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Postural orthostatic tachycardia syndrome and orthostatic hypotension in post-acute sequelae of COVID-19 during pregnancy: a case report

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Background Patients with post-acute sequelae of COVID-19 (PASC) often experience the addition of new symptoms after recovery from COVID-19 illness. These may include orthostatic intolerance and autonomic dysfunction, and postural orthostatic tachycardia syndrome has been described to occur in a proportion of patients with PASC.

Case summary In this report, we present a 32-year-old pregnant woman (G3P2) who experiences severe orthostatic symptoms as part of her PASC syndrome, which is decoupled from normal physiologic changes of pregnancy. At 25 weeks of gestation, she was evaluated for increasing episodes of dyspnoea, marked tachycardia with minimal exertion, intermittent non-exertional chest pain, and pre-syncope. This patient had a moderate course of COVID-19 at 12 weeks of gestation, for which she received monoclonal antibody therapy (casirivimab/imdevimab). The patient then had complete resolution of COVID-19 symptoms and felt well for 1 month prior to developing orthostatic symptoms at 25 weeks of gestation. Evaluation with a NASA Lean Test revealed marked orthostatic tachycardia, as well as delayed orthostatic hypotension. Given her COVID-19 illness 4 months prior, PASC involving autonomic dysfunction was diagnosed.

Discussion Patients with orthostatic symptoms in PASC should be carefully evaluated with dedicated active stand tests, such as the NASA Lean Test, to characterize the autonomic response to standing. In pregnant patients, an understanding of normal pregnancy physiology is crucial to correctly identify abnormal findings in such tests.

Keywords Hypotension • Tachycardia • 10 min NASA Lean Test • Pregnancy • Autonomic dysfunction • Case report

ESC Curriculum 5.1 Palpitations • 6.1 Symptoms and signs of heart failure

Learning points

- Active stand tests such as the NASA Lean Test should be considered in making a diagnosis of postural orthostatic tachycardia syndrome or orthostatic hypotension, including during pregnancy, to help determine appropriate treatment plans.
- An understanding of normal pregnancy physiology is important to interpret the results of active stand tests in pregnant patients.

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Primary specialties involved other than cardiology

'Obstetrics and Gynecology' is the other primary speciality involved.

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a clinical syndrome of orthostatic intolerance characterized by symptoms such as light-headedness and palpitations occurring when standing, accompanied by increased heart rate >30 b.p.m. and absence of orthostatic hypotension.[1,2] Postural orthostatic tachycardia syndrome has recently been identified in ~20% of patients with post-acute sequelae of COVID-19 (PASC). Autonomic changes are also seen in pregnancy, and diagnosing these conditions in pregnant patients may be more challenging. Utilizing diagnostic testing such as the NASA Lean Test can give insight into an individual's physiology by capturing late autonomic responses and helping to inform pharmacologic therapy that successfully addresses POTS symptoms while maintaining fetal safety during pregnancy.

Timeline

8 weeks of gestation	• A 32-year-old Caucasian female presented for her first obstetrics visit. • The patient had two prior full-term pregnancies, with gestational ages of 38 weeks and 41 weeks. The first child was born with neurogenic bilateral club feet.
12 weeks of gestation	• Patient presented for COVID-19 illness. • Patient was given monoclonal antibodies before discharge.
25 weeks of gestation	• Patient evaluated for increasing episodes of dyspnoea, resting tachycardia with minimal exertion, and intermittent non-exertional chest pain.
29 weeks of gestation	• A diagnosis of postural orthostatic tachycardia syndrome with delayed orthostatic hypotension was made after NASA lean testing. • Treatment began with midodrine 5 mg orally three times daily and metoprolol tartrate 6.25 mg orally twice daily, which was increased to 12.5 mg twice daily after 2 days.
31 weeks of gestation	• Heart rate improved but she still had symptomatic hypotensive episodes.
32 weeks of gestation	• Metoprolol tartrate was then increased to 25 mg every morning and 12.5 mg in the evening.
33 weeks of gestation	• Patient still experienced episodic light-headedness and hypotension with a heart rate increase from supine to standing. • Recommendation included metoprolol tartrate at 25 mg every morning and 12.5 mg in the evening, and midodrine at 5 mg twice daily, both medications to be taken throughout labour and delivery.
37 + 2 weeks of gestation	• Patient had an uncomplicated birth of a healthy baby girl. • NASA Lean Test was performed 30 h post-partum. She still had a tachycardic response to postural change, but her blood pressure remained stable.
3–6 months post-partum	• Patient stable with minimal change in heart rate and blood pressure from postural change.

Case summary

Patient presentation

A 32-year-old Caucasian female (G3P2) at 25 weeks of gestation was evaluated for increasing episodes of dyspnoea, tachycardia up to 160 b.p.m. with minimal exertion, intermittent non-exertional chest pain, and presyncope. This patient had COVID-19 at 12 weeks of gestation and then had complete resolution of COVID-19 symptoms and felt well for 1 month prior to developing these orthostatic symptoms.

The patient's pregnancy was complicated by a moderate course of COVID-19 at 12 weeks of gestation, and she presented to the emergency department with SpO_2 89% on room air, heart rate at 148 b.p.m., cough with exertion, and anosmia with hypogeusia. Before discharge, she was given casirivimab/imdevimab therapy.

At 25 weeks of gestation, a transthoracic echocardiogram revealed normal right and left ventricular function, and a workup for pulmonary embolism was negative. On physical examination, blood pressure was 116/68 mmHg, heart rate was 107 b.p.m., respiratory rate was 18 breaths/min, and SpO_2 was 100% on room air. She had a tachycardic but regular rhythm, no murmurs, rubs, or gallops, and no jugular venous distension.

Obstetric history included two prior full-term vaginal births. Previous diagnoses include obesity (current weight of 99.8 kg, body mass index 32.5 kg/m^2), a peripheral nerve disorder (neurogenic club feet as a child which did not require surgical intervention), gastroesophageal reflux disorder, and exercise-induced asthma as a child. The patient is an upper/middle-class woman currently working as an oncology nurse.

The patient had an uncomplicated birth of a healthy baby girl at 37 + 2 weeks after induction of labour for premature rupture of membranes. Three months following the birth, the patient remained in stable condition with minimal changes in heart rate and blood pressure as a result of postural change. In the months following the pregnancy, the patient remained on the same medication regimen of metoprolol tartrate and midodrine as recommended immediately following birth.

In light of the physiological changes of pregnancy and new-onset cardiovascular symptoms, the differential diagnoses included new-onset cardiomyopathy and pulmonary embolism. Other potential diagnoses included coronary artery disease, spontaneous coronary artery dissection, and anaemia. Her haemoglobin was 12.4 g/dL, and serum troponin I was undetectable. When considering her presenting symptoms including orthostatic intolerance, episodic exertional dyspnoea, and intermittent chest pain following a COVID-19 illness 4 months prior, PASC involving autonomic dysfunction was a possibility.

Work up

Chest computed tomography angiography imaging from 25 weeks of gestation showed no filling defects to suggest pulmonary emboli. There was no reflux of contrast into the intrahepatic inferior vena cava to suggest elevated right heart pressures. The heart size was normal without pericardial thickening or effusion.

A transthoracic echocardiogram demonstrated normal left ventricle size, wall thickness, wall motion, and systolic and diastolic function. Chest X-ray at 25 weeks performed due to complaints of shortness

Figure 1 NASA Lean Test at 29 weeks of gestation. (*A*) Systolic and diastolic blood pressure, and (*B*) heart rates measured at supine and standing positions over 10 min to confirm delayed orthostatic hypotension, with a marked drop in her blood pressure not seen until the 10th minute of standing upright. Mild shortness of breath observed from standing 2 min to standing 5 min. Slight light-headedness with mild shortness of breath observed from standing 6 min to standing 9 min. Dizziness, feeling flushed, black spots in vision observed at standing 10 min.

of breath showed faint patchy densities in the left base with a normal cardiomediastinal silhouette.

A comprehensive metabolic panel taken at 25 weeks of gestation revealed no electrolyte abnormalities, normoglycemia, and normal TSH levels. No further thyroid studies were done afterwards. All other metabolic panels throughout the course of the pregnancy were normal in terms of electrolytes, blood sugar, and TSH levels.

A NASA Lean Test was performed at 29 weeks (*Figure 1*). This active stand test measures heart rate and blood pressure while the patient is supine and then upright leaning against a wall for over 10 min. Recently,

this test served as a point-of-care method aiding in the diagnosis and treatment of myalgic encephalomyelitis/chronic fatigue syndrome.[3] The test is a variant of NASA research testing for orthostatic intolerance and became a superior measure of orthostatic tolerance by reducing muscular influences on venous return.[4] This test was initially used as opposed to orthostatic tests such as the tilt table test or the sit-to-stand test because we were evaluating for delayed orthostatic hypotension, which could be missed on another testing.

The results from the NASA Lean Test revealed a marked increase in heart rate by >30 b.p.m., from 115 b.p.m. supine to a maximum heart rate of 148 b.p.m. at the 10th minute of standing upright. Notably, while she was normotensive at baseline and for the first 9 min of the upright position, she became acutely hypotensive to 77/49 mmHg at the 10th minute. During testing, she developed symptoms of dyspnoea after standing for 2 min, light-headedness at 6 min, and then dizziness, faintness, and flushing at the 10th minute.

Management

Based on the NASA Lean Test results, a diagnosis of postural orthostatic tachycardia with delayed orthostatic hypotension was made, and treatment began with midodrine 5 mg orally three times daily to prevent hypotensive episodes. Given the marked orthostatic tachycardia, she was also started on low-dose metoprolol tartrate (6.25 mg orally twice daily), which was uptitrated to 12.5 mg twice daily after 2 days. She was counselled to wear compression socks and increase hydration with electrolyte powder and water. While traditionally patients with orthostatic symptoms are counselled to increase sodium intake, this was avoided due to concerns of unwanted hypertension with pregnancy and concomitant midodrine use.

The Heart Rhythm Society Expert Consensus Statement recognizes that treatment of POTS is inherently difficult due to a lack of any therapy having uniform success and the need for combination therapy.[1] This case explores the use of combination therapy further. Fludrocortisone is recommended for those with hypovolemia to increase sodium retention and expand the volume, but this effect might only last a few days.[1] For that reason, in combination with wanting to avoid hypertension with midodrine use as mentioned previously, this medication was not used. Midodrine use was in line with guideline recommendations to avoid orthostatic tachycardia and increase venous return, with daytime usage to avoid supine hypertension.[1] Beta-blockers have been recommended to lower standing heart rate and reduce symptoms of tachycardia and palpitations,[1] and thus metoprolol was also used in this case. Other agents such as the acetylcholinesterase inhibitor pyridostigmine or the alpha-2 agonist clonidine are thought to help treat orthostatic symptoms in the hyperadrenergic form of POTS[1] but were not explored in this case.

At 31 weeks, her heart rate had improved slightly on the metoprolol tartrate 12.5 mg dose but she still had symptomatic hypotensive episodes. After decreasing the metoprolol tartrate dose to 6.25 mg twice daily, her heart rate remained between 130–150 b.p.m. She ultimately was titrated to a metoprolol tartrate dose of 12.5 mg in the mornings and 6.25 mg in the evenings, as well as midodrine 5 mg 2–3 times per day for the next week.

At 32 weeks, her blood pressure was 100/60 mmHg in the office, with resting heart rate at 110–115 b.p.m. while supine and 140–150 b.p.m. while standing, with higher heart rates associated with dyspnoea. Metoprolol tartrate was then uptitrated to 25 mg every morning and 12.5 mg in the evening.

At 33 weeks, the patient continued to experience episodic light-headedness. Blood pressure was 118/80 mmHg and heart rate 107 b.p.m. supine. After 2 min standing, her heart rate increased to 144 b.p.m. and her blood pressure was 100/80 mmHg. Recommendations at 33 weeks included metoprolol tartrate at 25 mg every morning and 12.5 mg in the evening, and midodrine at 5 mg twice daily, both medications to be taken throughout labour and delivery.

Follow-up

The patient had an uncomplicated birth of a healthy baby girl at 37 + 2 weeks after induction of labour for premature rupture of membranes. Her labour course involved an epidural with no abnormal haemodynamic parameters seen. A NASA Lean Test was performed 30 h post-partum (*Figure 2*). She still had a tachycardic response to postural change, but unlike prior testing, her blood pressure remained stable. She continues to take metoprolol tartrate 12.5 mg every 6 h for tachycardia.

Discussion

Recently, POTS has been identified in ∼20% of cases of PASC, in which symptoms persist >4 weeks after the onset of COVID-19 illness.[5,6] It is postulated that the cytokine storm from COVID-19 results in sympathetic dysregulation, causing an abnormal autonomic response in POTS.[7] The relationship between heart rate variability due to this autonomic failure and inflammatory factors from infection has been well studied.[7] It is thought that the abnormal heart rate may result from these inflammatory mediators crossing the blood–brain barrier, causing brain damage, and triggering chronic neuronal dysregulation.[7] Autonomic dysfunction in POTS could also be a result of the virus itself or the immune response it stimulates, with immune-mediated neurological syndromes having been described.[8] In addition, there may also be an association with POTS and autoantibodies following COVID-19 illness,[9] which suggests an autoimmune component to PASC and POTS. Ultimately, further investigation may be needed to determine the exact biological relationship between the autonomic nervous system and the immune system, as the exact impact on heart rate variability found in secondary POTS has not been determined.[7] Cases linking infectious diseases like COVID-19 and secondary POTS may also help reveal mechanisms behind autonomic dysfunction.

Several case reports have identified POTS in patients after their COVID-19 illness.[10] However, the case discussed in this report is the first described in pregnancy. The first prospective study evaluating autonomic dysfunction in PASC used the head-up tilt table test, as opposed to the NASA Lean Test, and excluded pregnant patients.[6] It was deduced that the postural orthostatic intolerance observed in the subjects was significant and presumably PASC-related, as no patients reported a history suggestive of orthostatic intolerance or autonomic disease before their COVID-19 illness.[6] Here we make the diagnosis of orthostatic intolerance and PASC using the NASA Lean Test for a patient who is also pregnant. Based on the test results (*Figure 1*), this patient equivocally met the criteria for POTS, as diagnostic criteria require an absence of orthostatic hypotension. During testing, she developed delayed orthostatic hypotension, defined as a drop in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg that occurs >3 min after standing upright.

It is possible that pregnancy physiology contributed to this abnormal POTS presentation. There is mixed data suggesting that POTS does not affect pregnancy and pregnancy does not affect POTS,[11] and there are conflicting data to suggest that POTS can deteriorate during pregnancy due to increased baseline cardiac output and heart rate.[12] Overall, it is believed that pregnancy will have a variable effect on POTS with a wide range of clinical manifestations.[13] Normal blood pressures relative to pre-pregnancy baselines are dynamic; baseline blood pressures start at conception with a gradual decrease in average blood pressure starting at 6 weeks until there is a trough at 22–24 weeks around 10 mmHg below the baseline.[14] There is then a gradual return to baseline near term.[14] Given these haemodynamic alterations are autonomically mediated, in a patient with autonomic dysfunction, it is reasonable to conclude that these changes can be exacerbated. In reviewing the patient's symptoms throughout her pregnancy, she had peak symptoms at 25 weeks which coincided with her trough blood pressure. She

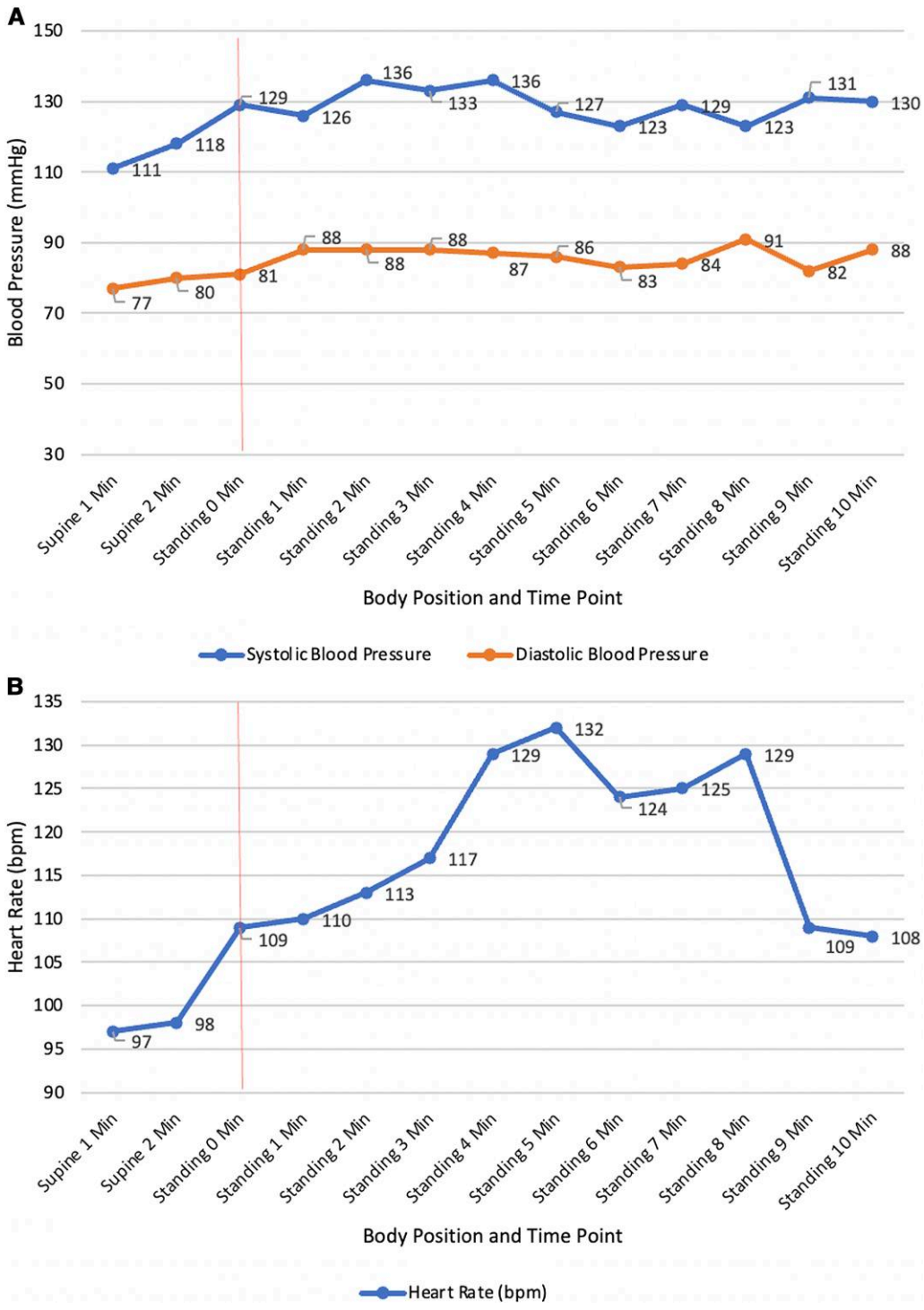

Figure 2 NASA Lean Test 30 h post-partum. (*A*) Systolic and diastolic blood pressure and (*B*) heart rates measured at supine and standing positions over 10 min showing tachycardic response to the position change and stable blood pressure without orthostatic hypotension. Mild shortness of breath observed from standing 1 min to standing 5 min. Diaphoresis and mild shortness of breath were observed at standing 6 min. Facial flushing, diaphoresis, and shortness of breath were observed from standing 7 min to standing 8 min, with symptoms improving from standing 9 min to standing 10 min.

had improvement of symptoms after this time point. While her improvements can be attributed to initiating medications, it is also possible the normal physiology of pregnancy contributed to the improvement in symptoms.

The decision to perform the NASA Lean Test 30 h post-partum was based on several factors. First, we wanted to ensure that the effects of the labour epidural analgesia had completely worn off. The second reason was to be temporally removed from the fluid shifts that take place

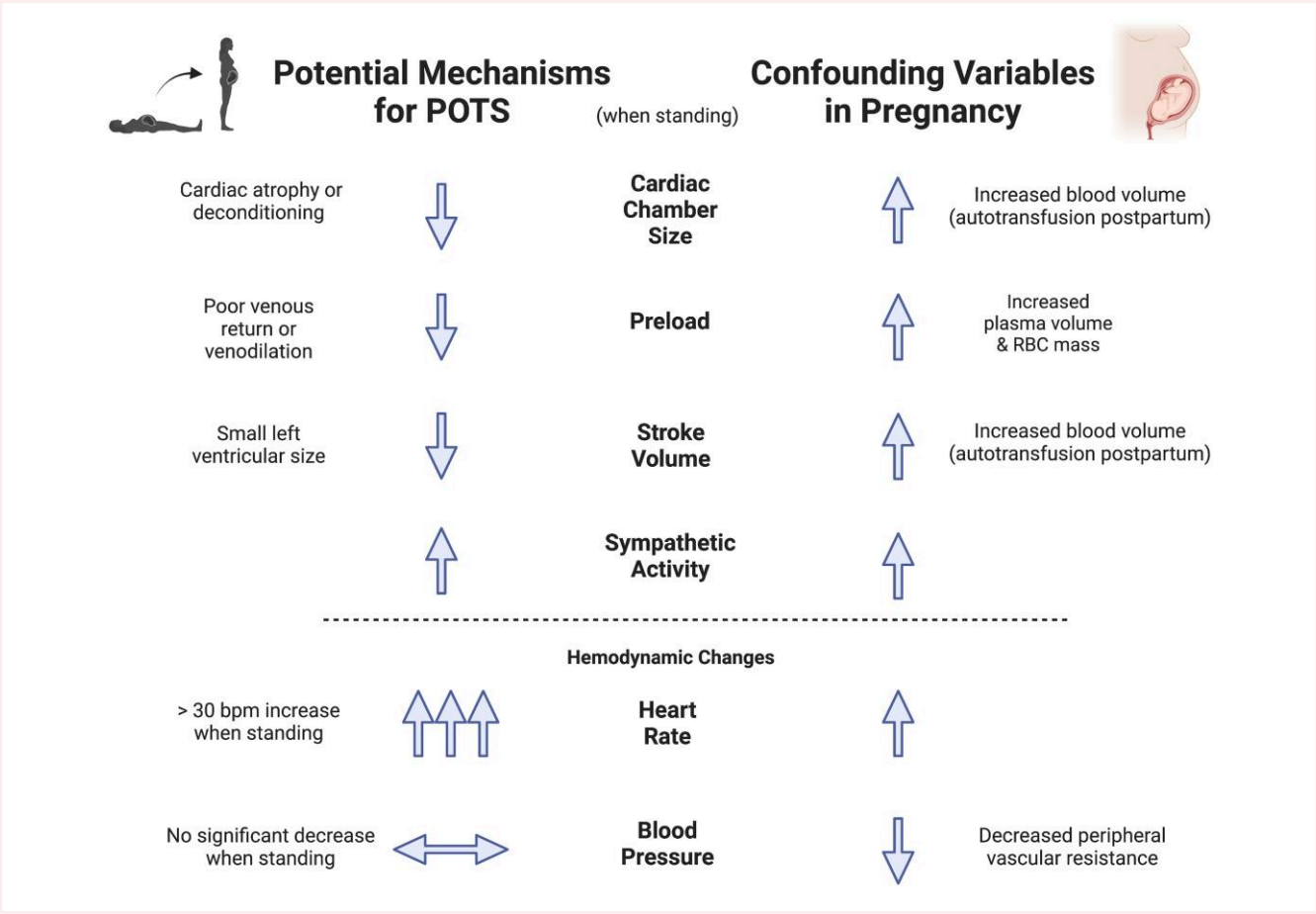

Figure 3 Potential mechanisms for postural orthostatic tachycardia syndrome and confounders consequent to physiological adaptations in pregnancy. As a result of physiological changes in pregnancy, there may be clinical manifestations of postural orthostatic tachycardia syndrome that differ from the standard presentation of postural orthostatic tachycardia syndrome in a non-pregnant individual.

in the immediate post-partum period. While fluid shifts continue to occur for up to several weeks post-partum, the largest shifts occur with the 500–1000 cc autotransfusion in the immediate post-partum period. The normalization of the NASA Lean Test could be confounded by being post-autotransfusion and the patient having increased intravascular volume, however, this is not likely to be a significant contributor as there is rapid increase in urine output in the post-partum period to maintain intravascular euvolemia. Possible mechanisms of POTS and confounders consequent to the physiology of pregnancy are outlined in *Figure 3*.

This case illustrates that haemodynamic manifestations of autonomic dysfunction may not always fit neatly into a diagnostic definition, and deeper investigations such as NASA Lean Tests are important to understanding an individual patient's physiology. It is thought that delayed orthostatic hypotension could be due to the gradual impairment of adaptive mechanisms during orthostasis, thus suggesting an early form of autonomic failure.[15] However, considering there may be different neurohormonal mechanisms of classical orthostatic hypotension and delayed orthostatic hypotension, it may be that normal pregnancy physiology exacerbated this abnormal presentation of POTS, as per the discussion above.[16] One other variable to consider in classical orthostatic hypotension which may influence delayed orthostatic hypotension is insulin resistance. There have been suggestions that patients with POTS may have a degree of insulin resistance and release more glucose-dependent insulinotropic peptide after glucose ingestion, which can contribute to the exacerbation of orthostatic symptoms through splanchnic vasodilation.[17] However, this was not further investigated in this case study.

Patients diagnosed with postural orthostatic tachycardia or orthostatic hypotension associated with PASC during pregnancy can benefit from combination therapy of midodrine (alpha-adrenergic agonist, pregnancy Class C) and metoprolol (beta-blocker, pregnancy Class C) while maintaining fetus safety. While formal autonomic nervous system testing can be helpful in centres where advanced testing is available, evaluation of an individual's physiology can easily be performed in the clinic using the NASA Lean Test or other similar tests, which may help capture delayed haemodynamic effects such as orthostatic hypotension.

Patient perspective

All the risks, benefits, and alternatives were discussed with the patient throughout her pregnancy. Of the medications used for treatment, they are all commonly used pharmacological therapies for the management of POTS and pose little to no risk to the pregnancy. The patient, therefore, agreed to the treatment plan. The patient was also comfortable receiving the diagnosis of POTS as there is no reliable data to suggest that there are any adverse maternal or fetal complications attributable to POTS.

Lead author biography

Justin Hanson is a second-year medical student at the David Geffen School of Medicine at UCLA and a researcher in the Division of Cardiology at the University of California Los Angeles. Justin also graduated with a bachelor's degree in Biological Sciences from Northwestern University.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written informed consent for the publication of this case report was obtained from the patient in line with the Committee on Publication Ethics (COPE) guidelines.

Conflict of interest: None declared.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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