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Intrauterine therapy of fetal tachyarrhythmias: Intraperitoneal administration of antiarrhythmic drugs to the fetus in fetal tachyarrhythmias with severe hydrops fetalis

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1 Introduction

Protracted periods of fetal tachyarrhythmia (supraventricular tachycardia, atrial flutter and atrial fibrillation) may cause congestive heart failure and fetal death in the presence of non-immune hydrops fetalis. If there are contraindications to immediate delivery, such as fetal immaturity, transplacental therapy of the fetus can be achieved by administering antiarrhythmic agents that can cross the placenta to the mother. This has proven to be successful in a number of cases [1, 2, 9, 11, 13].

Publications on fetal tachyarrhythmia and our own observations show that, particularly in tachyarrhythmias with advanced states of non immune hydrops fetalis, transplacental antiarrhythmic therapy of the fetus produces either no or only a temperary cardioversion in which the hydrops fetalis remains constant or continues to increase. In such fetal emergency conditions it seems advisable to give antiarrhythmic agents directly to the fetus in addition to the transplacental route. In the presence of marked ascites the intraperitoneal administration of antiarrhythmic drugs using ultrasound monitoring is technically simple, can be repeated and is most effective. This will be demonstrated on the basis of the following two cases with supraventricular tachycardia or atrial flutter, both associated with severe hydrops fetalis.

Curriculum vitae

ULRICH GEMBRUCH, *M. D., was born in 1954. From 1974 to 1980 he studied Medicine at the J.-W. Goethe-University of Frankfurt, FRG. In 1980 he was trained in cardiology at the Heart and Circulation Center of Rotenburg FRG, and from 1980 to 1981 in neonatalogy and pediatric cardiology at the Rheinische Friedrich-Wilhelms-University of Bonn, FRG. Since 1982 he has been working in the Department of Obstetrics and Gynecology of the University of Bonn. His main research interests include fetal cardiovascular physiology and pathophysiology, particularly fetal echocardiography and Doppler flow measurements.*

2 Case reports

Case 1: A 20-year-old gravida 2, para 1 in a 26+2 weeks gestation was referred because of supraventricular tachycardia (SVT) with ascites and polyhydramnios after an uneventful course of pregnancy.

Sonographic findings: inactive fetus, constant SVT about 250 bpm, non-immune hydrops fetalis with severe ascites, severe polyhydramnios, nor-

mal placenta (bipartietal diameter: 73 mm, frontooccipital diameter: 86 mm, abdominal transverse diameter: 78 mm; heart (short axis at atrioventricular valve level): 28 mm).

Therapy: Rapid digitalization with beta-methyldigoxin (digoxin level of January 31, February 3, 1986: 1.0 ng/ml). There was sustained SVT, increasing ascites (figure 1), presence of skin edema and rapidly advancing pericardial effusion (figures 2 and 3) even after additional daily oral administration of 360 mg verapamil.

It was decided to administer antiarrhythmic therapy directly to the fetus: from February 4, 1986 (72+2 weeks gestation) up to February 14, 1986 (28+5 weeks gestation) 12 intraperitoneal administrations of antiarrhythmic agents were carried out (except for February 8, 12, and 13, 1986 in the morning as well as in the evening) with the following doses being used: 10 µg betamethyldigoxin and 1 mg verapamil, and, in the last 4 punctures, an additional 7–10 mg propafenon. Within 5–15 minutes after these interventions cardioversion with sinus rhythm of 150 bpm was established, lasting a few hours, max. 36 hours. The digoxin concentration measured in the ascites fluid prior to the administration of drugs was between 0.6 ng/ml and 1.0 ng/ml. During this time the fetus became active again; in the meantime the maternal digoxin level could be increased to values between 1.4 ng/ml and 1.6 ng/ml; starting on January 12, 1986 the mother was given an additional 450 mg propafenon daily along with methyldigoxin and verapamil together with maintenance therapy of 400 µg betamethyldigoxin. From February 15, 1986 (28+2 weeks gestation) a constant sinus rhythm was recorded following oral medication (300 µg betamethyldigoxin, 360 g verapamil and 450 mg propafenon daily). A further increase in the dose of digitalis was not possible due to maternal signs of toxicity (first-degree AV-block, nausea, vomiting); there was no evidence of pericardial effusion on February 21, 1986 (29+5 weeks gestation), the ascites decreased slowly and had disappeared by the time of outpatient monitoring on March 26, 1986 (34+3 weeks gestation). On April 10, 1986 (36+5 weeks gestation) there was a spontaneous vaginal delivery: female infant 3080 grams, 50 cms long. Apgar score: 8/7/9 at 1, 5 and 10 minutes. After delivery the arrhythmia dit not reoccur even though the

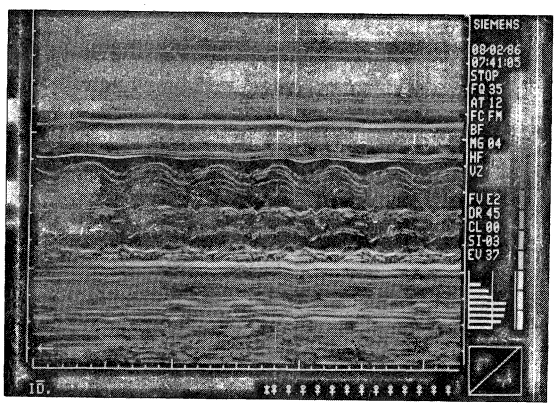

Figure 3. Pericardial effusion in the 28th week of gestation (case 1) demonstrated by a M-mode echocardiogram across both ventricular chambers the level of the chordae tendineae (Figures 1–3 from GEMBRUCH U, M HANSMANN, DA REDEL, R BALD: Ultraschall Klin Prax 2 (1987) 33).

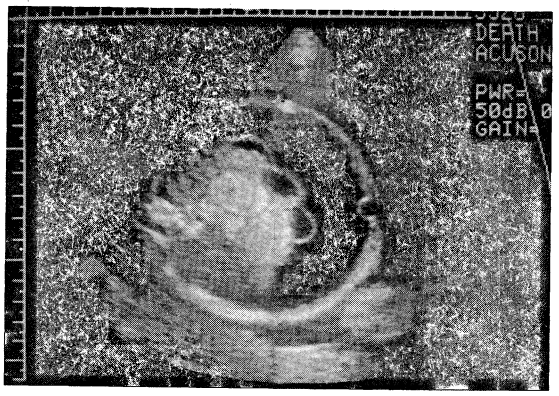

Figure 1. Massive ascites in the 28th week of gestation (transverse scan) (case 1).

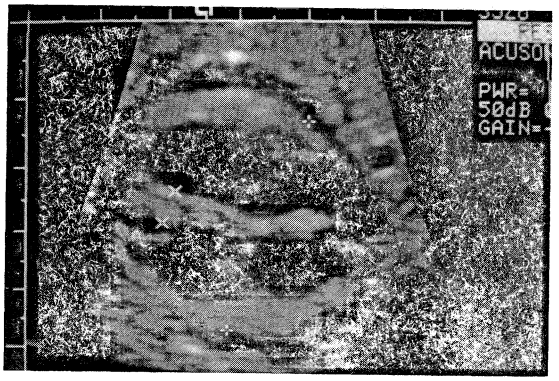

Figure 2. Cardiac four-chamber view with pericardial effusion in the 28th week of gestation (case 1).

antiarrhythmic therapy was discontinued. The child was treated with phenobarbital because of suspected seizures occuring twice in the neonatal period but is otherwise in good condition and has developed appropriately by age.

Case 2: A 23 year-old gravida 2, para 1, during the 33th week of gestation was admitted on August 29, 1986 because of bradyarrhythmia and non-immune hydrops fetalis with ascites and skin edema, cardiomegaly and a hydropic placenta.

Sonographic findings include: immobile fetus, atrial flutter at 300 to 350 bpm with 1 : 1 AV-conduction and periodic 2 : 1 AV-block; non-immune hydrops fetalis with massive ascites and slight skin edema, cardiomegaly, dilated veins, hepatomegaly, normal volume of amniotic fluid, slightly hydropic placenta (biparietal diameter: 90 mm, fronto-occipital diameter: 73 mm, abdominal transverse diameter: max. 130 mm; heart (short axis at AV-valve level): 60 mm).

Pulsed and 2-dimensional color Doppler-echocardiography showed severe regurgitation of the mitral and tricuspidal valves, possibly as a consequence of the pronounced dilatation of the cardiac structure.

Therapy: Rapid digitalization of the mother with betamethyldigoxin and additional daily oral administration of 900 mg propafenon (maternal digoxin level: on August 30, 1986: 1.6 ng/ml, on September 1, 1986: 2.7 ng/ml and on September 4, 1986: 1.6 ng/ml); because of the poor condition of the fetus it was decided to treat it directly. On August 30, 1986 150 ml of ascites was aspirated and intraperitoneal instillation of 18 µg betamethyldigoxin and 2 mg propafenon was performed. Eight minutes later, a sinus rhythm of 150 bpm was recorded several times for 5–20 seconds. On August 31, 1986 there was an intraperitoneal administration of 10 µg betamethyldigoxin and 2 mg propafenon. The atrial flutter persisted despite these measures, but on August 30, 1986 there was a constant 2 : 1 conduction block so that the ventricular frequency was 150 bpm. The color Doppler-echocardiography demonstrated better contractility with only slight regurgitation in the AV-valve area; the fetus became more lively, the effusion no longer increased. Unfortunately, because of the undesirable sympathomimetic cardiac effects in this case, high-dose intravenous tocolysis (max. 4 µg fenoterol/minute) had to be given from the day of admission because of early cervical dilatation. When the tocolysis was reduced, there was silent cervical dilatation to 5 cms in diameter. On September 6, 1986 (34th week gestation) immediately after prepartal aspiration of 300 ml ascites the delivery was carried out by cesarean section: hydropic female infant, 3650 grams, immediate intubation and respiration. Apgar score 2/4/7/7 at 1, 3, 5 and 10 minutes (digoxin concentration 17 hours after the last drug administration: maternal blood: 1.4 ng/ml; umbilical vein blood: 1.2 ng/ml). Following delivery and antiarrthythmic therapy, there was cardioversion of the neonate, sinus rhythm in a normal frequency and subsequent reduction of the ascites and skin edema. Later thereby, discontinuation of drugs and discharge. Through January 9, 1987 there has been normal growth and development.

3 Discussion

Intrauterine therapy of fetal tachyarrhythmia has out up to now been carried by the transplacental route. Antiarrhythmic agents administered to the mother reached the fetal compartments through the placenta. Agents of first choice with good placental crossing ability are the cardiac glycosides, which have not only an antiarrhythmic but also an positive inotropic effect. Also used are verapamil, propanolol, propafenon and in some cases, quinidine, procainamide, amiodarone and flecainide. On the one hand, when the latter antiarrhythmic agents are used, undesirable effects in the fetus may occur, particularly with already existing cardiac insufficiency due to the negative inotropic effects of some of these antiarrhythmic agents. It is still relatively unclear whether and to what extent these drugs cross the placenta [1, 2, 5, 11, 12, 13].

Successful cardioversion of fetal tachyarrhythmia by transplacental administration of antiarrhythmic agents has been described frequently. In the cases of advanced cardiac decompensation with the signs of severe non-immune hydrops fetalis, it would appear that this therapy seldom leads to constant cardioversion and remission of the fluid accumulation, even with high dose drug therapy. This could be due to the following: The early appearance of undesirable side effects from the antiarrthythmic agents to the mother which would not permit the dose to be increased; the transplacental crossing of the drugs from the maternal to the fetal compartments is hampered, viz. due to the abnormal state of the fetal circulation in cardiac insufficiency which may also lead to

placental changes resulting in hydrops placentae; the insufficient „sick" fetal heart is a poor responder to the antiarrhythmic therapy compared to that of an unaffected heart; in some cases, a sufficient drug level may not be reached if the fetus has already died prior to therapy; antiarrhythmic agents which are normally efficacious do not reach an effective level in the fetal compartments since they cannot or only cross the placenta in a limited manner.

All of these considerations make it seem favorable to carry out direct antiarrhythmic treatment of the fetus at least in the case of manifest heart failure. In the therapy of rhesus incompatibility the direct treatment of the fetus in the form of intraperitoneal blood transfusion has been reported by LILEY [10] in 1963. HANSMANN and LANG [6] did this for the first time using ultrasound monitoring in 1972. At present ultrasound guided direct interventions in the fetus are so highly developed that, for example, fetal effusion can be aspirated and fetal vessels punctured for diagnostic blood analysis or intravascular transfusion and exchange transfusion [3, 4, 7, 8].

Intravascular administration of antiarrhythmic agents can be carried out by ultrasound guided injections in the umbilical vein. This is technically difficult and in individual cases impossible, depending on the unfavorable location of the fetus and the placenta or the umbilical cord connection. In fetuses eligible for antiarrhythmic direct therapy with non-immune hydrops fetalis, there is always some ascites, so that an intraperitoneal administration of anti-arrthythmic agents is technically simple and can be easily repeated. In our first case, using concomitant high dose transplacental therapy, sustained periods of sinus rhythm of varying duration were observed 5–15 minutes after 12 intraperitoneal administrations of antiarrhythmic agents. This it may be assumed that the resorption of drugs from the ascites takes place rapidly. In the second case, 8 minutes afer injection, there was only a very brief period of sinus rhythm with a following flutter. Due to the apparently very rapid resorption of the drugs from the ascites we did not substantially exceed the dosing amounts for intravenous injections in the intraperitoneal administration of antiarrhythmic agents, in order to avoid fatal intrauterine effects which are difficult to monitor since we were unaware of the concentrations previously reached by the transplacental route in the fetal compartments.

4 Conclusion

Indications for direct administration of antiarrhythmic drup directly into the peritoneal fluid of the fetus, in addition to transplacental therapy, must include fetal emergency states due to non-immune hydrops fetalis secondary to tachyarrhythmia. By doing this, it is possible to reach high concentrations of antiarrhythmic agents in the fetal compartments more rapidly than by the transplacental route particularly in the case of drugs that only limitedly cross the placenta. Intraperitoneal therapy is also optimal therapy when no further increase in the dose of oral medication is possible due to side effects which might jeopardize the health of the mother. In such case, intraperitoneal administration of antiarrhythmic agents is an effective, technically simple, option which can be repeated at short intervals.

Summary

In cases of fetal tachyarrhythmia with congestive heart failure accompanied by signs of non-immune hydrops fetalis, the transplacental treatment of the fetus with antiarrhythmic agents by administration of drugs to the mother is only rarely successful. In the two cases reported, the cardioversion of a supraventricular tachycardia to a sinus rhythm or a constant 2 : 1 AV conduction block to a 1 : 1 AV conduction with atrial flutter could only be achieved after additional antiarrhythmic treatment directly administered to the fetus using ultrasound guidance. Drugs used include: beta-methyldigoxin, verapamil, propafenon, and they were administered according to the dosing amounts for intravascular injections. This was carried out 12 times in case 1 by the intraperitoneal route into the fetal ascites and twice in case 2. This led in both cases to varying durations of a sustained sinus rhythm after 5–15 minutes. This technically relatively simple procedure affords the option of rapidly achieving high concentrations, even when antiarrhythmic agents are administered which do not adequately cross the placenta. This direct treatment is indicated in cases of tachyarrhythmia with advanced signs of non-immune hydrops fetalis as a supplement to the high-dose transplacental therapy using antiarrhythmic agents.

Keywords: Fetal Doppler echocardiography, fetal echocardiography, fetal heart arrhythmia, fetal heart failure, fetal tachyarrhythmia, fetus, intrauterine therapy, non-immune hydrops fetalis, prenatal diagnosis, ultrasonography.

Zusammenfassung

Intrauterine Therapie fetaler Tachyarrhythmien: Intraperitoneale Antiarrhythmikagabe an den Feten bei fetalen Tachyarrhythmien mit schwerem Hydrops fetalis

Bei Vorliegen eines schweren nicht-immunologisch bedingten Hydrops fetalis infolge einer fetalen Herzinsuffizienz aufgrund fetaler Tachyarrythmien ist die alleinige transplazentare antiarrhythmische Behandlung des Feten via Mutter nur selten erfolgreich. In den beiden beschriebenen Fällen konnte die Kardioversion einer supraventrikulären Tachykardie in einen Sinusrhythmus bzw. die Überführung in eine konstante 2 : 1 AV-Überleitung bei zuvor vorhandender 1 : 1 AV-Überleitung bei Vorhofflattern nur durch eine zusätzliche Direktbehandlung des Feten erreicht werden. Hierbei wurden die Antiarrythmika (Beta-Methyldigoxin, Verapamil, Propafenon) Ultraschall-gesteuert intraperitoneal in den fetalen Ascites appliziert – gemäß der für die intravaskuläre Injektion üblichen, gewichtsbezogenen Dosierungsrichtlinien. Dieser Eingriff wurde bei einem Feten (supraventrikuläre Tachykardie) zwölfmal, bei dem anderen (Vorhofflattern) zweimal durchgeführt, wonach 5–15 Minuten später unterschiedlich lang anhaltende Sinusrhythmen auftraten. Diese technisch relativ einfache und daher oft wiederholbare intraperitoneale Antiarrhythmikagabe bietet die Möglichkeit, schnell hohe Antiarrhythmikakonzentrationen in den fetalen Kompartimenten zu erreichen, auch wenn die gewählten Medikamente schlecht plazentagängig sind. Indiziert ist diese Behandlung bei tachyarrhythmischen Feten mit schwerem Hydrops fetalis, zusätzlich zur üblichen hochdosierten transplazentaren Antiarrhythmikagabe. Sie scheint die Prognose auch für diese schwerkranken Kinder zu verbessern.

Schlüsselwörter: Fet, fetale Doppler-Echokardiographie, fetale Echokardiographie, fetale Herzinsuffizienz, fetale Herzrhythmusstörung, fetale Tachyarrhythmie, intrauterine Therapie, nicht-immunologischer Hydrops fetalis, pränatale Diagnostik, Ultraschall.

Résumé

Traitement in utéro des tachyarythmies fœtales: Injection fœtale intrapéritoneale de médicaments anti-arythmiques lors de tachyarythmies fœtales s'accompagnant d'hydrops fœtalis sévère

La traitement transplacentaire du fœtus par des agents antiarythmiques grâce à l'administration de médicaments à la mère n'est que rarement couronné de succès en cas de tachyarythmies fœtales avec défaillance cardiaque congestive s'accompagnant de signes d'hydrops fœtalis non immunologique. Dans les deux cas décrits la cardioversion d'une tachycardie supraventriculaire en rythme sinusal ou en conduction AV 2/1 constante alors qu'il existait avant une conduction AV 1/1 avec flutter auriculaire n'a pu être obtenue qu'après traitement antiarythmique additionel direct au fœtus en utilisant une surveillance échographique et des médicaments (bétaméthyldigoxine, verapamil, propafenon) injectés aux doses utilisées pour la voie intra-veineuse. Ce protocole a été réalisé 12 fois chez le premier fœtus par voie intrapéritonéale au niveau de l'ascite fœtale et deux fois chez le second aboutissant chez les deux fœtus à des périodes variables de rhythme sinusal continu au bout de 5 à 15 minutes. Cette méthodologie, techniquement relativement simple, soutient l'option de concentrations élevées rapidement obtenues, même lorsque les agents antiarythmiques administrés ne traversent pas suffisement le placenta. Le traitement direct est indiqué dans les cas de tachyarythmies s'accompagnant de signes graves d'hydrops fœtalis non immunologique comme complément d'une thérapeutique à haute dose par voie transplacentaire utilisant des agents antiarythmiques.

Mots-clés: Arythmie cardiaque fœtale, défaillance cardiaque fœtale, diagnostic prénatal, échocardiographie Doppler fœtale, échocardiographie fœtale, échographie, fœtus, hydrops fœtalis non immunologique, traitement in utero, tachyarythmie fœtale.

Medications used in this study:
Beta-Methyldigoxin (Lanitop®, Boehringer AG, Mannheim, FRG)
Verapamil (Isoptin®, Knoll AG, Ludwigshafen, FRG)
Propafenon (Rhythmonorm®, Knoll AG, Ludwigshafen, FRG)

References

[1] Allan LD, RH Anderson, ID Sullivan, S Campbell, DW Holt, M Tynan: Evaluation of fetal arrhythmias by echocardiography. Br Heart J 50 (1983) 240

[2] Bergmans MGM, GJ Jonker, HCLV Kock: Fetal supraventricular tachycardia. Review of the literature. Obstet Gynecol Surv 40 (1985) 61

[3] DAFFOS R., M CAPELLA-PAVLOVSKY, F FORESTIER: Fetal blood sampling during pregnancy with the use of a needle guided by ultrasound: a study of 606 consecutive cases. Am J Obstet Gynecol 153 (1985) 665

[4] DE CRESIPIGNY LC, HP ROBINSON, M QUINN, L DOYLE, A ROSS, M CAUCHI: Ultrasound guided fetal blood transfusion for severe rhesus isoimmunization. Obstet Gynecol 66 (1985) 529

[5] DUMESIC A, NH SILVERMAN, S TOBIAS, MS GOLBUS: Transplacental cardioversion for fetal supraventricular tachycardia with procainamide. N Engl J Med 307 (1982) 1128

[6] HANSMANN M, N LANG: Intrauterine Transfusion unter Ultraschallkontrolle. Klin Wochenschr 50 (1972) 930

[7] HANSMANN M: Ultraschallkontrollierte Therapie des Feten. Arch Gynecol 238 (1985) 1

[8] HANSMANN M, K FISCHER, U GEMBRUCH, R ULBRICH: Pränatale Blutsubstitution – Transfusion und Austausch – bei Pseudo-Anti-A-Erythroblastose infolge fetomaternaler Blutung. Ultraschall Klin Prax 1 (1986) 35

[9] KLEINMANN CS, RL DONNERSTEIN, CC JAFFE, GR DEVORE, EM WEINSTEIN, DC LYNCH, NS TALNER, RL BERKOWITZ, JC HOBBINS: Fetal echocardiography. A tool for evaluation of in utero cardiac arrhythmias and monitoring of in utero therapy: analysis of 71 patients. Am J Cardiol 51 (1983) 237

[10] LILEY AW: Intrauterine transfusion of fetus in haemolytic disease. Br Med J 11 (1963) 1107

[11] REDEL DA, HANSMANN M: Fetale Echokardiographie – ihre Anwendung in Diagnostik und Therapie. Gynäkologe 17 (1984) 41

[12] REY E, L DUPERRON, R GAUTHIER, M LEMAY, A GRIGNON, J LELORIER: Transplacental treatment of tachycardia-induced fetal heart failure with verapamil and amiodarone: A case report. Am J Obstet Gynecol 153 (1985) 311

[13] STEWART, PA, HM TONGUE, JW WLADIMIROFF: Arrhythmia and structural abnomalities of the fetal heart. Br Heart J 50 (1983) 550

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