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Effects of common pharmacologic agents on reproductive outcomes among male and female pregnancy planners

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BOSTON UNIVERSITY
SCHOOL OF PUBLIC HEALTH

Dissertation

**EFFECTS OF COMMON PHARMACOLOGIC AGENTS ON REPRODUCTIVE
OUTCOMES AMONG MALE AND FEMALE PREGNANCY PLANNERS**

by

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ABSTRACT

Infertility and spontaneous abortion (SAB) affect up to one-third of couples planning a family.¹⁻³ While common, there are few known risk factors. Medication use may play a role but the extent is unknown because, for most agents, use during reproduction has been understudied. The objective of this dissertation was to examine the associations between use of common pharmacologic agents and reproductive outcomes in three interrelated prospective cohort studies of pregnancy planners in Denmark, the United States, and Canada.

In study 1, we examined fecundability, the average per-cycle probability of conception and a measure of time-to-pregnancy (TTP), in relation to past contraceptive use. Exposures of interest included oral contraceptives, IUDs (hormonal, copper), rings, implants, patches, injectables, natural methods, and barrier methods. Among 9,350 female pregnancy planners, we first examined TTP by the last method of contraception used before pregnancy attempt. We then examined the association between total lifetime duration of use of hormonal contraceptive methods and TTP. On average, injectable users had the longest delay in the return of fertility (8 cycles), followed by OC, ring, implant and patch

(3 cycles), hormonal IUD (2 cycles), and copper IUD users (1 cycle). We did not find any evidence that long-term use of these methods was detrimental to fecundability.

Study 2 examined the association between male use of pain medications and fecundability among 1,065 couples planning pregnancy in North America. Medications examined include ibuprofen, acetaminophen, naproxen, and aspirin. We examined fecundability in relation to any use and cumulative monthly dose of each of these medications. Our study showed little evidence of a deleterious effect of male preconception use of common pain medications on fecundability.

In study 3, we examined use of pain medications between pregnancy conception and 12 gestational weeks and risk of SAB. Medications examined include ibuprofen, acetaminophen, naproxen, aspirin, and opioids. In the three cohorts of women recruited before conception, we observed 9,196 pregnancies and 1,597 SABs (17.4%). We found that low-dose use of ibuprofen, naproxen, or opioids before 12 weeks of gestation was associated with slightly increased risk of SAB. Overall, low-dose use of acetaminophen or aspirin did not appreciably increase risk of SAB.

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LIST OF ABBREVIATIONS

AMH.....	Anti-Mullerian Hormone
BMI.....	Body Mass Index
CI.....	Confidence Interval
COX.....	Cyclooxygenase
CPR.....	Civil Personal Registration
DKK.....	Danish Krone
DNRP.....	Danish National Registry of Patients
EAGeR.....	Effects of Aspirin in Gestation and Reproduction
FR.....	Fecundability Ratio
FSH.....	Follicle-stimulating Hormone
hCG.....	Human Chorionic Gonadotropin
HR.....	Hazard Ratio
ICD.....	International Classification of Disease
IQR.....	Interquartile Range
IUD.....	Intrauterine Device
LARC.....	Long-acting Reversible Contraceptives
LMP.....	Last Menstrual Period
MET.....	Metabolic Equivalent of Task
NSAID.....	Nonsteroidal Anti-inflammatory Drug
OC.....	Oral Contraceptive
OTC.....	Over-the-counter

PCP.....	Primary Care Provider
PG.....	Prostaglandin
PPV.....	Positive Predictive Value
PRESTO.....	Pregnancy Study Online
PSS.....	Perceived Stress Scale
SAB.....	Spontaneous Abortion
SF.....	Snart Forældre
SG.....	Snart Gravid
SSB.....	Sugar Sweetened Beverage
TAB.....	Therapeutic Abortion
TTP.....	Time-to-pregnancy
U.S.....	United States
USD.....	United States Dollar

1 INTRODUCTION

Infertility and spontaneous abortion (SAB) are common reproductive problems with few identified risk factors. Estimates of the prevalence of current infertility, defined as the inability to conceive during 12 months of regular unprotected intercourse, vary widely. In the United States, estimates range from 6.0%¹ to 15.5%² of women ages 15–44. Infertility can be attributed to one or both partners. It is thought that approximately 33% of infertility can be attributed to the female partner, 20% can be attributed to male partner, 39% can be attributed to both partners, and 8% remains unknown.³ The primary explanations for infertility are thought to be ovulatory disorders among females and reduced sperm motility among males.^{3,4} Known predictors of infertility include older maternal age⁵, and conditions such as pelvic inflammatory disease⁶ and endometriosis.⁷ Modifiable risk factors and cause of these reproductive disorders remain largely unknown.

Spontaneous abortion (SAB), defined as the loss of pregnancy before 20 weeks of gestation, is a common pregnancy outcome that affects approximately 20% of clinically recognized pregnancies.⁸ While there is substantial research on SAB, there are relatively few known risk factors.^{9,10} The methodological challenges in studying SAB have led to few consistent clinical recommendations to reduce risk of pregnancy loss. Examination of pharmacologic agents on SAB risk have often been conducted in large administrative databases^{11–13} or post-conception cohorts.^{14–16} These study designs often fail to capture SABs that occur before women visit healthcare providers and could result in considerable

bias.

Medication use among men and women of childbearing age is common.¹⁷⁻

¹⁹ In 2005, the majority of reproductive-aged women in the United States used over the counter or prescription medications.¹⁸ Because pharmacologic agents are used so widely periconceptionally, even small increases in the risk of infertility or SAB would have a large public health impact. Information about the reproductive safety of medications is often limited, even for common medications such as pain relievers.

Using prospectively collected data from Danish and North American pregnancy planners, this dissertation examined female pregravid use of contraceptives and fecundability (Chapter 2), male pain-reliever use and fecundability (Chapter 3), and early pregnancy use of pain-relievers and risk of spontaneous abortion (Chapter 4).

1.1 References

2 PREGRAVID CONTRACEPTION USE AMONG FEMALES AND FECUNDABILITY

2.1 Introduction

Long-acting reversible contraceptive (LARC) methods and the contraceptive ring have gained popularity among women wanting to avoid pregnancy.²⁰ These methods include intrauterine devices (IUDs), implants, and injectable contraceptives.²¹ In Europe, 10% of women used LARC methods in 2006.²² In the United States (U.S.), 2% of women ages 25–34 used LARC methods in 1995 compared with 11% in 2011–2013.²³ The contraceptive ring, an effective alternative to oral contraceptives (OCs), has had quick uptake since its approval in 2001²⁴ and was used by 7% of US women in 2006–2010.²⁰

These contraceptive methods often contain a progestin (OCs, implants, injectables, patches, rings, hormonal IUD) and estrogen (OCs, patches, rings) and have a variety of mechanisms of action including preventing ovulation (OCs, implants, injectables, patches, and rings), thinning the uterine lining to prevent implantation and thickening cervical mucus to prevent semen transport (OCs, hormonal IUD, implants, patches, rings, and injectables), and providing a barrier between sperm and egg (hormonal IUD and copper IUD). While the mechanisms of the IUDs are not fully understood, the copper IUD additionally damages sperm to prevent successful fertilization.²⁵ Effects of these contraceptives may persist after discontinuation and leading to delayed conception.

Research on contraception and fertility has focused primarily on OCs. Studies have consistently found slight delays in return of fertility after cessation of OC use.^{26,27} Women who use OCs for long durations may have increased fecundability when compared with short-term users,^{26,28} but results have been inconsistent.²⁹ Less is known about the association between ceasing use of alternative methods of contraception and fertility. When compared with barrier methods, IUDs (copper and hormonal combined) have been associated with slightly increased time to conception,^{27,30} but results are conflicting^{29,31} and could be confounded by parity. One study suggested that injectable use may be associated with increased time to conception.²⁹ Most studies examining less common contraceptive methods have been retrospective^{27,30} and/or underpowered.²⁹⁻³¹

There is limited information about fertility after use of IUDs, injectables, rings, implants, or patches. Using prospectively collected data, this study examines fecundability among women who discontinued contraception in order to conceive. As women delay childbearing, timing of return of fertility may be an important factor in contraceptive choice among pregnancy planners.

2.2 Methods

2.2.1 Study Population

To enhance sample size, data from three prospective cohort studies of pregnancy planners were pooled for this analysis: 1) In Denmark, Smart Gravid

(SG) (2007–2011)³² enrolled female pregnancy planners ages 18–49 years; 2) Snart Foraeldre (SF) (2011–2017), an extension of SG, also includes male partners;³³ 3) in the U.S. and Canada, Pregnancy Study Online (PRESTO) (2013–2017)³⁴ enrolls female pregnancy planners ages 21–45 and their male partners. Recruitment for SF and PRESTO is ongoing.

Participants in all studies were recruited primarily using advertisements on social media and health-related websites. Eligible women were in a relationship with a male partner, not pregnant, and not using contraception or fertility treatments.

All questionnaires were administered online. At baseline, participants reported exposure and covariate information including self-reported demographics, lifestyle factors, and medical history. Follow-up questionnaires were administered every two months for 12 months or until reported pregnancy. Over 80% of participants completed at least one follow-up questionnaire.^{34,35} The Danish Data Protection Board and Boston University Medical Center institutional review board approved the study protocol and participants provided online informed consent.

2.2.2 Assessment of Contraceptive Use

At baseline, participants reported the contraceptive method they used last, before beginning their conception attempt. Categories included barrier methods (condoms, diaphragm, sponge, jells/foams/creams/suppositories), OCs, hormonal IUDs, copper IUDs, patches, injectables, rings, implants, and natural

methods (withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, avoiding sex during fertile window). Recent users of hormonal methods were asked if they waited for a period of time after discontinuing this method before attempting to conceive.

In PRESTO, women also reported the total number of hormonal contraceptives (e.g. OCs, rings, implants, hormone IUDs) they have ever used, the name of each method, and their ages at initiation and cessation of each. In SF and SG, a detailed history of use was only collected for OCs. For PRESTO, duration was calculated separately for each type of hormonal contraceptive by summing the years of use.

2.2.3 Assessment of Pregnancy and Menstrual Cycles at Risk

At baseline, participants reported their usual menstrual cycle length, their date of last menstrual period (LMP), and the number of cycles they had been trying to conceive. At each follow-up, participants reported their LMP date, pregnancy status primarily confirmed using home pregnancy tests (>96%), and information about time-varying covariates. Total cycles at risk were calculated as (cycles trying to conceive at study entry) + [(LMP date from most recent follow-up questionnaire - date of baseline questionnaire)/cycle length] + 1.

2.2.4 Exclusions

Participants were excluded if they did not complete at least 1 follow-up questionnaire, if they reported insufficient or implausible menstrual cycle

information, or if they had been trying to conceive for >6 cycles at study entry. We also excluded women if they used a contraceptive method not examined (e.g. reversed sterilization). The final analytic sample included 3,966 women from SG, 2,367 women from SF, and 3,017 women from PRESTO for a combined total of 9,350 women (Figure 2.1).

2.2.5 Data Analysis

Women contributed at-risk cycles to the analysis beginning at study entry until reported pregnancy, initiation of fertility treatment, withdrawal, loss-to-follow-up, or 12 cycles, whichever occurred first. We first examined the association between fecundability and use of OCs, hormonal IUDs, copper IUDs, rings, implants, patches, injectables, and natural methods as the last method of contraception compared with barrier methods. Next, we compared fecundability after use of hormonal versus copper IUDs. We then examined fecundability for each method by cycle of pregnancy attempt compared with barrier methods as a method that presumably has no persistent effects upon cessation. Lastly, we examined the total duration of use of each hormonal method. Total duration was split into two-year categories and compared with <2 years of use.

We used proportional probabilities models to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs).³⁶ The FR is a measure of the average per-cycle probability of conception comparing users of a specific contraceptive method with the reference group. The proportional probabilities model adjusts for cycle at risk, taking into account average declining fecundability as fertile couples

conceive and are removed from the denominator over time.³⁷ We used the Andersen-Gill data structure to account for differences in attempt time at enrollment (0–6 cycles) and to reduce bias from left truncation.^{38,39} For example, if a woman entered the study with 3 cycles of attempt time and conceived during her 6th cycle, she would contribute cycles 4–6 to the analysis. We also used the weighted copy method to reduce convergence issues associated with the log binomial model.⁴⁰

Models were adjusted for potential confounders selected *a priori* based on the literature and a directed acyclic graph. These included cohort (SG, SF, PRESTO), age (<25, 25–29, 30–34, ≥35 years), education (≤12, 13–15, 16, ≥17 years), non-Hispanic white (yes versus no), income (< versus ≥ 50,000 USD/300,000 DKK per year), current smoking (yes versus no), BMI (<25, 25–29, ≥30 kg/m²), baseline intercourse frequency (<1, 1–3, ≥4 times per week), doing something to improve chances of conception (e.g. timing intercourse during the fertile window, monitoring cervical mucus) (yes versus no), physician diagnosed endometriosis (yes versus no), physician diagnosed uterine leiomyomata (yes versus no), physician diagnosed diabetes (yes versus no) and lifetime duration of hormonal contraceptive use (months; SG/SF: OCs only, PRESTO: all hormonal contraceptives)²⁶. Models were run with and without adjustment for menstrual cycle characteristics (regularity: yes versus no; length: ≤21, 22–35, ≥36 days; and flow heaviness: yes versus no) and parity (0, ≥1 births), as these may be causal intermediates.⁴¹

Results for most recent type of contraception were examined separately by cohort (SG, SF, PRESTO) to examine the impact of potential biases stemming from minor difference in data collection or differences by country, age (<30 versus ≥ 30 years) to determine any differences in delay by baseline fecundity, attempt time at study entry (0–2 versus 3–6 cycles) to examine changes in effect with increasing attempt time, and BMI (<30 versus ≥ 30 kg/m²) as effectiveness of hormonal contraceptives may vary by BMI.⁴² We also stratified by history of infertility (*i.e.*, *12 months of unprotected intercourse without conception*) (yes versus no), and parity (0 versus ≥ 1 births) to explore residual confounding by indication.

We used PROC MI to impute missing values for exposures and covariates to create five datasets. 2.4% of participants were missing last method of contraception. Duration of use for each type of hormonal contraceptive was imputed for between 0.2% (implants) and 17.1% of participants (OCs). We used PROC MIANALYZE to combine coefficient and standard error estimates.⁴³

2.3 Results

OCs (42.9%), barrier methods (30.9%), and natural methods (12.9%) were the most commonly-used last methods of contraception. The most commonly-used LARC methods were IUDs, with 5.4% and 3.7% of women last using the hormonal and copper IUD, respectively. Compared with users of all other methods, IUD users were more likely to be older and parous; injectable and implant users were less likely to identify as non-Hispanic white and more likely to

have a lower household income; and patch and injectable users were more likely to report lower educational attainment. Injectable users were also more likely than users of other methods to report a history of infertility or diabetes, and patch and implant users were more likely to report endometriosis (Table 2.1). 9,350 women contributed a total of 39,261 menstrual cycles and 6,215 pregnancies to the analysis.

2.3.1 Last Method of Contraception

Overall, after adjusting for potential confounders, use of OCs (FR=0.90, 95% CI: 0.85–0.95) or injectables (FR=0.73, 95% CI: 0.46–1.14) as the last method of contraception was associated with decreased fecundability compared with barrier methods. On average, last use of hormonal IUDs, copper IUDs, rings, implants, patches or natural methods was not meaningfully associated with fecundability compared with barrier methods. There was little difference in fecundability comparing the copper and hormonal IUDs. While adjustment for menstrual cycle characteristics did not appreciably change the results (data not shown), there is evidence of confounding by parity as adjustment attenuated the slight increase in fecundability observed when comparing the hormone and copper IUDs with barrier methods (Table 2.2).

Figure 2 and Table 3 display the cycle-specific probability of conception and FRs, respectively, for recent users of different methods of contraception (Figure 2.2). Compared with barrier methods, we observed varying delays in return of fertility for recent users. On average, return of fertility was delayed by 8

cycles for injectable users, 3 cycles for users of OCs, rings, implants, and patches, 2 cycles for copper IUD users, and 1 cycle for hormonal IUD users (Table 2.3).

Relative to barrier method use, use of OC as the last method of contraception was associated with decreased fecundability among women trying to conceive for 0–2 cycles at study entry (FR=0.85, 95% CI: 0.80–0.91) but not 3–6 cycles (FR=1.05, 95% CI: 0.93–1.17), consistent with a short-term delay in return of fertility. Results were similar when stratifying by age, BMI, parity and history of infertility (Table 2.4) and when analyzing the cohorts separately (Table 2.5).

2.3.2 Lifetime Duration of Use

In a subgroup analysis of PRESTO participants, there was no evidence of decreased fecundability with longer total lifetime duration of use of OCs, rings, injectables, hormonal IUDs, implants, and patches (Table 2.6).

2.4 Discussion

In this prospective cohort of pregnancy planners, we found that users of OCs and some LARC methods experienced short-term delays in return of fertility compared with barrier method users. On average, injectable users had the longest delay in the return of fertility (8 cycles), followed by OC, ring, implant and patch (3 cycles), hormonal IUD (2 cycles), and copper IUD users (1 cycle). We did not find any evidence that long-term use of these methods was detrimental to fecundability.

The delay in return of fertility we observed is consistent with our previous study examining OC use in a subset of the SG cohort.²⁶ Our results are also consistent with additional literature finding slight delays in return of fertility after use of OCs,²⁷ IUDs,^{27,30} and implants.²⁹ Use of OCs, rings, and patches inhibits ovulation^{25,44,45} and may suppress ovarian function immediately after discontinuation.⁴⁶ In cycle-specific analyses we observed reduced fecundability among participants who recently used these methods.

Our finding of reduced fecundability after injectable use was consistent with previous studies.^{29,47} The level of progestin in injectables inhibits ovulation and may result in suppressed ovarian function for much longer than 90 days, the recommended interval between injections.^{48,49} Women were likely attempting to conceive when the medication was still active. This would explain the reduced fecundability overall and the 8 cycle delay in the return of fertility. However, characteristics of injectable users were different than barrier method users. Residual confounding by unmeasured factors, such as overall health and reproductive health knowledge, may explain part of the observed association. Further, loss to follow-up was higher among injectable users than non-users. If use of injectables causes reduced fecundability, our results would underestimate the detrimental effect of injectables on fecundability.

The mechanisms by which IUDs prevent pregnancy is not fully understood. Previous research on IUDs and fecundability has primarily examined IUDs as one group and not separately by type.^{27,30,31} Overall, we did not observe

a meaningful difference in fecundability comparing hormonal and copper IUDs. We did, however, observe a slightly longer delay in return of fertility among hormonal IUD users. This difference may result from the progestin-induced thinning of the uterine lining that occurs with hormonal IUD use.⁵⁰

Previous studies, including one based on the SG cohort,²⁶ observed a small increase in fecundability after long-term OC use.^{26,28} As ovulation may cease during use,²⁵ some^{51,52} but not all^{53–55} studies suggest that long-term use may help to maintain ovarian reserve levels. Our analysis of PRESTO participants showed no detrimental effect of long-term OC use on fecundability but does not suggest any considerable improvement.

This study has several limitations. While the large sample allowed for evaluation of less common methods of contraception, there were still small numbers of users of injectables, rings, and implants, limiting precision of the results. As discussed, contraceptive choice may relate to underlying fertility and residual confounding may partially explain our results. While we adjusted for contraindications and demographic and lifestyle factors, residual confounding by unmeasured factors (e.g. undiagnosed reproductive disorders), is still possible. Further, some misclassification of the cycle of conception was likely. This calculation relies on reported menstrual cycle length and date of the LMP and accuracy may differ by last contraceptive method. For example, if women with irregular cycles were more likely to use OCs than barrier methods, and their cycle of conception was more likely to be misclassified, the results could be

biased in either direction. Additionally, a selection bias could occur if participation was related to both contraceptive use and fecundability; however, because women enrolled in the study before conception, selection bias arising from differential participation is likely to be minimal.

Because a detailed history of use of all types of hormonal contraceptives was collected in PRESTO only, precision was limited for duration analyses. Further, reporting of contraceptive methods is likely to be less accurate for methods used in the distant past as compared with recently-used methods. Nevertheless, since contraceptive history was collected before report of pregnancy, any misclassification is likely non-differential. The effect of this misclassification would be a bias towards the null in the longest duration categories, and an unpredictable bias in the intermediate categories.

We found that use of OCs, LARC methods, and the contraceptive ring was associated with transient delays in the return of fertility, with injectables showing the longest delay (approximately 8 menstrual cycles). Our findings indicate little effect of long-term use of these methods.

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Figure 2.1: Flow chart of enrollment and exclusions, Snart Gravid, Snart Forældre and PRESTO (N=13,466), 2007–2017

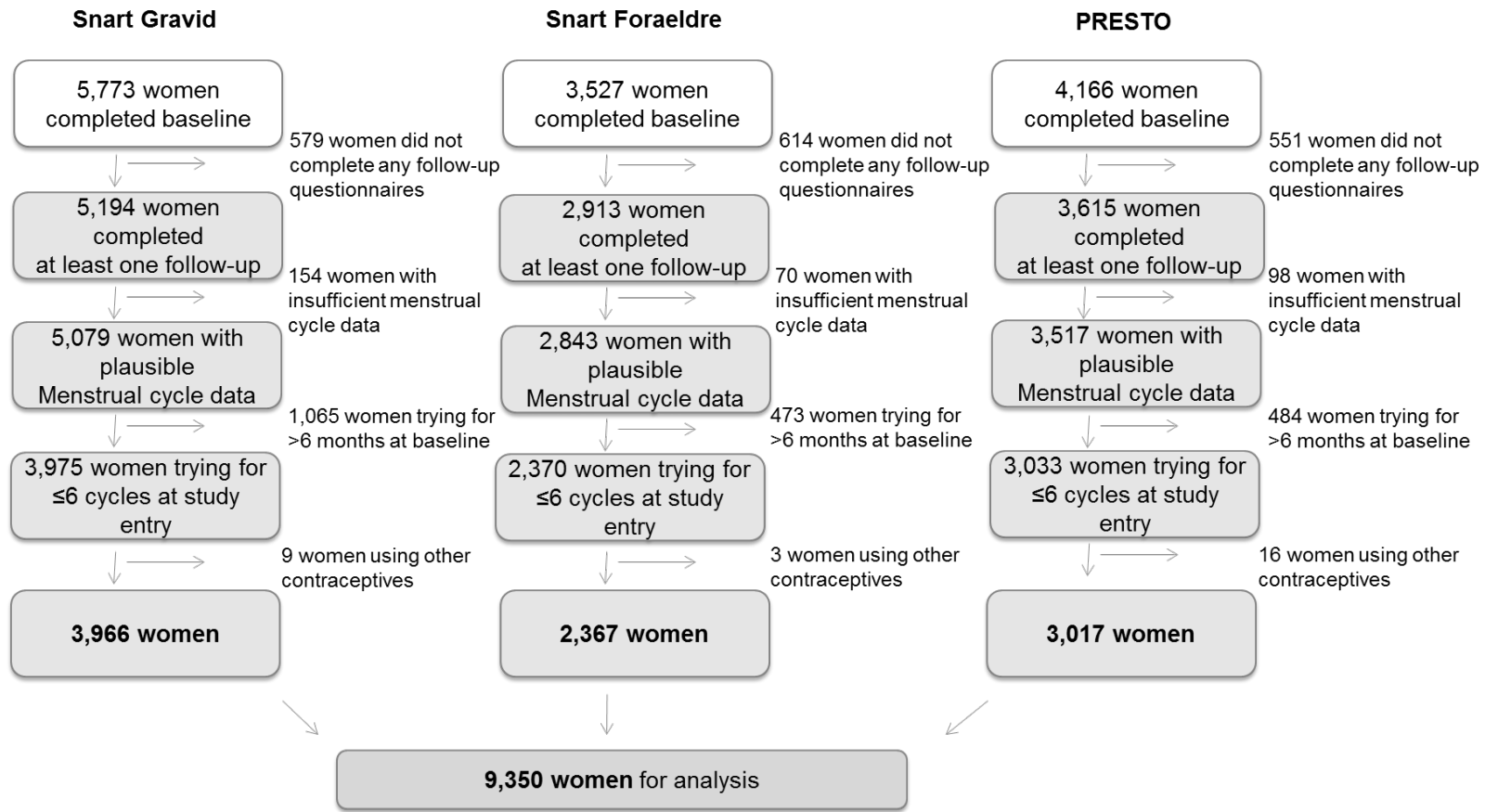


Table 2.1 Baseline characteristics of pregnancy planners by last method of contraception, Snart Gravid, Snart Forældre and PRESTO (N=9,350), 2007–2017

	Barrier	OC	Hormonal IUD	Copper IUD	Ring	Implant	Patch	Injectable	Natural [†]
Number of Participants N (%)	2,891 (30.9)	4,011 (42.9)	505 (5.4)	344 (3.7)	274 (2.9)	52 (0.6)	32 (0.3)	33 (0.4)	1,208 (12.9)
Cohort									
Snart Gravid	35.0	53.8	35.1	23.6	35.4	17.3	40.6	30.3	33.9
Snart Forældre	27.0	26.8	25.9	46.8	22.3	17.3	28.1	9.1	11.3
PRESTO	38.0	19.4	39.0	29.7	42.3	65.4	31.3	60.6	54.8
Age (years), mean	29.2	28.3	30.4	30.3	28.8	27.1	27.8	26.9	29.9
Partners age (years), mean	30.9	31.1	31.3	31.9	31.3	31.2	27.5	30.6	31.4
Non-Hispanic White, %	94.6	97.8	94.7	95.6	93.4	86.6	91.6	80.1	91.5
Annual household income <50,000 USD/<300,000 DKK, %	16.0	13.7	14.7	15.3	16.6	19.1	11.1	23.9	18.0
<College degree, %	28.4	33.1	30.2	25.1	32.1	36.9	41.8	50.8	25.8
Length of relationship (years), mean	5.9	5.1	5.8	5.5	4.7	4.7	4.8	4.4	5.6
BMI (kg/m ²), mean	24.9	24.7	25.6	24.6	25.2	28.4	21.8	27.6	25.1
Past smoker, %	21.0	19.3	19.9	18.0	20.9	27.2	19.6	15.1	23.2
Current smoker, %	9.0	13.9	14.0	16.5	10.5	4.4	14.1	28.4	10.8
Parous, %	31.6	28.2	58.0	54.2	27.2	38.1	19.8	39.0	33.1
Irregular menstrual cycle, %	22.6	23.8	20.0	15.8	20.5	24.8	22.1	30.2	19.8
Menstrual cycle length <22 days, %	0.7	1.5	1.0	0.0	0.7	0.0	0.0	3.7	0.6
Menstrual cycle length ≥36 days, %	9.1	9.1	6.7	5.7	8.0	9.5	5.5	1.2	7.1
Doing something to improve chances of conceiving, %	68.9	56.0	64.7	65.3	56.5	67.9	61.5	59.6	65.7
Intercourse frequency <1 time/week, %	20.1	15.6	14.6	13.6	16.1	22.3	17.0	21.9	20.6
Intercourse frequency ≥4 times/week, %	14.8	19.3	21.2	22.3	15.8	20.5	8.4	28.4	15.5
History of infertility, %	8.1	7.1	10.5	6.1	5.3	6.1	5.6	21.1	6.8
Diabetes, %	1.2	1.2	1.9	1.0	2.2	0.0	2.8	5.2	1.4
Uterine leiomyomata, %	1.7	2.5	1.7	1.6	3.4	2.2	5.5	3.7	2.2
Endometriosis, %	2.2	2.4	3.0	2.5	4.1	6.1	5.5	3.7	2.0

OC = Oral contraceptive, IUD = Intrauterine device, USD = U.S. dollars, DKK = Danish kroner.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal temperature, and avoiding sex when fertile.

Note 1. All characteristics except for age are age-standardized to the cohort at baseline.

Table 2.2 Last method of contraception and fecundability among pregnancy planners

Method	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b	Adjusted FR (95% CI) ^c
Barrier	11,784	1,916	Reference	Reference	Reference
OC	17,483	2,653	0.90 (0.85–0.95)	0.89 (0.84–0.94)	0.90 (0.85–0.95)
Hormonal IUD	1,830	381	1.20 (1.09–1.32)	1.22 (1.11–1.35)	1.11 (1.01–1.23)
Copper IUD	1,316	252	1.10 (0.98–1.23)	1.12 (0.99–1.26)	1.05 (0.93–1.18)
Ring	1,199	174	0.91 (0.78–1.05)	0.93 (0.80–1.07)	0.93 (0.80–1.07)
Implant	214	31	0.94 (0.68–1.30)	1.02 (0.74–1.41)	1.01 (0.73–1.39)
Patch	147	22	0.91 (0.62–1.33)	0.94 (0.64–1.37)	0.98 (0.67–1.44)
Injectable	181	17	0.67 (0.43–1.05)	0.73 (0.47–1.14)	0.73 (0.46–1.14)
Natural [†]	5,107	769	0.95 (0.87–1.02)	0.97 (0.89–1.05)	0.95 (0.87–1.02)
IUDs					
Copper IUD	1,316	252	Reference	Reference	Reference
Hormonal IUD	1,830	381	1.10 (0.96–1.27)	1.12 (0.97–1.31)	1.08 (0.93–1.26)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

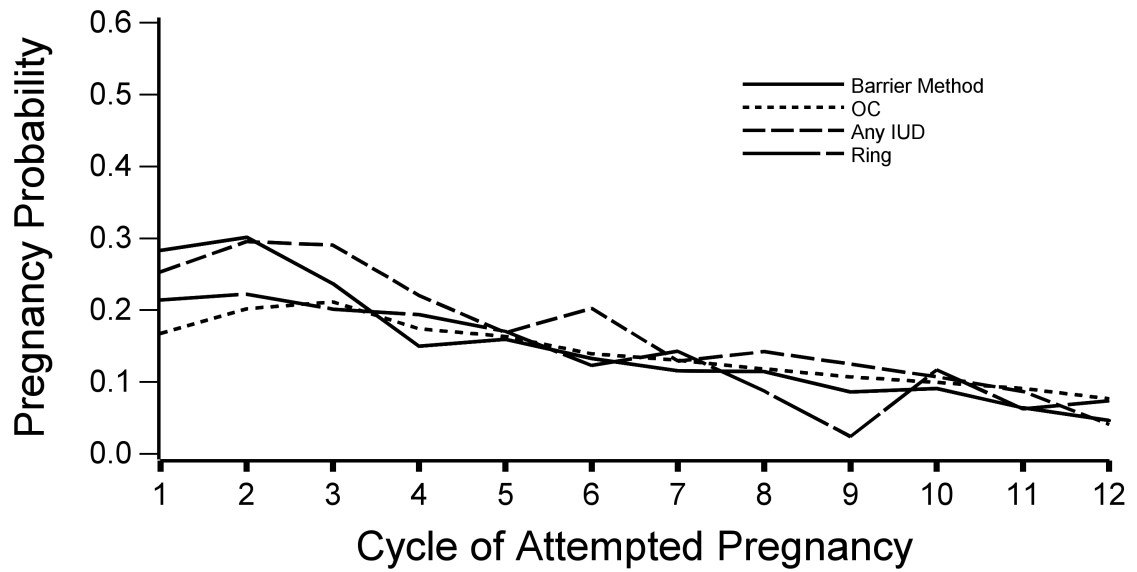
a Adjusted for study (SF, SG, PRESTO).

b Models adjusted for study, age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, and duration of hormonal contraception use.

c Models adjusted for variables in b, and parity.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

Figure 2.2 Per-cycle probability of conception by last method of contraception



IUD=Intrauterine device

Note: Additional LARC methods were not displayed due to the small number of users.

Table 2.3 Last method of contraception and fecundability among pregnancy planners by observed cycle of attempt

Method	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycles 5–8	Cycles 9–12
Barrier						
No. of cycles	664	1,350	1,376	1,329	4,633	2,432
No. of pregnancies	188	407	326	199	613	183
Adjusted FR (95% CI) ^a	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Adjusted FR (95% CI) ^b	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
OC						
No. of cycles	805	1,897	2,145	2,092	6,991	3,553
No. of pregnancies	135	383	454	364	976	341
Adjusted FR (95% CI) ^a	0.62 (0.50–0.75)	0.66 (0.58–0.75)	0.87 (0.76–0.99)	1.11 (0.94–1.31)	1.02 (0.92–1.12)	1.16 (0.97–1.38)
Adjusted FR (95% CI) ^b	0.68 (0.44–1.05)	0.68 (0.60–0.77)	0.87 (0.77–0.99)	1.12 (0.95–1.32)	1.01 (0.92–1.12)	1.12 (0.93–1.34)
Hormonal IUD						
No. of cycles	120	257	262	232	669	290
No. of pregnancies	32	72	79	53	120	25
Adjusted FR (95% CI) ^a	0.97 (0.71–1.34)	0.94 (0.76–1.16)	1.26 (1.02–1.55)	1.51 (1.16–1.98)	1.35 (1.13–1.61)	1.12 (0.75–1.66)
Adjusted FR (95% CI) ^b	0.89 (0.65–1.21)	0.86 (0.70–1.06)	1.19 (0.97–1.46)	1.33 (1.01–1.74)	1.27 (1.06–1.52)	1.05 (0.73–1.51)
Copper IUD						
No. of cycles	105	183	168	140	481	239
No. of pregnancies	25	58	46	29	68	26
Adjusted FR (95% CI) ^a	0.79 (0.55–1.13)	1.05 (0.83–1.32)	1.13 (0.87–1.47)	1.35 (0.95–1.91)	1.05 (0.83–1.32)	1.35 (0.92–1.99)
Adjusted FR (95% CI) ^b	0.78 (0.52–1.17)	1.01 (0.80–1.27)	1.10 (0.85–1.43)	1.27 (0.90–1.80)	0.99 (0.79–1.26)	1.22 (0.82–1.82)
Ring						
No. of Cycles	56	117	139	129	480	278
No. of pregnancies	12	26	28	25	64	19
Adjusted FR (95% CI) ^a	0.76 (0.45–1.27)	0.77 (0.55–1.09)	0.81 (0.56–1.16)	1.27 (0.87–1.85)	1.02 (0.80–1.30)	0.91 (0.57–1.43)
Adjusted FR (95% CI) ^b	0.82 (0.51–1.34)	0.74 (0.52–1.05)	0.83 (0.58–1.19)	1.36 (0.93–1.98)	1.04 (0.82–1.32)	0.92 (0.60–1.40)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

^a Adjusted for study (SF, SG, PRESTO).

^b Models adjusted for study, age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, and duration of hormonal contraception use.

^c Models adjusted for variables in b, and parity.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

Table 2.3 Continued. Last method of contraception and fecundability among pregnancy planners by observed cycle of attempt

Method	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycles 5–8	Cycles 9–12
Implant						
No. of cycles	8	20	32	27	81	46
No. of pregnancies	3	2	6	4	13	3
Adjusted FR (95% CI) ^a	1.32 (0.54–3.25)	0.35 (0.10–1.31)	0.81 (0.39–1.67)	1.05 (0.42–2.62)	1.30 (0.79–2.15)	0.93 (0.31–2.78)
Adjusted FR (95% CI) ^b	1.34 (0.57–3.14)	0.39 (0.10–1.43)	0.87 (0.42–1.79)	1.06 (0.43–2.60)	1.52 (0.92–2.50)	0.91 (0.34–2.44)
Patch						
No. of Cycles	3	15	19	19	59	32
No. of pregnancies	0	1	3	3	11	4
Adjusted FR (95% CI) ^a	--	0.22 (0.03–1.47)	0.66 (0.23–1.86)	1.02 (0.36–2.88)	1.41 (0.82–2.41)	1.57 (0.62–3.95)
Adjusted FR (95% CI) ^b	--	0.25 (0.04–1.63)	0.72 (0.26–2.01)	1.06 (0.37–2.98)	1.51 (0.88–2.58)	1.47 (0.60–3.64)
Injectable						
No. of cycles	2	8	15	22	78	56
No. of pregnancies	0	1	1	1	7	7
Adjusted FR (95% CI) ^a	--	0.43 (0.07–2.67)	0.29 (0.04–1.90)	0.32 (0.05–2.12)	0.71 (0.35–1.44)	1.77 (0.88–3.57)
Adjusted FR (95% CI) ^b	--	0.41 (0.07–2.53)	0.37 (0.06–2.39)	0.34 (0.05–2.29)	0.79 (0.39–1.61)	1.65 (0.76–3.58)
Natural[†]						
No. of cycles	266	598	651	622	1,946	1,024
No. of pregnancies	20	134	141	114	245	75
Adjusted FR (95% CI) ^a	0.83 (0.63–1.09)	0.78 (0.65–0.94)	0.90 (0.75–1.09)	1.24 (0.99–1.54)	1.00 (0.87–1.15)	1.02 (0.78–1.33)
Adjusted FR (95% CI) ^b	0.84 (0.62–1.15)	0.79 (0.66–0.94)	0.91 (0.77–1.09)	1.21 (0.97–1.51)	1.00 (0.87–1.16)	1.02 (0.80–1.30)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

a Adjusted for study (SF, SG, PRESTO).

b Models adjusted for study, age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, and duration of hormonal contraception use.

c Models adjusted for variables in b, and parity.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

Table 2.4 Last method of contraception and fecundability among pregnancy planners stratified by age and attempt time at study entry

Method	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b
Age<30				Age≥30				
Barrier	6,425	1,086	1.00 (Reference)	1.00 (Reference)	5,359	830	1.00 (Reference)	1.00 (Reference)
OC	11,099	1,707	0.89 (0.83–0.96)	0.89 (0.83–0.96)	6,384	946	0.90 (0.83–0.98)	0.91 (0.83–0.99)
Hormonal IUD	778	167	1.22 (1.05–1.40)	1.07 (0.92–1.23)	1,052	214	1.18 (1.04–1.35)	1.14 (1.00–1.30)
Copper IUD	537	117	1.21 (1.03–1.43)	1.12 (0.95–1.32)	779	135	1.01 (0.86–1.19)	0.98 (0.83–1.15)
Ring	781	112	0.87 (0.73–1.04)	0.89 (0.74–1.07)	418	62	0.96 (0.76–1.22)	0.97 (0.77–1.22)
Implant	140	21	0.95 (0.64–1.41)	0.98 (0.66–1.44)	74	10	0.89 (0.50–1.57)	0.98 (0.55–1.72)
Patch	94	13	0.83 (0.50–1.36)	0.90 (0.55–1.48)	53	9	1.03 (0.57–1.86)	1.07 (0.60–1.94)
Injectable	141	12	0.58 (0.34–0.99)	0.65 (0.38–1.11)	40	5	0.98 (0.44–2.22)	0.98 (0.44–2.19)
Natural [†]	2,443	400	0.97 (0.87–1.10)	0.97 (0.86–1.08)	2,664	369	0.91 (0.81–1.02)	0.93 (0.83–1.05)
IUDs								
Copper IUD	537	117	1.00 (Reference)	1.00 (Reference)	779	135	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	778	167	1.01 (0.82–1.24)	0.96 (0.78–1.19)	1,052	214	1.17 (0.96–1.42)	1.18 (0.96–1.46)
Trying 0–2 cycles at study entry				Trying 3–6 cycles at study entry				
Barrier	7,927	1,454	1.00 (Reference)	1.00 (Reference)	3,857	462	1.00 (Reference)	1.00 (Reference)
OC	11,962	1,914	0.84 (0.79–0.90)	0.85 (0.80–0.91)	5,521	739	1.08 (0.97–1.21)	1.05 (0.93–1.17)
Hormonal IUD	1,359	288	1.12 (1.00–1.25)	1.05 (0.94–1.17)	471	93	1.55 (1.27–1.89)	1.38 (1.13–1.69)
Copper IUD	944	199	1.08 (0.94–1.23)	1.03 (0.90–1.17)	372	53	1.19 (0.92–1.55)	1.14 (0.87–1.48)
Ring	769	127	0.89 (0.76–1.06)	0.92 (0.78–1.09)	430	47	0.95 (0.72–1.26)	0.94 (0.71–1.25)
Implant	160	23	0.86 (0.59–1.26)	0.91 (0.63–1.32)	54	8	1.28 (0.68–2.43)	1.46 (0.77–2.75)
Patch	106	14	0.73 (0.45–1.18)	0.82 (0.51–1.33)	41	8	1.71 (0.93–3.14)	1.60 (0.86–2.96)
Injectable	106	6	0.38 (0.18–0.82)	0.45 (0.21–0.97)	75	11	1.21 (0.70–2.08)	1.22 (0.71–2.11)
Natural [†]	3,673	585	0.90 (0.82–0.99)	0.90 (0.83–0.99)	1,434	184	1.11 (0.94–1.31)	1.10 (0.94–1.30)
IUDs								
Copper IUD	944	199	1.00 (Reference)	1.00 (Reference)	372	53	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	1,359	288	1.05 (0.89–1.23)	1.03 (0.88–1.22)	471	93	1.34 (0.98–1.83)	1.20 (0.85–1.70)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

a Model adjusted for study.

b Models adjusted for study, age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, duration of hormonal contraception use and parity.

Note 1: Stratified models for age were adjusted for a continuous age.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or body temperature, and avoiding sex when fertile.

Table 2.4 Continued. Last method of contraception and fecundability among pregnancy planners stratified by BMI and history of infertility

Method	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b
			BMI <30 kg/m ²				BMI ≥30 kg/m ²	
Barrier	9,639	1,651	1.00 (Reference)	1.00 (Reference)	2,145	265	1.00 (Reference)	1.00 (Reference)
OC	14,930	2,361	0.90 (0.85–0.96)	0.91 (0.86–0.96)	2,553	292	0.84 (0.71–0.98)	0.82 (0.69–0.96)
Hormonal IUD	1,408	323	1.26 (1.13–1.40)	1.14 (1.03–1.27)	422	58	1.01 (0.78–1.32)	0.97 (0.74–1.26)
Copper IUD	1,140	220	1.07 (0.94–1.21)	1.02 (0.90–1.16)	176	32	1.31 (0.94–1.81)	1.19 (0.86–1.64)
Ring	970	149	0.90 (0.77–1.05)	0.92 (0.79–1.07)	229	25	0.97 (0.66–1.42)	0.97 (0.66–1.42)
Implant	126	23	1.11 (0.77–1.60)	1.17 (0.81–1.68)	88	8	0.71 (0.37–1.39)	0.69 (0.35–1.34)
Patch	113	17	0.89 (0.58–1.37)	0.96 (0.62–1.48)	34	5	1.06 (0.47–2.37)	0.97 (0.43–2.17)
Injectable	114	13	0.75 (0.45–1.24)	0.76 (0.46–1.26)	67	4	0.57 (0.22–1.47)	0.77 (0.30–1.99)
Natural [†]	4,214	680	0.96 (0.88–1.05)	0.96 (0.89–1.05)	893	89	0.81 (0.64–1.02)	0.82 (0.64–1.03)
IUDs								
Copper IUD	1,140	220	Reference	Reference	176	32	Reference	Reference
Hormonal IUD	1,408	323	1.19 (1.02–1.38)	1.15 (0.98–1.34)	422	58	0.82 (0.54–1.23)	0.89 (0.67–1.19)
			No History of Infertility				History of Infertility	
Barrier	10,607	1,797	1.00 (Reference)	1.00 (Reference)	1,177	119	1.00 (Reference)	1.00 (Reference)
OC	16,344	2,504	0.88 (0.83–0.93)	0.89 (0.84–0.94)	1,139	149	1.13 (0.90–1.43)	1.06 (0.91–1.23)
Hormonal IUD	1,605	337	1.17 (1.06–1.30)	1.06 (0.95–1.17)	225	44	1.56 (1.14–2.14)	1.18 (0.74–1.88)
Copper IUD	1,197	236	1.09 (0.97–1.23)	1.03 (0.91–1.16)	119	16	1.20 (0.74–1.93)	1.06 (0.81–1.39)
Ring	1,117	168	0.90 (0.78–1.05)	0.92 (0.79–1.06)	82	6	0.66 (0.30–1.46)	0.86 (0.57–1.30)
Implant	203	28	0.87 (0.62–1.22)	0.93 (0.66–1.31)	11	3	2.39 (0.93–6.13)	1.42 (0.67–3.01)
Patch	138	21	0.88 (0.60–1.31)	0.97 (0.66–1.42)	9	1	1.29 (0.20–8.10)	1.07 (0.43–2.64)
Injectable	131	13	0.67 (0.40–1.12)	0.71 (0.43–1.18)	50	4	0.96 (0.37–2.46)	1.13 (0.72–1.78)
Natural [†]	4,651	731	0.95 (0.88–1.03)	0.95 (0.87–1.03)	456	38	0.82 (0.57–1.18)	0.94 (0.79–1.13)
IUDs								
Copper IUD	1,197	236	1.00 (Reference)	1.00 (Reference)	119	16	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	1,605	337	1.08 (0.93–1.26)	1.04 (0.89–1.22)	225	44	1.23 (0.74–2.05)	1.16 (0.71–1.88)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

a Model adjusted for study.

b Models adjusted for study, age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, duration of hormonal contraception use and parity.

Note 1: Stratified models for BMI were adjusted for a continuous BMI.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or body temperature, and avoiding sex when fertile.

Table 2.4 Continued. Last method of contraception and fecundability among pregnancy planners stratified by parity

Method	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b	No. of Cycles	No. of Pregs	Adjusted FR (95% CI) ^a	Adjusted FR (95% CI) ^b
	Nulliparous				Parous			
Barrier	8,355	1,219	1.00 (Reference)	1.00 (Reference)	3,429	697	1.00 (Reference)	1.00 (Reference)
OC	13,494	1,893	0.93 (0.87–1.00)	0.91 (0.85–0.98)	3,989	760	0.89 (0.81–0.97)	0.88 (0.80–0.96)
Hormonal IUD	796	133	1.13 (0.96–1.33)	1.12 (0.95–1.32)	1,034	248	1.07 (0.94–1.21)	1.09 (0.96–1.23)
Copper IUD	596	100	1.05 (0.88–1.27)	1.06 (0.88–1.28)	720	152	1.00 (0.86–1.16)	1.02 (0.87–1.20)
Ring	898	122	0.95 (0.80–1.13)	0.97 (0.82–1.15)	301	52	0.84 (0.65–1.10)	0.83 (0.64–1.07)
Implant	170	17	0.74 (0.48–1.17)	0.82 (0.52–1.28)	44	14	1.29 (0.84–1.98)	1.27 (0.82–1.96)
Patch	122	16	0.88 (0.56–1.38)	0.94 (0.60–1.49)	25	6	1.19 (0.61–2.34)	1.05 (0.53–2.08)
Injectable	136	10	0.56 (0.31–1.02)	0.60 (0.33–1.08)	45	7	0.97 (0.50–1.91)	1.07 (0.55–2.09)
Natural [†]	3,376	471	0.98 (0.89–1.09)	0.99 (0.91–1.06)	1,731	298	0.84 (0.74–0.96)	0.88 (0.78–1.00)
IUDs								
Copper IUD	596	100	1.00 (Reference)	1.00 (Reference)	720	152	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	796	133	1.11 (0.86–1.43)	1.14 (0.84–1.55)	1,034	248	1.06 (0.89–1.26)	1.07 (0.89–1.28)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

a Model adjusted for study.

b Models adjusted for study, age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, duration of hormonal contraception use and parity.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or body temperature, and avoiding sex when fertile.

Table 2.5 Last method of contraception and fecundability among pregnancy planners stratified by study

Method	No. of Cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a
SG				
Barrier	4,006	718	1.00 (Reference)	1.00 (Reference)
OC	9,401	1,450	0.86 (0.80–0.94)	0.87 (0.80–0.94)
Hormonal IUD	645	133	1.14 (0.96–1.34)	1.05 (0.89–1.24)
Copper IUD	326	59	1.01 (0.80–1.28)	0.90 (0.71–1.14)
Ring	445	64	0.80 (0.63–1.02)	0.83 (0.65–1.06)
Implant	25	6	1.29 (0.65–2.56)	1.52 (0.78–2.97)
Patch	80	7	0.53 (0.26–1.07)	0.56 (0.28–1.13)
Injectable	51	7	0.85 (0.43–1.69)	0.83 (0.42–1.64)
Natural [†]	1,683	271	0.89 (0.78–1.02)	0.89 (0.77–1.01)
IUDs				
Copper IUD	326	59	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	645	133	1.11 (0.85–1.46)	1.10 (0.83–1.46)
SF				
Barrier	2,894	551	1.00 (Reference)	1.00 (Reference)
OC	4,598	738	0.87 (0.79–0.96)	0.88 (0.79–0.97)
Hormonal IUD	433	107	1.22 (1.02–1.46)	1.06 (0.88–1.27)
Copper IUD	552	125	1.15 (0.97–1.36)	1.07 (0.90–1.27)
Ring	237	40	0.88 (0.66–1.18)	0.93 (0.70–1.25)
Implant	38	6	0.88 (0.43–1.82)	0.75 (0.36–1.57)
Patch	21	8	1.63 (0.95–2.82)	1.79 (1.04–3.11)
Injectable	22	2	0.50 (0.14–1.87)	0.53 (0.14–2.00)
Natural [†]	499	99	1.00 (0.81–1.23)	0.95 (0.78–1.16)
IUDs				
Copper IUD	433	107	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	552	125	1.05 (0.84–1.32)	0.98 (0.78–1.23)
PRESTO				
Barrier	4,884	647	1.00 (Reference)	1.00 (Reference)
OC	3,484	465	0.97 (0.87–1.08)	0.95 (0.85–1.06)
Hormonal IUD	752	141	1.25 (1.07–1.47)	1.19 (1.01–1.40)
Copper IUD	438	68	1.07 (0.85–1.34)	1.05 (0.84–1.32)
Ring	517	70	1.05 (0.84–1.32)	1.04 (0.83–1.30)
Implant	151	19	0.90 (0.59–1.37)	1.04 (0.68–1.59)
Patch	46	7	1.02 (0.52–2.00)	1.24 (0.64–2.42)
Injectable	108	8	0.63 (0.32–1.22)	0.72 (0.37–1.39)
Natural [†]	2,925	399	0.97 (0.87–1.09)	0.99 (0.88–1.11)
IUDs				
Copper IUD	438	68	1.00 (Reference)	1.00 (Reference)
Hormonal IUD	752	141	1.17 (0.90–1.51)	1.06 (0.86–1.31)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

^a Models adjusted for age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma, duration of hormonal contraception use and parity.

[†] Natural methods include withdrawal, calendar methods, monitoring cervical mucus or basal body temperature, and avoiding sex when fertile.

Table 2.6 Duration of use of hormonal contraceptives when pregnancy attempt began and fecundability, PRESTO (N=3,033), 2013–2017

Method		No. of Cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a
OC, years	<2	1,850	236	1.00 (Reference)	1.00 (Reference)
	2–3	1,881	270	1.09 (0.92–1.29)	1.10 (0.93–1.30)
	4–5	1,814	267	1.13 (0.94–1.34)	1.09 (0.90–1.30)
	6–7	1,607	230	1.08 (0.91–1.28)	1.09 (0.92–1.29)
	8–9	1,364	204	1.14 (0.96–1.36)	1.09 (0.92–1.31)
	10–11	1,308	180	1.04 (0.87–1.24)	1.02 (0.85–1.22)
	≥12	1,793	260	1.09 (0.92–1.29)	1.14 (0.95–1.35)
Hormonal IUD, years	<2	449	75	1.00 (Reference)	1.00 (Reference)
	2–3	579	104	1.00 (0.76–1.31)	0.92 (0.69–1.22)
	4–5	400	69	1.06 (0.79–1.42)	1.02 (0.75–1.41)
	≥6	173	27	0.88 (0.57–1.35)	0.86 (0.56–1.33)
	Ring, years	<2	1,505	215	1.00 (Reference)
2–3		600	92	1.08 (0.86–1.37)	1.16 (0.91–1.48)
4–5		322	46	0.99 (0.73–1.34)	0.99 (0.73–1.35)
6–7		195	35	1.21 (0.88–1.66)	1.25 (0.90–1.73)
≥8		121	16	0.92 (0.57–1.46)	1.04 (0.64–1.67)
Injectable, years		<2	967	127	1.00 (Reference)
	2–3	414	48	0.96 (0.69–1.33)	0.92 (0.69–1.23)
	4–5	237	11	0.43 (0.24–0.78)	0.53 (0.21–1.34)
	6–7	103	13	0.89 (0.50–1.58)	0.87 (0.53–1.42)
	≥8	96	10	0.84 (0.47–1.50)	0.82 (0.45–1.50)
	Patch, years	<2	1,060	151	1.00 (Reference)
2–3		262	33	0.84 (0.58–1.22)	0.84 (0.58–1.21)
4–5		122	16	0.94 (0.59–1.52)	0.79 (0.48–1.28)
≥6		80	9	0.76 (0.39–1.48)	0.73 (0.36–1.46)
Implant, years		<2	169	23	1.00 (Reference)
	≥2	237	29	0.92 (0.54–1.56)	1.03 (0.74–1.43)

FR=fecundability ratio, OC=Oral contraceptive, IUD=Intrauterine device

^aModels adjusted for age at baseline, education, race, income, BMI, intercourse frequency, current smoking, doing something to improve chances of conception, diabetes, endometriosis, uterine leiomyoma and parity.

3 MALE USE OF PAIN MEDICATION AND TIME-TO-PREGNANCY

3.1 Introduction

Pain-relievers are the most commonly-used medication among reproductive-aged men in North America. In 2002, more than 20% of U.S. men ages 18–44 years used over-the-counter analgesics during the past week.¹ There is evidence that use increases with age, even as men transition from their 20s to 30s.² Use is more common among physically active men, including athletes³ and blue collar workers.⁴

Analgesics generally reduce pain by inhibiting cyclooxygenase (COX)-1 and -2 enzymes that synthesize prostaglandins.^{5,6} Prostaglandins are found throughout the body and have a variety of actions, including helping to maintain homeostasis^{7,8} and causing pain and inflammation.⁷ While their role in male reproduction is not fully understood, prostaglandins are a component of semen and stimulate smooth muscle⁹ facilitating erection.^{10,11} Low prostaglandin levels have been associated with reduced sperm quality,¹² motility and penetration capacity,¹³ and fertility.¹⁴ Elevated COX-2 levels may also be detrimental as they have been associated with abnormal spermatogenesis.^{15,16}

Ibuprofen, aspirin, and naproxen—all non-steroidal anti-inflammatory drugs (NSAIDs)—have varied effects on COX-2 inhibition and prostaglandin synthesis,^{17–19} with potentially different effects on reproduction. Acetaminophen, the most commonly used non-NSAID pain-reliever,²⁰ is highly effective for pain relief but has limited effectiveness for inflammation.²¹ The effect of

acetaminophen on prostaglandin synthesis may vary by dose, with low doses increasing synthesis and high doses reducing synthesis.^{19,22–24}

There are limited data on the influence of pain medication use on male fertility. Ibuprofen exposure has been linked to decreased testosterone levels in male mice²⁵ and rats,²⁶ and exposure to aspirin or naproxen have been associated with reduced prostaglandin levels in male rats.^{27,28} Exposure to aspirin, however, has also been associated with improved reproductive parameters including better semen quality in animal studies.^{29–32} High doses of acetaminophen have been associated with abnormal testicular function³³ and decreased fertility in rodents.^{34,35} *In vitro* studies of human testes obtained from prostate cancer patients showed that exposure to acetaminophen or aspirin was associated with decreased testosterone and prostaglandin levels³⁶ Smarr et al. found that men with urinary acetaminophen concentrations greater than 73.5 ng/ml had a 35% reduction in fecundability compared with men having concentrations less than 5.44 ng/ml (fecundability odds ratio=0.65, 95% 0.45–0.94).³⁷ However, the authors did not control for indication for acetaminophen use.

Although pain medications are widely used, their effects on male fecundability have received limited epidemiologic study. In a prospective preconception cohort of North American pregnancy planners, we examined time-to-pregnancy (TTP) after male preconception use of acetaminophen, aspirin, ibuprofen, and naproxen.

3.2 Methods

3.2.1 Study population

We analyzed data from Pregnancy Study Online (PRESTO)³⁸ (2013–2017), an ongoing prospective cohort study of pregnancy planners in the United States (U.S.) and Canada. PRESTO enrolls female pregnancy planners ages 21–45 years and a sample of their male partners ages ≥ 21 years.

Female participants are recruited primarily using advertisements on social media. Eligible women are in a stable relationship with a male partner, not pregnant, and not using contraception or fertility treatments. Female participants completed a baseline questionnaire and follow-up questionnaires every two months for 12 months or until reported pregnancy, whichever came first. Over 80% of female participants completed at least one follow-up questionnaire.³⁸ Enrolled women are asked to invite their male partner to complete a one-time baseline questionnaire with information on sociodemographics, lifestyle factors, medication use, and medical history. All questionnaires were completed online. In the present report, we analyzed data from eligible males who enrolled between June 2013 and July 2017. The Boston University Medical Center institutional review board approved the study protocol and participants provided online informed consent.

3.2.2 Assessment of pain medication use

At baseline, men were asked if they used pain medication during the

previous 4 weeks. They were able to indicate the names of up to three medications using auto-complete text recognition software,³⁹ they recorded the names of up to three pain medications, as well as the total number of pills used of each type during the past month, and the reason for use. Medications were grouped by active ingredient. Categories included acetaminophen, aspirin, ibuprofen and naproxen. Men who reported ≥ 1 pill in the 4 weeks before baseline were considered users. These groupings were not mutually exclusive; men who took more than one type of pain medication (e.g. ibuprofen and acetaminophen) or took a medication that contained more than one active ingredient (e.g. “Excedrin Migraine”) were classified as exposed to each of the medications reported. Cumulative monthly dose was calculated as the number of pills used during the past 4 weeks multiplied by the dose of the active ingredient(s) in each pill and then summed for each active ingredient. The most commonly purchased dose was used for medication sold in varying strengths.

3.2.3 Assessment of pregnancy and menstrual cycles at risk

At baseline, females reported their menstrual cycle length, date of their last menstrual period (LMP), and the number of cycles they had been attempting conception. At each follow-up, females reported their LMP date and pregnancy status. Over 96% of participants reported using home pregnancy tests to confirm pregnancy. Total cycles at risk were calculated as: (cycles trying to conceive at study entry) + [(LMP date from most recent follow-up questionnaire - date of baseline questionnaire)/cycle length] + 1.

3.2.4 Assessment of covariates

On the male baseline questionnaire, participants reported data on sociodemographic, medical history, lifestyle factors, and indications for pain medication use. BMI was calculated as kg/m^2 , physical activity was calculated as metabolic equivalent of task (MET) hours/week and stress was assessed by the perceived stress scale (PSS-10).⁴⁰ Household income, female age and education, intercourse frequency, and doing something to improve chances of conception (e.g., timing intercourse during the fertile window, monitoring cervical mucus) were reported by the female partner on the female baseline questionnaire.

3.2.5 Exclusions

5,020 women completed the PRESTO baseline questionnaire. Of these women, we excluded 161 women with implausible menstrual cycle information and 881 women who had been trying to conceive for more than 6 cycles at study entry. Of the 3,978 remaining women, 2,186 invited their male partners to participate; 1,072 men enrolled. We excluded 7 men who used an NSAID other than those examined (i.e. celecoxib, diclofenac, meloxicam). 1,065 men were included in this analysis.

3.2.6 Data analysis

Couples contributed cycles to the analysis beginning at study entry until reported pregnancy (63.7%), initiation of fertility treatment (8.3%), withdrawal

(0.6%), loss-to-follow-up (13.7%), or 12 cycles (13.8%). We used proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs).⁴¹ The FR is a measure of the average per-cycle probability of conception comparing users of a specific pain medication with non-users of that medication. The model adjusts for each cycle at risk to account for the decline in average fecundability over time when more fertile couples conceive sooner and are removed from the denominator.⁴² We used the Andersen-Gill data structure⁴³ to account for left truncation bias that may result from women entering the study after ≥ 1 cycles of pregnancy attempt.^{44,45} For example, couples that entered the study with 1 cycle of attempt time and conceived during the 5th cycle contribute cycles 2 through 5 to the analysis. We used the “weighted copy method” to facilitate convergence of the log binomial model.⁴⁶

Due to the low number of participants exposed to some medications, models were adjusted for potential confounders selected using a hybrid approach to avoid overfitting. Covariates identified *a priori* were included one at a time in the unadjusted model; those that caused a $\geq 5\%$ change in any medication-specific point estimate were retained in the final models. Covariates evaluated included age (<25, 25–29, 30–34, ≥ 35 years), education (≤ 12 , 13–15, 16, ≥ 17 years), non-Hispanic white (yes versus no), income (< versus $\geq 50,000$ USD per year), BMI (<25, 25–29, ≥ 30 kg/m²), use of performance enhancing supplements (yes versus no), vigorous physical activity (MET hours/week), occupational exposure to high temperatures or toxic chemicals (yes versus no), work hours

(<45 versus \geq 45 hours/week), sleep hours (<7 versus \geq 7 hours/night), alcohol use (drinks/week), sugar-sweetened beverage intake (drinks/week), multivitamin use (yes versus no), smoking (current, past, never), physician-diagnosed anxiety (yes versus no), physician-diagnosed depression (yes versus no), PSS-10 score (range 0–40), physician-diagnosed migraine headaches (yes versus no), physician-diagnosed hypertension (yes versus no), fever during the past 3 months (yes versus no), past month antibiotic use (yes versus no), past month opioid use (yes versus no), frequency of primary care provider (PCP) visits (<3 versus \geq 3 visits per year), intercourse frequency (<1, 1–3, \geq 4 times per week), and doing something to improve chances of conception (yes versus no). Female covariates examined included age (<25, 25–29, 30–34, \geq 35 years), and education (\leq 12, 13–15, 16, \geq 17 years). Categorical variables were included as a set of indicator variables (e.g. 3 variables for age). Retained covariates included male age, BMI, household income, intake of sugar-sweetened beverages and alcohol, migraine headaches, fever, and doing something to improve chances of conception. We adjusted for indications for medication use including headache (yes versus no), muscular pain (yes versus no), illness (yes versus no), toothache (yes versus no), insomnia (yes versus no), surgery (yes versus no), and cardiovascular health (yes versus no), when applicable.

To examine potential confounding and explore effect measure modification by selected covariates, we conducted stratified and subgroup analyses. We stratified by male age (<30 versus \geq 30), attempt time at study entry

(0–2 versus 3–6 menstrual cycles), and male BMI (<30 versus ≥ 30 kg/m²). We also conducted analyses restricted to medication users who reported common indications for use (headache, muscular pain, illness). Additionally, we conducted an analysis restricted to the first observed menstrual cycle, which was the time period when exposure was assessed, to examine outcomes most proximate to exposure. We also conducted an analysis restricted to men who did not have a fever during the 3 months before baseline (N=908, 85.3%), as fever is a common indication for pain-reliever use and fever can adversely affect spermatogenesis.⁴⁷ Next, to compare use of each medication with non-use of *any* pain medication, we restricted the analysis to users of only one type of medication and all non-users. Lastly, we restricted analyses to users of only one type of medication and compared users of acetaminophen, aspirin, or naproxen to users of the most commonly-used medication, ibuprofen, to indirectly control for confounding by indication as these medications are often used for the same conditions.

Between 0.3% (naproxen) and 1.2% (acetaminophen) of participants were missing data on pain-reliever dose. Pregnancy status was missing for 4.7% of couples. Missing covariate data ranged from 0% (13 variables including age) to 8.7% (household income), with the exception of PSS score, fever, and indication for use which were missing for 50.2%, 52.1%, and 69.9% of participants, respectively. These items were added to the questionnaire 2–3 years after the study began and thus were “missing at random”.⁴⁸ We used PROC MI to impute missing data on exposure, covariates, and pregnancy status, and used PROC

MIANALYZE to combine coefficient and standard error estimates from five imputed datasets.⁴⁹

3.3 Results

At baseline, more than half (51.8%) of the 1,065 males reported using a pain medication during the previous month. The most commonly used analgesics were ibuprofen (36.7%) and acetaminophen (16.8%). Fewer men used naproxen (5.6%) and aspirin (4.4%). Among users, the median total monthly dose of each medication was 1,600 mg (interquartile range (IQR): 800–2,400 mg) of ibuprofen, 1,300 mg (IQR: 650–2,600 mg) of acetaminophen, 1,320 mg (IQR: 440–2,200 mg) of naproxen, and 1,000 mg (IQR: 650–1,950 mg) of aspirin. The most common indications for use were headache (80.0%) and muscular pain (37.8%). Ibuprofen (40.3%) and naproxen (53.8%) users were more likely to report use for muscular pain, acetaminophen users were more likely report use for an illness (9.1%), and aspirin users were more likely to report use for headache (93.3%) or cardiovascular health (8.3%) when compared with users of the other medications.

Compared with non-users of any pain medication, users were more likely to be non-Hispanic white and past smokers of cigarettes, and to report medical conditions including anxiety, depression, migraines, and hypertension. They were also more likely to report a fever within the 3 month-period before baseline and to have a history of infertility. When compared with all other groups, ibuprofen use was positively associated with educational attainment; naproxen use was

positively associated with occupational exposure to high temperatures or toxic chemicals, income, and lower educational attainment (Table 3.1).

A total of 1,065 couples contributed 5,096 cycles and 678 pregnancies to the analysis. Compared with unadjusted analyses, results were attenuated after adjusting for potential confounders, including indication for medication use (Table 2). Adjusted FRs were 1.23 for naproxen use (95% CI: 0.80–1.90), 1.15 for aspirin use (95% CI: 0.80–1.65), 0.93 for acetaminophen use (95% CI: 0.75–1.15) and 0.97 for ibuprofen use (95% CI: 0.81–1.17) when compared with non-users of each respective medication (Table 3.2). There was little evidence of an association between cumulative monthly dose and fecundability (Table 3.3).

Reduced fecundability was observed among obese (FR=0.79, 95% CI: 0.47–1.32) and younger (FR=0.68, 95% CI: 0.40–1.16) ibuprofen users compared with non-users, but these results were imprecise. Results for the examined medications were generally consistent across strata of pregnancy attempt time at study entry (<3 cycles vs. 3–6 cycles) (Table 3.4), and common indications for medication use (headache, muscular pain, or illness) (Table 3.5).

We conducted several sensitivity analyses. When we restricted to the first observed menstrual cycle, results were consistent with the overall results (data not shown). Among men without a fever during the past 3 months, for whom confounding by recent illness was less likely, results were consistent with our overall findings (results not shown). Finally, when we assessed use of single

medications relative to use of ibuprofen only (reference group), fecundability was slightly higher among users of naproxen only and aspirin only (Table 3.6).

3.4 Discussion

In this large prospective cohort of North American couples planning pregnancy, use of common pain medications at low cumulative doses over a 4-week period did not have a deleterious effect on male fecundability. While use of naproxen or aspirin was associated with slightly increased fecundability, numbers of users were small and results were attenuated after adjusting for demographics, lifestyle factors, and indications for medication use. Our results were consistent among couples with shorter pregnancy attempt times at enrollment (≤ 2 menstrual cycles), among users of a single pain medication compared with ibuprofen, and when analyses were restricted to the first observed menstrual cycle.

Our finding of no meaningful reduction in fecundability among male acetaminophen users disagrees with the 35% decrease reported by Smarr et al. among men with urinary acetaminophen concentrations >73.5 ng/ml compared with <5.44 ng/ml³⁷. The strong inverse association found may be explained by unmeasured confounding by indication for use, particularly fever and infections, which are strong potential confounders.⁵⁰ While urinary measurement of acetaminophen is presumably more accurate than self-reported medication use, capturing both medical and environmental exposures,^{50,51} a single spot urine sample measures only past-day exposure,⁵² a time interval that and may not be

etiologically relevant to conception.

There is no previous study examining male use of naproxen, ibuprofen, or aspirin and fecundability. NSAIDs block COX-1 and -2 enzymes, which help form prostaglandins.⁷ The role of COX-1 and -2 enzymes and the resulting prostaglandins in reproduction is not fully understood.

Our data provided no indication that male aspirin use deleteriously affected fertility. Aspirin's antiplatelet activity makes it different from other NSAIDs.^{53,54} While results have been inconsistent,⁵⁵⁻⁵⁷ some animal studies indicate that aspirin use may improve male reproductive parameters.²⁹⁻³²

A primary limitation of the study was low precision for naproxen and aspirin effects, stemming from small numbers of users, and the narrow range of doses. Additionally, information about medication use was obtained only at baseline. For some couples, this assessment occurred months before they reached a study endpoint. It is likely that exposure changed over time. To address this problem, we conducted a sensitivity analysis restricted to the first observed menstrual cycle. Results from this analysis were consistent with the main analysis. Further, because we measured total number of pills over the 4 week period, but lacked information about the timing of use and dosage patterns (e.g. chronic low dose, infrequent high dose), some misclassification of relevant exposure was inevitable. In addition, participants may have incorrectly recalled the name and dose of the medications used. All these sources of error were likely non-differential, as report of medication use occurred before the outcome

was known. Such non-differential misclassification would bias our effect estimates toward the null. Outcome misclassification, though less of a problem in this study, was also possible. Calculation of time-to-pregnancy relies on the female participant's report of LMP date and menstrual cycle length, which may be reported with error. Such misclassification is expected to be non-differential with respect to studied exposure because any errors in the female partner's reporting of LMP and menstrual cycle length are unlikely to be related to their male partners' medication use.

Indication for use was missing for a large percentage of users because questionnaire items about reasons for use were added after the study began. We used multiple imputation to deal with missing data and thus inferred indication when missing from other questionnaire items. Results were attenuated after adjusting for our imperfect measure of indication for use; we expect that our results would be attenuated further had we measured indication with less error. To reduce residual confounding by indication, we conducted an analysis restricted to men who did not have a fever during the past 3 months, since fever is associated with pain medication use and reduced semen quality. This analysis showed results similar to the main analysis. Further, results were similar when we compared use of each medication with ibuprofen use, the most commonly used pain medication. Such an analysis indirectly controls for indication for use because over-the-counter (OTC) pain-relievers have broadly similar indications.

As with many prospective cohort studies, we studied volunteers, recruiting

females and asking them to invite their male partners to participate. About 55% of men were invited by their female partners to participate, and of those invited, only 49% of males enrolled. Because the probability of conception was similar when comparing male and female pairs with female who participated alone, selection bias by participation is likely small. Selection bias by loss to follow-up is also unlikely to be a serious problem because medication users (90.4%) and non-users (88.9%) had similar proportions completing follow-up.

Given currently available evidence from the literature and from our findings, male preconception use of common OTC pain medications at low cumulative doses does not appear to have deleterious effects on fecundity.

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Table 3.1 Baseline characteristics of male pregnancy planners by pain medication use, PRESTO (N=1,065), 2013–2017

	Pain Medication Use		Type of Medication Use			
	No	Yes	Ibuprofen	Acetaminophen	Naproxen	Aspirin
Number of Participants N (%)	513 (48.2)	552 (51.8)	391 (36.7)	179 (16.8)	60 (5.6)	47 (4.4)
Age (years), mean	31.2	32.1	32.2	31.7	31.7	32.2
Partners age (years), mean	29.8	30.0	30.0	30.2	30.0	30.2
Non-Hispanic White, %	84.5	89.1	89.0	90.8	92.3	91.2
Annual household income <\$50,000	16.3	16.2	15.2	20.1	9.6	16.8
Annual household income >\$150,000	20.1	20.6	22.0	16.7	22.0	20.3
<College degree, %	29.0	26.4	26.4	29.6	33.7	29.4
Partner <College degree, %	15.1	15.9	15.0	16.2	14.3	16.5
Work >45 hrs/wk, %	28.3	34.8	32.9	34.8	39.4	37.8
Occupational exposure to high temperatures or toxic chemicals, %	24.2	26.0	25.9	28.9	32.4	25.2
BMI (kg/m ²), mean	27.4	27.9	27.7	28.1	28.7	28.4
Sleep <7 hrs/wk, %	31.6	34.8	32.5	38.7	35.5	40.6
Vigorous physical activity (MET-hrs/wk), mean	19.3	17.4	18.6	15.1	17.3	17.6
Multivitamin supplement use, %	31.3	39.2	40.3	35.7	51.2	34.0
Performance enhancing supplement use, %	10.8	9.0	10.8	7.6	6.7	13.1
Alcohol (drinks/wk), mean	5.9	6.5	7.1	6.1	5.1	6.7
Sugar sweetened beverages (drinks/wk), mean	4.2	4.2	3.8	5.2	3.7	4.9
Past smoker, %	17.6	24.2	24.4	27.4	28.3	23.6
Current smoker, %	5.5	5.0	5.0	6.1	6.1	4.5
Doing something to improve chances of conceiving, %	75.6	77.1	77.3	76.2	81.8	76.0
Intercourse frequency <1 time/week, %	21.2	18.5	18.5	18.1	23.7	10.7
Intercourse frequency ≥4 times/week, %	15.4	15.5	16.2	17.0	14.7	14.2
History of infertility, %	6.3	9.2	9.1	10.0	3.7	8.6
Perceived Stress Scale Score, mean	14.0	15.2	14.8	16.4	17.4	15.4
Diagnosis of anxiety, %	5.9	9.9	10.2	12.9	26.8	11.1
Diagnosis of depression, %	8.0	12.6	11.2	16.7	17.1	19.0
Migraine headaches, %	3.5	7.3	7.1	9.0	10.9	4.0
Hypertension, %	6.9	8.5	8.0	9.0	12.7	8.8

All characteristics except for age are age-standardized to the cohort at baseline.
 Note: Pain medication use was assessed during the 4 weeks before baseline.

Table 3.1 Continued. Baseline characteristics of male pregnancy planners by pain medication use, PRESTO (N=1,065), 2013–2017

	Pain Medication Use		Type of Medication Use			
	No	Yes	Ibuprofen	Acetaminophen	Naproxen	Aspirin
Hypertension, %	6.9	8.5	8.0	9.0	12.7	8.8
Fever, past 3 months, %	11.2	18.2	17.7	21.6	17.0	31.5
Antibiotic use, %	3.1	5.0	4.1	7.2	3.0	0.0
>3 PCP visits/year, %	5.0	7.9	7.8	9.5	14.9	5.6
Indication						
Headache, %	--	80.0	78.6	78.7	61.3	93.3
Muscular pain, %	--	37.8	40.3	38.8	53.8	30.9
Illness, %	--	6.8	6.9	9.1	3.0	8.5
Toothache, %	--	4.4	4.1	6.7	0.0	6.6
Insomnia, %	--	3.8	2.6	5.6	0.0	4.3
Surgery, %	--	3.1	2.3	4.6	1.4	4.5
Cardiovascular, %	--	1.9	1.4	0.5	0.0	8.3

All characteristics except for age are age-standardized to the cohort at baseline.

Note: Pain medication use was assessed during the 4 weeks before baseline.

Table 3.2 Baseline pain medication use and fecundability

Medication	No. of Cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)^a
Any pain medication				
Non-use	2,111	322	1.00 (Reference)	1.00 (Reference)
Any use	2,307	356	1.04 (0.91–1.19)	1.07 (0.93–1.23)
Ibuprofen ^b				
Non-use	2,773	431	1.00 (Reference)	1.00 (Reference)
Any use	1,645	247	0.98 (0.85–1.13)	0.97 (0.81–1.17)
Acetaminophen ^b				
Non-use	3,631	569	1.00 (Reference)	1.00 (Reference)
Any use	787	109	0.91 (0.75–1.09)	0.93 (0.75–1.15)
Naproxen ^b				
Non-use	4,209	636	1.00 (Reference)	1.00 (Reference)
Any use	209	42	1.36 (1.03–1.80)	1.23 (0.80–1.90)
Aspirin ^b				
Non-use	4,226	645	1.00 (Reference)	1.00 (Reference)
Any use	191	33	1.29 (0.93–1.78)	1.15 (0.80–1.65)

FR=fecundability ratio

a Models were adjusted for male age, BMI, household income, sugar sweetened beverage intake, alcohol intake, migraine headache, fever, and doing something to improve chances of conception.

b Adjusted for all variables in footnote “a” and mutually adjusted for the other types of pain medications and reported indications for use.

Note: Pain medication use was assessed during the 4 weeks before baseline.

Table 3.3 Baseline cumulative monthly dose of pain medication exposure and fecundability

Medication	No. of Cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a
Non-use	2,111	322	1.00 (Reference)	1.00 (Reference)
Any use				
Low exposure	1,357	226	1.12 (0.96–1.30)	1.13 (0.97–1.32)
Moderate exposure	950	130	0.93 (0.77–1.12)	0.98 (0.81–1.19)
Ibuprofen (mg) ^b				
Non-use	2,773	431	1.00 (Reference)	1.00 (Reference)
<2,000	983	161	1.05 (0.89–1.24)	1.01 (0.83–1.23)
≥2,000	662	86	0.87 (0.70–1.08)	0.91 (0.70–1.18)
Acetaminophen (mg) ^b				
Non-use	3,631	569	1.00 (Reference)	1.00 (Reference)
<2,000	515	73	0.92 (0.74–1.16)	0.92 (0.73–1.17)
≥2,000	272	36	0.87 (0.64–1.20)	0.95 (0.71–1.26)
Naproxen (mg) ^b				
Non-use	4,209	636	1.00 (Reference)	1.00 (Reference)
<1,500	139	29	1.43 (1.03–2.01)	1.26 (0.80–1.98)
≥1,500	70	13	1.23 (0.76–1.99)	1.19 (0.70–2.02)
Aspirin (mg) ^b				
Non-use	4,226	645	1.00 (Reference)	1.00 (Reference)
<1,500	131	21	1.21 (0.80–1.83)	1.09 (0.76–1.58)
≥1,500	61	12	1.44 (0.88–2.36)	1.29 (0.70–2.36)

FR=fecundability ratio

a Models were adjusted for male age, BMI, household income, sugar sweetened beverage intake, alcohol intake, migraine headache, fever, and doing something to improve chances of conception.

b Adjusted for all variables in footnote “a” and mutually adjusted for the other types of pain medications and reported indications for use.

Note: Pain medication use was assessed as total dose during the 4 weeks before baseline.

Table 3.4 Baseline pain medication use and fecundability stratified by age and attempt time at study entry

Medication	No. of Cycles	No. of Pregs	Age<30		Age≥30		Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a
			Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a	No. of Cycles	No. of Pregs		
Age<30								
Any pain medication								
Non-use	854	130	1.00 (Reference)	1.00 (Reference)	1,257	192	1.00 (Reference)	1.00 (Reference)
Any use	751	114	1.10 (0.88–1.39)	1.13 (0.89–1.44)	1,556	242	1.02 (0.86–1.21)	1.06 (0.89–1.26)
Ibuprofen ^b								
Non-use	1,107	175	1.00 (Reference)	1.00 (Reference)	1,666	256	1.00 (Reference)	1.00 (Reference)
Any use	498	69	0.94 (0.73–1.21)	0.68 (0.40–1.16)	1,147	178	1.01 (0.84–1.20)	1.10 (0.82–1.49)
Acetaminophen ^b								
Non-use	1,298	204	1.00 (Reference)	1.00 (Reference)	2,333	365	1.00 (Reference)	1.00 (Reference)
Any use	307	40	0.91 (0.66–1.24)	0.73 (0.43–1.25)	480	69	0.91 (0.72–1.16)	0.99 (0.76–1.23)
Naproxen ^b								
Non-use	1,541	230	1.00 (Reference)	1.00 (Reference)	2,668	406	1.00 (Reference)	1.00 (Reference)
Any use	64	14	1.51 (0.95–2.40)	1.21 (0.73–2.01)	145	28	1.31 (0.93–1.86)	1.28 (0.77–2.15)
Aspirin ^b								
Non-use	1,526	232	1.00 (Reference)	1.00 (Reference)	2,700	413	1.00 (Reference)	1.00 (Reference)
Any use	79	12	1.25 (0.74–2.12)	1.03 (0.57–1.85)	113	21	1.34 (0.89–2.02)	1.20 (0.75–1.90)
Trying 0–2 cycles at study entry								
Any pain medication								
Non-use	1,449	233	1.00 (Reference)	1.00 (Reference)	662	89	1.00 (Reference)	1.00 (Reference)
Any use	1,627	269	1.07 (0.92–1.26)	1.13 (0.97–1.33)	680	87	0.97 (0.73–1.28)	0.90 (0.66–1.21)
Ibuprofen ^b								
Non-use	1,900	316	1.00 (Reference)	1.00 (Reference)	873	115	1.00 (Reference)	1.00 (Reference)
Any use	1,176	186	0.97 (0.82–1.14)	0.92 (0.69–1.25)	469	61	1.04 (0.77–1.40)	0.99 (0.60–1.62)
Acetaminophen ^b								
Non-use	2,510	417	1.00 (Reference)	1.00 (Reference)	1,121	152	1.00 (Reference)	1.00 (Reference)
Any use	566	85	0.96 (0.78–1.19)	0.92 (0.72–1.19)	221	24	0.78 (0.51–1.19)	0.88 (0.57–1.37)
Naproxen ^b								
Non-use	2,922	474	1.00 (Reference)	1.00 (Reference)	1,287	162	1.00 (Reference)	1.00 (Reference)
Any use	154	28	1.22 (0.86–1.72)	1.14 (0.71–1.84)	55	14	1.83 (1.14–2.95)	1.51 (0.67–3.42)
Aspirin ^b								
Non-use	2,956	478	1.00 (Reference)	1.00 (Reference)	1,270	167	1.00 (Reference)	1.00 (Reference)
Any use	120	24	1.39 (0.96–2.00)	1.33 (0.81–2.18)	72	9	1.05 (0.55–1.99)	1.08 (0.56–2.09)
Trying 3–6 cycles at study entry								

a Models were adjusted for male age, BMI, household income, sugar sweetened beverage intake, alcohol intake, migraine headache, fever, and doing something to improve chances of conception.

b Adjusted for all variables in footnote “a” and mutually adjusted for the other types of pain medications and reported indications for use.

Note: Pain medication use was assessed during the 4 weeks before baseline.

Table 3.4 Continued. Baseline pain medication use and fecundability stratified by BMI

Medication	No. of Cycles	No. of Pregs	BMI <30 kg/m ²		BMI ≥30 kg/m ²		Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a
			Unadjusted FR (95% CI)	Adjusted FR (95% CI) ^a	No. of Cycles	No. of Pregs		
Any pain medication								
Non-use	1,586	255	1.00 (Reference)	1.00 (Reference)	525	67	1.00 (Reference)	1.00 (Reference)
Any use	1,593	260	1.05 (0.90–1.23)	1.07 (0.92–1.26)	714	96	1.07 (0.80–1.44)	1.06 (0.79–1.43)
Ibuprofen ^b								
Non-use	2,015	326	1.00 (Reference)	1.00 (Reference)	758	105	1.00 (Reference)	1.00 (Reference)
Any use	1,164	189	1.04 (0.88–1.22)	1.13 (0.86–1.50)	481	58	0.86 (0.64–1.17)	0.79 (0.47–1.32)
Acetaminophen ^b								
Non-use	2,609	435	1.00 (Reference)	1.00 (Reference)	1,022	134	1.00 (Reference)	1.00 (Reference)
Any use	570	80	0.85 (0.68–1.06)	0.89 (0.66–1.22)	217	29	1.06 (0.73–1.54)	0.97 (0.67–1.39)
Naproxen ^b								
Non-use	3,052	483	1.00 (Reference)	1.00 (Reference)	1,157	153	1.00 (Reference)	1.00 (Reference)
Any use	127	32	1.52 (1.12–2.06)	1.67 (1.15–2.42)	82	10	1.07 (0.57–2.01)	0.89 (0.57–1.39)
Aspirin ^b								
Non-use	3,071	493	1.00 (Reference)	1.00 (Reference)	1,155	152	1.00 (Reference)	1.00 (Reference)
Any use	108	22	1.39 (0.95–2.03)	1.44 (0.92–2.26)	84	11	1.22 (0.68–2.17)	0.97 (0.62–1.51)

FR=fecundability ratio

a Models were adjusted for male age, BMI, household income, sugar sweetened beverage intake, alcohol intake, migraine headache, fever, and doing something to improve chances of conception.

b Adjusted for all variables in footnote “a” and mutually adjusted for the other types of pain medications and reported indications for use.

Note: Pain medication use was assessed during the 4 weeks before baseline.

Table 3.5: Baseline pain medication use and fecundability, restricted to users who reported headaches, muscle pains, or illness as indications for use

Medication	No. of Cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)^a
Headache				
Ibuprofen				
Non-use	1,134	567	1.00 (Reference)	1.00 (Reference)
Any use	2,654	1,327	0.86 (0.63–1.18)	0.86 (0.62–1.19)
Acetaminophen				
Non-use	2,498	1,249	1.00 (Reference)	1.00 (Reference)
Any use	1,290	645	0.81 (0.61–1.08)	0.86 (0.63–1.16)
Naproxen				
Non-use	3,510	1,755	1.00 (Reference)	1.00 (Reference)
Any use	278	139	1.24 (0.80–1.93)	1.21 (0.80–1.85)
Aspirin				
Non-use	3,416	1,708	1.00 (Reference)	1.00 (Reference)
Any use	372	186	1.17 (0.76–1.73)	1.15 (0.77–1.73)
Muscle Pain				
Ibuprofen				
Non-use	402	201	1.00 (Reference)	1.00 (Reference)
Any use	1,324	662	0.99 (0.61–1.60)	0.93 (0.58–1.50)
Acetaminophen				
Non-use	1,164	582	1.00 (Reference)	1.00 (Reference)
Any use	562	281	0.95 (0.64–1.39)	0.93 (0.65–1.32)
Naproxen				
Non-use	1,492	746	1.00 (Reference)	1.00 (Reference)
Any use	234	117	1.41 (0.83–2.38)	1.22 (0.71–2.08)
Aspirin				
Non-use	1,640	820	1.00 (Reference)	1.00 (Reference)
Any use	86	43	1.28 (0.51–3.22)	1.27 (0.71–2.08)
Illness				
Ibuprofen				
Non-use	76	38	1.00 (Reference)	1.00 (Reference)
Any use	222	111	0.84 (0.40–1.75)	0.74 (0.33–1.61)
Acetaminophen				
Non-use	182	91	1.00 (Reference)	1.00 (Reference)
Any use	116	58	0.93 (0.42–2.09)	0.98 (0.56–1.70)
Naproxen				
Non-use	294	147	1.00 (Reference)	1.00 (Reference)
Any use	4	2	1.29 (0.34–4.90)	0.80 (0.32–2.05)
Aspirin				
Non-use	276	138	1.00 (Reference)	1.00 (Reference)
Any use	22	11	1.33 (0.39–4.45)	1.68 (0.23–12.08)

FR=fecundability ratio

a Models were adjusted for male age, BMI, household income, sugar sweetened beverage intake, alcohol intake, migraine headache, fever, and doing something to improve chances of conception. Models were mutually adjusted for the other types of pain medications.

Note: Pain medication use was assessed during the 4 weeks before baseline.

Table 3.6 Baseline pain medication use and fecundability, restricted to users of single medications compared with ibuprofen use

Medication	No. of Cycles	No. of Pregs	Unadjusted FR (95% CI)	Adjusted FR (95% CI)^a
Ibuprofen	1,259	196	1.00 (Reference)	1.00 (Reference)
Acetaminophen	376	55	0.99 (0.77–1.28)	0.98 (0.80–1.21)
Naproxen	127	28	1.36 (0.98–1.88)	1.25 (0.78–1.99)
Aspirin	69	15	1.40 (0.90–2.18)	1.25 (0.75–2.08)

FR=fecundability ratio

^a Models were adjusted for male age, BMI, household income, sugar sweetened beverage intake, alcohol intake, migraine headache, fever, and doing something to improve chances of conception. Results were also mutually adjusted for the other types of pain medications and reported indications for use.

Note: Pain medication use was assessed during the 4 weeks before baseline.

4 Female Use of Pain Medication in Pregnancy and Spontaneous Abortion

4.1 Introduction

Spontaneous abortion (SAB), defined as the loss of pregnancy before 20 weeks of gestation, is a common pregnancy outcome that affects approximately 20% of clinically recognized pregnancies.¹ About 50% of SABs are believed to have genetic cause.^{2,3} The mechanisms behind pregnancy loss are not fully understood, but systemic inflammation⁴ and reductions in uterine blood flow may contribute.⁵

Women commonly use medication for pain and inflammation during pregnancy. In 2005, almost 60% of U.S. pregnant women used an analgesic during their first trimester. Acetaminophen use was most common (54.2%), followed by use of ibuprofen (16.0%), and aspirin (3.8%).⁶

Over-the-counter pain medications generally relieve pain and inflammation by reducing prostaglandin (PG) synthesis,⁷⁻¹² with the strength of effect varying by medication type^{7-12,18,19} and dose.⁹⁻¹² The numerous PGs, differentiated by alphabetic/alphanumeric suffixes (e.g. PGA, PGF₂), are found throughout the body and perform a variety of actions, including maintaining homeostasis^{13,14} and causing inflammation and pain.¹³ During pregnancy, there is a rise in PGA and PGI₂ levels,^{15,16} and a decline in PGE and PGF₂ levels.¹⁷ PGA and PGI₂ act as vasodilators and reduced levels in pregnancy have been associated with hypertension, preeclampsia, and placental insufficiencies.^{18,19} Conversely, PGE₂ and PGF_{2a} have vasoconstrictive properties, and increased levels may restrict

blood flow to the uterus^{20,21} and the placenta^{22,23} which could affect viability of the fetus.²⁴

While acetaminophen, a non-NSAID pain reliever, is widely considered the first-line treatment for pain during pregnancy,^{25,26} research on its effects during reproduction is sparse. The few available studies have indicated no increased risk of SAB after use.^{26–28}

Epidemiologic research examining the association of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and naproxen, with SAB is conflicting. Some studies have found an increased risk of SAB after use of non-aspirin NSAIDs,^{27,29–31} while another found no increased risk after use of naproxen or ibuprofen.³² Early studies found an association between low-dose aspirin use and reduced risk of SAB.^{33,34} The more recent Effects of Aspirin in Gestation and Reproduction (EAGeR) randomized controlled trial, found no association between low-dose use and rate of clinical loss among women who experienced one to two previous pregnancy losses (HR=1.00, 95% CI: 0.73, 1.36).³⁶ When restricted to participants who experienced only one previous SAB that occurred during the past year, participants randomized to low-dose aspirin had a slightly higher live birth rate compared with placebo (HR=1.17, 95% CI: 1.01–1.37).³⁵ When examining primarily regular dose aspirin use, however, one observational post-conception cohort study found increased risk of SAB (HR=4.3, 95% CI: 1.3–14.2) when aspirin was used around the time of conception.²⁷

Little is known about the effects of opioid use during pregnancy. While

there is evidence of other adverse birth outcomes,^{36,37} to our knowledge, there are no studies examining SAB after use of opioids during early pregnancy.

Most prior studies of pain medication use in relation to SAB have been conducted using large administrative databases^{29,31,32} or post-conception pregnancy cohorts.^{26,27,33} Studies using administrative databases have substantial power to detect effects but are unable to examine over-the-counter medication use or control for confounding by variables unavailable in these databases (e.g. lifestyle factors). Lack of information on over-the-counter medication use may lead to substantial misclassification and preclude examination of infrequent use. More importantly, database studies and post-conception cohorts may fail to capture SABs that occur before women visit healthcare providers, introducing bias if exposure is differentially related to timing of loss.

The present study prospectively examines the association between pain medication use during early pregnancy and SAB risk in three large prospective cohorts of women enrolled pre-pregnancy in Denmark, the U.S., and Canada.

4.2 Methods

4.2.1 Data Collection

Data from three prospective cohort studies of pregnancy planners were combined for this analysis. 1) In Denmark, Smart Gravid (SG)³⁸ (2007–2011) enrolled female pregnancy planners ages 18–49 years; 2) Smart Foraeldre (SF) (2011–2017) is an expansion of SG that includes male partners,^{39,40} 3) In the

U.S. and Canada, Pregnancy Study Online (PRESTO)⁴¹ (2013–2017) enrolls female pregnancy planners ages 21–45 and their male partners. Recruitment and follow-up for SF and PRESTO are ongoing.

These three studies have similar designs and data collection procedures. Participants were recruited primarily using advertisements on health-related websites and social media. Eligible women were in a relationship with a male partner, not pregnant, and not using contraception or fertility treatments.

Questionnaires were administered online. Participants completed a questionnaire at baseline to report demographics, lifestyle factors, and medical history. Follow-up questionnaires were administered every two months until pregnancy or 12 months, whichever occurred first, to ascertain information on time-varying exposures (e.g. smoking status and alcohol consumption) and pregnancy status, identified by over 96% of participants using home pregnancy tests. Participants who conceived during follow-up completed an additional follow-up questionnaire during early (SG, SF, PRESTO; median 9 gestational weeks) and late (PRESTO; median 33 gestational weeks) pregnancy to ascertain data on pregnancy outcomes and exposures in pregnancy. Over 80% of participants completed at least one follow-up questionnaire.^{41,42} SF and SG participants provided their Civil Personal Registration (CPR) number, a ten-digit unique identifier assigned to all residents in Denmark⁴³ allowing for linkage to pregnancy outcome information in the Danish National Registry of Patients (DNRP).

PRESTO participants were linked to birth registers in selected U.S. states and Canadian provinces (19.3%) to identify viable pregnancies among participants who were still pregnant at study completion or lost to follow-up after conception. Self-reported data on SABs were obtained from follow-up questionnaires.

The Boston Medical Center institutional review board and the Danish Data Protection Board approved the study protocol and participants provided informed consent.

4.2.2 Assessment of covariates

On the baseline questionnaire, participants reported data on sociodemographics, reproductive history, medical history, anthropometrics, and lifestyle factors. On the follow-up questionnaires, participants reported time-varying data on lifestyle factors. Report of covariates occurred before the pregnancy outcome. BMI was calculated as weight (kg)/height (m)².

4.2.3 Assessment of SAB

On each follow-up questionnaire, women were asked if they were currently pregnant (yes, no, don't know) or if they experienced a pregnancy loss since the last questionnaire. Women who experienced an SAB, therapeutic abortion (TAB), or ectopic pregnancy reported the date and gestational week of pregnancy loss.

To obtain additional information about pregnancy outcomes in Denmark,

we linked participant CPR numbers to records in the DNRP. The DNRP provides information on inpatient and outpatient diagnoses and services including labor and delivery, SAB, and TAB, and weeks of gestation at pregnancy loss.

International Classification of Disease (ICD) 10th edition code DO03 was used to identify SABs and codes DO04-DO05 identified TABs. The positive predictive value for DNRP SAB diagnosis is excellent (97.4%).⁴⁴

In SG and SF, SAB was operationalized as 1) questionnaire report of a pregnancy loss at ≤ 20 gestational weeks and/or 2) questionnaire report of a viable pregnancy followed by a DNRP ICD-10 code for SAB at ≤ 20 gestational weeks, or 3) questionnaire report of a pregnancy and no subsequent ICD-10 code for SAB, TAB, or labor and delivery (presumed SAB). Of 1,204 SABs observed in SG and SF, 446 (37.0%) were identified only in the DNRP, 431 (35.8%) were identified only by questionnaire (*i.e.* early losses), and 151 (12.5%) were identified in both sources. Nearly 15% (N=176) of SG and SF participants reported a pregnancy on the early pregnancy questionnaire that was not found in the DNRP. We assumed these participants subsequently experienced an SAB and multiply imputed weeks of gestation as ≤ 12 because SABs later than 12 weeks' gestation typically would be identified in the DNRP. We conducted a sensitivity analysis excluding these women and observed similar results.

4.2.4 Assessment of pain medication use

Pain medication use was assessed at baseline and on each follow-up questionnaire. In SG and SF, participants were asked if they used any of 31 and

51 different pain medications during the past 4 weeks, respectively, and could check all that apply. In PRESTO, participants were asked if they used pain medication in the past 4 weeks. Users could indicate the names of up to 3 medications using auto-complete text recognition software.⁴⁵ For each reported medication, PRESTO and SF participants were asked how many pills they took during the past 4 weeks and SG participants were asked how many pills they used in categories (≤ 1 , 2–5, 6–8 per week; 2, ≥ 3 per day). SG categories were converted to monthly intake using the midpoint of the category scaled to a 28 day period.

Medications were categorized by active ingredient (acetaminophen, aspirin, ibuprofen, naproxen, opioids). Categories were not mutually exclusive; women who used medications with more than one active ingredient were considered users of both types. SG and SF questionnaires only included select opioid combination products; due to the incomplete ascertainment of exposure, opioids were only analyzed in PRESTO.

At baseline and each follow-up, cumulative past-month dose was calculated as the total number of pills used during the past 4 weeks multiplied by the dose of the active ingredient in each pill, summed by active ingredient. The most common dose was used for medications that are available in multiple strengths. For example, if a participant indicated using 2 “Excedrin Migraine” pills, this would contribute 2 x 250 mg of acetaminophen and 2 x 250 mg of aspirin; if a participant reported 3 “ibuprofen,” this would contribute 3 x 200 mg of

ibuprofen, the most common strength. Dose was not analyzed for opioids due to the small number of users.

The approximate date of conception was calculated as the first day of the last menstrual period +14 days. Use was assessed on any questionnaire completed between conception and 12 gestational weeks. Importantly, exposure information was reported before the pregnancy outcome was known, *i.e.* exposure information was not analyzed if it was reported concurrently with or after a pregnancy loss. To reduce potential for reverse causation, we only analyzed exposure on questionnaires that were completed between conception and >3 days before the reported date of SAB.⁴⁶

The majority of participants had one (52.2%) or two (11.7%) prospective exposure assessments during pregnancy; 36.1% of participants were missing exposure assessment during pregnancy. Figure 1 describes common scenarios for each number of exposure assessments. Participants who had one exposure assessment reported a pregnancy on a follow-up questionnaire, having conceived since the last data collection time point (scenarios A–B). Participants with two exposure assessments were pregnant at a prior follow-up but had not yet received a positive pregnancy test; they reported the pregnancy at the subsequent follow-up (scenarios C–D). Participants missing exposure assessment conceived and experienced an SAB between follow-up questionnaires (scenario F); or conceived after being lost to follow-up with a recorded live birth in the DNRP with no intervening pregnancy loss (SG & SF,

scenario E) (Figure 4.1).

For each medication, a participant was considered exposed if she used ≥ 1 pill during the pregnancy. Cumulative past-month dose was assigned as the reported monthly dose for participants with one prospective data collection time point during pregnancy, and the mean of reported monthly doses for participants with two prospective exposure assessments. For the 36.1% of women without exposure assessment during pregnancy, we used multiple imputation to complete missing exposure data in 5 datasets. We conducted the imputation separately for Danish and North American participants and included over 120 variables in the imputation models, including all information on pre-conception pain medication use. We conducted a sensitivity analysis omitting all participants with missing exposure assessment.

4.2.5 Exclusions

This study was restricted to the PRESTO, SF, and SG participants who had a clinically detectable pregnancy as reported on follow-up questionnaires or in the DNRP. Exclusions by study are detailed in Figure 4.2.

4.2.6 Data analysis

We conducted a time-to-event analysis using gestational weeks as the time scale. We first examined the association between use of acetaminophen, aspirin, ibuprofen, naproxen, or opioids (PRESTO) during pregnancy and SAB. We then examined the association between cumulative monthly dose and SAB,

grouped into two categories based on the distribution of reported use.

We used Cox proportional hazards regression models using gestational weeks as the time scale to estimate hazard ratios (HR) and 95% confidence intervals (CI), using the exact option in PROC PHREG to account for tied event times.^{47,48} The HR is approximately equal to average per-week risk of SAB comparing users of a specific pain medication with non-users of that medication. Participants were censored at gestational week of SAB, TAB, last follow-up, or 20 weeks, whichever occurred first. Proportional hazards was confirmed using log survivor plots.

Models were adjusted for potential confounders selected *a priori* based on the literature and a directed acyclic graph. These included study cohort (SG, SF, PRESTO), age (<25, 25–29, 30–34, 35–39, ≥40 years), education (≤12, 13–15, 16, ≥17 years), income (< versus ≥ 50,000 USD/300,000 DKK per year), non-Hispanic white (yes versus no), BMI (<18.5, 18.5–24, 25–29, ≥30 kg/m²), diagnosis of migraine headaches (yes versus no), diabetes (yes versus no), uterine leiomyoma (yes versus no) or thyroid disease (yes versus no), and cigarette smoking (yes versus no), alcohol use (yes versus no), or antibiotic use (yes versus no) during pregnancy (proxy for fever or infection). Models were mutually adjusted for the other types of pain medications.

To examine effect measure modification, results were examined separately by age (<30 versus ≥30 years), time to pregnancy (<6 versus 3–≥6 cycles), BMI (<30 versus ≥30 kg/m²) and history of SAB (yes versus no). To

identify any impact of difference in methodology by cohort, we examined results separately by study (SG, SF, PRESTO). Further, because the etiology of pregnancy loss may differ by weeks of gestation at loss,⁴⁹ we stratified by timing of loss (<8 versus ≥8 weeks). Next, we compared use of each pain medication with non-use of *any* pain medication by restricting to women who used only one type of pain medication during pregnancy or who did not use pain-relievers. To control for residual confounding by indication, we then compared users of aspirin, ibuprofen or naproxen to users of the most common medication, acetaminophen, as these medications are often used for the same indications. Finally, because we were unable to examine time-varying medication use to avoid potential immortal time bias that occurs when viable pregnancies have more time to accrue exposure,³² we conducted a sensitivity analysis to reduce the probability of this bias by limiting exposure assessment to any data collection time point that occurred at <8 weeks of gestation, instead of the <12 weeks of gestation used in our main analyses.

Thirty seven percent of participants were missing data on pain-reliever use during pregnancy. Missing covariate data ranged from <3% (age, race, education, BMI, migraine headaches) to 34% (smoking during pregnancy), with the exception of antibiotic use during pregnancy, which was missing for 66% of participants. Antibiotic use was not collected in SG and was thus “missing at random”.⁵⁰ We used PROC MI to impute missing values in five imputed datasets and PROC MIANALYZE to combine coefficient and standard error estimates.⁴⁸

4.3 Results

Among 13,901 pregnancy planners, we identified 9,196 pregnancies conceived without the use of fertility treatments and 1,597 SABs (Overall: 17.4%, SG: 17.5%, SF: 18.0%, PRESTO: 16.5%). Nearly half (45.1%) of pregnancies were exposed to one or more pain medications before 12 gestational weeks, most commonly acetaminophen (37.0%) or ibuprofen (17.5%) and less commonly aspirin (5.7%), opioids (3.7%, PRESTO) or naproxen (1.6%). Overall, cumulative monthly dose was low; the median dose was 2,000 mg (IQR: 500–3,500) for acetaminophen, 400 mg (IQR: 200–1,400) for ibuprofen, 250 mg (IQR: 250–3,500) for aspirin, 220 mg (IQR: 220–660) for naproxen, and 1 pill (PRESTO IQR: 1–2) for opioids.

Pain medication use, especially use of naproxen or ibuprofen, was more common in PRESTO compared with SG and SF. Pain medication use during pregnancy was associated with lower educational attainment, use of alcohol or tobacco during pregnancy, and indications such as migraine headache or antibiotic use during pregnancy (i.e., proxy for fever or infection). Diagnoses of uterine leiomyoma or thyroid disease were more common among naproxen and opioid users, and opioid users were more likely to have a higher BMI and a history of SAB, compared with non-users of these respective medications (Table 4.1).

After adjusting for potential confounders, the HRs for pain medication use and SAB were 1.04 (95% CI: 0.82–1.31) for acetaminophen, 1.06 (95% CI: 0.81–

1.39) for aspirin, 1.28 (95% CI: 1.11–1.47) for ibuprofen, 1.26 (95% CI: 0.61–2.57) for naproxen, and 1.66 (95% CI: 0.85–3.24) for opioids (PRESTO), compared with non-users of each respective medication. We observed consistent results after excluding women with missing exposure data (Table 4.2). We did not observe dose response relations, apart from naproxen, for which there were only 8 events in the high dose category, however, results were not consistent when restricted to participants with exposure assessment during pregnancy (Table 4.3).

SAB risk was higher for ibuprofen users <30 years (HR=1.55, 95% CI: 1.28–1.88) than for ≥30 years (HR=1.04, 95% CI: 0.84–1.28), compared with non-users of ibuprofen. Further, ibuprofen users had increased risk of early (HR=1.44, 95% CI: 1.19–1.73) but not late (HR=1.05, 95% CI: 0.85–1.30) SAB compared with non-users. For no other pain-relieving medications did the risk of SAB appear to differ by gestational week. Aspirin use was associated with increased risk of SAB among women without a history of SAB (HR=1.28, 95% CI: 0.90–1.82) but not among women with a history of SAB (HR=0.97, 95% CI: 0.52–1.80) (Table 4.4).

After stratifying by BMI (Table 4.4), time-to-pregnancy (Table 4.4), and cohort (Table 4.5), results were consistent with our overall findings. When restricted to users of a single medication, or to participants with exposure assessment before 8 gestational weeks, the results did not change appreciably (Table 4.6).

4.4 Discussion

In this large prospective cohort of Danish and North American women recruited during preconception, we found that use of ibuprofen, opioids, or naproxen before 12 weeks of gestation was associated with a small increased risk of SAB, after controlling for demographics, common indications for use of pain medications, and other covariates, although numbers of naproxen and opioid users were small. Overall, low cumulative dose of acetaminophen or aspirin did not affect risk of SAB. Among women without a history of SAB, aspirin use was associated with a slight increase in risk of SAB.

The lack of association between acetaminophen use and SAB risk is consistent with prior literature.^{27,28} It is important to note, however, that recent studies have suggested possible associations between in-utero exposure to acetaminophen and adverse infant and childhood outcomes including neurodevelopmental problems,^{51–53} asthma,^{54,55} and reduced anogenital distance^{56,57} in male offspring.

Results for ibuprofen and naproxen are consistent with most,^{27,29,30} but not all,³² previous studies that found an increased risk of SAB among users of non-aspirin NSAIDs. Ibuprofen and naproxen use, via alterations in PG synthesis,^{8,12} may upset the balance of PGA and PGI₂ upregulation^{15,16} and PGE and PGF₂ downregulation¹⁷ needed to sustain pregnancy.^{18–24} Ibuprofen was associated with increased risk of early (<8 gestational weeks) but not late (≥8 gestational weeks) pregnancy loss. Because ibuprofen is not recommended for pain-relief

during pregnancy,^{25,26} use may have occurred before the women knew they were pregnant, thereby increasing the risk of early loss proximate to exposure.

Overall, we did not observe any appreciable association between aspirin use and SAB risk, overall and by dose, and specifically among women with a history of SAB. Our results are consistent with the EAGeR randomized trial finding similar results when examining low-dose aspirin use among women with a prior SAB.^{35,58} Our result of slightly increased risk of SAB among aspirin users without a history of SAB was consistent with the Li et al. study, which examined regular-dose aspirin use in a post-conception cohort. It is possible that regular-but not low-dose aspirin use increases risk of SAB.

Little is known about the effect of opioid use during pregnancy on SAB risk. Our data showed an increased risk of SAB among PRESTO participants who reported opioid use. Bateman et al. found that in the U.S. opioids are prescribed during pregnancy for symptoms such as back pain, abdominal pain, joint pain, cough, or migraine headaches.⁵⁹ They found a high prevalence of opioid prescriptions for abdominal pain (31.9%),⁵⁹ a common symptom of SAB, indicating that reverse causation may explain the increase in risk we observed. To reduce this bias, we only assessed exposures reported on questionnaires completed >3 days before the reported date of SAB; however, this step may not have fully eliminated reverse causation. For example, if a woman took a medication for SAB pain and inaccurately recorded a later date at SAB, she may be incorrectly classified as a user. Since the early 2000s, the U.S. has

experienced a significant increase in opioid abuse and dependence.^{59,60} There may be lifestyle factors associated with opioid abuse that increase the risk of SAB. For example, opioid users may have poor nutrition⁶¹ or use illicit drugs,⁶² which could increase SAB risk.

This study has several limitations. Primarily, due to the timing of follow-up questionnaires, pregnancy exposure information was not collected for all participants. Using multiple imputation allowed us to address missing data and avoid a selection bias that could occur if we excluded these participants.

Secondly, exposure misclassification is also likely. We relied on participant report of pain reliever use, which was likely underreported or recalled with error. Exposure was most often assessed once during pregnancy and the timing, frequency, and dose of medication use could have varied greatly within 12 weeks of gestation. Because exposure was ascertained before the pregnancy outcome was known, these sources of exposure misclassification are unlikely to be differential. As such, we would expect our effect estimates to be biased towards the null, with the exception of the intermediate dose group, which could be biased in either direction. While we limited exposure assessment to <3 days before the date of SAB, if this date was incorrectly identified as a later date, differential misclassification of exposure is possible. This would result in an upward bias and could partially explain the increased risk of SAB observed among ibuprofen, opioid, and naproxen users compared with non-users. Further, while pain medication use during pregnancy was common, participants mainly

used low cumulative doses, precluding the interpretation of differences by dose. Likewise, aspirin, naproxen and opioid use was uncommon and opioid use could only be analyzed in PRESTO, thereby limiting our precision.

We assessed exposure between conception and 12 weeks of gestation, however, viable pregnancies often had a greater amount of time to be exposed to pain medications compared with pregnancies ending in SABs, possibly creating a downward bias.³² This potential bias would not explain the increased risk of SAB observed after ibuprofen, opioid, or naproxen use. Further, it is likely that we failed to observe early losses that occurred before pregnancy detection. Additionally while we had Danish registry data to ascertain SABs not reported on questionnaires, this information was unavailable in the PRESTO cohort. Nevertheless, we observed a similar risk of SAB in Denmark (17.7%) and North America (16.5%), indicating that the use of different sources of outcome information was unlikely to introduce appreciable bias. Further, we had more complete ascertainment of SABs compared with many post-conception cohorts (e.g. 4.8%,²⁶ 6.3%³³) or studies exclusively using administrative databases (e.g. 9.9%³²). Furthermore, some residual confounding by indication is likely because we did not know the specific indication for use. We assessed indication more generally using other questionnaire items (e.g. migraine headache, antibiotics as a proxy for infection), however, we were not able to adjust for indications such as abdominal cramping, which could lead to an upward bias.

Our study indicates that low cumulative dose use of ibuprofen, opioids,

and naproxen during pregnancy may be associated with a small increased risk of SAB, though numbers of naproxen and opioid users were low. Overall, low cumulative dose aspirin or acetaminophen use was not appreciably associated with SAB.

4.5 Funding

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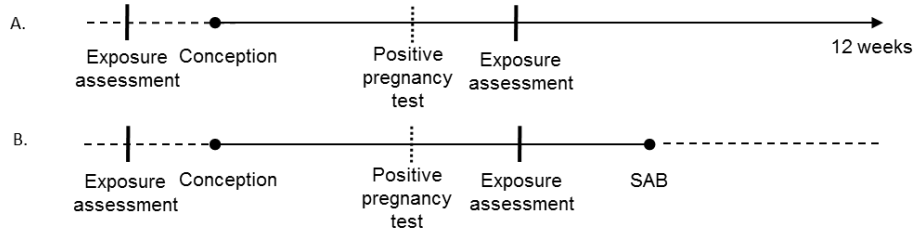
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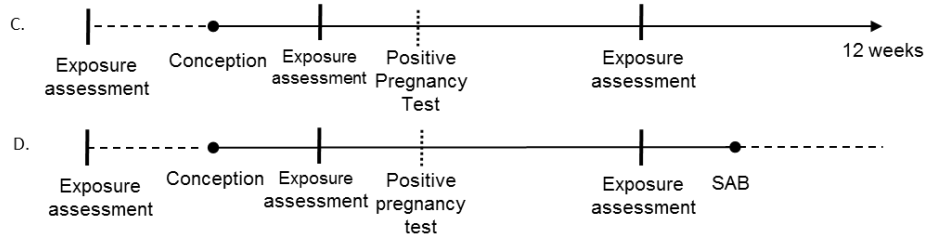
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Figure 4.1 Scenarios for exposure assessments during pregnancy, by number of prospective assessments available for analysis

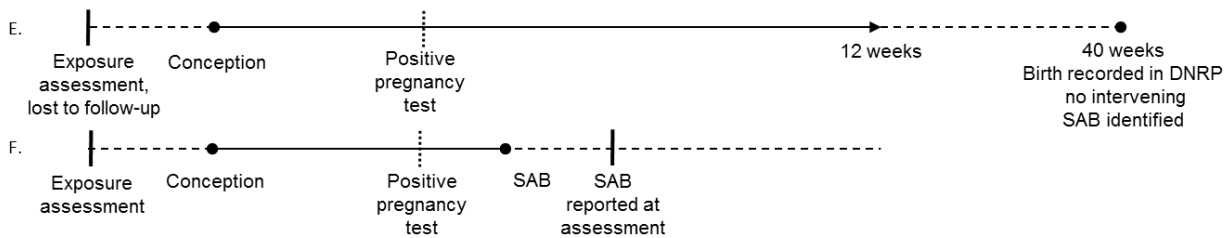
1 Exposure Assessment



2 Exposure Assessments



Missing Exposure Assessments



SAB=Spontaneous abortion

Note 1: Not drawn to scale. Follow-up questionnaires were administered every 8 weeks until reported pregnancy, then during early pregnancy.

Note 2: Solid horizontal line denotes pregnancy

Note 3: Viable pregnancies were censored at 20 weeks.

Figure 4.2 Flow chart of enrollment and exclusions, Snart Gravid, Snart Foraelldre and PRESTO, 2007–2017

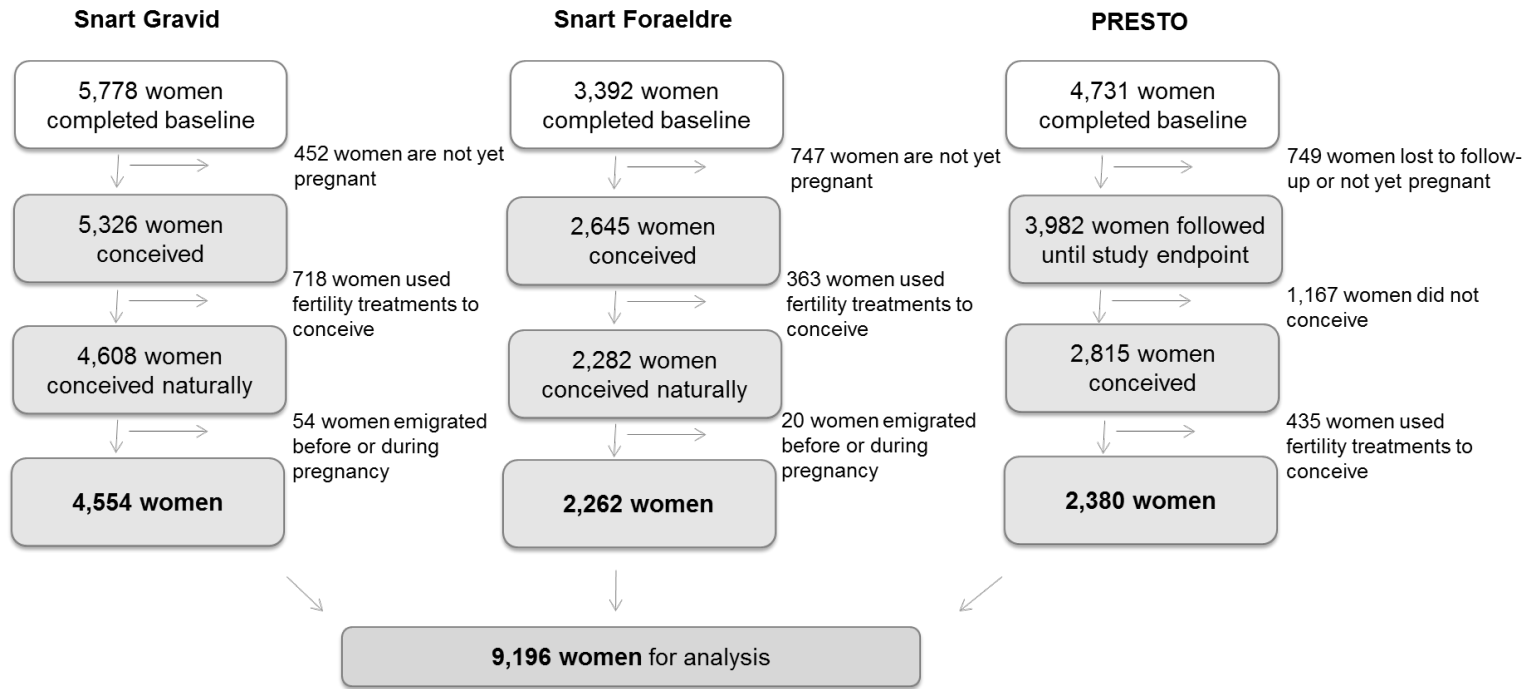


Table 4.1 Characteristics of participants by pain medication use before 12 gestational weeks, Snart Gravid, Snart Forældre and PRESTO (N=9,196), 2007–2017

	Pain Medication Use		Type of Medication Use				
	No	Yes	Acetaminophen	Aspirin	Ibuprofen	Naproxen	Opioids [†]
Number of Participants N (%)	5,052 (54.9)	4,144 (45.1)	3,398 (37.0)	520 (5.7)	1,612 (17.5)	146 (1.6)	89 (3.7)
Cohort							
Snart Gravid, %	49.0	50.2	52.3	53.1	47.3	27.4	--
Snart Forældre, %	27.5	21.0	22.9	21.4	20.1	9.6	--
PRESTO, %	23.5	28.8	24.8	25.6	32.6	63.0	100.0
Age (years), mean	28.7	28.6	28.6	28.8	28.7	28.2	28.6
Non-Hispanic White, %	96.4	96.3	96.9	95.4	95.7	92.2	75.2
Annual household income <50,000 USD/<300,000 DKK, %	15.4	16.0	16.0	16.6	17.3	15.4	25.0
<College degree, %	31.6	35.4	36.0	38.6	36.2	34.7	32.4
BMI (kg/m ²), mean	24.2	25.4	25.4	25.2	25.6	26.9	28.1
Physical activity (MET-hrs/wk), mean	41.7	36.5	36.4	34.6	37.3	38.9	34.7
Alcohol use during pregnancy, %	41.6	64.0	61.6	80.8	79.1	69.2	64.9
Smoked during pregnancy, %	7.9	13.8	14.0	18.4	15.8	11.1	10.0
Multivitamin supplement use, %	81.9	83.6	83.8	80.3	83.2	85.1	71.3
Antibiotic use during pregnancy, %	6.3	20.5	21.4	37.8	25.1	44.5	31.3
History of SAB, %	15.3	16.5	16.8	18.5	16.0	16.6	26.7
Migraine headaches, %	30.2	47.6	49.9	52.6	45.7	28.5	29.6
Diabetes, %	0.9	1.6	1.8	2.1	2.1	<2.0	0.0
Uterine leiomyoma, %	1.4	2.2	2.5	4.4	2.0	5.9	6.8
Thyroid disease, %	2.6	3.5	3.3	3.0	4.1	5.4	7.4
Time to pregnancy ≥6 months, %	45.7	48.8	49.0	53.1	52.1	49.8	58.8
Regular period, %	69.9	69.7	70.3	72.4	70.0	62.0	57.1
Did something to improve chances of conception, %	61.2	63.9	64.0	64.2	64.4	73.0	71.2

USD = U.S. dollars, DKK = Danish kroner, MET = metabolic equivalent of task

[†] Data from PRESTO are presented. SG and SF did not have complete ascertainment of opioids on participant questionnaires.

Note 1. All characteristics except for age and cohort are age-standardized to the study population at baseline.

Note 2. Column percentages are displayed

Note 3. Medication categories are not mutually exclusive.

Note 4. Antibiotic use was not collected in SG. Multiple imputation was used to complete missing data.

Table 4.2 Pain medication use before 12 gestational weeks and spontaneous abortion, Snart Gravid, Snart Forældre and PRESTO, 2007–2017

Medication	Full cohort using multiple imputation to complete missing exposure information (N=9,196)				Restricted to participants with exposure assessment during pregnancy (N=5,876)			
	No. of Pregs	No. of SAB	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a	No. of Pregs	No. of SAB	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Any pain medication								
Non-use	5,052	772	1.00 (Reference)	1.00 (Reference)	3,473	243	1.00 (Reference)	1.00 (Reference)
Any use	4,144	825	1.37 (1.09–1.71)	1.24 (0.99–1.55)	2,403	251	1.54 (1.29–1.83)	1.26 (1.05–1.52)
Acetaminophen								
Non-use	5798	940	1.00 (Reference)	1.00 (Reference)	3,916	322	1.00 (Reference)	1.00 (Reference)
Any use	3398	657	1.08 (0.85–1.36)	1.04 (0.82–1.31)	1,960	172	0.98 (0.81–1.19)	0.93 (0.77–1.13)
Aspirin								
Non-use	8,676	1,479	1.00 (Reference)	1.00 (Reference)	5,657	469	1.00 (Reference)	1.00 (Reference)
Any use	520	118	1.11 (0.85–1.45)	1.06 (0.81–1.39)	219	25	1.03 (0.64–1.68)	0.90 (0.57–1.45)
Ibuprofen								
Non-use	7,584	1,223	1.00 (Reference)	1.00 (Reference)	5,098	392	1.00 (Reference)	1.00 (Reference)
Any use	1,612	374	1.42 (1.23–1.64)	1.28 (1.11–1.47)	778	102	1.75 (1.39–2.18)	1.29 (1.02–1.63)
Naproxen								
Non-use	9,050	1,560	1.00 (Reference)	1.00 (Reference)	5,828	487	1.00 (Reference)	1.00 (Reference)
Any use	146	37	1.25 (0.62–2.52)	1.26 (0.61–2.57)	48	7	1.60 (0.75–3.41)	1.24 (0.58–2.65)
Opioids [†]								
Non-use	2,291	368	1.00 (Reference)	1.00 (Reference)	1,678	170	1.00 (Reference)	1.00 (Reference)
Any use	89	25	1.61 (0.90–2.88)	1.66 (0.85–3.24)	30	7	2.19 (1.01–4.75)	2.07 (0.93–4.61)

SAB=spontaneous abortion, HR=hazard ratio

[†] Opioids analyses were restricted to PRESTO participants. SG and SF did not have complete ascertainment of opioids on participant questionnaires.

^a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.3 Cumulative monthly dose of pain medication exposure before 12 gestational weeks and spontaneous abortion, Snart Gravid, Snart Foraeldre and PRESTO, 2007–2017

Medication	No. of	No. of	Unadjusted	Adjusted	No. of	No. of	Unadjusted	Adjusted
	Pregs	SAB	HR (95% CI)	HR (95% CI) ^a	Pregs	SAB	HR (95% CI)	HR (95% CI) ^a
	Full cohort using multiple imputation to complete missing exposure information (N=9,196)				Restricted to participants with exposure assessment during pregnancy (N=5,876)			
Non-use	5,052	772	1.00 (Reference)	1.00 (Reference)	3,427	239	1.00 (Reference)	1.00 (Reference)
Any use								
Low exposure	2,192	488	1.57 (1.27–1.94)	1.42 (1.15–1.75)	900	93	1.60 (1.26–2.03)	1.22 (0.94–1.59)
Moderate exposure	2,020	349	1.16 (0.91–1.47)	1.05 (0.82–1.34)	1,549	162	1.50 (1.23–1.83)	1.28 (1.02–1.59)
Acetaminophen (mg)								
Non-use	5,798	940	1.00 (Reference)	1.00 (Reference)	1,960	172	1.00 (Reference)	1.00 (Reference)
<3,000	1,855	408	1.22 (0.97–1.55)	1.17 (0.93–1.49)	797	70	1.05 (0.80–1.36)	0.93 (0.71–1.23)
≥3,000	1,543	249	0.92 (0.71–1.18)	0.88 (0.68–1.14)	1,163	102	0.94 (0.75–1.18)	0.93 (0.72–1.19)
Aspirin (mg)								
Non-use	8,676	1,479	1.00 (Reference)	1.00 (Reference)	5,657	469	1.00 (Reference)	1.00 (Reference)
<500	295	84	1.39 (0.98–1.96)	1.36 (0.95–1.94)	14	0	--	--
≥500	225	34	0.76 (0.52–1.10)	0.70 (0.48–1.03)	205	25	1.11 (0.68–1.82)	0.98 (0.61–1.58)
Ibuprofen (mg)								
Non-use	7,584	1,223	1.00 (Reference)	1.00 (Reference)	5,098	392	1.00 (Reference)	1.00 (Reference)
<1,000	1,066	274	1.58 (1.35–1.86)	1.43 (1.23–1.68)	322	47	1.98 (1.45–2.69)	1.38 (0.99–1.92)
≥1,000	546	100	1.11 (0.88–1.41)	1.00 (0.78–1.27)	456	55	1.58 (1.19–2.11)	1.23 (0.91–1.65)
Naproxen (mg)								
Non-use	9,050	1,560	1.00 (Reference)	1.00 (Reference)	5,828	487	1.00 (Reference)	1.00 (Reference)
<500	110	29	1.21 (0.54–2.72)	1.21 (0.53–2.79)	19	≤3	0.51 (0.07–3.69)	0.42 (0.06–3.00)
≥500	36	8	1.34 (0.63–2.86)	1.34 (0.63–2.87)	29	6	2.48 (1.11–5.57)	1.84 (0.81–4.16)

HR=hazard ratio

a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.4 Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by age, Smart Gravid, Smart Forældre and PRESTO, 2007–2017

Medication	No. of Pregs	No. of SAB	Age<30		Age≥30		Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
			Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a	No. of Pregs	No. of SAB		
Any pain medication								
Non-use	3,035	390	1.00 (Reference)	1.00 (Reference)	2,017	382	1.00 (Reference)	1.00 (Reference)
Any use	2,458	440	1.48 (1.13–1.93)	1.33 (1.01–1.75)	1,686	385	1.24 (1.01–1.53)	1.16 (0.94–1.43)
Acetaminophen								
Non-use	3,471	484	1.00 (Reference)	1.00 (Reference)	2,327	456	1.00 (Reference)	1.00 (Reference)
Any use	1,676	346	1.07 (0.83–1.38)	1.01 (0.77–1.33)	1,376	311	1.08 (0.84–1.40)	1.06 (0.82–1.39)
Aspirin								
Non-use	5,194	778	1.00 (Reference)	1.00 (Reference)	3,482	701	1.00 (Reference)	1.00 (Reference)
Any use	299	52	1.01 (0.69–1.49)	0.98 (0.66–1.45)	221	66	1.23 (0.81–1.86)	1.14 (0.77–1.70)
Ibuprofen								
Non-use	4,550	615	1.00 (Reference)	1.00 (Reference)	3,034	608	1.00 (Reference)	1.00 (Reference)
Any use	943	215	1.72 (1.43–2.08)	1.55 (1.28–1.88)	669	159	1.12 (0.92–1.37)	1.04 (0.84–1.28)
Naproxen								
Non-use	5,399	813	1.00 (Reference)	1.00 (Reference)	3,651	747	1.00 (Reference)	1.00 (Reference)
Any use	94	17	1.08 (0.40–2.89)	1.04 (0.37–2.91)	52	20	1.49 (0.75–2.96)	1.44 (0.72–2.90)

HR=hazard ratio

^a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.4 Continued. Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by time to conception, Snart Gravid, Snart Foraeldre and PRESTO, 2007–2017

Medication	No. of Pregs	No. of SAB	Time to conception <6 cycles		Time to conception ≥6 cycles		Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
			Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a	No. of Pregs	No. of SAB		
Any pain medication								
Non-use	2,744	410	1.00 (Reference)	1.00 (Reference)	2,308	362	1.00 (Reference)	1.00 (Reference)
Any use	2,121	387	1.34 (1.03–1.75)	1.25 (0.97–1.62)	2,023	438	1.37 (1.08–1.75)	1.24 (0.97–1.57)
Acetaminophen								
Non-use	3,134	489	1.00 (Reference)	1.00 (Reference)	2,664	451	1.00 (Reference)	1.00 (Reference)
Any use	1,731	308	1.12 (0.90–1.38)	1.08 (0.88–1.34)	1,667	349	1.03 (0.75–1.43)	1.00 (0.73–1.37)
Aspirin								
Non-use	4,622	747	1.00 (Reference)	1.00 (Reference)	4,054	732	1.00 (Reference)	1.00 (Reference)
Any use	243	50	1.08 (0.67–1.75)	1.02 (0.63–1.67)	277	68	1.12 (0.77–1.62)	1.07 (0.75–1.53)
Ibuprofen								
Non-use	4,094	635	1.00 (Reference)	1.00 (Reference)	3,490	588	1.00 (Reference)	1.00 (Reference)
Any use	771	162	1.34 (1.05–1.73)	1.24 (0.98–1.57)	841	212	1.45 (1.22–1.74)	1.32 (1.09–1.59)
Naproxen								
Non-use	4,792	775	1.00 (Reference)	1.00 (Reference)	4,258	785	1.00 (Reference)	1.00 (Reference)
Any use	73	22	1.37 (0.46–4.09)	1.42 (0.48–4.26)	73	15	1.14 (0.58–2.26)	1.11 (0.56–2.19)

HR=hazard ratio

^a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.4 Continued. Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by BMI, Snart Gravid, Snart Forældre and PRESTO, 2007–2017

Medication	No. of Pregs	No. of SAB	BMI <30 kg/m ²		BMI ≥30 kg/m ²		Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
			Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a	No. of Pregs	No. of SAB		
Any pain medication								
Non-use	4,475	677	1.00 (Reference)	1.00 (Reference)	577	95	1.00 (Reference)	1.00 (Reference)
Any use	3,421	675	1.37 (1.09–1.71)	1.23 (1.00–1.53)	723	150	1.28 (0.82–1.99)	1.25 (0.76–2.06)
Acetaminophen								
Non-use	5,100	812	1.00 (Reference)	1.00 (Reference)	698	128	1.00 (Reference)	1.00 (Reference)
Any use	2,796	540	1.09 (0.86–1.39)	1.05 (0.83–1.34)	602	117	0.97 (0.65–1.45)	0.97 (0.63–1.49)
Aspirin								
Non-use	7,463	1,254	1.00 (Reference)	1.00 (Reference)	1,213	225	1.00 (Reference)	1.00 (Reference)
Any use	433	98	1.16 (0.88–1.54)	1.10 (0.83–1.47)	87	20	0.91 (0.50–1.65)	0.86 (0.47–1.57)
Ibuprofen								
Non-use	6,590	1,056	1.00 (Reference)	1.00 (Reference)	994	167	1.00 (Reference)	1.00 (Reference)
Any use	1,306	296	1.42 (1.18–1.70)	1.27 (1.06–1.51)	306	78	1.36 (0.94–1.98)	1.32 (0.84–2.08)
Naproxen								
Non-use	7,783	1,327	1.00 (Reference)	1.00 (Reference)	1,267	233	1.00 (Reference)	1.00 (Reference)
Any use	113	25	1.22 (0.57–2.62)	1.19 (0.57–2.49)	33	12	1.35 (0.53–3.46)	1.48 (0.46–4.77)

HR=hazard ratio

a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.4 Continued. Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by timing of pregnancy loss, Snart Gravid, Snart Foraeldre and PRESTO, 2007–2017

Medication	No. of Pregs	No. of SAB	Pregnancy loss <8 weeks		Pregnancy loss ≥ 8 weeks		Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
			Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a	No. of Pregs	No. of SAB		
Any pain medication								
Non-use	4,671	391	1.00 (Reference)	1.00 (Reference)	4,661	381	1.00 (Reference)	1.00 (Reference)
Any use	3,812	493	1.55 (1.12–2.15)	1.37 (1.00–1.88)	3,651	332	1.17 (0.94–1.46)	1.09 (0.87–1.37)
Acetaminophen								
Non-use	5,340	482	1.00 (Reference)	1.00 (Reference)	5,316	458	1.00 (Reference)	1.00 (Reference)
Any use	3,143	402	1.17 (0.84–1.62)	1.12 (0.81–1.56)	2,996	255	0.96 (0.73–1.27)	0.93 (0.70–1.23)
Aspirin								
Non-use	8,012	815	1.00 (Reference)	1.00 (Reference)	7,861	664	1.00 (Reference)	1.00 (Reference)
Any use	471	69	1.07 (0.71–1.60)	1.02 (0.68–1.53)	451	49	1.19 (0.78–1.82)	1.15 (0.74–1.79)
Ibuprofen								
Non-use	7,005	644	1.00 (Reference)	1.00 (Reference)	6,940	579	1.00 (Reference)	1.00 (Reference)
Any use	1,478	240	1.64 (1.35–1.98)	1.44 (1.19–1.73)	1,372	134	1.14 (0.92–1.40)	1.05 (0.85–1.30)
Naproxen								
Non-use	8,352	862	1.00 (Reference)	1.00 (Reference)	8,188	698	1.00 (Reference)	1.00 (Reference)
Any use	131	22	1.28 (0.58–2.82)	1.22 (0.52–2.87)	124	15	1.23 (0.59–2.55)	1.33 (0.64–2.76)

HR=hazard ratio

^a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.4 Continued. Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by history of SAB, Snart Gravid, Snart Foraeldre and PRESTO, 2007–2017

Medication	No. of Pregs	No. of SAB	No history of SAB		History of SAB		Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
			Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a	No. of Pregs	No. of SAB		
Any pain medication								
Non-use	4,177	588	1.00 (Reference)	1.00 (Reference)	751	155	1.00 (Reference)	1.00 (Reference)
Any use	3,563	668	1.41 (1.21–1.64)	1.34 (1.13–1.58)	705	186	1.29 (0.97–1.70)	1.35 (1.01–1.80)
Acetaminophen								
Non-use	4,798	730	1.00 (Reference)	1.00 (Reference)	863	182	1.00 (Reference)	1.00 (Reference)
Any use	2,942	526	1.05 (0.87–1.27)	1.04 (0.86–1.25)	593	159	1.07 (0.76–1.50)	1.17 (0.84–1.65)
Aspirin								
Non-use	7,282	1,145	1.00 (Reference)	1.00 (Reference)	1,351	311	1.00 (Reference)	1.00 (Reference)
Any use	458	111	1.30 (0.92–1.82)	1.28 (0.90–1.82)	105	30	0.97 (0.56–1.65)	0.97 (0.52–1.80)
Ibuprofen								
Non-use	6,359	955	1.00 (Reference)	1.00 (Reference)	1,193	275	1.00 (Reference)	1.00 (Reference)
Any use	1,381	301	1.59 (1.26–2.00)	1.50 (1.19–1.90)	263	66	1.22 (0.74–2.00)	1.17 (0.77–1.77)
Naproxen								
Non-use	7,616	1,232	1.00 (Reference)	1.00 (Reference)	1,432	333	1.00 (Reference)	1.00 (Reference)
Any use	124	24	1.03 (0.58–1.82)	1.07 (0.58–1.98)	24	8	1.30 (0.43–3.90)	1.54 (0.48–4.94)

HR=hazard ratio

^a Models were adjusted for cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.5 Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by cohort, 2007–2017

Medication	No. of Pregs	No. of SAB	Unadjusted	Adjusted
			HR (95% CI)	HR (95% CI) ^a
SG				
Any pain medication				
Non-use	2,473	379	1.00 (Reference)	1.00 (Reference)
Any use	2,081	418	1.36 (1.11–1.66)	1.26 (1.03–1.54)
Acetaminophen				
Non-use	2,778	448	1.00 (Reference)	1.00 (Reference)
Any use	1,776	349	1.11 (0.89–1.40)	1.08 (0.85–1.36)
Aspirin				
Non-use	4,278	740	1.00 (Reference)	1.00 (Reference)
Any use	276	57	1.09 (0.71–1.67)	1.04 (0.67–1.63)
Ibuprofen				
Non-use	3,791	620	1.00 (Reference)	1.00 (Reference)
Any use	763	177	1.34 (1.02–1.76)	1.23 (0.94–1.60)
Naproxen				
Non-use	4,514	786	1.00 (Reference)	1.00 (Reference)
Any use	40	11	1.29 (0.29–5.66)	1.37 (0.31–6.09)
SF				
Any pain medication				
Non-use	1,391	216	1.00 (Reference)	1.00 (Reference)
Any use	871	191	1.54 (0.94–2.53)	1.25 (0.80–1.96)
Acetaminophen				
Non-use	1,484	240	1.00 (Reference)	1.00 (Reference)
Any use	778	167	1.12 (0.71–1.76)	1.00 (0.68–1.49)
Aspirin				
Non-use	2,151	369	1.00 (Reference)	1.00 (Reference)
Any use	111	38	1.89 (1.10–3.24)	1.60 (0.93–2.75)
Ibuprofen				
Non-use	1,938	314	1.00 (Reference)	1.00 (Reference)
Any use	324	93	1.65 (1.21–2.26)	1.45 (1.01–2.06)
Naproxen				
Non-use	2,248	402	1.00 (Reference)	1.00 (Reference)
Any use	14	5	1.64 (0.41–6.50)	1.50 (0.42–5.40)

HR=hazard ratio

^a Models were adjusted for age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.5 Continued. Pain medication use before 12 gestational weeks and spontaneous abortion, stratified by cohort, 2007–2017

Medication	No. of Pregs	No. of SAB	Unadjusted	Adjusted
			HR (95% CI)	HR (95% CI) ^a
PRESTO				
Any pain medication				
Non-use	1,188	177	1.00 (Reference)	1.00 (Reference)
Any use	1,192	216	1.24 (1.01–1.52)	1.18 (0.95–1.48)
Acetaminophen				
Non-use	1,536	252	1.00 (Reference)	1.00 (Reference)
Any use	844	141	0.96 (0.77–1.21)	0.95 (0.75–1.20)
Aspirin				
Non-use	2,247	370	1.00 (Reference)	1.00 (Reference)
Any use	133	23	0.79 (0.47–1.34)	0.80 (0.47–1.36)
Ibuprofen				
Non-use	1,855	289	1.00 (Reference)	1.00 (Reference)
Any use	525	104	1.34 (1.03–1.74)	1.25 (0.95–1.64)
Naproxen				
Non-use	2,288	372	1.00 (Reference)	1.00 (Reference)
Any use	92	21	1.17 (0.57–2.41)	1.11 (0.49–2.48)

HR=hazard ratio

^a Models were adjusted for age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

Table 4.6 Pain medication use before 12 gestational weeks and spontaneous abortion restricted to single medication users or participants with early exposure assessment

Medication	No. of Pregs	No. of SAB	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
Single medication use versus non-use				
Non-use	5,052	772	1.00 (Reference)	1.00 (Reference)
Any use	2,814	516	1.25 (1.04–1.50)	1.16 (0.96–1.41)
Acetaminophen	2,211	383	1.15 (0.92–1.44)	1.10 (0.87–1.38)
Aspirin	68	12	1.20 (0.68–2.10)	1.08 (0.61–1.89)
Ibuprofen	572	128	1.68 (1.37–2.06)	1.44 (1.17–1.77)
Naproxen	31	5	1.17 (0.42–3.28)	0.99 (0.34–2.85)
Single medication use versus acetaminophen				
Acetaminophen	2,211	383	1.00 (Reference)	1.00 (Reference)
Aspirin	68	12	1.04 (0.59–1.84)	0.97 (0.54–1.74)
Ibuprofen	572	128	1.48 (1.15–1.91)	1.37 (1.06–1.78)
Naproxen	31	5	1.07 (0.36–3.12)	0.98 (0.33–2.91)
<8 gestational weeks at exposure assessment				
Any pain medication				
Non-use	2,698	425	1.00 (Reference)	1.00 (Reference)
Any use	2,239	486	1.42 (1.08–1.86)	1.34 (1.04–1.73)
Acetaminophen				
Non-use	3,116	537	1.00 (Reference)	1.00 (Reference)
Any use	1,821	374	1.00 (0.70–1.43)	1.03 (0.75–1.42)
Aspirin				
Non-use	4,622	838	1.00 (Reference)	1.00 (Reference)
Any use	315	73	1.01 (0.66–1.55)	1.03 (0.69–1.55)
Ibuprofen				
Non-use	4,003	676	1.00 (Reference)	1.00 (Reference)
Any use	934	235	1.56 (1.31–1.85)	1.42 (1.19–1.69)
Naproxen				
Non-use	4,832	884	1.00 (Reference)	1.00 (Reference)
Any use	105	27	1.30 (0.61–2.75)	1.10 (0.53–1.29)

HR=hazard ratio

a Models were adjusted cohort, age, non-Hispanic white, income, education, BMI, use of cigarettes, alcohol, or antibiotics during pregnancy, diagnosis of migraine headaches, diabetes, uterine leiomyoma, or thyroid disease. Medication specific results were also mutually adjusted for the other types of pain medications.

5 CONCLUSION

This dissertation examined three potential risk factors for adverse reproductive outcomes among North American and Danish pregnancy planners.

In the first study, we examined pregravid contraceptive use in relation to TTP using data pooled from three prospective cohorts of pregnancy planners, SG, SF, and PRESTO. We found that use of OCs, LARC methods, and the contraceptive ring were associated with temporary delays in return of fertility. Our findings indicate little effect of long-term use of these methods on fertility. These results were consistent with previous research examining OCs,^{1,2} IUDs,^{2,3} and implants.⁴ This was the first study to examine fecundability after use of less common contraceptive methods, however, there were still a small number of users of implants, injectables, and patches, limiting precision of these results.

In study 2, we examined the association between pain reliever use and fecundability among 1,065 male pregnancy planners in PRESTO. Our study showed no strong deleterious effects of male preconception low-dose use of common pain medications on fecundability. Our results were not consistent with the one previous study examining acetaminophen exposure and fecundability; the authors observed reduced fecundability among men with the highest urinary concentrations of acetaminophen compared with the lowest.⁵ These conflicting results could result from differences in exposure assessment or control for confounding by indication (discussed in detail in Chapter 3). While pain medication use was common, limitations included the small number of users of

naproxen and aspirin, which reduced precision, and the low cumulative monthly dose, which limited our ability to examine dose-response relations. To our knowledge, this is the first study to examine fecundability after male use of ibuprofen, naproxen, and aspirin.

In study 3, we examined pain medication use during early pregnancy and risk of SAB. Among 9,196 women who conceived without fertility treatment in Denmark, the United States, and Canada, we observed 1,597 SABs (17.4%). Low cumulative dose of ibuprofen, naproxen, or opioids was associated with slightly increased risk of SAB, though numbers of naproxen and opioid users were small. Overall, our study showed no substantial deleterious effects of acetaminophen or aspirin use on risk of SAB. The lack of association between acetaminophen^{6,7} or aspirin^{33,34} use and SAB, and the association between NSAID^{6,8,9} use and SAB is consistent with prior literature. The use of a pre-conception cohort allowed for excellent ascertainment of SAB in comparison to previous studies using administrative databases¹⁰ or post-conception cohorts.^{6,11} The main limitation of this study was the large number of participants missing exposure assessment during pregnancy.

In summary, among a non-clinical population of predominately non-Hispanic white pregnancy planners, we found that selected pharmacologic agents commonly used by reproductive-aged women may increase risk of adverse reproductive outcomes.

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