Human Reproduction, Vol.32, No.1 pp. 103–111, 2017
Advanced Access publication on November 5, 2016 doi:10.1093/humrep/dew272

human reproduction

ORIGINAL ARTICLE *Infertility*

Preconception use of pain-relievers and time-to-pregnancy: a prospective cohort study

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Submitted on May 16, 2016; resubmitted on September 27, 2016; accepted on October 19, 2016

STUDY QUESTION: To what extent is preconception use of pain-relieving medication associated with female fecundability?

SUMMARY ANSWER: Women who used naproxen or opioids had slightly lower fecundability than women who did not use any pain-relieving medications; use of acetaminophen, aspirin and ibuprofen was not appreciably associated with fecundability.

WHAT IS KNOWN ALREADY: Over-the-counter pain-relieving medications are commonly used by women of reproductive age in the USA. Studies investigating the effects of pain-relieving medication use on ovulation, implantation and fecundability have shown conflicting results.

STUDY DESIGN, SIZE, DURATION: We analyzed data from an internet-based prospective cohort study of 2573 female pregnancy planners aged 21–45 years from the USA and Canada. Participants were enrolled and followed from June 2013 through September 2015. Participants completed a baseline questionnaire and bimonthly follow-up questionnaires until a reported pregnancy or for 12 months, whichever occurred first. Over 80% of participants completed at least one follow-up questionnaire.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Use of pain-relieving medication during the past month was assessed at baseline and on each follow-up questionnaire. Medications were categorized according to type (acetaminophen, aspirin, ibuprofen, naproxen and opioids) and total monthly dose. Self-reported pregnancy was assessed at each follow-up. Multivariable-adjusted fecundability ratios (FRs) and 95% CI were calculated using proportional probabilities regression. Models were adjusted for demographic, lifestyle and anthropometric factors; reproductive history; gynecologic morbidity; and indications for use of pain medications. Models were also run with and without adjustment for parity. After restricting to women with 6 or fewer months of attempt time at study entry, 1763 were included in the analyses.

MAIN RESULTS AND THE ROLE OF CHANCE: At baseline, 1279 (73%) women reported using ≥1 pain-relieving medications in the previous month. When compared with non-use of pain-relieving medications, FRs for use of naproxen and opioids at baseline were 0.78 (95% CI: 0.64–0.97) and 0.81 (95% CI: 0.60–1.10), respectively. A dose–response relation was observed between naproxen use and fecundability; FRs for use of <1500 and ≥1500 mg of naproxen were 0.85 (95% CI: 0.68–1.07) and 0.58 (95% CI: 0.36–0.94), respectively. Small numbers ($n = 74$) precluded the examination of opioid use by dose. Overall, there was little evidence of an association between fecundability and acetaminophen (FR 1.04, 95% CI: 0.92–1.18), aspirin (FR 1.00, 95% CI: 0.80–1.25), or ibuprofen (FR 1.00, 95% CI: 0.89–1.11). Similar results were observed when exposure information was updated over time.

LIMITATIONS, REASONS FOR CAUTION: Numbers of opioid users were small. Information collected on reason for use of pain medications was not specific to each type of pain medication. Therefore, we cannot rule out confounding by indication as an explanation of these results.

WIDER IMPLICATIONS OF THE FINDINGS: Use of naproxen and opioids was associated with a small reduction in fecundability, but there was little association between other pain-relieving medications and fecundability.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported through funds provided by National Institute of Child Health and Human Development, National Institute of Health (R21 HD072326, T32 HD052458). The authors have no conflicts of interest to disclose.

TRIAL REGISTRATION NUMBER: Not applicable.

Key words: fecundability / pain medications / time-to-pregnancy / non-steroidal anti-inflammatory drugs / acetaminophen / fertility / opioids / conception

Introduction

Over-the-counter pain-relieving medications are commonly used by reproductive-aged women (Turunen *et al.*, 2005; Werler *et al.*, 2005; Mitchell *et al.*, 2011). In 2005, a cross-sectional study found that 60% of pregnant women in the USA used analgesics during the 3 months before conception, most commonly acetaminophen (48%) and ibuprofen (21%) (Werler *et al.*, 2005). The effect of pain-relieving medication use on human reproduction is unclear.

Aspirin, ibuprofen and naproxen are non-steroidal anti-inflammatory drugs (NSAIDs) that prevent pain by inhibiting the enzymes that synthesize prostaglandins (PGs) (Orczyk and Behrman, 1972; Cashman, 1996). PGs are essential for reproduction as pre-ovulatory increases in PG levels facilitate ovulation (Tsafriri *et al.*, 1972; Clark *et al.*, 1978; Ando *et al.*, 1999) and implantation (Hurst and MacFarlane, 1981; Agrawal and Alvin Jose, 2009). There is evidence that inhibition of PG synthesis may vary by type of NSAID (Hurst and MacFarlane, 1981; Danon *et al.*, 1983; Meade *et al.*, 1993), suggesting differential effects on reproduction. One study found that ibuprofen was associated with reduced odds of anovulation, while naproxen was associated with slightly increased odds of anovulation, although results were imprecise (Matyas *et al.*, 2015).

The effects of aspirin use on pregnancy have been studied in women with a history of infertility or pregnancy loss. In the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, women with a previous miscarriage who were randomized to low-dose aspirin use had a reduced time-to-pregnancy (TTP) relative to women not randomized to low-dose aspirin (Schisterman *et al.*, 2015). Low-dose aspirin has also been shown to improve fertility among women with polycystic ovary syndrome (Zhao *et al.*, 2014). In IVF populations, results from double-blind RCTs have been conflicting (Dirckx *et al.*, 2009; Lambers *et al.*, 2009).

The most commonly used non-NSAID pain-reliever among US women during the preconception period is acetaminophen (Werler *et al.*, 2005), which has potent analgesic effects but limited anti-inflammatory effects (Botting, 2000). Compared with NSAIDs, acetaminophen has weak and varying effects on PG synthesis, with high levels of exposure inhibiting synthesis, and low levels of exposure stimulating synthesis (van Kolfschoten *et al.*, 1981, 1982; Boughton-Smith and Whittle, 1983; Danon *et al.*, 1983). In humans, acetaminophen has been shown to slightly reduce the odds of anovulatory cycles (Matyas *et al.*, 2015) and have little effect on female fecundability (Smarr *et al.*, 2016). In addition, frequent use of opioids has been associated with amenorrhea, and decreased ovarian and adrenal sex hormone production (Daniell, 2008).

To date, little is known about the effects of pain-relieving medication use on human fecundability. In a North American cohort of female pregnancy planners, we examined prospectively whether the type and monthly dose of analgesic use during the preconception period was associated with fecundability.

Materials and Methods

Study population

Pregnancy Study Online (PRESTO) is an ongoing web-based prospective cohort study of pregnancy planners that began in June 2013, recruiting participants primarily through online advertisements on social media and health-related websites (Wise *et al.*, 2015). Women aged 21–45 years who are not using contraception or fertility treatments, in a stable relationship with a male partner, and not currently pregnant are eligible to participate. For the present analysis, women were followed through September 2015.

Participants completed an online baseline questionnaire, providing detailed data on demographic, lifestyle and behavioral factors; anthropometrics; and reproductive and medical history. Online follow-up questionnaires were completed every 2 months for 12 months or until a reported pregnancy, whichever occurred first. Women who became pregnant were asked to complete early and late pregnancy questionnaires. Over 80% of participants completed at least one follow-up questionnaire (Wise *et al.*, 2015).

Ethical approval

The Boston University Medical Center institutional review board approved the study protocol and participants provided online informed consent.

Assessment of medication usage

On the baseline and follow-up questionnaires, women were asked whether they had used any pain-relieving medications during the previous 4 weeks. Participants who responded affirmatively were asked to provide the names of up to three medications using text-recognition software provided by the Slone Drug Dictionary (Kelley *et al.*, 2003), and the total number of pills taken for each medication. Pain-relieving medications reported under separate questions about medication use for migraine headaches or other diseases/indications were also considered.

Pain-relieving medications were grouped into five categories by active ingredient. Categories include acetaminophen, aspirin, ibuprofen, naproxen and opioids. Medications that included active ingredients from more than one category were included in multiple groups. For example, users of 'Excedrin Migraine' were classified as users of both acetaminophen and aspirin. All medications that contained at least one of these active ingredients were included in these classifications.

Total dose was calculated as the total number of pills multiplied by the dose of each active ingredient in each pill. Total monthly dose was calculated at baseline and updated every 2 months via follow-up questionnaire.

Assessment of pregnancy and cycles at risk

On the baseline questionnaire, participants reported their average menstrual cycle length, the date of their last menstrual period (LMP) and the number of cycles they had already been trying to conceive. On each additional follow-up questionnaire, participants reported their LMP date and pregnancy status. Total cycles at risk were calculated using the number of cycles trying to conceive at baseline, LMP dates before study entry and at each follow-up questionnaire, and usual cycle length. Participants contributed cycles to the analysis from study enrollment until reported conception, initiation of fertility treatments, loss to follow-up, or 12 months, whichever occurred first. Only observed cycles of attempted pregnancy were analyzed.

Exclusions

Of the 2573 women who completed the baseline questionnaire, we excluded 445 women without follow-up data, 49 women with insufficient or implausible menstrual cycle information and 28 women who were using a pain medication with unknown ingredients (e.g. 'cold medicine'). In addition, to avoid differential misclassification of medication use by subfertility, we excluded 288 women who had been trying to conceive for >6 cycles at study entry. The final analytic sample included 1763 women.

Data analysis

We first categorized pain medication use as a dichotomous variable (use versus non-use). We then evaluated type of medication use (acetaminophen, ibuprofen, aspirin, naproxen, opioids). We divided total dose of each medication at baseline into low and moderate exposure categories based on the distribution of use in the study population. Dose was not examined for opioids due to the small number of users ($n = 74$). The reference group for all analyses was non-use of pain-relieving medications in the previous 4 weeks. Primary analyses were based on baseline exposure data. Secondary analyses were based on exposure data updated over time using bimonthly follow-up questionnaires. To avoid recall bias, only medication use reported by women on the questionnaire(s) before the questionnaire on which they reported their pregnancy status was updated. For example, if a woman reported a pregnancy on her second follow-up questionnaire, data from both her baseline and first follow-up questionnaires would be used to model her medication use before her pregnancy. Women were permitted to contribute to more than one exposure category (21.8% used more than one type of pain medication).

Women contributed at-risk menstrual cycles to the analysis from study entry until a reported pregnancy or a censoring event (initiation of fertility treatment, loss to follow-up or 12 cycles of attempt time), whichever came first. Couples that did not conceive within 12 cycles of attempted conception were censored at 12 cycles, which is the typical amount of time after which couples seek infertility treatment. We used a proportional probabilities regression model to estimate the fecundability ratio (FR) and 95% CI (Weinberg *et al.*, 1989). The FR is a measure of the per-cycle probability of conception comparing exposed with unexposed women. An FR of <1.0 indicates reduced fecundability, or equivalently, increased TTP. By adjusting for cycle at risk, the proportional probabilities model takes into account the declining average fecundability of the cohort as fertile couples are removed from the denominator with increasing attempt time. To account for differences in attempt time at enrollment (0–6 cycles) and reduce bias from left truncation (Howards *et al.*, 2007; Schisterman *et al.*, 2013), we analyzed only observed cycles using the Andersen-Gill data structure (Therneau and Grambsch, 2000). For example, if a woman entered the study with two cycles of attempt time and conceived during her fourth cycle, she would contribute only cycles 3 and 4 to the analysis.

Models were adjusted for hypothesized confounders that were selected *a priori* based on the literature and the drawing of a causal directed acyclic graph. These variables included age (years), race/ethnicity (non-white versus white), household income (< versus ≥$50 000 USD per year), education (< versus ≥ college degree), physical activity (metabolic equivalent (MET)-hours/week), BMI (calculated as weight (kg)/height $(m)^2$), history of smoking (ever versus never), history of miscarriage (yes versus no) and doing something to improve chances of conception (e.g. charting menstrual cycles, using ovulation testing kits, monitoring cervical fluid). We also adjusted for potential indications for pain-relieving medication use, including pain severity during menses (none, mild, moderate, severe); last method of contraception-(intrauterine device (IUD), oral contraception, other); clinical diagnoses of anxiety (yes versus no), uterine leiomyomata (yes versus no), endometriosis (yes versus no) and migraine (yes versus no); use of antibiotics during the previous 4 weeks (proxy for fever or infection) (yes versus no); intercourse frequency (<1, 1–3, ≥4 times/week); menstrual cycle irregularity (able to predict about when next period will occur: yes versus no); and menstrual cycle length (<22, 22–35, ≥36 days, based on clinical definitions of polymenorrhea and oligomenorrhea; Speroff *et al.*, 1999). Medications were also mutually adjusted for each other. As parity may act as a causal intermediate (Weinberg, 1993; Howards *et al.*, 2012), models were fit with and without adjustment for parity (0, ≥1 births).

Results were stratified by age at study entry (<30 versus ≥30 years), pregnancy attempt time at study entry (<3 versus 3–6 cycles), use of a single pain medication type (e.g. acetaminophen only) versus using more than one type (e.g. acetaminophen and naproxen), menstrual cycle regularity (regular versus irregular), BMI (<30 versus ≥30 kg/m^2) and parity (0 versus ≥1 births).

We used PROC MI to impute missing values for exposures and covariates using 138 variables in the imputation model to create five imputed data sets (SAS 9.3, Cary, NC, USA). Total dose was imputed for 1.8% of participants, primarily women who reported analgesics in questionnaire fields for migraine or 'other' medications where pill number was not ascertained. Covariate data were imputed for <1% of participants. We used PROC MIANALYZE to combine coefficient and SE estimates from the five data sets (SAS Institute, 2008) .

Results

Of the 1763 women included in these analyses, 1279 (72.5%) reported use of a pain medication in the 4 weeks before the baseline questionnaire and 484 (27.5%) were non-users. Ibuprofen use was most common (50.1% of women), followed by use of acetaminophen (29.7%), naproxen (8.8%), aspirin (7.3%) and opioids (4.2%).

A total of 201 participants (11.4%) were lost to follow-up after completing one or more follow-up questionnaires. Pain medications were used by 72.6% of the 1562 participants who completed follow-up and 71.6% of the 201 participants who were lost to follow-up. Among users, the mean monthly dose of each medication was 1200 mg (range: 200–22 400 mg) of ibuprofen, 1300 mg (range: 250–40 000 mg) of acetaminophen, 1000 mg (range: 250–12 000 mg) of aspirin and 880 mg (range: 220–13 200 mg) of naproxen. Opioid users took an average of 4 pills (range: 1–300 pills). The maximum recommended daily dose is 3200 mg of ibuprofen, 4000 mg of acetaminophen (NCPDP, 2013) or aspirin (Bayer, 2014), and 1500 mg of naproxen (Roche, 2014), indicating a plausible range of use in a 4-week period.

Use of pain medications was positively associated with use of alcohol, tobacco, oral contraceptives (OCs) and antibiotics, and with anxiety, headaches, endometriosis and moderate or severe pain during menses compared with non-use (Table I). Use of analgesics was inversely associated with parity compared with non-use; however, users of acetaminophen and aspirin were more likely to be parous than users of

Table I Baseline characteristics of 1763 female pregnancy planners by type of pain medication used during the previous 4 weeks.

Characteristic[a]	Pain medication use		Type of medication use				
	No	Yes	Acetaminophen	Aspirin	Ibuprofen	Naproxen	Opioids
Number of women	484	1279	523	129	884	156	74
Age (years, mean)	29.9	30.1	30.2	30.1	30.1	29.9	29.4
Partners age (years, mean)	32.1	32.0	31.8	31.7	32.1	32.1	32.3
White, non-Hispanic (%)	84.3	86.6	86.2	87.9	87.1	84.3	80.6
Geographic region of residence (%)							
Midwest	13.0	14.0	13.8	11.3	12.4	14.4	17.0
Northeast	41.5	39.8	38.6	41.0	41.0	40.4	32.4
South	17.9	22.6	23.2	28.7	21.4	26.7	27.2
West	14.3	13.6	14.3	14.2	14.5	11.5	15.1
Canada	13.3	10.0	10.1	4.7	10.7	7.0	8.3
Annual household income <US$50 000 (%)	19.5	14.4	18.8	15.9	12.9	12.5	25.2
<College degree (%)	21.8	19.8	22.2	24.4	18.8	19.8	25.1
BMI (kg/m^2, mean)	25.9	26.4	26.8	26.9	26.3	27.2	28.1
Physical activity (MET-hours/week, mean)	41.9	39.0	38.4	38.8	39.9	39.1	37.9
Multivitamin or folic acid supplement use (%)	82.8	84.3	86.5	82.6	84.3	81.5	87.1
Ever smoker (%)	19.9	25.8	27.0	24.3	25.2	25.4	44.8
Alcohol intake (drinks/week, mean)	2.8	3.8	3.1	3.3	4.2	3.9	3.7
Parous (%)	35.6	27.0	31.3	28.9	24.4	21.3	22.6
Irregular menstrual cycles (%)	17.9	14.5	14.3	16.1	14.3	13.7	17.5
Menstrual cycle <22 days (%)	1.0	0.9	0.6	1.3	0.8	1.3	1.2
Menstrual cycle ≥36 days (%)	8.3	7.4	7.7	7.9	7.6	5.8	4.4
Doing something to improve chances of conceiving (%)	72.2	75.2	77.4	73.6	75.2	68.1	85.4
Intercourse frequency <1 time/week (%)	17.9	21.1	19.7	18.6	20.7	23.0	18.8
Last method of contraception: OCs (%)	31.9	38.1	37.8	41.8	37.9	42.3	39.0
Last method of contraception: IUD (%)	12.6	10.4	10.7	15.7	11.1	4.3	7.4
History of spontaneous abortion (%)	22.7	20.7	24.2	19.2	18.3	20.0	37.1
History of infertility (%)	7.5	6.5	7.6	9.6	5.6	5.7	6.7
Diagnosis of anxiety (%)	14.4	19.6	22.7	13.3	18.8	18.4	31.9
Moderate or severe pain during period (%)	24.5	48.4	48.6	42.0	49.8	53.3	57.1
Endometriosis (%)	1.6	2.7	2.3	0.0	3.0	2.5	5.1
Uterine leiomyomata (%)	2.3	2.4	2.4	2.7	2.5	1.5	2.8
Migraine headaches (%)	13.5	23.3	31.8	39.4	21.0	20.0	30.0
Antibiotic use (%)	4.9	8.8	9.8	14.3	8.5	9.7	26.1

OC, oral contraceptives; IUD, intrauterine device; MET, metabolic equivalent.
[a]All characteristics, with exception of age, are age standardized to the cohort at baseline.

other medications. Users of aspirin were more likely to have used antibiotics during the previous 4 weeks and were much more likely to have migraine headaches than users of other over-the-counter medications. Naproxen users were more likely to have pain during menses and use OCs as their last method contraception, and were less likely to report uterine leiomyomata, use an IUD as their last method of contraception, or report doing something to improve their chances of conception compared with acetaminophen, aspirin or ibuprofen users.

Opioid users were substantially different from users of other medications. Opioid use was associated with lower educational attainment when compared with users of the other pain-relievers examined, and lower household income when compared with users of aspirin, ibuprofen and naproxen. Likewise, opioid users were more likely to have smoked, have a diagnosis of anxiety, report a prior miscarriage, use multivitamins and be doing something to improve chances of conception when compared with users of over-the-counter pain medications (Table I).

The 1763 participants contributed a total of 7684 observed cycles and 1117 pregnancies to the analysis. Median follow-up was 4 cycles (interquartile range: 2–7) among users of pain-relieving medication and 3 cycles (interquartile range: 2–7) among non-users of pain-relieving

Table II Baseline and time-varying pain medication use during the past 4 weeks and fecundability among female pregnancy planners.

Exposure	Baseline analysis				Time-varying analysis			
	No. of cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]	No. of cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]
Non-use	2158	308	Reference	Reference	2400	334	Reference	Reference
Any use	5830	820	1.01 (0.90–1.14)	1.04 (0.92–1.18)	5588	784	1.00 (0.89–1.13)	1.03 (0.92–1.17)
Acetaminophen	2362	338	1.04 (0.92–1.18)	1.04 (0.92–1.18)	2377	340	1.04 (0.92–1.18)	1.03 (0.91–1.17)
Aspirin	577	78	1.01 (0.81–1.26)	1.00 (0.80–1.25)	547	75	0.99 (0.79–1.24)	0.97 (0.78–1.21)
Ibuprofen	3995	559	0.98 (0.88–1.09)	1.00 (0.89–1.11)	3673	521	0.97 (0.87–1.08)	0.99 (0.88–1.10)
Naproxen	840	86	0.75 (0.61–0.93)	0.78 (0.64–0.97)	781	75	0.68 (0.55–0.85)	0.71 (0.57–0.89)
Opioids	369	41	0.81 (0.60–1.09)	0.81 (0.60–1.10)	334	35	0.76 (0.55–1.05)	0.79 (0.57–1.09)

FR, fecundability ratio; Pregs, pregnancies. Specific medication categories are not mutually exclusive. Medication-specific results are additionally adjusted for each of the other pain medications.

[a]Adjusted for age, education, income, race/ethnicity, IUD or OCs as last method of contraception, BMI, smoking history, physical activity, intercourse frequency, history of spontaneous abortion, having irregular menstrual cycles, menstrual cycle length, pain severity during menses, doing something to improve chances of conceiving, diagnosis of anxiety, endometriosis, leiomyomata, migraine headaches and antibiotic use.

medication. Use of acetaminophen, aspirin and/or ibuprofen during the 4 weeks before baseline was not appreciably associated with fecundability compared with non-use. In contrast, use of naproxen at baseline, alone or in combination with another type of pain-relieving medication, was associated with a 22% reduction in fecundability (FR 0.78, 95% CI: 0.64–0.97). The FR for opioid use was 0.81 compared with non-use (95% CI: 0.60–1.10). Results examining time-varying medication use were similar to those examining baseline use (Table II). Including parity in the models, or adjusting for a six-category variable for menstrual cycle length, did not appreciably change the results.

Higher doses of naproxen use were associated with greater reduction in fecundability. Compared with non-users, FRs for baseline use of <1500 mg and ≥1500 mg of naproxen were 0.85 (95% CI: 0.68–1.07) and 0.58 (95% CI: 0.36–0.94), respectively. Use of aspirin, ibuprofen or acetaminophen was not appreciably associated with fecundability, regardless of dose (Table III). The number of opioid users was too small to examine associations by dose.

Results restricted to women trying to conceive for 0–2 cycles at study entry were similar to those found among all participants (Table IV).

To assess differences in single versus combined medication effects, and to examine residual confounding by conditions or pain severity requiring use of multiple types of pain-relieving medications, we stratified the data according to use of a single medication (e.g. aspirin only) and use of ≥2 medications (e.g. aspirin and ibuprofen). The FR for use of aspirin only at baseline was 1.27 (95% CI: 0.82–1.97) compared with non-use, and the FR for user of aspirin and ≥1 other medications was 0.96 (95% CI: 0.73–1.28). The FR for use of naproxen only was 0.81 (95% CI: 0.61–1.07), a slightly weaker association than that observed for all naproxen users (Table IV).

To examine further the impact of residual confounding by indication, we restricted the population to the 617 women who used ≥1 medications and had moderate or severe pain during menses. Users of naproxen (FR 0.70, 95% CI: 0.51–0.95) and opioids (FR 0.70, 95% CI: 0.46–1.07) had reduced fecundability compared with users of ibuprofen, showing stronger associations than those observed in the full population.

Among women with irregular cycles, FRs for use of acetaminophen and ibuprofen were 1.37 (95% CI: 0.93–2.01) and 1.33 (95% CI: 0.97–1.83), respectively; among women with regular cycles, those respective FRs were 1.02 (95% CI: 0.89–1.16) and 0.96 (95% CI: 0.85–1.08) (Table IV). Results did not vary by age, BMI or parity (results not shown).

Discussion

In this North American prospective cohort study of pregnancy planners, women who used naproxen alone or in combination with another pain-relieving medication had slightly lower fecundability compared with women who did not use any pain-relieving medications, after accounting for possible indications for use (e.g. menstrual pain). Further, a dose–response relation between naproxen use and fecundability was found. A small reduction in fecundability was also observed among opioid users, but precision was hampered by the low prevalence of opioid use in this cohort; thus, this finding should be interpreted with caution.

The association between naproxen use and fecundability has not been studied previously. Naproxen has been shown to decrease PGE2 secretion from cultured human endometrial cells from healthy women, making naproxen an effective treatment for dysmenorrhea (Carrarelli *et al.*, 2015) but potentially detrimental for ovulation and implantation (Hurst and MacFarlane, 1981; Ando *et al.*, 1999). Results from the present study may be influenced by residual confounding, as naproxen is often used to treat menstrual pain, which may indicate subclinical fertility problems (e.g. endometriosis). However, we found that the association between naproxen and reduced fecundability persisted after adjustment for minor, moderate and severe menstrual pain, which correlates with subclinical endometriosis (Missmer and Cramer, 2003). We also conducted an analysis restricted to medication users who experienced moderate or severe menstrual pain, comparing naproxen users with ibuprofen users, both of which have similar indications. The association between naproxen use and reduced fecundability became slightly stronger. We further examined use of naproxen only, which yielded a slightly weaker association than what was observed among all users of naproxen in combination with other pain medication types.

Table III Baseline and time-varying total dose of pain medication exposure during the past 4 weeks and fecundability among female pregnancy planners.

Exposure	Baseline analysis				Time-varying analysis			
	No. of cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]	No. of cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]
Non-use	2158	308	Reference	Reference	2400	334	Reference	Reference
Any use								
Low exposure	3898	548	1.00 (0.88–1.14)	1.00 (0.88–1.15)	3805	537	1.00 (0.86–1.17)	1.01 (0.89–1.14)
Moderate exposure	1911	268	1.00 (0.86–1.17)	1.10 (0.94–1.29)	1759	254	1.00 (0.88–1.13)	1.10 (0.94–1.28)
Type of medication								
Acetaminophen (mg)								
<2000	1577	224	1.01 (0.87–1.16)	0.99 (0.86–1.14)	1603	223	0.99 (0.86–1.14)	0.96 (0.84–1.11)
≥2000	785	114	1.12 (0.93–1.35)	1.19 (0.99–1.44)	774	117	1.15 (0.96–1.39)	1.21 (1.00–1.46)
Aspirin (mg)								
<1500	388	52	1.01 (0.78–1.32)	1.02 (0.68–1.55)	353	48	0.96 (0.73–1.25)	0.92 (0.70–1.20)
≥1500	215	27	0.90 (0.62–1.29)	0.99 (0.59–1.65)	194	27	0.96 (0.66–1.37)	1.01 (0.70–1.44)
Ibuprofen (mg)								
<2000	2967	407	0.96 (0.86–1.08)	0.96 (0.85–1.08)	2736	385	0.97 (0.87–1.10)	0.97 (0.86–1.09)
≥2000	1028	152	1.02 (0.87–1.21)	1.12 (0.94–1.32)	937	136	0.98 (0.82–1.16)	1.06 (0.89–1.26)
Naproxen (mg)								
<1500	607	69	0.82 (0.66–1.03)	0.85 (0.68–1.07)	574	58	0.71 (0.56–0.91)	0.74 (0.57, 0.94)
≥1500	233	17	0.54 (0.34–0.88)	0.58 (0.36–0.94)	207	17	0.59 (0.36–0.94)	0.63 (0.39, 1.01)

'Any use' categories are mutually exclusive groups of exposure in the highest exposure group of any medication (moderate exposure) and exposure to any medication in the lowest dose group and no exposure in the higher dose category (low exposure). Specific medication categories are not mutually exclusive. Medication-specific results are adjusted for each of the other pain medications.

[a]Adjusted for age, education, income, race/ethnicity, IUD or OCs as last method of contraception, BMI, smoking history, physical activity, intercourse frequency, history of spontaneous abortion, having irregular menstrual cycles, menstrual cycle length, pain severity during menses, doing something to improve chances of conceiving, diagnosis of anxiety, a diagnosis of endometriosis, diagnosis of leiomyomata, diagnosis of migraine headaches and antibiotic use during the past 4 weeks.

Given that users of naproxen with other pain medications may have greater potential for underlying fertility issues, the attenuated results in the naproxen-only group suggest that residual confounding by indication may partially explain these findings. Results restricted to women trying to conceive for between 0 and 2 cycles at study entry were similar to the overall results, providing evidence against reverse causation as an explanation of our findings. These stratified results also indicate that the association is likely consistent among observed and unobserved women during the first few cycles of attempt time.

Previous studies indicate that low levels of acetaminophen exposure increase PG synthesis in rats (van Kolfschoten *et al.*, 1981, 1982; Boughton-Smith and Whittle, 1983; Danon *et al.*, 1983), facilitating ovulation (Tsafriri *et al.*, 1972; Clark *et al.*, 1978; Ando *et al.*, 1999) and implantation (Hurst and MacFarlane, 1981; Agrawal and Alvin Jose, 2009). Studies of urinary acetaminophen concentrations in women found no association with fecundability (Smarr *et al.*, 2016). Matyas *et al.* (2015) found that use of acetaminophen or ibuprofen during the follicular phase of the menstrual cycle was associated with reduced odds of anovulatory cycles when compared with non-use. This evidence lends support to our findings of increased fecundability among women with irregular menstrual cycles who used acetaminophen or ibuprofen because women with irregular cycles would be more likely to experience anovulation (Laven *et al.*, 2004; Burgers *et al.*, 2010).

This study has several limitations. Women were not asked to report the indication for use of each pain medication; rather, information on indication for use was assessed more generally using other survey questions. Thus, residual confounding by indication is likely. Further, information on exact timing of medication use was not collected. These medications may have an effect on fecundability that varies over the phases of the menstrual cycle. If so, then the observed FR may underestimate the actual effect during susceptible periods. Non-differential misclassification of medication use from under-reporting would also contribute to underestimation of any real effect. We did not control for pain-relieving medication use by the male partner. If male medication use affects fecundability (Smarr *et al.*, 2016), and male and female medication use is positively correlated, then the observed associations may be confounded. Additionally, although pain-reliever use was common, there were few opioid users and the range of dose exposures was narrow, limiting the precision and inferences of our analyses on opioid use and dose.

Misclassification of TTP was also likely; the calculation of the cycle where conception occurred was dependent on a woman's reported LMP and average cycle length. If reporting accuracy differed by exposure status, a bias of unpredictable direction could have occurred. For example, women with irregular periods were less likely to use analgesics and may have been more likely to have a misclassified cycle of conception, which would have biased the FR toward the null.

Table IV Baseline pain medication use and fecundability among female pregnancy planners stratified by age, time trying to conceive at study entry and number of medications used.

Exposure	Baseline analysis							
	No. of cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a]	No. of cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)[a,b]
	Regular menstrual cycles				**Irregular menstrual cycles**			
Non-use	1717	260	Reference	Reference	441	48	Reference	Reference
Any use	5048	720	0.96 (0.85–1.09)	0.98 (0.86–1.12)	782	100	1.21 (0.88–1.66)	1.33 (0.96–1.84)
Acetaminophen	2067	299	1.01 (0.89–1.16)	1.02 (0.89–1.16)	295	39	1.17 (0.81–1.69)	1.37 (0.93–2.01)
Aspirin	487	67	1.02 (0.80–1.29)	1.00 (0.79–1.27)	90	11	0.91 (0.49–1.68)	0.69 (0.36–1.33)
Ibuprofen	3468	490	0.95 (0.85–1.07)	0.96 (0.85–1.08)	527	69	1.14 (0.85–1.55)	1.33 (0.97–1.83)
Naproxen	712	79	0.77 (0.62–0.96)	0.81 (0.65–1.01)	128	7	0.52 (0.25–1.08)	0.48 (0.23–1.00)
Opioids	306	35	0.82 (0.60–1.14)	0.81 (0.58–1.12)	63	6	0.80 (0.36–1.77)	0.93 (0.40–2.15)
	Trying to conceive 0–2 cycles at study entry				**Trying to conceive 3–6 cycles at study entry**			
Non-use	1435	222	Reference	Reference	723	86	Reference	Reference
Any use	3962	597	1.01 (0.88–1.16)	1.06 (0.91–1.22)	1868	223	1.03 (0.82–1.30)	0.98 (0.77–1.25)
Acetaminophen	1568	248	1.09 (0.94–1.26)	1.12 (0.97–1.29)	794	90	0.95 (0.74–1.21)	0.90 (0.70–1.15)
Aspirin	339	56	1.12 (0.87–1.44)	1.10 (0.86–1.42)	238	22	0.78 (0.51–1.20)	0.80 (0.52–1.23)
Ibuprofen	2709	409	0.99 (0.88–1.13)	1.00 (0.88–1.14)	1286	150	0.99 (0.80–1.22)	0.97 (0.78–1.12)
Naproxen	582	61	0.74 (0.58–0.95)	0.79 (0.62–1.02)	258	25	0.81 (0.55–1.20)	0.81 (0.55–1.19)
Opioids	243	23	0.65 (0.43–0.96)	0.63 (0.42–0.95)	126	18	1.14 (0.72–1.78)	1.22 (0.77–1.19)
	Use of 1 type of pain medication				**Use of ≥2 types of pain medication**			
Non-use	2158	308	Reference	Reference	2158	308	Reference	Reference
Any use	4076	588	1.02 (0.90–1.16)	1.06 (0.93–1.21)	1754	232	0.98 (0.83–1.14)	1.00 (0.85–1.20)
Acetaminophen	882	138	1.08 (0.91–1.27)	1.07 (0.90–1.26)	1480	200	1.13 (0.87–1.48)	1.14 (0.87–1.49)
Aspirin	64	14	1.44 (0.92–2.27)	1.27 (0.82–1.97)	513	64	0.91 (0.70–1.20)	0.96 (0.73–1.28)
Ibuprofen	2712	387	1.01 (0.90–1.14)	1.04 (0.92–1.18)	1283	172	0.95 (0.74–1.22)	0.96 (0.75–1.23)
Naproxen	397	45	0.78 (0.59–1.03)	0.81 (0.61–1.07)	443	41	0.73 (0.54–1.00)	0.76 (0.56–1.04)
Opioid	21	4	1.53 (0.64–3.68)	1.76 (0.75–4.15)	348	37	0.75 (0.54–1.05)	0.84 (0.59–1.18)

Except for analyses examining participants who use only one pain medication, specific medication categories are not mutually exclusive and the results are adjusted for each of the other pain medications.

[a]Adjusted for age, education, income, race/ethnicity, IUD or OCs as last method of contraception, BMI, smoking history, physical activity, intercourse frequency, history of spontaneous abortion, having irregular menstrual cycles, menstrual cycle length, pain severity during menses, doing something to improve chances of conceiving, anxiety, endometriosis, leiomyomata, migraine headaches and antibiotic use.

[b]Models for irregular menstrual cycles and trying 3–6 cycles at study entry adjusted for age, education, income, BMI, pain during periods, history of spontaneous abortion, diagnosis of anxiety, a diagnosis of endometriosis and diagnosis of leiomyomata.

This study relied on self-reported exposure and outcome information via questionnaire and thus may be subject to differential reporting errors. Insofar as exposure and outcome are assessed at different time points, and over 96% of participants reported using home pregnancy tests to confirm their pregnancies, this bias is likely to be small.

Finally, this study relied on self-selected volunteers participating in a web-based study in a diverse population. Thus, a selection bias could occur if participation is jointly related to analgesic use and probability of pregnancy. However, because women were not pregnant at the time of enrollment and comparisons were made within the study population and not with the general population, selection bias is unlikely.

This study has a number of strengths. PRESTO participants were enrolled during the preconception period and data were collected prospectively, thereby decreasing the likelihood of selection bias and differential exposure misclassification. PRESTO participants represent the full range of the fertility spectrum, from the most fertile to those identified as infertile after 12 months of observation. With the high prevalence of home pregnancy test use, there was low potential for differential recognition of pregnancy by exposure status. Loss to follow-up was low and did not differ appreciably by pain-reliever use (11.8% of non-users, 11.3% of users). Further, recall of TTP has been shown to be accurate using our study design (Radin *et al.*, 2015). Finally, we adjusted our associations for a wide range of potential confounders.

Our study suggests that use of naproxen during the preconception period is associated with a small reduction in female fecundability, with evidence of a dose–response relation. Opioid use was also associated with a decrease in female fecundability, but given the small numbers of users, the results were imprecise and warrant confirmation with additional data.

The high prevalence of analgesic use among reproductive-age women warrants further examination of the effect of different dosing regimens, indications for use, and timing of use of analgesics among women planning a pregnancy.

Authors' roles

K.A.M. performed data management, analyses and drafted manuscript. E.E.H. K.J.R. and E.M.M. planned and implemented the PRESTO study and assisted with analytic decision-making and compilation of the manuscript. A.K.W. assisted with data analysis and management, analytic decision-making and compilation of the manuscript. L.A.W. planned and implemented the PRESTO study, assisted with data analysis, and oversaw analytic decision-making and compilation of the manuscript.

Funding

Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Health (R21 HD072326, T32 HD052458).

Conflict of interest

The authors have no conflicts of interest to disclose.

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