

Successful in utero transesophageal pacing for severe drug-resistant tachyarrhythmia



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Sustained fetal tachyarrhythmia can evolve into a life-threatening condition in 40% of cases when hydrops develops, with a 27% risk of perinatal death. Several antiarrhythmic drugs can be given solely or in combination to the mother to achieve therapeutic transplacental concentrations. Therapeutic failure could lead to progressive cardiac insufficiency and restrict therapeutic options to either elective delivery or direct fetal administration of antiarrhythmic drugs, which may increase the risk of death. We report for the first time successful fetal transesophageal pacing to treat a hydropic fetus with drug-resistant tachyarrhythmia.

Key words: fetal, fetoscopy, pacing, surgery, tachyarrhythmia

A 28-year-old pregnant mother, at 27 5/7 weeks of gestation in her second pregnancy was referred after the discovery of a fetal tachyarrhythmia that had been discovered by fetal auscultation at routine follow-up evaluation. This pregnancy had been uneventful: ultrasound examinations were normal in the first and second trimester, and fetal movements remained normal. Fetal echocardiography diagnosed atrial flutter as the cause of tachyarrhythmia, with atrial and ventricular frequencies of 440 and 220 bpm, respectively, that were compatible with a 2:1 atrial flutter (Figure 1, A) and moderate mitral and tricuspid regurgitations, which were considered functional in the context.

The fetus was hydropic with moderate pericardial, thoracic, and peritoneal effusions. After a normal electrocardiogram and routine blood tests, the mother was hospitalized and given digoxin and flecainide.^{1–3} Serial follow-up echocardiography showed worsening of hydrops without return to sinus rhythm. On day 7, treatment was switched for amiodarone.⁴ Steroids (betamethasone) were also given for fetal lung maturation.

After 5 days of amiodarone, at 29 3/7 weeks of gestation, hydrops had worsened, with associating subcutaneous edema, with persisting atrial flutter, and with worsening tricuspid and mitral regurgitations. Given the failure of 2 lines of medical treatment and progressive hydrops, in utero transesophageal pacing (IUTP) was considered as a third-line option, along with elective delivery and third-line antiarrhythmic drugs by direct intracardial administration. The mother was counselled based on efficacy and safety of transesophageal pacing in newborn infants with atrial flutter^{5,6} and on the possible adverse events and inefficacy of third-line medical therapies and the growing risk of intrauterine fetal death.^{2,4} Preterm elective delivery was not considered a choice, given the early gestational age. Despite the associated risk of iatrogenic preterm premature rupture of the membranes and the

recent concerns raised by fetal anesthesia,⁷ this innovative treatment was advised by both cardiologists and perinatologists; the patient opted for fetoscopic IUTP.

At 29 4/7 weeks of gestation, after 2 weeks of antiarrhythmic therapy, a fetoscopy was performed under maternal epidural analgesia, continuous infusion of atosiban, and antibiotic prophylaxis by cefazolin. The video of the whole procedure is presented in the Appendix. Fetal anesthesia and paralysis were obtained by an injection of sufentanil and atracurium besylate (a curare) in the umbilical vein under ultrasound guidance. A 10F (3.3 mm) introducer (Pinnacle introducer; Terumo Medical Corporation, Somerset, NJ) was inserted in the amniotic cavity with a Seldinger technique, under continuous ultrasound guidance and aiming towards the fetal mouth. A 3-mm curved cannula receiving a 2-mm 0-degree semirigid fetoscope (Karl Storz GmbH, Tuttlingen, Germany) was inserted in the fetal esophagus. The position of the distal tip of the cannula was placed right above the heart under ultrasound guidance (Figure 2). The fetoscope was then retrieved from the cannula and replaced by a 6F (2 mm) bipolar pacing esophageal lead (FIAB Esokid 4S, Firenze, Italy) and positioned right behind the left atrium. The lead was connected to an asynchronous esophageal pacemaker (FIAB 2007, Firenze Italy). Pacing rate was increased incrementally until atrial capture, monitored by continuous echocardiography, and then increased to 640 beats/min at a pulse amplitude of 5 mA with 2-millisecond pulse width. Two 6-second bursts with these settings were not effective. Pacing parameters were then set at 10 mA/5 millisecond at the same cycle length. Two bursts of 6 seconds with these settings converted the rhythm to atrial fibrillation along with periods of sinus rhythm (Figure 1, B). Conversion to

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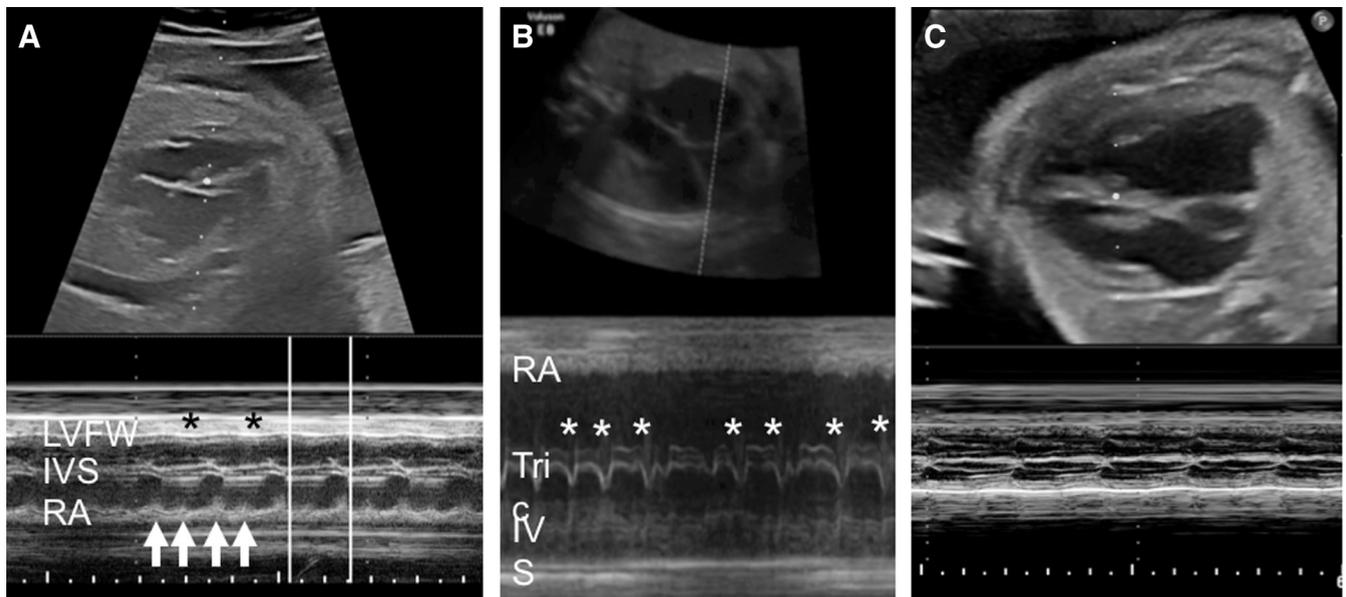
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FIGURE 1
M mode echocardiography



M mode echocardiography at referral demonstrates **A**, atrial flutter, **B**, right after in utero transesophageal pacing demonstrating atrial fibrillation, and **C**, on day 1 after in utero transesophageal pacing that demonstrated normal ventricular rate. *Arrows indicate ventricle systole; stars indicate auricular systole.*

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intermittent atrial fibrillation, auguring restoration of sinus rhythm, was considered a successful result⁵; the probe was retrieved, and the fetoscope was reinserted to visualize the absence of local damage on the esophageal walls. The complete intrauterine procedure lasted 18 minutes.

Postoperative follow-up evaluation 2 hours later found continuous sinus rhythm, without any paroxysmic bursts of atrial fibrillation, as confirmed by a normal cardiocography (Figure 3). The rest of the postoperative course was uneventful. The mother was discharged 4 days after surgery with signs of regressing hydrops and persistent sinus rhythm (Figure 1, C). Amiodarone was continued for 7 days and then replaced with digoxin that was continued up until delivery, with maternal serum levels within the lower therapeutic range.

Weekly ultrasound follow-up evaluation consistently found sinus rhythm at 140 beats/min, with a gradual resolution of hydrops over 2 weeks. At 32 weeks of gestation, hydrops had resolved completely, as did mitral and tricuspid regurgitations.

Labor was induced at 38 2/7 weeks of gestation that resulted in the vaginal delivery of a healthy 3660 g male neonate (Apgar score was 10 at 5 minutes; umbilical artery pH=7.25). Immediate neonatal cardiac assessment with electrocardiogram and echocardiography was considered normal. No antiarrhythmic treatment was indicated, and mother and child were discharged 2 days after delivery. At 1 month, Holter monitoring showed permanent sinus rhythm.

Commentary

Although postnatal management of tachyarrhythmia is well-established, its prenatal management is often challenging. Postnatal treatment options comprise antiarrhythmic drugs, external, intracardiac and transesophageal pacing, and even radiofrequency catheter ablation in older children.⁸ In the newborn infant, transesophageal pacing or external cardioversion are effective methods to restore sinus rhythm in drug-resistant or hemodynamically compromised cases, whereas prenatally, antiarrhythmic drugs are the only option so far, with an overall success of 50–80%.²

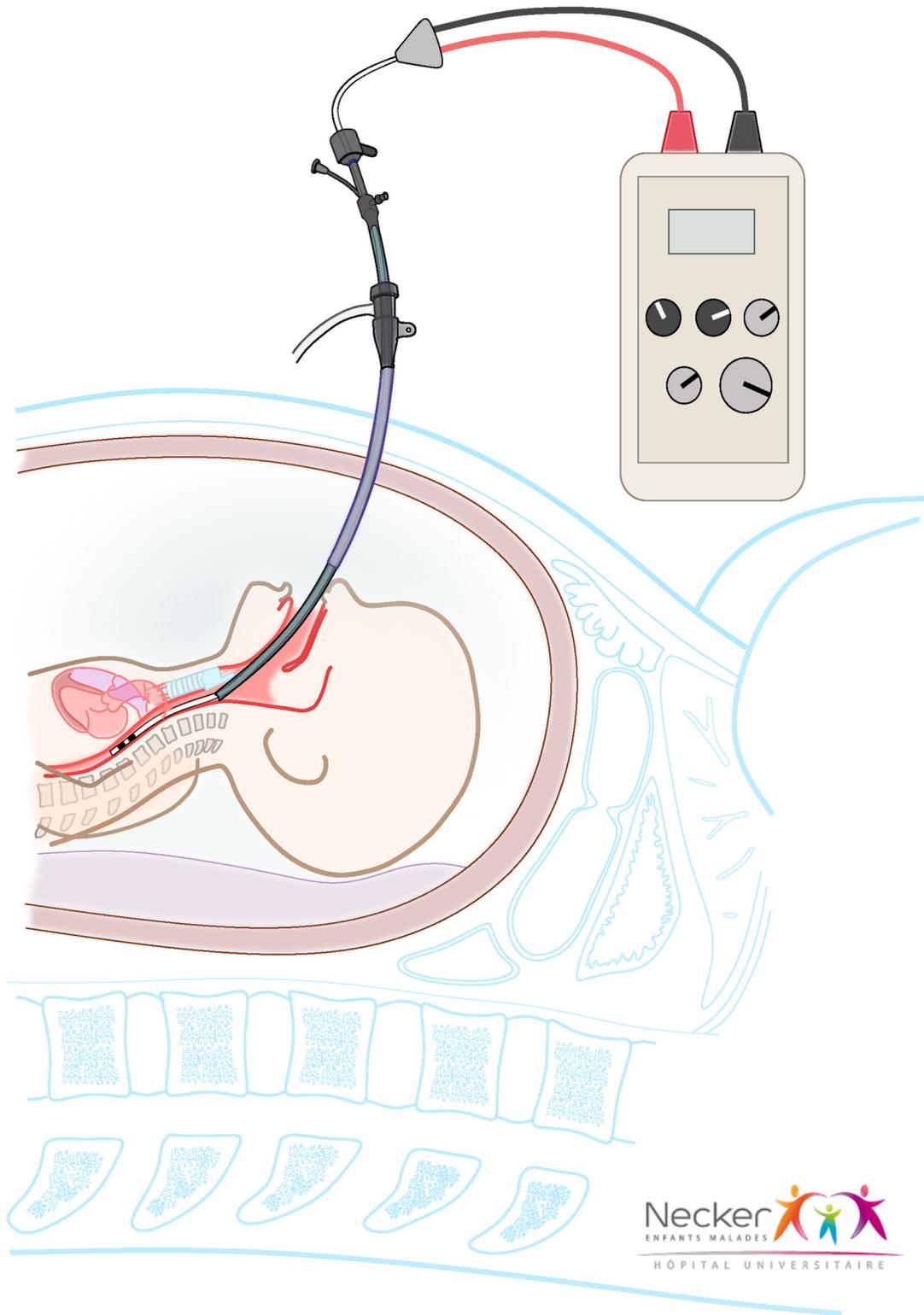
Attribution of success to in utero pacing

This case demonstrates the technical feasibility and possible efficacy of IUTP for atrial flutter. Given the evolution before surgery and the immediate effects of the procedure, IUTP can be credited for the successful outcome in our case.

The coincidence of a delayed effect of medical therapy exactly when pacing was performed is highly unlikely in our case. Conversion from atrial flutter to atrial fibrillation during antitachycardia pacing is a well-documented phenomenon, usually preceding the return to sinus rhythm,^{5,6} especially in the smallest individuals whose atrial myocardium mass is not sufficient to support sustained atrial fibrillation.⁹ Nonetheless, the success of pacing probably was potentiated by the 2 lines of preoperative antiarrhythmic drugs given over 2 weeks.

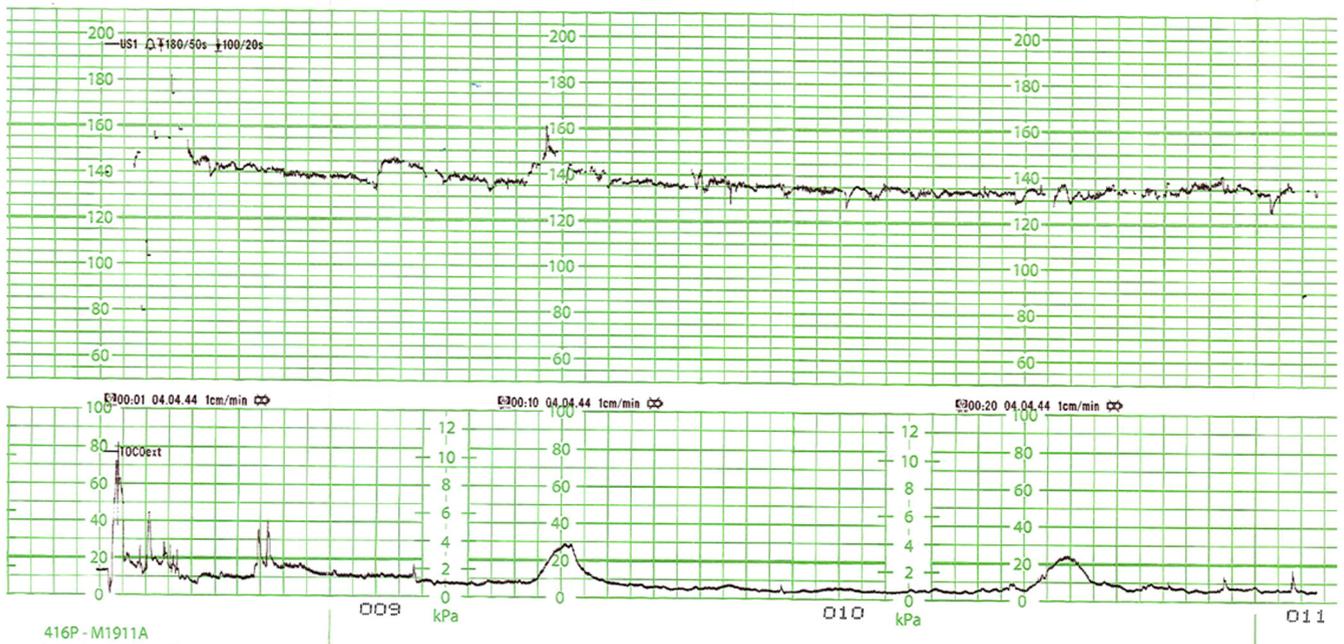
We acknowledge that the choice of drugs that was adopted in our case is debatable and that we cannot rule out the possibility that a different set of drugs could have avoided the need for IUTP. Indeed, uncertainties remain regarding

FIGURE 2
Schematic view



Schematic view of the fetoscopic approach of the fetal esophagus for in utero pacing.
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FIGURE 3
Cardiotocography performed 2 hours after surgery



Baseline heart rate is 135-140 beats per minute with normal oscillations during the 25-minute recording.

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the best first-line drug or combination of drugs and how to manage failure in the context of a potentially worsening fetal condition. An ongoing trial will attempt to answer these questions but is far from completion.¹⁰ Nonetheless, transplacental sotalol has been suggested as a safe and effective treatment for atrial flutter; despite the limited evidence of its efficacy in case of hydrops, it could have been a good candidate drug in first-line therapies in our case, alone or in combination.^{2,11-13}

Aside from sotalol, a few alternative third-line drugs or combinations of drugs could have been considered before IUTP, including direct intracardial or intramuscular administration.^{14,15} However, lethal accidents have been reported with the use of direct fetal administration.¹⁶

Safety of the procedure

The risks of IUTP are limited compared with other invasive prenatal cardiac interventions (such as percutaneous valvuloplasty,¹⁷ atrial septostomy,^{18,19} or

resection of pericardial teratomas²⁰) or extracardiac surgeries (such as endoscopic repair of myelomeningoceles).^{21,22} The risks of IUTP are those of the fetoscopic surgical approach of the esophagus and those of cardiac pacing.

Risks of fetoscopy. Technically, this surgical procedure is comparable with prenatal fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia;²³⁻²⁶ iatrogenic preterm premature rupture of the membranes and its associated morbidity are the main surgical complication, which occurs in 17% of cases. Given that the introducer's diameter, gestational age, and surgical route are close to the setting of fetoscopic endoluminal tracheal occlusion, a similar rate of preterm premature rupture of the membranes is to be anticipated with IUTP.

Specific risks of transesophageal pacing in the fetus. Postnatally, transesophageal pacing carries potential risks not only

of ventricular fibrillation, if the ventricle is captured instead of the atrium, but also of sinus node depression after reduction because of previous antiarrhythmic therapy. Therefore, postnatally, transesophageal pacing is performed under continuous electrocardiogram and with immediate access to an external defibrillator and external pacemaker. In our case, atrial capture was secured by ultrasound-guided placement of the pacing lead and continuous echocardiographic monitoring. The same lead offers the possibility of atrial escape pacing in the event of a prolonged pause after reduction, along with rescue intracardial injection of adrenalin.

Place of IUTP in the management of fetal tachyarrhythmia

The place of IUTP in the management of fetal tachyarrhythmia is to be balanced with the risks of medical therapy, the severity of the condition (ie, hydrops and cardiac failure),²⁷ and the cause of tachyarrhythmia.

Antiarrhythmic drugs can lead to increased morbidity. Despite their undisputed efficacy, antiarrhythmic drugs can lead to increased morbidity for the mother, fetus, and neonate. Among all potential antiarrhythmic drugs that can be used in fetal tachyarrhythmia, amiodarone carries the highest risk, given its potential impact on both the maternal and fetal thyroid functions. Although transplacental pharmacokinetics of antiarrhythmic drugs have been studied,²⁸ the resulting fetal concentrations can vary widely, especially in case of hydrops that reduces transplacental drug transfer.^{15,29,30} Furthermore, in case of atrial flutter specifically, medically slowing the atrial cycle can increase the ventricular response when 1:1 atrioventricular conduction occurs and lead to intractable ventricular dysfunction.

Transplacental antiarrhythmic drugs. The efficacy of transplacental antiarrhythmic drugs is delayed, sometimes requiring up to 3 subsequent lines of treatment, although the growing risks of cardiac failure, hydrops, and fetal death increase with time. Therefore, IUTP, which aims to restore sinus rhythm promptly, is a legitimate option in severe cases, in addition to transplacental antiarrhythmic therapy.

Two main causes of fetal tachyarrhythmia. The 2 main causes of fetal tachyarrhythmia are atrial flutter in 20–30% of cases and reentrant tachycardia that is mediated by an accessory pathway (atrioventricular reentrant tachycardia) in >60% of cases.^{31,32} In atrial flutter, the macro-reentrant circuit can be terminated easily by pacing, and recurrence is uncommon, which allows the withdrawal of antiarrhythmic therapy after reduction.³³ Although atrial flutter is the ideal candidate for IUTP, atrioventricular reentrant tachycardia is also amenable to pacing. In those cases, IUTP could be considered a rescue therapy in young fetuses or as an alternative to early delivery, along with transplacental drug therapy in order to minimize the risk of recurrence.

However, some rare fetal arrhythmias are not candidates for IUTP.³⁴ Ectopic

atrial tachycardia cannot be corrected by pacing, and permanent junctional reciprocating tachycardia that is mediated by decremental accessory pathway is too prompt to recur to be a good candidate for IUTP. Apart from fetal tachyarrhythmia, several rarer conditions could also benefit from IUTP: not only arrhythmia in long QT syndrome type 2 but also complete atrioventricular block³⁵ with very low escaping heart rate, where IUTP before delivery could facilitate perinatal management that often is facing profound hemodynamic instability.

Comment

IUTP is a potentially life-saving procedure that should be considered in the management of drug-resistant tachyarrhythmia, particularly atrial flutter, in combination with antiarrhythmic drugs. It is important that this message reaches the maternal-fetal medicine community to increase the awareness of the feasibility of this procedure. Indeed, these cases could be addressed to superspecialized centers instead of planning a semielective preterm delivery in a critical cardiac condition without considering this novel approach. ■

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