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Negligible risk of prenatal ductus arteriosus closure or fetal renal impairment after third-trimester paracetamol use: evaluation of the German Embryotox cohort

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Objective Risk of fetotoxicity after paracetamol exposure in the third trimester.

Design Observational cohort study and retrospective case assessment.

Setting Germany, 2008–2017.

Population Pregnant women exposed to paracetamol.

Methods Prospectively enrolled third-trimester pregnancies that had been exposed to paracetamol (604) were compared with pregnancies exposed to paracetamol in the first and/or second trimester only (1192). Exclusion criteria were exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) in the second or third trimester. Additionally, the Embryotox 'adverse drug reaction in pregnancy' database was screened for cases of fetotoxicity.

Main outcome measures The prenatal study end points focused on narrowing or closure of ductus arteriosus Botalli, late fetal death, and oligohydramnios. The postnatal end points included patent ductus arteriosus (PDA), primary pulmonary hypertension (PPHT), and impaired renal function.

Results In both cohorts, no fetus with intrauterine narrowing or closure of the ductus arteriosus Botalli was reported (0/604 versus 0/1192). Oligohydramnios was diagnosed at a similar frequency in both cohorts: 1.3% (8/604) versus 1.6% (19/1192). There was one stillbirth in the study cohort (1/604, 0.2%) and four stillbirths in the comparison cohort (4/1192, 0.3%). The rates of PDA in neonates were similar: 0.7% (4/615) versus 0.7% (9/1212). PPHT as well as serious postnatal renal disorders were reported once in each cohort. In 12 out of 96 retrospective cases, there were indicators for study end points; however, co-exposure to NSAIDs or complex situations weaken the assumption of paracetamol toxicity.

Conclusions Fetal cardiovascular or renal toxicity of maternal third-trimester paracetamol use appears to be negligible.

Keywords Closure of ductus arteriosus Botalli, ductus arteriosus, fetal renal impairment, fetus, oligohydramnios, paracetamol (acetaminophen), persistent fetal circulation, third trimester of pregnancy, stillbirth.

Tweetable abstract Paracetamol use in the third trimester does not seem to be associated with a relevant risk of fetotoxicity.

Linked article This article is commented on by RJ Wapner and AM Friedman, p. 1568 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15923.

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Introduction

Paracetamol (acetaminophen) has so far been considered as a medication of first choice throughout pregnancy if pain and fever need to be treated. Particularly in the third trimester, when nonsteroidal anti-inflammatory drugs (NSAIDs) carry the risk of the premature closure of the ductus arteriosus Botalli,[1–3] or fetal renal impairment leading to oligohydramnios,[4–6] paracetamol is the analgesic or antipyretic of choice. Recent publications have raised the question of an association between third-trimester paracetamol use and ductus arteriosus constriction in the fetus, however.[7,8]

Furthermore, paracetamol has been shown to be as effective as NSAIDs in the treatment of patent ductus arteriosus Botalli in newborns.[9–11] These observations have supported concerns about whether paracetamol can still be recommended as a safe treatment option during the third trimester. The aim of this project was to estimate the frequency of clinically relevant cardiovascular or renal adverse events in the fetus/infant exposed to paracetamol prenatally.

Methods

Data collection

The Embryotox institute in Berlin is a well-established publicly funded institution that offers risk assessment on drug use in pregnancy to health care professionals (HCPs) and their pregnant patients.[12] Relevant data on drug exposure (duration of treatment, dosage, and anatomical therapeutic chemical [ATC] codes), including co-medication as a potential confounding factor, treatment indications (Medical Dictionary for Regulatory Activities, MedDRA), and maternal medical history, are recorded in addition to the counselling process. Approximately 8 weeks after the expected date of delivery, a follow up is carried out via a standardised and detailed questionnaire sent to the person who initially contacted our institute. Again, information on maternal drug use in pregnancy is requested. Additionally, details on complications during pregnancy and delivery are collected. In Germany, pregnant women are offered three regular ultrasound examinations at 9–12, 19–22, and 29–32 weeks of gestation. In high-risk pregnancies, special ultrasound examinations are performed. Our follow up also includes neonatal outcome parameters, congenital anomalies, and the results of the third paediatric examination (U3) at the age of 4–5 weeks. In cases of adverse pregnancy outcomes or incomplete or implausible data, further details or medical records are requested.

In addition, the Embryotox institute serves as a national clearing house for suspected adverse drug reactions (ADRs) in pregnancy. We receive case reports for evaluation from HCPs, patients, and medical authorities. As adverse outcomes are over-represented among retrospective reports, they were evaluated separately. All retrospective data received between 1994 and 2018 were included.

Study design, definitions, and end points investigated

Prospective case reports ascertained and archived at Embryotox between January 2008 and December 2017 provide the basis for the observational study. In this context, prospective means that the pregnancy outcome was not known and no prenatal pathology had been diagnosed at the time of the initial contact with our institute.

The study cohorts were defined as follows:

- The study cohort included patients with systemic third-trimester paracetamol medication. Treatment may have started before or during the third trimester. Cases were excluded if exposed to NSAIDs, acetylsalicylic acid (ASA) >300 mg/day, or metamizole during the second or third trimester.
- The comparison cohort comprised patients systemically exposed to paracetamol at any time in the first and second trimester, but not in the third trimester. Cases may be exposed to NSAIDs, ASA, or metamizole only during the first trimester. Paracetamol cases already included in the exposed cohort (i.e. those also exposed during the third trimester) were excluded from the comparison cohort.

As a comparison cohort we chose paracetamol exposure exclusively before the third trimester. Using the same drug but in a different trimester of exposure follows the rationale that patients in both cohorts are presumably affected by similar health conditions, although patients in the comparison cohort suffer less during the third trimester or have decided not to take paracetamol.

Exposed pregnancies were included independent of the duration of paracetamol exposure. Exposure must be clearly assignable to trimesters, otherwise the cases were excluded, for example if paracetamol use was reported as 'rarely' or 'as needed' without further specification. Co-medication other than NSAIDs, ASA, or metamizole were allowed. In most instances, this co-medication was the reason to contact our institute. The first trimester was defined from 2^{+0} to 12^{+6} weeks of gestation, the second trimester was defined from 13^{+0} to 26^{+6} weeks of gestation, and the third trimester was defined as $>27^{+0}$ weeks of gestation. Gestational age was calculated by ultrasound determination in early pregnancy or, if not available, the first day of the last menstrual period (LMP). A completed follow up on course and outcome of pregnancy was a prerequisite for study inclusion. As this study focused on exposures and defined end points in the third trimester, pregnancies ending before 27^{+0} weeks of gestation (i.e. preterm infants, fetal death, and elective terminations of pregnancy) were excluded from both cohorts. Twin pregnancies with a loss of one embryo in the first trimester were included. Further selection criteria are shown in the flow chart (Figure 1).

Data analysis focused on the following end points:

- Prenatal study end points: intrauterine narrowing or closure of ductus arteriosus Botalli and possible associated conditions (signs of right ventricular overload or failure and tricuspid insufficiency), oligohydramnios, late fetal death or stillbirth after 27^{+0} weeks of gestation. Stillbirth was considered as an outcome parameter because it could result from impaired fetal circulation caused by the closure of the ductus arteriosus.
- Postnatal study end points: patent fetal ductus arteriosus Botalli (PDA), primary pulmonary hypertension (PPHT),

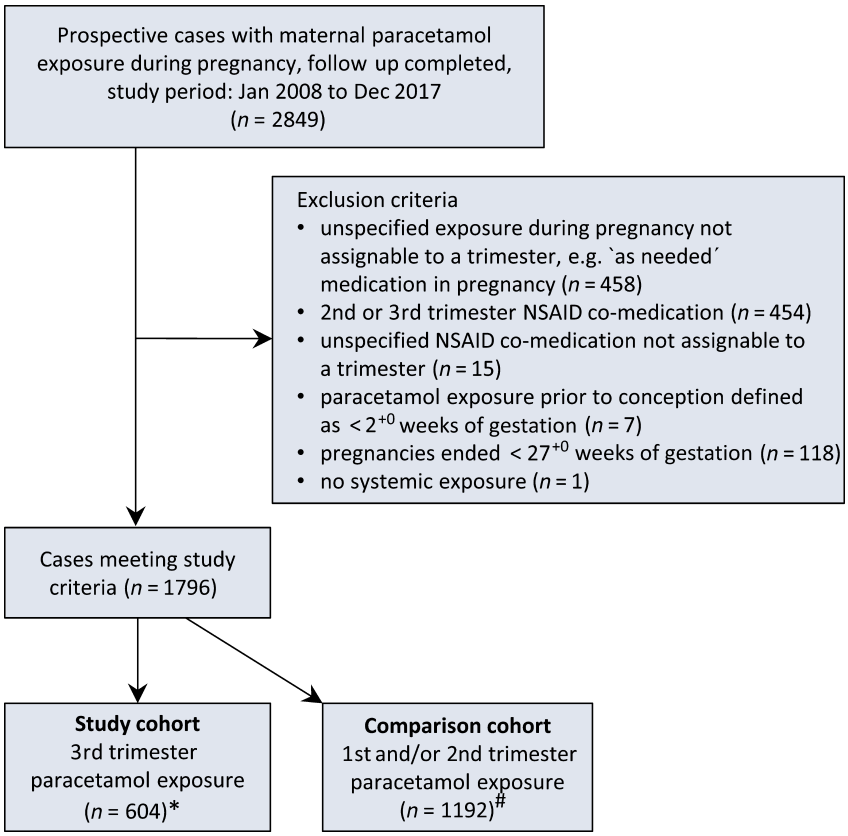

Figure 1. Flow chart depicting the selection criteria for the study cohort. *The study cohort included one triplet and 10 twin pregnancies. Number of liveborn infants *n* = 615; stillborn fetuses *n* = 1. #The comparison cohort included 31 twin pregnancies. Thereof, miscarriage of one twin in the first trimester was reported in 7 pregnancies. Number of liveborn infants *n* = 1212; stillborn fetuses *n* = 4. Thereof, one occurred in a twin pregnancy.

and medical conditions associated with renal disorders or impaired renal function in the newborn period. PDA was considered because it is discussed as a paradoxical reaction after intrauterine ductus arteriosus constriction.

The information about whether one of the defined end points was present was obtained through our standardised follow-up procedure. The diagnostic criteria and quality of care depend on the practice of individual HCPs and the hospital. Therefore, the returned follow-up data are reviewed case by case for plausibility and missing values. Study end points were only considered relevant in the study cohort if paracetamol exposure occurred before the diagnosis of outcome, and not after.

Infants and fetuses with major birth defects of genetic origin or caused during embryogenesis were not excluded from the study cohort.

Data analysis

Descriptive statistics were applied to compare maternal and infant characteristics between the study cohorts. Crude rates of the defined prenatal abnormalities were calculated by dividing the number of affected pregnancies by all pregnancies. For postnatal abnormalities, crude rates were calculated by dividing the affected infants by all liveborn infants. Descriptive analyses were calculated using R 3.3 (R Development Core Team, Vienna, Austria).

Participant and public involvement

There was no patient or public involvement in setting the research question, designing the study, or in the interpretation of the study results.

Funding

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Results

Our study cohort comprised *n* = 604 pregnancies with third-trimester paracetamol exposure resulting in 615

liveborn infants, including ten pairs of twins and one set of triplets. One pregnancy ended in stillbirth. The comparison cohort consisted of n = 1192 pregnancies exposed to paracetamol in the first and/or second trimester. Of these, 1212 infants were liveborn. The comparison cohort included 31 twin pregnancies, seven of which resulted in a first-trimester miscarriage of one twin. Four pregnancies ended as stillbirths.

Cohort characteristics

Exposure pattern of paracetamol in the third trimester

The majority of patients used paracetamol temporarily for acute pain or fever. A short-term exposure of ≤7 days was reported in 364/604 patients (60.3%), whereas 36/604 patients (6.0%) took paracetamol between 7 and ≤14 days, and 19/604 patients (3.1%) took paracetamol between 15 and ≤28 days. A more frequent or daily use was recorded in 31/604 patients (5.1%). The number of exposure days was not specified in a further 154/604 patients (25.5%). The median for the latest paracetamol exposure in pregnancy was 35^{+3} weeks of gestation (interquartile range, IQR, from 32^{+0} to 38^{+4} weeks of gestation) (Table S1).

Maternal and neonatal parameters

Maternal characteristics were similar in both cohorts (Table 1), but the median gestational age at first contact with our institute in the study cohort was later (12^{+1} weeks of gestation) than in the comparison cohort (10^{+0} weeks of gestation). As the study cohort focused on pregnancies exposed to paracetamol in the third trimester, a later gestational age at first contact appears plausible. For neonatal characteristics the median gestational age at birth was similar for both cohorts (39^{+3} weeks of gestation), as were further parameters (Table S2).

Fetotoxic end points

A summary of cases with defined study end points in the cohort exposed to paractamol in third trimester, including details on exposure, dosage, co-medication, treatment indication, and pregnancy outcome, is given in Table S3. Cases identified from the comparison cohort are summarised in Table S4. A very brief overview of all reported pre- and postnatal study end points is provided in Table 2.

Intrauterine narrowing or closure of the ductus arteriosus

Intrauterine narrowing or closure of the ductus arteriosus was not observed in the study cohort (n = 604), nor in the comparison cohort (n = 1192). Furthermore, there were no reports of possibly associated conditions, such as right ventricular dilatation, heart failure, or relevant tricuspid insufficiency.

Table 1. Maternal characteristics of the study cohorts

Cohorts	Paracetamol	Comparison
GW at first contact, *n*	604	1192
Median (IQR)	12^{+1} (7^{+0}–26^{+4})	10^{+0} (6^{+5} – 15^{+2})
Age (years), *n*	604	1192
Median (IQR), (min-max)	32 (30–36), (19–51)	32 (29–35), (15–44)
Pre-pregnancy BMI, *n*	593	1161
Median, (kg/m^2), (IQR)	22.9 (20.7–26)	22.2 (20.2–24.8)
Educational level, *n*	448	806
≤9 years, *n* (%)	17 (3.8)	40 (5)
>9 and ≤13.5 years, *n* (%)	216 (48.2)	374 (46.4)
Acadamic degree, *n* (%)	215 (48)	392 (48.6)
Smoking, *n*	600	1184
No, *n* (%)	518 (86.3)	1022 (86.3)
≤5 cig/day, *n* (%)	21 (3.5)	65 (5.5)
>5 cig/day, *n* (%)	61 (10.2)	97 (8.2)
Alcohol, *n*	600	1181
No, *n* (%)	539 (89.8)	1034 (87.6)
≤1 drink/day, *n* (%)	50 (8.3)	104 (8.8)
>1 drink/day, *n* (%)	11 (1.8)	43 (3.6)
Pregnancy wanted, *n*	482	931
Yes, *n* (%)	475 (98.5)	888 (95.4)
Indifferent, *n* (%)	7 (1.5)	38 (4.1)
No, *n* (%)	0 (0)	5 (0.5)
Previous pregnancies, *n*	602	1186
0, *n* (%)	240 (39.9)	480 (40.5)
1, *n* (%)	202 (33.6)	383 (32.3)
2, *n* (%)	96 (15.9)	191 (16.1)
≥3, *n* (%)	64 (10.6)	132 (11.1)
Previous deliveries, *n*	602	1185
0, *n* (%)	305 (50.7)	570 (48.1)
1, *n* (%)	223 (37)	450 (38)
2, *n* (%)	58 (9.6)	126 (10.6)
≥3, *n* (%)	16 (2.7)	39 (3.3)
Previous miscarriages, *n*	601	1184
0, *n* (%)	469 (78)	957 (80.8)
1, *n* (%)	88 (14.6)	165 (13.9)
≥2, *n* (%)	44 (7.3)	62 (5.2)
Previous children with birth defect, *n*	600	1184
0, *n* (%)	585 (97.5)	1157 (97.7)
1, *n* (%)	13 (2.2)	26 (2.2)
≥2, *n* (%)	2 (0.3)	1 (0.1)

BMI, body mass index; GW, gestational week; IQR, interquartile range; *n*, number of cases with available information.
The absolute number of parameters differ due to missing values.

Stillbirth

Of 604 pregnancies in the study cohort, one pregnancy (0.2%) ended in stillbirth at 29^{+2} weeks of gestation. This pregnancy was complicated by acute Crohn's disease, and several blood transfusions were necessary as a result of

Table 2. Study end points reported in both study cohorts

	Study cohort, paracetamol exposure 3rd trimester	Comparison cohort, paracetamol exposure 1st/2nd trimester
Prenatal end points	**Pregnancies, *n* = 604**	**Pregnancies, *n* = 1192**
Ductus arteriosus constriction/closure	0/604	0/1192
Stillbirth	1/604	4/1192
Oligohydramnios[a]	8/604	19/1192
Postnatal end points	**Liveborn infants, *n* = 615**	**Liveborn infants, *n* = 1212**
Patent ductus arteriosus[b]	4/615	9/1212
Primary pulmonary hypertension	1/615	1/1212
Renal disorder	1/615	1/1212

[a]Pregnancies with reported oligohydramnios independent from the gestational week (GW) at diagnosis are included. Further information on GW are listed in Tables S3 and S4.
[b]Three infants were born preterm in the study cohort and four infants were born preterm in the comparison cohort.

iron-deficiency anaemia (Table S3, case 9). In the comparison cohort, 4/1192 (0.3%) stillbirths were observed. Three fetal deaths were linked to other events (Table S4, cases 20, 21, 22); one fetus died at 32^{+3} weeks of gestation without previous complications in the third trimester (Table S4, case 23).

Oligohydramnios

Oligohydramnios was reported in 8/604 pregnancies (1.3%) of the study cohort and in 19/1192 (1.6%) of the comparison cohort. These numbers refer to all reported pregnancies with oligohydramnios, independent of gestational age at diagnosis. As the amniotic fluid volume decreases near term, it is not easy to assess possible pathologies associated with paracetamol intake in late pregnancy. In one pregnancy, transient oligohydramnios and placental insufficiency were observed already at 29 weeks of gestation after frequent paracetamol use during the entire pregnancy until delivery at 39^{+4} weeks of gestation (Table S3, case 2). Weekly ultrasounds after the diagnosis of oligohydramnios confirmed the normalisation of the amniotic fluid while paracetamol use continued.

Patent ductus arteriosus

Patent ductus arteriosus was reported in 4/615 (0.7%) newborns in the study cohort. PDA is known to occur at a higher prevalence in preterm infants. Of these four infants in the study cohort, three were born prematurely. Only one term-born infant, born at 37^{+4} weeks of gestation, was diagnosed with PDA, which closed spontaneously at day 4 after birth. Paracetamol medication was reported at 33 and 34 weeks of gestation. In the comparison cohort, 9/1212 (0.7%) newborns had a PDA: four were preterm and five were born at term.

Primary pulmonary hypertension

Primary pulmonary hypertension was described in one neonate in the study cohort born at 40^{+2} weeks of gestation. No cardiac involvement was mentioned but, in addition, the infant was affected by pneumonia. He was treated successfully and left hospital 5 days after birth. Maternal paracetamol use was limited to 1 day at 36^{+6} weeks of gestation. In the comparison cohort, one infant born at term was described as having PPHT, mild tricuspid insufficiency, and a PDA. No intervention was necessary. A control echocardiography at the age of 3 months was recommended.

Postnatal renal disorders

Bilateral renal hypoplasia and renal metabolic acidosis were diagnosed in one neonate from the study cohort (1/615, 0.2%). Paracetamol exposure occurred between 16 and 30 weeks of gestation. One neonate in the comparison cohort (1/1212, 0.1%) was diagnosed with a unilateral multicystic kidney.

Retrospective reports

We identified 96 retrospective reports with third-trimester paracetamol exposure in the Embryotox database. Nearly all cases had relevant co-medication and paracetamol exposure was not primarily suspected to be linked to the observed symptoms. In (altogether) 12 of the 96 case reports the observed pathology corresponded to the end points of our cohort study. Three of the 96 neonates were born at 41 weeks of gestation with right ventricular hypertrophy and PPHT, possibly resulting from prenatal ductus arteriosus constriction. In the first case, 500–2000 mg/day paracetamol had been taken because of headaches twice per week throughout pregnancy. In the second case, 2500 mg/day paracetamol had been taken for 4 days at 39 weeks of gestation for otitis. In the third case, paracetamol use was reported to be taken as needed between 16 and 24 weeks of gestation and again for 2 days at 39 weeks of gestation, at a dose of 500–1000 mg/day. Prenatal screening for ductus arteriosus abnormalities was not performed in these three pregnancies. There was no concomitant NSAID medication reported. The condition of the three infants improved within a few weeks.

Oligohydramnios was noted in one pregnancy at 36 weeks of gestation. Paracetamol and diclofenac had been used for 5 days at 33 weeks of gestation. This pregnancy ended in stillbirth at 39 weeks of gestation, possibly due to premature placental abruption and umbilical cord complications. A

further four pregnancies resulted in late stillbirths after third-trimester paracetamol exposure plus analgesic NSAID co-medication. In the first case, paracetamol, ASA, and ergotamine had been used for migraine at 38 weeks of gestation. In the second case, back pain was treated with diclofenac 150 mg/day and paracetamol 500 mg/day for 3 days at 39 weeks of gestation. In the third case, analgesics had been used as needed throughout pregnancy up to 36 weeks of gestation, when paracetamol 1000 mg/day, metamizole 1000 mg/day, and sumatriptan 100 mg/day were taken for 2 days. In a fourth pregnancy, a combined analgesic preparation consisting of ASA, paracetamol, and caffeine had been used at high doses at 40 weeks of gestation (5000, 4000, and 1000 mg/day, respectively).

Four neonates had PDA: two were born before and two after 37 weeks of gestation. One of the term-born infants had an atrial septal defect and an oral cleft; the other was affected by atrial and ventricular septal defects. One premature infant was born at 35 weeks of gestation and on the third day of life, PDA was still present. The second premature infant with PDA was born at 28 weeks of gestation. During pregnancy, acute myeloid leukaemia had been diagnosed in the mother and multiple co-medication was necessary, including paracetamol, metamizole, and diclofenac between 25 and 28 weeks of gestation. PDA closure was performed with ibuprofen 11 days after birth.

Discussion

Main findings

Our study compared 604 prospectively enrolled pregnancies with third-trimester paracetamol exposure with 1192 pregnancies exposed in the first and/or second trimester only. This cohort study did not indicate an increased risk for prenatal cardiovascular and renal toxicity after maternal paracetamol use in the third trimester. In particular, there was no indication for prenatal constriction of the ductus arteriosus, although paracetamol is increasingly used for the effective treatment of PDA in neonates.

Strengths and limitations of the study

Strengths and limitations of observational pregnancy outcome studies have been discussed in detail elsewhere.[13,14] Embryotox studies using prospectively enrolled pregnancies are based on detailed follow-up questionnaires covering the course, complications, and outcome of pregnancy, delivery, and paediatric examinations. A case-by-case plausibility test of exposure and outcome data followed by calls to the attending HCPs in cases of missing or implausible questionnaire entries ensure that reliable high-quality data sets are obtained. A strength of our study is that we report information on all drug exposures including over-the-counter drugs. The Embryotox cohort may not be representative of the general population of pregnant women in Germany. Educational achievement is usually higher in women seeking advice at Embryotox.[15] However, possible selection bias is reduced by using controls from the same data pool with a similar procedure of assessment. Descriptive statistics have demonstrated that maternal characteristics did not differ between study cohorts (Table 1), making any bias unlikely. Nevertheless, interpreters of our results should keep in mind that specific study end points are rare events and paracetamol exposure pattern was heterogeneous (Table S1). The proportion of women who used paracetamol for 7 days or less in the third trimester was 60%. One would not necessarily expect adverse fetal effects after short-term exposure. Looking at the study cases affected there was no indication that the duration of paracetamol intake had an impact on the outcomes.

Interpretation of results

Paracetamol is considered an atypical cyclooxygenase inhibitor with analgesic and antipyretic effects, but without anti-inflammatory properties. Interestingly, paracetamol seems equally effective as NSAIDs such as indomethacin or ibuprofen in the treatment of PDA in preterm infants.[9–11] This led to the fear that paracetamol might have similar effects prenatally.

Prenatal closure of the ductus arteriosus leads to right ventricular overload and may result in ventricular dilation and an increase of pulmonary vascular resistance and PPHT in the newborn.[16] Fetal death may occur by heart failure if the closure is irreversible and not detected in time by ultrasound screening. Thus, in cases of repeated use of NSAIDs in the third trimester, echocardiography is recommended. No intrauterine narrowing or closure of the ductus arteriosus, nor any possibly associated heart conditions, were reported among the 604 patients exposed to paracetamol in the third trimester in our study; however, we are aware of the fact that patients with third-trimester paracetamol exposure are not monitored regularly for ductus constriction as paracetamol is not considered a critical medication. Therefore, cases of ductus narrowing may have been overlooked, but it is unlikely that clinically relevant or even fatal cases would have been missed. On the other hand, there were 12 out of 96 cases in our ADR database with cardiovascular or renal pathology in the fetus or neonate, and four of the 12 cases even resulted in stillbirths. Although causality cannot be excluded, the role that paracetamol played in these cases is rather questionable. Considering the worldwide recommendation of paracetamol as the analgesic of choice in the third trimester and its widespread use, these few cases in the German Embryotox ADR database along with the findings of the prospective cohort study do not support the assumption of relevant fetotoxicity.

In 1983, Momma et al. compared the potency of different NSAIDs and paracetamol to constrict the ductus

arteriosus in full-term pregnant rats at dosages adjusted to those used in humans. Acidic NSAIDs, e.g. indomethacin and ibuprofen, caused the most pronounced constriction, in contrast to mild constriction with paracetamol. Much higher paracetamol doses were required to demonstrate a significant constriction.[17]

Ductus constriction may also occur spontaneously. Reliable prevalence data are scarce. A case series reported by Leal et al. described five fetuses with ductus arteriosus closure: no drug use was reported in three cases and two occurred after indomethacin treatment.[18] Evaluating fetal echocardiographies, Luchese et al. (2003) identified 20 fetuses with prenatal ductus constriction in a population comprising 7000 pregnant women: 13/7000 (0.2%) were assessed as 'idiopathic' and seven were diagnosed after NSAID use in the second or third trimester.[19] In a further echocardiography study, Lopes et al. (2016) identified 45 fetuses with ductus arteriosus constriction or closure among 26 000 patients. An association with previous NSAID use was reported in 29 cases (group A). In 8/26 000 (0.03%), ductus constriction was classified as spontaneous (group B). In a further eight cases with previous maternal drug use, neither paracetamol nor other suspected medications were reported (group C).[20]

Primary pulmonary hypertension in newborns may be related to intrauterine ductus arteriosus constriction.[16,21–24] In the study cohort, we identified only one report of PPHT in a term neonate with pneumonia. A single paracetamol dose taken approximately 4 weeks before delivery makes a causal association unlikely.

Interestingly, there are studies showing a higher incidence of PDA in newborns exposed to antenatal NSAID treatment, especially with indomethacin. A paradoxical effect due to ischaemic damage of the ductus arteriosus vessel walls after intrauterine constriction shortly before birth was discussed.[25,26] Taking prematurity into account, third trimester paracetamol exposure did not result in a higher incidence of PDA in our study (0.7% both cohorts).

Not to overlook an unrecognised closure in fatal outcomes, we included stillbirth as study end point. Among third trimester exposed pregnancies, one stillbirth occurred. The complex clinical situation at 29^{+2} weeks of gestation (Table S3, case 9) makes a causal relationship between paracetamol exposure and fetal death unlikely.

Reduced amniotic fluid volume may be caused by disturbed renal function; however, oligohydramnios may also originate from other reasons. Near term, amniotic fluid decreases physiologically.[27] Renal damage leading to oligohydramnios is a known adverse effect after continuous NSAID use in the second and third trimester.[28,29] Rates of oligohydramnios were unsuspicious in the study (1.3 versus 1.6%). The majority of cases were observed near term, at term or after due date and the decrease of amniotic fluid was presumably physiological in most of these cases. Only in one pregnancy (1/604), an oligohydramnios in association with placental insufficiency was observed in early third trimester (29 weeks of gestation) after regular paracetamol use (Table S3, case 2). Oligohydramnios was reversible while paracetamol use continued.

Only one newborn (1/615) was affected with a postnatal renal disorder, i.e., bilateral renal hypoplasia and renal metabolic acidosis. Thus, persistent renal impairment does not appear significantly associated with third trimester paracetamol use.

Being the largest study so far with focus on ductus arteriosus our results contribute to the lively discussion whether paracetamol can still be considered a medication of choice during late pregnancy. However, especially near term, repeated doses of paracetamol should not be taken uncritically.

Conclusion

Based on our prospective cohort study and the very few and inconclusive ADR reports collected over 25 years, the fetal cardiovascular and renal risk of paracetamol in the third trimester appears negligible. Therefore, paracetamol continues to be an analgesic and antipyretic of first choice during pregnancy, in particular during the third trimester.

Disclosure of interests

All listed authors declare that they have no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

KD and CS had the idea for this study. KD, CS, JF, RM and EB developed the study approach and wrote the study protocol. EB performed data exports and contributed statistical support. JF, KD, SP and KM validated and analysed the data. KD, SP, SH and CS provided clinical expert interpretation of results. KD and CS wrote the first draft of the manuscript and all listed authors critically revised subsequent manuscript drafts and contributed essential discussion points. All authors approved the final draft of the manuscript.

Details of ethics approval

The study received ethics approval from the ethical committee of the Charité—Universitätsmedizin Berlin, Germany (ref. EA2/129/18, 14 August 2018).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of third trimester paracetamol exposure.

Table S2. Neonatal characteristics of the study cohorts.

Table S3. Study cohort with third trimester paracetamol exposure. Cases with defined study end points.

Table S4. Comparison cohort. Cases with defined study end points.■

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