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Patterns of Prescription Medication Use during the First Trimester of Pregnancy in the United States, 1997–2018

Martha M. Werler[1,*], **Stephen M. Kerr**[2], **Elizabeth C. Ailes**[3], **Jennita Reefhuis**[3], **Suzanne M. Gilboa**[3], **Marilyn L. Browne**[4], **Katherine E. Kelley**[1], **Sonia Hernandez-Diaz**[5], **Rashida S. Smith-Webb**[1], **Michelle Huezo Garcia**[1], **Allen A. Mitchell**[2],

The National Birth Defects Prevention Study and Birth Defects Study To Evaluate Pregnancy exposureS

[1]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA

[2]Slone Epidemiology Center at Boston University School of Medicine, Boston, Massachusetts, USA

[3]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[4]Birth Defects Registry, New York State Department of Health; Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York, USA

[5]Department of Epidemiology, Harvard TH Chan School of Public Health, Harvard University, Cambridge, Massachusetts, USA.

Abstract

The objective of this analysis was to describe patterns of prescription medication use during pregnancy, including secular trends, with consideration of indication, and distributions of use within demographic subgroups. We conducted a descriptive secondary analysis using data from 9,755 women whose infants served as controls in two large United States case–control studies from 1997–2011 and 2014–2018. After excluding vitamin, herbal, mineral, vaccine, i.v. fluid, and topical products and over-the-counter medications, the proportion of women that reported taking at least one prescription medication in the first trimester increased over the study years, from 37% to 50% of women. The corresponding proportions increased with increasing maternal age and years of education, were highest for non-Hispanic White women (47%) and lowest for

[*]Correspondence: Martha M. Werler (werler@bu.edu).

AUTHOR CONTRIBUTIONS

M.M.W., S.M.K., E.C.A., J.R., S.M.G., M.L.B., K.E.K., S.H.-D., and A.A.M. wrote the manuscript and designed the research. M.M.W., S.M.K., K.E.K., R.S.S.-W., and M.H.G. performed the research. S.M.K., R.S.S.-W., and M.H.G. analyzed the data.

CONFLICT OF INTEREST

Dr. Mitchell is a member of the Pregnancy Advisory Board for Biogen's Tecfidera Pregnancy Registry. Dr. Werler serves as a diagnostic adjudicator for Novartis pregnancy registries. All other authors declared no competing interests for this work.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Hispanic women (24%). The most common indication for first trimester use of a medication was infection (12–15%). Increases were observed across the years for medications used for indications related to nausea/vomiting, depression/anxiety, infertility, thyroid disease, diabetes, and epilepsy. The largest relative increase in use among women was observed for medications to treat nausea/vomiting, which increased from 3.8% in the earliest years of the study (1997–2001) to 14.8% in 2014–2018, driven in large part by ondansetron use. Prescription medication use in the first trimester of pregnancy is common and increasing. Many medical conditions require treatments among pregnant women, often involving pharmacotherapy, which necessitates consideration of the risk and safety profiles for both mother and fetus.

Treating conditions with medications in pregnant populations deserves special attention. On the one hand, alleviating symptoms related to maternal conditions with pharmacologic treatments is generally a benefit to the mother. On the other hand, most medications cross the placenta, thereby extending exposure to the developing fetus and raising the possibility of harm.[1]

The potential teratogenicity of medications has been a concern for decades, when the use of thalidomide in pregnancy was associated with birth defects in offspring, most notably missing or shortened limbs.[2] Over this same time period, the availability of medications to treat chronic and acute conditions has markedly increased. Commensurate with the expansion of treatments, use of medications during pregnancy has increased.[3] Previous reports have shown this increase across pregnancy as a whole, and for the first trimester when the majority of organogenesis occurs.[3]

In this study, we describe patterns of prescription (Rx) medication use in pregnancy, using data collected from 2 United States, population-based case–control studies, with data collected from pregnancies with deliveries from 1997 to 2011 and 2014 to 2018. Secular trends of medication used for common indications and distributions of use within demographic subgroups were examined.

METHODS

Study population

The National Birth Defects Prevention Study (NBDPS) and its extension the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) are multistate, population-based case–control studies of birth defects. NBDPS included pregnancies with due dates from 1997 to 2011 and, following a 2-year hiatus, BD-STEPS included those with due dates from 2014 to 2018.[4,5] Cases comprised pregnancies affected with selected major structural birth defects ascertained from state birth defect surveillance programs in Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina, New Jersey, Texas, and Utah. Liveborn infants without structural birth defects (controls) were contemporaneously ascertained from the same catchment areas as cases. For this descriptive study, we restricted the study population to mothers of liveborn control subjects from the 7 study centers with data collected up to 2018 (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, and New York). Institutional review board approvals at each

study site and informed consents from each participant were obtained. Participation rates ranged from 64% in early NBDPS to 39% in BD-STEPS.

Data collection

Questions about demographic, reproductive, medical, dietary, and other factors were asked via standardized telephone interview. In NBDPS, interviews were conducted within 24 months of estimated delivery date (median = 7 months). In BD-STEPS, the vast majority (> 98%) of interviews were conducted within 18 months (median = 7 months). For medications, women were asked about use for specific conditions, use of specific medication groups (e.g., antibiotics), use of specific medication, and an overarching question about use of any other medications. If a woman reported taking a medication in response to an indication query, but could not remember its name, the interviewer read a list of commonly used medications for that indication in order to aid recall. Prompts for some indications and medications changed over the years, as shown in Table S1. In addition, the timeframe about which use was queried changed; it encompassed 3 months before through the end of pregnancy in NBDPS and 1 month before through the third month of pregnancy in BD-STEPS. For each medication that was reported as taken, the name, start and stop dates, duration, and frequency of use were recorded.

The Slone Epidemiology Center Drug Dictionary was used to code and classify reported medications and link products to active ingredient components and pharmacologic classes, with oversight by a pharmacist (author K.E.K.).[6] If a mother could not recall the name of a medication but reported its indication, it was coded as “not otherwise specified” within its corresponding indication (e.g., asthma) or class (e.g., anti-infective). Medications that are available in different formulations (e.g., “albuterol” and “albuterol sulfate”) were grouped together. Medications with multiple indications were counted within each corresponding indication group (e.g., promethazine was counted as an anti-nauseant and antihistamine). Medications with multiple active ingredients (e.g., doxylamine/pyridoxine) were counted as a single entity. Vitamin, herbal, mineral, vaccine, i.v. fluid, and topical products, and over-the-counter (OTC) medications were not considered in this analysis. Medications whose availability switched from Rx to OTC were considered as Rx when dates of use preceded the switch date plus 90 days (e.g., loratadine (Claritin) was approved for OTC November 27, 2002; use before February 25, 2003, was classified as Rx). Medications that could be dispensed as Rx or OTC (e.g., ibuprofen) were classified as OTC under the assumption that the vast majority are obtained OTC.

Data analysis

To determine the timing of medication exposures in relation to pregnancy, dates of use were compared to an estimated date of pregnancy onset (estimated due date minus 266 days). If dates of use were unknown for a given medication, it was excluded. Although NBDPS collected data on medication use at any time in pregnancy, the BD-STEPS was limited to the first trimester only. Thus, for this descriptive analysis, exposures were tabulated only for the first trimester (defined as 30 days before through 90 days after the onset of pregnancy). The month before pregnancy was included to account for uncertainty regarding the date of pregnancy onset. Medications were categorized according to indication.

For Rx medications in the first trimester, the proportion of women taking ≥ 1, the average number of Rx medications taken, and the most commonly used medications were compared across four birth year groups in NBDPS (1997–2001, 2002–2006, and 2007–2011) and the BDSTEPS birth years (2014–2018). The proportion taking ≥ 1 and the average number of Rx medications taken were compared across study sites (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, and New York), age groups (< 20, 20–24, 25–29, 30–34, and ≥ 35 years), highest level of education (less than high school, high school, or at least some post-secondary), and race/ethnicity groups. Based on maternal report and serving as proxies for socio-cultural contexts, categories for race/ethnicity were non-Hispanic Black (subsequently referred to as “Black”), Hispanic, non-Hispanic White (referred to as “White”), and Pacific Islander, Asian, Native American and other (referred to as “other”). For the proportion taking ≥ 1 medications, tests for trend were calculated across groups of years, maternal age, and maternal level of education with Cochran-Armitage tests; tests for differences across race/ethnicity groups and study sites were calculated with least squares means from logistic regression models. For the average number of medications taken, tests for trend and differences were calculated with Jonkheere-Terpstra and Kruskal–Wallis tests, respectively.

Comparisons of Rx medication use across birth year groups were also performed according to the indication most commonly ascribed to a given medication. For example, metformin was categorized as a treatment for type 2 diabetes mellitus, the indication for which it is US Food and Drug Administration (FDA)-approved, although it can also be used for polycystic ovary syndrome and other off-label indications. We calculated the proportions of women taking any medication and specific medications for infection, depression/anxiety, nausea/vomiting, fertility, thyroid disease, diabetes, and epilepsy. We did not examine medications for pain because most are OTC and not included in this analysis; we did, however, calculate proportions of women taking opioid-containing medications.

RESULTS

After exclusion of 310 women due to incomplete interviews, the study population comprised 9,755 women. Table 1 shows that a majority of the study population had at least a high school education, were non-Hispanic White, and were over 25 years of age.

For Rx medications in the first trimester, only slight increases were observed for the proportion of women taking ≥ 1 (37–38%) and the average number taken (0.6–0.7) across the NBDPS years (Figure 1a,b). After 2 years between studies (2012–2013), larger increases were observed for the 2014–2018 (BD-STEPS) group of years; 50% of women took ≥ 1 and the average number taken was 0.9. Both the corresponding proportions of women and averages increased with increasing maternal age and years of education. White women had the highest and Hispanic women had the lowest intakes. Use also varied across study centers, most notably for California where use was lowest; 30% of women took ≥ 1 and the average number taken was 0.4. For both the proportion taking ≥ 1 medication and the average number of medications taken, tests of trend over study year, maternal age, and maternal education were $P < 0.0001$. Differences in medication use for each race/ethnic group vs. all others and each study site vs. all others were apparent ($P < 0.0001$).

Figure 2a–g show trends of medication use according to indication. Specifically, proportions of any medication taken and specific medications taken in the first trimester are shown for the following indications (albeit the most commonly ascribed indication): infection, nausea/vomiting, depression/anxiety, fertility, thyroid disease, diabetes, and epilepsy. Of the indications presented, medications taken for infection were most common, ranging from 11% to 15% of women, in a U-shaped curve across calendar year groupings. This pattern appears to be driven by amoxicillin and “unknown antibiotic,” and to a lesser extent, trimethoprim/sulfamethoxazole.

Medications taken for nausea/vomiting showed a steady increase, from 4% of women in the first NBDPS birth year group (1997–2001) to 15% of women in BDSTEPS (2014–2018). Ondansetron accounts for the majority of this pattern, increasing from no use in 1997–2001 to almost 10% of women in 2014–2018. Doxylamine and pyridoxine are each available OTC, but the combination was approved by the FDA as a single prescription product in 2013, which likely accounts for the rise in use detected in 2014–2018. Promethazine use also increased to a lesser degree, which was evident earlier (1997–2001 to 2002–2006).

Medication use for depression or anxiety increased over the study period, with any medication rising from 3.7% in 1997–2001 to 6% of women in 2014–2018. With the exception of fluoxetine and paroxetine, use of medications indicated for depression/anxiety increased, including any selective serotonin re-uptake inhibitors, sertraline, bupropion, and both escitalopram and citalopram. Use of fertility medications also increased more than 1.5-fold; in 1997–2001, 4% of women reported first trimester fertility medication use compared to 7% in 2014–2018. Progesterone was the most commonly taken medication, followed by clomiphene, both of which increased across the time period. In contrast, use of leuprolide decreased from 1% in 1997–2011 to 0.6% in 2014–2018.

For thyroid disorder medications, levothyroxine comprised over 90% of reported use. A sharp rise in use was observed for levothyroxine (1.5–4.6% of women). For diabetes, metformin rose steeply (0.2–1.9%), whereas insulin vacillated between 0.4% and 0.8%, with some evidence of an increase in use. Use of medications that are indicated for epilepsy more than doubled (0.8% to almost 2%). Clonazepam, topiramate, and lamotrigine all increased over the study period, but the increase for clonazepam was most apparent, rising from 0.1% to 0.8%. Use of diazepam decreased slightly.

Use of any opioid-containing medication was reported by 2.2% of women across all years of NBDPS (1997–2011) and increased steadily to 3.5% in BDSTEPS 2014–2018 (Figure 2g). Codeine in combination with acetaminophen was the most commonly reported opioid and fluctuated in use over time, but was highest in 2014–2018 (1.7%). Hydrocodone with acetaminophen use was reported by ~ 0.5% of women in 1997–2001 and 2014–2018, which was slightly lower than the intervening years.

In addition to the most commonly taken medications within indication groups, the top specific medications taken in the first trimester within each birth year grouping are shown in Table 2. Of the 35 most commonly taken medications in 2014–2018, most were in the top 35 in earlier periods with some notable exceptions. Ondansetron was the most commonly

used Rx medication, which was taken by 9.5% of women in 2014–2018. The next most commonly taken Rx medications were levothyroxine and amoxicillin, each of which were taken by half or fewer women in any given birth year group. Metformin was in the top 35 list for the latter 2-year groupings, but ranked considerably lower in prior years.

DISCUSSION

Data from the US-based NBDPS and BD-STEPS case–control studies show Rx medication use in the first trimester of pregnancy has steadily increased over the past two decades. Increases were evident for medications taken for nausea/vomiting, depression/anxiety, infertility, thyroid disease, diabetes, and epilepsy. Although some specific medications decreased over the study period, they tended to be replaced by other medications, as evidenced by increases in the use of medications overall for all indications, except those for infection. For example, paroxetine use decreased after 2007 when warnings were added against use in pregnancy, whereas sertraline and bupropion use increased. Indeed, sertraline and bupropion accounted for 70% of the increase in first trimester antidepressant/antianxiety medication use from 1997–2001 to 2014–2018 years. The largest relative increase over time was observed for nausea or vomiting treatments, for which any first trimester use more than tripled over the same time period, driven largely by ondansetron (0–9.5%) and to some extent by the combination of doxylamine and pyridoxine (0% to almost 3%), which was approved by the FDA in 2013 for nausea and vomiting of pregnancy (NVP).[7]

The increases in medication use are consistent, roughly, with increases in diagnoses of depression/anxiety, infertility, subclinical thyroid disease, and diabetes in women of childbearing ages.[8–15] In contrast, urinary tract infections in pregnancy appear to be stable over NBDPS years and we could find no reports showing overall infections have changed in pregnancy.[16] Although slight increases in self-reported NVP were reported in the late 1990s and early 2000s, the proportion of women with NVP that report Rx treatment has sharply increased.[17,18] Prescription NVP treatments (e.g., promethazine) have been available across all years of the study, raising the question as to what is driving the increase in Rx treatment; patient and clinician preferences likely play a role. In consideration of the most commonly used Rx medications, it is not surprising that they include medications taken for common conditions in pregnancy (e.g., infection, nausea/vomiting, depression/anxiety, sinus congestion, and asthma). Pain is another common condition in pregnancy, and 2 opioids were among the 35 most frequently used medications in all study year groupings – codeine/acetaminophen and hydrocodone/acetaminophen. Although that list in Table 1 is populated by the 2014–2018 ranking, these 2 opioids were among the top 35 in all year groupings. We did not examine the range of medications taken for pain, although they are by far the most commonly taken medications in pregnancy because they are primarily OTC.[19]

In addition to the occurrence and diagnosis of treatable conditions, other factors influence use of medications. Access to healthcare provider for medication prescription, provider treatment patterns, insurance coverage, financial means, and patient desires all likely play a role. These factors vary by geographic region, race/ethnicity, age, and education and may explain the observed variations in medication use during pregnancy. Increasing rates of medication use among older, White, and more educated women, as has been documented in

other studies, exceed differences based on the prevalence of underlying conditions, raising questions of whether these differences may reflect health care inequities, particularly for more marginalized groups.[3,19]

Medication use in this study was based on maternal report generated from a detailed and structured interview. Relative to medical record and claims data sources, maternal interview data carry both strengths and limitations. The NBDPS and BD-STEPS interviews ask about timing and frequency of use of medications, regardless of how they were acquired. Medical records and claims data typically include only prescribed treatments and lack detail on whether the medication was actually used and, if so, how often or for how long. Maternal report is vulnerable to recall inaccuracies. Previous studies have shown the sensitivity of maternally reported medication use is lower for medications taken intermittently and with longer intervals between data collection and the time of use.[20,21] Specificity of medication reporting is generally higher than sensitivity. If NBDPS/BD-STEPS reported medication use has low sensitivity and high specificity, use would be higher than presented here. In addition, participation rates of eligible women declined over all study years, raising the possibility that medication use is higher in women who do participate than those who do not, inflating observed prevalence of use over time.

In NBDPS/BD-STEPS, not all reports of medication use were linked to the reason for taking them. In this analysis, we grouped medications according to most common indication (when reported) and not necessarily the reason for which any medication was taken. Many medications are strongly correlated with one indication (e.g., albuterol and asthma); whereas others might be taken for multiple indications (e.g., promethazine and either nausea/vomiting, insomnia, or allergy; metformin, and either diabetes or polycystic ovary syndrome). Our approach of examining multiple specific medications in selected relevant indications helps identify patterns of pharmacologic treatment for those indications.

Queries based on specifically named medications have been shown to enhance recall, particularly for medications that are taken episodically or shared.[22] Because questions in the interview about specific medications and indications were added over time, some portion of increasing use may be due to missing data before these changes were made to the interview. However, the use of some medications for which prompts were added, either as specific prompts or within added indications, increased before changes to the interview were implemented. For example, levothyroxine use steadily increased across all study periods, but the prompt for medications taken for thyroid disease was not added until 2010. Specific prompts for ondansetron and many other nausea/vomiting treatments were added to the interview in 2014 when overall use and ondansetron use specifically, increased dramatically, but increases were already evident from 2002–2006 to 2007–2011. Conversely, changes in prompts for anti-infection medications may explain the observed increase in use from the latter NBDPS years and for BD-STEPS. Specifically, both NBDPS and BD-STEPS interviews asked about treatments for several types of infections (kidney, bladder, urinary tract infection, pelvic inflammatory disease, and sexually transmitted disease), but the BD-STEPS interview added a prompt “did you take any antibiotics, and if so, what was the name of the medication?” to capture use for a broader range of infections. Another example of the interview likely influencing increased reporting is clonazepam, for which a

specific prompt was added in 2014. It is worth noting that we classified clonazepam as an anti-convulsant for this analysis, but it is also approved for panic attacks and is increasingly prescribed for the treatment of generalized anxiety, depression, and insomnia. Like opioid-containing medications, clonazepam and other benzodiazepines are addictive and subject to abuse, raising the possibility that increasing clonazepam use might partly be attributed to increasing substance use disorder across the study years.[23] The BD-STEPS interview included lamotrigine as a possible medication for depression or anxiety or for migraines. Of note, use of clonazepam, topiramate, and lamotrigine during pregnancy were observed to be increasing in US Medicaid subscribers from 2006 to 2013.[24] Opioid use overall was shown to be increasing during pregnancy in NBDPS and among women of childbearing ages; this trend is evident for any opioid-containing product and for the combination product hydrocodone with acetaminophen for the NBDPS years (1997–2011).[25,26] A recent report showed opioid use is declining in women of childbearing age, which we also observed for hydrocodone/acetaminophen in BD-STEPS.[26] On the other hand, we observed an increase in codeine/acetaminophen use in BD-STEPS.

Previous reports on both prescription and OTC medication use from the NBDPS described trends of use at any time during pregnancy and the first trimester.[3,19] The present study is restricted to first trimester only, because data on use later in pregnancy were not collected in BD-STEPS. Of note, trends of medication use any time in pregnancy in those studies were strongly correlated with use during the first trimester. Our observed pattern of more medication use in older and more educated women differs from reports from study populations outside the United States in which younger and less educated women were more common users.[27,28]

Similar to the present findings, other studies in the United States observed anti-infectives to be the most commonly prescribed medication during pregnancy.[3,29,30] Studies from other countries of trimester-specific medication use also reported anti-infectives to be the most commonly prescribed medication in the first trimester, including in Canada, Norway, Sweden, and Denmark.[31–36] In concordance with our findings, use of anti-infectives, NVP, anti-depression/anxiety, fertility, anti-diabetic and thyroid medications appear to be increasing outside of the United States.[24,33,37–41] However, demographic patterns of medication use among pregnant women in other countries differed from those presented here, owing to variations in prescribing patterns of specific products.[27]

In conclusion, we found that prescription medication use in the first trimester of pregnancy is common and increasing. Reasons may include contemporaneous increases in underlying indications, greater surveillance of thyroid levels, cultural trends of patient and clinician preferences, and the addition of specific prompts to the interview. Appropriate treatment of many medical conditions is essential among pregnant women, which often involves pharmacotherapy, thus the risk and safety profiles of medication treatments must consider both mother and fetus. Evidence of relative safety to the developing fetus for most medications is lacking and could be informed by further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA SHARING AND DATA ACCESSIBILITY

The study questionnaires and process for accessing the data used in this study are described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book may be made available upon request.

References

1. Feghali M, Venkataramanan R & Caritis S Pharmacokinetics of drugs in pregnancy. Semin. Perinatol 39, 512–519 (2015). [PubMed: 26452316]
2. Lenz W A short history of thalidomide embryopathy. Teratology 38, 203–215 (1988). [PubMed: 3067415]
3. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C & Hernández-Díaz S Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am. J. Obstet. Gynecol 205, 51.e1–51.e8 (2011).
4. Reefhuis J et al. The national birth defects prevention study: a review of the methods. Birth Defects Res. Part A – Clin. Mol. Teratol 103, 656–669 (2015).
5. Tinker SC et al. Next steps for birth defects research and prevention: the birth defects study to evaluate pregnancy exposureS (BD-STEPS). Birth Defects Res. A Clin. Mol. Teratol 103, 733–740 (2015). [PubMed: 25846741]
6. Kelley K, Kelley TP, Kaufman DW & Mitchell AA The Slone drug dictionary: a research driven pharmacoepidemiology tool. Pharmacoepidemiol. Drug Saf 12, 168–169 (2003).
7. Slaughter SR, Hearns-Stokes R, van der Vlugt T & Joffe HV FDA approval of doxylamine–pyridoxine therapy for use in pregnancy. N. Engl. J. Med 370, 1081–1083 (2014). [PubMed: 24645939]
8. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S & Goodwin RD Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. Psychol. Med 48, 1308–1315 (2018). [PubMed: 29021005]
9. Mallhi AK, Sullivan K & Zhang J Changes in the association between overweight and depression across three major ethnic groups, 2005–2018. J. Psychiatr. Res 151, 564–570 (2022). [PubMed: 35636033]
10. Haight SC, Byatt N, Moore Simas TA, Robbins CL & Ko JY Recorded diagnoses of depression during United States delivery hospitalizations, 2000–2015. Obstet. Gynecol 133, 1216–1223 (2019). [PubMed: 31135737]
11. Snow M, Vranich TM, Perin J & Trent M Estimates of infertility in the United States: 1995–2019. Fertil. Steril 118, 560–567 (2022). [PubMed: 35710598]
12. Hollowell JG et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and nutrition examination survey (NHANES III). J. Clin. Endocrinol. Metab 87, 489–499 (2002). [PubMed: 11836274]

13. Bardenheier BH, Imperatore G, Devlin HM, Kim SY, Cho P & Geiss LS Trends in pre-pregnancy diabetes among deliveries in 19 U.S. States, 2000–2010. Am. J. Prev. Med 48, 154–161 (2015). [PubMed: 25326417]
14. Deputy NP, Kim SY, Conrey EJ & Bullard KM Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth – United States, 2012–2016. MMWR Morb. Mortal. Wkly Rep 67, 1201–1207 (2018).
15. Huybrechts KF et al. National trends in antidepressant medication treatment among publicly-insured pregnant women. Gen. Hosp. Psychiatry 35, 265–271 (2013). [PubMed: 23374897]
16. Johnson CY, Rocheleau CM, Howley MM, Chiu SK, Arnold KE & Ailes EC Characteristics of women with urinary tract infection in pregnancy. J. Womens Health (Larchmt) 30, 1556–1564 (2021). [PubMed: 34491115]
17. Louik C, Hernandez-Diaz S, Werler MM & Mitchell AA Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr. Perinat. Epidemiol 20, 270–278 (2006). [PubMed: 16879499]
18. Schrager NL, Adrien N, Werler MM, Parker SE, Van Bennekom C & Mitchell AA Trends in first-trimester nausea and vomiting of pregnancy and use of select treatments: findings from the National Birth Defects Prevention Study. Paediatr. Perinat. Epidemiol 35, 57–64 (2021). [PubMed: 32623767]
19. Werler MM, Mitchell AA, Hernandez-Diaz S & Honein MA Use of over-the-counter medications during pregnancy. Am. J. Obstet. Gynecol 193, 771–777 (2005). [PubMed: 16150273]
20. Pisa FE, Casetta A, Clagnan E, Michelesio E, Vecchi Brumatti L & Barbone F Medication use during pregnancy, gestational age and date of delivery: agreement between maternal self-reports and health database information in a cohort. BMC Pregnancy Childbirth 15, 310 (2015). [PubMed: 26608022]
21. van Gelder MMHJ, van Rooij IALM, de Walle HEK, Roeleveld N & Bakker MK Maternal recall of prescription medication use during pregnancy using a paper-based questionnaire: a validation study in The Netherlands. Drug Saf 36, 43–54 (2013). [PubMed: 23315295]
22. Mitchell AA, Cottler LB & Shapiro S Effect of questionnaire design on recall of drug exposure in pregnancy. Am. J. Epidemiol 123, 670–676 (1986). [PubMed: 3953545]
23. Research C for DE and FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class FDA. Published October 2, 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class>. Accessed November 17, 2022
24. Cohen JM et al. Prevalence trends and individual patterns of antiepileptic drug use in pregnancy 2006–2016: a study in the five Nordic countries, United States, and Australia. Pharmacoepidemiol. Drug Saf 29, 913–922 (2020). [PubMed: 32492755]
25. Interrante JD et al. Risk comparison for prenatal use of analgesics and selected birth defects, National Birth Defects Prevention Study 1997–2011. Ann. Epidemiol 27, 645–653.e2 (2017). [PubMed: 28993061]
26. Summers AD et al. Opioid prescription claims among women aged 15–44 years—United States, 2013–2017. J. Opioid Manag 17, 125–133 (2021). [PubMed: 33890276]
27. Lupattelli A et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open 4, e004365 (2014).
28. Smolina K, Hanley GE, Mintzes B, Oberlander TF & Morgan S Trends and determinants of prescription drug use during pregnancy and postpartum in British Columbia, 2002–2011: a population-based cohort study. PLOS ONE 10, e0128312 (2015). [PubMed: 26011706]
29. Andrade SE et al. Prescription drug use in pregnancy. Am. J. Obstet. Gynecol 191, 398–407 (2004). [PubMed: 15343213]
30. Haas DM et al. Prescription and other medication use in pregnancy. Obstet. Gynecol 131, 789–798 (2018). [PubMed: 29630018]
31. Engeland A, Bjørge T, Klungsøyr K, Hjellvik V, Skurtveit S & Furu K Trends in prescription drug use during pregnancy and postpartum in Norway, 2005 to 2015. Pharmacoepidemiol. Drug Saf 27, 995–1004 (2018). [PubMed: 29920833]

32. 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 3, 43–50 (2011). [PubMed: 21386973]

33. Bjørn AMB, Nørgaard M, Hundborg HH, Nohr EA & Ehrenstein V Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark. Clin. Epidemiol 3, 149–156 (2011). [PubMed: 21607016]

34. Malm H, Martikainen J, Klaukka T & Neuvonen PJ Prescription drugs during pregnancy and lactation—a Finnish register-based study. Eur. J. Clin. Pharmacol 59, 127–133 (2003). [PubMed: 12700878]

35. Lacroix I et al. Prescription of drugs during pregnancy: a study using EFEMERIS, the new French database. Eur. J. Clin. Pharmacol 65, 839–846 (2009). [PubMed: 19365629]

36. Gagne JJ, Maio V, Berghella V, Louis DZ & Gonnella JS Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy. Eur. J. Clin. Pharmacol 64, 1125–1132 (2008). [PubMed: 18685836]

37. de Jonge L, Bos HJ, van Langen IM, de den Berg LTW, J.-v. & Bakker MK Antibiotics prescribed before, during and after pregnancy in The Netherlands: a drug utilization study. Pharmacoepidemiol. Drug Saf 23, 60–68 (2014). [PubMed: 23913654]

38. Cesta CE et al. Antidiabetic medication use during pregnancy: an international utilization study. BMJ Open Diabetes Res. Care 7, e000759 (2019).

39. Taylor PN et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat. Rev. Endocrinol 14, 301–316 (2018). [PubMed: 29569622]

40. Turunen S, Vääräsmäki M, Leinonen M, Gissler M, Männistö T & Suvanto E The increased trend of medical treatment for thyroid diseases during pregnancy: a 13-year National Study. Eur. Thyroid J 10, 230–236 (2021). [PubMed: 34178709]

41. Charlton RA et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG 122, 1010–1020 (2015). [PubMed: 25352424]

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

- Use of specific medications in pregnancy have been reported in relation to pregnancy outcomes, but reports on patterns of use in recent years is lacking.

WHAT QUESTION DID THIS STUDY ADDRESS?

- What medications are most commonly taken in pregnancy for infection, depression/anxiety, nausea/vomiting, fertility, thyroid disease, diabetes, and epilepsy, and how has use trended over time? What are the demographic patterns of use?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

- This study shows distinct trends of increasing medication use in pregnancy for the treatment of nausea/vomiting and depression/anxiety, with 15% and 5% use, respectively, in 2014–2018. It also shows overall medication use varies according to maternal age, years of education, race/ethnicity, and state of residence.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

- Clinicians must consider the risks and safety of both mother and fetus, when prescribing medications in pregnancy. The observed increases in some medications raise questions regarding the reasons for such increases, and emphasizes the need for careful discernment when treating medical conditions in pregnant women.

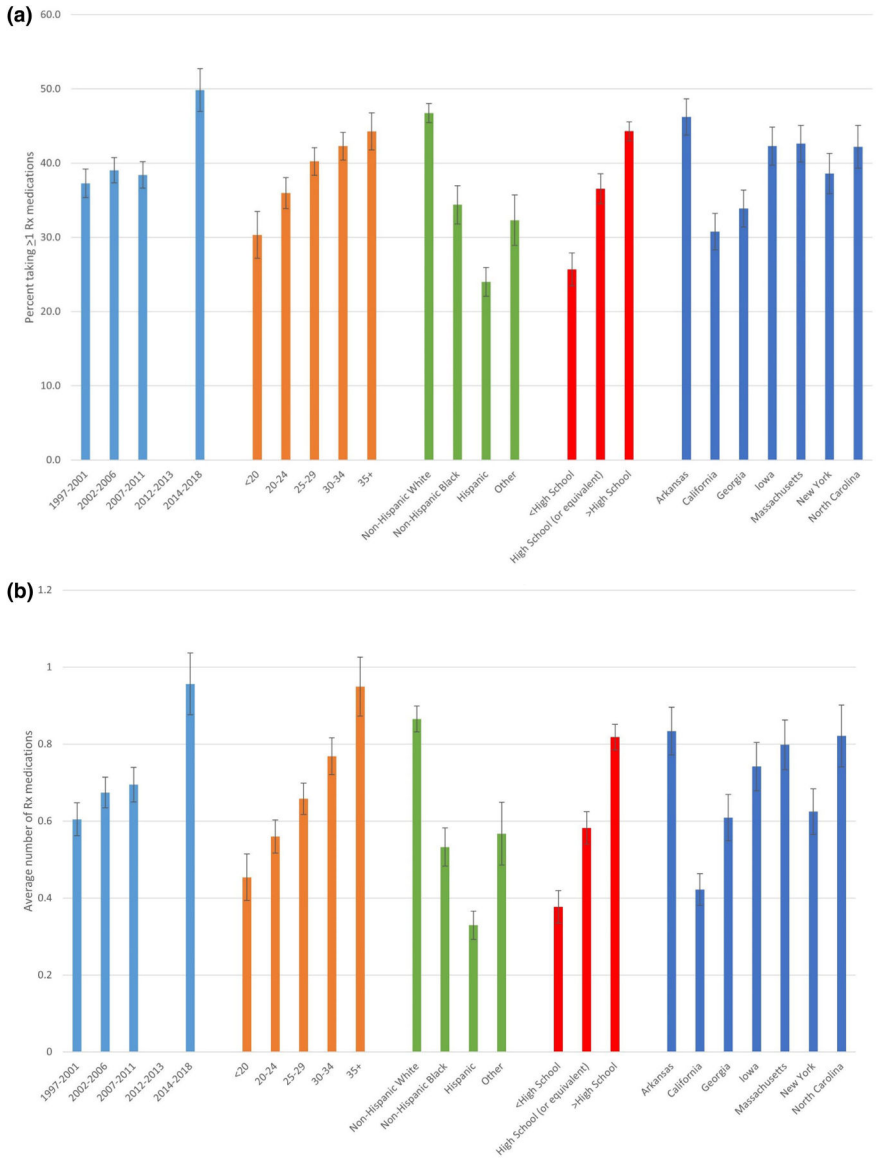

Figure 1.

Prescription medication use in first trimester*, National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy Exposures (2014–2018). (a) Percent taking >1 medication (error bars indicate 95% confidence intervals). (b) Average number of prescription medications taken (error bars indicate 95% confidence intervals). *First trimester, 30 days before to 90 days after pregnancy onset.

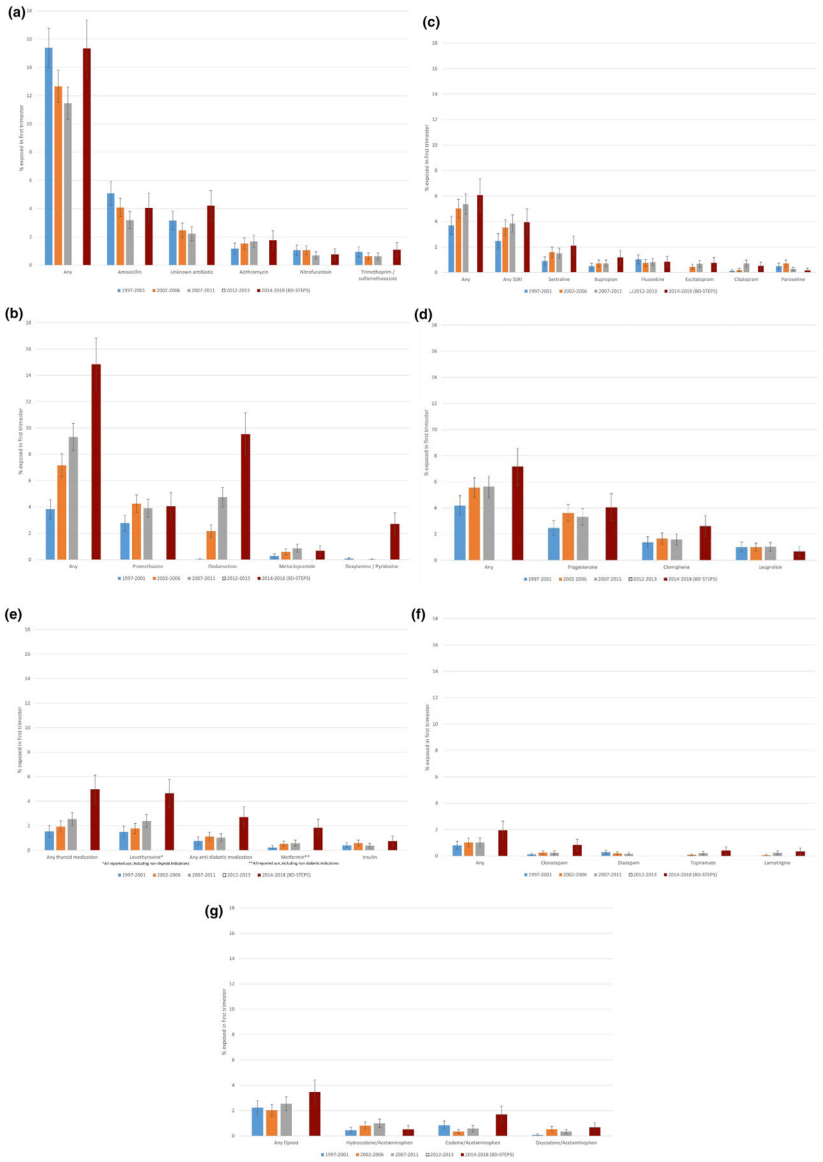

Figure 2.

Prescription medication use in first trimester* over time, National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy Exposures (2014–2018). (a) Anti-infective medication use. (b) Anti-nausea/vomiting medication use. (c) Antidepressant/anxiety medication use. (d) Fertility medication use. (e) Thyroid and anti-diabetic medication. * All reported use, including non-thyroid indications. ** All reported use, including non-diabetic medications. (f) Anti-convulsant medication use, including non-seizure indications. (g) Opioid medication use. *First trimester, 30 days before to 90 days after pregnancy onset. (Error bars represent 95% confidence intervals.)

Table 1

Demographic factors among 9,755 women from National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy exposureS (2014–2018) studies[a]

		Rx med in T1[b]	
Characteristic	**Total**	**Number**	**Percent**
Overall	9755	3874	39.7
Birth year (5-year intervals)			
1997–2001	2457	916	37.3
2002–2006	3200	1249	39.0
2007–2011	2912	1118	38.4
2012–2013			
2014–2018	1186	591	49.8
Maternal age when child was born			
< 20	811	246	30.3
20–24	2054	739	36.0
25–29	2663	1071	40.2
30–34	2673	1130	42.3
35+	1554	688	44.3
Maternal race/ethnicity (category)			
Non-Hispanic White	5889	2753	46.7
Non-Hispanic Black	1300	447	34.4
Hispanic	1838	441	24.0
Other	721	233	32.3
Maternal education when child was born			
Less than high school	1453	373	25.7
High school	2184	798	36.5
More than high school	6037	2674	44.3
Study center			
Arkansas	1621	749	46.2
California	1355	417	30.8
Georgia	1390	471	33.9
Iowa	1438	608	42.3
Massachusetts	1563	666	42.6
New York	1241	479	38.6
North Carolina	1147	484	42.2

Rx, prescription medication.

[a] Live births only.

[b] Rx med in T1, prescription medication use in the first trimester (30 days before to 90 days after pregnancy onset).

Table 2

Most common prescription medications taken in the first trimester,[a] by frequency in 2014–2018, National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy Exposures (2014–2018)

	2014–2018		2007–2011		2002–2006		1997–2001	
Medication	**No.**	**Percent**	**No.**	**Percent**	**No.**	**Percent**	**No.**	**Percent**
Ondansetron	113	9.5	138	4.7	69	2.2	1	0.0
Levothyroxine	55	4.6	70	2.4	57	1.8	37	1.5
Unknown antibiotic	50	4.2	65	2.2	79	2.5	78	3.2
Amoxicillin	48	4.0	93	3.2	131	4.1	125	5.1
Promethazine	48	4.0	114	3.9	136	4.3	68	2.8
Progesterone	48	4.0	97	3.3	116	3.6	61	2.5
Albuterol	34	2.9	92	3.2	92	2.9	69	2.8
Loratadine[b]	33	2.8	117	4.0	56	1.8	27	1.1
Doxylamine/pyridoxine	32	2.7	1	0.0	0	0.0	2	0.1
Clomiphene	31	2.6	47	1.6	53	1.7	34	1.4
Cetirizine[c]	28	2.4	61	2.1	47	1.5	10	0.4
Unknown oral contraception	26	2.2	45	1.5	56	1.8	26	1.1
Sertraline	25	2.1	44	1.5	51	1.6	22	0.9
Metformin	22	1.9	17	0.6	17	0.5	6	0.2
Azithromycin	21	1.8	49	1.7	49	1.5	29	1.2
Codeine/acetaminophen	20	1.7	17	0.6	11	0.3	21	0.9
Fluticasone[d]	17	1.4	19	0.7	21	0.7	16	0.7
Bupropion	14	1.2	21	0.7	23	0.7	12	0.5
Trimethoprim/sulfamethoxazole	13	1.1	18	0.6	20	0.6	23	0.9
Letrozole	12	1.0	7	0.2	2	0.1	0	0.0
Fluoxetine	10	0.8	24	0.8	24	0.8	25	1.0
Cephalexin	10	0.8	15	0.5	16	0.5	26	1.1
Clonazepam	10	0.8	7	0.2	8	0.3	3	0.1
Ethinyl estradiol/norgestimate	9	0.8	40	1.4	86	2.7	47	1.9

Medication	2014–2018		2007–2011		2002–2006		1997–2001	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Nitrofurantoin	9	0.8	20	0.7	34	1.1	26	1.1
Escitalopram	9	0.8	20	0.7	14	0.4	0	0.0
Leuprolide	8	0.7	30	1.0	32	1.0	25	1.0
Metoclopramide	8	0.7	25	0.9	19	0.6	7	0.3
Hydrocodone/acetaminophen	6	0.5	29	1.0	26	0.8	11	0.4
Citalopram	6	0.5	21	0.7	6	0.2	3	0.1
Doxycycline	3	0.3	22	0.8	7	0.2	4	0.2
Follitropin alfa	2	0.2	31	1.1	32	1.0	14	0.6
Gonadotropin chorionic	2	0.2	14	0.5	26	0.8	32	1.3
Fexofenadine[e]	2	0.2	29	1.0	26	0.8	15	0.6
Paroxetine	2	0.2	8	0.3	23	0.7	12	0.5

Became available over-the-counter during the following study years:

[a] First trimester, 30 days before to 90 days after pregnancy onset.

[b] Loratadine – 11/27/2002.

[c] Cetirizine – 11/16/2007.

[d] Fluticasone – 7/23/2014.

[e] Fexofenadine – 1/24/2011.