Title

Most Frequently Reported Prescription Medications and Supplements in Couples Planning Pregnancy: The LIFE Study

Journal

Reproductive Sciences, 25(1)

ISSN

1933-7191

Authors

Palmsten, Kristin
Flores, Katrina F
Chambers, Christina D
et al.

Publication Date

2018

DOI

10.1177/1933719117702249

Peer reviewed

Reproductive Sciences
2018, Vol. 25(1) 94-101

DOI: 10.1177/1933719117702249
journals.sagepub.com/home/rsx
SAGE

Most Frequently Reported Prescription Medications and Supplements in Couples Planning Pregnancy: The LIFE Study

Kristin Palmsten, ScD[1], Katrina F. Flores, MPH[2], Christina D. Chambers, PhD, MPH[1,2], Lauren A. Weiss, PhD[3], Rajeshwari Sundaram, PhD, MS[4], and Germaine M. Buck Louis, PhD, MS[4]

Abstract

Objective: To identify frequently reported prescription medications and supplements among couples planning pregnancy because there is a lack of descriptive information on these agents in women and men who are trying to conceive. **Methods:** Five hundred one couples enrolled in the Longitudinal Study of Infertility and the Environment, which took place between 2005 and 2009. Participants reported prescription medications as well as prescription and over-the-counter supplements used through interviews at study enrollment and through daily dairies during the 12-month follow-up. We identified prescription medications and supplements prospectively reported by $\geq$1% of women and men at baseline and from daily journal information grouped into 3-month preconception follow-up intervals while couples tried for pregnancy. **Results:** The 5 most reported prescription medications among women were levothyroxine (5.8%), cetirizine (2.6%), fluticasone (2.4%), escitalopram (1.8%), and fluoxetine (1.8%) and for men were lisinopril (2.0%), mometasone (2.0%), fexofenadine (1.8%), atorvastatin (1.6%), and montelukast (1.6%). The most reported supplements were multivitamins (63.3%, 43.5%) and fish oil (13.2%, 9.4%) for women and men, respectively, and prenatal vitamins (22.0%) for women. For women during the first 3 months of follow-up, prenatal vitamins (6.0%) and antibiotics (1.2%-2.6%) were among the most frequently started medications. During the next 3 months, clomiphene (4.5%) was the most frequently initiated medication. **Conclusions:** Couples trying for pregnancy reported a variety of prescription medications and supplements, and they differed by gender. Preconception guidance should address medication and supplement use to avoid potential exposures associated with adverse reproductive and perinatal outcomes.

Keywords

dietary supplements, fecundity, fertility, medication, preconception care

Introduction

Certain medications and supplements may affect female fecundity, male fecundity, or adverse pregnancy outcomes.[1-6] Although medication and supplement use is common in the United States among women of childbearing ages and adult men,[7,8] little is known about which medications and supplements are used by people trying to conceive.

Preconception counseling provides an opportunity to promote healthy behaviors and optimize medication use with the goal of preventing adverse reproductive and perinatal outcomes.[9,10] The Food and Drug Administration's 2015 Pregnancy and Lactation Labeling Rule,[11] which requires drug labels to include a new subsection on infertility related to the drug, and the lack of guidance regarding the impact of specific medications/supplements on fertility in the Center for Disease Control and Prevention's preconception guidelines,[12] underscores the public's need for information on the impact of medications and supplements on fertility. Knowing which medications and supplements are frequently reported by couples trying to conceive is important for guiding research on the impact of these exposures on fecundity. Furthermore, it is important to characterize the agents being used during sensitive windows as a step toward developing research on adverse perinatal outcomes to inform preconception guidance.

[1] Department of Pediatrics, University of California, San Diego, La Jolla, CA, USA
[2] Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, USA
[3] Department of Medicine, University of California, San Diego, La Jolla, CA, USA
[4] Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD, USA

Corresponding Author:
Kristin Palmsten, Department of Pediatrics, University of California, San Diego, 9500 Gilman Drive #0828, La Jolla, CA 92093, USA.
Email: kpalmsten@ucsd.edu

To our knowledge, there are no previous studies that prospectively describe medication and supplement utilization exclusively in men planning a pregnancy or in women planning a pregnancy. Descriptive information on medication and supplement use is available for nonpregnant women of reproductive ages,[13-16] although prevalence estimates cannot necessarily be generalized to the minority of women in this group who are planning a pregnancy. Furthermore, information on medication and supplement utilization in the months before pregnancy is available from women who went on to have pregnancies but does not address usage in women who did not conceive.[13,17-22]

Given the absence of data on medications and supplements used by couples planning pregnancy, the objective of this prospective study was to identify the most frequently reported prescription medications and supplements by a cohort of couples planning pregnancy.

Methods

Design and Study Population

The data are from the Longitudinal Study of Infertility and the Environment (LIFE), which has been described in detail elsewhere.[23] This prospective cohort study was conducted between 2005 and 2009 and enrolled couples discontinuing contraception to become pregnant. Couples were sampled from 16 counties in Michigan or Texas. The eligibility criteria were couples in a committed relationship, women aged 18 to 40 years and men aged at least 18 years, able to communicate in English or Spanish, menstrual cycles between 21 and 42 days, no hormonal contraceptive injections in the past year, no physician-diagnosed infertility or sterility, planning a pregnancy, and off contraception less than 2 months. The 501 couples who enrolled in the study were followed up until a recognized pregnancy occurred, up to 12 months of attempting pregnancy, or withdrawal from the study (n = 100). Human subject's approval was granted and all couples provided informed consent. Secondary use of the data for the current study was approved by the institutional review board of University of California, San Diego.

Data Collection

Each partner participated, separately, in an in-person interview at enrollment to provide information on demographics, health, and reproductive history. Also, information was obtained on baseline prescription medications and supplements. Specifically, participants were asked, "Are you currently taking any prescription medications, including prescription vitamins?" Then they were asked to list the names of these prescriptions. During the baseline interview, participants were asked to provide bottles for all medications they were taking to help verify usage whenever possible. Additionally, participants were asked, "In the past 3 months, did you take any of the following supplements more than once a week?" Participants then responded yes or no to 9 supplements, including multivitamins, and were asked to specify the names of any other supplement use. Information on supplements was combined with information on prescription vitamins.

To establish time to pregnancy, women used the Clearblue home fertility monitor (SPD Swiss Precision Diagnostics GmbH, Switzerland), for timing intercourse with ovulation, and the Clearblue digital home pregnancy test, which can detect 25 mIU/mL human chorionic gonadotropin (hCG).[24] Because certain tetracycline antibiotics can give false fertility monitor results, couples were asked to log the type and date of any prescription medication use while trying for pregnancy in standardized daily journals either online or in hard copy. Specifically, there was a standard open-ended prompt in the daily journal asking if any prescription medications were started, and if medications were started, participants were instructed to list the medications. This daily journal information was used to assess medications initiated during the preconception follow-up.

Analysis

We reported frequencies and means of cohort demographics, lifestyle factors, and comorbidities, by partner, and time to pregnancy. We identified prescription medications and supplements reported by at least 1% of women and men, separately, at baseline. We also identified prescription medications initiated by at least 1% of women and men, separately, during the 3-month preconception follow-up intervals using the information from daily journals. We presented the percentage of women and men who reported each of these medications and supplements. In the follow-up analysis, couples who had a recognized pregnancy or withdrew from the study during a 3-month follow-up interval were excluded from the subsequent interval. Participants could initiate the same medication in different follow-up intervals. We also presented the number of women and men who reported using any medications and supplements reported by at least 1% of women and men, respectively.

Results

Cohort Characteristics

The mean age was 30 years for women (standard deviation 4.1 years) and 32 years (standard deviation 4.9 years) for men (Table 1). The majority of participants were non-Hispanic white (81.2% for women and 82.2% for men), had a college education or higher (75.6% for women and 62.1% for men), and were overweight or obese (53.1% for women and 79.6% for men). In the 12 months before baseline, 16.4% of women and 23.8% of men smoked, and 5.6% of women and 23.1% of men reported having 4 to 5 alcoholic drinks or more on a typical occasion. At baseline, 4.0% of women and 10.4% of men reported high blood pressure and 8.2% of women and 15.6% of men reported high cholesterol. Among women, 7.8% reported having hypothyroidism, 8.0% reported having

Table 1. Characteristics for Women and Men: LIFE Study, 2005 to 2009.[a]

Characteristics	Women	Men
Age, mean (±SD), years	30.0 (4.1)	31.8 (4.9)
Race/ethnicity, n (%)		
Non-Hispanic white	407 (81.2)	412 (82.2)
Hispanic	50 (10.0)	48 (9.6)
Non-Hispanic blacks	23 (4.6)	25 (5.0)
Other[b]	17 (3.4)	14 (2.8)
Missing	4 (0.8)	2 (0.4)
Education, n (%)		
Less than college	121 (24.2)	187 (37.3)
College or greater	379 (75.6)	311 (62.1)
Missing	1 (0.2)	3 (0.6)
Health insurance, n (%)		
No	40 (8.0)	43 (8.6)
Yes	461 (92.0)	458 (91.4)
BMI, n (%)		
Underweight (≤18.5)	12 (2.4)	17 (3.4)
Normal weight (18.5-24.9)	218 (43.5)	78 (15.6)
Overweight (25.0-29.9)	136 (27.1)	203 (40.5)
Obese (≥30.0)	130 (25.9)	196 (39.1)
Missing	5 (1.0)	7 (1.4)
Smoking in the past 12 months, n (%)		
No	419 (83.6)	382 (76.2)
Yes	82 (16.4)	119 (23.8)
Number of alcoholic beverages on a typical occasion in the past 12 months, n (%)		
None	127 (25.3)	73 (14.6)
1 drink	108 (21.6)	63 (12.6)
2 to 3 drinks	237 (47.3)	249 (49.7)
4 to 5 drinks or more	28 (5.6)	116 (23.2)
Missing	1 (0.2)	–
Participation in a regular vigorous exercise program in the past 12 months, n (%)		
No	301 (60.1)	290 (57.9)
Yes	200 (39.9)	211 (42.1)
High blood pressure, n (%)		
No	481 (96.0)	448 (89.4)
Yes	20 (4.0)	52 (10.4)
Missing	0 (0.0)	1 (0.2)
High cholesterol, n (%)		
No	460 (91.8)	422 (84.2)
Yes	41 (8.2)	78 (15.6)
Missing	0 (0.0)	1 (0.2)
Diabetes, n (%)		
No	494 (98.6)	486 (97.0)
Yes	6 (1.2)	14 (2.8)
Missing	1 (0.2)	1 (0.2)
Hypothyroid disease, n (%)		
No	462 (92.2)	497 (99.2)
Yes	39 (7.8)	4 (0.8)
Mood disorder, n (%)		
No	460 (91.8)	487 (97.2)
Yes	40 (8.0)	12 (2.4)
Missing	1 (0.2)	2 (0.4)
Anxiety disorder, n (%)		
No	463 (92.4)	480 (95.8)
Yes	38 (7.6)	21 (4.2)
Gravidity, n (%)		
0	210 (41.9)	215 (42.9)
1 to 2	221 (44.1)	226 (45.1)
≥3	68 (13.6)	58 (11.6)
Missing	2 (0.4)	2 (0.4)
Couples' time to pregnancy,[c] n (%)		
No recognized pregnancy within the study period or withdrew	154 (30.7)	–
0 to <3 cycles	213 (42.5)	–
≥3 to <6 cycles	89 (17.8)	–
≥6 to <9 cycles	30 (6.0)	–
≥9 to <12 cycles	15 (3.0)	–

Abbreviations: BMI, body mass index; LIFE, Longitudinal Study of Infertility and the Environment; SD, standard deviation.
[a]N = 501.
[b]Includes Non-Hispanic Asian, Non-Hispanic American Indian, and Non-Hispanic other.
[c]Menstrual cycles until pregnancy.

a mood disorder, and 7.6% reported having anxiety; 2.8% had more than 1 of these 3 underlying comorbidities. The majority of couples had an hCG-recognized pregnancy within the study period (69.3%).

Baseline Prescription Medications and Supplements

At the time of the baseline interview, 48.1% of women and 32.3% of men reported using any prescription medication or prescription vitamin. For women, the 5 most reported prescription medications were (in descending order) levothyroxine (5.8%) indicated for hypothyroidism, cetirizine (2.6%; an antihistamine), fluticasone (2.4%; an inhaled or intranasal corticosteroid), escitalopram (1.8%) and fluoxetine (1.8%), both selective serotonin reuptake inhibitor antidepressants, and metformin (1.8%), an oral antidiabetic agent (Table 2). The top 5 prescription medications reported by men were (in descending order): lisinopril (2.0%; an angiotensin-converting enzyme inhibitor antihypertensive), mometasone (2.0%; a corticosteroid), fexofenadine (1.8%; an antihistamine), atorvastatin (1.6%; a statin cholesterol-lowering medication), and montelukast (1.6%; a leukotriene receptor antagonist asthma medication). A total of 116 women (23.2%) reported using at least 1 of the 18 medications reported by at least 1% of women at baseline and 31 (6.2%) reported using more than 1 at baseline. There were 88 men (17.6%) who reported using at least 1 of the 20 medications reported by at least 1% of men at baseline and 35 (7.0%) reported using more than 1 at baseline.

Multivitamins (63.3% for women and 43.5% for men) were the most frequently reported supplement at baseline (Table 3). Furthermore, prenatal vitamins with or without docosahexaenoic acid were reported by 22.0%. At baseline, 376 (75.0%) women reported using prenatal vitamins, multivitamins, or folic acid supplements. Of 6 supplements from the structured

Table 2. Most Frequently Reported Medications at Baseline for Women and Men: LIFE Study, 2005 to 2009.[a]

Medication Name	n	%
Women		
Levothyroxine	29	5.8
Cetirizine	13	2.6
Fluticasone propionate	12	2.4
Escitalopram	9	1.8
Fluoxetine	9	1.8
Metformin	9	1.8
Albuterol	8	1.6
Fluticasone propionate/salmeterol	8	1.6
Montelukast	8	1.6
Fexofenadine	7	1.4
Sertraline	7	1.4
Bupropion	6	1.2
Phentermine	6	1.2
Amoxicillin	5	1.0
Budesonide	5	1.0
Drospirenone/ethinyl estradiol	5	1.0
Methyldopa	5	1.0
Thyroid	5	1.0
Men		
Lisinopril	10	2.0
Mometasone	10	2.0
Fexofenadine	9	1.8
Atorvastatin	8	1.6
Montelukast sodium	8	1.6
Albuterol	7	1.4
Fenofibrate	7	1.4
Fluticasone propionate	7	1.4
Fluticasone propionate/salmeterol	7	1.4
Hydrocodone/acetaminophen	7	1.4
Hydrochlorothiazide	6	1.2
Methylphenidate	6	1.2
Omeprazole	6	1.2
Azelastine	5	1.0
Cetirizine	5	1.0
Desloratadine	5	1.0
Metformin	5	1.0
Metoprolol	5	1.0
Sertraline	5	1.0
Simvastatin	5	1.0

Abbreviation: LIFE, Longitudinal Study of Infertility and the Environment.
[a]Medications reported by ≥1% of the cohort.

Table 3. Most Frequently Reported Vitamins and Supplements Used More Than Once a Week in the 3 Months Before Baseline for Women and Men: LIFE Study, 2005 to 2009.[a,b]

	Women		Men	
Vitamin or Supplement Name	n	%	n	%
Multivitamin[c,d,e]	317	63.3	218	43.5
Prenatal vitamin with or without DHA	110	22.0	–	–
Prenatal vitamin with DHA	14	2.8	–	–
Fish oil[c,f]	66	13.2	47	9.4
Protein shake[c]	37	7.4	45	9.0
Folic acid[d]	18	3.6		
Echinacea[c]	17	3.4	15	3.0
Calcium	16	3.2		
Ginkgo biloba[c,g]	5	1.0	15	3.0
Vitamin C	13	2.6	14	2.8
Creatine[c,g]	–	–	14	2.8
Energy drink	–	–	12	2.4
Glucosamine with or without chondroitin	–	–	11	2.2
Glucosamine with chondroitin	–	–	5	1.0
St John's wort[c]	6	1.2	8	1.6
Iron[d]	7	1.4	–	–
Vitamin B_{12}	7	1.4	–	–
Vitamin not otherwise specified	7	1.4	–	–
Weight loss supplement	5	1.0	6	1.2
Vitamin B complex	–	–	6	1.2
Ginseng	–	–	5	1.0

Abbreviations: LIFE, Longitudinal Study of Infertility and the Environment; DHA, docosahexaenoic acid.
[a]Cell counts of <5.
[b]Agents reported by ≥1% of the cohort.
[c]Supplement from the structured interview.
[d]Includes individuals who reported multivitamins at baseline when asked the question: "Are you currently taking any prescription medications, including prescription vitamins?"
[e]Two women had missing information.
[f]Two men had missing information.
[g]One man had missing information.

interview (fish oil, protein shakes, creatine, echinacea, St John's wort, and ginkgo biloba), 21.2% of women and 20.0% of men reported using at least 1 and 4.2% of women and 5.8% of men reported using more than 1 of these supplements at baseline.

Preconception Follow-Up

For women during the first 3 months of preconception follow-up, prenatal vitamins (6.0%), hydrocodone with acetaminophen (2.6%), and several antibiotics (1.2%-2.6%) were among the most frequently started agents (Table 4). For women who did not have a recognized pregnancy and did not withdraw from the study in the first 3 months, medications that may be used in fertility treatment, including clomiphene (4.5%), medroxyprogesterone (3.0%), and progesterone (2.6%), as well as azithromycin (3.0%; an antibiotic), were among the most frequently initiated medications in the next 3 months. For the 86 women who were not censored in the first 9 months, 8.1% started clomiphene in the final 3 months of follow-up.

For men during the first 3 months of preconception follow-up, several antibiotics (1.0%-2.0%) and hydrocodone with acetaminophen (1.2%) were among the most frequently initiated medications. For the other follow-up intervals, less than 1% of men initiated any 1 medication.

Discussion

To our knowledge, this is the first study to report the types of prescription medications and supplements being used by couples trying for pregnancy. Given that approximately 20% of women and men used at least 1 of the frequently reported medications at baseline and more than 7% used 2 or more of

Table 4. Most Commonly Reported Initiated Medications From Daily Journals Before Pregnancy During the 1-Year Study Follow-Up for Women and Men: LIFE Study, 2005 to 2009.[a,b]

Medication Name	1 to <3 Months (n = 501), n (%)	3 to <6 Months[c] (n = 267), n (%)	6 to <9 Months[c] (n = 133), n (%)	9 to <12 Months[c] (n = 86), n (%)
Women				
Prenatal vitamin	30 (6.0)	–	–	–
Amoxicillin	13 (2.6)	–	–	–
Azithromycin	13 (2.6)	8 (3.0)	–	–
Hydrocodone/ acetaminophen	13 (2.6)	5 (1.9)	–	–
Amoxicillin/potassium clavulanate	9 (1.8)	–	–	–
Clomiphene citrate	9 (1.8)	12 (4.5)	10 (7.5)	7 (8.1)
Fluconazole	8 (1.6)	–	–	–
Ciprofloxacin	7 (1.4)	–	–	–
Diphenhydramine	7 (1.4)	–	–	–
Metformin	7 (1.4)	–	–	–
Naproxen	7 (1.4)	–	–	–
Nitrofurantoin	7 (1.4)	5 (1.9)	–	–
Fexofenadine	6 (1.2)	–	–	–
Fexofenadine/ pseudoephedrine	6 (1.2)	–	–	–
Ibuprofen	6 (1.2)	–	–	–
Levofloxacin	6 (1.2)	–	–	–
Progesterone	6 (1.2)	7 (2.6)	6 (4.5)	–
Trimethoprim/ sulfamethoxazole	6 (1.2)	–	–	–
Valacyclovir	6 (1.2)	–	–	–
Medroxyprogesterone	–	8 (3.0)	7 (5.3)	–
Men				
Azithromycin	10 (2.0)	–	–	–
Amoxicillin	7 (1.4)	–	–	–
Hydrocodone/ acetaminophen	6 (1.2)	–	–	–
Fexofenadine	5 (1.0)	–	–	–
Naproxen	5 (1.0)	–	–	–
Penicillin	5 (1.0)	–	–	–
Prednisone	5 (1.0)	–	–	–

Abbreviation: LIFE, Longitudinal Study of Infertility and the Environment.
[a]Cell counts of <5.
[b]Medications reported by ≥1% of the cohort.
[c]Excludes couples who were censored due to pregnancy or withdrawal from the study before the start of the interval.

these medications, preconception guidance should address usage to avoid potential exposures associated with adverse outcomes.[12,25] Research focused on the potential impact of commonly used medications on fecundity and adverse perinatal outcomes is needed to better inform preconception guidance.

Allergy and asthma medications were among the most frequently reported medications by both men and women. Hypothyroid medication and antidepressants were the most frequently reported medications by women, whereas antihypertensive and cholesterol-lowering medications were the most frequently reported medications by men. These medications are also among the most commonly used medications in the general population for similarly aged individuals.[7] Differences in the most reported medications by gender reflect different underlying diagnoses. Hypothyroidism and mood and anxiety disorders were reported in approximately 8% of women and were far less common in men, whereas high blood pressure and high cholesterol were more common in men. Multivitamins, fish oil, protein shakes, echinacea, and vitamin C were the most frequently reported supplements for both women and men, as well as prenatal vitamins and calcium supplements for women.

Given its continual usage while trying for pregnancy, the daily journals captured several medications that are typically used on a short-term basis including antibiotics and analgesics. Agents that may be used in fertility treatments were frequently initiated in women. Infertility is typically diagnosed after 12 months of unprotected intercourse without conception or after 6 months if the female partner is older than 35 years. In this cohort, 17 women reported that they initiated clomiphene before 6 months of study follow-up. Although we do not know the circumstances under which these mediations were used, clomiphene may be indicated for anovulatory infertility.

Levothyroxine, the treatment for hypothyroidism, and metformin, an oral antihyperglycemic agent, were top medications among women at baseline. These medications may be prescribed to increase fertility under certain circumstances[26,27]; however, we do not know participants' indications for these medications. Hypothyroidism impacts female fertility,[28] and levothyroxine may be prescribed in infertile women who have subclinical hypothyroidism.[26] Metformin increases the probability of clinical pregnancy in women with polycystic ovary syndrome.[27]

We assumed that couples taking fertility medications would have been excluded from the study, as they would have been diagnosed as experiencing infertility. We think it is an important observation to find some women using fertility agents without a formal infertility evaluation (at least as reported to the study), and we do not have information as to how such prescriptions were obtained.

There is relatively little information on the impact of the other frequently reported medications and supplements on fecundity. Most of this literature focuses on animal models and human semen parameters. Studies on the impact of antidepressant use on fecundity in women and men and on pregnancy loss are inconclusive because of potential confounding by depression, depression severity, or factors associated with depression. Selective serotonin reuptake inhibitor antidepressants are associated with sexual dysfunction in both women and men[29] and may decrease male fecundity by impacting semen parameters.[30] A prospective cohort study reported that antidepressant use among women during a particular menstrual cycle is associated with reduced probability of conceiving.[3] Antidepressants are also associated with miscarriage in some but not all studies,[5,31,32] and any substantial increased risk of birth defects overall or cardiac birth defects, in particular, associated with selective serotonin reuptake inhibitors has been ruled out by recent studies.[21,33] Many antihypertensives are associated with sexual dysfunction, and animal models have suggested a

link between several classes of antihypertensives and male infertility.[34] Animal models suggest that statins may have an adverse effect on female fertility[35] and atorvastatin is associated with changes in semen parameters.[36] However, no studies have assessed the association between statin use and human fecundity. Although some animal data suggested that statins may be teratogenic, recent observational data do not demonstrate an increased risk of birth defects following first-trimester statin use.[37] There are no studies of methylphenidate and fecundity in humans, although chronic administration of the medication to male mice reduces fecundity.[38]

Both women and men may use supplements with the intention of enhancing fertility, despite the lack of robust evidence to support a benefit.[39,40] Multivitamin use in women has been associated with increased fecundity,[41] and the LIFE study previously reported that both male and female preconception adherence to daily vitamin intake was associated with reduced pregnancy loss.[42] However, multivitamin and prenatal formulations contain different types and amounts of nutrients, which make it difficult to determine the individual effects of single nutrients.[39] The US Preventive Services Task Force recommends that all women take multivitamins containing folic acid at least 1 month prior to conception to prevent neural tube defects.[43] 3 out of 4 women reported using prenatal supplements, multivitamins (which were assumed to contain folic acid), or folic acid at baseline in this study of women planning pregnancy. This figure is higher than what has been reported from population-based surveys of women who had pregnancies,[44] in which up to 50% of pregnancies may be unplanned.[45,46]

This study has some limitations. First, this study relied solely on self-report of daily prescription medication and supplement use. Prompts for specific types of medications were not used,[47] and medical records were not used as an additional source for exposure information. Therefore, underreporting of medication and supplement use is a potential limitation. However, medication bottles were requested from participants at baseline to reduce reporting errors. Underreporting of use during follow-up was minimized by prospective reporting and the daily journals. Second, medication descriptive information is limited to prescriptions. Participants were not queried about over-the-counter medication information because these medications are not known to affect fertility monitor results. Third, we did not have reliable information to report duration of use or dose and we did not have information regarding the indication for medications and supplements used. Finally, the absolute number for several of the agents is small and a larger study size would have provided more robust information. Although linking these medications with outcomes is of great interest, the objective of this study is descriptive, that is, to identify the most commonly used medications/supplements in couples planning pregnancy. The next step is to evaluate the association between specific commonly used agents and time to pregnancy, although there is limited statistical power to do so in this study.

This study was conducted in response to the knowledge gap regarding medication use among couples trying to conceive. A major strength of this study is that medication use was collected prospectively and before a pregnancy outcome was known. Consequently, the possibility that couples reported medication use differently according to pregnancy status was avoided. The population-based sampling framework and that levels of drinking,[48] smoking,[48] overweight/obesity in females,[49] high blood pressure,[50] and mood disorders[51] in the LIFE study are similar to levels in individuals of childbearing ages in the United States suggest that the types of medications and supplements frequently reported in this study may generalize to couples planning pregnancy in the United States.

Information regarding the impact of frequently used agents on fertility is often limited to studies in animals or on semen parameters. Consequently, it is critical to evaluate the impact of commonly used medications and supplements on both female and male fecundity. Although the Food and Drug Administration's 2015 Pregnancy and Lactation Labeling Rule requires a new subsection on infertility related to the drug for medications approved in 2001 and later,[11] most frequently reported medications in this study were approved before 2001 and do not have this requirement. Additionally, supplements are not covered by the Pregnancy and Lactation Labeling Rule.

In this study, couples planning pregnancy reported medications in line with the most commonly used medications by similarly aged individuals in the general population. This finding highlights the need to understand the impact of these exposures on fertility and adverse perinatal outcomes and provide women, men, and clinicians with resources for preconception guidance.

Acknowledgments

The authors would like to thank Manroop Budwal for her assistance with literature searches for this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The LIFE study was funded by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (contracts N01-HD-3–3355, N01-HD-3–3356, and NOH-HD-3–3358). K. Palmsten is supported by a career development award from the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development, National Institutes of Health (K99HD082412).

References

1. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. *Ann Rheum Dis*. 2015;74(10):1836-1841.
2. Sands K, Jansen R, Zaslau S, Greenwald D. Review article: the safety of therapeutic drugs in male inflammatory bowel disease patients wishing to conceive. *Aliment Pharmacol Ther*. 2015; 41(9):821-834.

3. Casilla-Lennon MM, Meltzer-Brody S, Steiner AZ. The effect of antidepressants on fertility. *Am J Obstet Gynecol*. 2016;215(3): 314.e1-e5.
4. Obican S, Scialli AR. Teratogenic exposures. *Am J Med Genet C Semin Med Genet*. 2011;157C(3):150-169.
5. Almeida ND, Basso O, Abrahamowicz M, Gagnon R, Tamblyn R. Risk of miscarriage in women receiving antidepressants in early pregnancy, correcting for induced abortions. *Epidemiology*. 2016; 27(4):538-546.
6. Smarr MM, Grantz KL, Sundaram R, et al. Urinary paracetamol and time-to-pregnancy. *Hum Reprod*. 2016;31(9):2119-2127.
7. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. *JAMA*. 2015;314(17):1818-1831.
8. Bailey RL, Fulgoni VL III, Keast DR, Dwyer JT. Examination of vitamin intakes among US adults by dietary supplement use. *J Acad Nutr Diet*. 2012;112(5):657-663.e4.
9. Hood JR, Parker C, Atrash HK. Recommendations to improve preconception health and health care: strategies for implementation. *J Womens Health (Larchmt)*. 2007;16(4):454-457.
10. Cragan JD, Friedman JM, Holmes LB, Uhl K, Green NS, Riley L. Ensuring the safe and effective use of medications during pregnancy: planning and prevention through preconception care. *Matern Child Health J*. 2006;10(suppl 5):S129-S135.
11. US Food and Drug Administration. Pregnancy and lactation labeling final rule. 2014. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. Accessed March 25, 2017.
12. Center for Disease Control and Prevention. Preconception health and health care, clinical care for women, exposures. 2014. https://www.cdc.gov/preconception/careforwomen/exposures.html. Accessed March 25, 2017.
13. Tinker SC, Broussard CS, Frey MT, Gilboa SM. Prevalence of prescription medication use among non-pregnant women of childbearing age and pregnant women in the United States: NHANES, 1999–2006. *Matern Child Health J*. 2015;19(5):1097-1106.
14. Chuang CH, Hillemeier MM, Dyer AM, Weisman CS. The relationship between pregnancy intention and preconception health behaviors. *Prev Med*. 2011;53(1-2):85-88.
15. Ailes EC, Dawson AL, Lind JN, et al; Centers for Disease Control and Prevention (CDC). Opioid prescription claims among women of reproductive age—United States, 2008–2012. *MMWR Morb Mortal Wkly Rep*. 2015;64(2):37-41.
16. Dawson AL, Ailes EC, Gilboa SM, et al. Antidepressant prescription claims among reproductive-aged women with private employer-sponsored insurance—United States 2008–2013. *MMWR Morb Mortal Wkly Rep*. 2016;65(3):41-46.
17. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. *Am J Obstet Gynecol*. 2004;191(2):398-407.
18. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol*. 2005;193(3 pt 1):771-777.
19. Stephansson O, Granath F, Svensson T, Haglund B, Ekbom A, Kieler H. Drug use during pregnancy in Sweden—assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol*. 2011;3:43-50.
20. Palmsten K, Hernandez-Diaz S, Chambers CD, et al. The most commonly dispensed prescription medications among pregnant women enrolled in the U.S. Medicaid Program. *Obstet Gynecol*. 2015;126(3):465-473.
21. Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014; 370(25):2397-2407.
22. Maats FH, Crowther CA. Patterns of vitamin, mineral and herbal supplement use prior to and during pregnancy. *Aust N Z J Obstet Gynaecol*. 2002;42(5):494-496.
23. Buck Louis GM, Schisterman EF, Sweeney AM, et al. Designing prospective cohort studies for assessing reproductive and developmental toxicity during sensitive windows of human reproduction and development—the LIFE Study. *Paediatr Perinat Epidemiol*. 2011;25(5):413-424.
24. Johnson S, Cushion M, Bond S, Godbert S, Pike J. Comparison of analytical sensitivity and women's interpretation of home pregnancy tests. *Clin Chem Lab Med*. 2015;53(3): 391-402.
25. Center for Disease Control and Prevention. Preconception health and health care, clinical care for men, exposures. 2014. https://www.cdc.gov/preconception/careformen/exposures.html. Accessed March 25, 2017.
26. Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. *Fertil Steril*. 2015;104(3):545-553.
27. Sinai Talaulikar V, Tang T, Yasmin E. Role of metformin in women's health: review of its current place in clinical practice and emerging indications for future. *Obstet Gynecol Surv*. 2016; 71(5):307-317.
28. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. *Hum Reprod Update*. 2003;9(2): 149-161.
29. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol*. 2009;29(3):259-266.
30. Norr L, Bennedsen B, Fedder J, Larsen ER. Use of selective serotonin reuptake inhibitors reduces fertility in men. *Andrology*. 2016;4(3):389-394.
31. Andersen JT, Andersen NL, Horwitz H, Poulsen HE, Jimenez-Solem E. Exposure to selective serotonin reuptake inhibitors in early pregnancy and the risk of miscarriage. *Obstet Gynecol*. 2014;124(4):655-661.
32. Johansen RL, Mortensen LH, Andersen AM, Hansen AV, Strandberg-Larsen K. Maternal use of selective serotonin reuptake inhibitors and risk of miscarriage—assessing potential biases. *Paediatr Perinat Epidemiol*. 2015;29(1):72-81.
33. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ*. 2015;350:h1798.
34. Samplaski MK, Nangia AK. Adverse effects of common medications on male fertility. *Nat Rev Urol*. 2015;12(7):401-413.
35. Vitagliano A, Noventa M, Quaranta M, Gizzo S. Statins as targeted "magical pills" for the conservative treatment of endometriosis: may potential adverse effects on female fertility represent

the "dark side of the same coin"? A systematic review of literature. *Reprod Sci*. 2016;23(4):415-428.
36. Pons-Rejraji H, Brugnon F, Sion B, et al. Evaluation of atorvastatin efficacy and toxicity on spermatozoa, accessory glands and gonadal hormones of healthy men: a pilot prospective clinical trial. *Reprod Biol Endocrinol*. 2014;12:65.
37. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ*. 2015;350: h1035.
38. Fazelipour S, Jahromy MH, Tootian Z, Kiaei SB, Sheibani MT, Talaee N. The effect of chronic administration of methylphenidate on morphometric parameters of testes and fertility in male mice. *J Reprod Infertil*. 2012;13(4):232-236.
39. Buhling KJ, Grajecki D. The effect of micronutrient supplements on female fertility. *Curr Opin Obstet Gynecol*. 2013;25(3): 173-180.
40. Buhling KJ, Laakmann E. The effect of micronutrient supplements on male fertility. *Curr Opin Obstet Gynecol*. 2014;26(3): 199-209.
41. Grajecki D, Zyriax BC, Buhling KJ. The effect of micronutrient supplements on female fertility: a systematic review. *Arch Gynecol Obstet*. 2012;285(5):1463-1471.
42. Buck Louis GM, Sapra KJ, Schisterman EF, et al. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: the LIFE study. *Fertil Steril*. 2016;106(1): 180-188.
43. US Preventive Services Task ForceFolic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;150(9):626-631.
44. Weiss LA, Chambers CD. Associations between multivitamin supplement use and alcohol consumption before pregnancy: pregnancy risk assessment monitoring system, 2004 to 2008. *Alcohol Clin Exp Res*. 2013;37(9):1595-600.
45. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008–2011. *N Engl J Med*. 2016;374(9):843-852.
46. Mumford SL, Sapra KJ, King RB, Louis JF, Buck Louis GM. Pregnancy intentions—a complex construct and call for new measures. *Fertil Steril*. 2016;106(6):1453-1462.
47. Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *Am J Epidemiol*. 1986;123(4):670-676.
48. Schoenborn CA, Adams PF, Peregoy JA. Health behaviors of adults: United States, 2008–2010. *Vital Health Stat* 10. 2013; (257):1-184.
49. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA*. 2010; 303(3):235-241.
50. Yoon SS, Gu Q, Nwankwo T, Wright JD, Hong Y, Burt V. Trends in blood pressure among adults with hypertension: United States, 2003 to 2012. *Hypertension*. 2015;65(1):54-61.
51. Pratt LA, Brody DJ. Depression in the U.S. household population, 2009–2012. *NCHS Data Brief*. 2014;(172):1-8.