ORIGINAL ARTICLE

Herbal supplement use among reproductive-aged women in an academic infertility practice

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Objective: To address the knowledge gap surrounding herbal medicine and supplement usage patterns and supplement-prescription medication interactions among patients seeking treatment for infertility.
Design: Cross-sectional survey study.
Setting: Academic infertility practice.
Patient(s): Ninety-five reproductive-aged patients.
Intervention(s): Not applicable.
Main Outcome Measure(s): Use of herbal medications and supplements, baseline demographics, history of infertility treatments, and potential supplement-medication interactions.
Result(s): We surveyed 95 participants with a median age of 35 years. Overall, 68.4% of patients reported ever having used supplements or herbal medicines in the past. Current use of herbal supplements and vitamins was reported by 53.7% and 93.7% of participants, respectively, with a median of 2 (range 19) supplements used per person. There were no significant associations between patient demographics, comorbidities, or infertility treatments with increased rates of supplement use. The most commonly used herbal supplements were: green tea (n = 14), chamomile (n = 12), peppermint (n = 9), turmeric (n = 8), elderberry (n = 7), ginger (n = 7), maca (6) with the most common modalities being pills/capsules (23.8%) and tea (42.3%). The most common reasons for use were: general health and wellness (24.5%), immune support (16.2%), stress (14.0%), and fertility (15.0%). Patients used maca (n = 5), chasteberry (n = 3), goji berry (n = 2), ginger (n = 2), yam-based progesterone (n = 2), and combination product (n = 2) for fertility purposes. A total of 7.9% of patients learned about these products from their general health care provider, and 33.3% of supplements were disclosed by patients to their provider. We identified 41 moderate-risk supplement-drug interactions, with 12 of these interactions attributed to infertility therapies. Based on the interaction checker, the most commonly proposed mechanisms of interaction were CYP3A4 and CYP2C19 inhibition. In terms of safety in pregnancy, cannabidiol and chasteberry were suggested to be "possibly unsafe in pregnancy," and red raspberry leaf "likely unsafe in pregnancy" without direct medical supervision.
Conclusion(s): We found over two thirds of women seeking treatment for infertility reported past and over half reported current herbal medicine and supplement use. Notably, the Natural Medicines Interaction Checker suggested high rates of moderate-risk supplement-drug interactions and possible harmful effects in early pregnancy. Our results call for further investigation of clinically relevant supplement interactions with infertility therapies. (Fertil Steril Rep® 2022;■:■–■. ©2022 by American Society for Reproductive Medicine.)
Key Words: infertility, herbal supplements, supplement-medication interaction

The Center for Disease Control's (CDC) 2017 National Health and Nutrition Examination Survey estimated that, on average, 57% of the United States population uses dietary supplements, with botanicals or "herbal supplements" comprising 5.1–8.3% of these supplements (1). Across national studies, women are consistently more likely to report using supplements, with 49% of reproductive-aged women reporting ever having used dietary supplements (1–4).

Overall, there remains a paucity of published studies that have specifically explored women's use of complementary and alternative medicines (CAM) for fertility enhancement or female-specific diseases and diagnoses (5–9). A systematic review analyzing CAM use in infertility clinics worldwide from 1999 to 2010 reported a prevalence of CAM use ranging from 29% to 91%, with the most common method of CAM being herbal medicine

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(6). A prospective cohort study of 428 couples in infertility clinics found that 29% of couples used a CAM modality for infertility treatment, with 17% specifically using herbal therapies over the course of 18 months (8).

The existing studies on alternative medicine use to address infertility often lack information about which specific supplements patients were taking, what comorbidities the patients had, and other medications they were using (6, 8, 9). These data are essential to truly determine the safety profile of these supplements. Herbal remedies reported to enhance fertility, such as *Viter agnus-cactus*, black cohosh, and *Angelica*, have been shown to have adverse effects ranging from gastrointestinal distress to ovarian hyperstimulation (10). Concurrent use of herbal medicines with prescription medications is reported among 20%–30% of prescription drug users in the United States; there is evidence via in vitro and in vivo studies that herbal therapies can act as metabolic inhibitors or inducers of prescription medications when used in combination (11). The herbal therapy with the most interaction evidence is St. John's Wort which acts as a CYP3A inducer causing metabolic effects on a wide range of medications, from hormonal therapies to antiretrovirals and antimicrobials (11, 12). Risks of herbal-drug interactions span from side effects (eg, bleeding, cardiotoxicity, hypoglycemia, hypotension) to altered pharmacokinetics (eg, decreased absorption, increased metabolism) of medications (12). Understanding the use of these herbal supplements could help guide clinical counseling on the safety of these products and their potential supplement-medication interactions. This study aimed to fill in some of the gaps regarding herbal supplement use in women's health care by directly assessing herbal medicine and supplement use among patients seeking care in an assisted reproductive medicine clinic.

MATERIALS AND METHODS

Subjects and Setting

We conducted a cross-sectional study of reproductive-aged women (14–45 years) presenting to the University of Colorado Reproductive Endocrinology and Infertility Clinic in Denver, Colorado.

Data Collection

We created an electronic REDCap survey for this study, with all study data collected and managed using REDCap electronic data capture tools (13, 14). The survey collected baseline demographic and clinical information about the participants, including their medical comorbidities and prescription medications. Participants were then asked about their current and past herbal medication and supplement use. We provided participants with a list of herbal medications and supplements based on the most commonly purchased supplements in the United States as reported by the American Botanical Council in 2020 (15), in addition to commonly used herbal products for female-specific complaints such as blue and black cohosh, chasteberry, yam-based products, primrose, and raspberry leaf (9, 10, 16). We also provided participants a free-form response section to list combination products and other supplements and prescription medications not included in the provided list. We then assessed the methods of herbal medicine use (eg, pills, tea, tinctures), motivations for use (eg, general health and wellness, gynecological concerns), sources of information used when deciding to start an herbal medication (eg, friends, health care providers), and whether participants disclosed herbal medication or supplement use to their health care care providers.

We piloted this survey among 20 clinic participants for readability, understandability, and completion time. Electronic advertising efforts were used to recruit participants from patients seen at the Aurora and Colorado Springs clinic sites of the University of Colorado Reproductive Endocrinology and Infertility department from November 2020 to December 2020. We advertised the study to eligible patients via direct E-mail communications twice during this time period. Additionally, from January 2021 to July 2021, patients had the option of filling out the online survey via a quick response code given to them during their in-person clinic visit. Participants were remunerated a $10 gift card for the completion of the survey.

Analyses

We used IBM SPSS(version 28) statistical software for all data analyses. We used descriptive statistics and content analysis for participant baseline characteristics and the kinds and types of alternative medicines commonly used. We then used Chi-square and independent medians tests to compare baseline characteristics of herbal medicine users to nonusers for categorical and continuous outcomes, respectively. We also evaluated for potential supplement-drug interactions using the Natural Medicines Interaction Checker, a peer-reviewed scientific database for natural medicines. We included interactions if they were determined to be "moderate-risk" or higher, meaning "use cautiously or avoid combination; warn patients that a significant interaction or adverse outcome could occur" (17). For this study, given the paucity of directly relevant published data, we a priori selected a sample size of 100 participants, as this was within the average sample size of comparable studies performed in reproductive endocrine clinics within a similar timeframe (8).

We obtained approval for this study from the Colorado Multiple Institutional Review Board at the University of Colorado Anschutz Medical Campus (#20-1153). All participants provided informed consent as a part of the survey completion. This study was funded using institutional funds from the Reproductive Endocrinology and Infertility Division at the University of Colorado.

RESULTS

Between January 2021 and July 2021, we surveyed 100 patients, with a total of 95 participants meeting the inclusion criteria. The median age of the participants was 35 (range 24–45) years old, and most were white (85.3%), nonHispanic (88.3%), born in the United States (83.2%), and with private insurance (92.6%). A little over half of the participants (58.9%) reported having an infertility diagnosis and 15.8% reported polycystic ovary syndrome (PCOS). The most commonly reported treatments used for infertility were

in vitro fertilization (26.3%), intrauterine insemination (24.2%), letrozole (16.8%), clomiphene citrate (11.6%), and other hormonal injections (9.5%). (Table 1)

Overall, 65 patients (68.4%) reported ever having used supplements or herbal medicines in the past, with a mean of 5.07 supplements used per person. Current use of herbal supplements and vitamins was reported by 51 (53.7%) and 89 (93.7%) of subjects, respectively, with a median of 2 (range 1–9) supplements used per person. Of the respondents who answered, "no" to the question "do you currently use supplements or herbal medicines" (n = 53), when presented with a list of herbal medicines, nine participants (17.0%) reported using at least one of these products.

The most commonly used herbal supplements were: green tea (n = 14), chamomile (n = 12), peppermint (n = 9), turmeric (n = 8), elderberry (n = 7), ginger (n = 7), maca (6), garlic (6), goji berry (5), cranberry/echinacea (4), and cannabidiol (CBD)/Ashwagandha/Ginseng/Vitex/Combination product (3). The most common modalities of herbal supplement use were tea (42.3%), pills/capsules (23.8%), food (14.6%), powder (9.8%), and tincture (6.5%). Participants reported learning about these products from their friends and family (43.9%), the internet (28.0%), alternative medicine providers (20.2%), and general health care providers (7.9%). Only 33.3% of supplements were disclosed by patients to their provider, and over half (54.5%) of the participants reported that they would continue using these products during pregnancy.

Participants cited the following reasons for their herbal supplement use: general health and wellness (24.5%), immune support (16.2%), stress (14.0%), and fertility (15.0%). Only 1.7% of patients reported using herbal supplements and medications to address their PCOS. Patients reported using maca (n = 5), chasteberry (n = 3), goji berry (n = 2), ginger (n = 2), yam-based progesterone (n = 2), and combination product (n = 2) for fertility purposes. Other supplements patients used for fertility purposes included CoQ10, DHEA, inositol, raspberry leaf tea, and plants from their garden (Fig. 1).

The most commonly reported comorbidities among our cohort were anxiety (n = 34), depression or other mood disorder (n = 20), headache/migraines (n = 17), and thyroid disease (n = 18). We found no significant associations between reported current or previous use of herbal medicines or supplements and patient demographics, comorbidities, previous number of pregnancies, or type of infertility treatment ($P>.05$, Chi-square and independent medians tests). Most participants (69.5%) reported current use of at least one prescription medication, most commonly levothyroxine (n = 28), selective serotonin reuptake inhibitors (n = 13), and hormonal therapies such as progestins or combined hormonal contraceptives (n = 7). Roughly one third (31%) of participants reported using both prescription medications and herbal supplements concurrently.

We identified 41 moderate-risk supplement-medication interactions and no high-risk interactions using the Natural Medicines Interaction Checker (17). Among the moderate-risk supplement-medication interactions, 12 of these

TABLE 1

Patient Demographics and Clinical Characteristics

Patient Demographics	Total (N = 95) Median (range) or % (n)
Age (y)	35 (24–45)
Race:	
White	85.3 (81)
Black/African American	6.3 (6)
Asian	7.4 (7)
American Indian or Alaskan native	1.1 (1)
Other	2.1 (2)
Ethnicity	
Hispanic or Latino	11.7 (11)
NonHispanic	88.3 (83)
Born in the United States	
Yes	83.2 (83)
No	16.8 (17)
Gravidity	1 (0–6)
Nulligravid	41.1 (39)
Parity	0 (0–2)
Nulliparous	66.3 (63)
Education	
Less than high school	0.0 (0)
High school/GED	5.3 (5)
College	32.6 (31)
Graduate	46.3 (44)
Postdoctorate	15.8 (15)
Household Income	
$0–50,000	9.5 (9)
$50,000–75,000	12.6 (12)
$75,000–100,000	17.9 (17)
$100,000+	60.0 (57)
Insurance: % (n)	
Uninsured	3.2 (3)
Medicare/Medicaid/CHIP	4.2 (4)
Private	92.6 (88)
Clinical Characteristics	
Takes prescription medications	69.5 (66)
Medications or Therapies for Infertility Treatment	
Metformin	4.2 (4)
Clomiphene citrate	11.6 (11)
Letrozole	16.8 (16)
IUI	24.2 (23)
IVF	26.3 (25)
Hormonal injections	9.5 (9)
Other	7.4 (7)
N/A	26.3 (25)
Missing	13.6 (13)
Health Conditions	
Anxiety	35.8 (34)
Autoimmune disorder	11.6 (11)
Depression/other mood disorder	21.1 (20)
Endometriosis	4.2 (4)
Fibroids	8.4 (8)
Headaches/Migraines	17.9 (17)
Infertility	58.9 (56)
Insomnia	6.3 (6)
Obesity	7.4 (7)
PCOS	15.8 (15)
Thyroid disease	18.9 (18)
UTIs	5.3 (5)
Menstrual disorder	3.2 (3)
None	8.4 (8)

GED = General Equivalency Diploma; CHIP = Children's Health Insurance Program; IUI= intrauterine insemination; IVF = in vitro fertilization; PCOS = polycystic ovary syndrome

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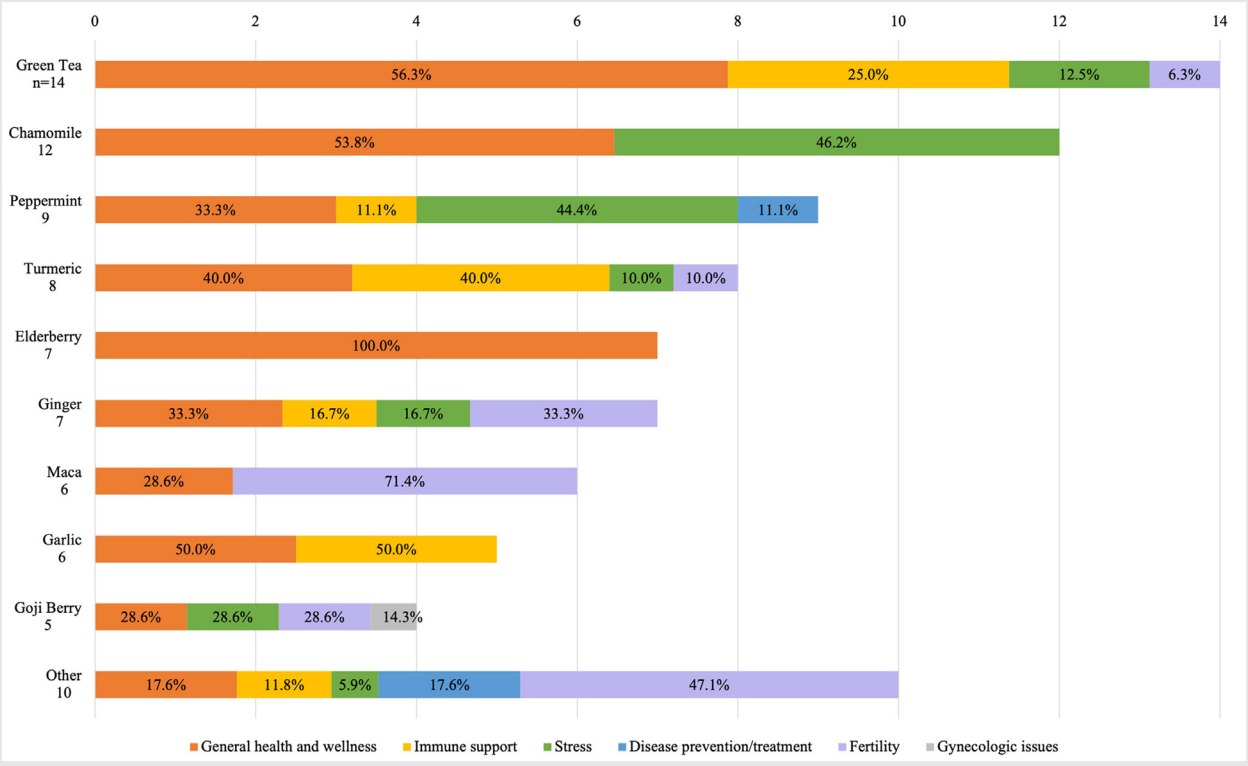
FIGURE 1



Patients using a supplement (N)/ % using a supplement for a condition.

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interactions were attributed to infertility therapies. The most common interactions were via CYP3A4 and CYP2C19 inhibition between letrozole and common herbal supplements, including CBD, chamomile, cranberry, echinacea, garlic, and peppermint (Table 2). Theoretical risks of these interactions include increased levels of drugs like letrozole that are metabolized by CYP3A4. In turn, letrozole inhibits CYP2C19 and may increase the levels of herbal supplements by increasing their potential therapeutic and adverse effects. Other potential adverse effects of these interactions are increased levels of proton pump inhibitors, antidepressant and antipsychotic medications, and analgesics secondary to Cytochrome P450 inhibition and reduced metabolism of Cytochrome P450 substrates.

No moderate-risk interactions were detected between herbal supplements and clomiphene citrate. Unfortunately, we could not assess interactions between herbal supplements and commonly used medications for in vitro fertilization and intrauterine insemination, as these medications are not currently included in the Natural Medicines Interaction Checker. We also assessed potential risks from continued supplement use in pregnancy and found potential use of CBD and chasteberry that were suggested to be "possibly unsafe in pregnancy," and red raspberry leaf suggested to be "likely unsafe in pregnancy" (18–22).

DISCUSSION

Our cross-sectional survey study among 95 reproductive-aged female patients at an academic infertility practice found that most patients (68.4%) had used supplements in the past, and over half (53.7%) were currently using nonvitamin supplements. A comparable prospective study among 100 patients at an infertility practice in Australia similarly found 66% of their patients were using complementary medicines, with 29% using herbal remedies (23), whereas a private infertility clinic in the United Kingdom reported 40% of their patients used CAM with 5% using herbal therapies (24).

The demographics of supplement and herbal medicine users in our study were comparable to the findings of eight article reviews of users of CAM for fertility enhancement in the United States, Australia, and England. Typically, women were older, with a median age of 35 years, with high educational attainment, working as professionals, and earning high incomes (6). Additional associations with increased CAM use include an increased number of years trying to conceive and use in vitro fertilization (IVF) (6, 8). We found no significant associations between patient demographics, comorbidities, previous number of pregnancies, or type of infertility treatment with increased rates of previous or current supplement use in our study. Lack of association or significance may be secondary to the homogeneity of our study

TABLE 2

Moderate-risk herbal supplement interactions per patient.

Herbal supplement	Letrozole	Levothyroxine	Proton Pump Inhibitors	Antidepressants/ Antipsychotics	Antihypertensives	Analgesics
Ashwagandha		may increase side effects of thyroid hormone				
CBD	CYP3A4 CYP2C19			CYP2C19 (SSRI) CYP3A4 (SSRI)		
Chamomile	CYP3A4		Pantoprazole (CYP3A4)	CYP2D6 (SNRI)	Metoprolol (CYP2D6)	Ibuprofen/diclofenac (CYP2C9)
Cranberry	CYP3A4			CYP3A4 (SSRI)		
Echinacea	CYP3A4			CYP1A2(Olanzapine) CYP3A4(Quetiapine)		
Garlic	CYP3A4					
Goji Berry			Pantoprazole (CYP2C19, CYP3A4)	CYP2D6 (SNRI)	Metoprolol (CYP2D6, additive hypotensive effects with goji root bark)	
Green Tea				-Caffeine withdrawal can increase medication levels (Lithium)		
Peppermint	CYP3A4			Quetiapine (CYP3A4)		Ibuprofen/diclofenac (CYP2C9)
Turmeric			Pantoprazole (CYP3A4)			
Ginger						Ibuprofen/diclofenac (increase anti-platelet effects)

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population in addition to our small sample size. Future research with more heterogenous and diverse patient populations may better elucidate the individual characteristics associated with increased likelihood of herbal medication and supplement use.

The most commonly used supplements among our participants to address their infertility were: maca, chasteberry, goji berry, ginger, yam-based progesterone, and combination products. Two similar United States-based studies found that patients with infertility were most commonly using chasteberry, soy, evening primrose, yam extract, and raspberry tea (9, 16). There appears to be a general continuity across the limited available studies in terms of what herbal medicines patients use to address their infertility. Many of these supplements, like black cohosh, have reported phytoestrogenic components whereas others, like chasteberry, are theorized to increase luteal phase progesterone synthesis; however, few supplements have randomized control data evaluating their effectiveness for these therapeutic claims (10, 25, 26). Interestingly, most participants in our study reported using supplements for general health and wellness, immune support, and stress as opposed to addressing infertility. A questionnaire study of 400 patients with infertility in the UK found that 10% of their patients felt that CAM was helpful for infertility, 13% felt that CAM helped them psychologically, and 22% felt it had helped them to relax (24). Thus, the high prevalence of herbal supplement use among patients experiencing infertility may not only be to specifically target their infertility but also to help patients cope with the significant stressors and lack of control that may go along with a diagnosis of infertility and to improve their general health for conception and pregnancy.

In our cross-sectional study, only 33.3% of supplements were disclosed by patients to their general health care provider. These disclosure rates are similar to a prospective study of 100 patients at a fertility clinic in which 42% of responders reported discussing the use of their complementary medicines with a health professional: 31% with their general provider and 26% with their fertility specialist. In this Australian based-study, patients learned about complementary therapies from their general practitioner (18%) along with family members (22%) and friends (16%) (23), whereas, in our Colorado-based cohort, patients learned about supplements from their friends and family (43.0%) and the internet (26.8%), with only 7.9% having learned about these products from their general health care provider. Thus, despite more Australian patients learning about CAM from their providers, the disclosure rates across studies are still very low, indicating possible discrepancy and lack of agreement on how to assess or ask about CAM use.

Underreporting of supplements and alternative therapies is likely to impact clinical care, as supplements and other alternative medicines have the potential to interact with medications and can cause adverse medical effects (27, 28). Although research on the adverse effects of herbal medicines is often limited to animal models or human case reports, these adverse effects can have significant health impacts. There have been case reports of teas used to promote fertility causing bradycardia and edema (29) and lead poisoning from infertility supplements (30). Although there is some evidence for efficacy of these herbal medicines (10, 31), patients continue to use these herbal medicines and supplements in spite of reliable efficacy data. Since the passage of the Dietary Supplement and Health and Education Act in 1994, dietary supplements have been exempt from prescreening or any safety and efficacy studies before they are released to the public. Under the Dietary Supplement and Health and Education Act, the Food and Drug Administration (FDA) may take action if a product poses a direct health threat and only after adverse health effects have already occurred. As supplements and herbal medicines in the United States are self-regulated by their manufacturers and distributors with minimal to no oversight from the FDA, it falls to the health care providers and researchers to determine the safety of CAM among their patients (32, 33).

In terms of the safety of herbal supplements among our study population, we identified 41 moderate-risk supplement-medication interactions using Natural Medicines Interaction Checker (17). Twelve of these interactions were attributed to infertility therapies, most commonly via CYP3A4 and CYP2C19 inhibition between letrozole and common herbal supplements. Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme (34). The Natural Medicines Interaction Checker determines interactions based on the mechanism of action of herbal compounds and medications with similar mechanisms of action. For instance, CBD has been found to increase levels of drugs that are metabolized by CYP3A4, thus increasing plasma levels of the CYP3A4 substrates such as tacrolimus, citalopram, and methadone (35–37). However, there are no available clinical studies to determine if there is a true change in letrozole plasma levels or other infertility medications because these data are based on the extrapolation of known mechanisms of action and interactions of similar medications.

A prospective study found that concurrent use of CAM among patients undergoing IVF was associated with a 30% lower ongoing pregnancy and live birth rate over a 12-month period, although CAM users underwent more IVF cycles. Still, this study didn't specifically identify what CAM products patients were using (38). In our cohort, two patients reported using yam-based progesterone. Natural progesterone is isolated from diosgenin, a sterol extracted from the *Dioscorea* species of yam. Intake of diosgenin may affect serum progesterone levels (39). Given that progesterone supplementation does impact the outcome in frozen embryo transfer, it is possible that patients who take diosgenin, especially without notifying their infertility providers, may have altered progesterone serum levels or altered implantation window or both and thus may end up with lower pregnancy rates during either a programmed or natural frozen embryo transfer (40). Our study is the first to our knowledge to elucidate the potential for herbal-drug interactions among infertility medications and calls for further clinical studies to be performed to directly assess these interactions.

The safety of herbal supplements in pregnancy is also a common concern among our reproductive-aged patient population seeking fertility. Many supplements patients report

taking have minimal to no evidence of their effects in pregnancy, especially early pregnancy. Nevertheless, over half (54.5%) of patients in our study reported that they would continue using their herbal supplement products during pregnancy. The FDA has a clear stance on avoiding CBD in pregnancy, although its statement includes both marijuana and CBD, with further evidence needed on CBD itself (19). In pregnancy, there is minimal evidence that chasteberry (*Vitex agnus-castus*) may have estrogenic or progesteronic activity, even potentially acting as a uterine stimulant (41); thus, it is recommended to use with caution during pregnancy and in the first trimester only (42). Raspberry leaf (*Rubus idaeus)* has long been widely used among women during pregnancy. However, the evidence of use is limited to one randomized control trial and an observational study that did not show negative fetal or pregnancy outcomes but also did not demonstrate benefit (43). Importantly, the only clinical studies of this product include use in the third trimester of pregnancy and do not analyze the effects of raspberry leaf on organogenesis (44).

Limitations of our study include a possible lack of generalizability as we recruited a convenience sample among patients in a private infertility clinic in Colorado. Our study population may have over-represented patients who are more likely to be using medications and have a greater number and/or severity of medical conditions, given the clinical recruitment site. However, given the very limited data available on this topic, even a convenience sample can add granularity to the minimal data on specific herbal medication and supplement use among reproductive-aged females. Additionally, commonly used medications for IVF (menotropins, follitropins, gonadotropins) and intrauterine insemination (human chorionic gonadotropin, leuprolide) were not included in the Natural Medicines Interaction Checker, and thus, interactions among these medications were not able to be determined which may underestimate the magnitude of potential herbal-drug interactions.

Although this study may have limited generalizability, the level of detail we captured with our survey still helps address a major knowledge gap within the field regarding what specific supplements and herbal medicine are commonly used. Further, by providing participants with an actual list of commonly used herbal medicines and supplements, we were able to capture users of these substances who reported not using supplements or herbal medicines with a simple yes/no style question. However, we may still have under-captured herbal medicine and supplement use because of the wide variety of formulations and product names available on the market.

CONCLUSIONS

In our cross-sectional study, over two thirds of reproductive-aged women reported past and over half reported current herbal medicine and supplement use. Notably, the Natural Medicines Interaction Checker suggested high rates of moderate-risk supplement-drug interactions and possible harmful effects in early pregnancy. Understanding the use of herbal supplements could guide clinical counseling of patients regarding potential drug interactions with supplements and could also influence education efforts among patients and providers regarding increased disclosure of supplement use. Our results call for further investigation of clinically relevant supplement interactions with infertility therapies.

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