Ivabradine-sensitive incessant atrial tachycardia during pregnancy: a case report

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Background
Automaticity is the dominant mechanism in maternal focal atrial tachycardia (FAT) during pregnancy and if incessant, can cause tachycardia-induced cardiomyopathy. Medication failure for FATs is common, however, for the subgroup due to increased automaticity ivabradine sensitivity has been described and may represent a valuable treatment option. Little data are available regarding the safety profile of ivabradine during pregnancy.

Case Summary
We report the case of a 38-year-old woman with background of peripartum cardiomyopathy and incessant atrial tachycardia with deteriorating ventricular function during her second pregnancy unresponsive to betablockade and demonstrating the immediate successful rate-controlling effect of ivabradine.

Discussion
Early recognition of persistent maternal FAT is essential due to its frequent association with tachycardia-mediated cardiomyopathy. Our case report highlights the challenges of providing an equally safe and effective treatment of these notoriously difficult to treat arrhythmias during pregnancy. Ivabradine in combination with a betablocker can be effective for abnormal automaticity but its safety profile during pregnancy remains uncertain.

Keywords
Ivabradine-sensitive atrial tachycardia • Focal atrial tachycardia • Abnormal automaticity • Tachycardia-induced cardiomyopathy • Peripartum cardiomyopathy • Case report

Introduction
Focal atrial tachycardias (FATs) are defined as organized atrial rhythms >100 b.p.m. initiated from a discrete origin and spreading over both atria in a centrifugal pattern. The term includes a pathophysiological heterogeneous group of arrhythmias caused by abnormal ectopic automaticity, triggered activity, or micro-reentrants. Automaticity is the dominant mechanism in maternal FAT during pregnancy1 and if incessant, can cause tachycardia-induced cardiomyopathy.2 Medication failure for FATs is common, however, for the subgroup due to

Learning points
• Ivabradine is an efficient alternative treatment option for rate control in a subset of incessant focal atrial tachycardia resistant to betablockers also in pregnant patients.
• The limited available data for ivabradine use during pregnancy does not suggest a major teratogenic risk in humans but the safety profile remains uncertain and foetal monitoring for structural abnormalities and growth restrictions is advised in pregnant women exposed to ivabradine.
increased automaticity ivabradine sensitivity has been described and may represent a valuable treatment option. Little data are available regarding the safety profile of ivabradine during pregnancy.

Peripartum cardiomyopathy is a rare form of heart failure manifesting in the last trimester or early postpartum period. It often presents as dilated cardiomyopathy with systolic dysfunction which can be complicated by arrhythmias or thromboembolic events. Pathophysiology remains unclear but research suggests vascular-hormonal pathways in patients with underlying predisposition.

We report the case of a 38-year-old female with a background of peripartum cardiomyopathy and incessant atrial tachycardia during her second pregnancy unresponsive to betablockade and demonstrating the immediate successful rate-controlling effect of ivabradine.

Timeline

Case presentation

A 38-year-old European woman with type I diabetes mellitus and corrected hypothyroidism and negative family history of dysrhythmias or cardiomyopathies was first noted to have a persistent asymptomatic tachycardia 110–120 b.p.m. during the third trimester of her first pregnancy. The 12-lead electrocardiogram (ECG) at the time confirmed P-wave morphology consistent with a sinus tachycardia with normal intrinsic atrioventricular conduction and narrow QRS complex. Reversible causes were ruled out and the tachycardia was attributed to the pregnant state. After delivery of her first son, the tachycardia persisted postpartum over several months and she was referred to Cardiology for suspected inappropriate sinus tachycardia. Apart from the elevated heart rate the physical exam was normal. A transthoracic echocardiogram (TTE) 8 months after delivery demonstrated a dilated left ventricle (LV) with severely impaired function [ejection fraction (EF) 15%], presence of an apical thrombus and an interatrial shunt. A cardiac magnetic resonance imaging (MRI) confirmed the echocardiographic findings and additionally diagnosed an ischaemic scar in the apex (figure 1) but coronaries were unobstructed on ECG-gated computed tomography coronary angiogram. A genetic screen within the 100 000 Genomes project did not reveal any abnormalities in the 84 genes associated with dilated cardiomyopathy known at the time. The main differential diagnosis was a late diagnosis of peripartum cardiomyopathy with secondary LV thrombus formation complicated by embolic myocardial
infarction, or myocarditis and a paradoxical coronary embolic event facilitated by the interatrial defect. With optimal medical heart failure therapy and Warfarin the left ventricular function fully recovered, the left ventricular thrombus resolved completely, and heart rate normalized within 6 months. A persistent foramen ovale closure was performed after recovery of LV function and thrombus resolution based on the differential diagnosis of paradoxical embolism. Warfarin was ceased. An attempt to wean the heart failure medication resulted in progressive LV dilatation (as documented in a routine follow-up cardiac MRI) within 3 months after stopping her betablocker and angiotensin-converting enzyme-inhibitor (ACEI) and were therefore reinstated. The patient remained asymptomatic throughout.

Three years later the patient became pregnant with her second child, requiring suspension of ACEI therapy. Bisoprolol was continued and she was closely monitored with clinical and echo surveillance by the Pregnancy Heart Team. Towards the beginning of the third trimester, the patient noted palpitations and a repeated TTE found a mildly impaired left ventricular EF of 46% (compared to previously 57%) and a heart rate of 120 b.p.m. No overt clinical signs of heart failure were present. The 12-lead ECG (Figure 2) demonstrated a regular organized atrial rhythm with 1:1 conduction to the ventricles with discrete monomorphic P waves separated by isoelectric intervals with upright P waves in the inferior leads, negative in aVL and I, and biphasic negative–positive in V1–V2. The electrocardiographical features were consistent with a left-sided FAT with suspected origin from the superior mitral annulus using the Kistler algorithm. A further up-titration of Bisoprolol to maximum dose failed to control her heart rate, worsened her fatigue, and caused loss of hypoglycaemia awareness.

Given the deterioration in LV function in the context of a persistent atrial tachycardia and the previous cardiomyopathy during her first pregnancy, treatment to rate control the arrhythmia was mandated; however, options in this circumstance were limited by the safety profile of commonly used antiarrhythmic drugs. Ivabradine was discussed considering the higher incidence of autonomic FATs during pregnancy and the recent evidence of its efficiency in this particular subset of arrhythmias. In view of the limited available data regarding the teratogenic risk of ivabradine, this option was reviewed with the Pregnancy Heart Team and pharmacists, as well as the patient. It was felt that the benefits would outweigh the risks and ivabradine was started at a dose of 5 mg twice daily. A three-lead 24 h Holter ECG was fitted and recording started parallel to commencing the treatment. The effect was observed ~6 h after the first dose with a successful reduction of the average heart rate to ~100 b.p.m. (Figure 3). Ivabradine was further increased to the target dose of 7.5 mg twice daily. A repeated TTE under improved rate control demonstrated an improved left ventricular function (LV EF 55%).

The patient was scheduled for obstetric foetal ultrasound scans at gestation Weeks 28, 32, and 36, which revealed no abnormalities, and had an uncomplicated vaginal delivery of a 3900 g healthy male infant at term. A 12-lead ECG 1 month postpartum showed spontaneous resolution of the atrial tachycardia and confirmed normal sinus rhythm.
Ivabradine was stopped and her betablocker continued. The ACEI has been reinstituted after the pregnancy. She has been symptom free since delivery.

Discussion

The term FAT includes a diverse group of arrhythmias caused by abnormal ectopic automaticity, triggered activity, as well as micro-re-entries. The incidence of associated structural heart disease is higher in FATs than in other paroxysmal supraventricular tachycardias and if incessant can cause tachycardia-induced cardiomyopathy.

During pregnancy abnormal automaticity was found to be the dominant mechanism for maternal FATs and they often manifest around a gestation age of 24–25 weeks. They can be accompanied by tachycardia-induced cardiomyopathy, but prognosis is generally good with the improvement of LV function and spontaneous resolution of the arrhythmia after delivery in the majority of patients. The underlying reason for this apparent transient predisposition for automatic FATs during pregnancy remains open but is likely multifactorial. First,
it has been described that the involved cells at sites of abnormal automaticity have nodal-like electrophysiological properties with both spontaneous automaticity (Phase 4 depolarization) and adenosine sensitivity. Their proarrhythmogenic potential may be unmasked by the increased beta-adrenergic sensitivity associated with normal pregnancy. Also the increase of plasma volume during pregnancy with subsequent autonomic adaptations and mechanical stress and stretch of the atrial walls may facilitate the occurrence of arrhythmias. Last but not least, animal studies found an up-regulation of If channels during pregnancy contributing to the normal increase in heart rate in pregnancy but possibly also predisposing for automatic FATs.

In adults with recurrent or incessant FATs catheter ablation is the first-line treatment as medication alone is often insufficient to control the tachycardia. In contrast, during pregnancy pharmacotherapy is usually preferred as a bridge to delivery and invasive treatments are reserved for highly symptomatic refractory arrhythmias. Recently, several case reports and series describe an ivabradine sensitivity for the subgroup of atrial tachycardias due to automaticity with or without tachycardia-induced cardiomyopathy. There are no well-controlled studies in pregnant women to inform about ivabradine-associated risks. In the large clinical trials of ivabradine in humans for indications of heart failure (SHIFT trial) and coronary artery disease (BEAUTIFUL and SIGNIFY trial) 3 women became pregnant and another 21 during post-marketing surveillance. For those with available follow-up information, there were no reports of foetal abnormality but two cases of growth restriction and premature birth. More recently a case series from the German Embryotox database including 38 women exposed to ivabradine in the first trimester or throughout the entire pregnancy, most commonly used for supraventricular tachycardias, did not find any major teratogenic risk.

Currently, the FDA recommends limiting its use during pregnancy if the benefit outweighs the risk and while under monitoring for preterm birth during the third trimester. The British National Formulary (BNF) of the National Institute for Health and Care Excellence (NICE) currently advises against its use in pregnant patients.

**Conclusion**

Our case demonstrates the importance of early recognition of persistent maternal FAT due to its frequent association with tachycardia-mediated cardiomyopathy. It highlights the challenges and difficulties of providing an equally safe and effective treatment of these notoriously ‘difficult to treat’ arrhythmias during pregnancy. Also it further contributes to the growing evidence of effective use of ivabradine in combination with a betablocker in suspected FATs due to abnormal automaticity. This has been recently acknowledged by inclusion of ivabradine in the latest ESC Guidelines for the management of supraventricular tachycardias in adults. However, there is no recommendation for the use in pregnant patients. Benefits and risks of ivabradine use must be thoroughly discussed with the Pregnancy Heart Team and the patient in view of the unclear safety profile during pregnancy.

**Lead author biography**

Johanna B. Tonko underwent her Medical Studies at the Medical University in Vienna, Austria, and the Université Paris Descartes, France. She completed her general internal medicine and general cardiology training in Zurich Switzerland 2013–2019. She has been a Clinical and Research Fellow for interventional electrophysiology and cardiac devices at Guy’s and St Thomas Hospital and King’s College London since 2020.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.
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 consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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