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SHORT REPORT

Maternal paracetamol intake and fetal ductus arteriosus constriction or closure: a case series analysis

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Recent case reports describe an association between maternal paracetamol intake and fetal ductus arteriosus constriction or closure. To put these cases into perspective and explore causality, a structured literature search was conducted. The World Health Organization Uppsala Monitoring Centre (WHO–UMC) causality tool was applied to the cases retrieved. The search resulted in 12 papers with 25 case descriptions, of which one case was classified as unlikely, nine as possible, 11 as probable and four as certain. Consequently, we concluded that a causal relationship between maternal paracetamol intake and fetal ductus arteriosus constriction or closure is likely. These findings suggest that pharmacovigilance studies on paracetamol safety during pregnancy are warranted to quantify the event and put the current findings into clinical perspective. Although analgesia during pregnancy and during the peripartum period is of obvious relevance, alternative analgesics such as opioids or other nonsteroidal anti-inflammatory drugs also have side effects.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Recent case reports have described an association between maternal paracetamol intake and fetal ductus arteriosus constriction or closure, but no structured search and causality assessment of these case reports have been conducted.

WHAT THIS STUDY ADDS

- A structured search on this topic resulted in 12 reports, describing 25 different cases of the association between maternal paracetamol exposure and fetal ductus arteriosus constriction/closure.
- Using the World Health Organization Uppsala Monitoring Centre (WHO-UPC) causality tool, one case was classified as unlikely, nine as possible, 11 as probable and four as certain. Consequently, we conclude that a causal relationship between maternal paracetamol intake and fetal ductus arteriosus constriction or closure is likely.

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Introduction

Paracetamol (acetaminophen) is the most commonly used over-the-counter (OTC) drug to treat mild-to-moderate pain or fever. Pharmaco-epidemiological data suggest that exposure to paracetamol is also very common (37–53%) during pregnancy [1–3].

Although it is well documented that paracetamol has analgesic and antipyretic activities, its mechanisms of actions are still not fully understood. The central analgesic effects are, in part, mediated through activation of descending serotonergic pathways and the formation of an active metabolite influencing cannabinoid receptors [4]. There is also inhibition of central prostaglandin synthesis by competitive inhibition of the peroxidase enzyme part of the prostaglandin H2 synthase (PGHS) enzyme complex, which also includes **cyclooxygenase**. Besides these central effects, paracetamol has nonselective (competitive) inhibitory activity on the PGHS enzyme. As it is competitive, this inhibitory action relates only to physiological, low arachidonic acid concentrations [4–7]. This explains the difference between paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin or ibuprofen, which have stronger peripheral anti-inflammatory, and anti-thrombotic effects [4, 5].

Data on the pharmacokinetics (PK) and pharmacodynamics (PD) of paracetamol during pregnancy have been generated. During pregnancy, there is an important increase in the volume of distribution and metabolic clearance of paracetamol. As a consequence, and when administering normal doses (up to 4 g day^{-1}), it is reasonable to anticipate that the analgesic effect of paracetamol will decrease faster, while use of higher doses may result in an increased formation of oxidative toxic metabolites [8]. Paracetamol crosses the placenta and results in fetal exposure, but without an impact on fetal breathing or movements [8–10].

The epidemiological data on the association between fetal paracetamol exposure and atopy, neurocognition and fertility were recently summarized [1–3]. However, none of these papers discussed the potential association of maternal paracetamol intake and fetal ductus arteriosus constriction. We recently described two such cases [11]. Here, we report on the results of a structured literature search from which we performed a case series analysis to explore causality and put these case observations into clinical perspective.

Methods

A structured search was performed on 10 June 2018 by the first author (K.A.), using 'pregnancy and acetaminophen/paracetamol' and 'fetal ductus' or 'fetal ductus closure, or constriction' as keywords, in the electronic resources PubMed, Web of Science and Google Scholar, without language restrictions. The hits were subsequently screened on the title and, when needed, the abstract or full report. Only cases with acetaminophen/paracetamol in monotherapy (no simultaneous intake of other drugs known to be associated with fetal ductus arteriosus closure, such as NSAIDs) were retained. All retrieved documents were subsequently screened for potential relevant references and citations, using the same search engines.

In the cases retained, causality between maternal paracetamol intake and fetal ductus arteriosus constriction or closure was graded independent by two authors (K.A., P.M.), using the World Health Organization Uppsala Monitoring Centre (WHO-UHC) causality assessment system. This tool has been developed to assess causality in case reports, and uses different causality categories (*certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable*).

The related assessment criteria for the different causality categories are provided in the WHO-UHC document and all these points should be reasonably complied with [12]. Taking the fetal-maternal clinical setting and the maturational aspects (higher likelihood in late pregnancy) related to the risk of ductal closure for NSAIDs into account, the rechallenge criterion was not considered [13]. Differences in classification between the two assessors were subsequently discussed until agreement was reached.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [14], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [15].

Results

Using 'pregnancy and acetaminophen/paracetamol' and 'fetal ductus' or 'fetal ductus closure, or constriction' as keywords, a PubMed, Web of Science and Google Scholar search resulted in 20 and 12, 6 and 0, and 217 and 100 hits, respectively. Using these hits and the subsequent citation and reference analysis, we retrieved 12 reports that described 25 cases on the association between maternal paracetamol intake (as monotherapy) and fetal ductus arteriosus constriction/closure. These reports were published between 2005 and 2018. The most relevant maternal, fetal and/or neonatal clinical characteristics are summarized in Table 1 [11, 16–26].

In these 25 cases, causality between maternal paracetamol intake and fetal ductus arteriosus constriction/closure was graded, and was classified in one case as unlikely (*very long time interval between exposure and diagnosis not compatible with the pathophysiology*), in nine cases as possible (*no pre-exposure normal fetal ultrasound described in the reports and no 'normalization' before delivery described*), in 11 cases as probable (*no pre-exposure normal fetal ultrasound, constriction during exposure with subsequent normalization after paracetamol exposure was stopped*) and in four cases as certain (*normal pre-exposure fetal ultrasound findings, fetal ductus arteriosus constriction or closure during or shortly after exposure described in the reports*) (Table 1).

Two postnatal cases were diagnosed in early neonatal life (<24 h) with a clinical and ultrasound syndrome compatible with 'preterm' fetal ductal closure. A prenatal diagnosis was

Table 1

Summary of the most relevant maternal, fetal and/or neonatal clinical characteristics of retained cases, and the causality assessment scores attributed [11, 12, 16–26]

Author, year	Number	Paracetamol exposure	Outcome (fetal/maternal/neonatal)	WHO-UCM score [10]
Araújo *et al.* 2014 [16]	1	*Dose:* 1000 mg every 6 h for 2 weeks *Week of GA:* 32 *Indication:* pain	*Fetal:* Arrhythmia at 32 weeks with abnormal fetal ultrasound (right ventricular hypertrophy, restricted DA). Partial normalization of ultrasound 1 week after cessation of paracetamol *Maternal:* Elective caesarean at 38 weeks *Neonatal:* Pulmonary hypertension with subsequent confirmed normalization of ultrasound findings	Probable (n = 1)
Becquet *et al.* 2018 [11]	2	*Case 1:* *Dose:* 1000 mg every 6 h, intermittent *Week of GA:* 32 *Indication:* Repeated headaches *Case 2:* *Dose:* 1000 mg day^{-1} for 1 week at 34 weeks, and 1000 mg day^{-1} for 3 days at 36 weeks' GA *Week of GA:* 34–36 *Indication:* Muscular pain	*Fetal:* Routine ultrasound normal before 26 weeks and after 34 weeks. Restriction of DA at 35 weeks *Maternal:* Labour induction *Neonatal:* Right ventricular hypertrophy, pulmonary artery pressure (2 h postnatal), with subsequent recovery and discharge on day 10 *Fetal:* Ultrasound normal at 22 weeks and 33 weeks, at 37 weeks DA restriction. *Maternal:* Labour induction *Neonatal:* Hypertrophied, hypokinetic right ventricle with moderate tricuspid regurgitation, DA closed, progressive normalization and discharge on day 5	Certain (n = 2)
Capuruço & Leite, 2016 [17]	2	*Case 1 and 2:* *Dose:* 500 mg, every 6 h, for >1 week *Week of GA:* 32 (n = 1) and 34 (n = 1) *Indication:* Not reported	*Fetal:* Moderate tricuspid valve regurgitation, dilated right atrium, DA narrowing with high systolic and diastolic velocity and poor pulsatility index (n = 2), normalized DA and pulsatility index (n = 2) 7–10 days after paracetamol was stopped *Maternal:* Emergency caesarean (n = 1) or labour induction with vaginal delivery (n = 1) *Neonatal:* Term, asymptomatic (n = 2)	Probable (n = 2)
Diez & Bazan, 2009 [18]	1	*Dose:* 500 mg, every 8 h, for 4 days *Week of GA:* 32 *Indication:* Flu	*Fetal:* Normal ultrasound at 23 weeks, 4 days after paracetamol intake fetal ductal constriction and relative oligohydramnios at 32 weeks; 2 weeks after stopping paracetamol intake normalization of fetal ultrasound at 34 weeks *Maternal:* elective caesarean at 39 weeks. *Neonatal:* term, normal findings.	Certain (n = 1)
Genovese *et al.* 2015 [19]	1	*Dose:* 500 mg every 6 h for 4 days *Week of GA:* 33 *Indication:* Lumbar pain	*Fetal:* 34 weeks ultrasound fetal heart abnormality, right ventricular hypertrophy, pulmonary hypertension, DA constriction *Maternal:* Semi-elective caesarean at 34^{4} weeks *Neonatal:* Right ventricular hypertrophy, DA constriction, subsequent regression over 15 days	Possible (n = 1)
Gewillig *et al.* 2017 [20]	4/27	*Dose:* – *Week of GA:* 32, 24, 25, 21	*Fetal:* Closure DA (n = 2), constricted (n = 1), kinking (n = 1), moderate dilated right atrium (n = 2), severe tricuspid valve regurgitation (n = 2), severe right	Possible (n = 4)

(continues)

Table 1

(Continued)

Author, year	Number	Paracetamol exposure	Outcome (fetal/maternal/neonatal)	WHO-UCM score [10]
		Indication: –	ventricular hypertrophy (n = 1), right ventricular hypocontractility, tricuspid valve thickening (n = 1), pulmonary artery dilatation, cardiomegaly, pericardial effusion (n = 1), pulmonary valve thickening (n = 1) *Maternal:* Spontaneous at 40 weeks (n = 1), induction at 35 weeks and 37 weeks (n = 2), or caesarean at 39 weeks (n = 1) *Neonatal:* Cyanosis (n = 3), asymptomatic (n = 1), moderate (n = 1) or severe (n = 1) right atrium, mild (n = 1) or severe (n = 1) tricuspid valve regurgitation, moderate right ventricular dilatation (n = 2), severe right ventricular hypertrophy (n = 2), pulmonary stenosis (n = 1), pulmonary atresia (n = 1), pulmonary valve agenesis (n = 1), angioplasty for pulmonary artery atresia (3 months) (n = 1), tricuspid valve repair at 3 weeks, and subsequent replacement at 5 weeks (n = 1), pulmonary valve replacement (7 year) (n = 1)	
Nygaard *et al.* 2009 [21]	1/3	*Dose:* (Minimal) *Week of GA:* 'Early pregnancy' *Indication:*–	*Fetal:* – *Maternal:* – *Neonatal:* Term with postnatal cyanosis, respiratory distress. Postnatal ultrasound showed right ventricular hypertrophy, tricuspid regurgitation, closure DA. Discrete hypertrophy at 7 months	Unlikely (n = 1)
Pérez *et al.* 2016 [22]	1	*Dose:* – *Week of GA:* 32 *Indication:* Renal colic disease, several admissions during pregnancy, including double J stent	*Fetal:* ultrasounds normal until 32 weeks, DA constriction. Ultrasound improved within 48 hours, normalized 1 week after paracetamol stop. *Maternal:* – *Neonatal:* Term, normal	Certain (n = 1)
Schierz *et al.* 2018 [23]	1	*Dose:* 3000 mg day^{-1}, 4 days *Week of GA:* 38 *Indication:* Pain Polyphenol-rich diet	*Fetal:* Systolic heart murmur, triad of DA closure, severe cardiomyopathy, right ventricular dysfunction *Maternal:* Emergency caesarean *Neonatal:* Cardiomyopathy regressed after 2 months	Possible (n = 1)
Suhag *et al.* 2008 [24]	1	*Dose:* 1000 mg day^{-1}, prolonged *Week of GA:* 29 *Indication:* Back pain	*Fetal:* Ultrasound at 29 weeks showed DA constriction, reduced pulsatility index, biventricular hypertrophy. Normalization of ductus constriction and pulsatility index 1 week after paracetamol cessation *Maternal:* – *Neonatal:* –	Probable (n = 1)
Veneziano *et al.* 2009 [25]	2	*Case 1:* *Dose:* 'High' *Week of GA:* 39 *Indication:* Skeletal-muscle pain *Case 2:*	*Fetal:* Acute fetal right decompensation, oligohydramnios, fetal distress, DA closure *Maternal:* Emergency caesarean (n = 1) or induction (n = 1) *Neonatal:* Favourable neonatal outcome (n = 2)	Possible (n = 2)

(continues)

Table 1
(Continued)

Author, year	Number	Paracetamol exposure	Outcome (fetal/maternal/neonatal)	WHO-UCM score [10]
		Dose: – *Week of GA:* 'Term' *Indication:* –	*Fetal:* Unexplained right heart dilatation, no cardiac decompensation, DA restriction *Maternal:* Labour induction and vaginal delivery *Neonatal:* Favourable neonatal outcome	
Wood *et al.* 2005 [26]	8	*Dose:* Self-directed paracetamol intake for <36 h before fetal ultrasound *Week of GA:* 24–35 *Indication:* Back pain	*Fetal:* Total DA closure with cardiomegaly, tricuspid valve regurgitation, abnormal venous Doppler, mild pericardial effusion, ascites (n = 1). Moderate-to-severe DA constriction, 1 week after stopping paracetamol normalized DA flow patterns (n = 7) *Maternal:* Emergency caesarean (first case), others unreported *Neonatal:* Normal (n = 8), but closed ductus in first case	Possible (n = 1) Probable (n = 7)

DA, ductus arteriosus; GA, weeks of gestational age; Incl., including; WHO-UMC, World Health Organization Uppsala Monitoring Centre– = Not reported

made in 23 (fetal ductal closure: five; fetal ductal constriction: 18) cases, with induction or emergency delivery in at least 12 cases (Table 1). In the cases with a fetal diagnosis of ductal constriction that were not immediately delivered (n = 12), normalization of these fetal findings were described in all but two cases (elective caesarean at term [16] and subsequent caesarean, after prenatal lung maturation at 34 weeks, respectively [19]).

Discussion

In this case series analysis, we retrieved and discussed 25 cases of fetal ductus arteriosus constriction or closure, and thereby provided evidence on the likely causal relationship with maternal paracetamol intake.

Although robust data on its incidence are absent, fetal ductus arteriosus constriction or closure is rare, with two recent retrospective case series on, respectively, 45 and 22 consecutive cases in datasets of 26 000 (0.17%) and 1602 (1.4%) referrals for fetal echocardiography [20, 27]. The specific setting of fetal physiology necessitates patency of the fetal ductus arteriosus to bypass fetal blood flow from the pulmonary artery to the systemic circulation under low pressure and low resistance settings. Fetal ductus arteriosus constriction or closure will result in high pressure, transpulmonary blood flow with subsequent right ventricular hypertrophy, disturbed lung blood vessel development, and cardiac decompensation with hydrops [20, 27]. This fetal ductus arteriosus patency is maintained by circulating prostaglandins of placental origin, and occurs in a setting of low fetal oxygen tension.

As a result of these mechanisms and their link with prostaglandins, it seems likely that the best-known and quantified risk factor for fetal ductus constriction or closure is maternal NSAID intake, especially when this occurs in late pregnancy. Koren *et al*. quantified this risk with an odds ratio of 15.04 (95% confidence interval 3.29, 68.68), using the data on clinical studies that evaluated the efficacy of NSAIDs as tocolytic agents in the third trimester of pregnancy [13]. However, many cases still remain unexplained, or have been suggested to be associated with other drugs, such as naphazoline, fluoxetine, isoxsuprine, caffeine or paracetamol [20, 27]. Other suggested mechanisms relate to a high polyphenol intake, associated with a 'Mediterranean' diet [23].

The epidemiological findings on the association between paracetamol and ductus constriction or closure are further supported by animal experimental PK/PD observations, as described by Tanaka *et al*. [28]. These authors quantified the impact of systemic NSAIDs, topical NSAIDs and also systemic paracetamol on fetal ductal constriction in a near-term rat model. This also included a dose- or concentration-related effect of paracetamol on the extent of ductal constriction [28]. Finally, the findings of an association between paracetamol and the fetal patent ductus are in line with the accumulating evidence on its use for postnatal ductus closure in preterm neonates [29, 30].

Although we are confident that the retrieved evidence on the association between maternal paracetamol and fetal

ductus dysfunction and its causality (mechanism, time-dependent observations and reversal, although no data on re-exposure) is robust, we remain cautious about how to put these findings into clinical perspective, and how to quantify these effects on their incidence and severity (constriction to closure) compared with NSAIDs (odds ratio 15.04). Pain during pregnancy and delivery remains a relevant problem, and NSAIDs (fetal ductus constriction or closure, oligohydramnios, platelet dysfunction) and other analgesics, such as opioids (sedation, neonatal abstinence syndrome) are also associated with relevant and more commonly observed side effects. Moreover, in the majority of cases, the constriction was a transient finding. The current case series analysis therefore also provides evidence that a conservative approach in the setting of fetal ductus arteriosus constriction is a reasonable option, with normalization in a relevant portion of cases that were not immediately delivered. At the very least, these findings suggest that further analyses on the safety of paracetamol in pregnancy are warranted (atopy, neurocognition and behaviour, fertility) and that fetal ductal constriction or closure should also be considered [1–3]. This may include reanalysis of the existing cohorts with cases of unexplained ductus closure [27] and exploration of existing pharmacovigilance databases to search for confirmation or rejection of the current signal, and putting these findings into clinical perspective. This clinical perspective is relevant, as analgesia during pregnancy and during the peripartum period is of obvious importance, and alternative analgesics, such as opioids or other NSAIDs, also have side effects.

Competing Interests

There are no competing interests to declare.

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