# Paracetamol/Acetaminophen During Pregnancy Induces Prenatal Ductus Arteriosus Closure

Odile Becquet, MD,[a] Damien Bonnet, MD, PhD,[b,c] Yves Ville, MD, PhD,[c,d] Karel Allegaert, MD, PhD,[e,f] Alexandre Lapillonne, MD, PhD[a,c]

Paracetamol or acetaminophen (APAP) is commonly used as a first line treatment of pain and fever in pregnancy. In view of new evidence that reveals that APAP medication during pregnancy may be associated with impaired outcomes, safety of the use of APAP during pregnancy should be questioned. The causality between maternal APAP treatment and prenatal ductus arteriosus closure was qualified as certain by using the World Health Organization Uppsala Monitoring Center causality assessment system in a short series of 2 clinical cases. Because the fetal ductus arteriosus closure can lead to fetal loss or life-threatening cardiac failure in the newborn, the use of APAP, specifically after the sixth month of pregnancy, should be as limited as possible.

Paracetamol or acetaminophen (APAP) is commonly used as first-line treatment of pain and fever in pregnancy.[1] It is considered safe compared with nonsteroidal antiinflammatory drugs (NSAIDs), which increase the risk of malformations, bleeding, and prenatal closure of the ductus arteriosus (DA).[1] The most common reason for prenatal closure of DA is the maternal administration of NSAIDs or other medications that affect prostaglandin E synthesis during the third trimester of gestation. Approximately 60% of mothers who had infants with intrauterine DA closure received NSAIDs drugs and/or corticosteroids, according to the authors of a recent large series systematic literature review.[2]

New evidence reveals that APAP medication during pregnancy may be associated with neurodevelopmental and attention-deficit/hyperactivity disorders, increased risk of wheezing, and higher incidence of asthma among offspring.[3] In view of recent data revealing that APAP confer comparable efficacy as ibuprofen for patent DA closure of premature infants,[4] safety of the use of APAP during pregnancy with regard to prenatal closure of the DA should be questioned. The authors of only 1 previous publication reported prenatal DA closure after maternal treatment with APAP,[5] but causality could not be determined because maternal treatment was associated with numesolide, which is well known to induce prenatal closure of the DA.[6] We report for the first time a short series of clinical cases for which causality between prenatal DA closure and maternal APAP treatment has been assessed by using a validated causality assessment system.

## CASES

Two neonates were diagnosed with a prenatal DA closure possibly after maternal APAP treatment. In the first case, the neonate was born from a 32-year-old woman (weight: 69 kg, BMI: 23.8) who had previously given

abstract

*Departments of [a]Neonatology and [d]Obstetrics, and [b]M3C-Necker, Congenital and Pediatric Cardiology, Hôpital Universitaire Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; [c]Paris Descartes University, Paris, France; [e]Intensive Care and Department of Surgery, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, Netherlands; and [f]Department of Development and Regeneration, Katholieke Universiteit Leuven, Leuven, Belgium*

Dr Becquet collected data, drafted the manuscript, and had access to all of the primary data; Dr Bonnet had access to all of the primary data, provided expertise in reviewing the data, and provided significant scientific input; Dr Ville had access to all of the primary data and provided expertise in reviewing the data; Dr Allegaert provided significant scientific input and critically reviewed the manuscript for important intellectual content; Dr Lapillonne served as the coordinator for the study, had access to all of the primary data, and drafted the manuscript; and all authors participated in the review, revision, and approval of the final manuscript as submitted and agree to be accountable for all aspects of the work.

**DOI:** https://doi.org/10.1542/peds.2017-4021

Accepted for publication Feb 26, 2018

Address correspondence to Alexandre Lapillonne, MD, PhD, Department of Neonatology, Necker Enfants Malades Hospital, 149 Rue de Sèvres, 75015 Paris, France. E-mail: alexandre.lapillonne@aphp.fr

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).



**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**To cite:** Becquet O, Bonnet D, Ville Y, et al. Paracetamol/Acetaminophen During Pregnancy Induces Prenatal Ductus Arteriosus Closure. *Pediatrics*. 2018;142(1):e20174021

birth to 2 daughters at term after uneventful pregnancies. During her third pregnancy, she suffered repeated headaches during the first weeks and was prescribed paracetamol (maximum dosage of 1 g every 6 hours). Routine ultrasound examinations were normal until 26 weeks' gestation. Isolated fetal supraventricular tachycardia was discovered at 33 weeks' gestation, which responded well to flecainide given to the mother until she gave birth. At 34 weeks' gestation, fetal heart rate and cardiac anatomy and function were normal under flecainide treatment. Because of the recurrent headaches, the mother took 1 g of paracetamol once. Two days later, at 35 weeks' gestation, the pediatric cardiologist reported right ventricular dilatation, tricuspid regurgitation, and color Doppler indicated restriction of the fetal DA. On the basis of this information, labor was induced and an apparently healthy male infant was born with an appropriate adaptation to extrauterine life. Echocardiography at 2 hours of life revealed right-ventricular hypertrophy, pulmonary artery pressure of 20 mm Hg, bicuspid aorta, and totally closed DA. The left ventricular function was normal. The results of a Holter electrocardiogram were also normal without signs of supraventricular tachycardia or underlying causes. The boy was discharged from the hospital at 10 days in good condition with no treatment.

In the second case, the 27-year-old mother (weight: 45 kg, BMI: 16.9) had no previous medical history and was having an uneventful pregnancy with normal routine ultrasound examinations at 22 and 33 weeks' gestation. Because of fetal cardiac ventricular asymmetry, she was referred to a pediatric cardiologist at 37 weeks' gestation. Cardiac anatomy was normal with right ventricular dilatation, tricuspid regurgitation, and color Doppler indicated fetal DA restriction. A healthy female neonate (birth weight: 2210 g; <10th percentile) was born at 37 weeks' gestation after the induction of labor. Her Apgar scores were 9, 10, and 10 at 1, 3, and 5 minutes, respectively. The birth pH was 7.37 and lactic acid was 3.4 mmol/L. Echocardiography at 2 hours of life revealed a hypertrophied and hypokinetic right ventricle with a moderate tricuspid regurgitation (systolic pulmonary artery pressure = 60 mm Hg) and right-to-left shunt through a patent foramen ovale. The DA was completely closed. Daily echocardiograms revealed progressive normalization of pulmonary pressure. Finally, the infant was discharged from the hospital on day 5 of life in good condition. In-depth postnatal questioning revealed self-medication with APAP for transient muscular pain at the dose of 1 g per day once a day for 7 days at 34 weeks' gestation and for 3 consecutive days at 36 weeks' gestation but revealed no underlying chronic diseases.

Permission of collection and of use of medical records of our unit has received authorization by the National Committee on Personal Data and Privacy (Commission Nationale de l'Informatique et des Libertés) under the agreement 1825522.

## DISCUSSION

We graded causality between maternal APAP treatment and prenatal DA closure by using the World Health Organization Uppsala Monitoring Center (WHO-UMC) causality assessment system that was developed as a practical tool for assessing causality in case reports.[7] In this system, causality is classified as "certain," "probable or likely," "possible," "unlikely," "conditional or unclassified," and "unassessable or unclassifiable" by considering clinical-pharmaceutical aspects of the case history as well as quality of the documentation of the observation. In our short series of cases, causality was qualified as "certain" (Table 1) by all authors individually. In both cases, the maternal history revealed no other plausible cause for prenatal DA restriction, and the timing of the self-medication was exactly in-between 2 ultrasound examinations, the first being normal and the second revealing the DA restriction. Specifically, in case 1, causality was qualified as "certain" despite the concomitant treatment with flecainide. Indeed, the causality between maternal flecainide treatment and prenatal DA closure is unlikely because the ultrasound examination performed after the start of the treatment with flecainide was normal and because there is no case of prenatal DA closure reported with this drug, which is widely used for the prenatal treatment of fetal supraventricular tachycardia.[8]

Several clinical and experimental reasons support the causality of maternal APAP treatment of the prenatal DA closure. Firstly, the pharmacologic properties of APAP support the association because APAP crosses the placenta freely, inhibits cyclooxygenase-1 and cyclooxygenase-2, and in turn inhibits the synthesis of the vasodilator prostaglandins.[10] Secondly, there are also reports of APAP promoting prenatal ductal constriction in animal models.[9,11,12] Finally, APAP use in preterm infants has been recently demonstrated to be as effective as NSAIDs in closing the DA.[4,13]

Interestingly, severity at birth was mild in both of our cases. As suggested by others,[14] we believe that this is because of the close obstetric management and timely delivery. Prevention of heart failure and fetal hydrops is key in improving neonatal outcome[2] because severe pulmonary hypertension, dysfunction of the right ventricle, and tricuspid regurgitation generate inappropriate pulmonary perfusion, atrial right-to-left shunting,

**TABLE 1** In an Attempt to Determine Causality Between Maternal APAP Treatment and Prenatal DA Closure, the WHO-UMC Causality Assessment System Was Used

| Causality Term | Assessment Criteria of the WHO-UMC System | Criteria in Clinical Cases |
|---|---|---|
| Certain | Event or laboratory test abnormality with a plausible time relationship to drug intake | In both cases, the timing of the mother's APAP use was in-between 2 ultrasound examinations, the first being normal and the second revealing a DA restriction. In case 1, the DA closure was observed 2 d after the maternal treatment. |
| | Cannot be explained by disease or other drugs | The in-depth postnatal questioning of both mothers revealed no history of medications or diets known to close the DA prenatally |
| | Response to withdrawal is plausible (pharmacologically or pathologically) | The adverse event (ie, prenatal DA restriction) did not improve (eg, reopening of DA) after the drug was stopped; the DA was confirmed postnatally. The absence of a positive response to withdrawal was expected because the DA usually does not reopen after withdrawal of APAP or NSAID unless prostaglandin E1 is used. |
| | The event is definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon) | APAP promotes fetal ductal constriction in animal models[9] and postnatal DA closure in preterm infants.[4] |
| | A rechallenge is satisfactory, if necessary | In the recommendations for the use of the WHO-UMC system, it is stated that to be qualified as "certain," rechallenge information with a satisfactory outcome is requested unless the evidence in the report is already convincing without a re-exposure. In both case, a rechallenge would not have been ethical and was not possible because the DA remained closed and delivery was induced. |

Assessment criteria necessary for qualifying causality as "certain" and the correspondent criteria in the clinical cases are depicted. Adapted from the World Health Organization Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. Available at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. Accessed August 30, 2017.

and in turn severe neonatal hypoxia and cyanosis.

Despite the broad usage of APAP during pregnancy (40%–50%),[1] the prevalence of DA prenatal closure is low.[2] Several reasons might explain this apparent discrepancy. The dose of paracetamol reported (or suggested) by researchers to close the DA in preterm infants is high (ie, 60 mg/kg per day for 3 consecutive days) and corresponds to a dose unlikely to be taken by pregnant women (ie, ~3 g per day of paracetamol for 3 consecutive days). Assessing APAP plasma concentrations of the newborn or the mother would have been interesting in this context, but this was unfortunately not possible in the cases presented above. Altered pharmacokinetics in pregnant women with low BMI, altered arachidonic status, or other yet undiscovered factors may be necessary to promote this association.[1,15] Experimental and human data reveal that the clinical efficacy of APAP on DA closure is dependent on the duration and dose.[9] Finally, we cannot exclude that the incidence of constriction and/or closure of the fetal DA is underestimated because it may be transient or partial during pregnancy (and therefore underdiagnosed by routine ultrasound examinations) or because it may lead to a mild postnatal clinical presentation that is not diagnosed postnatally.

Our short case series demonstrates that APAP treatment during pregnancy is likely an underdiagnosed and yet-unrecognized cause of prenatal DA closure and may explain some of the so-called "idiopathic" cases. Because the fetal DA closure can lead to fetal loss or life-threatening cardiac failure in the newborn, we believe that it is crucial to perform further studies to determine the exact role and risk of APAP treatment during the sixth month of pregnancy, and we suggest that APAP treatment during pregnancy should be as limited as possible.

## ABBREVIATIONS

APAP: paracetamol or acetaminophen
DA: ductus arteriosus
NSAID: nonsteroidal antiinflammatory drug
WHO-UMC: World Health Organization Uppsala Monitoring Center

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

## REFERENCES


1. Allegaert K, van den Anker JN. Perinatal and neonatal use of paracetamol for pain relief. *Semin Fetal Neonatal Med*. 2017;22(5):308–313
2. Ishida H, Kawazu Y, Kayatani F, Inamura N. Prognostic factors of premature closure of the ductus arteriosus in utero: a systematic literature review. *Cardiol Young*. 2017;27(4):634–638
3. Tiegs G, Karimi K, Brune K, Arck P. New problems arising from old drugs: second-generation effects of acetaminophen. *Expert Rev Clin Pharmacol*. 2014;7(5):655–662
4. Terrin G, Conte F, Oncel MY, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2016;101(2):F127–F136
5. Simbi KA, Secchieri S, Rinaldo M, Demi M, Zanardo V. In utero ductal closure following near-term maternal self-medication with nimesulide and acetaminophen. *J Obstet Gynaecol*. 2002;22(4):440–441
6. Prefumo F, Marasini M, De Biasio P, Venturini PL. Acute premature constriction of the ductus arteriosus after maternal self-medication with nimesulide. *Fetal Diagn Ther*. 2008;24(1):35–38
7. World Health Organization Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. Available at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. Accessed August 30, 2017
8. Hill GD, Kovach JR, Saudek DE, Singh AK, Wehrheim K, Frommelt MA. Transplacental treatment of fetal tachycardia: a systematic review and meta-analysis. *Prenat Diagn*. 2017;37(11):1076–1083
9. El-Khuffash A, Jain A, Corcoran D, et al. Efficacy of paracetamol on patent ductus arteriosus closure may be dose dependent: evidence from human and murine studies. *Pediatr Res*. 2014;76(3):238–244
10. 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(3):201–232
11. Momma K, Takao A. Transplacental cardiovascular effects of four popular analgesics in rats. *Am J Obstet Gynecol*. 1990;162(5):1304–1310
12. Peterson RG. Consequences associated with nonnarcotic analgesics in the fetus and newborn. *Fed Proc*. 1985;44(7):2309–2313
13. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics*. 2011;128(6). Available at: www.pediatrics.org/cgi/content/full/128/6/e1618
14. Soslow JH, Friedberg MK, Silverman NH. Idiopathic premature closure of the ductus arteriosus: an indication for early delivery. *Echocardiography*. 2008;25(6):650–652
15. Allegaert K, Olkkola KT, Owens KH, Van de Velde M, de Maat MM, Anderson BJ; PACIA Study Group. Covariates of intravenous paracetamol pharmacokinetics in adults. *BMC Anesthesiol*. 2014;14:77

# Paracetamol/Acetaminophen During Pregnancy Induces Prenatal Ductus Arteriosus Closure

Odile Becquet, Damien Bonnet, Yves Ville, Karel Allegaert and Alexandre Lapillonne

*Pediatrics* originally published online June 7, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

# Paracetamol/Acetaminophen During Pregnancy Induces Prenatal Ductus Arteriosus Closure

Odile Becquet, Damien Bonnet, Yves Ville, Karel Allegaert and Alexandre Lapillonne

*Pediatrics* originally published online June 7, 2018;