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Acetaminophen use in pregnancy: examining prevalence, timing and indication of use in a prospective birth cohort

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Abstract

Background: Previous studies of prenatal acetaminophen use have not addressed what indications and maternal co-factors describe acetaminophen use.

Objective: The objective of this study is to describe these parameters in a well-characterized, prospective birth cohort.

Methods: Data were drawn from the MotherToBaby study of pregnant women enrolled from 2004–2018. Daily acetaminophen diaries were calculated for all exposed women with complete dose and duration information. Descriptive statistics were used to assess maternal characteristics associated with acetaminophen use. Prevalence by two-year interval was described, and linear regression was used to test for trend. Indication of use and dose per indication were summarized.

Results: Of 2,441 subjects 1,515 (62%) reported use of acetaminophen. Over the 15-year period, there was a decline in use of 2.5% for each 2-year period (test for trend= 0.001) with 58% reporting acetaminophen use in 2017–2018. Among women with acetaminophen use in pregnancy (n=1,515), 58% reported less than 10 days of use, 13% reported 10–19 days of use, 9% reported 20–44 days of use, and 9% reported 45 or more days of use. Twelve percent had undefined duration of use. Increasing duration of exposure was associated with tobacco use, obesity, self-reported depression or anxiety, and antidepressant use. The most frequently reported indication was headache, however, indication varied by duration of use, with more women reporting use for sleep or pain/injury in the categories with the longest duration of use. Median dose per exposed day was highest among those reporting use for sleep, and higher doses were more frequently reported for arthritis, injury and pain.

Conclusion: Acetaminophen is used by the majority of pregnant women, and some continue use for many weeks in pregnancy. Given the heterogeneity in duration of use, indication and dose, studies that estimate the risk of adverse outcomes associated with acetaminophen must carefully consider these factors.

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Keywords

Acetaminophen; pregnancy; prevalence; indications for use

Background

Pregnant women experience the same fevers, inflammation and pain during pregnancy that occur outside of pregnancy. Acetaminophen has been considered the preferred over-the-counter analgesic for use in pregnancy compared to the alternative non-steroidal anti-inflammatory drugs (NSAIDs) which have been associated with increased risks of select birth defects and premature closure of the ductus arteriosus.[1] It has been previously reported that between 40% and 65% of pregnant women use acetaminophen,[1–7] with estimates of 3% to 20% of women reporting use in all three trimesters.[3,8] An emerging set of studies have signaled modest, yet concerning associations between acetaminophen and select pregnancy and childhood adverse outcomes, including preeclampsia,[9,10] preterm birth,[9] asthma (review and meta-analysis[11]) and neurodevelopmental disorders[3–8,12–14] (review and meta-analysis[15]). However, interpretation of these findings as causally related to prenatal acetaminophen exposure has been problematic. Based on this ambiguity, specifically with respect to a reported increased risk of neurodevelopmental disorders, the Society for Maternal Fetal Medicine[16] and the U.S. Food and Drug Administration[17] have declined to update safety recommendations for acetaminophen use in pregnancy. These decisions were made in part due to the potential for confounding by indication and lack of information regarding gestational timing, frequency and dose of acetaminophen use in previous studies, all of which are critical in attributing causality to the exposure.

Given the widespread use of acetaminophen in pregnancy, the public health implications of previously reported relationships, if causal, are profound. In order to rigorously study the safety of prenatal acetaminophen exposure, it is necessary to understand the epidemiology of the exposure, particularly the indications for use, the frequency and timing of exposure, and comorbidities associated with use. The objective of this study was to use well-characterized data from the U.S. and Canada-wide MotherToBaby Pregnancy study to describe the use of acetaminophen in pregnancy. We specifically focused analyses on duration, dose and indication for use, and sociodemographic characteristics and comorbidities associated with higher levels of exposure with the goal of informing future epidemiologic studies of acetaminophen use during pregnancy and risk of maternal and child outcomes.

Methods

Description of the study cohort

MotherToBaby, a service of the Organization of Teratology Information Specialists, provides evidence-based information about the risks of medications, chemicals, herbal products, illicit drugs, and diseases in pregnancy. MotherToBaby also conducts prospective studies to assess a spectrum of adverse pregnancy and birth outcomes in pregnant women exposed to diseases or therapeutic agents relative to unexposed pregnancies. Details of study design and subject recruitment have been previously described.[18–22] Briefly, subjects residing in the United

States or Canada that speak English or Spanish are recruited through three primary mechanisms: 1) invitation to participate after a pregnant woman spontaneously contacts the MotherToBaby counseling service; 2) direct-to-healthcare provider promotion for specific diseases, or 3) direct-to-consumer recruitment through the Internet/social media.

Between 2004–2018, 4,233 women enrolled in MotherToBaby pregnancy study either as non-diseased controls for studies of women with autoimmune conditions or asthma, or for studies assessing vaccine safety (influenza, TDaP). Two hundred and fifty-six women (6%) were lost to follow up prior to delivery, either due to failure to respond to attempts to conduct scheduled interviews (62%) or withdrawal of consent (38%). As these individuals did not have the opportunity to provide full accounting of potential acetaminophen exposure, they were excluded from the sample. Women with autoimmune diseases or asthma were eligible to enroll in the influenza or TDaP vaccine studies. In order to report on a population representative of the general population, we randomly down-sampled women with autoimmune diseases and asthma to represent 3% and 10% of the study population, respectively.[23,24] The final analytic sample consisted of 2,441 women (Figure 1). The MotherToBaby pregnancy study was approved by the University of California, San Diego Institutional Review Board.

Study design and data collection

Upon enrollment in pregnancy, participants complete up to four telephone interviews to assess maternal characteristics, health history, pregnancy exposures and complications. An outcome interview is conducted at the end of pregnancy and a spectrum of adverse pregnancy and birth outcomes are captured from interview and medical records abstraction. In the enrollment interview, women are queried about their family medical history, previous pregnancy outcomes, socioeconomic and demographic characteristics of the woman and her partner, all prescription and non-prescription medication exposures during pregnancy, tobacco and alcohol use. In each subsequent interview, women update exposure histories, and pregnancy events. The exposure histories include start and stop dates, dose, dosage changes, frequencies and indications for all medications, herbal supplements, vitamins, occupational exposures, and prenatal care testing or other procedures.

Exposure and covariates

Exposures—Acetaminophen (as a single agent or from combination products) was quantified for all exposed women with complete dose and duration information. Daily exposure (yes/no): we created daily exposure diaries based on reported start and stop dates that were overlaid with last menstrual period (LMP) date to determine exact gestational timing. Daily diaries were created from day 0 (LMP) through 280 days; women who delivered prior to 280 days had stop dates as reported, while pregnancies that extended after 280 days were censored at Day 280. Multiple exposures to acetaminophen on the same day were collapsed. From the daily diary, information from all subjects with any acetaminophen exposure was summed into count variables of 1) any exposure, 2) any exposure in each of the three trimesters, 3) cumulative exposure categorized as <10 days, 10-<20 days, 20-<45 days, 45+ days. Dosage: for each exposure, subjects reported the number of units (e.g.- pills, mL, etc) and dosage of each unit, from which total dosage per administration was calculated.

In instances where dosage was not provided, dosage was calculated from the product type (e.g.- if a subject reports 2 pills of Excedrin® extra strength, the assigned dose was 250mg × 2= 500mg per administration). Daily dose diaries were then created from dosage information overlaid with daily exposure variables. Multiple exposures to acetaminophen in a single day were summed, and average dose per exposed day was calculated. Indication: for each reported exposure, women are asked to report the indication for exposure. Reported indications were attributed to categories: headache, pain, cold/flu, fever, migraine, sleep, injury, and arthritis. When multiple indications were reported for a single exposure (e.g.- pain and fever), all were coded.

Covariates—Covariates for description include maternal age, pre-pregnancy body mass index (BMI), education, race, Hollingshead socioeconomic status,[25] whether the pregnancy was planned, parity, number of previous spontaneous abortions, and number of previously terminated pregnancies. Subjects reported use of prenatal vitamins, and from start dates, we determined whether vitamins were started prior to LMP. Exposure to any alcohol in pregnancy, the last week of alcohol consumption in pregnancy, and tobacco use in pregnancy were reported. Additionally, antidepressant use during gestation was reported. With respect to comorbidities, a history of depression, anxiety, other mental health conditions, diabetes, hypertension, autoimmune disease, and asthma were self-reported. In 2016, the Edinburgh Postnatal Depression Scale (EPDS)[26] and the State Trait Anxiety Inventory (STAI)[27] were added to MotherToBaby studies at the enrollment visit to measure current symptoms of depression and anxiety, respectively. They were available for a subset of the study sample (n=160). The EPDS was dichotomized at 10 (mild depressive symptoms)[28] and the STAI-state score was dichotomized at 45 for symptoms of anxiety.[29,30]

Statistical analysis

Data were summarized by any use, and then by duration of use categories. The prevalence of any use, and any use by trimester was summarized into 2-year periods (with the exception of 2004–2008, which were collapsed into one category to maintain stability in the sample size). To test for linear trend across years, we performed linear regression with a continuous variable representing each 2-year increment. The prevalence of use in one, two or all three trimesters was reported. To assess maternal characteristics with exposure, univariate summaries were performed. Indications for use were summarized and reported by overall frequency and by duration of use. Average dose per exposed day was summarized by indication. All analyses were conducted in SAS 9.4. (SAS Institute, Cary, NC).

Results

Of 2,441 subjects in the analysis, 1,515 (62%) reported use of acetaminophen in pregnancy. Of the reported acetaminophen, 97% was over the counter and 3% was prescription. Regular Tylenol®/acetaminophen/paracetamol (75%) was the highest reported product, followed by extra strength Tylenol®(18%) and Tylenol® cold and sinus preparations (4%) (data not shown).

Prevalence by 2-year period and trimester of use

When examined by 2-year periods, there was a slight decline (2.5%/2-year period) in reported prevalence over time, with estimates as high as 70% in 2009–2010, reducing to 58% in 2017–2018 (Figure 2; P-trend=0.001). Prevalence of acetaminophen use was similar in the first or second trimesters over time (28–45% over the period), while use in the third trimester was consistently ~10% lower than first or second trimester use in each period.

Prevalence by trimester of use

Of women who reported any acetaminophen use with complete information on timing of use (Table 1), over two-thirds reported use in trimester 1, two-thirds reported use in trimester 2, and slightly over one-half reported use in the third trimester.

We also quantified use by the numbers of trimesters of use reported; of women who used acetaminophen, 40% used only in one trimester, 30% of women reported use in two trimesters, and 30% reported use in all three trimesters. Of women who reported use in all three trimesters (n=401), 30% used for less than 10 days total, 26% used for 10–20 days, 21% used for 20–44 days, and 23% used acetaminophen for 45 days or more in gestation. Further, of women who used acetaminophen for 20–44 days, only 61% used in all three trimesters, and of women with 45+ days of use, only 63% used acetaminophen across all three trimesters (data not shown).

Characteristic of women with any acetaminophen use

Women who used acetaminophen in pregnancy were more often obese (≥ 30 mg/kg^2), identified as White, and were multiparous (Table 2). They were more likely to use tobacco in pregnancy, and were more likely to report use of antidepressants in pregnancy. Acetaminophen users more often self-reported depression, anxiety, and other mental health conditions, although their current EPDS and STAI scores in the small subset with those measures available did not differ from women without acetaminophen use. Additionally, women who used acetaminophen in pregnancy were more likely to have hypertension, autoimmune conditions, and asthma.

Characteristics of women by duration of use

From those reporting use of acetaminophen, 177 (12%) did not provide complete information on start and stop dates and frequency of use to calculate duration and were classified as having ‘undefined’ exposure duration. From those with incomplete information, 9 were missing stop dates; the other 168 participants gave full start dates and stop dates, but only provided a frequency of ‘PRN’. From the 1,515 women who reported any use in pregnancy (Table 2), 58% reported less than 10 days of use, 13% reported between 10 and 19 days of use, 9% reported 20–44 days of use, 9% reported 45 or more days of exposure, and 12% had use of undefined duration. Of the four defined duration categories, women in the longest duration of use category were more likely to be obese and to use tobacco and antidepressants in pregnancy, and to self-report depression or anxiety. Women in the top two duration categories were more likely to identify as White, and women in the lowest duration of use category were more likely to be primiparous. The four categories of defined duration did not differ on other comorbidities, including EPDS or STAI scores.

Indication and dose

Among 1,515 women who reported acetaminophen use, 34 did not report an indication. Headaches were the top reported indications for use (50%), followed by pain (19%), cold or flu (17%), fever (8%), sleep or cramps (1% each; Table 3).

When indication was examined by duration of use (Table 4), the proportion of users with an indication of fever were higher in the lowest duration of use category and decreased with increasing duration. The proportions of reported indications in the middle two duration categories were fairly consistent, while the highest duration category had proportionally more users reporting sleep as an indication, as well as pain/injury. Women who were categorized as undefined duration of use were predominantly using acetaminophen for headaches or migraine.

When examining the average dose per exposed day (Table 3), the highest median dose was reported by those indicating use for sleep (910 mg/day). While the median doses for the other indications did not differ (650 mg/day), the interquartile ranges (IQR), signifying the heterogeneity in doses, was highest among women who reported indications of arthritis, injury and pain. The most commonly reported indication (headaches) had the least variability in dose (IQR=378 mg).

Comment

Principal findings: Acetaminophen is the most widely used medication during pregnancy; however, given the recent literature reporting associations with adverse pregnancy and offspring outcomes, it is critical to understand the frequency, timing, dose and indication for use. These parameters inform multivariable analysis when estimating the associated risk of adverse outcomes in the pregnancy and offspring, and to date, have not been adequately reported. We found an overall prevalence of 62% of women reporting any acetaminophen use in pregnancy between 2004–2018, although there was a linear decline in prevalence observed over this period. When characterized by duration, 58% of acetaminophen-exposed women reported less than 10 days of use, and 18% of acetaminophen exposed subjects reported greater than 20 days of use in pregnancy. This latter duration was of interest based on previous studies that characterized 20–30 days of acetaminophen use as ‘long term’ exposure.[5,8,13] Any acetaminophen use and longer durations of use were both higher among those with tobacco use in pregnancy, self-reported depression or anxiety, and antidepressant use. Although headaches or migraines accounted for the largest proportion of reported indications, higher doses per exposure day were observed in those indicating use for arthritis, sleep, fever or cold/flu.

Strengths of the study—In our cohort, 97% of acetaminophen use was from products purchased over-the-counter. While unsurprising, this reinforces the need for well-characterized, maternal-reported sources of data in order to study prenatal acetaminophen use. Administrative data, which benefits from large sample sizes, is often inadequate to study exposures like acetaminophen that are largely acquired over the counter. Further, administrative data often does not capture indication or dates of use outside of prescription or fill dates, which do not necessarily align to medications taken on an as-needed basis. The

MotherToBaby pregnancy study has a long history of prospectively enrolling women in pregnancy and collecting self-reported prescription and over the counter medications.[18,19,22,31] Our practice of collecting detailed information on each exposure, including start and stop date, dose and changes in dose, frequency and indication all lent to this project.

Limitations of the data—MotherToBaby is a self-selected sample, and tends to over-represent women who self-identify as White and who have higher socioeconomic status, planned pregnancies, and receive prenatal care. Thus, although our overall prevalence estimates were similar to previously reported literature,[1–7] these estimates may not be generalizable to samples that differ on these characteristics or other unmeasured factors that are associated with self-selection into the study. Also, although most women enrolled prior to 20 weeks of gestation, and there was little difference in gestational week of enrollment by duration of acetaminophen use, some women had longer recall periods than other women, which may lead to some misclassification of exposure.

Interpretation—Our prevalence of any acetaminophen use was slightly higher than the five recent pregnancy cohorts which described acetaminophen exposure (Danish National Birth Cohort (DNBC), Norwegian Mother and Child Cohort Study (MOBA), Auckland Birthweight Collaborative (ABC), Avon Longitudinal Study of Parents and Children (ALSPAC), and Infance y Medio Ambiente (INMA), where prevalence estimates were between 40% and 56%.[3–7] Similarly, estimates of the prevalence of >20 days of medication (11% of the full sample) were much higher than reported from DNBC[3] (4% of participants) or MOBA[8] (1% for 22+ days of exposure). Further, MotherToBaby prevalence estimates of use in all three trimesters (16% of the full sample) was higher than the estimates reported from the DNBC (10%[3] of full sample) and in (MOBA (2%[8] of full sample). It is important to note that characterizing duration of exposure by number of trimesters is potentially misleading. When we examined duration of use by number of trimesters, only 44% of women with use in all three trimesters had over 20 days of exposure, and 30% had less than 10 days of total exposure, leading to tremendous heterogeneity in that variable. Further, 39% of individuals with 20–44 days of use and 37% of individuals with 45+ days of use did not use acetaminophen in all three trimesters, leaving many ‘long-term’ users out of that highest use (all three trimesters) category. If relying upon the number of trimesters of use to proxy for duration of use, this heterogeneity in exposure definition would likely bias results, with some results possibly moving away from the null depending on the categories of exposure into which individuals were misclassified.[32] Further, there is a tremendous amount of developmental variation across trimesters, and certain trimesters may not have etiologic relevance to the outcome of interest. This highlights the need for more granular assessment of use than a count of the number of exposed trimesters.

This study was one of few to collect information on indication for each record of acetaminophen use. From this cohort, we found a variety of expected indications (such as headache/migraine and pain), but also less expected indications such as sleep (for which women reported use of Tylenol® PM). Further, the median dose per exposed day varied greatly by indication, increasing from 575 mg/day for migraines to over 900 mg/day. Additionally, indications like sleep were disproportionally reported among women with

longer durations of use (≥45 days), potentially leading to very high cumulative doses across gestation. In the recent cohort studies, some did not report any indication,[4,6] and others did not have specific indications for acetaminophen, but rather reported for conditions associated with analgesics such as fever, maternal joint disease, headaches, and infection/inflammation.[3,7] The Norwegian MOBA cohort did query specific indications for use. Among their sample who used acetaminophen for over 28 days, the proportions of use were headache or migraine (63%), pain (20%), fever (20%) and cold/flu (12%) (not mutually exclusive categories).[5] In our sample of women who used acetaminophen for >20 days, the proportions of the same indications were relatively similar: headache/migraine (52%), pain (27%), fever (4%), and cold/flu (13%). Additionally, 3% of our acetaminophen users reported the indication as sleep. Given the heterogeneity in reported indications by duration of use, as well as the increase in average dose associated with indications reported for longer durations of use, it is important to capture actual indication and dose for each report of exposure, as residual confounding may otherwise bias results.

Maternal comorbidities were also of interest in this study. Asthma, hypertension, and autoimmune diseases were all more frequently reported among women who also reported acetaminophen use, but did not differ by duration of use. However, self-reported mental health conditions, such as depression, anxiety and other conditions, were more frequently reported by both any exposure and duration of exposure, with higher prevalence of these conditions in women with longer durations of reported acetaminophen. Compared with women who did not use acetaminophen, women who used acetaminophen for more than 44 days had almost three times the prevalence of self-reported depression, four times the prevalence of anxiety, and three times the prevalence of other mental health disorders. Antidepressant use followed the same pattern, where women who used acetaminophen for the longest duration had five times the prevalence of antidepressant use compared with women who did not use acetaminophen. Interestingly, depression and anxiety screening scales did not differ by use or duration of use, although sample sizes were quite small in the subset with EPDS and STAI measures. It is possible that symptoms of anxiety and depression rated on these scales may be adequately controlled by antidepressants. Our results, while in need of replication in a larger sample, highlight the need for very good measures of past and current mental health disorders, as residual confounding is of great concern, particularly when estimating the effects of acetaminophen on risk for offspring neurodevelopmental outcomes.

Conclusions

In the MotherToBaby pregnancy cohort, we found that women who use acetaminophen, particularly for the longest durations, were more likely to have a history of depression and anxiety and use antidepressants. Additionally, high doses are being reported for indications such as pain and sleep, which may be comorbidities of mental health disorders. These findings suggest that researchers should consider confounding by indication and comorbidities, particularly with longer durations of use, and make great efforts to collect information on these important covariates.

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Synopsis

Study question:

What is the prevalence of acetaminophen use in pregnancy, and what indications and maternal co-factors describe prevalence and duration of use?

What's already known:

Acetaminophen is the most common medication in pregnancy, used by one-half to two-thirds of pregnant women.

What this study adds:

This prospective birth cohort found that 1234562% of women enrolled between 2004–2018 used acetaminophen, and 11% reported use for more than 20 days during pregnancy. The reported indication varied by duration of use, and maternal comorbidities such as self-reported anxiety, depression and antidepressant use were higher in those with longer durations of use.

Social media quote:

Almost two-thirds of women in a prospective cohort used acetaminophen at some point in pregnancy, and 11% reported over 20 days of use. Those with more acetaminophen use also reported more anxiety, depression, and antidepressant use.

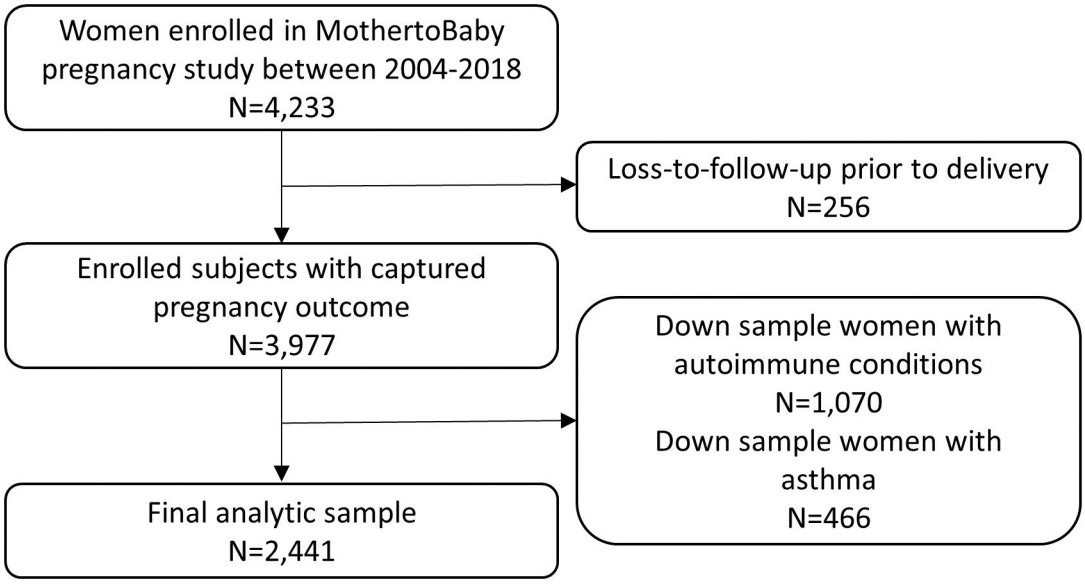

Figure 1.
Creation of analytic sample from MotherToBaby Pregnancy study (2004–2018).

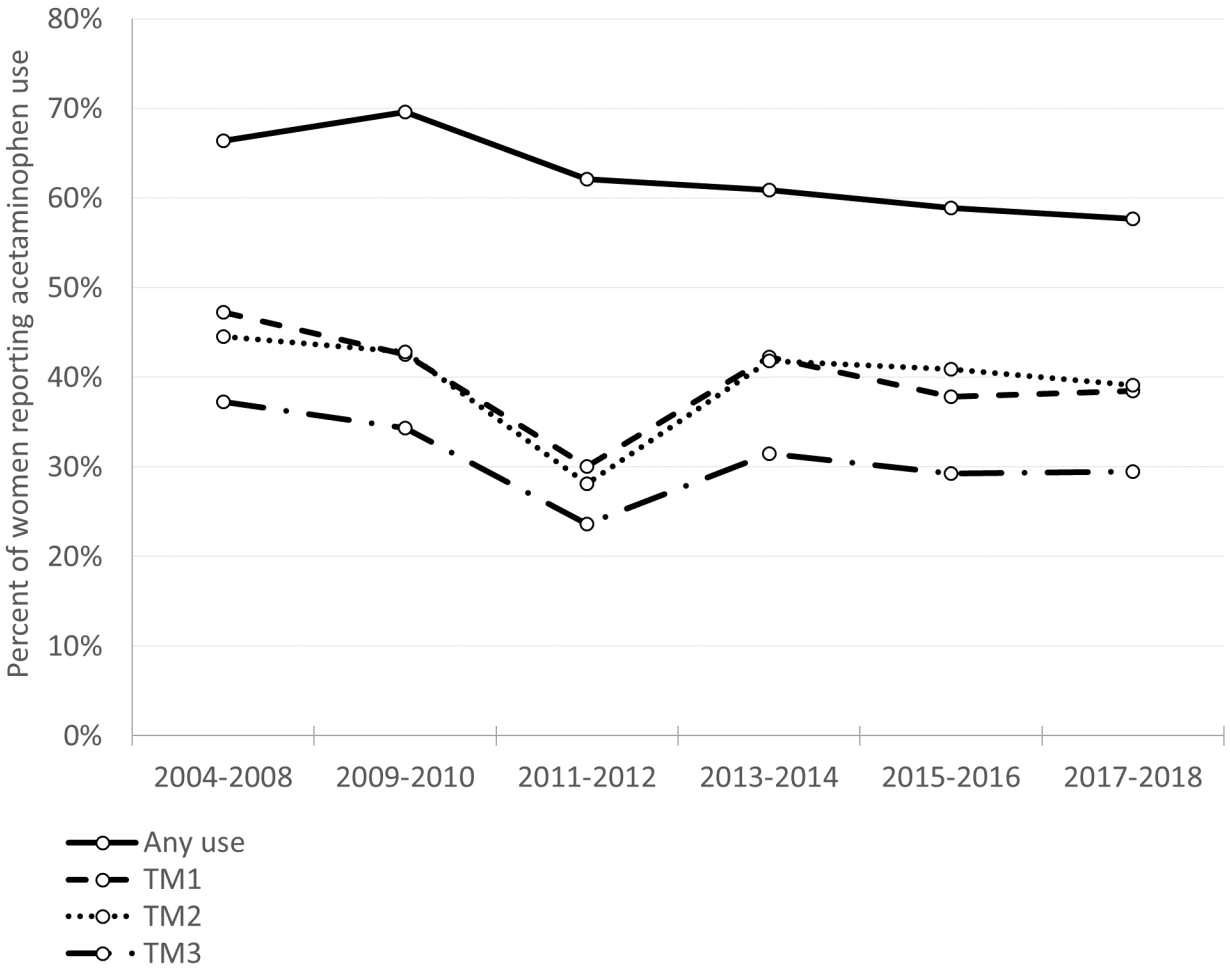

Figure 2.
Prevalence of any acetaminophen use in women enrolled in MotherToBaby pregnancy study between 2004–2018 (P-trend=0.001).

Table 1.

Prevalence of acetaminophen use by trimester (2004–2018) and by cumulative trimesters

	N	% of full sample (n=2,441)	% of acetaminophen users (n=1,338)[a]
Any acetaminophen use			
Trimester 1	915	38	68
Trimester 2	917	38	69
Trimester 3	711	30	53
Number of trimesters of use			
1 trimester	534	22	40
2 trimesters	403	17	30
all 3 trimesters	401	16	30

[a]177 women with any use could not be classified by trimester due to missing information and are excluded from analyses

Table 2.

Maternal characteristics by prenatal acetaminophen use exposure category (n=2,441) from women enrolled in MotherToBaby pregnancy study between 2004–2018

	Any use of acetaminophen, n=2,441 (n,%)		Acetaminophen stratified by duration of use,[a] n=1,515 (n,%)				
	None	Any	<10 days	10-<20 days	20-<45 days	≥45 days	Undefined
	926 (38)	1515 (62)	874 (58)	191 (13)	137 (9)	136 (9)	177 (12)
Maternal characteristics							
Gestational week of enrollment (mean, sd)	21 (10)	21 (10)	20 (9)	22 (9)	20 (9)	22 (9)	20 (10)
Maternal age >= 34 years	337 (36)	531 (35)	305 (35)	72 (38)	47 (34)	48 (35)	59 (33)
Pre-pregnancy BMI							
<24.9 mg/kg^2	649 (70)	938 (62)	574 (66)	119 (62)	89 (65)	63 (46)	93 (53)
25–29.9 mg/kg^2	153 (17)	344 (23)	177 (20)	38 (20)	33 (24)	41 (30)	55 (31)
>=30 mg/kg^2	105 (11)	226 (15)	119 (14)	33 (17)	15 (11)	32 (24)	27 (15)
missing	19 (2)	7 (1)	4 (1)	1 (1)	0 (0)	0 (0)	2 (1)
Education category							
<12 years	46 (5)	67 (4)	37 (4)	10 (5)	5 (4)	3 (2)	12 (7)
12–15 years	206 (22)	389 (26)	198 (23)	50 (26)	35 (26)	48 (35)	58 (33)
>15 years	673 (73)	1059 (70)	639 (73)	131 (69)	97 (71)	85 (63)	107 (61)
missing	1 (0.1)	0 (0.0)					
Race							
White	650 (70)	1200 (79)	677 (78)	145 (76)	123 (90)	116 (85)	139 (79)
Black	56 (6)	71 (5)	43 (5)	10 (5)	3 (2)	6 (4)	9 (5)
Asian/Pacific Islander	72 (8)	57 (4)	37 (4)	12 (6)	3 (2)	2 (2)	3 (2)
Native American	4 (0)	12 (1)	5 (1)	2 (1)	4 (3)	0 (0)	1 (1)
Other	31 (3)	30 (2)	22 (3)	2 (1)	0 (0)	5 (4)	1 (1)
decline	113 (12)	145 (10)	90 (10)	20 (11)	4 (3)	7 (5)	24 (14)
Socioeconomic status[b]							
Low	106 (12)	180 (12)	106 (12)	16 (8)	11 (8)	18 (13)	29 (16)
decline	26 (3)	24 (2)	11 (1)	6 (3)	0 (0)	4 (3)	3 (2)
Pregnancy was unplanned	214 (23)	359 (24)	206 (24)	43 (23)	32 (23)	40 (29)	38 (21)
Parity							

	Any use of acetaminophen, n=2,441 (n,%)		Acetaminophen stratified by duration of use,[a] n=1,515 (n,%)				
	None	Any	<10 days	10-<20 days	20-<45 days	≥45 days	Undefined
	926 (38)	1515 (62)	874 (58)	191 (13)	137 (9)	136 (9)	177 (12)
0	519 (56)	741 (49)	464 (53)	84 (44)	59 (43)	52 (38)	82 (46)
1	274 (30)	472 (31)	254 (29)	67 (35)	45 (33)	53 (39)	53 (30)
2+	133 (14)	301 (20)	155 (18)	40 (21)	33 (24)	31 (23)	42 (24)
Previous spontaneous abortion	232 (25)	376 (25)	205 (24)	55 (29)	40 (29)	37 (27)	39 (22)
Previous terminated pregnancy	75 (8)	134 (9)	80 (9)	15 (8)	9 (7)	16 (12)	14 (8)
Pregnancy exposures							
Prenatal vitamins in pregnancy	896 (97)	1464 (97)	850 (97)	183 (96)	130 (95)	132 (97)	169 (96)
Prenatal vitamins before conception	525 (57)	880 (58)	521 (60)	110 (58)	78 (57)	78 (57)	93 (52)
Any alcohol use in pregnancy	418 (45)	717 (47)	431 (49)	90 (47)	61 (45)	67 (49)	68 (38)
Last gestational week alcohol use in pregnancy (median, IQR)	2.7 (20)	3.3 (27)	3.1 (27)	3.9 (29)	4.1 (29)	6.9 (34)	2.6 (14)
Tobacco use in pregnancy	28 (3)	79 (5)	38 (4)	8 (4)	8 (6)	14 (10)	11 (6)
Antidepressant use in pregnancy	25 (3)	109 (7)	53 (6)	17 (9)	7 (5)	23 (17)	9 (5)
Medical comorbidities[c]							
Depression	115 (12)	297 (20)	153 (18)	35 (18)	32 (23)	49 (36)	28 (16)
Anxiety	59 (6)	177 (12)	86 (10)	25 (13)	19 (14)	33 (24)	14 (8)
Other mental health conditions	28 (3)	85 (6)	44 (5)	9 (5)	9 (7)	14 (10)	9 (5)
Diabetes	12 (1)	25 (2)	10 (1)	4 (2)	2 (2)	3 (2)	6 (3)
Hypertension	29 (3)	73 (5)	40 (5)	9 (5)	4 (3)	11 (8)	9 (5)
Autoimmune conditions	14 (1)	57 (4)	26 (3)	5 (3)	6 (4)	8 (6)	12 (7)
Asthma	72 (8)	172 (11)	93 (11)	20 (11)	16 (12)	20 (15)	23 (13)
EPDS >= 10[d]	5 (8)	13 (14)	8 (13)	2 (22)	2 (22)	1 (8)	0 (0)
STAI (State score) >= 45[d]	4 (6)	12 (13)	8 (13)	1 (11)	0 (0)	3 (25)	0 (0)

[a] 177 women did not provide enough information to calculate duration of use and have a duration noted as 'undefined'

[b] Low socioeconomic status is Hollingshead categories of 4 or 5

[c] Self-reported medical history of current or resolved conditions

[d] The EPDS and STAI were added to later cohorts and only available in 160 women

Table 3.

Average acetaminophen dose (mg) per exposed day by indication[a]

	n	%	median (mg)	IQR
Sleep	25	1.4	910	595
Arthritis	3	0.2	650	2175
Injury	3	0.2	650	1773
Pain	331	19.1	650	581
Cold/flu	300	17.3	650	542
Fever	136	7.9	650	505
Cramps	24	1.4	650	433
Headache	857	49.5	650	378
Migraine	51	2.9	575	653

[a]Women could have reported multiple indications which were each coded, and some women did not report an indication

Table 4.

Prevalence of reported indication for acetaminophen use, stratified by duration of use

	Undefined	<10 days	10-<20 days	20-<45 days	≥45 days
Count of reported indications	n=200	n=1,118	n=285	n=203	n=195
Headache/Migraine	76%	53%	54%	53%	50%
Cold/flu	8%	19%	19%	15%	11%
Pain/Injury	13%	17%	19%	25%	29%
Fever	1%	10%	5%	4%	4%
Cramps	1%	1%	2%	2%	1%
Sleep	2%	1%	1%	2%	5%

Women could report multiple indications for each exposure occurrence. Thirty-four subjects did not report an indication