection of small size effects on the outcomes, and the prospective design, minimizing the potential for recall bias. Database-recorded ADHD diagnoses and prediction for ADHD medication are likely to be an accurate reflection of the prevalence of ADHD.[14] Moreover, the robustness of the findings was enhanced by the inclusion of a wide range of covariates in the regression models, including fever or inflammation/infection during pregnancy, and mother's mental health problems, which are known risk factors for neurodevelopmental impairment and important potential confounders for the association of interest.[14]

What this paper adds

- Animal data suggest that therapeutic doses of paracetamol may alter cognition and behaviour.
- Epidemiological studies suggest a weak to moderate association between antenatal exposure to paracetamol and neurodevelopment or attention-deficit–hyperactivity disorder, but limitations in the studies' design and weakness of the observed associations prevent causal inference.
- Given the current knowledge, paracetamol is still to be considered safe in pregnancy and should remain the first line for the treatment of pain and fever.

However, as suggested by Cooper et al. in the editorial associated with the study,[14] the interpretation of the relationship is not straightforward. About 30% of the eligible mothers were excluded for missing one or more telephone interviews, which means that the sample may not be representative because ADHD is thought to be largely heritable and dropout may be different depending on the ADHD status of the parents. In addition, the possibility of residual confounding factors, such as indication for drug use, ADHD-related genetic factors, maternal psychopathology, or co-medication, cannot be excluded. Since the observed associations are moderate, they might disappear if further adjustment for unmeasured or imperfectly measured confounders is applied.

Recently, investigators involved in a prospective birthweight longitudinal study in New Zealand looked at the possible association between drugs commonly taken during pregnancy and ADHD.[11] Data on drug use were obtained by interview-administered questionnaires with the mother soon after the child's birth. ADHD symptoms were evaluated through questionnaires administered to parents at age 7 years and 11 years, and to the child at age 11 years, using the SDQ and Conners' Behavioural Rating Scale Revised Long Format scales. Data were available for a subgroup of 871 infants of European descent. Paracetamol was used by 49.8% of the study mothers (anti-inflammatory drugs 1.3%, aspirin 5.3%, antacids 17.4%, and antibiotics 23.5%). Statistically marginal significant differences were observed in the total SDQ scores derived at 7 years of age (maternal questionnaire) and at 11 years of age (child questionnaire). SDQs showed moderately higher values for children who were exposed to paracetamol during pregnancy. There were no statistically significant differences associated with any of the other drugs (anti-inflammatories: −1.3 [95% CI −3.5 to 0.9]; aspirin: 0.5 [95% CI −1.5 to 2.4]; antacids: −0.1 [95% CI −1.0 to 0.7]; and antibiotics: 1.2 [95% CI 0.4 to 2.0]). Children of mothers who used paracetamol during pregnancy were also at increased risk of having symptoms of ADHD at 7 years (but not at 11y) as defined by Conners' Rating System at the univariable level (difference of continuous parental Conners' scores: 1.6; 95% CI 0.3–2.9), but the significance was lost at the multivariable level.

This study suggests that the findings could be specific to paracetamol as there were no associations found with other commonly used drugs in pregnancy. However, the effect observed is weak and marginally significant, as a small

amount of residual confounding would suffice to generate spurious effect. The specificity of the effect could have been influenced by the weak prevalence of use of the other medicinal products. The study has, in addition, potential sources of bias such as a low follow-up rate, and the absence of information on the ADHD status of the parents. Finally, no information was collected on dosage or trimester use of paracetamol during pregnancy. Therefore it seems hazardous to infer clinical relevance from this study.

A few months before the publication of the Danish cohort study, the results of a sibling-control study evaluating the long-term neurodevelopmental effects of in utero exposure to paracetamol became available.[12] The study is a subproject of the Norwegian Mother and Child Cohort study (MoBa) conducted by the Norwegian Institute for Public Health. The authors prospectively examined a potential association between prenatal exposure to paracetamol and psychomotor development (communication, fine and gross motor development), externalizing and internalizing behaviour problems, and temperament (emotionality, activity, sociability, and shyness) in children after 3 years of follow-up. The sibling-control design allowed a separation of the effect of shared environmental and genetic confoundings (i.e. familial confoundings) from the effect of the medication. Within the MoBa, 2919 same-sex sibling pairs were identified as matching the inclusion criteria. The children were classified with regard to paracetamol in utero exposure either as: 'not exposed'; 'exposed for 1 to 27 days' (short-term exposure); or 'exposed for ≥28 days' (long-term exposure). The pairs of siblings were considered concordant when both were equally exposed (both exposed or both unexposed), and discordant on exposure when the siblings differed on exposure (one exposed for ≥28d, the other not exposed or exposed <28d). Ibuprofen was used as a secondary predictor. The potential association between prenatal paracetamol use and outcomes of interest was assessed using generalized linear regression on the intrapair differences. The mean difference in developmental outcomes in a discordant sibling pair was estimated by the beta (β) parameter.

The main indications reported in case of long-term exposure were as follows: headache or migraine (63.4%); back pain and pelvic girdle pain (19.5%); fever (19.5%); and influenza or cold (12.2%). The sibling-controlled adjusted analysis showed that long-term prenatal exposure to paracetamol (≥28 cumulative days) was associated with increased risk for the majority of the outcomes. The statistically significant effects in the adjusted models concerned the following items: delayed age of walking onset (β=0.26; 95% CI 0.06–0.45); gross motor development (β=0.24; 95% CI 0.12–0.51); communication skills (β=0.20; 95% CI 0.01–0.39); externalizing behaviour problems (β=0.24; 95% CI 0.12–0.37); internalizing behaviour problems (β=0.14; 95% CI 0.01–0.28); and active temperament (β=0.22; 95% CI 0.11–0.36).

Short-term exposure was associated with poor gross motor development and delayed motor milestone (age at onset of walking), but the effects were smaller than with long-term use. As a comparison, the cohort analyses on the total MoBa cohort only found a few weak associations between paracetamol exposure and the child's neurological development, with no specific trend related to the exposure duration. This suggests an underestimation of the effect in the cohort analysis as compared to the sibling-controlled analysis. Moreover, the high intraclass correlations observed suggest a strong familial confounding on the measured outcomes.

Assuming a prevalence of 6% for behavioural and psychomotor problems and 4% for language disorders in the general population of preschool children, the authors calculated the relative risks for disorders to be 1.69 for behavioural problems, 1.67 for psychomotor problems, and 1.51 for language disorders.

The major strength of the study lies in the sibling-control design, which naturally adjusts for familial confounding, and stable selection factors (e.g. socio-economic status). Additional strengths are the large sample size, the adjustment for indication (fever, infections, muscle pain, headache), and other potential confounders (e.g. co-medication, maternal depression, alcohol use).

Interestingly, ibuprofen was not associated with neurodevelopmental outcomes, which could suggest a specific effect of paracetamol that would be less likely to be confounded by indication. However, the absence of a significant association for ibuprofen might be because of the insufficient power. Indeed, the number of discordant pairs of same-sex siblings for ibuprofen was 155 (all exposures), whereas for paracetamol there were 805 and 134 discordant pairs for short- and long-term exposure respectively. Other limitations to the comparison between ibuprofen and paracetamol include the lack of information on the pattern of ibuprofen exposure. Ibuprofen is usually not recommended during pregnancy and contraindicated in the third trimester. A shorter average exposure or a more limited exposure to ibuprofen is therefore expected in the third trimester as compared to paracetamol.

The authors also identified limitations such as the low participation rate in MoBa that could potentially cause a selection bias and the assessment by self-reporting potentially leading to misclassification (e.g. smoking during pregnancy may be underestimated). The possibility of residual confounding because of unmeasured or imperfectly measured variables (e.g. unreported infections or illness) was not ruled out.

One of the main limitations is certainly the use of 'soft' outcomes, which can be prone to differential misclassification and do not have a simple clinical interpretation. Psychomotor, behaviour, and temperament problems detected at 3 years of age will not systematically translate into clinical disorders with time. Externalizing behaviour could be associated later in development with ADHD or other disorders such as opposition or anxiety disorders, but they could also result in an absence of any disorder. A longer follow-up or linkage with other available databases may be

envisaged to identify those children receiving ADHD/HKD diagnoses and further assess the clinical relevance of the findings. Recently Damkier et al.[15] have also criticized the translation of questionnaire-based scores of neurodevelopment into a single continuous scale variable. In their opinion, clinically meaningful interpretation of such data in terms of regression analyses are subject to underlying assumptions that cannot be verified.

Furthermore, the different classes of pregnancies showed important difference in patterns of paracetamol use, as indicated by the median difference in discordance of exposure between sibling discordant pairs (2d vs 37d in short- and long-term discordant pairs respectively). Some differences in other characteristics like smoking, alcohol use, and maternal depression were also observed. Pregnancies with long-term exposure to paracetamol differed from other pregnancies and it is possible that residual confounding could, at least partly, explain the reported association.

In both the Danish and the Norwegian studies, prolonged use resulted in stronger associations but both faced limitations in determining paracetamol exposure. Only data on the cumulative number of days/weeks of exposition could be collected, which might not adequately reflect the overall burden of exposure. The cut-off date set at 28 days cumulative exposure in the Norwegian study (based on the association between paracetamol and cryptorchidism)[16] might not be the most relevant choice. As a result, it is not clear which dosage is associated with the observed effects (one-off intensive use or regular moderate dosing).

Finally, although the authors mention a trend towards a third trimester effect in the Norwegian study and a stronger association for use during both second and third trimester in the Danish study, neither could clearly identify a period at risk.

In sum, exposure to paracetamol in utero was associated with a moderate (if not weak) statistically significant increased risk of ADHD/HKD disorders (Danish and New Zealand cohort studies[10,11]) or neurodevelopmental detrimental effects (Norwegian sibling-controlled study[12]) for the children. Though the three studies evaluate outcomes related to neurological development, they do not all overlap and are not directly supportive of each other. A major strength of the Danish and Norwegian studies is their large sample size. Furthermore, the use of a sibling-controlled design in the Norwegian study allowed to partially control for familial and hereditary confounding. Nonetheless, in each of the three studies, potentially unidentified or not fully controlled confounding factors could have an unpredictable impact on the moderate association observed. In addition, sound ascertainment of the ADHD/HKD diagnosis, including the pervasive aspect, is essential, but this has not been sufficiently addressed in the two concerned studies. Therefore, these findings need to be confirmed before a firm conclusion can be drawn. It must also be borne in mind that, in addition to possible specific effects on early brain maturation, postnatal effects might also occur. Moreover, other environmental factors such as mode of parenting, attachment style, or socio-economic status might also ameliorate or exacerbate those effects.

ANIMAL STUDIES

Several recent animal studies report that cognition and behaviour are affected by therapeutic doses of paracetamol. These data point towards different potential mechanisms that may support effects of paracetamol on neurological development.

Paracetamol administration in mice during neonatal brain development was shown to subsequently affect cognitive function, and alter analgesic and anxiolytic response in adult male mice.[17] The dose administered in this study (2×30mg/kg bodyweight, 4h apart) corresponds to a human equivalent dose (HED) of 4.9mg/kg bodyweight using the body surface area normalization method.[18] Subcutaneous administration of this clinically relevant dose of paracetamol at postnatal day 10, resulted in altered locomotor activity, and a failure to acquire spatial learning in adulthood without affecting thermal nociceptive responding or anxiety-related behaviour. However, when mice exposed neonatally received paracetamol during adulthood, they failed to exhibit paracetamol-induced antinociceptive and anxiogenic-like behaviour.

Moreover, in the same study, levels of brain-derived neurotrophic factor (BDNF) in the neonatal brain were affected. BDNF is a neurotrophin that is widely expressed in the brain with a distinct ontogeny pattern during the brain growth spurt. It promotes neuronal survival and also regulates cell migration, axonal and dendritic outgrowth, and formation and function of synapses. In humans, the brain growth spurt begins during the third trimester of pregnancy and continues throughout the first 2 years of life, whereas in rodents the brain growth spurt is confined to the neonatal period, spanning the first 3 to 4 weeks of life and peaking around postnatal day 10. Therefore, the observed behavioural and cognitive alterations in adulthood might to some extent be caused by paracetamol-induced changes in BDNF levels in key brain regions at a critical time during development.

BDNF is also known to interact with the endocannabinoid system,[19] which is involved in the development of the brain. In particular, the cannabinoid receptor CB1 is required for normal axonal growth and fasciculation.[20] Embryonic CB1-receptor signalling may participate in the correct establishment of neuronal connectivity. Consequently, manipulations of the endocannabinoid system during critical stages of brain development might have persistent neurobehavioural consequences.

In a study by Gould et al.,[21] acute intraperitoneal administration of paracetamol (100mg/kg bodyweight, HED: 8.1mg/kg) enhanced social behaviour in adult male mice. This was associated with elevated cortical levels of endocannabinoids. The behavioural effects of paracetamol were, however, distinct from a full CB1 agonist, which suppressed locomotor activity.

Interestingly, indirect activation of cannabinoid CB1 receptors is suggested by several authors as a mechanism

of action of the analgesic effect of paracetamol. In particular, it has been shown that analgesic activity of paracetamol in rats is blocked by CB1 or CB2 antagonists,[22,23] and analgesic activity is lost in $CB1^{-/-}$ knockout mice.[24] Why paracetamol fails to elicit cannabimimetic effects in humans is unknown. Gould et al.[21] seem to point to species differences since they demonstrated strain-specific differences in mice. They also suggest that other indirect actions of paracetamol, including enhanced serotonin (5-HT) neurotransmission, may outweigh any CB1-mediated effects in some mouse strains.

Indeed, another hypothesis is that the analgesic actions of paracetamol are substantially linked to various neurotransmitter systems. The analgesic activity of paracetamol is decreased by inhibitors of serotonin, endogenous opioids, endogenous cannabinoids, and, possibly, acetylcholine. In addition, the activity of some neurotransmitters like substance P, glutamate, and, possibly, noradrenaline is inhibited by paracetamol.[25]

In a recent review, Homberg et al.[26] emphasized the role of both 5-HT and BDNF in development and brain maturation. Moreover, they suggested a mutual interaction between BDNF and 5-HT to be central to the maintenance of neuroplasticity. Hence, interference of paracetamol with these two systems during critical stages of brain development might be expected to have persistent neurobehavioural consequences.

Furthermore, in rats, therapeutic doses of paracetamol cause significant changes in neurotransmission in the brain structures involved in cognitive processes. In male Wistar rats, repeated subcutaneous paracetamol treatment of 10 or 50mg/kg bodyweight per day (HED: 1.6 or 8.1mg/kg respectively) for 8 weeks resulted in significant modulation of neurotransmission, with subtle changes in behaviour and working memory.[27] Significant differences in the content of monoamines and metabolites between the experimental groups suggest that major changes after paracetamol administration were related to serotonergic and noradrenaline neurotransmission in the prefrontal cortex, hypothalamus, and the striatum. A shift in the metabolism of dopamine was also observed. In the same rat model, an 8-week paracetamol treatment significantly affected the balance of amino acids in the striatum, prefrontal cortex, and hypothalamus.[28] Such pronounced changes in amino acid levels might significantly affect the metabolism and transport of other neurotransmitters, and thereby cause cognitive and behavioural impairment.

In the mammalian brain, noradrenergic transmission is closely related to anxiety and plays an essential role in the regulation of fundamental brain functions such as attention, consolidation, and retrieval of some types of memory.[27] The shift in the metabolism of dopamine-neurotransmitter involved in movement may be responsible for the observed alterations of motor activity. Hence, the observed changes in neurotransmission may explain the discrete alterations in animal behaviour.

A study in mice by Ishida et al.[29] pointed to dose-dependent effects for either inhibition of cyclooxygenase-2 (COX-2) or increased serotonergic neuronal activity based on their observations that intraperitoneal paracetamol injections of high-dose paracetamol (302.3mg/kg bodyweight, HED: 24.5mg/kg) caused spatial memory deficits in the water maze, whereas low-dose paracetamol (15.1mg/kg, HED: 1.2mg/kg) improved water maze performance. These results are consistent with previous findings suggesting that endogenous COX-2 participates in memory formation.[30]

Taken together, evidence from non-clinical studies show that cognition and behaviour may be affected by therapeutic doses of paracetamol during early development. This is supported by findings in neonatal mice corresponding to the third trimester of pregnancy in humans. The other studies that we discussed, however, report effects observed in adult animals. It is difficult to translate these findings into human risk for paracetamol use during pregnancy, and currently no firm conclusion can be drawn with respect to the relevance of these observations for humans. The alleged association of paracetamol use and neurodevelopmental alterations may reflect underlying inhibition of endogenous COX-2, 5-HT agonism, and endocannabinoid system interactions. The critical window of exposure is nevertheless not established, and the exact neuromodulatory abilities of paracetamol and potential impact on behaviour or cognition are still poorly defined.

CONCLUSION

A review of the available non-clinical data indicates that neuronal development may be affected by therapeutic doses of paracetamol, and several plausible mechanisms have been suggested. Additional studies are needed to substantiate the proposed hypotheses regarding the underlying mechanism(s) and the clinical relevance of the observed effects, including their reversibility.

In the light of the currently available epidemiological data, no causal relationship between paracetamol in utero exposure and ADHD/HKD or neurodevelopmental issues can be concluded. The observed effects are at most moderate and could either be explained by unmeasured genetic or environmental confounders in the case of the studies on ADHD, or have an unclear clinical impact that might fade out over time (Norwegian study).

Additional carefully designed studies are necessary to confirm or disprove the association. Randomized clinical trials are not feasible in the pregnant population for ethical reasons. Therefore, only longitudinal cohort studies could generate exploitable information. A prospective ascertainment of exposure and outcome is important for avoiding reverse causality and recall bias. Confounding by indication and severity can seriously compromise the interpretation of the results, and should be tackled by collecting detailed data during pregnancy. In order to control for familial confoundings, the study design should allow separating effects of prenatal exposure to paracetamol from familial effects, as was done in the Norwegian study. Contrasting maternal and

paternal exposure, as proposed by Smith,[31] could further help investigate the causal inferences. Moreover, every effort should be made to obtain good quality data of key potential confounders (e.g. maternal stress, co-medication) for reducing the impact of residual confounding. Above all, studies' outcomes should be carefully selected to characterize the clinical relevance of the effect. Given the complex heterogeneity of AHDH/HKD, it is of the utmost importance to validate the diagnoses on the basis of clinical criteria as well as evaluation of neuropsychological assessment.[32] Perhaps neurophysiological recordings might be considered.[33] To the extent possible, subgroup analysis per trimester, exposure duration, and cumulative dose would be needed to allow practical clinical conclusions.

Based on currently available evidence, we conclude that paracetamol is still to be considered safe in pregnancy, and it remains the first line treatment for pain and fever. For the indication of fever, no restriction beyond the standard recommendations should be made to the use of paracetamol in pregnant females, since untreated fever may lead to uterine contractions and early delivery.[34] For the indication of pain, the following recommendation is proposed: that paracetamol should be used only if clinically needed and at the lowest effective dose for the shortest possible time, and at the lowest possible frequency. Care should be taken to avoid raising poorly founded concerns among pregnant females because of the risk of switching to other analgesic/antipyretic drugs with less favourable risk profile (e.g. non-steroidal anti-inflammatory drugs).[35]

ACKNOWLEDGEMENTS

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of the Belgian Agency for Medicines and Health Products (FAMHP) or any other public institution the authors might be working for.

REFERENCES

1. Thorpe PG, Gilboa SM, Hernandez-Diaz S, et al. Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. *Pharmacoepidemiol Drug Saf* 2013; **22**: 1013–8.
2. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet C Semin Med Genet* 2011; **157C**: 175–82.
3. Arguello B, Salgado TM, Fernandez-Llimos F. Assessing the information in the summaries of product characteristics for the use of medicines in pregnancy and lactation. *Br J Clin Pharmacol* 2015; **79**: 537–44.
4. Charlton R, De Vries C. Systematic Overview of Data Sources for Drug Safety in Pregnancy Research Consultancy EMA/2010/29/CN Prepared for the European Medicines Agency, June 2012. Available from: http://www.encepp.eu/structure/documents/Data_sources_for_medicines_in_pregnancy_research.pdf (accessed 13 November 2014).
5. Werler MM, Mitchell A, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol* 2005; **193**: 771–7.
6. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open* 2014; **4**: e004365.
7. Mosha D, Mazuguni F, Mrema S, Abdulla S, Genton B. Medication exposure during pregnancy: a pilot pharmacovigilance system using health and demographic surveillance platform. *BMC Pregnancy Childbirth* 2014; **14**: 322.
8. Levy G, Garrettson LK, Soda DM. Letter: Evidence of placental transfer of acetaminophen. *Pediatrics* 1975; **55**: 895.
9. Prescrire R. Paracetamol during pregnancy: no particular danger for the child. *Prescrire Int* 2012; **21**: 186–7, 190.
10. Liew Z, Ritz B, Rebordosa C, Lee P-C, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr* 2014; **168**: 313–20.
11. Thompson J, Waldie K, Wall C, Murphy R, Mitchell EA, ABC Study Group. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PLoS ONE* 2014; **9**: e108210.
12. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013; **42**: 1702–13.
13. Streissguth AP, Treder RP, Barr HM, et al. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratology* 1987; **35**: 211–9.
14. Cooper M, Langley K, Thapar A. Antenatal acetaminophen use and attention-deficit/hyperactivity disorder: an interesting observed association but too early to infer causality. *JAMA Pediatr* 2014; **168**: 306–7.
15. Damkier P, Pottegård A, dePont Christensen R, Hallas J. Annotations and reflections: pregnancy and paracetamol: methodological considerations on the study of associations between in utero exposure to drugs and childhood neurodevelopment. *Basic Clin Pharmacol Toxicol* 2014; **116**: 2–5.
16. Jensen MS, Rebordosa C, Thulstrup AM, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology* 2010; **21**: 779–85.
17. Viberg H, Eriksson P, Gordh T, Fredriksson A. Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicol Sci* 2014; **138**: 139–47.
18. Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *FASEB J* 2008; **22**: 659–61.
19. D'Souza DC, Pittman B, Perry E, Simen A. Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans. *Psychopharmacology* 2009; **202**: 569–78.
20. McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLoS ONE* 2014; **9**: e89566.
21. Gould GG, Seillier A, Weiss G, et al. Acetaminophen differentially enhances social behavior and cortical cannabinoid levels in inbred mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **38**: 260–9.
22. Dani M, Guindon J, Lambert C, Beaulieu P. The local antinociceptive effects of paracetamol in neuropathic pain are mediated by cannabinoid receptors. *Eur J Pharmacol* 2007; **573**: 214–5.
23. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol* 2006; **531**: 280–1.
24. Mallet C, Daulhac L, Bonnefont J, et al. Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. *Pain* 2008; **139**: 190–200.
25. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013; **21**: 201–32.
26. Homberg JR, Molteni R, Calabrese F, Riva MA. The serotonin-BDNF duo: developmental implications for the vulnerability to psychopathology. *Neurosci Biobehav Rev* 2014; **43**: 35–47.

27. Blecharz-Klin K, Piechal A, Pyrzanowska J, Joniec-Maciejak I, Kiliszek P, Widy-Tyszkiewicz E. Paracetamol–the outcome on neurotransmission and spatial learning in rats. *Behav Brain Res* 2013; **253**: 157–64.

28. Blecharz-Klin K, Joniec-Maciejak I, Piechal A, Pyrzanowska J, Wawer A, Widy-Tyszkiewicz E. Paracetamol impairs the profile of amino acids in the rat brain. *Environ Toxicol Pharmacol* 2014; **37**: 95–102.

29. Ishida T, Sato T, Irifune M, Tanaka K, Nakamura N, Nishikawa T. Effect of acetaminophen, a cyclooxygenase inhibitor, on Morris water maze task performance in mice. *J Psychopharmacol* 2007; **21**: 757–67.

30. Rall JM, Mach SA, Dash PK. Intrahippocampal infusion of a cyclooxygenase-2 inhibitor attenuates memory acquisition in rats. *Brain Res* 2003; **968**: 273–6.

31. Smith GD. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol* 2008; **102**: 245–56.

32. Sonuga-Barke EJS, Coghill D. The foundations of next generation attention-deficit/hyperactivity disorder neuropsychology: building on progress during the last 30 years. *J Child Psychol Psychiatry* 2014; **55**: e1–5.

33. Lenartowicz A, Delorme A, Walshaw PD, et al. Electroencephalography correlates of spatial working memory deficits in attention-deficit/hyperactivity disorder: vigilance, encoding, and maintenance. *J Neurosci* 2014; **34**: 1171–82.

34. Hoffman BL, Horsager R, Roberts S. Williams Obstetrics, Study Guide. 24th edn. New York, NY: McGraw-Hill Education, 2014.

35. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 9th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2011.