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. 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). 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. New evidence reveals that APAP confer comparable efficacy as ibuprofen for patent DA closure of premature infants, 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, but causality could not be determined because maternal treatment was associated with numesolide, which is well known to induce prenatal closure of the DA. 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

Paracetamol/Acetaminophen During Pregnancy Induces Prenatal Ductus Arteriosus Closure.

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. Officially, atrial right-to-left shunting, and tricuspid regurgitation, should be considered as Doppler signs of the prenatal DA closure. 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. The baby was having an uneventful pregnancy and was qualified as “certainty” by our follow-up. In this system, causality is classified as certain, possible, or unclassifiable. In our short series of cases, causality was qualified as “certainty” (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 “certainty” 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.

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. Secondly, there are also reports of APAP promoting prenatal ductal constriction in animal models. As shown in Table 1, APAP use in preterm infants has been recently demonstrated to be as effective as NSAIDs in closing the DA.

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 because severe pulmonary hypertension, dysfunction of the right ventricle, and tricuspid regurgitation generate inappropriate pulmonary perfusion, atrial right-to-left shunting,
and in turn severe neonatal hypoxia and cyanosis.

Despite the broad usage of APAP during pregnancy (40%–50%), the prevalence of DA prenatal closure is low. 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. Experimental and human data reveal that the clinical efficacy of APAP on DA closure is dependent on the duration and dose. 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

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