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Acetaminophen is not Safe in Pregnancy

*Katsuhiro Toda**

Department of Orthopedic Surgery, Kitahiroshima Town Toyohira Hospital, Japan

Abstract

A narrative review of risks of acetaminophen to the fetus is conducted. Prenatal exposure to acetaminophen is associated with cerebral palsy, autism spectrum disorder, communication problems, hyperactivity/impulsivity symptoms, attention-deficit/hyperactivity disorder, attention and executive function problems, language delay, lower intelligence quotient, behavioral problems, shorter anogenital distance in male infants, decreased relative numbers of hematopoietic stem cells in cord blood, wheeze, and asthma. Paternal preconception acetaminophen use for 8 day or more is associated with ADHD. A systematic review and meta-analysis showed significant association between prenatal acetaminophen exposure and child asthma risk. Exposure for 29 day or more is probably danger. However, we cannot assert that exposure for 28 day or less is safe. At the present moment, any public organizations or academic associations have not declared the danger of acetaminophen in pregnancy. Each article has poor power to show risks of acetaminophen, however, the integration of the articles that showed adverse effects of acetaminophen may have power to show them. We should recognize that acetaminophen is danger in pregnancy. However, acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy. Fever and pain during pregnancy themselves are probably associated with adverse gestational outcomes. Acetaminophen should be used at the lowest effective dosage and for the shortest time. We should use acetaminophen in pregnancy only when needed and no safer option for pain or fever relief is available. I would like public organizations or academic associations to declare danger (or safety) of acetaminophen in pregnancy.

Keywords: Acetaminophen; Paracetamol; Adverse effects; Pregnancy; Cerebral palsy; Autism spectrum disorder; Attention-deficit/hyperactivity disorder; Language delay; Intelligence quotient; Shorter anogenital distance; Asthma

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Correspondence:
Katsuhiro Toda, Department of Orthopedic Surgery, Kitahiroshima Town Toyohira Hospital, 4705, Azaka, Kita-Hiroshima Town, Yamagata-Gun, Hiroshima, 731-1222, Japan, Tel: 81-826-84-1155; Fax: +81-826-84-1015; E-mail: goutattack@yahoo.co.jp

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Introduction

Acetaminophen is recommended as the safest analgesic and antipyretic medicine for pregnant women, and it is widely used all over the world. Recent studies suggest that acetaminophen is a hormone disrupter (i.e., it interferes with sex and thyroid hormone function essential for normal brain development) and thus may not be considered a safe drug during pregnancy [1]. Recently many adverse effects of acetaminophen on the fetus have been reported. A narrative review of risks of acetaminophen to the fetus is conducted and the situation of the world on the issue is explained.

Cerebral palsy

A cohort study showed that prenatal exposure to paracetamol ever in pregnancy was associated with increased risk of overall Cerebral Palsy (CP) (adjusted Odds Ratio [aOR] 1.3, 95% Confidence Interval [CI] 1.0-1.7) and unilateral spastic CP (aOR 1.5, 95% CI 1.0-2.2) [2].

Autism spectrum disorder and communication problems

Paracetamol has been widely prescribed since the mid-1990s during circumcision. Using all available country-level data (n=8) for the period 1984 to 2005, prenatal use of paracetamol was correlated with autism/Autism Spectrum Disorder (ASD) prevalence (r=0.80). For studies including boys born after 1995, there was a strong correlation between country-level (n=9) autism/ASD prevalence in males and a country's circumcision rate (r=0.98). A very similar pattern was seen among U.S. states and when comparing the 3 main racial/ethnic groups in the U.S. [3].

A prospective cohort study showed that children exposed to prenatal paracetamol for more than 28 days had poorer gross motor development (β 0.24, 95% CI 0.12-0.51), communication (β 0.20, 95% CI 0.01-0.39), externalizing behavior (β 0.28, 95% CI 0.15-0.42), internalizing behavior (β 0.14, 95% CI 0.01-0.28), and higher activity levels (β 0.24, 95% CI 0.11-0.38) at 3 years of age [4]. Children exposed prenatally to short-term use of paracetamol (1-27 days) also had poorer gross

motor outcomes (β 0.10, 95% CI 0.02-0.19), but the effects were smaller than with long-term use [4].

A total of 64,322 children and mothers enrolled in the Danish National Birth Cohort were followed for average 12.7 years [5]. Prenatal use of acetaminophen was associated with an increased risk of ASD accompanied by hyperkinetic symptoms (Hazard Ratio [HR] 1.51, 95% CI 1.19-1.92), but not with other ASD cases (HR 1.06, 95% CI 0.92-1.24) [5]. Longer duration of use (i.e., use for >20 weeks in gestation) increased the risk of ASD or infantile autism with hyperkinetic symptoms almost twofold [5].

The spanish birth cohort study included 2,644 mother-child pairs recruited during pregnancy [6]. Ever-exposed offspring had higher risks of presenting more hyperactivity/impulsivity symptoms (Incidence Rate Ratio [IRR] 1.41, 95% CI 1.01-1.98) [6]. Childhood Autism Spectrum Test (CAST) scores were increased in ever-exposed males (β 0.63, 0.09-1.18) [6]. Increased effect sizes of risks by frequency of use were observed for hyperactivity/impulsivity symptoms (IRR 2.01, 0.95-4.24) in all children, and CAST scores in males (β 1.91, 0.44-3.38) [6].

The Norwegian Mother and Child Cohort Study (51,200 pregnancies) showed that long-term (≥ 28 days) paracetamol exposure during pregnancy was associated with communication problems(Odds Ratio [OR]1.38, 95% CI 0.98-1.95) and delayed motor milestone attainment (OR 1.35, 95% CI 1.07-1.70) at 18 months of age [7]. Short-term exposure (<28 days) was not associated with increased risks [7].

A review that examined risk factors of ASD reported that β2-adrenergic receptor agonists and paracetamol had also lately been associated with increased rate of ASD but the data was too preliminary and inconclusive [8].

Andrade published a review [9] including 2 studies that showed a risk of ASD [5] and adverse developmental outcomes [4]. He concluded as follows: The empirical data are very limited, but whatever empirical data exist do not support the suggestion that the use of acetaminophen during pregnancy increases the risk of autism in the offspring [9].

Attention-deficit/hyperactivity disorder

Liew et al. [10] studied 64,322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002. Acetaminophen use during pregnancy was assessed prospectively *via* 3 computer-assisted telephone interviews during pregnancy and 6 months after child birth. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of Hyperkinetic Disorders (HKDs) (HR 1.37, 95% CI 1.19-1.59), use of Attention-Deficit/Hyperactivity Disorder (ADHD) medications (HR 1.29, 95% CI 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio 1.13, 95% CI 1.01-1.27) [10]. Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes (i.e., HKD diagnosis, ADHD medication use, and ADHD-like behaviors; P trend <0.001) [10].

Participants were members of the Auckland Birth weight Collaborative Study, a longitudinal study of 871 infants of European descent sampled disproportionately for small for gestational age [11]. Children of mothers who used acetaminophen during pregnancy were at increased risk of ADHD at 7 and 11years of age (Conners' Parent Rating Scale-Revised) [11].

The Spanish birth cohort study included 2,644 mother-child pairs recruited during pregnancy [6]. Ever-exposed offspring had higher risks of presenting more hyperactivity/impulsivity symptoms (IRR 1.41, 95% CI 1.01-1.98) [6]. CAST scores were increased in ever-exposed males (β 0.63, 0.09-1.18) [6]. Increased effect sizes of risks by frequency of use were observed for hyperactivity/impulsivity symptoms (IRR 2.01, 0.95-4.24) in all children, and CAST scores in males (β 1.91, 0.44-3.38) [6].

Gervin et al. [12] have conducted an epigenome-wide association study (*n*=384 cord blood samples). Analyses identified significant differences in DNA methylation (*n*=6,211 CpGs) associated with prenatal exposure to paracetamol for more than 20 days in children diagnosed with ADHD compared to controls [12]. In addition, these samples were differentially methylated compared to samples with ADHD exposed to paracetamol for less than 20 days (*n*=2,089 CpGs) and not exposed to paracetamol (*n*=193 CpGs) [12].

Diagnoses were obtained from the Norwegian Patient Registry for 112,973 offspring from the Norwegian Mother and Child Cohort Study, including 2,246 with ADHD [13]. The HR for more than 29 days of maternal acetaminophen use was 2.20 (95% CI 1.50-3.24) [13]. Use for <8 days was negatively associated with ADHD (HR 0.90, 95% CI 0.81-1.00) [13]. Acetaminophen use for fever and infections for 22 to 28 days was associated with ADHD (HR 6.15, 95% CI 1.71-22.05) [13]. Paternal and maternal use of acetaminophen were similarly associated with ADHD [13]. Short-term (1-7 days) paternal preconception use was not negatively associated with ADHD (HR 1.10, 95% CI 0.92–1.30); paternal preconception use for 29 days or more and 8-28 day was as strongly associated with ADHD (29 day or more HR 2.06, 95% CI 1.36–3.13: 8-28 days HR 1.81, 95% CI 1.26–2.60) as the corresponding maternal prenatal use [13].

A review reported as follows: It appears possible that the use of acetaminophen during pregnancy is itself responsible for the increased risk of ADHD [14]. This suggests that acetaminophen may not be as safe in pregnancy as is widely believed. However, since fever during pregnancy may itself be associated with adverse gestational outcomes, given the present level of uncertainty about the ADHD risk with acetaminophen, it is suggested that, until more data are available, the use of acetaminophen in pregnancy should not be denied in situations in which the need for the drug is clear [14].

Hoover et al. [15] conducted a systematic review that assessed the relationship of prenatal acetaminophen exposure and the development of attention deficit disorders or hyperactivity. They concluded as follows: While there does appear to be a mild correlation between prenatal acetaminophen use and the development of ADHD symptoms in children, current data do not provide sufficient evidence that prenatal acetaminophen exposure leads to development of ADHD symptoms late in life [15]. Acetaminophen is a preferred option for pain management during pregnancy when compared with other medications such as non-steroidal anti-inflammatory drugs or opioids for pyretic or pain relief [15].

Attention and executive function problems

Liew et al. [16] studied 1,491 mothers and children enrolled in the Danish National Birth Cohort (1996-2002). Children prenatally exposed to paracetamol were also at a higher risk for subnormal Overall Attention (OR 1.5, 95% CI 1.0-2.5), selective attention

difficulties (OR 1.5, 95% CI 1.0-2.4), and parent-rated subnormal executive function (metacognition index, OR 1.5, 95% CI 0.9-2.3) in 5-year-olds [16]. The risks for subnormal overall attention or executive unction were elevated with longer duration of paracetamol use in pregnancy [16].

Language delay

A population-based pregnancy cohort study including 754 women who enrolled in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study in pregnancy week 8-13 [17]. Both the number of acetaminophen tablets and urinary acetaminophen concentration were associated with greater Language Delay (LD) in girls but not in boys [17]. The a aOR for LD among girls whose mothers reported >6 (3,000 mg; I confirmed it to the authors.) *vs.* 0 acetaminophen tablets was 5.92 (95% CI 1.10-31.94) [17]. The OR for LD in girls whose mothers' urinary acetaminophen was in the highest compared to the lowest quartile was 10.34 (95% CI 1.37-77.86) [17].

Lower intelligence quotient (IQ)

Liew et al. [18] studied 1,491 mothers and children enrolled in the Danish National Birth Cohort (1996-2002). Children born to mothers using acetaminophen without reporting fever scored on average 3.4 points lower (95% CI, 0.30-6.6 points) on performance IQ in 5-year olds compared with offspring of mothers who neither experienced fever nor took acetaminophen [18]. Children born to mothers reporting fever without using acetaminophen also scored lower on verbal (2.7 points, 95% CI -0.19 to 5.6) and performance IQ (4.3 points, 95% CI 0.30-8.3); IQ scores were not affected if mothers with fever used acetaminophen [18].

Behavioral problems

Stergiakouli et al. [19] studied 7,796 mothers enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective birth cohort, between 1991 and 1992 along with their children and partners. Maternal prenatal acetaminophen use at 18 (n=4,415; 53%) and 32 weeks of pregnancy (n=3,381; 42%) was associated with higher odds of having conduct problems (Risk Ratio [RR] 1.42, 95% CI 1.25-1.62) and hyperactivity symptoms (RR 1.31, 95% CI 1.16-1.49), while maternal acetaminophen use at 32 weeks was also associated with higher odds of having emotional symptoms (RR 1.29, 95% CI 1.09-1.53) and total difficulties (RR 1.46, 95% CI 1.21-1.77) [19]. Stergiakouli et al. [19] found the associations between maternal prenatal acetaminophen use and all the Strengths and Difficulties Questionnaire domains unchanged even after adjusting for maternal postnatal or partner's acetaminophen use [19].

Shorter anogenital distance in male infants

Prospective cohort study with recruitment of pregnant women at ~12 post-menstrual weeks of gestation from a single UK maternity unit between 2001 and 2009 [20]. Of 2,229 recruited women, 1,640 continued with the infancy study after delivery, of whom 676 delivered male infants and completed a medicine consumption questionnaire [20]. Paracetamol exposure during 8-14 weeks of gestation, but not any other period, was associated with shorter Anogenital Distance (AGD) (by 0.27 SD, 95% CI 0.06-0.48, P=0.014) from birth to 24 months of age [20]. This reduction was independent of body size [20].

A total of 117 infertile men (mean age: 35.3 ± 17.4) and 56 fertile men (mean age: 44.8 ± 9.7) were recruited [21]. The infertile men possessed significantly shorter mean AGD and penile length compared to the fertile controls (AGD: 31.8 *vs.* 44.6 mm, penile length: 107.1 *vs.* 119.5 mm, p<0.01) [21]. The difference in AGD persisted even after accounting for ethnic and anthropomorphic differences [21]. After adjusting for demographic and reproductive variables, for each 1 cm increase in a man's AGD, the sperm density increases by 4.3 million sperm per mL (95% CI 0.53-8.09, p=0.03) and the total motile sperm count increases by 6.0 million sperm (95% CI 1.34-10.58, p=0.01) [21].

Decreased relative numbers of hematopoietic stem cells in cord blood

The Prince (Prenatal Determinants of Children's Health) study, a population-based prospective pregnancy cohort study initiated in 2011 [22]. A total of 518 healthy pregnant women with singleton pregnancies were recruited during the first trimester [22]. Paracetamol intake, particularly during the third trimester, resulted in decreased relative numbers of hematopoietic stem cells in cord blood, independent of maternal age, first-trimester body mass index, parity, gestational age and birth weight (-0.286, 95% CI -0.592 to 0.021, p=0.068) [22].

Wheeze and asthma

Sordillo et al. [23] included 1,490 mother-child pairs in Project Viva, a longitudinal prebirth cohort study. Prenatal acetaminophen was associated with increased asthma (OR 1.26, 95% CI 1.02-1.58) in early childhood (3-5 years of age, n=1,419) but not mid childhood (7-10 years of age, n=1,220) [23].

Magnus et al. [24] used information from the Norwegian Mother and Child Cohort Study, including 53,169 children for evaluation of current asthma at 3 years, 25,394 for current asthma at 7 years and 45,607 for dispensed asthma medications at 7 years in the Norwegian Prescription Database. There were independent modest associations between asthma at 3 years with prenatal paracetamol exposure (adjusted relative risks 1.13, 95% CI 1.02-1.25) and use of paracetamol during infancy (adjusted relative risks 1.29, 95% CI 1.16-1.45) [24]. The results were consistent for asthma at 7 years [24]. The associations with prenatal paracetamol exposure were seen for different indications (pain, respiratory tract infections/influenza and fever) [24]. Maternal pain during pregnancy was the only indication that showed an association both with and without paracetamol use [24]. Maternal paracetamol use outside pregnancy and paternal paracetamol use were not associated with asthma development [24].

An Italian birth cohort study reported that the association between maternal paracetamol use during pregnancy and infant wheezing was mainly, if not completely explained by confounding [25].

A systematic review and meta-analysis of longitudinal studies reported that any paracetamol use during the first trimester was related to increased risk of childhood asthma (5 studies, pooled OR1.39, 95% CI 1.01-1.91) but there was marked between-study heterogeneity (I(2)=63%) and only one of these studies adjusted for maternal respiratory tract infections [26]. However, the association during early pregnancy exposure was highly variable between studies and exposure during infancy appears to be moderately confounded by respiratory tract infections [26]. The authors concluded that there was insufficient evidence to warrant changing guidelines on early life paracetamol exposure at this time [26].

Lourido-Cebreiro et al. [27] conducted a systematic review to analyze the relationship between paracetamol and asthma. The

exposure to paracetamol during pregnancy was analyzed in several cohort studies, showing an association between the prenatal exposure to paracetamol with suffering from asthma or presence of wheezing in childhood, especially for persistent wheezing [27]. Nevertheless, a recent study concluded that the relationship between asthma and paracetamol was explained, at least in part, by confounding factors [27]. They concluded that there were many arguments that suggested a relationship between the use of paracetamol with the appearance of asthmatic symptoms, however the evidence was inconclusive [27].

Fan et al. [28] conducted a systematic review and meta-analysis. A total of 13 articles of more than 1,043,109 individuals were included in the meta-analysis. A statistically significant association between prenatal paracetamol exposure and child asthma risk was found [28]. The data showed that prenatal paracetamol exposure could increase the risk of child asthma (OR 1.19, 95% CI 1.12-1.27, P<0.00001) in a random-effect model [28]. Six studies reported paracetamol exposure during the first trimester of pregnancy [28]. Fan et al. [28] found that paracetamol exposure during the first trimester of pregnancy was associated with increased risk of child asthma (OR 1.21, 95% CI 1.14-1.28, P<0.00001) [28]. Furthermore, Fan et al. [28] observed that paracetamol exposure during the 2-3 trimesters of pregnancy was also associated with child asthma risk (OR 1.13, 95% CI 1.04-1.23, P=0.005) [28].

Castro-Rodriguez et al. [29] retrieved systematic reviews on these topics in children (aged 1 to 18 years) to summarize the principal findings on risk and protective factors for childhood asthma. They drew two articles [26,30] and concluded as follows: Current findings do suggest mild-to-moderate causal effects of certain modifiable behaviors or exposures during pregnancy (maternal weight gain or obesity, maternal use of antibiotics or paracetamol, and maternal stress), the perinatal period (birth by Caesarean delivery), or postnatal life (severe respiratory syncytial virus infection, overweight or obesity, indoor exposure to mold or fungi, and outdoor air pollution) on childhood asthma, but this suggestive evidence must be confirmed in interventional studies or (if interventions are not feasible) well-designed prospective studies [29].

A systematic review and meta-analysis was undertaken of studies reporting the association between paracetamol use in pregnancy and subsequent asthma in childhood [30]. The pooled random effects OR for the risk of current wheeze in the children of women who were exposed to any paracetamol during any stage of pregnancy was 1.21 (95% CI 1.02-1.44) [30].

A systematic review and meta-analysis of longitudinal studies reported that any paracetamol use during the first trimester was related to increased risk of childhood asthma (5 studies, pooled OR 1.39, 95% CI 1.01-1.91) but there was marked between-study heterogeneity (I(2)=63%) and only one of these studies adjusted for maternal respiratory tract infections [26]. However, the association during early pregnancy exposure was highly variable between studies and exposure during infancy appears to be moderately confounded by respiratory tract infections [26]. The authors concluded that there was insufficient evidence to warrant changing guidelines on early life paracetamol exposure at this time [26].

The Spanish Pediatric Societies reported that current evidence was insufficient to discourage the use of paracetamol during gestation or in children with or at risk of asthma [31].

Decreased atopy

The Family Atherosclerosis Monitoring in early life study is a general, population-based Canadian birth cohort that prospectively evaluated prenatal and early-life traits and their association with atopy and/or allergic disease [32]. The study population included 901 babies, 857 mothers and 530 fathers [32]. Prenatal maternal exposure to dogs (OR 0.60, 95% CI 0.42-0.84) and acetaminophen (OR 0.68, 95% CI 0.51-0.92) was associated with decreased atopy [32].

Fetal activity

A longitudinal study was performed in 20 women between 30 and 34 weeks' gestation with uncomplicated pregnancies [33]. A 1-hour ultrasound was performed and recorded to document baseline fetal breathing and body movements [33]. All the subjects were then given a 1,000 mg dose of oral acetaminophen [33]. One hour later, a second 1 hour ultrasound was performed [33]. There was no significant effect of acetaminophen on the number of episodes or time spent in fetal breathing or body movements when each activity parameter was analyzed separately [33]. In addition, there was no effect when fetal breathing and body movements were combined into a single composite activity score [33].

Discussion

An article of Ystrom et al. [13] is worthy of attention because paternal preconception acetaminophen use is associated with ADHD. I believe that it indicates the risk of acetaminophen to the fetus.

The safety evaluation and recommendation of acetaminophen are greatly different.de Fays reported that no firm conclusion could be made on the relevance of published epidemiological studies to humans and paracetamol was still to be considered safe in pregnancy and should remained the first-line treatment for pain and fever in the context of current knowledge [34]. Hoover et al. [15] reported that acetaminophen was a preferred option for pain management during pregnancy when compared with other medications such as nonsteroidal anti-inflammatory drugs or opioids for pyretic or pain relief [15]. Vlenterie et al. [7] reported that caution was warranted when considering long-term use of paracetamol during pregnancy; however, women with severe pain conditions should not be deprived of appropriate pharmacotherapy. Aminoshariae et al. [1] reported that available evidence suggested that indiscriminate usage of this drug was not warranted and its administration to a pregnant patient should be considered with great caution. A review reported as follows [35]: Nine prospective cohort studies fulfilled all inclusion criteria. Data pooling was not appropriate due to heterogeneity in outcomes [35]. All included studies suggested an association between prenatal acetaminophen exposure and the neuro developmental outcomes; ADHD, ASD, or lower IQ [35]. Longer duration of acetaminophen use was associated with increased risk [35]. Associations were strongest for hyperactivity and attention-related outcomes [35]. Little modification of associations by indication for use was reported [35].

Long-term use and/or a lot of usage probably increase the occurrence of adverse effects. Critical point of occurrence of adverse effects is unknown. Because some articles reported the relationship between the number of days of medication and occurrence of adverse effects, it is reviewed. Longer exposure (i.e., use for >20 weeks in gestation) increased the risk of ASD or infantile autism with hyperkinetic symptoms almost twofold [5]. Exposure during 8-14 weeks of gestation, but not any other period, was associated with shorter AGD [20]. Prenatal exposure for more than 28 days

had poorer gross motor development, externalizing behavior, internalizing behavior, and higher activity levels [4]. Short-term exposure (1-27 days) also had poorer gross motor outcomes, but the effects were smaller than with long-term use [4]. Long-term (≥ 28 days) exposure was associated with communication problems and delayed motor milestone attainment [7]. Short-term exposure (<28 days) was not associated with increased risks [7]. Exposure for more than 20 days showed significant differences in DNA methylation compared to exposure for less than 20 days [12]. HR of ADHD for more than 29 days of maternal acetaminophen use was 2.20 [13]. Use for <8 days was negatively associated with ADHD [13]. Acetaminophen use for fever and infections for 22 to 28 days was associated with ADHD (HR 6.15, 95% CI 1.71-22.05) [13]. Short-term (1-7 days) paternal preconception use was not negatively associated with ADHD; paternal use for 29 days or more and 8-28 day was associated with ADHD [13]. Based on these articles, exposure for 29 day or more is probably danger. However, we cannot assert that exposure for 28 day or less is safe. Bornehag et al. [17] reported that the a aOR for LD among girls whose mothers reported >6 (3,000 mg) *vs*. 0 acetaminophen tablets was 5.92 (95% CI 1.10-31.94). Daily dose or cumulative dose may affect the results. Acetaminophen should be used at the lowest effective dosage and for the shortest time.

At the present moment, any public organizations or academic associations have not declared the danger of acetaminophen in pregnancy. In 2013, the Spanish Pediatric Societies reported that current evidence was insufficient to discourage the use of paracetamol during gestation or in children with or at risk of asthma [31]. In 2015, the U.S. Food and Drug (FDA) announced it has reviewed possible risks of pain medicine use during pregnancy and stated: "Based on our evaluation of these studies, we believe that the weight of evidence is inconclusive regarding a possible connection between acetaminophen use in pregnancy and ADHD in children [36]." The FDA did not subsequently make a statement about safety (or danger) of acetaminophen in pregnancy. In 2017, the Society for Maternal-Fetal Medicine: Publications Committee made a statement about safety of acetaminophen in pregnancy [37]. I am afraid that the cited articles ([4,10], etc.) are only one part of articles which showed risks of acetaminophen in pregnancy. I sent a letter to the editor, however, it was rejected. In 2017, the letter to the editor was published as a review in Scandinavian Journal of Pain [38].

Many articles that showed the danger of acetaminophen in pregnancy was published after my article [38] were published. We cannot conduct a meta-analysis of different adverse effects such as CP, ADHD, ASD, asthma, and low IQ scores. Each article has poor power to show risks of acetaminophen, however, the integration of the articles that showed adverse effects of acetaminophen may have power to show them.

We should recognize that acetaminophen is danger in pregnancy. However, it does not mean the prohibition of the use of acetaminophen. Acetaminophen is the safest medicine as analgesics for nociceptive pain and antipyretics in childhood and pregnancy [38]. There is no alternative medication of acetaminophen. Acetaminophen should not be withheld from children or pregnant women for fears it might develop adverse effects. Fever and pain during pregnancy themselves are probably associated with adverse gestational outcomes. Evidence of acetaminophen risks is inconclusive. However, the warning is necessary about acetaminophen use in childhood and pregnancy. For example, few physicians recognize fibromyalgia and some pregnant women with fibromyalgia receive acetaminophen over a long period in Japan. Acetaminophen is not effective for non-nociceptive pain (neuropathic pain) such as fibromyalgia, but effective for nociceptive pain. Acetaminophen should be used at the lowest effective dosage and for the shortest time. We should recognize risks of acetaminophen. When we know the possible, rare but serious complications, we should use acetaminophen in pregnancy only when needed and no safer option for pain or fever relief is available. Health care providers should help inform the general lay public about this difficult dilemma.

To my knowledge, any obstetricians do not explain the adverse effects of acetaminophen to pregnant women and some pregnant women receive acetaminophen over a long period. In order to protect the fetus, I would like public organizations or academic associations to declare danger (or safety) of acetaminophen in pregnancy.

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