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Review

Postural Orthostatic Tachycardia Syndrome during pregnancy: A systematic review of the literature

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ABSTRACT

Purpose: Postural Orthostatic Tachycardia Syndrome is most commonly seen in women of child bearing age, however little is known about its effects in pregnancy.
Method: A systematic review was conducted in March 2015 and updated in February 2018. Medline, Embase, PsychInfo, CINHAL, and the Cochrane Library were searched from database inception. The ClinicalTrials.gov site and bibliographies were searched. MeSH and Emtree headings and keywords included; Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, and were combined with pregnancy and pregnancy related subject headings and keywords. Searches were limited to English. Eligible articles contained key words within the title and or abstract. Articles were excluded if Postural Orthostatic Tachycardia Syndrome was not pre-existing.
Results: Eleven articles were identified as eligible for inclusion. Studies were appraised using the PRISMA 2009 guidelines. The overall quality of evidence was poor using the NHMRC Evidence Grading Matrix, which was attributed to small sample sizes and mostly observational studies, emphasizing the need for future high quality research. Findings in this review must be used with caution due to the poor quality of the literature available.
Conclusions: Postural Orthostatic Tachycardia Syndrome should not be a contraindication to pregnancy. Symptom course is variable during pregnancy and the post-partum period. Continuing pre-conception medication may help symptoms, with no significant risks reported. Obstetric complications, not Postural Orthostatic Tachycardia Syndrome, should dictate mode of delivery. Postural Orthostatic Tachycardia Syndrome did not appear to affect the rate of adverse events. These results are important in determining appropriate management and care in this population.

1. Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is a condition of the autonomic nervous system that is five times more likely to affect women, and occurs most often in child bearing age (Kimpinski et al., 2010; Glatter et al., 2005; Raj, 2006; Kanjwal et al., 2009; Blitshteyn et al., 2012; Benrud-Larson et al., 2002; Low et al., 2009). The prevalence of POTS is unknown due to difficulty with diagnosis, however it is estimated that between 500,000 and 3,000,000 Americans are affected (Mar and Raj, 2014; Robertson, 1999; Mustafa et al., 2012; Pavlik et al., 2016). It is characterized by symptoms of orthostatic tachycardia including tachycardia, palpitations, syncope or pre-syncope, light headedness, cognitive dysfunction, nausea, exercise or heat intolerances, and fatigue (Benarroch, 2012; Pavlik et al., 2016). It is heterogeneous in nature with patients often displaying multiple, non-specific symptoms with varying degrees of functional impairment (Benarroch, 2012; Kavi et al., 2012). In severe cases, morbidity and functional disability may be similar to that of chronic obstructive pulmonary disease or heart failure (Pramya et al., 2012; Blitshteyn et al., 2012). Misdiagnosis is common due to inconsistency in clinical presentation, difficulty with diagnosis, and lack of awareness or acceptance of the reality of the condition (Pavlik et al., 2016).

In adults, the current criteria for a POTS diagnoses is: the presence of excessive tachycardia and symptoms of orthostatic intolerance for more than six months, an increase of 30 beats per minute or heart rate > 120 beats per minute on Head Up Tilt test within 10 min of

Abbreviations: POTS, Postural Orthostatic Tachycardia Syndrome; CS, caesarean section

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standing, an absence of orthostatic hypotension, and improvements of symptoms upon recumbence (Pavlik et al., 2016; Benarroch, 2012; Busmer, 2013; Thieben et al., 2007). An extensive history is essential so that physiological conditions such as pheochromocytoma, or psychological conditions such as conversion disorder can be excluded before a diagnosis of POTS can be made (Busmer, 2013; Benrud-Larson et al., 2002; Thieben et al., 2007).

Similar conditions to POTS have been described since 1871 when Jacob Mendes Da Costa observed orthostatic symptoms in soldiers which he diagnosed as Irritable Heart Syndrome (Da Costa, 1871). Similar symptoms were later described by Sir Thomas Lewis, Robert D. Rudolf, and Paul Wood (Mathias et al., 2012; Rudolf, 1916; Lewis, 1918). Other diagnoses for these symptoms include Da Costa Syndrome, Soldier's Heart, neurasthenia, anxiety neurosis, effort intolerance, neurocirculartory asthenia (Mathias et al., 2012; Low et al., 2009; Wood, 1941). POTS was finally defined by Ronald Schondorf and Phillip Low at the Mayo Clinic in 1993 (Schondorf and Low, 1993).

Current research is predominantly focused on the general diagnosis and management of this complex condition. This includes an exploration of pharmacological management (Busmer, 2013; Benarroch, 2012), which has been noted to be of particular concern to patients. Common medications may include fludrocortisone, β-blockers such as propranolol, midodrine (Busmer, 2013; Benarroch, 2012; Garland et al., 2015; Pavlik et al., 2016; Sheldon et al., 2015), ivabradine (Pavlik et al., 2016; Busmer, 2013; Garland et al., 2015; Sheldon et al., 2015), selective serotonin reuptake inhibitors (Busmer, 2013; Garland et al., 2015), clonidine (Pavlik et al., 2016; Sheldon et al., 2015), desmopressin (DDAVP) (Pavlik et al., 2016; Garland et al., 2015), methyldopa, modafinil (Sheldon et al., 2015; Garland et al., 2015), and pyridostigmine (Benarroch, 2012; Garland et al., 2015; Pavlik et al., 2016; Sheldon et al., 2015). The medications prescribed for the management of POTS vary in their safety profiles and, whilst the potential harm from medications during pregnancy may be alleviated with appropriate choice of medication and monitoring, the lack of guidelines for pharmacological management in POTS and pregnancy may pose a risk to both mother and baby (Lide and Haeri, 2015).

A small number of previous studies have shown links between POTS and gynecological disorders. A study by Peggs et al. (2012) assessed the gynecological history and menstrual cycle lightheadedness of POTS patients compared to healthy controls. This study found significantly higher rates of amenorrhea, lightheadedness in all phases of the menstrual cycle and particularly in the follicular phase, dysfunctional uterine bleeding, endometriosis, galactorrhea, uterine fibroids, and ovarian cysts (Peggs et al., 2012).

In 2015, the Heart Rhythm Society released an international consensus statement to provide guidance to clinicians in the diagnosis and management of POTS (Sheldon et al., 2015). However, there are no clinical guidelines found in the available literature for the management and treatment of POTS during pregnancy, leaving patients and clinicians uncertain of the appropriate management. Patients may turn to the academic literature or the internet causing confusion. This may increase the potential risk to the mother and or fetus, and may adversely affect the patient-clinician relationship. As POTS is more common in women of child-bearing age, there is an urgent need to more closely examine the physical and psychological management of POTS during pregnancy.

The aims of this paper are to: evaluate the quality of the evidence available surrounding pre-existing POTS in pregnancy, determine what is currently known about pre-existing POTS and pregnancy, and specify areas where further research is needed.

2. Sources

A search of the available evidence was conducted in March 2015 and updated in February 2018. The electronic databases Medline, Embase, PsychInfo, CINHAL, and the Cochrane Library were searched from database inception. These databases index a wide range of qualitative and quantitative journals across a number of different health disciplines. The search strategy was constructed using both subject and keyword word searching and translated for each specific database. Subject headings, keywords and phrases included; 'Postural* Tachycardia Syndrome', 'Postural Tachycardi* Syndrome', as well as 'Orthostatic Intolerance'. These were combined using the Boolean operator 'AND' with 'pregnancy' related subject headings and keywords. Details of the complete search strategies can be found in Appendix A. The search was limited to English language citations. Librarians from the University of Newcastle and Hunter New England Health Libraries, John Hunter Hospital were consulted to ensure satisfactory search techniques. The ClinicalTrials.gov site was searched to identify any relevant unpublished studies. A search of the literature available on the Dysautonomia International (www.dysautonomiainternational.org) and PoTS UK (www.potsuk.org) websites was also conducted, as well as contacting the board of directors and chairperson from each website to assist in identifying other relevant studies. Manual searching of relevant bibliographies was completed to ensure all articles were captured. Where only abstracts were available, attempts to contact the authors were made to ensure the full body of knowledge was identified.

2.1. Inclusion criteria

Searches were limited to original research articles published in the English language. The terms 'pregnancy' and 'postural tachycardia syndrome' or 'postural orthostatic tachycardia syndrome' were required to appear in any part of the title or abstract

2.2. Exclusion criteria

Studies were excluded if the full text was not available, and if POTS was diagnosed during pregnancy or post-partum due to differences in clinical management.

3. Study selection

Ninety-eight articles were identified in the literature search. Eleven studies met the inclusion criteria. Of these, eight were case reports that included one to seven patients. Three of the studies, including one case report, employed retrospective chart reviews. One study used self-administered questionnaires that asked about symptoms and medication use during the pre-conception, pregnancy and post-partum periods, and mode of delivery. Two of the case reports included a brief review of the literature, one focusing on previous cases reported in the literature, and the other on medications reported in the previous literature. Seven studies were conducted in the United States, three in the United Kingdom and one in India. Sample sizes ranged between one and 51 participants.

The one case report that was excluded was due to the diagnosis of POTS being made during the post-partum period. Five conference abstracts were excluded as no full text was available. This decision was made by one of the authors (KM) and confirmed by another of the authors (CC). Fig. A summarizes the retrieval process and study selection.

3.1. Quality appraisal

The McMasters Critical Review Form for Quantitative Studies was selected to appraise the methodological quality of the 11 selected studies (Law et al., n.d.). This critical appraisal tool was chosen as it provides a consistent checklist for the different methodological designs presented across the articles included in this review. The studies scored between six and eight out of ten, with the majority of points lost in the following sections: detailed sample description, informed consent, and reliable and valid outcome measures. Appendix B summarizes the

scores.

The strength of evidence was determined using the National Health and Medical Research Council (NHMRC) Evidence Grading Matrix, which provides a rating between A (excellent) and D (poor). These are based on the volume of evidence, consistency, clinical impact, generalizability, and applicability to the Australian healthcare context (NHMRC, 2009). The overall rating of the evidence reviewed was Grade D (poor) as outlined in Appendix C. This was due to the evidence predominantly being level III (case-control and retrospective cohort studies) or IV (case studies) according to the NHMRC Evidence Hierarchy (NHMRC, 2009). Despite this, all 11 articles were included due to the small number of articles to draw from.

The PRISMA 2009 checklist for systematic reviews was utilized in the writing of this review to ensure quality and transparency in reporting (Moher et al., 2009).

4. Results

Each article was independently reviewed by two of the authors (KM, CC). Any discrepancies in the findings were discussed and resolved by returning to and reassessing the articles in question. The general quality of the reviewed articles was poor. The sample sizes were very small; five studies reported on single cases, two studies reported on two cases, and the remaining four studies contained seven, ten, 22 and 51 participants. Table A provides an overview of the included studies. The majority of the studies were observational. There were no longitudinal analyses, so temporality and casualty cannot be inferred. Furthermore, potential confounders were not taken into account in the majority of the studies. The results below are presented in this context, as descriptive examples of the potential course, treatments and experiences of POTS during pregnancy.

Five main areas were covered by the articles and these are outlined below.

4.1. Symptom course during pregnancy

Eight of the 11 studies addressed symptom course during pregnancy. These studies showed the course of POTS symptoms during pregnancy and the post-partum period to be variable. It is difficult to predict the course for an individual patient. There seemed to be a general trend towards an exacerbation of symptoms in the first trimester, an improvement of symptoms in the second trimester, and a variable course in the third trimester and the post-partum period (Kimpinski et al., 2010; Lide and Haeri, 2015). This pattern or trend of the variable symptoms course appeared in multiple studies: ten patients by Blitshteyn et al. (2012), 51 patients by Kimpinski et al. (2010) and 22 patients by Kanjwal et al. (2009). Both Blitshteyn and Kanjwal reported 60% to 68% of their patients respectively remained either stable or experienced improved symptoms during pregnancy, with only 40% and 31% of patients respectively experiencing a worsening of symptoms (Blitshteyn et al., 2012; Kanjwal et al., 2009). Three studies suggested that improvements in POTS symptoms may be naturally occurring due to the increase in fluid, blood and plasma levels in pregnancy, as well as subsequent increases in cardiac output and blood pressure. This was particularly seen in the later trimesters (Kimpinski et al., 2010; Kanjwal et al., 2009; Glatter et al., 2005).

By six months post-partum, 50–69% of patients in the studies by Blitshteyn et al. (2012) and Kanjwal et al. (2009) reported their symptoms remained stable or improved, whilst 27–50% reported worsening of symptoms (Kanjwal et al., 2009; Blitshteyn et al., 2012). Glatter et al. (2005) reported that one patient felt better at six months post-partum than before pregnancy, possibly due to the increase in upper body resistance training with caring for a newborn (Kanjwal et al., 2009). This improvement was also reported in the case study by Pramya et al. (2012).

At one year post-partum, 40% of patients felt their symptoms were unchanged, 10% reported an improvement in experienced symptoms, and 50% described worsening symptoms (Blitshteyn et al., 2012). At 22 months post-partum, one patient reported a significant reduction in syncope but remained disabled by other POTS symptoms (Kanjwal et al., 2009).

4.2. Medication use

The limited evidence suggests that medication use in pregnancy appeared to be safe under close observation of the physician, where it was decided that the benefit outweighed the risk. Medications utilized for the treatment of POTS during pregnancy reported in the literature included beta blockers (propranolol, metoprolol) (Blitshteyn et al., 2012; Powless et al., 2010; Pramya et al., 2012; Kanjwal et al., 2009; McEvoy et al., 2007; Corbett et al., 2006), fludrocortisone (Blitshteyn et al., 2012; Powless et al., 2010; Kanjwal et al., 2009; McEvoy et al., 2007), midodrine (Blitshteyn et al., 2012; Powless et al., 2010; Kanjwal et al., 2009; Glatter et al., 2005), pyridostigmine (Blitshteyn et al., 2012; Powless et al., 2010), and selective serotonin reuptake inhibitors (Kanjwal et al., 2009). Ondansetron was used to successfully treat hyperemesis gravidarum (Kanjwal et al., 2009). Phenylephrine was recommended during labour for hemodynamic stability (Kodakkattil and Das, 2009; Jones and Ng, 2008; McEvoy et al., 2007).

Across the ten studies that addressed medication use in pregnancy and delivery, no reported adverse events or complications related to medication use were identified. Blitshteyn et al. (2015) reported that birth weight was slightly below the population average. Although not statistically significant, this was thought to be related to the use of beta blockers (Blitshteyn et al., 2012). Patients who did not require medication for treatment of POTS prior to pregnancy were less likely to report exacerbation of symptoms during pregnancy and were less likely to require treatment (Lide and Haeri, 2015; Powless et al., 2010). Patients who continued using medications during pregnancy were less likely to experience exacerbations and were more likely to remain stable or report improved POTS symptoms (Blitshteyn et al., 2012).

Lide and Haeri (2015), in their medication review, highlighted that there are currently no clinical guidelines for the use of medication to treat POTS in pregnancy and that treatment is individualized to the patient and their symptomology (Lide and Haeri, 2015). The authors suggested that propranolol should be considered as the first line treatment in POTS and pregnancy due to its safe pregnancy and lactation profile (Lide and Haeri, 2015). Other medications may be used but require close monitoring of mother and baby (Lide and Haeri, 2015).

4.3. Anesthesia and analgesia during delivery

Seven of the 11 case studies, involving between one and seven patients, addressed anesthesia and analgesia during delivery. Three case studies focused specifically on the anesthetic management of patients with POTS. These case studies reported that anesthesia and analgesia, along with the increased stress of labour on the autonomic nervous system, can prove particularly challenging to the POTS patient. Four of the case studies reported physiological changes including hemodynamic instability and tachycardia throughout labour. These case studies also consistently reported that early analgesia with close monitoring of hemodynamic status may reduce tachycardia and associated complications (Lide and Haeri, 2015; Kodakkattil and Das, 2009; McEvoy et al., 2007). Early consultation with an anesthetist or anesthesiologist was recommended (Corbett et al., 2006; McEvoy et al., 2007; Kodakkattil and Das, 2009; Lide and Haeri, 2015).

Epidural (bolus and or infusion) with phenylephrine during delivery was described in four studies and was used to prevent reactive tachycardia in the presence of peripheral vasodilation causing hypotension (McEvoy et al., 2007; Jones and Ng, 2008; Kodakkattil and Das, 2009; Corbett et al., 2006). McEvoy et al. (2007) recommend phenylephrine as the first line treatment in this setting, over labetalol which must be

titrated in smaller doses and its effects in the pregnant POTS patients may be unpredictable (McEvoy et al., 2007). Corbett et al. (2006) cautioned against the use of epinephrine due to an increased risk of causing tachycardia, especially in patients with hyperadrenergic POTS (Corbett et al., 2006). This author also suggested that epidural appears to be safer than spinal anesthesia which may cause sudden changes in systemic vascular resistance and subsequent hemodynamic instability (Corbett et al., 2006). Fluid loading may also be useful in maintaining hemodynamic stability (Jones and Ng, 2008; McEvoy et al., 2007; Corbett et al., 2006).

Powless et al. (2010) described two of their seven patients giving birth without anesthesia and analgesia and without complications (Powless et al., 2010). These findings highlight the need for each individual patient to be assessed during pregnancy, and the importance of close monitoring during labour to avoid unnecessary intervention or a delay in appropriate management of pain and associated hemodynamic changes.

4.4. Mode of delivery

There remain no clear recommendations regarding the mode of delivery for women experiencing POTS. Glatter et al. (2005) was the first to report on two cases of severe POTS in pregnancy and recommended that patients undergo a caesarean section (CS) to reduce the extreme physical stressed placed on the mother during labour (Kanjwal et al., 2009). However subsequent case studies have shown that vaginal delivery can be achieved without major complications with appropriate planning, monitoring and pain management (Lide and Haeri, 2015; Blitshteyn et al., 2012; Powless et al., 2010; Pramya et al., 2012; Kanjwal et al., 2009; Kodakkattil and Das, 2009). Only one patient elected to have a CS and this was reported to be based on the previously published recommendations by Glatter et al. (2005) (Glatter et al., 2005; Powless et al., 2010). Twelve patients across six studies were reported to have delivered by CS, nine of whom were recommended to undergo CS for obstetric complications unrelated to POTS including breech position and an active phase arrest (Powless et al., 2010; Blitshteyn et al., 2012; Kanjwal et al., 2009; Corbett et al., 2006), and three due to the obstetricians recommendations based on an increase in POTS symptoms (Glatter et al., 2005; Jones and Ng, 2008). Only one patient had an instrument assisted delivery using forceps which was recommended to reduce hemodynamic fluctuations in the second stage of labour caused by the Valsalva maneuver (McEvoy et al., 2007). Labour was induced in one patient due to maternal syncope, and the patient delivered vaginally with no complications (Kodakkattil and Das, 2009). All other reported patients delivered vaginally with no complications (Lide and Haeri, 2015; Blitshteyn et al., 2012; Powless et al., 2010; Pramya et al., 2012; Kanjwal et al., 2009).

4.5. Complications and adverse events

Complications and adverse events rates amongst women with POTS were generally found to be similar to that of the general population (Kimpinski et al., 2010; Pramya et al., 2012) at around 8% (Kimpinski et al., 2010), although sample sizes in these studies were small. No clinically important differences were found in the study by Kimpinski et al. (2010) between 61 nulliparous and 51 parous women with pre-existing POTS (Kimpinski et al., 2010). No complications or adverse events were reported to be POTS related, including during pregnancy (Kimpinski et al., 2010; Pramya et al., 2012; Kanjwal et al., 2009; Kodakkattil and Das, 2009), during vaginal or CS delivery (Lide and Haeri, 2015; Kanjwal et al., 2009; Kodakkattil and Das, 2009; McEvoy et al., 2007), or to mother or baby (McEvoy et al., 2007; Kimpinski et al., 2010; Blitshteyn et al., 2012). Three studies concluded that POTS should not be considered a contraindication to pregnancy with pregnancy itself appearing to be relatively safe (Kimpinski et al., 2010; Kanjwal et al., 2009; Blitshteyn et al., 2012). Kanjwal et al. (2009) reported that risk factors for the mother should be assessed as per normal obstetric practices (Kanjwal et al., 2009).

The retrospective study by Blitshteyn et al. (2012) reported higher rates of miscarriage (59.9%) compared to the general population (31%) (Blitshteyn et al., 2012). Even after excluding one woman with a history of 13 miscarriages at less than ten weeks gestation and no history of clotting, autoimmune or genetic disorders, the rate remained high (41%) (Blitshteyn et al., 2012). This finding was not supported in other studies and requires further consideration before an association can be made between POTS and miscarriage in pregnancy (Blitshteyn et al., 2012).

Blitshteyn et al. (2012) also noted higher rate of hyperemesis gravidarum or severe vomiting (59%) when compared to the general population (0.5–2%) possibly due to co-morbid migraine which was also common amongst their participants (30%) (Blitshteyn et al., 2012).

General complications and adverse events to the mother and/or baby reported across seven case studies in the literature included hyperemesis gravidarum (Glatter et al., 2005; Kanjwal et al., 2009; Blitshteyn et al., 2012), gestational hypertension (Powless et al., 2010; McEvoy et al., 2007), threatened preterm labour (Kodakkattil and Das, 2009), complete heart block requiring insertion of a permanent pacemaker (Kanjwal et al., 2009), oligohydramnios at term (Powless et al., 2010), preterm rupture of the membranes (Powless et al., 2010), chronic placental abruption (Powless et al., 2010), breech presentation (Powless et al., 2010), miscarriage (Kimpinski et al., 2010), placenta previa resulting in miscarriage (Kimpinski et al., 2010), placental abruption with malpresentation resulting in a peripartum hysterectomy (Kimpinski et al., 2010), fetal distress syndrome (Blitshteyn et al., 2012), Down Syndrome (Kanjwal et al., 2009), asymptomatic ostium secundum atrial septal defect (Kanjwal et al., 2009), and a small ventricular septal defect with spontaneous closure (Kanjwal et al., 2009). None of these complications reported were considered to be related to POTS. The mother's preconception health was not always disclosed which may cause a potential bias towards POTS as a risk factor. In the case of Down Syndrome, the mother was of advanced age (37 years old) which is a well-known risk factor for Down Syndrome (Kanjwal et al., 2009). The authors noted that the etiology of the complete heart block was unclear, and may not be POTS related (Kanjwal et al., 2009). Despite the limitations of the studies, POTS is not considered to increase the risk of complications and adverse events (Kimpinski et al., 2010; Pramya et al., 2012).

5. Discussion

The findings presented in this review were not unexpected due to the heterogeneous nature of POTS. Since symptoms and management of POTS varies from patient to patient, it is reasonable to expect that the experience of pregnancy and labour would also be quite variable in its course. However it was surprising to find an absence of research into, or acknowledgement of, the patient perspective with POTS and pregnancy. Of the 11 studies reviewed, only Glatter et al. (2005) appeared to mention from observation the women's improvement in physical and mental wellbeing after the birth of their child, speculating this may have occurred with the change in focus from their health to baby's wellbeing and increase upper body training with caring for a child (Kanjwal et al., 2009). This is important to note as evidence suggests that maternal chronic illness is related to poorer perinatal health outcomes (Tyer-Viola and Lopez, 2014).

It is imperative that future research explores the patient experience to be able to better understand the patients' needs, as currently no studies on pregnancy and POTS address this issue. Understanding the patient experience will help shape and inform future quantitative research, identify patient-centered priorities of antenatal and postnatal care, and illuminate the issues that are most important to patients. From this, clinical guidelines can be created for POTS and pregnancy, reducing uncertainly for both patient and clinician.

Due to the small number of studies available over the past ten years, patients and clinicians are often left to approach the management of the pregnancy by trial and error based on cases of patients who may not share the same POTS symptomology or cause, and on recommendations that may now be out of date. This was demonstrated in the study by Powless et al. (2010) where a patient elected to have a CS despite its risks and without obstetric indications (Powless et al., 2010) based on an earlier outdated study of only two cases of severe POTS (Kanjwal et al., 2009). Patients and clinicians may be left uncertain of the appropriate course of action for the individual, or with contradictory information that can be confusing and affect the patient – clinician relationship. This is particularly important when considering medications in the pregnant POTS patient. Whilst the relative safety of the medications reported in the literature is recognized, safety profiles are still viewed with a certain amount of subjectivity depending on the individual physician's experience, knowledge and specialty. Patients are often managed by multiple specialists with varying opinions on the relative safety of the medications in pre-conception, pregnancy, labour and breastfeeding which may lead to increased ambiguity regarding safety, particularly from the patient's point of view. Furthermore many medications used in the treatment of POTS, such as ivabradine, modafinil or pyridostigmine, have not been sufficiently and rigorously explored for safety in pregnant or lactating women and caution must be used. The cause and course of POTS may differ significantly between each patient and therefore treatment and management of both POTS and pregnancy is highly individual (Lide and Haeri, 2015; Kimpinski et al., 2010). Blitshteyn et al. (2012) noted patients and clinicians need to be aware of the existing data to aid in the development of a management plan for pre-conception, pregnancy and labour, which may help reduce anxieties and help patients prepare for the possibilities of symptom exacerbation (Blitshteyn et al., 2012).

The long list of serious general complications reported in the literature is of concern given the small sample sizes. Without the patients preconception health status and medications disclosed, it is difficult to be able to confidently conclude that these complications were not attributed to POTS. Given the complexities of POTS, the various medications utilized during pregnancy, and the variable course of pregnancy in general, it may be possible that there are unknown risks associated with POTS in pregnancy. Further research into complications in pregnancy with POTS is warranted.

Although during quality appraisal the majority of the studies received a favorable score with the McMasters checklist, the NHMRC score indicates that the overall quality of the evidence is poor. This is primarily due to the majority of studies being case reports with very limited patient numbers. These provide interesting insights but are unable to be used to produce generalizable evidence based guidelines with translatable clinical practice recommendations for patients with a diagnosis of POTS who wish to become, or who are pregnant.

This systematic review highlights the need for more rigorous high quality research into POTS during pregnancy. Future research in this area is vital to improve the care and consistency of patients with POTS considering pregnancy or who are pregnant. Whilst this review may be used to inform clinical care, large prospective studies with longitudinal follow-up are needed to objectively and comprehensively address the questions faced by this population. These question include, but are not limited to: short and long term effects of pregnancy on POTS, POTS symptom course during pregnancy, duration of symptom exacerbation, rates of pregnancy induced hypertensive disorders, risk of antenatal and postnatal mental health disorders in the POTS population, appropriate medication to treat POTS during pregnancy, the possible short and long term effects of medication on the fetus, the potential for the requirement of an obstetrician who specializes in high risk pregnancies, and the exploration of lived experience of pregnancy and POTS symptoms as perceived by the women themselves. Addressing pregnancy in women diagnosed with POTS is vital in ensuring patients and their families are adequately prepared during the preconception stage and throughout pregnancy and labour, as well as ensuring patients feel confident in the management of the POTS and pregnancy. However, without further research, this goal is unlikely to be met.

Clinical guidelines for POTS and pregnancy need to be developed to provide expert consensus for clinicians. A consumer's guide to the clinical guidelines would also be recommended given the concerns of this group of patients and the confusion that may be encountered particularly concerning medication and mode of delivery. It is acknowledged however that producing these kinds of studies may be extremely difficult given the prevalence of POTS.

5.1. Conclusion

The findings of this systematic review must be used with caution due to the overall small number and poor quality of articles discussing pre-existing POTS in pregnancy. However, based on the evidence available, the symptom course of POTS appears to be variable during pregnancy and the post-partum period. Patients who required medication pre-conception may benefit from continuing medication in pregnancy to help stabilize or improve symptoms. It is consistently recommended that patients receive an early review with an obstetrician and an anesthetist. Early initiation of pain relief may reduce the risk of hemodynamic instability during labour. Mode of delivery should be based on obstetric complications rather than on a diagnosis of POTS. Vaginal delivery appears to be safe in the absence of obstetric complications and with close monitoring. Adverse events do not appear to be higher than the general public. Current knowledge suggests patients and clinicians should be reassured that POTS does not appear to be a contraindication to pregnancy. Further high quality research is crucial in improving knowledge and quality of care of patients with pre-existing POTS who are, or wish to become pregnant.

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Conflict of interest

Kate Morgan declares that she has no conflict of interest. Dr. Catherine Chojenta declares that she has no conflict of interest. Dr. Meredith Tavener declares that she has no conflict of interest. Ms. Angela Smith declares that she has no conflict of interest. Professor Deb Loxton declares that she has no conflict of interest. The authors alone are solely responsible for the content and writing of this paper.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Informed consent

For this type of study formal consent is not required.

Author contributions

K. Morgan: Project development, Data collection, Data analysis, Manuscript writing/editing.

C. Chojenta: Project development, Data analysis, Manuscript writing/editing.

M. Tavener: Project development, Manuscript writing/editing.

A. Smith: Search design, Manuscript writing/editing.

D. Loxton: Project development, Manuscript writing/editing.

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Condensation

Although evidence regarding Postural Orthostatic Tachycardia Syndrome in pregnancy is scarce and of poor quality, it suggests the condition may be safe with close monitoring.

Source of the work

This work was completed at The University of Newcastle, Newcastle, New South Wales, Australia.

Appendix A. Search strategy

Medline (search updated 14/Feb/2018).

Line	Search term	Results
1	Postural Orthostatic Tachycardia Syndrome	328
2	("postural orthostatic tachycardia syndrome" or "postural tachycardia syndrome").ti,ab,kw.	648
3	(orthostatic adj (tachycardia or intolerance)).ti,ab,kw.	1327
4	exp Posture/	68,505
5	exp Tachycardia/	44,937
6	4 and 5	335
7	1 or 2 or 3 or 6	1739
8	exp Pregnancy/	826,342
9	exp Pregnancy complications	391,368
10	Pregnancy Outcome/	44,347
11	pregnan*.ti,ab,kw.	463,795
12	(labo?r or antenatal or ante-natal or neonat* or postnatal* or post-natal* or primigravid* or post-partum or postpartum or obstetric* or childbearing or child-bearing or nulliparous or parous or gyn?ecolog*).ti,ab.	591,015
13	8 or 9 or 10 or 11 or 12	1,304,499
14	7 and 13	35
15	limit 14 to english language	33

Embase (search updated 20/Feb/2018).

Line	Search term	Results
1	postural orthostatic tachycardia syndrome	1204
2	("postural orthostatic tachycardia syndrome" or "postural tachycardia syndrome").ti,ab.	1107
3	(orthostatic adj (tachycardia or intolerance)).ti,ab.	2024
4	Postural tachycardia syndrome	963
5	1 or 2 or 3 or 4	2593
6	exp pregnancy/	733,507
7	exp pregnancy complication/	128,970
8	pregnancy outcome/	46,963
9	pregnan*.ti,ab.	615,926
10	(labo?r or antenatal or ante-natal or neonat* or postnatal* or post-natal* or primigravid* or post-partum or postpartum or obstetric* or childbearing or child-bearing or nulliparous or parous or gyn?ecolog*).ti,ab.	801,834
11	6 or 7 or 8 or 9 or 10	1,510,353
12	5 and 11	52
13	Limit 12 to English language	51

PsychINFO (search updated 20/Feb/2018).

Line	Search term	Results
1	("postural orthostatic tachycardia syndrome" or "postural tachycardia syndrome").ti,ab.	59
2	(orthostatic adj (tachycardia or intolerance)).ti,ab.	96
3	tachycardia/	245
4	syndromes/	13,333
5	autonomic nervous system disorders	97
6	4 or 5	13,611

7	3 and 6	30
8	1 or 2 or 7	116
9	exp pregnancy/	22,824
10	obstetrical complications/or pregnancy outcomes/	2167
11	pregnan*.ti,ab.	41,297
12	(labo?r or ante-natal or neonat* or postnatal* or post-natal* or primigravid* or post-partum or postpartum or obstetric* or childbearing or child-bearing or nulliparous or parous or gyn?ecolog*).ti,ab.	81,829
13	9 or 10 or 11 or 12	111,329
14	8 and 13	0

CINAHL (search updated 20/Feb/2018).

Line	Query	Results
S1	(MH “Postural Orthostatic Tachycardia Syndrome”)	149
S2	TI (“postural orthostatic tachycardia syndrome” or “postural tachycardia syndrome”) OR AB (“postural orthostatic tachycardia syndrome” or “postural tachycardia syndrome”)	243
S3	TI (“orthostatic tachycardia” or “orthostatic intolerance”) OR AB (“orthostatic tachycardia” or “orthostatic intolerance”)	300
S4	S1 OR S2 OR S3	397
S5	(MH “Pregnancy+”)	166,264
S6	(MH “Pregnancy Complications”)	14,344
S7	(MH “Pregnancy Outcomes”)	18,027
S8	TI pregnan* OR AB pregnan*	95,702
S9	TI (labour or labor or antenatal or ante-natal or neonat* or postnatal* or post-natal* or primigravid* or post-partum or postpartum or obstetric* or childbearing or child-bearing or nulliparous or parous or gynecolog* or gynaecolog*) OR AB (labour or labor or antenatal or ante-natal or neonat* or postnatal* or post-natal* or primigravid* or post-partum or postpartum or obstetric* or childbearing or child-bearing or nulliparous or parous or gynecolog* or gynaecolog*)	128,070
S10	S5 OR S6 OR S7 OR S8 OR S9	266,912
S11	S4 AND S10	11
S12	S4 AND S10 Narrow by Language: - English	11

Cochrane Database (search updated 21/Feb/2018).

Line	Search term	Results
1	MeSH descriptor: [Postural Orthostatic Tachycardia Syndrome] this term only	19
2	“postural orthostatic tachycardia syndrome” or “postural tachycardia syndrome”	68
3	“orthostatic tachycardia” or “orthostatic intolerance”	162
4	MeSH descriptor: [Posture] explode all trees	3934
5	MeSH descriptor: [Tachycardia] explode all trees	1621
6	#4 and #5	24
7	#1 or #2 or #3 or #6	179
8	MeSH descriptor: [Pregnancy] explode all trees	5948
9	MeSH descriptor: [Pregnancy Complications] explode all trees	9556
10	MeSH descriptor: [Pregnancy outcome] this term only	3080
11	Pregnan*:ti,ab	25,551
12	Labor or labour or antenatal or ante-natal or neonat* or postnatal* or post-natal* or primigravid* or post-partum or postpartum or obstetric* or childbearing or child-bearing or nulliparous or parous or gynecolog* or gynaecology*	71,991
13	#8 or #9 or #10 or #11 or #12	83,703
14	#7 and #13	3

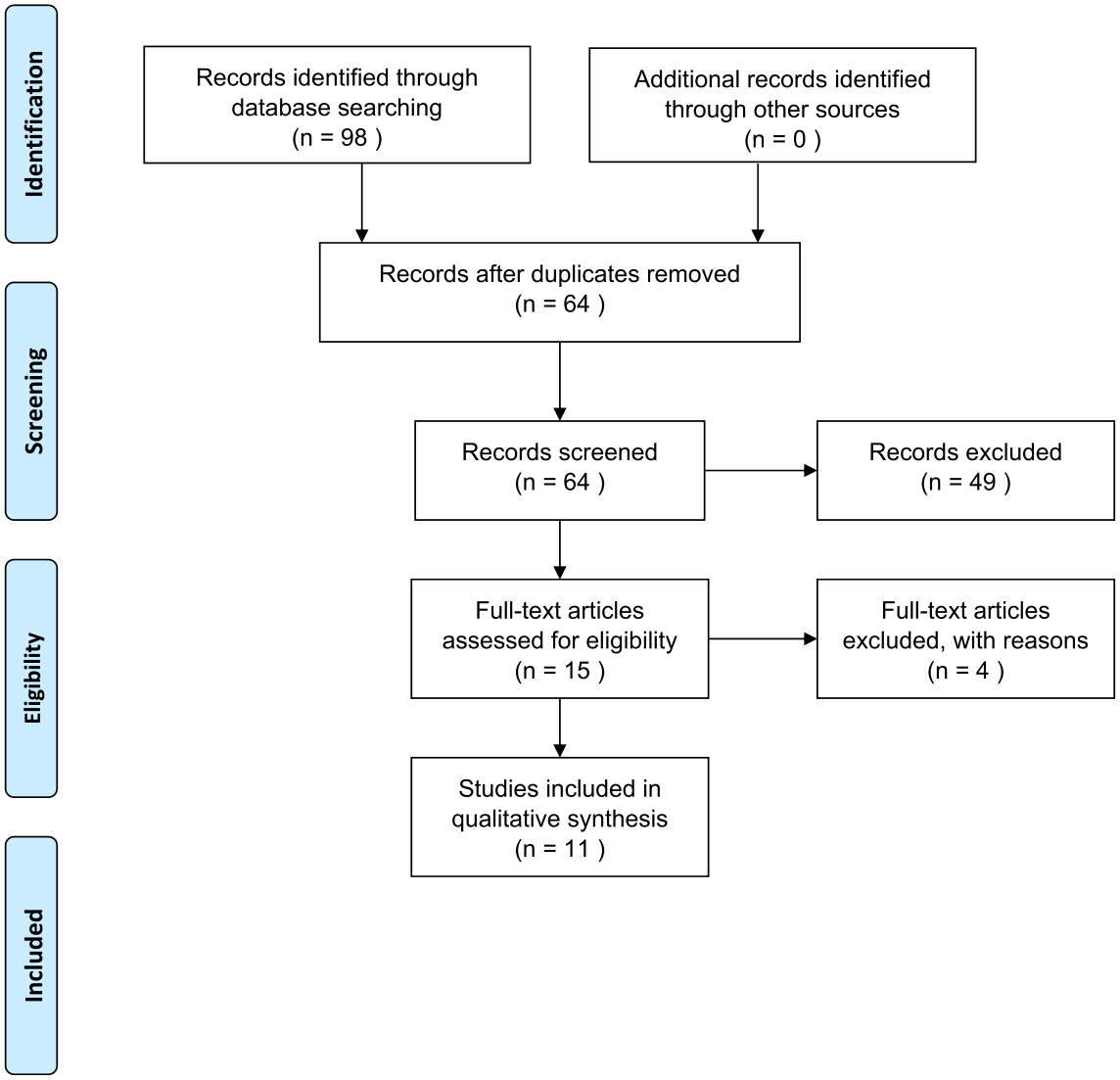

Fig. A. PRISMA flowchart (Moher et al., 2009) showing the retrieval process of articles included in the systematic review.

Table A
Overview of included studies.

Reference	Study design/number of cases	Medications use during pregnancy	Symptoms course of POTS in pregnancy	Antenatal complications	Mode of delivery	Labour analgesia/ anesthesia	Neonatal outcomes	Postnatal POTS symptoms
Kimpinski et al., 2010 (Kimpinski et al., 2010)	retrospective chart review/51 women - 116 pregnancies, parous Vs nulliparous	–	variable	miscarriage, placenta previa, placental abruption and malpresentation resulting in peripartum hysterectomy	–	–	live birth, no complications to baby	improved
Lide & Haeri, 2015 (Lide and Haeri, 2015)	case report/2	propranolol commenced at 15 weeks	1 exacerbation at 15 weeks	–	spontaneous vaginal	epidural without complication	live birth, no complications to baby	stable
		propranolol commenced at 10 weeks	1 exacerbation at 10 weeks	hyperemesis garvidarum	spontaneous vaginal	epidural without complication	live birth, no complications to baby	stable
Blitshteyn et al., 2012 (Blitshteyn et al., 2012)	self-reported questionnaires with longitudinal follow up/10 women - 42 pregnancies, 25 miscarriages, 17 live births	fludrocortisone, β-blockers, midodrine	variable - unchanged 20%, improved 40%, worsened 40%	hyperemesis garvidarum, tachycardia, hypotension, fatigue, presyncope, anaemia, pre-eclampsia	vaginal, emergency cesarean section, forceps delivery	epidural, general, unknown	prematurity (< 32 weeks), fetal distress syndrome	unchanged 20–40%, improved 10–30%, worsened 50%
Kanjwal et al., 2009 (Kanjwal et al., 2009)	retrospective chart review/22	β-blockers, midodrine, selective serotonin reuptake inhibitors, fludrocortisone	variable - unchanged 13%, improved 55%, worsened 31%	hyperemesis gravidarum, complete heart block	vaginal, cesarean section	–	Down's Syndrome, asymptomatic ostium secundum atrial septal defect, ventricular septal defect	unchanged 69%, worsened 27%, depression
Glatter et al., 2005 (Kanjwal et al., 2009)	case report/2	midodrine	variable - decompensation at 6 months, placed on bedrest at 7 months	hyperemesis gravidarum, severe dyspnoea, tachycardia, syncope	elective cesarean section at 37 weeks due to maternal clinical decompenssation	epidural without complication	live birth, no complications to baby	improved
		–	variable - decompensation at 6 months, bedrest at 30 weeks	hyperemesis gravidarum, syncope, tachycardia, premature labour at 30 weeks	elective cesarean section at 37 weeks due to maternal clinical decompenssation	–	live birth, no complications to baby	improved
Powless et al., 2010 (Powless et al., 2010)	retrospective chart review/7 women, 9 pregnancies	β-blockers, midodrine, fludrocortisone, pyridostigmine	variable	gestational hypertension, preterm premature rupture of membranes with premature onset of labour, oligohydramnios, chronic placental abruption, breech presentation, premature rupture of membranes	spontaneous vaginal, induced vaginal, elective cesarean section	epidural	live births	–
Pramya et al., 2012 (Pramya et al., 2012)	case report/1	metoprolol	stable	–	spontaneous vaginal	epidural without complication	live birth, no complications to baby	stable
McEvoy et al., 2007 (McEvoy et al., 2007)	case report/1	fludrocortisone, propranolol	stable	pregnancy induced hypertension	assisted forceps	epidural	live birth, no complications to baby	–
Corbett et al., 2006 (Corbett et al., 2006)	case report/1	metoprolol	worsened	–	emergency cesarean section for active phase arrest	epidural, proceeding to general analgesia post delivery for haemodynamic instability	live birth, no complications to baby	improved
Kodakkattil & Das, 2009 (Kodakkattil and Das, 2009)	case report/1	–	unchanged	threatened preterm labour, syncope with seizure	induced vaginal	epidural without complication	live birth, no complications to baby	stable
Jones & Ng, 2008 (Jones and Ng, 2008)	case report/1	–	worsened	–	elective cesarean section at 38 weeks	epidural without complication	live birth, no complications to baby	–

Appendix B. McMaster Critical Review Form for quantitative studies scores (Law et al., n.d.)

No	Reference	McMaster quantitative critical appraisal scoring items										
		1	2	3	4	5	6	7	8	9	10	Score
1	Kimpinski et. Al. 2010	Y	Y	Case-control	Y	Y	N/A	Y	Y	Y	Y	8/10
2	Glatter et. Al. 2005	Y	Y	Case study	Y	N/A	N/A	Y	Y	Y	Y	7/10
4	Kanjwal et. Al. 2009	Y	Y	Single case design	Y	N/A	CT	Y	Y	Y	Y	7/10
5	Blitshteyn et. Al. 2012	Y	Y	Single case design	Y	N/A	N/A	Y	Y	Y	Y	7/10
8	Pramya et. Al. 2012	Y	Y	Case study	Y	N/A	N/A	Y	Y	Y	Y	7/10
12	Lide and Haeri 2015	Y	Y	Case study	Y	N/A	N/A	Y	Y	Y	Y	7/10
13	Powless et. Al. 2010	Y	Y	Single case design	Y	N/A	N/A	CT	Y	Y	Y	6/10
14	McEvoy et. Al. 2007	Y	Y	Case study	Y	N/A	N/A	Y	Y	Y	Y	7/10
15	Corbett et. Al. 2006	Y	Y	Case study	Y	N/A	Y	Y	Y	Y	Y	8/10
16	Kodakkattil and Das 2009	Y	Y	Case study	Y	N/A	CT	Y	N/A	Y	Y	6/10
17	Jones and Ng 2008	Y	Y	Case study	Y	N/A	Y	Y	Y	Y	Y	8/10

Y = Yes, N = No, CT = Cannot tell, N/A = not applicable.
Item 1: Was the purpose stated clearly?
Item 2: Was the relevant background literature reviewed?
Item 3: Describe the study design.
Item 4: Was the design appropriate for the study?
Item 5: Was the sample described in detail? Was informed consent obtained?
Item 6: Were outcome measures reliable and valid?
Item 7: Was the intervention described in detail?
Item 8: If appropriate, were results reported in terms of statistical significance? Were analysis methods appropriate?
Item 9: Were all participants accounted for? If any participants dropped out from the study, were they accounted for?
Item 10: Were study conclusions appropriate given the study methods and results?

Appendix C. NHMRC Evidence Grading Matrix with overall scores from the review (NHMRC, 2009)

Component	A	B	C	D	Overall score
	Excellent	Good	Satisfactory	Poor	
Volume of evidence	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias	D
Consistance	All studies consistant	Most studies consistant and inconsistence may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistant	D
Clinical impact	Very large	Substantial	Moderate	Slight or restricted	D
Able to gener-alise	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population	B
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context	C

Appendix D. PRISMA 2009 Checklist (Moher et al., 2009)

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3–4
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5–7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	11–12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9–12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9–12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9–12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of the review or each meta-analysis done, including confidence intervals and measures of consistency.	9–12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11–12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23–26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23–26

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26–27
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Appendix E. List of included studies

1. Blitshteyn S, Poya H, Bett GC. Pregnancy in postural tachycardia syndrome: clinical course and maternal and fetal outcomes. J Matern Fetal Neonatal Med. 2012;25(9):1631–1634.
2. Corbett WL, Reiter CM, Schultz JR, Kanter RJ, Habib AS. Anaesthetic management of a parturient with the postural orthostatic tachycardia syndrome: a case report. BJA: The British Journal of Anaesthesia. 2006;97(2):196–199.
3. Glatter KA, Tuteja D, Chiamvimonvat N, Hamdan M, Park JK. Pregnancy in postural orthostatic tachycardia syndrome. Pacing Clin Electrophysiol. 2005;28(6):591–593.
4. Jones TL, Ng C. Anaesthesia for caesarean section in a patient with Ehlers-Danlos syndrome associated with postural orthostatic tachycardia syndrome. Int. 2008;17(4):365–369.
5. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Outcomes of pregnancy in patients with preexisting postural tachycardia syndrome. Pacing Clin Electrophysiol. 2009;32(8):1000–1003.
6. Kimpinski K, Iodice V, Sandroni P, Low PA. Effect of pregnancy on postural tachycardia syndrome. Mayo Clinic Proceedings. 2010;85(7):639–644.
7. Kodakkattil S, Das S. Pregnancy in woman with postural orthostatic tachycardia syndrome (POTS). J Obstet Gynaecol. 2009;29(8):764–765.
8. Lide B, Haeri S. A Case Report and Review of Postural Orthostatic Tachycardia Syndrome in Pregnancy. American Journal of Perinatology Reports. 2015;5(1):e033.
9. McEvoy MD, Low PA, Hebbar L. Postural orthostatic tachycardia syndrome: Anesthetic implications in the obstetric patient. Anesth Analg. 2007;104(1):166–167.
10. Pramya N, Puliyathinkal S, Sagili H, Jayalaksmi D, Reddi Rani P. Postural orthostatic tachycardia syndrome complicating pregnancy: a case report with review of literature. Obstetric Medicine (1753-495X). 2012;5(2):83–85.
11. Powless CA, Harms RW, Watson WJ. Postural tachycardia syndrome complicating pregnancy. J Matern Fetal Neonatal Med. 2010;23(8):850–853.

Appendix F. Excluded studies and reason for exclusion

1. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Postpartum postural orthostatic tachycardia syndrome in a patient with the joint hypermobility syndrome. Cardiol Res Pract. 2009;2009:187543

   Exclusion reason: Patient developed POTS in the post-partum period.

2. Kimpinski K, Iodice V, Low PA. Postural Tachycardia Syndrome associated with peripartum cardiomyopathy. Auton Neurosci. 2010;155(1–2):130–131

   Exclusion reason: Patient developed POTS in the post-partum period.

3. Lide B, Haeri S. A Case Report and Review of Postural Orthostatic Tachycardia Syndrome in Pregnancy. AJP Reports. 2014;5(1):e33-e36

   Exclusion reason: Links to 2015 article of the same entitled (included article).

4. Peggs KJ, Nguyen H, Enayat D, Keller NR, Al-Hendy A, Raj SR. Gynecologic disorders and menstrual cycle lightheadedness in postural tachycardia syndrome. International journal of gynaecology and obstetrics: The official organ of the International Federation of Gynaecology and Obstetrics. 2012;118(3):242–246

Exclusion reason: Participants were required to have a diagnosis of POTS for at least six months prior to enrolling in the study, however pregnancy was assessed historically with no record of whether patients had a pre-existing diagnosis of POTS before pregnancy.

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Glatter, K.A., Tuteja, D., Chiamvimonvat, N., Hamdan, M., Park, J.K., 2005. Pregnancy in postural orthostatic tachycardia syndrome. Pacing Clin. Electrophysiol. 28 (6), 591–593.

Jones, T.L., Ng, C., 2008. Anaesthesia for caesarean section in a patient with Ehlers-

Danlos syndrome associated with postural orthostatic tachycardia syndrome. Int. J. Obstet. Anesth. 17 (4), 365–369. http://dx.doi.org/10.1016/j.ijoa.2008.04.003.
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