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RESEARCH ARTICLE

Maternal medicine

Symptoms of postural orthostatic tachycardia syndrome in pregnancy: a cross-sectional, community-based survey

Kate M. Bourne[1] | Kara A. Nerenberg[1,2] | Lauren E. Stiles[3,4] | Cyndya A. Shibao[5] | Luis E. Okamoto[5] | Emily M. Garland[5] | Alfredo Gamboa[5] | Amanda Peltier[5] | André Diedrich[5] | Italo Biaggioni[5] | Robert S. Sheldon[1] | Paul S. Gibson[2,6] | Angela J. Kealey[1] | Satish R. Raj[1,5]

[1]Department of Cardiac Sciences, Libin Cardiovascular Institute, University of Calgary, Calgary, Alberta, Canada

[2]Department of Medicine, University of Calgary, Calgary, Alberta, Canada

[3]Stony Brook University School of Medicine, Stony Brook, New York, USA

[4]Dysautonomia International, East Moriches, New York, USA

[5]Vanderbilt Autonomic Dysfunction Center, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[6]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Alberta, Canada

Correspondence
Satish R. Raj, HRIC GAC70, 3280 Hospital Dr NW, Calgary, AB T2N 4Z6, Canada.
Email: satish.raj@ucalgary.ca

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Abstract

Objective: To evaluate the relationship between postural orthostatic tachycardia syndrome (POTS) and pregnancy.

Design: Cross-sectional survey.

Setting: International.

Sample: A total of 8941 female patients with a diagnosis of POTS.

Methods: Data from the survey were analysed using descriptive measures and stratified for comparisons.

Main outcome measures: Symptom course of POTS during pregnancy. Secondary outcomes included pregnancy loss, POTS onset during pregnancy and the impacts of a comorbid diagnosis of Ehlers–Danlos syndrome or an autoimmune disorder on symptoms during pregnancy.

Results: Overall, 40.8% (n = 3652) of participants reported one or more pregnancies. Most participants experienced worsening of symptoms in the first (62.6%) and third (58.9%) trimesters and 3 months after pregnancy (58.7%), and 81.1% experienced worsening symptoms at any point in their pregnancy. Most participants with worsening symptoms in the first trimester also experienced worsening symptoms in the second (61.6%) and third (68.1%) trimesters, but if they improved in the first trimester then this improvement persisted in the second and third trimesters. Of participants who reported that POTS was triggered by a specific event (41.3%), 8.1% reported pregnancy as the trigger for the onset.

Conclusions: Postural orthostatic tachycardia syndrome symptoms in the first trimester of pregnancy may help predict symptom course throughout the duration of pregnancy. Some individuals may experience an initial onset of POTS during pregnancy. This novel information may guide clinicians in counselling patients with POTS who are planning pregnancy.

KEYWORDS
autoimmune disorder, Ehlers–Danlos syndrome, first trimester, gestation, postural orthostatic tachycardia syndrome, pregnancy, survey, symptoms

1 | INTRODUCTION

Postural orthostatic tachycardia syndrome (POTS) is a syndrome of heterogenous aetiology leading to chronic orthostatic intolerance.[1] Individuals with POTS experience an increase in heart rate of ≥30 bpm (or ≥40 bpm if 12–19 years of age) within 10 min of standing, in association with chronic orthostatic symptoms lasting at least 3 months or longer, and in the absence of orthostatic hypotension (≥20/10 mmHg decrease in blood pressure within 3 min of upright posture).[2,3]

This article includes Author Insights, a video abstract available at: https://players.brightcove.net/3806881048001/default_default/index.html?videoId=6319977749112

POTS primarily affects females of reproductive age, and although the true prevalence is unknown, it is estimated to affect up to 1% of the North American population.[4]

Despite a primarily female demographic, there are minimal data evaluating the impact of POTS on pregnancy or the impact of pregnancy on POTS. Literature regarding POTS and pregnancy is limited, in part, by small sample sizes.[5,6] Some studies report an overall improvement in POTS symptoms throughout the course of pregnancy,[7,8] but with variable symptom response. These studies were of small sample size, making it difficult to generalize findings and translate them to clinical care. Further, a significant minority of patients with POTS are also diagnosed with a range of autoimmune disorders,[9] as well as Ehlers–Danlos Syndrome (EDS), a systemic connective tissue disorder (although the underlying mechanism of these relationships has not yet been identified identified),[9–11] which may both impact pregnancy.

Using a cross-sectional, community-based online survey of patients with POTS, this study aimed to evaluate the impact of pregnancy on POTS: specifically, the symptom course of POTS during pregnancy, and the impacts of either autoimmune disorders or EDS on the symptom course of POTS in pregnancy. In addition, differences between patients who identified pregnancy as the event leading to the initial onset of POTS and those who did not were also evaluated. Together, these findings may aid clinicians in the management of patients with POTS who are pregnant or who are considering pregnancy.

2 | METHODS

2.1 | Survey design and delivery

A comprehensive questionnaire was developed in partnership between Vanderbilt University Medical Center (Nashville, TN, USA) and Dysautonomia International (New York, USA), a patient advocacy group. Members of Dysautonomia International's Patient Advisory Board were engaged to help develop and test the questionnaire in an iterative process.[9] All questions about the impact of POTS on pregnancy were included (Table S1), as there are no core outcome sets for research on POTS in pregnancy. The survey was written in English and delivered in an online format. Participants reported that the time taken to complete the survey was 45–90 minutes, and they had the option to save the survey and return later. Questionnaire results were stored in a secure Research Data Capture (REDCap) electronic database at Vanderbilt University.[12] This is a retrospective study. This study received ethics approval from both the Vanderbilt University Institutional Review Board (IRB#140303) and the University of Calgary Conjoint Health Research Ethics Board (REB15-2922).

2.2 | Study participants

The inclusion criteria were a self-reported physician diagnosis of POTS and the ability to complete an English language survey on an electronic device using an internet connection. Patients with POTS were recruited primarily through Dysautonomia International's website and social media channels. Patients with POTS provided electronic informed consent (or parent/guardian consent in addition to participant assent if the patients were <18 years of age) to complete the survey.

2.3 | Analysis

Survey data collected between July 2015 and June 2022 were included in this analysis. Data were exported from REDCap and imported into SPSS Statistics 28 (IBM, Armonk, NY, USA) for analysis.[12] patients with POTS were included in this analysis if they indicated that their biological sex at birth was female, were post-menarche and disclosed their pregnancy history. Participants were excluded from the 'comorbidity analysis' if they did not respond to the comorbidities section of the survey. Patients with POTS were excluded from the total number of respondents to each question if they did not answer a question or answered 'prefer not to say'. Participants who answered 'not applicable (N/A)' or 'not sure' regarding questions on pregnancy symptoms were excluded from those analyses. Participants who indicated a diagnosis of one of more autoimmune disorders (Table S2) were grouped into a composite autoimmune variable (POTS + AI). Participants who did not report a diagnosis of an autoimmune disorder were grouped as POTSnoAI. Participants with diagnoses of both EDS (POTS + EDS) and POTS + AI were grouped together in a composite POTS + EDS + AI variable and compared with participants without EDS and AI (POTSnoEDSnoAI). Symptom comparisons among participants with POTS + EDS and POTSnoEDS, participants with POTS + AI and POTSnoAI, and participants with and without the onset of POTS during/after pregnancy, excluded any participants who gave 'N/A' and 'not sure' responses. Specific numbers of patients who responded to the individual questions are reported. Continuous data are presented as means ± standard errors of the mean. Categorical data are presented as percentages and number of participants who answered each question, or percentages only, if the number of participants is included in a table or figure.

2.4 | Statistical analyses

Descriptive analyses including total number and percentage of participants for categorical variables and measures of central tendency for continuous variables were performed. Wilcoxon rank sum tests were conducted to evaluate differences between group of patients with POTS (i.e. POTS + EDS and POTSnoEDS, POTS + AI and POTSnoAI, POTS + EDS + AI and POTSnoEDSnoAI, and those with and without initial POTS onset during pregnancy), for nonparametric continuous variables. Pearson's chi-square tests were conducted to evaluate differences between these groups for

categorical variables. Symptom responses with categories of 'better', 'same' or 'worse' were grouped into two categories: 'better/same' or 'worse', for statistical comparisons; $p < 0.05$ was considered statistically significant.

2.5 | Patient and public involvement

The study questionnaire was developed by Vanderbilt University in partnership with Dysautonomia International. Members of Dysautonomia International's Patient Advisory Board participated in the development of the questionnaire to ensure that questions were relevant to patients and reflected patient priorities. Dysautonomia International reviewed the study results and helped to identify the key results to highlight in this article, as well as relevant points to include in the discussion. Dysautonomia International will also assist with knowledge translation, through sharing the study results to the patient community and members of the public.

3 | RESULTS

3.1 | Participants

A total of 14 455 participants consented to complete the survey (Figure 1). Participants who did not report a physician diagnosis of POTS and those who reported their biological sex as male were excluded. Participants were also excluded if they were pre-menarche, did not disclose their menstrual status or did not disclose their pregnancy history. A total of 8941 female, post-menarche patients with POTS and with a known pregnancy history were included in this analysis.

3.2 | Patient demographics and comorbidities

The majority of participants were white (93.3%), non-Hispanic (95.2%) and 18 years of age or older (90.7%) (Table S3). The mean age at the onset of POTS symptoms was 20.8 ± 0.1 years. POTS + EDS was reported in 25.4% of participants. POTS + AI was reported by 17.1% of participants. POTS + EDS + AI was reported by 5.6% of participants.

3.3 | Symptoms

Commonly reported symptoms in this study cohort (at the time of survey completion) included light-headedness (99.0%), tachycardia/palpitations (97.4%), headache (95.2%), difficulty concentrating (94.6%) and presyncope (94.0%; Table S3). A more in-depth analysis of symptom profiles in individuals with physician-confirmed POTS who responded to this survey was recently published by Shaw et al.[9]

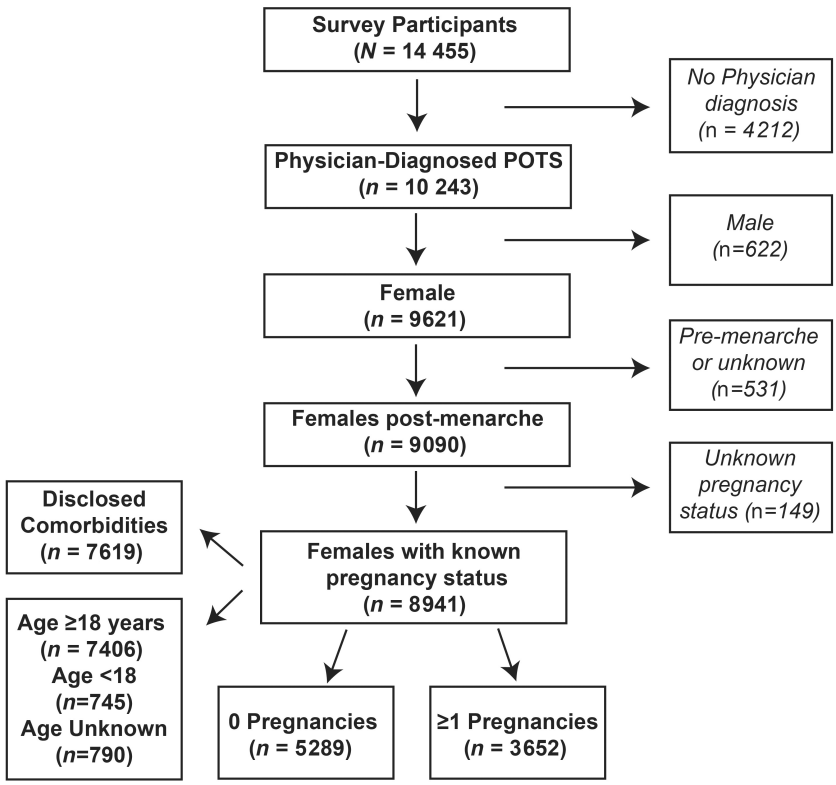

FIGURE 1 Participant flow diagram. A total of 8941 females with a physician diagnosis of postural orthostatic tachycardia syndrome (POTS) participated in this analysis.

TABLE 1 Mean number of pregnancies, live births and pregnancy losses in POTS + EDS, POTS + AI and POTS + EDS + AI.

		Pregnancies		Live births		Pregnancy losses	
Group	**Comparison**	**Mean**	***p***	**Mean**	***p***	**Mean**	***p***
POTS + EDS	POTS + EDS	2.80 ± 0.07	0.9	1.80 ± 0.04	0.003	0.93 ± 0.06	0.001
	POTSnoEDS	2.72 ± 0.03		1.95 ± 0.02		0.74 ± 0.03	
POTS + AI	POTS + AI	2.95 ± 0.07	0.005	2.00 ± 0.05	0.08	0.93 ± 0.07	<0.001
	POTSnoAI	2.69 ± 0.03		1.9 ± 0.02		0.75 ± 0.03	
POTS + EDS + AI	POTS + EDS + AI	2.91 ± 0.14	0.3	1.78 ± 0.08	0.1	1.11 ± 0.1	<0.001
	POTSnoEDSNoAI	2.66 ± 0.04		1.91 ± 0.03		0.71 ± 0.03	

3.4 | Pregnancies

In total, 3652 patients (40.8%) reported one or more pregnancies. Among patients with POTS who had been pregnant at least once, the mean number of pregnancies was 2.73 ± 0.03. Overall, 89.3% of participants reported one or more live births (mean 1.91 ± 0.02/patient) and 44.2% of participants reported one or more pregnancy losses (mean 0.78 ± 0.02/patient).

Fewer patients with POTS + EDS (36.9%) had been pregnant compared with patients with POTSnoEDS (42.0%) ($p < 0.001$; Table S4). Patients with POTS + EDS had fewer live births and more pregnancy losses than patients with POTSnoEDS. The mean number of pregnancies was similar (Table 1). More patients with POTS + AI (52.4%) had been pregnant compared with patients with POTSnoAI (38.3%) ($p < 0.001$). Patients with POTS + AI had more pregnancies and more pregnancy losses than patients with POTSnoAI. Live births were similar between POTS + AI and POTSnoAI (Table 1). Patients with POTS + EDS + AI had more pregnancy losses than patients who with POTSnoEDSnoAI (Table 1). The number of pregnancies and live births did not differ between these groups.

3.5 | POTS symptom course during pregnancy

A summary of the question structure is provided in Table S1. Overall, a significant proportion of participants reported N/A for their POTS symptoms during pregnancy: first trimester, 39.9% (1446 of 3620); second trimester, 45.2% (1631 of 3612); third trimester, 45.5% (1641 of 3603); post-pregnancy, 43.4% (1565 of 3608); and with subsequent pregnancies, 54.7% (1963 of 3586).

Excluding participants who reported N/A during pregnancy, the majority of patients with POTS experienced a worsening of POTS symptoms in the first trimester (62.6%) and in the third trimester (58.9%), when compared with their typical POTS symptoms (Table 2). In the second trimester, just under half of patients experienced a worsening of symptoms (48.2%) compared with typical POTS symptoms. In contrast, a significant minority of participants experienced an improvement in their POTS symptoms during the first (20.0%), second (34.8%) and third (26.4%) trimesters.

TABLE 2 Postural orthostatic tachycardia syndrome (POTS) symptoms during and after pregnancy, and with subsequent pregnancies, compared with POTS symptoms prepregnancy.

Time frame	**Improved POTS symptoms (%)**	**Same POTS symptoms (%)**	**Worse POTS symptoms (%)**
First trimester (T1) (total *n* = 1606)	20.0	17.3	62.6
Second trimester (T2) (total *n* = 1511)	34.8	17.0	48.2
Third trimester (T3) (total *n* = 1518)	26.4	14.7	58.9
Post-pregnancy (total *n* = 1636)	24.8	16.5	58.7
Subsequent pregnancies (total *n* = 1065)	12.0	35.4	52.6

Most participants who experienced improved POTS symptoms during the first trimester (*n* = 271) also experienced improved POTS symptoms in the second (77.1%; Figure 2A) and third trimesters (62.7% Figure 2B). Conversely, most participants who experienced a worsening of POTS symptoms in the first trimester (*n* = 683) experienced a continued worsening of POTS symptoms in the second (61.6%; Figure 2C) and third (68.1%; Figure 2D) trimesters, relative to their baseline prepregnancy POTS symptoms.

Of participants who experienced no change in POTS symptoms during the first trimester (*n* = 250), 46.4% continued to have no change during the second trimester, whereas 37.2% experienced a worsening of symptoms. In the third trimester, 52.8% of participants with no change in POTS symptoms during the first trimester experienced a worsening of symptoms. Overall, 81.1% of participants (*n* = 1138) experienced a worsening of their POTS symptoms at some point during pregnancy.

A majority of patients also reported a worsening of their POTS symptoms during the 3 months after delivery, when compared with their typical prepregnancy POTS symptoms (58.7%; Table 2). Furthermore, a majority of patients with POTS and multiple pregnancies reported that their symptoms worsened during subsequent pregnancies, when compared with symptoms during their earlier pregnancies (52.6%).

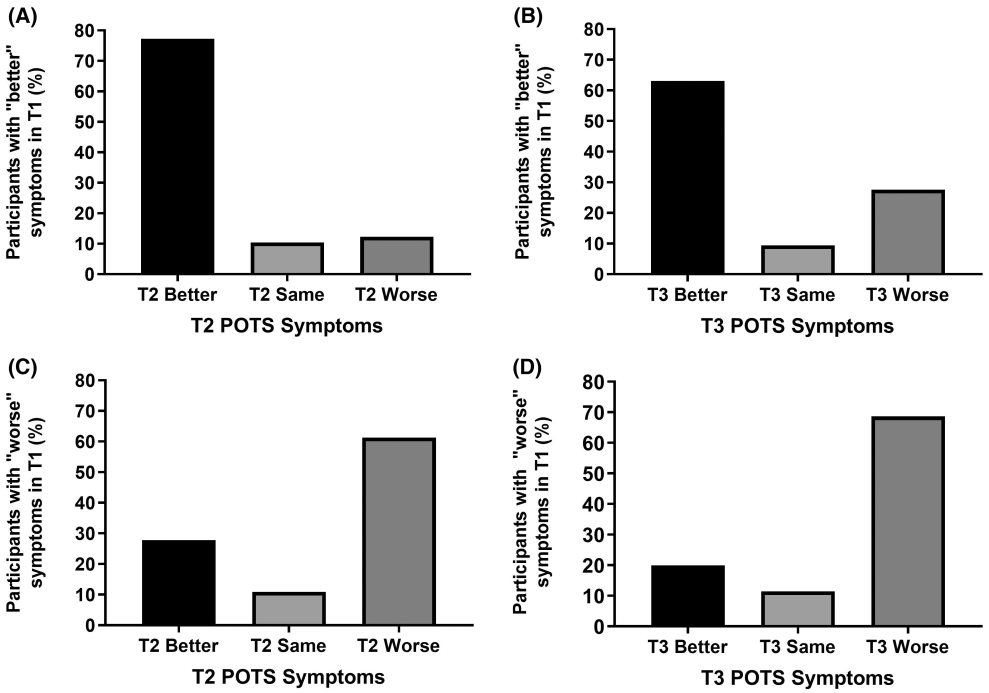

FIGURE 2 (A, B) Postural orthostatic tachycardia syndrome (POTS) symptoms in the second trimester (T2) and third trimester (T3) for participants who had better POTS symptoms in the first trimester (T1), compared with prepregnancy POTS symptoms. (C, D) Symptoms in T2 and T3 for participants who had worse POTS symptoms in T1, compared with prepregnancy POTS symptoms.

There was no statistically significant difference in the worsening of symptoms between POTS + EDS patients and POTSnoEDS patients at any point in pregnancy, or with subsequent pregnancies (Table S5). A larger proportion of patients with POTS + EDS (63.4%) had worse POTS symptoms during the postpartum period than patients with POTSnoEDS (56.6%) (p = 0.02). There were no statistically significant differences in the worsening of symptoms between patients with POTS + AI and patients with POTSnoAI at any point in pregnancy, during the postpartum period or in subsequent pregnancies (Table S6).

3.6 | Initial onset of POTS during pregnancy

Overall, 41.3% of patients with POTS reported that POTS symptoms started within 3 months of a 'specific event' (Table S7). Of those patients, 8.1% reported that their initial onset of POTS was during or within 3 months of (during/after) pregnancy. Similar proportions of patients with POTS + EDS and patients with POTSnoEDS (8.0%) reported that the initial onset of POTS was during/after pregnancy (p = 0.8). This is equivalent to 3.1% of all participants with POTS + EDS, and 3.4% of all participants with POTSnoEDS. Similar proportions of patients with POTS + AI (7.0%) and patients with POTSnoAI (8.3%) reported that the initial onset of POTS was during/after pregnancy (p = 0.3). This is equivalent to 3.1% of all participants with POTS + AI and 3.4% of all participants with POTSnoAI.

The mean number of pregnancies (2.70 ± 0.09 per patient vs 2.74 ± 0.03 per patient, p = 1.0) did not differ between patients who reported pregnancy as a trigger for their initial onset of POTS and those who did not. However, the mean number of live births was higher (2.06 ± 0.06 per patient vs 1.89 ± 0.02 per patient, p = 0.02) and the mean number of pregnancy losses was lower (0.66 ± 0.08 per patient vs 0.79 ± 0.02 per patient, p = 0.009) in patients with POTS who reported the onset of POTS during/after pregnancy.

Participants who reported the initiation of POTS symptoms during/after pregnancy were more likely to have worsening symptoms in the second (62.5% vs 46.7%, $p < 0.001$) and third (68.0% vs 58.2%, p = 0.01) trimesters of pregnancy, compared with participants with POTS not triggered during/after pregnancy. The rates of worsening symptoms in the first trimester did not differ between the two groups (66.7% vs 62.2%, p = 0.3). Post-pregnancy symptoms were also more likely to be worse in the group with the onset of POTS during/after pregnancy (67.8% vs 56.7%, p = 0.002), as well as with subsequent pregnancies (69.2% vs 50.2%, $p < 0.001$), compared with those without the onset of POTS during/after pregnancy. A summary of symptom responses in participants who reported the onset of POTS during/after pregnancy is shown in Table S8.

4 | DISCUSSION

4.1 | Main findings

This is the largest evaluation of pregnancy symptoms in females with POTS, with 3652 females reporting one of more pregnancies. Most participants reported that their POTS

symptoms worsened in the first and third trimesters of pregnancy, with just under half reporting a worsening of symptoms in the second trimester, compared with baseline. Among those who experienced improved POTS symptoms in the first trimester, most continued to have improved POTS symptoms throughout the pregnancy. Conversely, most participants with worsening POTS symptoms in the first trimester had continuing worsened symptoms in the second and third trimesters. The trajectory of POTS symptoms in the first trimester may inform prognosis regarding POTS symptoms throughout the remainder of the pregnancy. Most participants also reported a worsening of POTS symptoms in the postpartum period and during subsequent pregnancies. Some individuals experienced a new onset of POTS during or shortly after pregnancy.

4.2 | Strengths and limitations

This international evaluation of POTS in pregnancy is approximately 50 times larger than prior studies,[5–8,13–15] and provides a more comprehensive assessment of the patient experience of POTS and pregnancy than past studies. The results of this large survey may aid clinicians in the counselling patients with POTS who are pregnant or are considering pregnancy.

As these survey data were self-reported, both misclassification and selection biases are possible. Patients with POTS self-reported a physician diagnosis of POTS. Therefore, it is possible that the specific diagnostic criteria may not have been met for each participant. Patients with POTS could have also reported inaccurate information, although there would be little motivation for intentional misrepresentation. The time between pregnancy and the time of survey completion was also variable and could have led to a recall bias. Many participants are likely to have been pregnant before they developed POTS. A not applicable (N/A) option was included in the symptom questions, allowing each participant to indicate that POTS symptoms were not applicable to their pregnancy.

Participants were primarily recruited through online social media. Although the use of social media is very common, not everyone will have been aware of the survey. Participants in the survey had to be able to read English or had the resources for translation. These two factors may have reduced the representativeness of the study population, and the generalisability of the results.

4.3 | Interpretation

4.3.1 | Symptom course

Common POTS symptoms are detailed in the first article published on this survey.[9] A systematic review of POTS and pregnancy found that POTS symptoms worsened during the first trimester and improved during the second trimester, with variable symptom course in the third trimester,[5] which are consistent with our findings. Kimpinski et al. found worse symptoms of orthostatic intolerance in the first trimester, with improvement in the second and third trimesters, in a group of 51 patients with POTS.[8] Kanjwal et al. studied 22 patients with POTS, reporting that 55% had improved POTS symptoms, 13% had no change in symptoms and 31% had worsening POTS symptoms throughout their pregnancies.[7] Another small study of ten patients with POTS found 40% with worse POTS symptoms, 20% with unchanged symptoms and 40% with improved symptoms throughout the overall pregnancy.[13] We are able to provide a broader assessment of symptom course throughout pregnancy as a result of our much larger study sample.

4.3.2 | Initial onset of POTS during pregnancy

Pregnancy losses were lower in participants who reported that the initial onset of POTS was during or within 3 months after pregnancy. The reason for this is unknown. It is possible that patients who developed POTS during or shortly after pregnancy could have avoided future pregnancies. Alternatively, they could have managed their future pregnancies more closely, reducing the risk of pregnancy loss. Participants whose onset of POTS was during/after pregnancy were more likely to have worsening symptoms in their second and third trimesters as well as worsening symptoms with subsequent pregnancies, compared with patients without the onset of POTS during pregnancy. The onset of POTS during/after pregnancy may lead to more significant POTS symptoms throughout the entire pregnancy and during the postpartum period.

4.3.3 | Pregnancies

One or more pregnancies were reported by 41% of participants. At least one pregnancy loss was reported by 44.2% of participants who had been pregnant, with a mean of 0.78 ± 0.02 pregnancy losses per patient. A similar proportion of pregnancy losses (43%) was reported in a large study in Israel.[16] A study of 51 patients with POTS found a much lower pregnancy loss rate of 7% (eight losses out of 116 total pregnancies) among 10% of all participants (five of 51),[8] much lower than the 44% of participants in this current survey. Our large sample size may more accurately reflect the actual pregnancy loss rate with POTS of 0.78 ± 0.02 per patient.

4.3.4 | Comorbid EDS

Ehlers–Danlos Syndrome (EDS) was present in 25% of females with POTS, similar to prior studies.[11] Hypermobile EDS is most commonly associated with POTS.[10] Symptoms during pregnancy were similar among patients with POTS whether or not they had EDS. A larger proportion of POTS + EDS reported worse POTS symptoms in the postpartum period.

Patients with POTS + EDS had higher rates of pregnancy losses prior to 24 weeks of gestation than participants without EDS. Previously, small studies have provided conflicting results regarding pregnancy loss and EDS.[17,18]

4.3.5 | Comorbid autoimmune disorders

One or more comorbid autoimmune disorders were reported by 17.1% of participants. The course of POTS symptoms during pregnancy did not differ between patients with POTS with or without an autoimmune disorder. However, patients with POTS with autoimmune disorders had both higher rates of pregnancies and pregnancy losses. Increased risk of pregnancy loss has been documented in several autoimmune diseases.[19,20]

4.3.6 | Implications for clinical care

Clinicians should screen patients with POTS for EDS and autoimmune conditions commonly seen in POTS (including coeliac disease, Hashimoto's thyroiditis, lupus, rheumatoid arthritis and Sjogren's syndrome), and these conditions should be optimally treated as well as possible before or early in pregnancy in an effort to reduce the risk of pregnancy loss. Patients with POTS contemplating pregnancy should be advised that their POTS symptoms are likely to worsen during pregnancy. Clinicians should work with patients to optimise treatment and reduce symptoms as much as possible both prior to and during pregnancy, including medications that are not contraindicated during pregnancy, and non-pharmacological treatments to decrease the symptom burden.[2,21] Prevention of syncope is especially important.[22]

5 | CONCLUSION

This study, which could not have happened without the partnership with Dysautonomia International, reports on a large sample of patients with POTS, characterizing their symptom course during pregnancy. Most patients with POTS experience a worsening of POTS symptoms during pregnancy. POTS symptoms in the first trimester of pregnancy may help predict the course of symptoms throughout the duration of pregnancy. Some individuals may experience an initial onset of POTS during pregnancy. Comorbid EDS or autoimmune disorders may put patients with POTS at increased risk of pregnancy loss. Additional research is needed to understand the reasons for the worsening of POTS symptoms during pregnancy, and to develop the evidence base to improve clinical care for patients with POTS during pregnancy.

AUTHOR CONTRIBUTIONS

LES and SRR planned and developed the survey, with feedback from CAS, LO, EMG, AG, AP, AD, and IB. LES performed the survey recruitment. KMB performed the data analysis for this article. KMB drafted the article, with editing feedback from KAN, LES, CAS, LO, EMG, AG, AP, AD, IB, RSS, AJK, PSG, and SRR.

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CONFLICT OF INTERESTS STATEMENT

KMB, KAN, LES, CAS, LEO, EMG, AG, AD, AJK and PSG, have no conflicts of interest to report. AP is a consultant for Alnylam, Catalyst, and Argenx. IB is a consultant for Theravance Biopharma Inc., Ammeal Pharmaceuticals, Regeneron, and Takeda Pharmaceutical. RSS is a Cardiac Arrhythmia Network of Canada (CANet) Network Investigator. SRR is a consultant for Lundbeck NA Ltd. Theravance Biopharma Inc., Amneal Pharma, Servier Affaires Medicales, Regeneron, and argenx BV, is the chair for the Data Safety and Monitoring Board for Arena Pharmaceuticals, is a CANet Network Investigator, and is a member of the Medical Advisory Board of Dysautonomia International and PoTS UK, both without financial compensation. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information for this article.

ETHICS APPROVAL

This study received ethical approval from both the Vanderbilt University Institutional Review Board (IRB#140303) and the University of Calgary Conjoint Health Research Ethics Board (REB15-2922).

ORCID

Kate M. Bourne https://orcid.org/0000-0002-8355-0002
Kara A. Nerenberg https://orcid.org/0000-0003-3243-5765

Lauren E. Stiles https://orcid.org/0000-0002-2090-3149
Cyndya A. Shibao https://orcid.org/0000-0002-4518-6801
Luis E. Okamoto https://orcid.org/0000-0001-6914-7287
Emily M. Garland https://orcid.org/0000-0001-9525-2929
Alfredo Gamboa https://orcid.org/0000-0002-8676-687X
Amanda Peltier https://orcid.org/0000-0003-1097-7715
André Diedrich https://orcid.org/0000-0001-5643-0294
Italo Biaggioni https://orcid.org/0000-0001-7667-7083
Robert S. Sheldon https://orcid.org/0000-0003-0742-8379
Satish R. Raj https://orcid.org/0000-0002-5890-3785

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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