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Patterns of yeast infections and antifungal use in the first trimester of pregnancy: Findings from the Birth Defects Study to Evaluate Pregnancy exposureS, 2014-2019

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Abstract

Background: Yeast infections are common during pregnancy. Understanding their current prevalence and corresponding treatments during pregnancy is important. We used data from a US population-based retrospective study of recently pregnant people to describe patterns of first trimester maternal yeast infections and antifungal use.

Materials and Methods: Using a cohort of control participants from the Birth Defects Study to Evaluate Pregnancy exposureS, self-reports of first trimester yeast infections and antifungal use were collected via computer-assisted telephone interviews for births during 2014-2019. We described maternal characteristics and examined prevalence of yeast infections and antifungal use overall, and by study site and birth year. Tests for trend were used to evaluate changes over the study period.

Results: After exclusions, there were 1,524 control participants included in our sample. First trimester yeast infections (9.8%) and antifungal use (8.6%) were common. More participants reported prescription (52.7%) than over-the-counter (45.0%) antifungals; most users reported a topical antifungal (72.5%). Prevalence of yeast infections and antifungal use increased modestly, but non-significantly, over the study period, ranging from 7.8% to 10.9% for yeast infections and 7.2% to 9.8% for antifungal use. Prevalence of topical and over-the-counter antifungals

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significantly increased over the study period; use of oral and prescription antifungals modestly decreased.

Conclusions: In our cohort, first trimester yeast infections and antifungal use were relatively common and modestly increased throughout the study period, although this trend was not significant. We observed significant increases for topical and over-the-counter antifungals. Additional research is needed to investigate the reasons behind these prevalence changes.

Keywords

pregnancy; antifungal; yeast infection; Birth Defects Study to Evaluate Pregnancy exposureS

Introduction:

Fungal infections, such as vaginal yeast infections, are common in pregnancy. Previous studies suggest that 10-39% of pregnant people report fungal infections, but these studies largely took place outside the United States (U.S.).¹⁻⁴ Previous studies suggest that rising estrogen levels during pregnancy increase yeast infection risk by increasing glycogen production, which allows fungal cells to better adhere to the vaginal wall.^{5,6} Estrogen levels increase significantly in the first trimester and continue increasing steadily throughout pregnancy, suggesting a higher risk of infection among pregnant people compared to non-pregnant people.⁷ Additionally, a study by Kumwenda and colleagues demonstrated that high estrogen levels may also encourage fungal cells such as *C. albicans* to evade the immune system, promoting infection.⁵

Many different antifungal medications, both topical and oral, can be used to treat yeast infections. International and U.S. national guidelines recommend pregnant people use only topical antifungal medications.⁸⁻¹⁰ Although one-dose oral medications such as fluconazole are an effective and convenient treatment for these infections, some studies suggest positive associations between these medications and birth defects.¹¹⁻¹³ However, these associations are much stronger among those who use higher doses of fluconazole to treat systemic fungal infections.¹⁴ Studies of maternal use of other antifungal medications during early pregnancy have identified increased risk of some birth defects, including central nervous system defects and some congenital heart defects.^{15,16}

To date, no studies have evaluated demographic patterns of yeast infections and antifungal medication use during pregnancy in the U.S. It is important to study these patterns to not only understand how guidelines may have affected which medications are prescribed to pregnant people with a yeast infection, but to target areas for research concerning the effects of yeast infections and its treatment on adverse pregnancy and birth outcomes.

Materials and Methods:

The Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) is an on-going, population-based, multi-site, case-control study in the U.S. whose original aim is to investigate risk factors for a range of major structural birth defects. BD-STEPS includes pregnancies with dates of birth between January 2014 and August 2015 and between

July 2016 and December 2019.¹⁷ Cases were ascertained from birth defect surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New York, and North Carolina. Participant ascertainment included the entire state for Iowa and Arkansas, and select counties for California, Georgia, Massachusetts, New York, and North Carolina. This analysis utilized information from the pregnant people and their offspring who comprise the control group of live born infants without a major structural birth defect. Because our analysis only used controls, we treated our study as a retrospective cohort. Control infants were randomly selected from birth certificates in the same year and catchment area as the case infants. Institutional review boards at each study site and the Centers for Disease Control and Prevention approved this project and participants provided informed consent.

Participants completed a computer-assisted telephone questionnaire in English or Spanish between 6 weeks and 24 months (those with delivery dates before August 2015) or between 6 weeks and 18 months (those with estimated delivery dates after July 2016) following the delivery date. Interviewers asked about demographic factors, chronic diseases, other illnesses, medication use during pregnancy, and pregnancy history. For interview questions regarding genitourinary infections, participants were asked if they had a first trimester yeast infection and if they took medications to treat their infection. If participants reported affirmatively, they were asked whether the infection was diagnosed by a doctor, if medication used was prescription or over-the-counter, and if medication was used topically or orally. Specific medication names were not reported.

First trimester yeast infections and antifungal medication use were defined as occurring any time from the month before pregnancy through the third month of pregnancy. The month before pregnancy was included in the exposure window to account for potential inaccuracies in estimating the timing of conception. We excluded participants missing yeast infection information (51 participants).

In our analysis, we assessed maternal characteristics among participants who reported a yeast infection and those unexposed to a yeast infection in the first trimester. We assessed: age at delivery (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other race), educational attainment at delivery (years; 0-11, 12, 13-15, 16+), body mass index (kg/m²; underweight [<18.5], healthy [$18.5-25$], overweight [$25-30$], obese [$30+$]), parity (previous livebirths/stillbirths; 0, 1, 2+), pre-pregnancy diabetes or gestational diabetes (yes, no), periconceptional (defined as the month before through the first month of pregnancy) multivitamin use (yes, no), first trimester urinary tract infection (yes, no), maternal hypertension (yes, no), first trimester smoking or e-cigarette use (yes, no), first trimester alcohol use (yes/no), time to interview (days), and study site. We described whether the yeast infection was doctor diagnosed, as well as the route of administration and method of receipt (prescription or over-the-counter) for antifungal medication use. Finally, we estimated prevalence of yeast infections and first trimester antifungal use overall, and by study site and birth year. Due to variations in prevalence, we standardized for study site according to the geographic distribution of the entire population of cases and controls in BD-STEPS (N=4,250). Standardization was used for estimating prevalence by birth year. We used the Cochran-Armitage test for trend to determine whether any changes over the study period were statistically significant.

Results:

We included 1,524 participants in our analysis: 149 (9.8%) reported a first trimester yeast infection, 121 (7.6%) reported the yeast infection was diagnosed by a doctor, and 131 (8.6%) reported use of an antifungal medication. Only 18 participants reported an untreated yeast infection. All participants who reported using an antifungal medication also reported a yeast infection. Of the 121 participants who reported a doctor-diagnosed yeast infection, 90% reported using an antifungal medication. Demographic factors differed between participants who did and did not report first trimester yeast infections for a few variables; participants who reported first trimester yeast infections more frequently reported younger age at delivery, non-Hispanic Black race/ethnicity, first trimester cigarette or e-cigarette use, first trimester genitourinary infections and first trimester antibiotic use (Table 1). Given that 88% of those who reported first trimester yeast infections also reported antifungal use, demographic factors were similar for those who reported yeast infections and those who reported antifungals (data not shown). New York and Massachusetts participants reported the highest and lowest prevalence, respectively, of yeast infections and antifungal use.

Table 2 reports the route of administration and method of receipt for each antifungal medication reported. Approximately half (52.7%) of participants reported using a prescription antifungal, and 45.0% reported using an over-the-counter medication. Among those who reported prescription medications, 52.2% reported topical prescriptions. Of the 59 participants who reported over-the-counter medications, almost all reported topical antifungals (94.9%).

Variations in the prevalence of yeast infections and doctor-diagnosed yeast infections were observed across sites. New York participants reported having the highest and Massachusetts participants having the lowest prevalence for each category (Figure 1). We observed that not all yeast infections were diagnosed by a doctor, but the prevalence of infections and doctor-diagnosed infections differed by less than 1.5% overall. While this was true for most sites, larger differences in prevalence were observed for Arkansas and Georgia participants. The prevalence of first trimester antifungal use ranged from 5.4% in Massachusetts to 11.4% in New York. Among those reporting antifungal use, there were differences by site in the use of prescription or over-the-counter medications (Figure 2a). Arkansas participants had the highest prevalence of over-the-counter antifungal use, with Iowa participants having the lowest. Additionally, New York participants had the highest prevalence of prescription antifungal medication use, with Massachusetts having the lowest. Except for participants in Georgia, participants in each other study site reported a much higher prevalence of topical than oral antifungals (Figure 2b).

Due to variations in prevalence, we standardized the analysis by study site when estimating prevalence by birth year. The standardized prevalence was similar to the crude, and the interpretation of results remained the same. The prevalence of yeast infections, doctor-diagnosed infections, and antifungal medication use showed modest, but non-significant increases ($p>0.05$) over the study period (Figure 3). Looking by route of administration, however, revealed that reports of oral medications did not change significantly over the study

period ($p=0.17$), while topical medication use significantly increased from 4.3% to 8.0% ($p=0.03$) (Figure 4a). Similarly, we observed that while the use of prescription antifungal medications did not change significantly over the study period ($p=0.73$), the prevalence of over-the-counter medication use increased, rising from 2.4% to 5.4% ($p=0.04$; Figure 4b). While prescription antifungals were more prevalent in 2014, this changed by 2018, when over-the-counter antifungals became more prevalent.

Discussion:

We described the patterns of first trimester yeast infections and antifungal medication use during 2014-2019. Overall, we report that yeast infections and antifungal use were relatively common in the first trimester with 9.8% of study participants reporting a yeast infection in the first trimester, 7.9% reporting a doctor-diagnosed yeast infection, and 8.6% reporting antifungal use to treat their yeast infection. Overall, we observed that prescription antifungal medication was slightly more common than over-the-counter medication use, and that most participants reported use of topical medications. The prevalence of infections and medication use did not statistically significantly change over the course of the study period, although topical and over-the-counter antifungal medication use significantly increased.

Reports of yeast infections and antifungal use varied by some maternal demographics. We observed that those who reported yeast infections and treatment were more frequently younger at delivery and reported non-Hispanic Black race/ethnicity than those without first trimester yeast infections. Understanding the differences in prevalence of yeast infections in pregnancy could lead to new opportunities for its prevention, which could reduce maternal and fetal morbidity and decrease antifungal use in pregnancy.

We observed wide variations in prevalence of first trimester yeast infections (overall and doctor-diagnosed) and antifungal medication use across study sites, with New York participants reporting a yeast infection prevalence twice as high as Massachusetts participants. Participants from New York and Massachusetts both reported approximately 86% of infections were doctor-diagnosed. Interestingly, New York and Massachusetts participants had similar prevalence of over-the-counter antifungal use (4.2% vs. 3.7%), but considerably different levels of prescription antifungal prevalence (7.5% vs. 1.7%). Of those who reported prescription antifungals, prevalence among Massachusetts participants who reported topical and oral antifungals was the same (50%), whereas it differed for New York participants (68% vs. 28%) with 4% of New York participants reporting use of both topical and oral antifungals. These between-site differences may be due to variations in prescribing patterns, access to healthcare providers, or differences in demographics. We observed that 8.2% of Massachusetts participants reported non-Hispanic Black race/ethnicity, compared to 13.2% of New York participants (data not shown). Given higher prevalence of yeast infections among non-Hispanic Black participants overall, this may explain some of the between-site differences that we observed. It is worth noting that prevalence varied across all sites; rates of yeast infections and antifungal use in Georgia were similar to those in New York, and rates in Iowa were only slightly higher than in Massachusetts. Few studies have evaluated the differences in medication prevalence by geographic region.¹⁸ A study assessing secular trends of nausea and vomiting in pregnancy and selected treatments also

found wide variation in the prevalence of reported treatments across regions in the U.S., similar to our results, demonstrating that other medications also vary by geographic area.¹⁹ From our data alone, it is unclear why we observed differences in antifungal medication prevalence between study sites. Further research should evaluate differences in prescribing patterns, patient preferences, and other factors that could affect these results.

We observed that prevalence of first trimester antifungal use modestly, yet non-significantly, increased over the study period, with the prevalence ranging from 7.3% in 2014 to 9.4% in 2019. Although the prevalence of antifungal medication use, overall, did not significantly change, we observed significant increases in topical and over-the-counter antifungals over the study period. Although antifungal use overall increased over the study period, prescription medication use modestly decreased. Our findings are not consistent with the studies that reported that prescription medication use in the U.S. has increased over the last several decades. Werler and colleagues recently published a study, using data from the National Birth Defects Prevention Study and BD-STEPS, which reported that the use of prescription medications increased from 37% to 50% between 1997 and 2018.²⁰ Additionally, a study by Mitchell and colleagues analyzed the trends of first trimester medication use from 1976 to 2008 and observed that the prevalence of prescription medication use increased by 60% over three decades.²¹

Guidelines from the Centers for Disease Control and Prevention dating as far back as 2007 suggest that pregnant people should use only topical azoles to treat their yeast infections.^{9,10,22,23} It is unclear how to interpret our findings in the context of these guidelines. Fluconazole, a convenient one-dose oral treatment only available by prescription, is a first-line treatment for yeast infections in the general population.⁹ However, fluconazole is contraindicated during pregnancy due to reports of birth defects after treatment in the first trimester.^{11–13} This emerging evidence on the teratogenicity of fluconazole during the study period may have contributed to the slight decreases in prevalence of oral and prescription antifungals and the significant increase in the prevalence of topical and over-the-counter antifungals over the study period.

BD-STEPS is a population-based study that includes a diverse sample in terms of geography and demographics. Our analysis was restricted to pregnancies that ended in a live birth without a major structural birth defect. While a recent meta-analysis identified an association between oral fluconazole use during pregnancy and spontaneous abortion,¹¹ very few studies have explored yeast infection or antifungal use and the risk of miscarriage. Therefore, the prevalence of antifungal medication use among all pregnancies may be higher than we observed.

The BD-STEPS questionnaire included specific questions about yeast infections, medications used to treat these infections, along with information on route of administration, method of receipt, and if doctors diagnosed the reported infection. Such questions may improve recall of these exposures. Although some BD-STEPS participants had up to two years to complete the interview, 80% of those in our analysis completed the interview within 12 months of the delivery date. A study by Van Gelder, which included births from 2009-2010, reported that antifungal medication use was accurately retrospectively reported

in pregnancy, with a specificity of 98%,²⁴ suggesting pregnant people correctly recall antifungal medication use during the BD-STEPS time period. BD-STEPS did not collect information about the specific dates of a yeast infection during pregnancy or the antifungal medication name, dose, or frequency of use. We were unable to report the most common specific antifungal medications reported, how often they were taken, or more specific dates on when yeast infections occurred during the first trimester.

We believe this is the first study to describe patterns of yeast infections and antifungal medication use during the first trimester of pregnancy. We observed that the prevalence of yeast infections and any antifungal medication use non-significantly increased over the time period from 2014-2019. Additionally, the prevalence of topical and over-the-counter medications significantly increased, while the prevalence of oral and prescription antifungal medications non-significantly decreased.

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Data availability statement:

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

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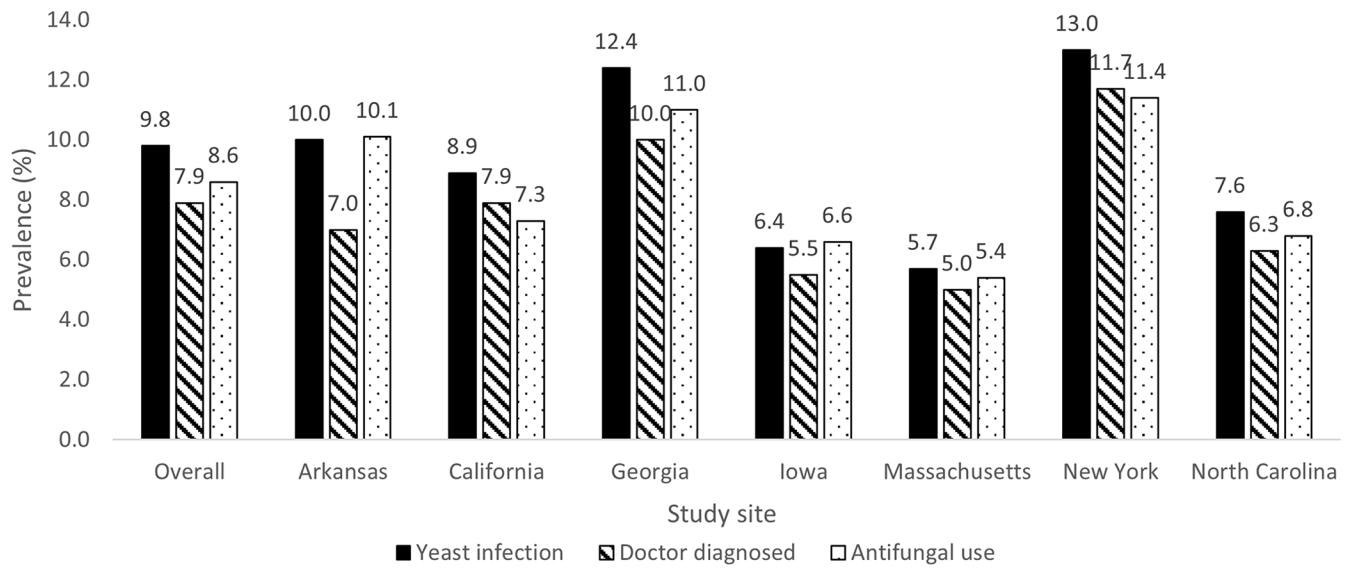


Figure 1.
First trimester prevalence of yeast infections, doctor-diagnosed infections, and antifungal use by study site (2014-2019).

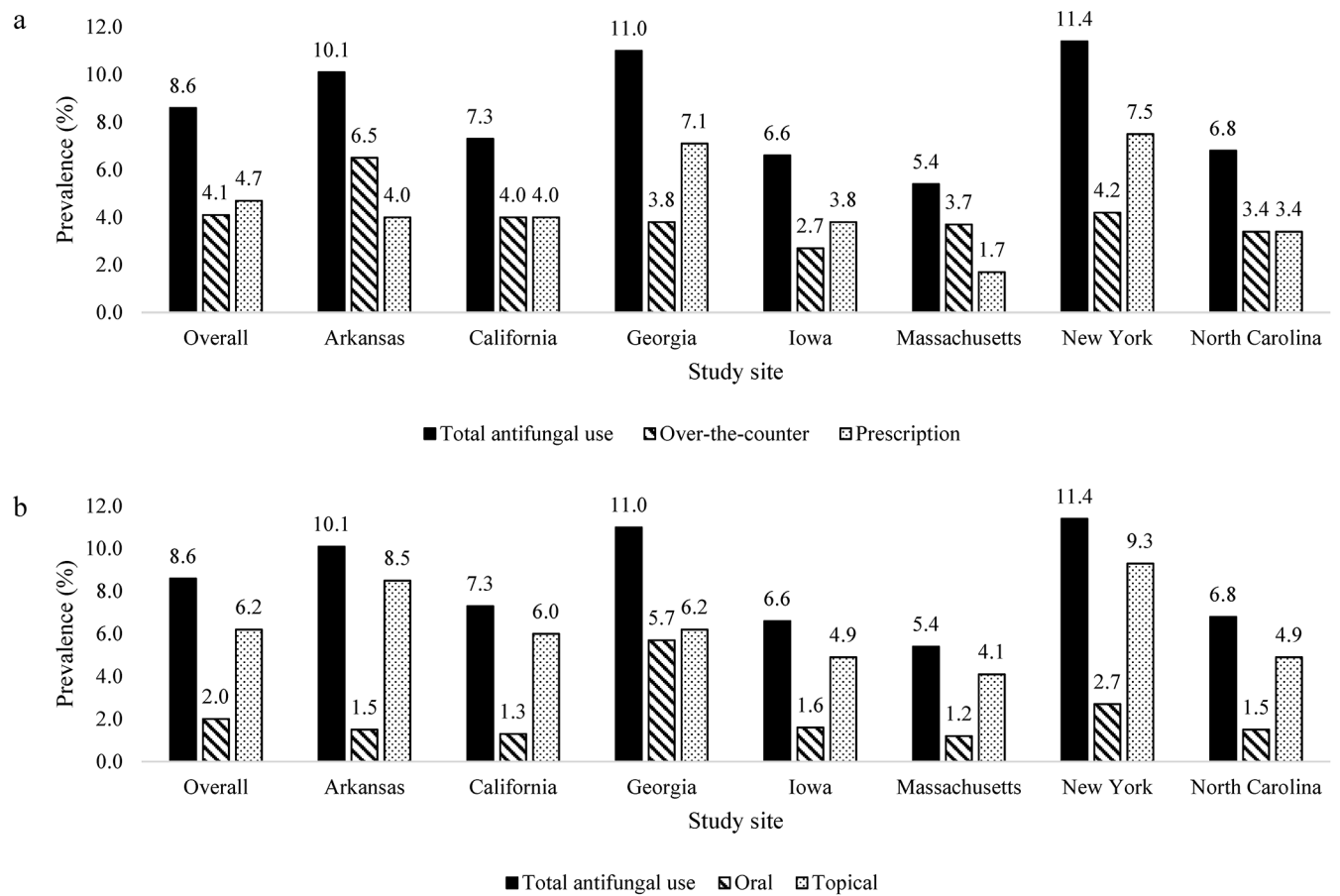


Figure 2.

a. First trimester prevalence of antifungal use, by study site and method of receipt (2014-2019). There were 3 participants who reported use of both over-the-counter and prescription antifungals. b. First trimester prevalence of antifungal use and route of administration, by study site (2014-2019). There were 4 participants who reported use of both oral and topical antifungals.

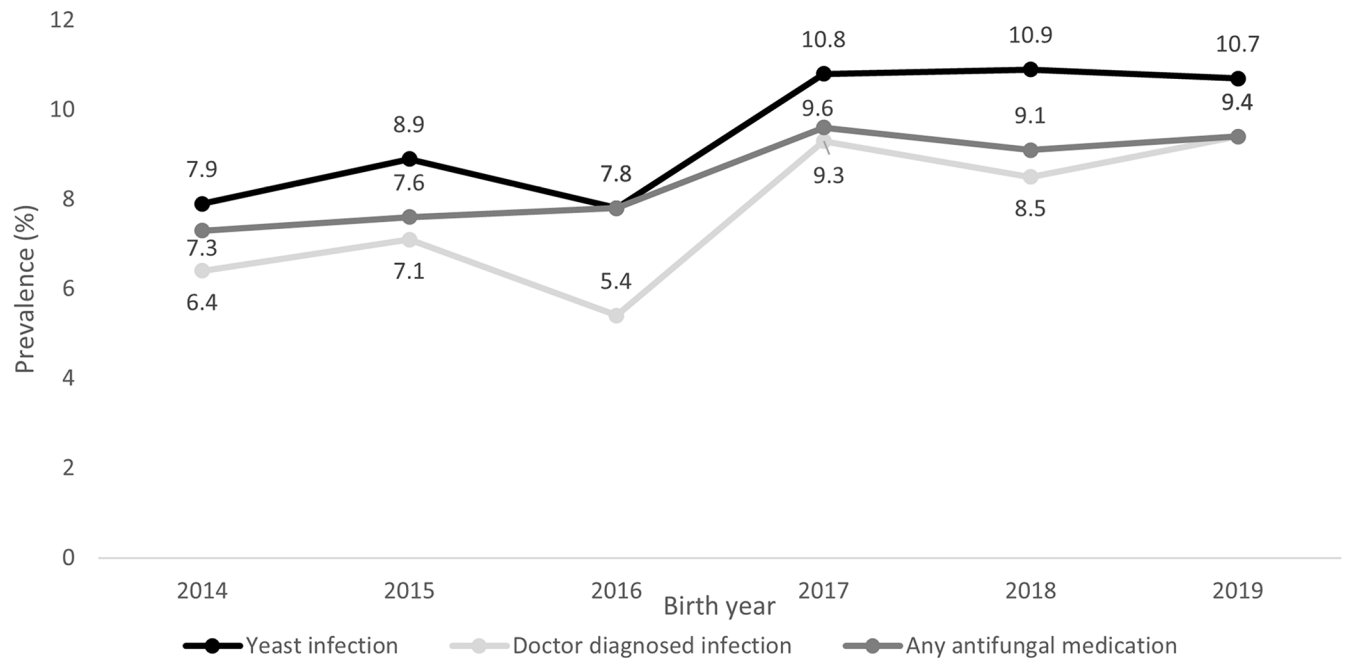


Figure 3.

Prevalence of yeast infections and antifungal medications, by birth year, standardized by study site (2014-2019). Cochran-Armitage test for trend: Yeast infection, $p=0.11$; doctor-diagnosed infection, $p=0.11$, any antifungal medication, $p=0.19$.

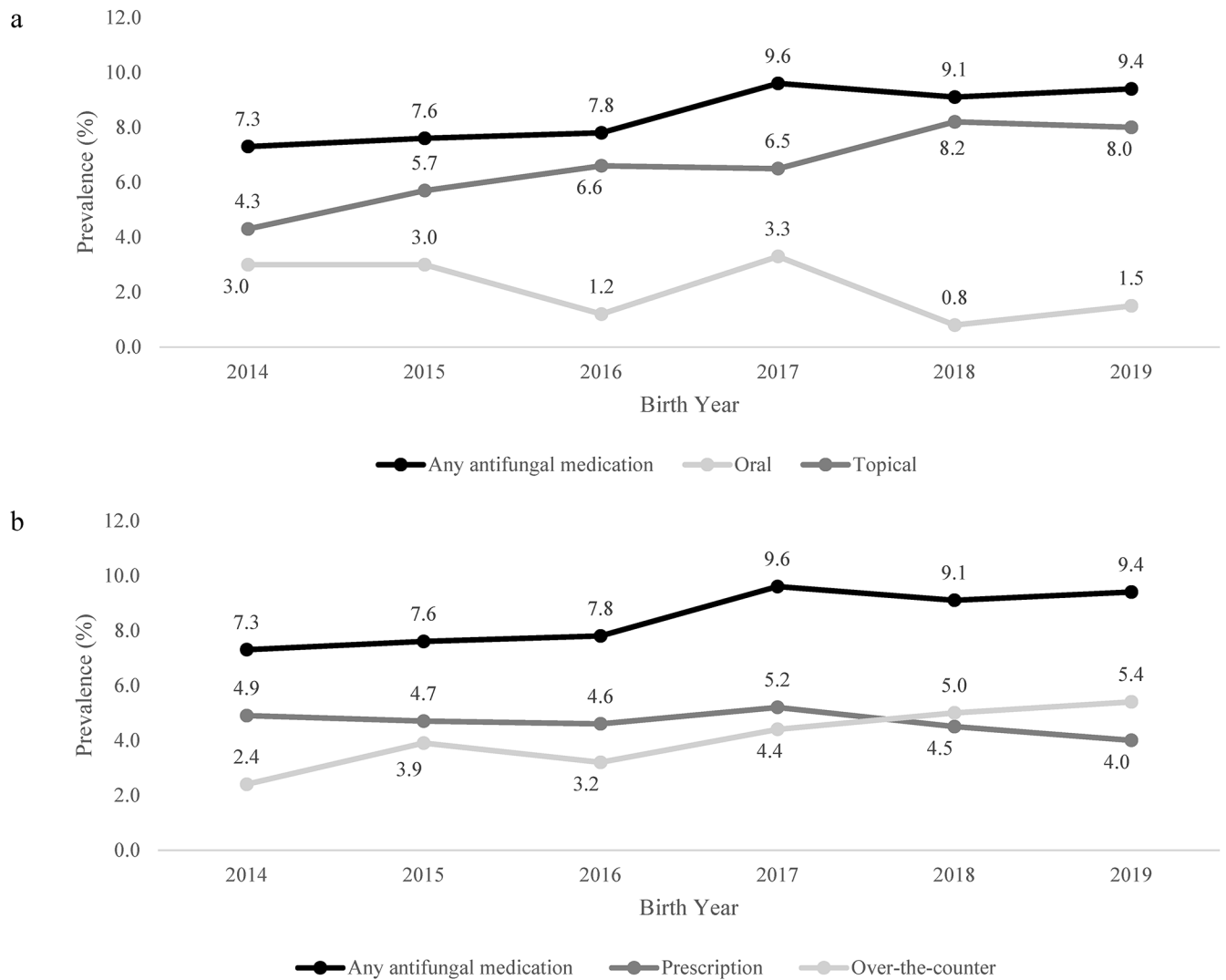


Figure 4.

a. Prevalence of first trimester antifungal use by study period, by route of administration, standardized by study site (2014-2019). Four participants who reported use of both oral and topical antifungals. Cochran-Armitage test for trend: any use, $p=0.19$; oral, $p=0.17$; topical, $p=0.03$. b. Prevalence of first trimester antifungal medication use, by method of medication receipt, standardized by study site (2014-2019). Three participants who reported use of both over-the-counter and prescription antifungals. Cochran-Armitage test for trend: any, $p=0.19$; prescription, $p=0.73$, over-the-counter, $p=0.04$.

Table 1.

Maternal characteristics of participants who reported first trimester yeast infections in BD-STEPS (2014-2019) among 1,524 participants

Characteristic	First trimester yeast infection	No yeast infection during pregnancy
	n=149	n=1375
	mean (SD)	mean (SD)
Maternal age (years) ^a	28.7 (5.8)	30.2 (5.5)
	n (%)	n (%)
Maternal race/ethnicity		
Non-Hispanic White	69 (46.3)	736 (53.5)
Non-Hispanic Black	33 (22.2)	164 (11.9)
Hispanic	37 (24.8)	356 (25.9)
Other	10 (6.7)	117 (8.5)
Missing	0 (0)	2 (0.2)
Maternal education		
0-11 years	21 (14.1)	139 (10.1)
12 years	34 (22.8)	209 (15.2)
13-15 years	33 (22.2)	322 (23.4)
16+ years	52 (34.9)	625 (45.5)
Missing	9 (6.0)	80 (5.8)
Body mass index (kg/m ²)		
Underweight (<18.5)	8 (5.4)	30 (2.2)
Normal (18.5-<25)	59 (39.6)	586 (42.6)
Overweight (25-<30)	36 (24.2)	345 (25.1)
Obese (30+)	35 (23.5)	285 (20.7)
Missing	11 (7.4)	129 (9.4)
Parity		
0 previous births/stillbirths	52 (34.9)	505 (36.7)
1 previous birth/stillbirth	51 (34.2)	454 (33.0)
2+ previous births/stillbirths	43 (28.9)	398 (29.0)
Missing	3 (2.0)	18 (1.3)
Diabetes		
Pre-pregnancy diabetes	3 (2.0)	21 (1.5)
No diabetes	140 (94.0)	1261 (91.7)
Missing	2 (1.3)	13 (1.0)
Periconceptional multivitamin use ^b		
Yes	110 (73.8)	1014 (73.8)
No	32 (21.5)	318 (23.1)
Missing	7 (4.7)	43 (3.1)
First trimester genitourinary infection ^c		
Yes	27 (18.1)	137 (10.0)

Characteristic	First trimester yeast infection	No yeast infection during pregnancy
	n=149	n=1375
	mean (SD)	mean (SD)
No	118 (79.2)	1227 (89.2)
Missing	4 (2.7)	11 (0.8)
First trimester antibiotic use ^C		
Yes	34 (22.8)	163 (11.9)
No	92 (61.7)	1197 (87.1)
Missing	5 (3.4)	33 (2.4)
Maternal hypertension		
Yes	23 (15.4)	198 (14.4)
No	125 (83.9)	1174 (85.4)
Missing	1 (0.7)	3 (0.2)
First trimester smoking or e-cigarette use ^C		
Yes	21 (14.1)	129 (9.4)
No	119 (79.9)	1173 (85.3)
Missing	9 (6.0)	73 (5.3)
First trimester alcohol use ^C		
Yes	71 (47.7)	641 (46.6)
No	68 (45.6)	657 (47.8)
Missing	10 (6.7)	77 (5.6)
Time to interview		
0-6 months	52 (34.9)	514 (37.4)
7-12 months	72 (48.3)	649 (47.2)
13-18 months	24 (16.1)	194 (14.1)
19-24 months	1 (0.7)	15 (1.1)
Missing	0 (0)	3 (0.2)
Study site ^a		
Arkansas	21 (14.1)	178 (13.0)
California	14 (9.4)	137 (10.0)
Georgia	27 (18.1)	183 (13.3)
Iowa	12 (8.1)	171 (12.4)
Massachusetts	14 (9.4)	228 (16.6)
New York	45 (30.2)	289 (21.0)
North Carolina	16 (10.7)	189 (13.8)

^a There were no missing values for maternal age and study site.

^b Periconceptional is defined as the period from the month before through the first month of pregnancy

^c First trimester is defined as the month before through the third month of pregnancy

Table 2.

Prevalence of antifungal medications reported during pregnancy among 1,524 participants (2014-2019)

	Any first trimester antifungal use
	n (%)
Any antifungal medication	131 (100.0)
Prescription *	69 (52.7)
Oral	30 (22.9)
Topical	36 (27.5)
Both oral and topical	2 (1.5)
Over-the-counter	59 (45.0)
Oral	1 (0.8)
Topical	56 (42.7)
Both oral and topical	2 (1.5)
Both prescription and over-the-counter	3 (2.3)
Oral	0 (0)
Topical	3 (2.3)
Both oral and topical	0 (0)

* One participant did not report whether their prescription medication was oral or topical.