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ORIGINAL ARTICLE

Supplement use by women during pregnancy: data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

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Abstract Women of reproductive age commonly use integrative treatments. However, the reproductive safety for most complementary products lacks systematic study. We aimed to study the use of supplements by women in a prospective pregnancy registry. The Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics was established to evaluate the reproductive safety of atypical antipsychotics. Exposed and control participants were systematically queried about the use of vitamins and supplements. Slightly greater than half (53.2 %) of the participants eligible for analysis (N=534) were using at least one vitamin or supplement at the time of enrollment, not including prenatal vitamins or folic acid. The most common supplements used were omega-3 fatty acids (38.0 %), vitamin D (11.0 %), calcium (8.2 %), and iron (4.7 %). Probiotics and melatonin were used by 2.6 and 0.9 %, respectively. In this prospective pregnancy registry, we found that over half of the participants were taking supplements or vitamins other than prenatal vitamins and folic acid. These findings underscore the need for active query on the part of health care providers about the use of supplements during pregnancy, and the need to obtain rigorous reproductive safety and efficacy data for supplements used by pregnant women and reproductive aged women.

Keywords Supplements · Pregnancy · Antipsychotics · Vitamin · Integrative

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Introduction

The use of integrative therapies is commonplace in the USA. Integrative medicine, also referred to as complementary, includes modalities and treatments that are considered outside of conventional Western medicine and is usually used along with conventional treatments (Clarke et al. 2015). Approximately one third of American adults reported using at least one vitamin or supplement in the past month (Clarke et al. 2015). Data show that women use integrative treatments more often than men, and use is common throughout the reproductive years (Elkins et al. 2005; Radimer et al. 2004; Tindle et al. 2005; Unutzer et al. 2000; Weissman et al. 1984).

Considering approximately half of pregnancies in the USA are unplanned, it is expected that many women will conceive on an integrative treatment that they might not actively select to use during a pregnancy (Sedgh et al. 2014). In other situations, women may opt to use integrative treatments during pregnancy and lactation. Examples of evidence-based use of supplements during pregnancy include prenatal vitamins and folic acid. However, for the majority of supplements available on the market, reproductive safety information is sparse. Therefore, more complete information informing the use of supplements during pregnancy is essential for women to make appropriate risk/benefit decisions about their use.

The motivation to use supplements during pregnancy is complex. For some, demonstrated or perceived specific obstetrical or fetal health benefits may motivate use. On the other hand, pregnant women may believe that a "natural" therapy is a safer treatment option than a prescription medication, and they may take supplements in lieu of standard treatments, even when the supplement in question is understudied or unstudied for both efficacy and safety of use during pregnancy.

Prospective pregnancy registries have emerged over the past few decades as a reliable method of collecting important

reproductive safety data for a particular medication or class of medications (Chambers et al. 1996; Clarke et al. 2015; Cohen et al. 2015). Several registries have been established to evaluate a broad range of medications for a variety of indications (http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm; Chambers et al. 1996; Cole et al. 2007; Schou et al. 1973). In general, registries thus far have primarily focused on the reproductive safety of prescription medications, without addressing vitamins or supplements that many pregnant women also utilize. Likewise, the new US FDA pregnancy and lactation labeling system announced in December 2014 should help patients and physicians weigh the costs and benefits of prescription medications during pregnancy, but the regulation does not apply to vitamins and supplements. The potential risks or benefits of vitamins and supplements that are widely being used by pregnant women are often less known than those of prescription medications, and rigorous, adequately powered studies do not inform most supplement use during pregnancy.

In 2008, the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics was established to obtain reproductive safety data regarding fetal exposure to second-generation antipsychotics. The Registry is the first hospital-based registry in North America for second-generation antipsychotics which systematically and prospectively evaluates risk of malformations among infants exposed and unexposed in utero to second-generation antipsychotics. While the primary objective of this registry is to obtain reproductive safety data for infants exposed to second-generation antipsychotics, this cohort contains prospectively acquired information on medication, supplement, and vitamin usage, as well as comprehensive data regarding maternal, obstetrical, and neonatal health outcomes. The objective of this report was to present data from the National Pregnancy Registry for Atypical Antipsychotics regarding the prevalence of dietary supplement and vitamin use during pregnancy in a cohort with psychiatric diagnoses.

Methods

The Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics was established in 2008 to evaluate the reproductive safety of second-generation antipsychotic medications. More detailed information regarding the methodology for the Registry has been described elsewhere (Cohen et al. 2015). Briefly, this ongoing prospective cohort study follows pregnant women 18–45 years old who are exposed and unexposed to second-generation antipsychotics during pregnancy (Cohen et al. 2015). The exposed group consists of women who have used one or more second-generation antipsychotics during pregnancy. The comparison group consists primarily of women with a history of psychiatric illness being treated with a variety of psychotropics other than second-generation antipsychotics. Participants are recruited across the USA and Canada

Table 1 Characteristics of the study cohort (N=534)

	Valid number	Number	Percent	Mean (±STD)
Age (years)	531			32.3 (±5)
Body mass index (kg/m^2)	518			27.8 (±6.4)
<25.0	518	207	40	
25.0–<30.0	518	154	30	
≥30.0	518	157	30	
Married	525	400	76	
College educated	522	320	61	
Caucasian	523	476	91	
Planned pregnancy	521	368	71	
1+ prior pregnancy	525	334	64	
Cigarette use during 1st trimester	531	113	21	
Alcohol use during 1st trimester	528	136	26	
Illicit drug use during 1st trimester	527	35	7	
Prenatal vitamin use during 1st trimester	531	517	97	
Primary psychiatric diagnosis				
Bipolar disorder	502	272	54	
Depression	502	99	20	
Anxiety	502	47	9	
Schizophrenia/Schizoaffective disorder	502	18	4	
Psychosis	502	6	1	

primarily through health care provider referrals, consultations at the Massachusetts General Hospital Center for Women's Mental Health, and the Center's website (www.womensmentalhealth.org). All participants in the Registry provide verbal informed consent, and all study procedures were approved by the Massachusetts General Hospital Institutional Review Board.

Participants were interviewed by trained research assistants across pregnancy: at enrollment, 7 months of gestation, and 3 months postpartum. The initial interview ascertains information regarding demographic characteristics, medication use and dosage changes, social habits (i.e., smoking, alcohol consumption, and illicit drug use), medical and psychiatric history, and family history of birth defects. Since the initial interview addresses the use of any supplements or vitamins, women who completed the initial interview between November 14, 2008, and July 7, 2015, were eligible for inclusion in this analysis. Women were specifically asked about the use of any vitamins and supplements.

Results

From November 14, 2008, to July 7, 2015, a total of 544 women were enrolled in the Registry, and $N=534$ women were eligible for this analysis. Ten participants were lost to follow-up for their first interview following enrollment and were therefore considered ineligible for this analysis. The cohort consisted of mostly Caucasian (91 %), married (76 %), and college-educated (61 %) women. The majority of pregnancies followed in this Registry were planned (71 %), and most women had been pregnant at least once prior to the current pregnancy (64 %). Among registry participants, bipolar disorder (54 %) was the most commonly reported primary psychiatric diagnosis, followed by depression (20 %) and anxiety (9 %). Please see Table 1 for further information regarding study participant characteristics.

Approximately half (53.2 %) of the study population was using at least one vitamin or supplement at the time of enrollment. The most common supplements used by the women in the Registry were omega-3 fatty acids (38.0 %), followed by vitamin D (11.0 %), and calcium (8.2 %). All supplements used by participants at baseline, excluding prenatal vitamins and folic acid, are recorded in Table 2.

Table 2 Use of vitamins and supplements in a psychiatrically ill population during pregnancy ($N=534$)

Supplement	Number	Percent
Any supplementation[a]	284	53.2
No supplementation	250	46.8
Omega-3 DHA/EPA	203	38.0
Vitamin D	59	11.0
Calcium	44	8.2
Iron	25	4.7
Probiotic	14	2.6
Vitamin B12	12	2.2
Vitamin B6	9	1.7
Vitamin C	8	1.5
Melatonin	5	0.9
Vitamin B complex	5	0.9
Coenzyme Q10	4	0.7
Cranberry	4	0.7
Biotin	3	0.6
Fiber	3	0.6
Magnesium	3	0.6
Ginkgo biloba	2	0.4
Zinc	2	0.4
Ambrotose	1	0.2
Choline	1	0.2
Colloidal minerals	1	0.2
Flax seed oil	1	0.2
Ganoderma mushroom	1	0.2
Garlic	1	0.2
Ginseng	1	0.2
Iodine	1	0.2
L-Lysine	1	0.2
Magnesium Taurate	1	0.2
Niacin	1	0.2
Riboflavin	1	0.2
Spirulina	1	0.2
St. John's wort	1	0.2
Vitamin B1	1	0.2
Vitamin E	1	0.2

[a] Women taking two or more supplements are included in all applicable categories in the table above

Discussion

In this prospective pregnancy registry designed to assess the effect of in utero atypical antipsychotic use, we found that over half of the participants were taking supplements or vitamins other than prenatal vitamins and folic acid. It is unknown whether the participants' health care providers had recommended or were aware of the supplement use. Therefore, this report underscores the need for active query on the part of health care providers about the use of supplements and non-prescription medications by pregnant women. These data also emphasize the need to obtain rigorous reproductive safety and efficacy data for supplements used by pregnant women and women of reproductive age.

As with prescription medications, prospective data are optimal to inform the risks and benefits of supplements during pregnancy. Prospective registries allow the collection data

regarding confounding variables and increase accuracy over subject recall. US FDA guidelines have recently modified the reproductive safety classification system from a simplified pregnancy letter category to a more comprehensive delineation of available data on fetal exposure. This shift underscores the importance of having high-quality human data to allow women and their health care providers to make individualized risk-benefit assessments for use during pregnancy.

Another aspect that needs to be included in the safety assessment of supplements during pregnancy is purity and quality assurance (Larimore and O'Mathúna 2003). The supplement and vitamin industry is not regulated to the same degree by the US FDA as prescription medications. This raises concerns about whether contents are precisely labeled, and the level of purity or presence of contaminants.

Strengths of this study include prospective assessment, rather than retrospective recall, the study of an important subgroup of women with psychiatric disorders, and active query about the use of supplements and non-prescription treatments. There are also important limitations. Use of supplements was determined by maternal report only, and this was a secondary analysis of a data set designed to assess pregnancy outcomes after exposure to atypical antipsychotic medications. The participants were primarily women with psychiatric disorders, and the majority were married and college educated; therefore, results may not be generalizable to the general population.

Future research is needed to fully assess the use of complementary treatments by pregnant women, including but not limited to supplements. For example, data regarding the use of mind-body therapies, exercise, acupuncture, massage, and other somatic treatments would help us to understand risks and benefits more fully. It is important to characterize whether women meet recommendations for certain guidelines regarding supplementation during pregnancy, such as for folic acid supplementation and exercise. It is essential to delineate potential risks posed during pregnancy of integrative treatments, or lack thereof. Not only is safety impactful, but also demonstration of potential benefits for obstetrical and neonatal outcomes would assist pregnant patients and their health care providers in selecting treatments for indications of use during pregnancy.

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Compliance with ethical standards

Conflict of interest Marlene Freeman has received other research support from GlaxoSmithKline plc, National Institute of Mental Health, Takeda/Lundbeck, Patient Centered Outcomes Research Institute, and the Department of Defense; has received consulting fees from Takeda, Lundbeck, Otsuka, JDS Therapeutics, Genetech Inc., and Johnson & Johnson; and has received medical editing stipends from DSM Nutritionals and GOED Omega-3 Newsletter.

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Ms. Sosinsky and Moustafa declare that they have no competing interests.

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Ethics approval and consent to participate All participants in the Registry provide verbal informed consent, and all study procedures were approved by the Massachusetts General Hospital Institutional Review Board.

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