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Original article

Prenatal acetaminophen use in women with autoimmune disorders and adverse pregnancy and birth outcomes

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Abstract

Objectives. Most women may have temporary pain for which they use analgesics, but those with autoimmune disorders have chronic pain that may be exacerbated for some during pregnancy. This study aimed to determine whether prenatal acetaminophen use was associated with an increased risk of adverse pregnancy and birth outcomes in women with autoimmune disorders.

Methods. Participants were enrolled between 2004 and 2018 in the MotherToBaby cohort study and limited to women with an autoimmune disorder ($n = 1821$). Self-reported acetaminophen use was characterized over gestation for indication, timing of use and duration. Cumulative acetaminophen use through 20 and 32 weeks was categorized into quintiles, with no acetaminophen use as the reference category. The association between acetaminophen quintile and preeclampsia or pregnancy-induced hypertension, small for gestational age and preterm birth was examined using adjusted multiple log-linear regression.

Results. Overall, 74% of women reported acetaminophen use during pregnancy. The most often reported indication for using acetaminophen was headache/migraines, followed by pain and injury. Risk of preeclampsia was 1.62 (95% CI: 1.10, 2.40) times greater for those in the fifth quintile of cumulative acetaminophen use through 20 weeks compared with those with no acetaminophen use. There were no associations with lower use quintiles, nor for the other outcomes.

Conclusion. The highest quintile of cumulative acetaminophen was associated with a modestly increased risk for preeclampsia. Some women with autoimmune conditions have pain throughout pregnancy; clinicians and patients should discuss approaches to best avoid high levels of acetaminophen in their pain management strategies.

Key words: acetaminophen, prenatal, autoimmune, preterm birth, preeclampsia, small for gestational age

CLINICAL SCIENCE

Rheumatology key messages

- Seventy-four per cent of pregnant women with autoimmune conditions used acetaminophen.
- Increased risk of preeclampsia and pregnancy-induced hypertension was noted for the highest dosage of acetaminophen.
- Guidelines on frequency and quantity of acetaminophen use during pregnancy need to be clarified.

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Introduction

Approximately 40–65% of pregnant women use acetaminophen at some point in their pregnancy [1–7]. Physicians, particularly in the USA, frequently and routinely suggest the use of acetaminophen for a wide range of conditions during pregnancy when other analgesics are contraindicated [7]. Two previous studies from a cohort in Denmark reported an increased risk of preeclampsia [8, 9] and preterm birth [8], with no increased risk of small for gestational age or low birthweight offspring.

A recent study reported that the highest dosage of acetaminophen among women from the general population was reported by women using it for sleep, and the most frequent indications of use were arthritis, injury and pain [7, 10]. Pain management during pregnancy can be particularly challenging for women with autoimmune conditions, as several of the medications used to control underlying disease outside of pregnancy are contraindicated (e.g. MTX) [11]. In addition, other medications used for symptom management are associated with adverse pregnancy outcomes. Oral corticosteroids may be associated with preterm birth [11, 12], gestational hypertension and gestational diabetes [11, 13]. NSAIDs are often used for symptom management outside of pregnancy, but have been associated with increased risk of spontaneous abortion in early pregnancy, as well as premature closure of the ductus arteriosus with third trimester use [13]. Due to these limitations, women with autoimmune conditions that contribute to pain and/or inflammation may use more acetaminophen during pregnancy than women without autoimmune conditions. Previous studies report increased risk of adverse birth outcomes among women with RA [14, 15], IBD [16, 17] and SLE [18, 19]. However, little consideration has been given to whether acetaminophen use in women with autoimmune conditions increases the risk of these outcomes.

This study had two primary aims. First, to characterize the prevalence and predictors of acetaminophen use in pregnant women with autoimmune conditions. Second, to determine whether acetaminophen use is associated with adverse pregnancy and birth outcomes, including preterm birth, small for gestational age and preeclampsia, in women with autoimmune conditions.

Methods

Study population

The MotherToBaby study is a prospective cohort study with the objective of evaluating a variety of adverse pregnancy and birth outcomes in women who are pregnant and exposed to diseases or therapeutic agents relative to those who were unexposed. The study population is composed of pregnant women recruited in the USA or Canada through invitation after contacting MotherToBaby counselling, their health care provider, or internet and social media. Women were enrolled between 2004 and 2018 and completed up to four telephone surveys assessing maternal factors, medical history, exposures and pregnancy complications. An outcome interview updated late gestation information and pregnancy outcomes. Medical records from obstetricians and specialty providers were requested and used to validate maternal report when possible. This study was restricted to participants who had a live birth, enrolled prior to 20 weeks of gestation and reported an autoimmune disorder (RA, psoriasis, IBD, SLE, other: multiple sclerosis, type I diabetes, antiphospholipid syndrome, celiac disease, Raynaud's syndrome, Sjögren's syndrome) ($n = 1827$) at baseline. After excluding five women missing gestational weeks at birth and one woman having a gestational age under 20 weeks, the final sample consisted of 1821 women. The University of California, San Diego Institutional Review Board approved the MotherToBaby pregnancy study, and all women previously provided informed consent.

Study exposure

All medications, including non-prescription medications, were self-reported at each phone interview, including start and stop dates, frequency, dosage and reason for use (indication). We created daily diaries specific to acetaminophen use by overlaying all reports of acetaminophen use (including acetaminophen containing products) and the corresponding dosages onto a gestational calendar from estimated last menstrual period through delivery. Daily dose of acetaminophen was calculated from the frequency and reported dosage. In the instance of multiple acetaminophen-containing products used in the same day, dosages were summed. The cumulative dose of acetaminophen use at both 20 weeks of pregnancy (for preeclampsia models) and 32 weeks of pregnancy (for preterm birth and small for gestational age models) was summed.

Study outcomes

Women in the MotherToBaby study completed an outcome interview that captured gestational age at delivery, birthweight of the baby and updated information on preeclampsia/pregnancy-induced hypertension. The risk of preeclampsia begins at 20 weeks; thus acetaminophen use prior to 20 weeks was assessed. To ensure all women had the same potential for exposure when assessing small for gestational age and preterm birth, cumulative acetaminophen use through 32 weeks was assessed. Deliveries prior to 32 weeks were excluded from analyses. The mother was the unit of analysis for preeclampsia and preterm birth models. For the 68 multiple births in the cohort, the infant was the unit of analysis in models of small for gestational age.

Covariates

Covariates included self-reported asthma, diabetes, arthritis, IBD, psoriasis, SLE, other autoimmune diseases, hypertension, depression, fibromyalgia, anxiety and other mental health disorders (all yes/no). Information on demographic, anthropometric and behavioral characteristics included maternal age, race (White, Black, Asian, Other), ethnicity (Hispanic/non-Hispanic), years of education (categorical), high/low socioeconomic status classified by Hollingshead criteria (high/low), prepregnancy body mass index and tobacco use during gestation (yes/no). Medications used for autoimmune disorders, including oral corticosteroids, conventional

synthetic (cs)DMARDs and/or biologic (b)DMARDs, and asthma medications were summarized according in 20- and 32-week use, corresponding to the outcome specific exposure window.

Statistical analysis

From cumulative dose of acetaminophen through 20 and 32 weeks, we categorized exposure into quintiles. Quintiles were selected due to the wide range of dosages; smaller categories had excessive variation between the lowest and highest dosage within a range, but quintiles provided ranges of acetaminophen that allowed for meaningful interpretation of the results. Comparison of covariates by the cumulative exposure quintiles at 32 weeks was performed with χ^2 analysis for categorical variables and ANOVA for continuous variables. Descriptive statistics were used to evaluate trends across time from 2004 to 2018 in the prevalence of acetaminophen use overall and by trimester, using Cochran–Armitage trend tests. Prevalence of acetaminophen use by trimester (any/none) as well as numbers of trimesters of use were described. To examine indications for acetaminophen use, text-string mining using a pattern match function to group indications was used. Once groups of indications were identified, the median daily dose and median number of days of use were calculated by indication. Separate multivariable log-linear regressions with robust standard errors were used to estimate adjusted risk ratios for each outcome. The reference was no acetaminophen use. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

The cohort was composed of women with autoimmune disorders, which were predominantly RA and IBD (Table 1). Slightly more than half of participants were using a csDMARD and/or bDMARD, and 34% were using oral corticosteroids for symptom control. Between 2004 and 2018, 74% of pregnant women with autoimmune conditions in the MotherToBaby study used acetaminophen at some point in pregnancy. Over this time period, there was a significant decline in the prevalence of acetaminophen use during pregnancy (Fig. 1), with prevalence of acetaminophen use decreasing from 81.7% to 68.4% ($P < 0.01$). Additionally, there was a decrease of acetaminophen use during the first ($P < 0.01$) and second trimesters ($P < 0.01$), but there was no change in the prevalence of third trimester acetaminophen use ($P = 0.18$).

The majority (78.6%) of women who used acetaminophen used it in their first trimester of pregnancy (Table 2). Additionally, the majority of acetaminophen users reported using acetaminophen in only one trimester of pregnancy (37.9%), followed by those reporting use in all three trimesters (34.4%). The most commonly reported reasons women with autoimmune disorders took acetaminophen during pregnancy was for headaches or migraines ($n = 890$), followed by pain/injury ($n = 482$) and RA ($n = 357$), as shown in Table 3. The highest dosage was reported among women using acetaminophen for cold/flu/sinus infection (537.3 mg/day), followed by fever (500.0 mg/day), and pain/injury and RA (median dosage in both was 487.5 mg/day).

When assessed through 20 weeks of use, 31% of women had no use. The other quintiles had ranges of 163–650, 661–983, 2000–5850, 5896–20 000 and 20 057–490 000 mg. When assessing cumulative use through 32 weeks, 26% ($n = 473$) of women had no use. Exposures per quintile were as follows: 163–975, 1000–2750, 2780–7467, 7475–29 668 and 30 000–784 000 mg. Of note, a standard capsule contains 325 mg of acetaminophen, Extra Strength contains 500 mg, for a typical dose of 650–1000 mg. In the lower quintiles, the ranges correspond to 0.5 capsules taken one time over 20 weeks. In the highest category, the upper range was reported as taking 3500 mg/day across 32 weeks of pregnancy, or seven capsules of Extra Strength acetaminophen taken every day for 32 weeks of pregnancy, which was verified through the participant's self-report of medication intake. As acetaminophen use increased (Table 1), education level decreased, while BMI category, alcohol and tobacco use increased. Neither race/ethnicity nor socioeconomic status differed by acetaminophen quintile. Prevalence of hypertension, fibromyalgia, RA, SLE and IBD increased as acetaminophen use increased. Prevalence of mental health conditions, including depression, anxiety and other mental health conditions all increased as acetaminophen use increased. Lastly, prevalence of use of oral corticosteroids and asthma medications increased as quintiles of acetaminophen increased. There was no clear pattern between prevalence of csDMARD and/or bDMARD use and cumulative use of acetaminophen.

Among women with autoimmune disorders, acetaminophen use in the fifth quintile was associated with 1.62 (95% CI: 1.10, 2.40) times greater risk of preeclampsia or pregnancy-induced hypertension relative to no acetaminophen use (Table 4). Results for all other quintiles crossed the null. There was no association between acetaminophen use and small for gestational age offspring or preterm birth.

Discussion

In this study, 74.0% of women used acetaminophen, which is higher than that among the general population of pregnant women (62%) [10] from this same birth cohort. Women with autoimmune conditions in the highest quintile of acetaminophen use in this study had a 62% (95% CI: 1.10, 2.40) greater risk of preeclampsia or pregnancy-induced hypertension compared with women with no acetaminophen use. There was no increased

Table 1 Maternal characteristics by acetaminophen use among women with an autoimmune condition in the MotherToBaby cohort

Characteristic	No acetaminophen use	Cumulative acetaminophen use at 32 weeks				
		1st quintile (163–975 mg)	2nd quintile (1000–2750 mg)	3rd quintile (2780–7467 mg)	4th quintile (7475–29 668 mg)	5th quintile (30 000–784 000 mg)
	n = 473 (26.0%)	*n* = 276 (15.2%)	*n* = 263 (14.4%)	*n* = 270 (14.8%)	*n* = 270 (14.8%)	*n* = 269 (14.8%)
Maternal characteristics						
Gestational age at enrolment, mean (S.D.), weeks	12.2 (4.4)	12.1 (4.2)	11.8 (4.3)	12.2 (4.5)	11.6 (4.2)	11.8 (4.3)
Maternal age, mean (S.D.), years	32.8 (4.4)	32.4 (4.4)	32.5 (4.6)	32.6 (4.7)	32.7 (4.5)	32.9 (4.4)
Pre-pregnancy BMI, *n* (%)						
$<$24.9 mg/kg^2	304 (64.4)	161 (58.3)	170 (64.6)	155 (57.6)	138 (51.3)	135 (50.4)
25–29.9 mg/kg^2	100 (21.2)	59 (21.4)	52 (19.8)	57 (21.2)	69 (25.7)	73 (27.2)
$\geq$30 mg/kg^2	68 (14.4)	56 (20.3)	41 (15.6)	57 (21.2)	62 (23.1)	60 (22.4)
Missing, *n*	1	0	0	1	1	1
Education, *n* (%)						
Less than high school	12 (2.5)	1 (0.4)	3 (1.1)	1 (0.4)	3 (1.1)	6 (2.2)
High school graduate/trade school	28 (5.9)	16 (5.8)	10 (3.8)	16 (5.9)	13 (4.8)	32 (11.9)
Some college	89 (18.8)	63 (22.8)	53 (20.2)	52 (19.3)	65 (24.1)	76 (28.3)
College degree	185 (39.1)	119 (43.1)	107 (40.7)	118 (43.7)	91 (33.7)	94 (34.9)
Post-college graduate	159 (33.6)	77 (27.9)	90 (34.2)	83 (30.7)	98 (36.3)	61 (22.7)
Race/ethnicity, *n* (%)						
Non-Hispanic White	383 (81.7)	232 (85.3)	219 (84.6)	233 (86.6)	225 (84.3)	222 (83.2)
Non-Hispanic Black	14 (3.0)	14 (5.2)	10 (3.9)	9 (3.4)	8 (3.0)	9 (3.4)
Hispanic	47 (10.0)	17 (6.3)	21 (8.1)	16 (6.0)	24 (9.0)	23 (8.6)
Asian	15 (3.2)	5 (1.8)	7 (2.7)	10 (3.7)	6 (2.3)	5 (1.9)
Pacific Islander/Native American	6 (1.3)	4 (1.5)	2 (0.8)	1 (0.4)	4 (1.5)	6 (2.3)
Other	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Missing, *n*	4	4	4	1	3	2
Socioeconomic status, *n* (%)						
Low	29 (6.3)	17 (6.2)	21 (8.1)	9 (3.4)	15 (5.7)	25 (9.5)
High	432 (93.7)	256 (93.8)	240 (92.0)	255 (96.6)	248 (94.3)	239 (90.5)
Missing	12	3	2	6	7	5
Alcohol during pregnancy, *n* (%)	197 (41.7)	108 (39.1)	118 (44.9)	120 (44.4)	143 (53.0)	120 (44.6)
Tobacco during pregnancy, *n* (%)	24 (5.1)	30 (10.9)	14 (5.3)	19 (7.0)	23 (8.5)	36 (13.4)

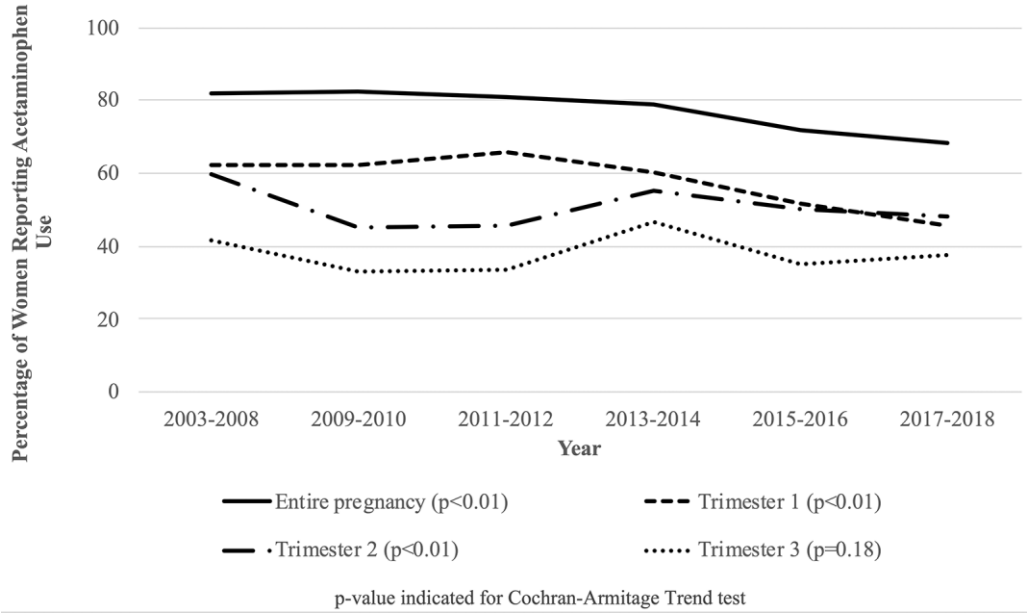
(continued)

Table 1 Continued

Characteristic	No acetaminophen use	Cumulative acetaminophen use at 32 weeks				
		1st quintile (163–975 mg)	2nd quintile (1000–2750 mg)	3rd quintile (2780–7467 mg)	4th quintile (7475–29 668 mg)	5th quintile (30 000–784 000 mg)
	n = 473 (26.0%)	*n* = 276 (15.2%)	*n* = 263 (14.4%)	*n* = 270 (14.8%)	*n* = 270 (14.8%)	*n* = 269 (14.8%)
Medical comorbidities, *n* (%)						
Hypertension	38 (8.0)	28 (10.1)	20 (7.6)	28 (10.4)	31 (11.5)	37 (13.8)
Asthma	96 (20.3)	54 (19.6)	41 (15.6)	50 (18.5)	67 (24.8)	68 (25.3)
Type II diabetes	20 (4.2)	8 (2.9)	5 (1.9)	11 (4.1)	10 (3.7)	10 (3.7)
Fibromyalgia	6 (1.3)	7 (2.5)	5 (1.9)	7 (2.6)	9 (3.3)	21 (7.8)
Autoimmune disorder, *n* (%)						
IBD	145 (30.7)	91 (33.0)	99 (37.6)	98 (36.3)	74 (27.4)	65 (24.2)
Psoriasis	89 (18.8)	54 (19.6)	42 (16.0)	37 (13.7)	49 (18.2)	44 (16.4)
RA	240 (50.7)	147 (53.3)	119 (45.3)	139 (51.5)	149 (55.2)	178 (66.2)
SLE	14 (3.0)	2 (0.7)	6 (2.3)	7 (2.6)	10 (3.7)	15 (5.6)
Other autoimmune disease	105 (22.2)	54 (19.6)	58 (22.1)	67 (24.8)	65 (24.1)	53 (19.7)
Mental health comorbidities, *n* (%)						
Depression	90 (19.0)	50 (18.1)	45 (17.1)	60 (22.2)	77 (28.5)	83 (30.9)
Anxiety	71 (15.0)	30 (10.9)	37 (14.1)	47 (17.4)	50 (18.5)	57 (21.2)
Other mental health conditions	25 (5.3)	9 (3.3)	4 (1.5)	15 (5.6)	13 (4.8)	31 (11.5)
Other medications, *n* (%)						
Asthma medications	33 (7.0)	23 (8.3)	11 (4.2)	20 (7.4)	25 (9.3)	32 (11.9)
Oral corticosteroids	124 (26.2)	105 (38.0)	74 (28.1)	91 (33.7)	106 (39.3)	128 (47.6)
Disease modifying antirheumatic	216 (45.7)	167 (60.5)	140 (53.2)	133 (49.3)	142 (52.6)	154 (57.3)

The univariate analysis of sociodemographic characteristics shows that there was an association between quintile of acetaminophen use and education, prepreganacy BMI, anxiety, depression, fibromyalgia, other mental health conditons, RA, SLE, hypertension, fibromyalgia, asthma medications and oral corticosterioids. Additionally, it shows the majority of the study cohort was well educated, white women in the high socioeconomic status category.

Fig. 1 Prevalence of acetaminophen use among women with an autoimmune condition by trimester



Acetaminophen use in pregnant women with an autoimmune condition decreased from the start of the mother to baby cohort in 2003 to 2018. When examining acetaminophen use by trimester, we see that acetaminophen use decreased across in the first and second trimesters, but not in the third trimester.

Table 2 Prevalence of acetaminophen use by trimester of pregnancy among women with an autoimmune condition

Indication	*n*	% of full sample (*n* = 1821)	% of acetaminophen users (*n* = 1348)
Any acetaminophen use			
Trimester 1	1060	58.2	78.6
Trimester 2	938	51.5	69.6
Trimester 3	695	38.2	51.6
Number of trimesters of use			
Use in one trimester	511	28.1	37.9
Use in two trimesters	395	21.7	29.3
Use in all three trimesters	464	25.5	34.4

The majority of pregnant women with autoimmune conditions took acetaminophen in their first trimester of pregnancy, and then the second trimester was the next most common response. When examining if acetaminophen was used in all trimesters compared with only one or two trimesters, the largest proportion of women took acetaminophen in only one trimester, with all three trimesters being the second largest proportion.

risk of small for gestational age offspring or preterm birth.

Acetaminophen use during pregnancy in this cohort significantly declined from 81.7% in 2004 to 68.4% in 2018 ($P < 0.01$), and this was particularly true for any acetaminophen use in the first and second trimesters of pregnancy. The decrease in acetaminophen use during this time observed for women in this study is similar to the trend seen among all pregnant women [10] and may be due to the increasing number of warnings about the harmful effects of acetaminophen on the liver in recent years [20, 21], although none of the warnings specifically targeted pregnant women. Most women in this study used acetaminophen during their first trimester of pregnancy (77.4%), which could be due to women taking it before they realized they were pregnant or believing it would minimally affect the fetus. Alternatively, some autoimmune disorders remit in pregnancy for a subset of individuals [22], which may have contributed to declining use as pregnancy progressed.

In addition to musculoskeletal pain, previous literature demonstrates that women with chronic inflammatory

Table 3 Most common indications for acetaminophen and mean cumulative use through 37 weeks of pregnancy

Indication	*n*[a]	Daily dose of acetaminophen, median, mg	Number of days acetaminophen taken, median
Headache/migraines	890	371.7	7.0
Pain/injury	482	487.5	26.0
RA	357	487.5	55.0
Cold/flu/sinus infection	255	537.3	6.0
Fever	124	500.0	4.5
Sleep	30	394.5	103.0
Cramps	21	325.0	15.0

[a]Women can report >1 indication for acetaminophen use. The most common reported reason for women with autoimmune conditions to take acetaminophen during pregnancy was for headaches and migraines, followed by pain and injury. However, the highest median daily dose of acetaminophen was reported for cold, flu or sinus infections followed with the second highest median daily dose being used for fever. When looking at the number of days a woman with an autoimmune disorder took acetaminophen during pregnancy, the highest number of median days was for sleep, followed by RA.

Table 4 Relative risk by quintile of cumulative acetaminophen use in the MotherToBaby cohort, 2004–2018

Model	Outcome, *n* (%)	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)	Test for trend (adjusted model)
Preeclampsia and pregnancy-induced hypertension[b]				
No acetaminophen use	47 (8.5)	1.00 (reference)	1.00 (reference)	**0.02**
1st quintile	26 (10.1)	1.19 (0.75, 1.88)	1.09 (0.69, 1.71)	
2nd quintile	25 (10.6)	1.26 (0.79, 1.99)	1.21 (0.77, 1.90)	
3rd quintile	28 (11.1)	1.31 (0.84, 2.04)	1.16 (0.74, 1.82)	
4th quintile	30 (12.0)	1.42 (0.92, 2.18)	1.26 (0.82, 1.92)	
5th quintile	43 (17.3)	**2.04 (1.39, 3.00)**	**1.62 (1.10, 2.40)**	
Small for gestational age				
No acetaminophen use	42 (9.0)	1.00 (reference)	1.00 (reference)	0.79
1st quintile	25 (8.8)	0.98 (0.58, 1.64)	0.98 (0.59, 1.63)	
2nd quintile	17 (6.5)	0.72 (0.41, 1.27)	0.70 (0.39, 1.26)	
3rd quintile	23 (8.5)	0.95 (0.57, 1.56)	0.90 (0.54, 1.51)	
4th quintile	25 (9.2)	1.02 (0.61, 1.71)	0.96 (0.57, 1.59)	
5th quintile	31 (11.4)	1.27 (0.81, 1.99)	1.10 (0.68, 1.79)	
Pre-term birth				
No acetaminophen use	49 (10.6)	1.00 (reference)	1.00 (reference)	0.86
1st quintile	37 (13.6)	1.28 (0.86, 1.91)	1.18 (0.79, 1.76)	
2nd quintile	23 (8.9)	0.84 (0.52, 1.35)	0.86 (0.53, 1.38)	
3rd quintile	25 (9.4)	0.89 (0.56, 1.40)	0.83 (0.53, 1.32)	
4th quintile	30 (11.4)	1.07 (0.70, 1.64)	0.94 (0.60, 1.45)	
5th quintile	42 (16.1)	**1.52 (1.03, 2.23)**	1.20 (0.81, 1.78)	

[a]Adjusted for maternal age, tobacco use, race/ethnicity, pre-pregnancy BMI, depression, anxiety, other mental health disorders, arthritis, IBD, SLE, other autoimmune diseases, oral corticosteroids, and disease modifying antirheumatic. [b]Uses cumulative dose of acetaminophen at 20 weeks of pregnancy. Bold text indicates statistical significance. The models by quintile of acetaminophen use show risk of developing preeclampsia among women with an autoimmune disorder is 1.62 (95% CI: 1.10, 2.40) times greater for those in the fifth quintile of acetaminophen use compared with those with no acetaminophen use. Additionally, there was a positive test for trend for the preeclampsia and pregnancy-induced hypertension model across quintiles of acetaminophen use. There was no association between small for gestational age or preterm birth with acetaminophen use in the adjusted models. RR: relative risk.

rheumatic diseases are almost two times more likely to experience migraine headaches than the general population [23]. Indeed, the most commonly reported indications for acetaminophen use in this cohort were headaches/migraines, followed by pain/injury. This is in accord with our previous findings [10] among the full

pregnancy cohort, in which the main reason for acetaminophen use was for headaches or pain. In this study of women with autoimmune conditions, the highest dosage of acetaminophen was taken for fever; however, median duration of use was short (4.5 days). The largest median number of days of acetaminophen use was for sleep during pregnancy (103 days), which was also observed in our previous work [10]. It is unclear whether it is understood by individuals using preparations for sleep such as Tylenol PM that it contains acetaminophen, and other therapies for sleep should be discussed with clinicians.

The increased risk of preeclampsia and pregnancy-induced hypertension among women who used acetaminophen in their third trimester has been seen among women in the Danish National Birth Cohort [9]. An acetaminophen–preeclampsia or pregnancy-induced hypertension association is biologically plausible as acetaminophen changes the oxidative state of the enzyme prostaglandin endoperoxide H_2 synthase [24–26]. Thus, acetaminophen potentially results in the increased risk in preeclampsia, particularly at high dosages. 'It should be noted that due to a variety of immunogenetic factors, exacerbated systemic endothelial dysfunction in the mother's vasculature may result in progression of preeclampsia, and acetaminophen use may therefore be a result of aggravated inflammation' [27]. Although we tried to mitigate reverse causation by only summarizing acetaminophen through 20 weeks in models of preeclampsia, we cannot rule out the possibility that early pathogenesis of preeclampsia resulted in use of acetaminophen.

Strengths of the study include the data source, which captures detailed self-report of over-the-counter and prescription medications. Our group has previously reported that for medications taken on an 'as-needed' basis, such as acetaminophen or oral corticosteroids, maternal report provides a more complete capture of use than reliance solely on medical records [28]. Further, MotherToBaby pregnancy studies request obstetric and specialty-provider medical records (with receipt in ~75% of pregnancies) to verify maternal-reported information, with protocols for resolution of discordant information.

Our findings should be considered in light of the limitations. Most women in this study were of high socioeconomic status, White, and had high levels of education, which may limit generalizability of these results to all women with autoimmune conditions. Further, over half of the participants were using csDMARDs (due to the study aims of the parent study) and/or bDMARDs, and thus may have had better controlled disease than women not using csDMARDs and/or bDMARDs and requiring less use of medications needed for symptom relief, including acetaminophen. Further, select autoimmune disorders as well as oral corticosteroids have been associated with preeclampsia [29, 30]. Although models were adjusted for the specific autoimmune disorder and oral corticosteroids, residual confounding by disease severity may be influencing our findings, particularly among individuals in the highest quintiles of use. Additionally, while this study enrolled a large sample size of women with autoimmune conditions, the adverse birth outcomes being assessed for this study are rare and lead to thin strata in the models. This could lead to imprecision of effect estimates for the outcomes of preeclampsia, small for gestational age and preterm birth. Lastly, NSAIDs, which are known to be associated with adverse outcomes [13] and are generally contraindicated during late-term pregnancy, were also not examined in this study, but future directions will look to quantify NSAID use in this population.

Women with autoimmune disorders have pain that may be exacerbated during pregnancy, prompting acetaminophen use. The results of this study show an increased risk of preeclampsia and pregnancy-induced hypertension for those who took the highest dosage of acetaminophen compared with no acetaminophen use. Therefore, women with autoimmune conditions who require high, prolonged use of acetaminophen during pregnancy should be monitored more closely for preeclampsia and hypertension, and pain management strategies should be discussed with their clinicians.

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Ethics: The University of California San Diego Institutional Review Board approved the study, and women provided oral and written informed consent.

Data availability statement

Due to prior commitments for access to the data from previous studies under which the data was collected, the raw data files cannot be posted online; however, investigators who wish to access the analytic code can contact G.B. at gbandoli@ucsd.edu.

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