The Fetal Pacemaker: Will It Ever Work?

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Introduction

Fetal hydrops is a non-specific entity from various fetal and maternal disorders that results in tissue edema and effusions in multiple cavities of the body. Approximately 50% of fetuses with hydrops fetalis die in utero with current medical care. (Matthew E. Abrams 2007) Hydrops is classically divided into immune and non-immune types. Immune hydrops is due to maternal hemolytic antibodies, while non-immune hydrops includes all other etiologies. The use of immunoprophylaxis and prevention of Rhesus disease has drastically declined the occurrence of immune hydrops, with the current majority of cases being of non-immune causes (>75%). This condition is associated with a high rate of fetal morbidity and mortality, with few treatment methods available (Matthew E. Abrams 2007).

Testing for maternal antibodies should take place within the first trimester of pregnancy and the fetal heart should be examined at 16 weeks with an echocardiogram. Current recommendations for abnormal findings such as increased PR interval, heart block. (Josephine Patricia Dhar 2006) The majority of fetal hydrops is currently caused by congenital heart problems (13.7%), abnormalities in heart rate (eg tachyarrythmias) (10.4%), twin-twin transfusions, congenital anomalies, chromosomal abnormalities, congenital viral infections, congenital anemia and congenital chylothorax (Matthew E. Abrams 2007).

A notable cause of hydrops is a complete atrioventricular conduction block that may be the result of autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndromes. Neonatal lupus erythematosus is an isoimmune disease that occurs with passage of anti-Ro/SS-A and anti-La/SS-B antibodies through the placenta. These antibodies travel through the fetal circulation binding to fetal tissue causing congenital heart blocks and non-cardiac neonatal lupus. Lab studies in NLE show elevated liver enzymes and thrombocytopenia. Maternal antibodies have no effect on the fetus at 6 to 8 months of gestation and NLE subsides, however CHB still remains an important issue leading to significant mortality and morbidity.

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CHB occurs in 2% of cases, with incidence increasing to 20% in infants born to mothers with previous CHB due to anti-Ro/SSA and anti-La/SSA antibodies. CHB is a serious irreversible condition that is caused by anti-Ro/SSA and anti La/SSB antibodies that bind to cardiac tissue within the fetus resulting in myocarditis and fibrosis of the atrioventricular node. Cardiac injury occurs most often between 16-24 wks gestation and presumed to arise from transplacental passage of maternal IgG auto antibodies. Maternal antibodies bind to fetal Ro/SSA and La/SSB antigens that are expressed during the development of fetal cardiac conduction tissue. Once bound, inflammation ensues and apoptosis occurs extensively leading to scarring and ultimately fetal heart block. It has been shown that a disrupted calcium homeostasis induces death of the cardiomyocytes (Josephine Patricia Dhar 2006). The adverse effects of these antibodies can convert a normal rhythm into a complete heart block in as quickly as 7 days.

Diagnosis and Workup

Currently, ultrasound technologies are available for accurate recognition and diagnosis of fetal hydrops and are the cornerstone of fetal imaging. Sonograms of hydrops fetalis are likely to show fluid collection of the pleural, pericardial and peritoneal spaces. Polyhydramnios and an edematous thick placenta are often present. Diagnostic criteria for fetal hydrops includes: fluid accumulation in at least 2 serous cavities or 1 serous effusion and generalized anasarca. A single site of fluid accumulation may be sufficient to diagnose as long as there is a strong association with preexisting pathology. Ultrasonographic findings are subsequently used for follow-up imaging to observe progress of the disease in utero.

The workup of hydrops fetalis should be initiated if hydrops is suspected or if there is a history of previously affected fetuses. Maternal blood typing along with antibody screening by ELISA is recommended in immune related hydrops fetalis. The use of echocardiography to monitor fetal PR intervals is the current recommendation for antibody positive mothers. Monitoring should be weekly during 16 to 26 weeks gestation and biweekly from 26-32 weeks gestation. Furthermore, a high antibody titer should draw attention to a risk of hemolysis and anemia. Fetal anemia can now be safely analyzed by non-invasive doppler ultrasonography which is less tramatic than prior methods of

direct fetal blood sampling. Fetal anemia requires an ultrasound guided intravascular fetal blood transfusion

Nonimmune-related hydrops fetalis can result from numerous causes, and workup should be directed at the mother initially—specifically searching for hereditary or metabolic diseases, infections and medications. Blood tests should be performed to test for blood counts, thalassemias, G6PD deficiency, fetal-maternal transfusion and screening of TORCH infections. Furthermore, amniocentesis should be performed to obtain a fetal karyotype as well as cultures, AFP levels and lecithin-sphingomyelin ratios (Hamdan 2007).

Treatment

Treatment involves interventional fetal therapy that is focused on the etiology; however, modalities differ for both immune and non-immune hydrops fetalis. Initial treatment for immune-related hydrops fetalis should be aimed at correcting underlying fetal anemia. Fetal blood sampling and subsequent ultrasound guided in-utero blood transfusion is indicated for anemia that presents together with fetal hydrops. It has been shown that intravascular blood transfusions have a better prognosis than intraperitoneal transfusions because hypdrops interferes with peritoneal absorption. With IVT, 70-85% of fetuses with hydrops and 85-95% of fetuses without hydrops can survive.

Considering the complexity of treating non-immune hydrops fetalis, treatment is grouped into non-invasive and invasive. Non-invasive treatment includes the use of antiarrhythmic drugs, antibiotics, and correction of underlying maternal disease. Positive inotropic agents such as digoxin can be used in cases of fetal cardiac failure and SVT. Digoxin is transferred to the fetus transplacentally when given to the mother. Data is scarce regarding the use of antiarrhythmic agents in fetal arrhythmias; however, many options are available including quinidine, verapamil, amiodarone, adenosine, procainamide, sotalol, and flecainide. Loop diuretics (e.g.: furosemide) are used to treat fetal edema by promoting kidney excretion of excess water.

The use of glucocorticoids has been explored in cases of autoantibody-associated congenital heart block. A comparison study was conducted in which 28 of 50 pregnancies with fetal heart block were treated with fluorinated steroids while the remainder received no treatment. It was found that 100% of the third degree heart blocks were irreversible, and that there was no change in mortality, prematurity, degree of block, or need for pacing with the addition of steroids. There was however an improvement of effusions, ascites and hydrops in the steroid group. (Saleeb S. 1999) The use of maternal steroid therapy in fetal heart block still remains questionable due to associated complications. Dexamethasone was shown to cause oligohydramnios, intrauterine growth restriction, adrenal suppression, and poor brain development. (Breur 2004)

Invasive treatment that is available is usually reserved for severe cases of hydrops fetalis and outcomes depend on available resources and experience of the technician. Procedures include: amnioreduction, cord occlusion in cardiac twins, thoracocentesis of pleural effusions and vesicoamniotic drainage. These interventions hold a risk of complications and are not curative of hydrops fetalis. A new intervention utilizing intrauterine monolithic fetal pacemakers is currently being studied with promising results. (Hamdan 2007)

History of the Pacemaker

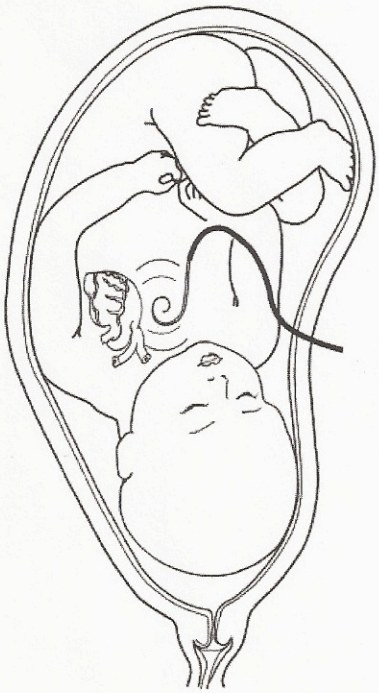
An artificial pacemaker is a device that uses electrical impulses via electrodes attached to myocardium to establish an adequate heart rate. The concept of pacing ones heart was reported as early as 1889 by J.A. McWilliam in the British Medical Journal in which an asystolic heart was ventricularly paced at a rate of 60-70 beats per minute. In 1928, Dr Mark C. Lidwell developed a technique of placing electrodes into a cardiac chamber, which was used to revive a still-born infant after ten minutes of pacing. Albert Hyman led the revolution in pacemaker history with the development of an electromechanical device that he coined as an "artificial pacemaker." During this time period much of the research on pacemakers was not published because of controversial views of interfering with nature by artificially stimulating the heart. The first external pacemaker design is attributed to John Hopps in the 1950s, which used a transcutaneous method of pacing. Early pacemaker designs were large, inconvenient, and were associated with patient discomfort. The development of the silicon transistor in 1956 allowed for the creation of the first wearable external pacemaker one year later. Advances led to the first clinical implantation of a pacemaker in 1958 via electrodes placed by thoracotomy. Transvenous pacing was subsequently studied in Sweden and France and became the mainstay of treatment. Although advancements had been made in technique, short battery life remained a large problem before the development of the lithium iodide cells in 1970. Current pacemakers offer adequate battery life, microchips that allow for external programming, and improved casing designs.

Pacemakers are currently being used for cardiac conditions such as sinus node dysfunction, bifascicular block, trifascicular block, third degree AV block, and Stokes-Adams conduction block. The success of pacemakers has been demonstrated in numerous studies in both adult and neonatal populations, however; the use of fetal pacemakers has not yet been applied. Neonatal pacemakers are being used for early intervention and treatment of congenital complete heart block with success. In a study led by Kelle in 2007, it was shown that "implantation of a dual-chamber epicardial pacemaker in neonates with congenital heart block is technically feasible and results in excellent outcomes in patients with structurally normal hearts and that system longevity at 6 years is excellent." (Kelle A. 2007.)

Currently, it is known that hydrops with a third degree heart blocks approaches a mortality of 100% despite treatment with steroids. The prospect of fetal pacing looks promising, and should be further explored as a treatment option for congenital complete heart block. Interventional pacing and heart rate support should theoretically correct the hemodynamic derangement and effectively clear the anasarca and pulmonary edema associated with CHB.

It has been shown that ventricular pacing should take place for a minimum of 2 to 4 weeks prior to delivery to achieve hemodynamic stability. This defines the necessary length of functionality needed for the fetal pacemaker system. In 2003, Dell'Orfano et al suggested the development of a prototype fetal pacemaker to be implanted via closed thorax over the wire deployment with ultrasound guidance, fetoscopy, or direct vision surgery. This fetal pacing system should avoid umbilical cord complications by bypassing umbilical vasculature and prevention of cord knotting or constriction by utilization of a low profile device. Another prerequisite entails in utero deployment with avoidance of thoracotomy or hysterectomy. The device

should be able to function for a minimum of 2 to 4 weeks or until delivery is plausible. A proposed method of delivery for an epicardial pacing is percutaniously via a subxiphoid incision—similar techniques have been used in adults. Additionally, unipolar electrical stimulation of the fetal heart is feasible due to the favorable conduction pathways. Electrical currents will pass through the high salt content of the amniotic fluid and through the fetal skin which has low electrical impedance due to underlying edema (Joseph Dell'Orfano 2003).



Fetal Pacemaker

A proof of concept article was published in 2003 showing successful use of the above described pacing system. In this study, complete AV block was artificially induced with ethanol in 11 Sprague rats. A J-wire was advanced through a 1cm subcostal incision and across diaphragm into the thorax. A pacing lead was then passed over the J-wire and positioned in close proximity to the mediastinum. Pacing was successful in 10 of the 11 rats, with ventricular capture and QRS widening. The mean QRS complex changed from 50.2ms pre-pacing to 95.1ms post-pacing. There were no complications caused by deployment, and the authors expect that fetal deployment will be associated with even less risk due to underlying pleural effusion that acts as a buffer against organ perforation during needle deployment. Movement of the fetus was also considered as a mode of deployment failure, but it is well known that a hydroptic fetus ceases to move thereby reducing the risk of dislodgment (Joseph Dell'Orfano 2003).

Some obstacles that must be taken into consideration were discussed by Fayn et al in 2005. These include the following 3 failure modes of the monolithic fetal pacemaker: primary positioning failure due to device length, angle of deployment and displacement due to somatic growth. The major finding in this study showed that the distance between the amniotic space and the pericardium has little variation in regards to gestational age. Data shows minimal changes in amniotic-to-pleural distance that followed a slope of 0.06 cm per week with a maximal change of 0.28 cm within 4 weeks—the time needed for resolution of the hydrops. This change is estimated to be much less in hydroptic fetuses with slower growth rates than healthy fetuses. Additionally, dislodgement of the electrodes due to somatic growth along with primary positioning failure was associated with minimal risk (Fayn E. 2005).

Conclusions

Hydrops fetalis that is associated with congenital complete heart block is a serious condition that has a poor prognosis. This condition leads to fetal mortality in 100% of cases. Unfortunately, current medical interventions are lacking and fail to address the underlying pathophysiology of the heart block. In utero pharmaceutical intervention with the use of steroids in previous studies showed no change in mortality, prematurity, degree of block, or need for pacing. Additionally, neonatal surgical intervention with dual chamber epicardial pacemakers has shown limited resolution of congenital complete heart block in regards to mortality and morbidity. Therefore, it may be assumed that intrauterine pacing should provide the greatest efficacy in reducing fetal demise from CHB. The monolithic fetal pacemaker holds the greatest potential for success in treatment of CHB, with positive results in prototypical lead designs. Recent studies in this field have recognized the importance of fetal pacemakers as an early intervention of hydrops associated with CHB. Further exploration of fetal heart pacing is imperative in regards to the future of interventional fetal medicine.

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