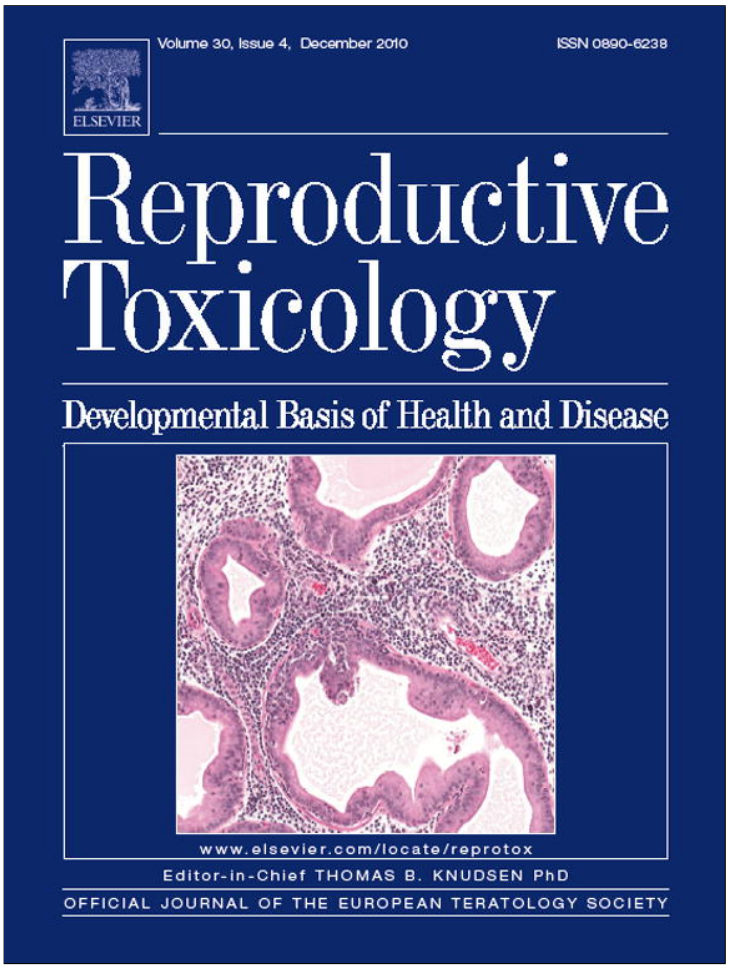

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Review

A review of the literature on the effects of acetaminophen on pregnancy outcome

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ABSTRACT

Acetaminophen is commonly used during pregnancy. Experimental animal studies do not suggest increased malformations after therapeutic use of single-ingredient acetaminophen during pregnancy. Cohort studies in humans in which exposure is prospectively ascertained show no detectable increase in congenital malformation risk associated with single-ingredient acetaminophen use during pregnancy. A case–control study identified an association between acetaminophen use during pregnancy and risk of gastroschisis in the offspring, but the study was limited by recall bias, unblinded interviewers, possible misclassification of gastroschisis, confounding by indication, difficulty in separating out the effects of combination products, and possible selection bias. Two case–control studies failed to identify a statistically significant association between acetaminophen use during pregnancy and gastroschisis. No other malformation has been shown to be causally associated with single-ingredient acetaminophen. A reported association between pre-eclampsia, preterm birth, and acetaminophen may be explained by reverse causation. Concerns expressed about childhood asthma and prenatal acetaminophen use has been addressed in a separate review. The use of single-ingredient acetaminophen during pregnancy can be justified based on outcome data. Data on the effects of acetaminophen cannot necessarily be extended to acetaminophen combination products.

Contents

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1. Introduction

Acetaminophen is commonly recommended for use during pregnancy and a large proportion of pregnant women are exposed to this medication. Over the many decades of use of acetaminophen, questions about its safety in pregnancy have been addressed by studies in different populations using different designs, but because of ubiquitous use of this medication and limitations of earlier studies, new studies continue to address the question. Acetaminophen is used as an analgesic and antipyretic, and use during pregnancy may be a marker for inflammatory or infectious disorders, which may have independent effects on pregnancy outcome. In addition, study of acetaminophen effects may be complicated by the frequent inclusion of acetaminophen with other medications in over-the-counter preparations.

The objective of this paper is to review the experimental and epidemiological studies on pregnancy outcome after single-ingredient acetaminophen use. Acetaminophen is an old drug, and there are few experimental animal studies that would meet modern standards of design and performance. Most of the epidemiology studies used retrospective ascertainment of exposure, although there are some good quality studies in which prospectively ascertained exposure information is available. In spite of the challenges of studying this ubiquitous medication, a clearer and more reassuring picture is emerging of acetaminophen safety. Data on childhood asthma and acetaminophen use during pregnancy is the subject of a separate review (Scialli AR, Ang R, Breitmeyer J, Royal MA, Submitted). Information on childhood cancer after prenatal exposure to acetaminophen appears restricted to a review of five case reports [1] and is not further considered.

2. Methods

Key word searches were performed in November, 2009 in BioBase; Biological Abstracts; CAB Abstracts; DART; Embase (EMB); International Pharmaceuticals Abstracts; Life Sciences Collection; PubMed/Medline; Medline Preprints; Inside Conferences; Analytical Abstracts; Engineering Index; Toxline; Reprotox®; TERIS; and Shepard's Catalog. Citations and reference lists within the key publications were reviewed to identify and review any additional relevant publications. We considered all studies involving acetaminophen; whether administered as a single product or as part of a combination product. We will note those studies in which combination products were included; data on the safety of single-ingredient acetaminophen do not necessarily extend to acetaminophen combination products.

3. Experimental animal studies

3.1. Pregnancy studies with viability/morphology end points

Lubawy and Garrett [2] treated pregnant Sprague–Dawley rats by gavage with acetaminophen, aspirin, or 0.5% methylcellulose vehicle. Treatments were by gavage on GD 8–19 (sperm positive day = GD 0). Aspirin and acetaminophen doses were 125 or 250 mg/kg bw/day. Fetal and placental weight and fetal length were recorded on GD 21, and resorption sites were counted. There was no mention of staining for resorption sites or of teratologic evaluation of fetuses. Twenty-one dams/group were treated according to the methods; however, the results are given for 18, 21, 15, 17, and 16 pregnant rats in the vehicle control, 125 mg/kg/day aspirin, 250 mg/kg/day aspirin, 125 mg/kg/day acetaminophen, and 250 mg/kg/day acetaminophen groups, respectively. No information is given on the missing animals, which presumably were not pregnant or died, nor is information provided on clinical signs, feed consumption, or water consumption. Dam weights were comparable among groups except in the 250 mg/kg/day aspirin group, in which dam weight gain on GD 8–20 was 14% less than in the vehicle control group. The number of resorptions was calculated based on total number of implantation sites, without regard to litter, and was reported to be increased in the 250 mg/kg bw/day aspirin group (44% of implantation sites) and in the 125 mg/kg/day acetaminophen group (16% of implantation sites). No resorptions were reported in the vehicle control group or in the 250 mg/kg/day acetaminophen group. Viable fetuses per litter, calculated from the number of viable fetuses and the number of litters, were 7.8, 9.9, 5.3, 7.4, and 9.7 in the vehicle control, aspirin 125 mg/kg/day, aspirin 250 mg/kg/day, acetaminophen 125 mg/kg/day, and acetaminophen 250 mg/kg/day groups. The numbers of litters with at least one resorption in these groups were 0/18, 3/21, 12/15. 4/17, and 0/16. The authors did not compare these proportions statistically, but by individual Fisher test between each dose group and the vehicle control performed by us, the proportions are different for the 250 mg/kg bw/day aspirin group and for the 125 mg/kg/day acetaminophen group. The authors report that mean fetal weight, fetal length, and placental weight were lower in the 250 mg/kg bw/day aspirin group, and that mean fetal length was lower in the 125 mg/kg bw/day acetaminophen group than in the control group. The analysis was performed using analysis of variance or a *t*-test, without regard to litter of origin. The lack of litter analysis and the lack of dose-relatedness of the putative acetaminophen effects raise questions about the interpretability of this report.

Acetaminophen was also evaluated in peri- and postnatal studies in mice. Continuous exposure to 1.0% acetaminophen during pregnancy via the diet in mice caused a reduction in the number of litters and a decreased number of live male pups per litter, but did not affect the proportion of pups born alive or the absolute pup weight. This dietary level results in acetaminophen intake of 1430 mg/kg bw/day, equivalent to 1.7 times the maximum human daily dose based on body surface area. There were no treatment-related gross or histologic abnormalities noted in adult offspring of treated mice. There were no signs of embryotoxicity at lower doses [3–5].

A Japanese paper cited in a secondary source reported no adverse outcome on mouse fetuses after treatment of pregnant dams with a combination preparation containing 43% acetaminophen at a dose level of 387 mg [6]. The other ingredients in the preparation were ethenzamide and caffeine. No additional details were available.

More typical developmental toxicology studies were published by Burdan using acetaminophen in combination with caffeine, with or without isopropylantipyrine (a non-steroidal anti-inflammatory drug) [7,8]. The two- or three-drug combination represented an over-the-counter preparation marketed in Europe, Central America, and South America. Pregnant Wistar rats were gavaged with the combination on GD 8–14 (plug = day 1). Three doses were used in a fixed ratio of ingredients: the lowest dose was 3.5 mg/kg bw/day acetaminophen + 0.7 mg/kg bw/day caffeine ± 2.14 mg/kg bw/day

isopropylantipyrine. The mid and high doses were 10 and 100 times the low dose. The results of both studies showed a decrease in fetal and placental weight per litter in the high dose (350 mg/kg bw acetaminophen + 70 mg/kg bw/day caffeine ± 214 mg/kg bw/day isopropylantipyrine). Decreases in maternal weight gain (without differences in feed consumption or water intake) were identified at all doses in the acetaminophen + caffeine study [8]. There were no differences between groups in litter size and in pup viability. These data were not shown in the three-drug study. There were no differences between groups in either study in the incidence of visceral or skeletal malformation. A study with a similar design using acetaminophen alone at these same doses had been published by the author in an overseas journal from which the abstract was obtained [9]. A decrease in fetal body length and "histological adaptive changes of the fetal liver" were described in the 350 mg/kg bw/day acetaminophen group. Only external malformations were apparently evaluated in this study.

3.2. Effects on the ductus arteriosus

Momma and Takeuchi [10] tested the ability of 24 non-steroidal anti-inflammatory drugs, including acetaminophen, to constrict the ductus arteriosus in the fetuses of full-term Wistar rats. Pregnant animals were gavaged on GD 21 (plug day not defined). Four hours later, the rats were killed by cervical dislocation, and fetuses were removed by cesarean section. Fetuses weighing more than 5.5 g were immediately frozen in acetone at–80 °C. The fetal thorax was sectioned and the inner diameters of the pulmonary artery and ductus arteriosus were measured. The ratio between these diameters was used as the outcome metric and was compared with the ratio between vessels of fetuses from untreated rats. The number of litters appears to have been 1, 2, or 3 for each dose, but is not further specified. The acetaminophen doses were 10, 100, and 1000 mg/kg bw, with 9, 10, and 10 fetuses, respectively, at each dose. Results were presented in graphic form, without indication of statistical comparisons. It appears that acetaminophen produced ductal constriction in a dose-dependent manner, with 10 mg/kg being a no effect level and 100 mg/kg bw as a lowest effect level. There appeared to be about a 25% decrease in the ductus arteriosus/pulmonary artery ratio at 10 mg/kg bw acetaminophen and about an 80% reduction at the 1000 mg/kg bw dose. The reliability of this study is decreased by lack of information on the number of litters contributing data and possible litter effects that were not evaluated.

A subsequent study with a similar design used 8–15 fetuses from 2 to 6 pregnant rats per evaluation period [11]. Dams were given acetaminophen 14 mg/kg bw by oral gavage (similar to the clinical dose on a mg/kg bw basis) and fetuses were evaluated 1, 4, 8, and 24 h later. Ductal diameter decreased about 9%, which the authors reported as statistically significant. Right ventricular volume was described as increasing about 40% at 4 h, but the figure showing these data did not indicate a statistically significant alteration in this parameter.

The 1983 Momma and Takeuchi study was cited in a review by Peterson as showing a "weak effect" of acetaminophen on the ductus arteriosus of the rat [12]. This review article presents data from the author's laboratory that appear to have appeared only in abstract [13]. Acetaminophen 20 mg/kg was given intramuscularly (i.m.) to a chronically catheterized pregnant ewe at 125 days gestation, producing a maternal peak plasma concentration of 9 μg/mL and a fetal peak plasma concentration of 4.5 μg/mL (estimated from a graph). A large increase in fetal left pulmonary artery flow occurred with a starting flow of <5 mL/min and peak flow of 140 mL/min at 90 min after treatment about 60 min after peak acetaminophen concentration in the fetus. Left pulmonary artery flow decreased to baseline by 180 min after treatment. An increase in pulmonary artery pressure and in cardiac rate accompanied the changes in pulmonary artery flow. Infusion of 5 μg prostaglandin E_1 was said to have reversed the changes in pulmonary artery hemodynamics even when injected at the peak of the drug effect. The presentation of these data in a review article without the usual amount of experimental and analytic detail makes it difficult to evaluate the reliability of the results.

3.3. Comparisons to human exposure

Recommendations for acetaminophen therapy limit the daily dose to 4000 or about 67 mg/kg/day for a 60-kg woman. Experimental animal studies have shown adverse effects on growth [10] and ductal constriction [10] at dose levels 1.5–2 times higher on a weight basis. The mechanism of ductal constriction is presumably prostaglandin synthetase inhibition, and ductal constriction has been seen in human fetuses after maternal therapy with other non-steroidal anti-inflammatory agents such as indomethacin. As discussed below, adverse effects on fetal growth or neonatal well-being have not been identified in epidemiology studies, although there is a single case report of transient ductal constriction in a human pregnancy [14].

4. Human studies and reports

4.1. Cohort studies

4.1.1. The Seattle study

A longitudinal study was conducted on a consecutive group of 1529 pregnant women receiving prenatal care in 1974–1975 in the greater Seattle area [15]. The sample of mothers was predominantly Caucasian (86%), married (87%), and well educated (61% with some college), which was felt to be representative of the Seattle population. Mothers were enrolled and interviewed at home during their 5th month of pregnancy. Follow-up data were available for a cohort of 421 of the offspring at 4 years of age. The study was undertaken to evaluate the effects of prenatal aspirin and acetaminophen on intelligence quotient (IQ) and attention in the exposed children. Aspirin, acetaminophen, and other drug use information was obtained by self-report at the 5th month of the pregnancy. Estimated frequency of use was categorized as none, 1 per month, 2 per month, 1 per week, several per week, daily, and several per day. Of the 421 mother–child pairs available for analysis at age 4 years, 229 (54.4%) had never used aspirin, and 238 (56.5%) had never used acetaminophen. Aspirin and acetaminophen were the two most frequently used medications during pregnancy in the interviewed women, and the most common indication was treatment of headache. Child IQ at 4 years of age was significantly and negatively correlated with prenatal aspirin exposure with evidence of a dose–response effect. Acetaminophen was not associated with an increased risk of either IQ or attentional deficits. Physical growth parameters were not associated with either aspirin or acetaminophen exposure.

In this study, only 421 (28%) of the mother/child pairs were available for the postpartum interview. No distinction was made between aspirin or acetaminophen taken as single ingredients or as components of combination products.

4.1.2. The National Collaborative Perinatal Project

Heinonen et al. used data from the National Collaborative Perinatal Project, which monitored around 58,000 pregnancies during which medication exposures were recorded at the initial prenatal visit and were ascertained before pregnancy outcome was known [16]. Possible associations of medication exposures with congenital malformations were identified by comparing the malformation incidence for individual agents with the overall incidence in the

sample. There were 226 pregnancies exposed to acetaminophen during the first 4 lunar months of pregnancy and 781 pregnancies with acetaminophen exposure any time during pregnancy. Eighteen malformed children were in the acetaminophen group of whom 17 were exposed during the first trimester. Of these, eight children had dislocated hips, and six children had clubfoot. The incidence of malformation in the acetaminophen-exposed group was not statistically higher than expected.

The National Collaborative Perinatal Project considered only live births; malformations among stillborn infants or abortuses were not included. Malformations were grouped by organ system (e.g., central nervous system, cardiovascular, musculoskeletal), which may have made it difficult to identify specific etiologically homogeneous abnormalities within an organ system. Exposure to acetaminophen as a single ingredient was not distinguished from exposure to combination products.

4.1.3. The Kaiser study

Li et al. found no association between acetaminophen use and miscarriage in a prospective population-based cohort study of 1055 women members of the Kaiser Permanente Medical Care Program (San Francisco, CA) [17]. Women were recruited and interviewed after their positive pregnancy test. This study is limited by the low participation rate; only 39% of women who were contacted agreed to participate. No distinction was made between single ingredient and combination product exposures.

4.1.4. The Danish National Birth Cohort

A prospective cohort study of acetaminophen exposure in pregnant women was conducted using the Danish National Birth Cohort (DNBC), a population-based study that enrolled 101,041 pregnant women from 1996 to 2003 [18]. Approximately 60% of invited eligible women participated. Eligibility criteria were that the women speak Danish well enough to participate in interviews and intended to carry their pregnancy to term. Participating women completed a self-administered enrolment questionnaire and four telephone interviews: two during pregnancy and two when their children were 6 and 18 months old. Women with multiple births ($n = 2080$), unknown outcome, unknown date of outcome, who emigrated ($n = 78$), and those enrolled after pregnancy outcome or enrolment date missing ($n = 693$) were excluded from the analysis leaving a total of 98,190. There were 98,140 evaluable women in the miscarriage database, 81,004 in the stillbirth database, and 63,871 in the liveborn database [19]. Pregnancy outcomes were ascertained using national registers of hospitalizations and births.

Although the 60% participation rate is low, there appeared to have been no bias resulting from non-participation in the study, as the effect of non-participation was evaluated for effect sizes of certain exposures, and odds ratios were not biased by participation or non-participation. Acetaminophen exposure (prescription and non-prescription, alone or in combination products) was identified from the interview responses and categorized by trimester. Cox proportional regression models adjusted for mother's age, socioeconomic status, pre-pregnancy body-mass index (BMI), cigarette use, birth order, coffee intake, and sex of child were used to compute hazard ratios. For miscarriage risk, the model also was adjusted by the history of previous abortions. Other variables were explored as potential confounders.

Rebordosa et al. reported the acetaminophen hazard ratio for congenital abnormalities in 88,142 pregnant women who had liveborn singletons and who provided information on acetaminophen use during the first trimester. Those women with stillbirths, abortions, ectopic pregnancies, hydatidiform mole, and multiple births were excluded. There were 3784 liveborn singletons (4.3%) who had congenital abnormalities, the majority of whom were children with an isolated congenital abnormality ($n = 2460$, 65%). Pregnant women who had a child with a congenital abnormality were similar to the cohort as a whole in terms of demographic variables, lifestyle factors, clinical and reproductive history of acute and chronic diseases during pregnancy, and history of previous abortions.

Among the pregnant women in the sample 44,144 (50.3%) took acetaminophen at least once during their pregnancy and of these, 26,424 (29.9%) used acetaminophen during the first trimester. Those who used acetaminophen during the first trimester were more likely to use it during later trimesters than were women who did not use acetaminophen in the first trimester. The distribution of subgroups of congenital abnormalities was similar among those exposed to acetaminophen and those who were not.

Exposure to acetaminophen during the first trimester or any trimester was not associated with a higher prevalence of any congenital abnormality. Congenital anomalies were identified based on the International Classification of Diseases, 10th edition (ICD-10). The distribution of subgroups of congenital abnormalities was similar among women who took acetaminophen during the first trimester and among the unexposed; these defects included gastroschisis (hazard ratio 0.91, 95% confidence interval 0.55–4.09) and congenital heart disease (Cardiac septal defects hazard ratio 1.02, 95% confidence interval 0.83–1.25; Ventricular septal defects hazard ratio 1.05, 95% confidence interval 0.81–1.35). There was an increased hazard ratio for the ear, face, and neck subgroup, particularly medial fistula-sinus-cyst (0.08% exposed and 0.04% unexposed, hazard ratio 2.15, 95% confidence interval 1.17–3.95), but this finding may have occurred by chance given the large number of comparisons made and the fact that this association has not been reported elsewhere. When the analysis was limited to the critical period of the first trimester for the development of most congenital abnormalities (i.e., second or third months of development), there was also no effect on the hazard ratio with acetaminophen use.

Of the 98,140 women in the miscarriages database, 50,702 described use of acetaminophen and 47,438 did not. Exposure by trimester was balanced: first ($n = 28,484$), second ($n = 20,501$), and third ($n = 25,792$). Women who delivered liveborn children reported having used acetaminophen on average during 9.4 weeks of their pregnancy. The decision to use only duration of acetaminophen exposure prevented differentiation between regular daily use and sporadic, infrequent use. Acetaminophen use, whether by trimester or at any time during the pregnancy, was not associated with an increased hazard ratio for miscarriage, stillbirth, low birth weight (LBW, less than 2.5 kg), or being small for gestational age (SGA, less than 10th percentile). Acetaminophen use appeared to increase the hazard ratio (1.55, 95% confidence interval 1.16–2.07) for preterm birth only in women with pre-eclampsia; the study authors noted that this association may have been spurious because acetaminophen would be used to treat the headache that may precede and accompany pre-eclampsia. Additionally, women with pre-eclampsia are more likely to be delivered preterm for therapeutic reasons. Acetaminophen use was not associated with an increased hazard ratio for the preterm birth complications of bronchopulmonary dysplasia, intracranial hemorrhage, retinopathy of prematurity, perinatal infections, and anemia of prematurity. The authors concluded that the results provided no strong reason for a change in the clinical practice of recommending acetaminophen during pregnancy.

Data from 63,833 women with liveborn singletons in the DNBC database who completed the three postnatal telephone interviews at the 12th and 30th weeks and at 6 months were also analyzed for an association between prenatal acetaminophen exposure and the risk for developing pre-eclampsia [20]. Pre-eclampsia was defined as "definitive" if it met the ICD-10 diagnosis of gestational hypertension (blood pressure: systolic $\geq$140 or diastolic $\geq$90 mmHg on at least 3 occasions) in combination with proteinuria of $\geq$0.3 g/L,

as "registry" if cases were reported from the National Hospital Discharge Registry (independent of the interview), and as "probable" if either the registry or the interview was positive. Acetaminophen exposure was determined in terms of weeks of use and number of pills per week. Acetaminophen use was reported by 35,992 women (56.4%) on one or more occasions during pregnancy with 19,630 exposed in the first trimester, 15,041 exposed in the second trimester, and 20,838 exposed in the third trimester. "Definite" pre-eclampsia was seen in 1113 (1.7%), "probable" in 2772 (4.3%), and "registry" in 1646 (2.6%). First trimester acetaminophen use was associated with an increased risk of gestational hypertension, and acetaminophen use in the third trimester was associated with an increased risk of early (≤32 weeks), late (after 32 weeks), and severe (BP > 180/110 or eclampsia) disease regardless of the definition used. There appeared to be an increase in the risk estimate with increasing number of acetaminophen doses, although this putative dose–response effect was not examined statistically. The highest relative risk was for early pre-eclampsia in the third trimester (relative risk = 1.39, 95% confidence interval: 1.21–1.59). The authors postulated a contributory role for acetaminophen in the oxidative stress process observed with pre-eclampsia; however, they could not exclude so-called reverse causation, in which the headache of pre-eclampsia (or incipient pre-eclampsia) causes the use of acetaminophen, rather than the other way around.

The study authors observed that the DNBC database provides "the most accurate evaluation" demonstrating the lack of a potential teratogenic effect from acetaminophen. A strength of the DNBC database is the high rate of successful follow-up in the Danish health system and that with a minimum follow-up of 3 years (mean of 5.2 years), most congenital abnormalities will have been identified in this study population. The overall prevalence of congenital abnormalities in this study (4.3%) is consistent with the control rates observed in other studies. Even with a large population of exposed pregnancies, however, the power to identify increases in the occurrence of individual malformations was limited. Other limitations of this study were the inclusion of acetaminophen combination products, the use of ICD-10 codes, which lump defects into broad groups that may not be etiologically related, and the exclusion of pregnancy terminations and stillbirths in the evaluation of malformations.

4.2. Case–control studies

4.2.1. All congenital malformations

Nelson et al. presented a case–control study to compare medication histories of 458 mothers of malformed babies (175 with major and 283 with minor malformations) and 911 mothers of non-malformed babies [21]. There was no significant difference between the proportions of women in each group exposed to acetaminophen in the first trimester (4/19 vs. 9/27, cases vs. controls) or any time in pregnancy (19/458 vs. 27/911, cases vs. controls). Medication information was available for 88% of the pregnancies. The consideration of all major and minor malformations together may have obscured increases in individual malformation categories. Other limitations of this study are the consideration of only live births and the lack of distinction between single-ingredient and combination product exposures.

Jick et al. used data from Group Health Cooperative of Puget Sound insurance records involving live births to 6837 women [22]. There were 481 women with prescriptions for acetaminophen, of whom three (0.4%) bore infants with a congenital disorder. The authors concluded that no strong associations between acetaminophen and congenital disorders were found. This study is limited by considering only prescription medication use, which probably represented combination products, and by not considering stillborn infants or abortuses.

Aselton et al. reported an analysis conducted on data collected from Group Health Cooperative of Puget Sound insurance records [23]. The study included 6509 mothers, 350 of whom filled prescriptions for acetaminophen. For the 21 congenital disorders observed, none of the 15 drugs studied had use prevalence more than twice that among nonusers. There were 2 infants (0.6%) with congenital disorders born to mothers who used acetaminophen alone. There were 347 infants born to women who received a combination prescription for acetaminophen and codeine among whom 3 (0.9%) had congenital disorders. This study is limited by considering only prescription medication use and lack of information on stillborn infants or abortuses.

Thulstrup et al. studied the possible association between any congenital abnormality or fetal growth problem and maternal acetaminophen use using a case–control design [24]. Data from the North Jutland Pharmaco-Epidemiological Prescription Database in Denmark were used with record linkage to a population-based prescription database. The study included 123 women who received a prescription for acetaminophen some time during pregnancy and/or 30 days before conception and 13,329 controls who did not receive any prescription drugs. An association was reported in a sub-population of women who were prescribed acetaminophen up to 30 days prior to conception and during the first trimester (adjusted odds ratio 2.3, 95% confidence interval 1.0–5.4) based on six exposed newborns with malformations, although there were no apparent patterns to these malformations (ventricular septal defect, two congenital hip dislocations, stenosis of tear duct, unspecified hernia, and megalocornea). Among the sub-cohort of primiparous women who received acetaminophen up to 30 days prior to conception and during the first trimester, the proportion of malformations was 4.2% compared to 5.6% for the controls (an odds ratio of 0.7).

No significant associations were seen between acetaminophen use and low birth weight (adjusted odds ratio 1.05, confidence interval 0.25–4.31), or preterm delivery (adjusted odds ratio 0.59, confidence interval 0.22–1.61). The authors found no evidence for an association between low birth weight or preterm delivery and acetaminophen in the sub-cohort of primiparous women who received a prescription for acetaminophen up to 30 days prior to conception and during the first trimester. The authors noted that the study was limited by the small sample size of the case group, and the type of congenital malformations reported were felt to point toward random findings rather than a causal link. Additionally, the overall prevalence of malformations in the control group of this study was much higher than the prevalence in a prospective Danish database (4.3% [18]). The selection of mothers requiring an acetaminophen prescription introduced the confounding factor of a concurrent medical condition such as underlying infection for which acetaminophen was used as an antipyretic. The failure to distinguish single-ingredient from combination products and the lack of information on terminated pregnancies are other limitations.

Feldkamp et al. presented a case–control study from the National Birth Defects Prevention Study, a population-based study using birth defects ascertained from centers in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah [25]. Birth defects were collected through each center's surveillance program and medical records of children reviewed to confirm eligibility for the study. Cases were children with any of the specific predefined malformations. Control children were selected randomly from all live births. Mothers were interviewed about exposures during pregnancy with specific questions about the use of acetaminophen-containing products, including timing of exposure, for 3 months prior to conception until the end of pregnancy. About 70% of eligible women agreed to participate. Women were considered exposed if they used an acetaminophen-containing product during any period from the first day of the

last menstrual period through 12 weeks gestation. Women using combination products were excluded. Information was also collected on infection and febrile episodes, and the analysis separately considered infection with and without fever. There were 11,610 cases and 4500 controls. Acetaminophen use during the first 12 weeks of pregnancy was identified in 46.9% of mothers of case children and 45.8% of mothers of control children. There were no statistically significant increases in any malformation associated with acetaminophen use. There were no statistically significant increases in neural tube defects, amniotic band defects, gastroschisis, or cardiac defects, abnormalities for which associations were suggested in prior studies (discussed below). When the analysis was restricted to women who took acetaminophen for febrile disorders, acetaminophen use was associated with a statistically significant protective effect for anencephaly or craniorachischisis, encephalocele, anotia/microtia, cleft lip with or without cleft palate, and gastroschisis.

4.2.2. Neural tube defects

Lynberg et al. used data from the Atlanta Birth Defects Case–Control Study, a retrospective study involving parents of infants with serious birth defects interviewed postpartum by telephone [26]. Seventy percent of eligible parents agreed to participate. Mothers were questioned about drug exposure from 1 month prior to conception to 3 months after conception. There were 4929 infants with birth defects in the case group and 3029 normal control infants matched for race, quarter of birth, and hospital of birth. The study evaluated 385 infants with neural tube defects. An association between acetaminophen and neural tube defects was found (odds ratio 3.1, 95% confidence interval 1.2–8.5). Stronger associations were found for every other drug studied: aspirin (odds ratio 6.2, 95% confidence interval 2.7–14.0), decongestants (odds ratio 8.6, 95% confidence interval 2.6–28.4), and antibiotics (odds ratio 3.8, 95% confidence interval 1.6–9.5), suggesting recalls bias or perhaps confounding by indication. Single-ingredient acetaminophen exposures were not separated from combination product exposures in this study. Stillborn cases were included, but terminated pregnancies did not contribute to the database.

Shaw et al. reported data from the California Birth Defects Monitoring Program [27]. Medical records were examined to identify infants diagnosed with a neural tube defect. Interviews were conducted with mothers of 538 case children and mothers of 539 non-malformed controls. The participation rate was 89%. Women were asked about drug exposure in the 3 months prior to conception, the first trimester, and during the second and third trimesters together. No association was found between acetaminophen use during pregnancy and neural tube defects. There were 144 cases and 141 controls exposed to acetaminophen, giving an odds ratio of 1.05 (95% confidence interval 0.80–1.38). No distinction was made between single-ingredient and combination product exposures. Stillbirths but not abortuses were included.

4.2.3. Renal anomalies

Abe et al. conducted a population-based case–control study specifically evaluating the association between congenital renal anomalies and maternal febrile illness and medication use in the first trimester [28]. This study used retrospective data from the Atlanta Birth Defects Case–Control Study and Metropolitan Atlanta Congenital Defects Program, both of which were conducted by the Centers for Disease Control and Prevention. In total, 192 live- or stillborn infants with renal anomalies were enrolled, with 3029 infants without renal anomalies matched by race, year of birth, and hospital of birth. Only 31% of eligible women participated. The study found an association between renal anomalies and aspirin use (adjusted odds ratio 3.45, 95% confidence interval 1.36–8.75) but no statistically significant association between renal anomalies and use of acetaminophen (adjusted odds ratio 1.48, 95% confidence interval 0.56–3.86) or antibiotics (adjusted odds ratio 1.97, 95% confidence interval 0.96–4.02). This study was limited by low sample size; only 10 (5.2%) of the case infants were exposed to antipyretics or antibiotics. Single-ingredient acetaminophen was not separated from combination exposures. Pregnancy terminations were not considered.

4.2.4. Amniotic band defects

Werler et al. looked specifically at amniotic band defects. Data from the Boston University Slone Epidemiology Center Birth Defects Study were used [29]. The study was conducted in pediatric tertiary care hospitals in Boston, Philadelphia, and Toronto and identified live and stillborn infants with major abnormalities. Exposures were ascertained mostly using in-person interviews conducted within 6 months of delivery. Mothers were questioned after birth about acetaminophen use in the first trimester, cigarette use, and socioeconomic and demographic data. Eighty-four cases of amniotic band defects were identified and compared to 12,227 controls with other major malformations. In order to exclude subjects with possible unidentified amniotic band defects, 4697 of these controls were excluded. The participation rate was 62%. First trimester acetaminophen use was found to be significantly associated with amniotic band defects affecting the limbs (adjusted odds ratio 2.1, 95% confidence interval 1.1–3.9) and with non-limb amniotic band defects (adjusted odds ratio 3.4, 95% confidence interval 1.1–10.3). No association was found with amniotic band defects of the body wall complex type (adjusted odds ratio 0.4, 95% confidence interval 0.1–1.4). Significant associations were also found between amniotic band defects and low socioeconomic status. No association was found between amniotic band defects and maternal cigarette smoking. The authors acknowledged that this study was limited by its lack of dosing information and may have been confounded by indication for medication usage, especially by infection or fever. Single-ingredient exposures were not distinguished from acetaminophen combination products and abortuses were not included.

4.2.5. Gastroschisis

In a case–control study from the Slone Epidemiology Unit, 76 cases of gastroschisis were compared to 2142 controls with other malformations [30]. The participation rate was 79%. An association was reported with first trimester acetaminophen use (adjusted odds ratio 1.7, 95% confidence interval 1.0–2.9) although a stronger and statistically significant association was found with pseudoephedrine (adjusted odds ratio 3.2, 95% confidence interval 1.3–7.7). There were 51 acetaminophen-exposed cases. Medical records were available for only half the cases, raising the possibility of misclassification of gastroschisis. The authors noted that there may have been confounding by indication for medication usage and difficulty separating single agent use from drug combinations (particularly acetaminophen and pseudoephedrine).

In a subsequent follow-up case–control study, 206 cases of gastroschisis and 126 cases of small intestinal atresia were compared to 798 controls from the Slone Epidemiology Unit database [31]. The controls included infants with malformations outside the gastrointestinal tract and non-malformed infants. Control mothers were matched by age to mothers in the gastroschisis group, because gastroschisis is strongly associated with young maternal age. The participation rate was 78%. Telephone interviews were conducted within 6 months of delivery questioning medication use and illnesses during pregnancy. The interviewer was not blinded to case or control status Statistical adjustments were made for family income, maternal education level, cigarette smoking, and illicit drug use. Reported maternal use of pseudoephedrine, aspirin, and acetaminophen were more frequent in the gastroschisis cases

than in controls. Most pseudoephedrine use was in combination with acetaminophen. A significant association was found between acetaminophen use (whether in combination products or alone) and gastroschisis (odds ratio 1.5, 95% confidence interval 1.1–2.2); however, the association was also noted with pseudoephedrine alone (odds ratio 1.8, 95% confidence interval 1.0–3.2) and the pseudoephedrine–acetaminophen combination (odds ratio 4.2, 95% confidence interval 1.9–9.2). No association was found between acetaminophen use and small intestinal atresia (odds ratio 1.0, 95% confidence interval 0.6–1.6). This study was limited by the possibility of recall bias, the unblinded interviewers, possible misclassification of gastroschisis, confounding by indication, difficulty in separating out the effects of combination products, and possible selection bias (20–30% of women refused to participate). Particularly problematic in the study authors' view was the fact that the use of products such as aspirin, pseudoephedrine, and acetaminophen could have been a marker for an infection that increased gastroschisis risk. This possibility of confounding by underlying infection was evaluated by identifying clusters of gastroschisis cases. When such a cluster analysis was performed, the association with acetaminophen and gastroschisis approached the null.

Torfs et al. conducted a case–control study of gastroschisis using births from March, 1989 to August, 1990 in the California Birth Defects Monitoring Program [32]. There were 110 cases and 220 healthy controls matched by ethnic background and age within one year. Seventy-seven percent of eligible mothers agreed to participate. Mothers were administered a 2-h structured in-person questionnaire. Questions covered medicinal use as well as socioeconomic and activity-based questions. In this study, no association between acetaminophen usage and gastroschisis was identified. Mothers of 28 cases (25.5%) of gastroschisis reported exposure to acetaminophen compared with mothers of 56 controls (25.5%), odds ratio 1.0 (95% confidence interval 0.59–1.69). Significant associations were found between gastroschisis and aspirin, ibuprofen, pseudoephedrine, and phenylpropanolamine usage along with some environmental exposures such as "solvents," colorants, and X-rays. Single-ingredient acetaminophen was not distinguished from combination products and only liveborn children were included.

4.2.6. Cardiac malformations

Zierler and Rothman performed a case–control study of congenital heart disease and exposure to a variety of medications during pregnancy [33]. Cases were derived from the New England Regional Infant Cardiac Registry and from death certificates. Control infants were randomly selected from birth certificates. The participation rate was 76%. Mothers responded to a 14–15 min telephone questionnaire concerning medication use during pregnancy. Interviews were conducted around 13 months after delivery. Obstetrical records for about three-quarters of the pregnancies were reviewed to obtain additional exposure information. Prevalence odds ratios for acetaminophen were 0.93 (90% confidence interval 0.69–1.2) and 1.4 (90% confidence interval 0.58–3.4) for questionnaire and obstetric record-derived exposures, respectively, consistent with a lack of effect of acetaminophen exposure on cardiovascular malformations. This study did not distinguish between single-ingredient and combination exposures and did not include information on stillborn infants or abortuses.

Cleves et al. analyzed possible associations between muscular ventricular septal defects and maternal use of acetaminophen or non-steroidal anti-inflammatory drugs during all stages of pregnancy [34]. Data from the CDC National Birth Defects Prevention Study were used, derived from population-based birth defect registries in eight US states. Mothers completed an extensive interview covering preconceptional, periconceptional, and pregnancy exposures to medication. The participation rate was 93%. Specific questions relating to acetaminophen use were asked. Mothers of 168 cases and 692 controls were included in the analysis; 92.3% of mothers reported exposure to acetaminophen some time during pregnancy. The 7.7% of women without reported exposure to acetaminophen all had missing data on acetaminophen use. Acetaminophen use during the first trimester of pregnancy was reported by 62% of case mothers and 57% of control mothers. Reported use of acetaminophen increased to 77% of case mothers and 72% of control mothers for the month prior to delivery. Significant associations were not detected between the occurrence of ventricular septal defects and maternal use of acetaminophen adjusting for maternal fever. Single-ingredient acetaminophen exposure was not distinguished from combination products and only liveborn infants were considered.

4.2.7. Stillbirth and preterm birth

Pastore et al. looked at the possible relationships between medications and stillbirths by using data from a case–control study of stillbirths in California [35]. A total of 332 cases of fetal deaths after 20 weeks gestation and infant deaths within 24 h of birth were compared to 357 control births matched by maternal age and county. Seventy-six percent of eligible mothers participated. About half of the mothers were exposed to acetaminophen (45% of cases, 54% of controls) with no significant relationships found between stillbirth and acetaminophen exposure even when examined by trimester of exposure. An association between prescription pain medication use in the first 2 months of pregnancy and stillbirth was found (adjusted odds ratio 7.5, 95% confidence interval 2.3–24.1); however when acetaminophen was examined specifically, no relationship was found (adjusted odds ratio 1.3, 95% confidence interval 0.8–2.0). Use of acetaminophen alone was not distinguished from use of combination products.

Czeizel et al. analyzed the population-based Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSA) database between 1980 and 1996 ($n = 38{,}151$ liveborn infants) [36]. The authors identified a significant 2.6-fold reduction in the proportion of preterm births (3.5% vs. 9.2%, adjusted $p = 0.01$) with maternal acetaminophen exposure during pregnancy. In general, two controls without congenital abnormalities were selected from the National Birth Registry of the Central Statistical Office for each case with abnormalities, matched by sex, birth week, and district of parents' residence. The participation rate was 83%. Only 173 (0.45%) mothers received acetaminophen during their pregnancy at a daily dose of 300–1000 mg for between 3 and 8 days (mean 4 days) with the peak usage during the 5th and 6th months of pregnancy. No distinction was made between single-ingredient and combination product exposures.

4.3. Case series of overdoses

The maximum recommended dose of oral acetaminophen is 1000 mg 4 times/day or about 67 mg/kg bw/day for a 60-kg woman. For an individual dose, 20 mg/kg by mouth is considered a large therapeutic dose and is associated with a peak plasma concentration of 20 mg/L [37]. Overdose is characterized by a plasma acetaminophen concentration of $\geq$150 mg/L at 4 h after ingestion, the concentration at which specific treatment to prevent hepatotoxicity is indicated [38].

Using cases referred to a Teratology Information Service (TIS) in collaboration with the London National Poisons Information Services, McElhatton et al. conducted a prospective study to investigate the outcome of pregnancy in 300 women who had self-administered an acetaminophen overdose between 1984 and 1992 [39]. This study was an expanded follow-up of a previous review

Table 1
Congenital malformations in liveborn infants after acetaminophen overdose.

Maternal Drug Overdose (acetaminophen dose); other drug in combination	Time of exposure		Plasma acetaminophen mg/L [time (h)]	Congenital malformation
	Trimester	Weeks		
Acetaminophen (not known)	3	32	37 [?]	Systolic murmur
Acetaminophen (5 g)	3	30	45 [4]	Small port wine stain on occiput
Acetaminophen (12–15 g)	3	28	105 [4]	Cleft lip and palate
Acetaminophen (not known)	3	28	None	Premature with bilateral inguinal hernias
Coproxamol: acetaminophen (13 g); dextropropoxyphene 1.3 g	3	28	30 [4]	Positional talipes
Acetaminophen (12.5 g); ibuprofen 3.2–12.8 g	3	27	153 [?]	Soft palate defect
Acetaminophen (7.5 g); dihydrocodeine (not known)	2	26	59 [?]	Spina bifida occult and bilateral squint
Acetaminophen (20 g)	2	26	126 [5]	Hypospadias
Acetaminophen (5 g)	2	20	50 [4]	Ptosis left eye
Acetaminophen (not known)	2	18	None	Severe bilateral talipes
Panadeine: acetaminophen (5–10 g); codeine 80–160 mg	2	16	None	Mild positional talipes

From McElhatton et al. [39]. Peak plasma acetaminophen concentration after a 20 mg/kg therapeutic dose is 20 mg/L [37].

of 115 cases [40]. Acetaminophen overdose was the most common reason for referral to the TIS. Overdose was defined as any consumption of a drug not for therapeutic purposes. The women enrolled in the study completed a questionnaire within 2 weeks of the referral to the TIS and were followed up within 2 months after the expected time of delivery to determine pregnancy outcome.

Of the 300 acetaminophen overdoses, 90 also involved other drugs. Of these, 65 involved acetaminophen combination products. The overdoses were relatively balanced across the trimesters (39% in the first, 34% in the second, and 26% in the third). The 300 pregnancies resulted in 219 normal liveborn infants (including two sets of twins), 11 liveborn infants with malformations, 16 spontaneous miscarriages, two late fetal deaths, and 54 elective abortions.

Individual acetaminophen exposure data, gestational age and outcomes from this study are presented in Appendix 1. None of the 11 infants with malformations was exposed in the first trimester (Table 1). The malformations (*n*) from second trimester acetaminophen exposure included talipes or clubfoot deformities (2), spina bifida occulta and bilateral squint (1), hypospadias (1), and left eye ptosis (1). The malformations from third trimester acetaminophen exposure included palatal defects (2), talipes (1), systolic murmur (1), small port wine stain (1), and bilateral inguinal hernias (1).

All of the spontaneous miscarriages and one fetal death occurred subsequent to a first trimester overdose. The other fetal death occurred after a second trimester overdose. Nearly two thirds of the spontaneous terminations occurred within 3 weeks of the overdose. None of the liveborn infants were reported to have any clinical signs of renal or hepatotoxicity, at least up to 6 weeks of age. Post mortem examinations in three aborted fetuses did not show signs of renal or hepatic damage. Thirty-three mothers were treated with acetylcysteine and 16 with methionine, but such treatment did not appear to influence toxicity outcomes. There was no correlation between the amount of acetaminophen reportedly taken, the maternal acetaminophen blood levels measured, and the subsequent maternal and/or fetal toxicity. Based upon the results, the authors concluded that in the absence of severe maternal toxicity, there is no overall increase in fetal toxicity.

Riggs et al. at the Rocky Mountain Poison and Drug Center conducted an evaluation of 113 pregnant women who had overdosed on acetaminophen from 1976 to 1985 [41]. All subjects were entered prospectively into the study after telephone consultation with the treating physician. Three women were excluded due to false-positive pregnancy tests. Follow-up data were available for 60 of 110 women. Forty-eight women were lost to follow-up and two were excluded due to an uninterpretable acetaminophen level. Women were treated with acetylcysteine according to the Rumack–Matthew nomogram or empirically (without a prior acetaminophen level) if the acetaminophen ingestion history was 7.5 g or more.

The 60 women were categorized by trimester at the time of the acetaminophen overdose: there were 19 women in the first trimester, 22 women in the second trimester, and 19 women in the third trimester. Six of 19 women who took overdoses during the first trimester had spontaneous abortions after the overdose, and eight of 19 women underwent an elective abortion during the first trimester. There were five normal term infants in the first trimester group. There were no maternal deaths. Two of the 22 women in the second trimester group had spontaneous terminations of pregnancy. One of them had been assaulted before admission and had a spontaneous termination the day after admission. She also required intubation for respiratory failure and bilateral pneumonia, suffered a cardiac arrest after self-extubation, and did not respond to resuscitative efforts. An autopsy revealed no hepatic damage. One woman had an elective abortion and 19 delivered normal infants (one was premature). One of the 19 women whose overdose occurred in the third trimester delivered a stillborn infant 2 days after the overdose. The fetal acetaminophen level was 330 μg/mL. The remaining 18 women delivered normal term infants (15), normal premature infants (3), or a term infant (1) with "mild positional deformity of the feet." A comparison of the incidence of spontaneous abortion or fetal death by trimester and comparison of those with toxic versus nontoxic acetaminophen levels, peak alanine aminotransferase level, or total number of acetylcysteine doses received revealed no statistically significant differences.

4.4. Case reports

Appendix A presents a tabular summary of individual acetaminophen dose data from case reports and case series including cases of acetaminophen overdose, which represent most of the cases. No pattern of malformations was noted. Of the 85 pregnancies presented, 10 resulted in fetal or neonatal malformations, 6 resulted in fetal or infant death (mostly from complications of prematurity), two spontaneously aborted, and four were electively aborted without information on possible malformations in the embryo. There was one child with hepatic injury and one child with constriction of the ductus arteriosus.

5. Discussion

Experimental animal studies have not suggested an increase in congenital malformations associated with acetaminophen treatment although some studies have shown fetotoxicity at dose levels about twice the maximum recommended human dose on a weight

Table 2
Observational human acetaminophen studies with breakdown of population by trimester.

Population	End points	Number of subjects by trimester exposed/unexposed or case/control			Main findings[d]	Reference
		1st	2nd	3rd		
Cohort studies						
Seattle	IQ	421[a]			No effect	Streissguth et al. [15]
USA	Congenital abnormalities	226/50056			No increase	Heinonen et al. [16]
San Francisco	Miscarriage	172/762[b]			No increase	Li et al. [17]
Denmark	Pregnancy outcomes	26424/61718	19737/68405	25020/63122	No increase in malformation, stillbirth, low birth weight. Preterm birth in women with pre-eclampsia: HR 1.55 (95% CI 1.16–2.07) Pre-eclampsia: RR 1.39, (95% CI 1.21–1.59)	Rebordosa et al. [18,19]
Case–control studies						
United Kingdom	Congenital abnormalities	13/1356			No association	Nelson and Forfar [21]
Seattle	Congenital abnormalities	481/6356			No association	Jick et al. [22]
Seattle	Congenital abnormalities	697/5812			No association	Aselton et al. [23]
Denmark	Congenital abnormalities	55/13327	111/13327[c]	111/13327[c]	No association	Thulstrup et al. [24]
USA	Congenital abnormalities	11,610/4500			No association for individual malformation groups	Feldkamp et al. [25]
Atlanta	Neural tube defects	23/2661			OR 3.1, 95% CI 1.2–8.5	Lynberg et al. [26]
California	Neural tube defects	285/792			No association	Shaw et al. [27]
Atlanta	Renal malformations	52/3169			No association	Abe et al. [28]
Boston, Philadelphia, Toronto	Amniotic band defects	7007/5304			Amniotic band: Affecting limb: OR 2.1, 95% CI 1.1–3.9 Not affecting limb: OR 3.4, 95% CI 1.1–10.3	Werler et al. [29]
Boston, Philadelphia, Toronto	Gastroschisis	1126/1092			OR 1.7, 95% CI 1.0–2.9	Werler et al. [30]
USA and Canada	Gastroschisis	506/624			OR 1.5, 95% CI 1.1–2.2	Werler et al. [31]
California	Gastroschisis	84/246			No association	Torfs et al. [32]
Massachusetts	Cardiac malformations	84/199			No association	Zierler and Rothman [33]
USA	Cardiac malformations	463/397			No association	Cleves et al. [34]
California	Stillbirths	177/512	219/470	173/516	No association	Pastore et al. [35]
Hungary	Gestational age, birth weight	173/37928[b]	173/37928[b]	173/37928[b]	2.6-fold reduction in preterm birth with acetaminophen	Czeizel et al. [36]

[a] Pregnancy up until the fifth month.
[b] Entire pregnancy.
[c] Second and third trimesters grouped together.
[d] Based on statistical testing. HR = hazard ratio, RR = relative risk, OR = odds ratio, CI = confidence interval.

basis. Acetaminophen may constrict the fetal rat ductus arteriosus, also at higher than the recommended human dose level on a weight basis.

Table 2 presents a summary of the observational human studies discussed in this review, with study populations broken down by trimester of acetaminophen exposure for reviewer convenience. Appendix A presents a tabular summary of individual acetaminophen dose data from case series and reports.

Acetaminophen use during pregnancy has been evaluated in several cohort and case–control studies without evidence for an increase in the overall rate of congenital malformations or other adverse pregnancy outcome and without consistent findings of an increase in any individual type of congenital malformation. The largest cohort study on the issue of acetaminophen exposure and the risk of congenital malformations is the prospective cohort study of the Danish National Birth Cohort [18], which evaluated the effect of acetaminophen use on the relative risk for congenital abnormalities among 88,142 pregnant women who had liveborn singletons. In this study, exposure to acetaminophen during the first or any trimester was not associated with a higher prevalence of any congenital abnormality. There was no increased risk for the development of gastroschisis, amniotic band defects, neural tube defects, or congenital heart disease. Limitations of this study included a 60% participation rate, although analysis of nonparticipants did not suggest resulting bias, the consideration of combination products, use of ICD-10 codes for diagnosis, and the exclusion of abortions and stillbirths.

Although an association of acetaminophen use during pregnancy and gastroschisis was identified by Werler et al. [30,31], these authors called attention to the difficulty in separating effects of combination productions such as pseudoephedrine/acetaminophen and of adjusting for indication for acetaminophen use. A cluster analysis revealed that the association between acetaminophen alone and gastroschisis approached the null. Torfs et al., a similarly powered case–control study of gastroschisis demonstrated an association with pseudoephedrine and aspirin; however, the authors did not find an association with acetaminophen [32]. The large case–control study from the National Birth Defects Prevention Study, which considered only acetaminophen taken as a single product, also found no significant association between acetaminophen exposure and gastroschisis or other individual malformations [25]. There are no other individual malformations for which acetaminophen has been shown to be causally associated.

Prenatal acetaminophen exposure does not appear to be associated with miscarriage, stillbirth, low birth weight, smallness for gestational age, or preterm birth complications (bronchopulmonary dysplasia, intracranial hemorrhage, retinopathy of prematurity, perinatal infections, and anemia of prematurity) [17–19]. Acetaminophen exposure during the third trimester was

associated with pre-eclampsia/preterm birth [18,19] but not with placental abruption; however the association was not confirmed in another study in which the proportion of preterm births was 3.5% in mothers who had acetaminophen treatment during pregnancy, compared to 9.2% in those who had not [36]. An association between acetaminophen, pre-eclampsia, and preterm birth may be spurious due to acetaminophen use to treat the headache related to pre-eclampsia and the frequent clinical decision to deliver the fetus prematurely as part of the management of pre-eclampsia.

The experimental animal studies and epidemiology studies taken together support the conclusion that therapeutic use of acetaminophen does not increase the risk of adverse pregnancy outcome. Use of acetaminophen as the analgesic and antipyretic of choice during pregnancy appears to be justified by the safety data.

Conflict of interest

Supported by Cadence Pharmaceuticals, Inc.

Appendix A. Individual acetaminophen dose data from case series or reports.

Dose	Highest maternal blood or plasma concentration	Other exposures	Gestational age	Outcome		Reference
				Mother	Baby	
15 g	Not reported	Not reported	18 days	Not reported	Term delivery	Flint et al. [42]
10 g	Not reported	Not reported	18 days	Not reported	Term delivery	
12.5 g	Not reported	Not reported	18 weeks	Not reported	Term delivery	
25 g	Not reported	Not reported	19 weeks	Not reported	Term delivery	
1 g	Not reported	Nimesulide	37 weeks	Not reported	Constricted ductus arteriosus, heart failure, normal at 6 weeks	Simbi et al. [14]
19 g	Not reported	None prior to delivery	Term	Anemia	No evidence of liver injury	Sancewicz-Pach et al. [43]
>35 g	40.43 mg/L	N-acetylcysteine	31 weeks	Hepatic necrosis, death	Premature delivery, neonatal death	Wang et al. [44]
>4 g/day, chronic	234 mg/L	N-acetylcysteine	27 weeks	Recovered	Discharged without evidence of liver injury	Horowitz et al. [45]
>4 g/day, chronic	Undetectable 48 h later	N-acetylcysteine	22 weeks	Recovered	Previable delivery, died without evidence of liver injury	
Not reported	176 mg/L	N-acetylcysteine	37 weeks	Recovered	Discharged without evidence of liver injury	
Not reported	Term	N-acetylcysteine	Unknown	Recovered	Discharged without evidence of liver injury	
7.5 g	59 mg/L	Cefadroxil, codeine, co-danthramer, clotrimazole, acyclovir	26 weeks	Not reported	Term delivery, spina bifida occulta, strabismus	McElhatton et al. [40]
12–15 g	105 mg/L	Dihydrocodeine	28 weeks	Not reported	Term delivery, cleft lip and palate	
15 g	Nor reported	Dihydrocodeine, methionine, amphetamine, barbiturates, flurazepam, promethazine, diamorphine, diazepam	34 weeks	Not reported	Term delivery, withdrawal syndrome	
Unknown	69 mg/L	N-acetylcysteine	29 weeks	Not reported	Premature delivery at 33 weeks, respiratory distress	
15 and 50 g	448 mg/L	N-acetylcysteine	31 and 32 weeks	Hepatic injury	Induced premature delivery, jaundice, hypoglycemia, “respiratory problems”; normal at 6 months of age	
6 g	Not reported	Aspirin, hepatitis B (at 16 weeks)	36 weeks	Not reported	Term delivery, pyloric stenosis at 8 weeks of age	
37.5 g	170 mg/L	None	7–8 weeks	No symptoms	Spontaneous abortion 2 weeks later	

(Appendix A *Continued*)

Dose	Highest maternal blood or plasma concentration	Other exposures	Gestational age	Outcome		Reference
				Mother	Baby	
Unknown	363 mg/L	N-acetylcysteine	12 weeks	Nausea and vomiting	Spontaneous abortion 2 weeks later	
2.6 g/day chronically	Not reported	Dextropropoxyphene, oral contraceptive, prednisolone, Crohn's disease	All of pregnancy	Not reported	Elective abortion of anencephalic fetus	
25 g	Not reported	None	16 weeks	Not reported	Elective abortion at 21 weeks, normal fetus	
10 g	Not reported	None reported	12 weeks	Not reported	Elective abortion	
10–13 g	Not reported	None reported	21 weeks	Not reported	Elective abortion	
50 g	Not reported	None reported	18 weeks	Not reported	Elective abortion	
Unknown	Not reported	None reported	10 weeks	Not reported	Elective abortion	
Unknown	225 mg/L	N-acetylcysteine	3 weeks	Not reported	Normal	
47.5 g	87 mg/L	N-acetylcysteine	3 weeks	Not reported	Normal	
23 g	Not reported	None	4 weeks	Not reported	Normal	
6.5 g	Not reported	None	5–6 weeks	Not reported	Normal	
10 g	Not reported	None	6 weeks	Not reported	Normal	
3.25 g	Not reported	None	7 weeks	Not reported	Normal	
15 g	60 mg/L	None	7 weeks	Not reported	Normal	
9.5 g	35 mg/L	None	8 weeks	Not reported	Normal	
5–10 g	Not reported	Antidepressant	10 weeks	Not reported	Normal	
10 g	Not reported	Methyldopa, ethanol	12 weeks	Not reported	Normal	
2 g	Not reported	Phenylpropanolamine	12 weeks	Not reported	Normal	
3.6 g	Not reported	None	12 weeks	Not reported	Normal	
1 g	Not reported	Diazepam, avomine, vallergan	12 weeks	Not reported	Normal	
24 g	222 mg/L	None	12 weeks	Not reported	Normal	
10 g	75 mg/L	None	16 weeks	Not reported	Normal	
12 g	Not reported	None	17 weeks	Not reported	Normal	
9 g	51 mg/L	None	17 weeks	Not reported	Normal	
15 g	290 mg/L	None	18 weeks	Not reported	Normal	
7.5 g	Not reported	None	20 weeks	Not reported	Normal	
10 g	170 mg/L	None	20 weeks	Not reported	Normal	
30 g	210 mg/L	N-acetylcysteine	26 weeks	Not reported	Normal	
12.5 g	115 mg/L	None	28 weeks	Not reported	Normal	
12.5 g	Not reported	None	28 weeks	Not reported	Normal	
10 g	Not reported	Codeine	28 weeks	Not reported	Normal	
3 g	Not reported	Diphenhydramine	32 weeks	Not reported	Normal	
40–50 g	214 mg/L	None	32–34 weeks	Not reported	Normal	
30 g	64 mg/L	None	34 weeks	Not reported	Normal	
14 g	125 mg/L	None	35 weeks	Not reported	Normal	
6 g	18 mg/L	None	35 weeks	Not reported	Normal	
25 g	121 mg/L	N-acetylcysteine	36 weeks	Not reported	Normal	
6 g	<5 mg/L	Chlorpheniramine	36 weeks	Not reported	Normal	
Unknown	Not reported	Methionine	37 weeks	Not reported	Normal	
7.5 g	50 mg/L	Ipecac	37 weeks	Not reported	Normal	
5–6 g	Not reported	None	39 weeks	Not reported	Normal	
5 g	Not reported	None	40 weeks	Not reported	Normal	
1.2 g/day, chronic	Not reported	Codeine, carisoprodol, aspirin, phenytoin, cefoxitin	35 weeks	Hepatic injury, recovered	Preterm delivery, hepatic injury with coagulopathy and intracranial bleeding	Kurzel [46]
50 g	448 mg/L	N-acetylcysteine	32 weeks	Hepatic injury, recovered	Hypoglycemia, jaundice	Rosevear and Hope [47]
36 g	340 mg/L	N-acetylcysteine	16 weeks	Normal	Normal	Robertson et al. [48]
64 g	198.5 mg/L (10 h later)	N-acetylcysteine, vitamin K	15.5 weeks	Hepatic necrosis, respiratory distress, recovered	Premature delivery (32 weeks)	Ludmir et al. [49]
20 g	280 mg/L	Ethanol	36 weeks	Normal	Normal	Roberts et al. [50]
25 g	236 mg/L	N-acetylcysteine, vitamin K	20 weeks	Jaundice, resolved	Normal delivery at 41 weeks, jaundice treated with phototherapy	Stokes [51]
29.5 g	56 mg/L (20 h later)	N-acetylcysteine (after fetal demise)	27–28 weeks	Hepatic injury, DIC, recovered	Fetal demise; fetal liver acetaminophen 250 μg/g	Haibach et al. [52]

(Appendix A *Continued*)

Dose	Highest maternal blood or plasma concentration	Other exposures	Gestational age	Outcome		Reference
				Mother	Baby	
32.5 g	159.5 mg/L	Aspirin, caffeine, quinine, methionine	29 weeks	Liver necrosis,	Premature delivery; hyaline membrane disease, exchange transfusion, infant death at 3 months of age of unknown cause	Lederman et al. [53]
Not reported	Not reported	Vitamin B6, doxylamine, propoxyphene	8 weeks	Not reported	Large perineal mass, hip dislocation, death at day 7	Williams et al. [54]
1.95–3.25 g/day	Not reported	Propoxyphene, phenobarbital	"Throughout pregnancy"	Not reported	Widely spaced sutures, beaked nose, micrognathia, bifid uvula, curved overlapping toes	Golden and Perman [55]
22.5 g	200 mg/L	None	36 weeks	Normal	Normal	Byer et al. [56]
Not reported	Not reported	Propoxyphene, dicyclomine, phenobarbital, amitriptyline	Preconception to 1 month after conception	Not reported	Anophthalmia (n)	Golden et al. [57]
1.3 g/day	Not reported	None	All of pregnancy	Normal	Polyhydramnios; neonatal renal failure and death.	Char et al. [58]
Up to 1.2 g/day, chronic	Not reported	Salicylamide, aspirin, caffeine	0–6 weeks	Not reported	Single artery and vein in umbilicus, dextrocardia, shortened left forearm, absent left thumb	McNeil [59]
0.2 g	Not reported	Salicylamide, aspirin, caffeine, chlorpheniramine	Early pregnancy	Not reported	Harelip, cleft palate	
1.2 g/day, chronic	Not reported	Salicylamide, aspirin, caffeine, multivitamin	0–12 weeks	Not reported	Hand and foot deformities	
Not reported	Not reported	None	10–12 weeks	Normal	Congenital cataracts	Harley et al. [60]

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