



Flecainide is a safe and effective treatment for pre-excited atrial fibrillation rapidly conducted to the ventricle in pregnant women: a case series

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Background

Pregnancy is associated with an increased incidence of cardiac arrhythmias likely due to hormonal, haemodynamic, and autonomic changes. Yet, there is little data available regarding the efficacy and safety of anti-arrhythmic agents to prevent pre-excited atrial fibrillation (AF) in pregnant women.

Case summary

We report on three pregnant women who developed AF rapidly conducted to the ventricle through an overt accessory pathway as the first manifestation of Wolff–Parkinson–White syndrome.

Discussion

All patients were treated with flecainide with neither arrhythmias recurrence nor adverse events of the treatment. Mechanisms of action and clinical efficacy of flecainide are discussed.

Keywords

Wolff–Parkinson–White syndrome • Flecainide • Malignant arrhythmia • Pre-excited atrial fibrillation • Sudden cardiac death • Ventricular fibrillation • Case series

Learning points

- Flecainide is effective to prevent Wolff–Parkinson–White associated arrhythmias without any foetal complications. Physicians should consider flecainide use during pregnancy even when pre-excited atrial fibrillation occurs.
- Electrophysiological study and catheter-based ablation should be considered in patients remaining symptomatic despite flecainide use.

Introduction

Pregnancy is associated with an increased incidence of cardiac arrhythmias likely due to hormonal, haemodynamic, and autonomic changes.¹ Arrhythmias generally occur with pre-existing symptoms but can also

manifest for the first time during pregnancy.² Supraventricular tachycardias (SVT) are the most common cause of cardiac arrhythmias in pregnant women and their clinical course is generally benign. However, because blood pressure during SVT is lower than normal, SVT can lead to foetal adverse events including respiratory distress,

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small foetus for gestational age, and prematurity. Because atrial fibrillation (AF) can be transmitted rapidly to the ventricle through an accessory pathway, life-threatening malignant ventricular arrhythmias affecting both the foetus and the pregnant woman may occur.

The two primary medical treatment options for SVT are the use of anti-arrhythmic medications and catheter ablation therapy. While radiofrequency catheter ablation is routinely performed there is still some reluctance to use intra-cardiac catheters in pregnant women. Radiation exposure can harm the foetus and complications associated with ablation techniques are not uncommon. The use of anti-arrhythmic agents is therefore recommended as first-line therapy over ablation techniques for the treatment of SVT in pregnant women.³ However, there is little data available regarding the efficacy and safety of anti-arrhythmic agents for the prevention of pre-excited AF in pregnant women.

Here, we report three cases in which pregnant women developed AF rapidly conducted to the ventricle through an overt accessory pathway as the first manifestation of Wolf–Parkinson–White (WPW) syndrome and were successfully treated with flecainide. There was no arrhythmia recurrence associated with the use of flecainide and foetal monitoring demonstrated no adverse events of the treatment in all cases. Mechanisms of action and clinical efficacy of flecainide are discussed.

Timeline

| Patient | 1 | 2 | 3 |
|--------------------------|--|--|--|
| Prior to pregnancy | Brief episodes of palpitations | Asymptomatic | Asymptomatic |
| At presentation | <ul style="list-style-type: none"> Dizziness, palpitations followed by cardiac arrest secondary to ventricular fibrillation (VF) Electrocardiogram (ECG) after VF was converted to sinus rhythm (SR) revealed left-sided accessory pathway | <ul style="list-style-type: none"> Palpitations, presyncope-ECG: irregular wide complex tachycardia converted to SR after 100 mg flecainide Electrocardiogram after SR resumed showed evidence of left-sided accessory pathway | <ul style="list-style-type: none"> Palpitations and dizziness-ECG: normal Holter monitoring: regular narrow QRS tachycardia followed by irregular wide QRS tachycardia |
| Follow-up until delivery | Asymptomatic with 300 mg flecainide | Asymptomatic with 200 mg flecainide | Asymptomatic with 150 mg flecainide |
| After delivery | Electrophysiological study (EPS): left-lateral accessory pathway. Anterograde effective refractory period of the accessory pathway (AERPAP) = 210 ms | EPS: left-lateral accessory pathway and AERPAP = 240 ms | EPS: antero-septal accessory pathway that conducted only in the retrograde conduction |

Case presentation

Case 1

Patient 1 was a 33-year-old pregnant primipara (27 weeks of gestation) admitted to the intensive care unit for dizziness and palpitations. She had a clinical history of brief periods of palpitation prior to her pregnancy, typically lasting seconds. At admission, physical

examination showed regular tachycardia with normal blood pressure (100/70 mmHg) and no evidence of respiratory failure. Electrocardiogram (ECG) showed narrow QRS complex tachycardia (rate 180 b.p.m.). Ventricular fibrillation (VF) occurred a few minutes later, briefly preceded by an irregular tachycardia with wide QRS complexes. Sinus rhythm resumed after the delivery of two external shocks at 150 and 300 J (Figure 1A) and ECG revealed a left-sided accessory pathway (Figure 1B). Flecainide (300 mg daily, prolonged-release capsules) was started and continued until the end of pregnancy. Five days after initiation of the treatment flecainide plasma level was 0.316 mg/L and increased up to 0.56 mg/L 2 months later (normal range for flecainide plasma level: 0.2–0.8 mg/L). Monthly foetal monitoring revealed normal growth, and vaginal delivery occurred at Week 37 without complications. The patient presented recurrent palpitations related to narrow QRS tachycardia 1 month after delivery. An electrophysiological study (EPS) was performed 1 month later, demonstrating the presence of a left anterolateral accessory pathway and an effective anterograde refractory period of 240 ms. This accessory pathway was successfully ablated and to our knowledge she had no further events or complications.

Case 2

A 32-year-old pregnant (10 weeks of gestation) multipara was admitted to the intensive care unit for palpitations and presyncope. She

had a clinical history of post-partum thyroiditis. At admission, physical examination showed irregular tachycardia with normal blood pressure (95/65 mmHg) and no evidence of respiratory failure ECG showed irregular wide QRS complex tachycardia with right bundle branch morphology suggestive of AF conducted to the ventricles (Figure 2A). Intravenous flecainide (100 mg) effectively restored sinus rhythm and ECG demonstrated a left-sided accessory pathway (Figure 2B). Transthoracic echocardiography was unremarkable. Blood samples showed low thyroid-stimulating hormone (TSH)



Figure 1 (A) Electrocardiogram recordings from the automated external defibrillator. Irregular wide QRS complex tachycardia degenerated into ventricular fibrillation (black-filled arrow) that is converted to sinus rhythm after two external shocks. (B) Electrocardiogram recording after external defibrillation reveals manifested accessory pathway.

levels without elevated T3 or T4 suggesting thyrotropic action by human chorionic gonadotropin. Oral flecainide at a daily dose of 200 mg (prolonged-release capsules) was started and maintained at this dose until delivery, since sequential flecainide blood levels remained in the normal range (0.38 mg/L at Week 20 and 0.23 mg/L at Week 32). ECG showed the disappearance of the pre-excitation pattern and the patient remained free of symptoms during follow-up (Figure 2C). Monthly foetal monitoring revealed normal growth, and vaginal delivery occurred at term with no maternal or foetal complications. An EPS was performed 4 months after delivery and demonstrated the presence of a postero-lateral accessory pathway with an anterograde effective refractory period measured at 210 ms. Ablation of the accessory pathway was performed with immediate success. While the accessory pathway reappeared 2 months later, a re-do procedure was successfully performed. To our knowledge, she had no further events or complications.

Case 3

A 26-year-old pregnant (28 weeks of gestation) multipara consulted a cardiologist following episodes of palpitation and dizziness. She reported suffering similar symptoms during her first pregnancy but did not seek medical assistance. Cardiac and respiratory examination were normal. Electrocardiogram demonstrated normal sinus rhythm with narrow QRS complexes and no pre-excitation. Transthoracic echography showed no evidence of cardiopathy. Fourteen-day Holter monitoring showed intermittent pre-excitation and a symptomatic (palpitations and lipothymia) episode of regular narrow QRS tachycardia with a heart rate of 235 b.p.m. converting to rapid and irregular wide QRS complexes tachycardia that spontaneously resumed to sinus rhythm (Figure 3). Oral flecainide at a daily dose of 150 mg (prolonged-release capsules) was started and continued throughout pregnancy, and the patient had no

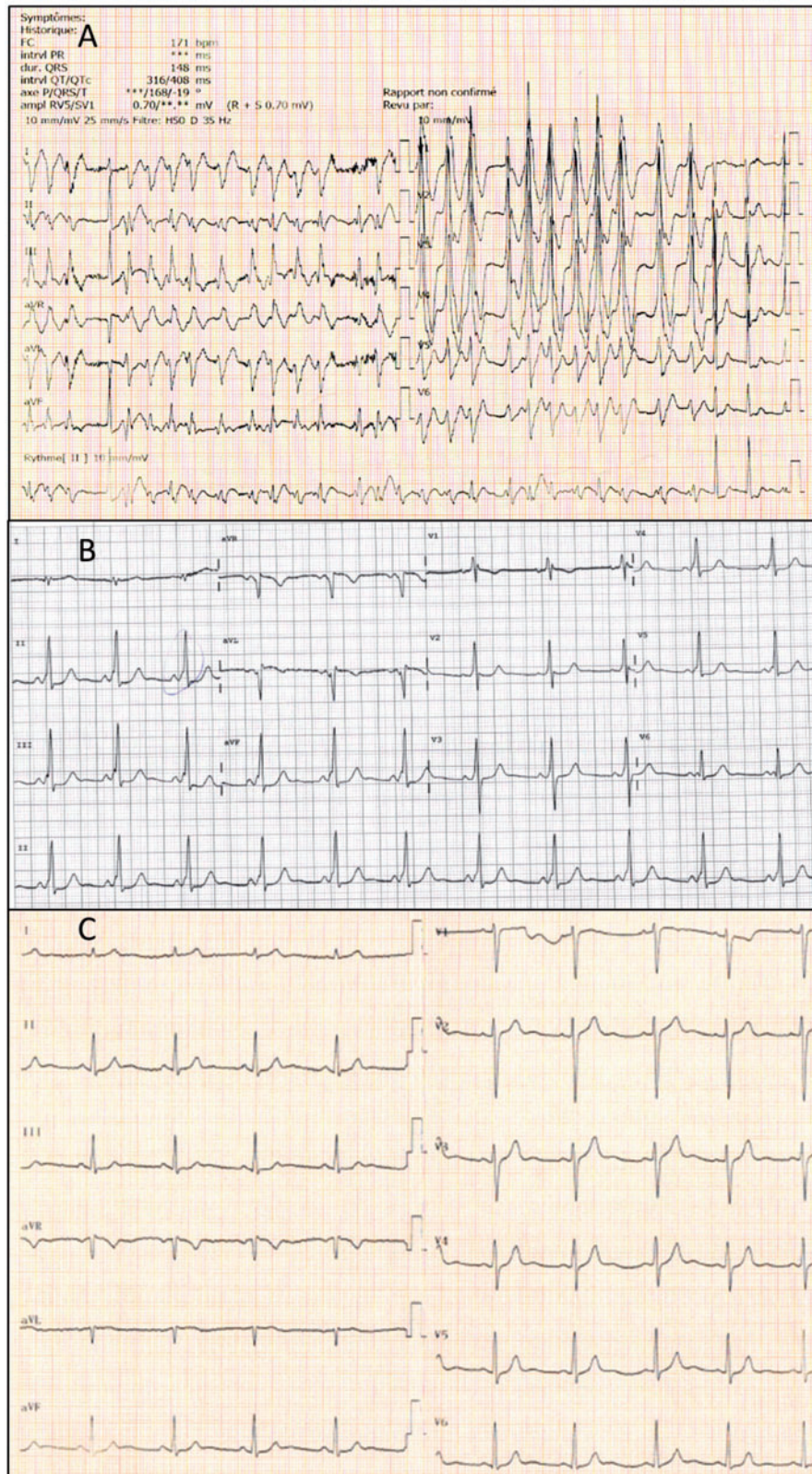


Figure 2 (A) Electrocardiogram on admission was suggestive of atrial fibrillation conducted to the ventricles through an accessory pathway. Minimum pre-excited RR interval was 250 ms (black-filled solid star). (B) Electrocardiogram after termination of atrial fibrillation episode with the infusion of 100 mg flecainide revealed the presence of a left-sided accessory pathway. (C) Electrocardiogram during follow-up and while the patient was taking oral flecainide showed the disappearance of the pre-excitation.

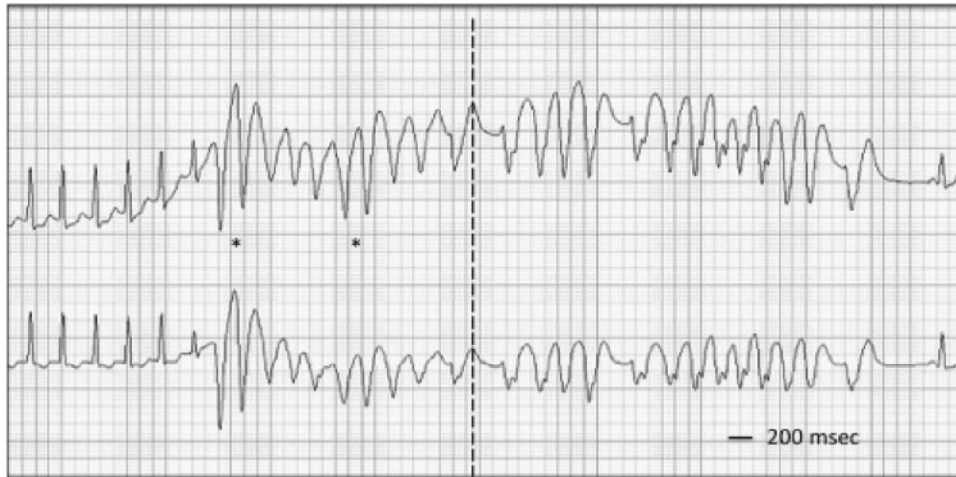


Figure 3 Holter monitoring revealed rapid (cycle length = 255 ms) regular narrow QRS tachycardia converted to rapid irregular wide tachycardia (black-filled star) that eventually resumed to sinus rhythm with short PR interval. Note that minimum RR intervals during irregular tachycardia were 180 ms. Paper speed is 50 mm/s.

symptom recurrence. An EPS was performed 3 months after vaginal delivery, demonstrating the presence of an antero-septal accessory pathway that conducted only in the retrograde direction and that was successfully ablated. To our knowledge, she had no further events or complications.

Discussion

In this case series of pregnant women, we found that flecainide was effective to prevent WPW-associated malignant arrhythmias without any foetal complications.

Pregnancy is associated with an increased risk of SVT that can potentially lead to adverse maternal and/or foetal outcomes. Atrioventricular nodal re-entrant tachycardia and orthodromic atrioventricular re-entrant tachycardia associated with WPW syndromes are the two most frequent causes of SVT in pregnant women. Manifest accessory pathways occur in 0.1–0.3% of the general population and symptoms related to WPW syndrome are generally linked to atrioventricular re-entrant tachycardia (AVRT). Rarely anterograde conduction through an accessory pathway can occur during AF with the potential of degenerating into VF if conduction is particularly rapid. In the presence of an accessory pathway with anterograde conduction it is estimated that the 10-year risk of sudden cardiac death ranges between 0% and 0.15%.⁴ Previous history of symptomatic tachycardia, young age, multiple accessory pathways, refractory periods of the accessory pathway <240 ms, and shortest pre-excited RR intervals ≤250 ms have been associated with an increased risk of malignant arrhythmias. Ventricular fibrillation can also be the first manifestation of the WPW syndrome as it occurred in the Patient 1. Patients 2 and 3 did not present with VF or sudden cardiac death but very short (≤250 ms) pre-excited RR that occurred during AF (Figures 2A and 3A) undoubtedly

predisposed them to VF. It is noteworthy that Patient 3 had intermittent pre-excitation on the 24-h Holter monitoring which is usually associated with a benign form of WPW. Intermittent pre-excitation is associated with longer effective refractory periods.⁵ However, even in these low-risk patients some have SPRRI <250 ms making them vulnerable to developing fast conducted pre-excited AF.⁵ Kappenberger *et al.* reported rapid pre-excited ventricular response to AF in a patient with intermittent pre-excitation and proposed that some accessory pathway may be extremely sensitive to catecholamines.⁶ Electrophysiological study revealed that the accessory pathway conducted only in the retrograde direction before and after isoproterenol. We considered two main hypotheses to explain the lack of anterograde conduction. First high sympathetic tone that probably occurred during the episode of palpitation might have facilitated anterograde conduction through the accessory pathway. Second catheter manipulation might have resulted in mechanical modulation of the accessory pathway. Nonetheless, it remains also possible that irregular wide QRS complex tachycardia recorded in this patient (Figure 3) corresponded to ventricular tachycardia rather than pre-excited AF.

Randomized clinical studies have demonstrated that medication targeting the accessory pathway is effective in preventing re-entrant tachycardias associated with WPW syndrome.³ Flecainide acetate is a sodium channel-blocking drug that decreases the rate of rise of phase 0 but has little effect on the duration of the action potential. Flecainide prolongs the effective refractory period of the right atrium, the right ventricle, and the atrio-ventricular node and has greater electrophysiological effects on accessory pathways. Neuss *et al.*⁵ investigated the electrophysiological effects of flecainide on accessory pathways in 12 patients with WPW syndrome. Intravenous administration of 100 mg flecainide increased the ventriculo-atrial block by

an average of 130 ms in 10 of 11 patients with retrograde conduction through the accessory pathway. They also found that intravenous administration of 100 mg flecainide resulted in a complete block of the accessory pathway in sinus rhythm in 7/12 patients, as occurred in Patient 2 in our series. Additionally, rapid atrial pacing induced AF with rapid ventricular response in five patients, and flecainide slowed ventricular response in three and complete block of the accessory pathway in two of these patients, as occurred in Patient 1 in our series. Kappenberger *et al.*⁶ reported similar findings in nine patients with severe WPW syndrome, in which 2 mg/kg flecainide increased shortest ventricular responses during pre-excited AF from 218 to 320 ms and converted AF to sinus rhythm in four patients. The usefulness of flecainide in treating patients at risk of malignant arrhythmias is further supported by its ability to prevent AF recurrence.⁷ Flecainide exhibits properties capable of preventing malignant arrhythmias by both preventing AF or AVRT-induced AF, and increasing the RR interval of pre-excited AF. We found no evidence in the literature of patients presenting with pre-excited AF, while taking flecainide but SVT recurrence has been reported in up to 30% of the patients.³ The use of flecainide in pregnant women appears safe, as it has not been associated with malformative syndromes and is currently used to treat severe foetal arrhythmias.⁸

Catheter-based approaches have been proven effective for the prevention of tachycardias associated with WPW. However, performing accessory pathway ablation in pregnant women exposes the foetus and the women to potentially harmful radiation and side effects of the ablation technique. Zero-fluoroscopy catheter ablation for severe arrhythmia in pregnant women is possible and has been reported in a single case in a small series, but this technology still exposes the patient and the foetus to vascular access, catheter manipulation, and the delivery of radiofrequency energy with an incidence of complications as high as 3%.^{3,9–11} Physicians should also be aware that the failure rate of accessory pathway ablation ranges between 5% and 7% and may be delayed after apparent immediate success.³

In conclusion, this case series supports the use of flecainide as a reasonable therapeutic option for the treatment of WPW-associated malignant arrhythmias in pregnant women. We strongly believe these data should be provided to pregnant women suffering from malignant pre-excited tachycardia in order to respect shared decision-making process. We strongly believe flecainide should be preferred over ablation in low-volume centres. Ablation with zero or near-zero fluoroscopy should be reserved to highly trained operators that can offer such a procedure with a high likelihood of success and minimal risk of complications.

If flecainide is preferred over catheter-based ablation we recommend, before hospital discharge, to titrate flecainide until therapeutic blood concentration is achieved. Then flecainide blood concentration should be measured every 2–3 months in order to ascertain flecainide blood levels are maintained within therapeutic ranges. Special attention should be given during the third trimester when the volume of distribution increases.

Lead author biography



Samuel Chauveau is a cardiac electrophysiologist working in Lyon, France. After obtaining his medical degree in France in 2012 he worked two years as a fellow-researcher in the laboratory of Biophysics and Biology (*Prs Ira S. Cohen and Michael R. Rosen*, Stony Brook, NY, USA). He also gained expertise in managing patients with inherited cardiac

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Supplementary material

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

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

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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