MANAGEMENT OF RHESUS ALLOIMMUNIZATION IN PREGNANCY pdf

1: Management of rhesus alloimmunization in pregnancy | Read by QxMD

Related topics, including a discussion of the Rhesus system, diagnosis and prevention of Rh(D) alloimmunization, diagnosis and management of pregnant women with non-Rh(D) alloimmunization (eg, Kell), in utero transfusion, and neonatal issues, are reviewed in detail separately.

Controversies in Rh prophylaxis. Who needs Rh immune globulin and when should it be given? Am J Obstet Gynecol The prevention of Rh immunization. Transfus Med Rev Prevention of Rho D alloimmunization. Lack of transmission of human immunodeficiency virus through Rho D immune globulin human. Management of rhesus alloimmunization in pregnancy. Obstet Gynecol Maternal anti-D prophylaxis during pregnancy does not cause neonatal haemolysis. Monoclonal anti-D development programme. Transpl Immunol Pharmacokinetics and safety of recombinant anti-RhD in healthy RhD-negative male volunteers. Transfus Med On the immunologic basis of Rh immune globulin anti-D prophylaxis. Immunol Lett Prevention of Rh alloimmunization. J Obstet Gynaecol Can Standards for blood banks and transfusion services. American Association of Blood Banks. Rh isoimmunization during pregnancy antenatal prophylaxis. Can Med Assoc J Anti-D administration in pregnancy for preventing rhesus alloimmunisation. Comparison of the efficacy of different methods for the prevention of anti-D allo-immunization during pregnancy targeted strategy limited to risk situations or associated with systematic prevention in the 3rd trimester. Anti-D immunoglobulin in RhD prophylaxis. Br J Obstet Gynaecol National Institute for Clinical Excellence. Guidance on the use of routine anti-D prophylaxis for RhD-negative women. May be viewed at www. Mol Diagn Whether your application is business, how-to, education, medicine, school, church, sales, marketing, online training or just for fun, PowerShow. And, best of all, most of its cool features are free and easy to use. You can use PowerShow. Or use it to find and download high-quality how-to PowerPoint ppt presentations with illustrated or animated slides that will teach you how to do something new, also for free. Or use it to upload your own PowerPoint slides so you can share them with your teachers, class, students, bosses, employees, customers, potential investors or the world. Most of the presentations and slideshows on PowerShow. You can choose whether to allow people to download your original PowerPoint presentations and photo slideshows for a fee or free or not at all. There is truly something for everyone!

MANAGEMENT OF RHESUS ALLOIMMUNIZATION IN PREGNANCY pdf

2: Mangement of Rh Disease and Isoimmunization

With the dawn of the new millennium, medical science has made little impact on the major complications of pregnancy. The one notable exception is rhesus alloimmunization and its associated fetal/neonatal consequenceâ€"hemolytic disease of the newborn.

Most women who become alloimmunized do so as a result of fetomaternal hemorrhage of less than 0. Several first- and second-trimester clinical events may cause Rh D alloimmunization. Ectopic pregnancy also is associated with alloimmunization in susceptible women. Threatened abortion infrequently causes alloimmunization, clinical procedures, which may breach the integrity of choriodecidual space, also may cause Rh D alloimmunization. Likewise, cordocentesis and other percutaneous fetal procedures pose a risk for fetomaternal hemorrhage. Failure to Prevent Rh D Alloimmunization: In spite of recommendations for immunoprophylaxis, 0. There are two primary reasons for the continuing problem. One reason is failure to implement recommended immunoprophylaxis protocol, resulting in preventable Rh D alloimmunization. The second reason if the small rate 0. This problem may become the largest single cause of new Rh D alloimmunization, because alloimmunization from other causes has decreased proportionally 4. Preventable Rh D alloimmunization occurs in susceptible Rh D-negative women for the following three reasons: Failure to administer an antenatal dose of anti-D immune globulin at weeks of gestation. Failure to recognize clinical events that place patients at risk for alloimmunization and failure to administer anti-D immune globulin appropriately. Failure to administer or failure to administer timely anti-D immune globulin postnatally to women who have given birth to an Rh D-positive or untyped fetus. Routine screening of all women for excessive fetomaternal bleeding at the time of delivery is now recommended by American Association of Blood Banks AABB. Typically this initially involves a sheep rosette test that is read qualitatively as positive or negative. If negative, one vial of Rh I G micro g is given. If positive, the bleed is quantitated with a Kleihauer-Betke stain or fetal cell stain by flow cystometry. Consultation with the blood bank pathologist to determine the number of doses is encouraged 5. Controversy surrounds the use of Rh I G for threatened abortion. It is probably not indicated when only spotty vaginal bleeding occurs but it should be used in patients with significant clinical bleeding; dose can be repeated in week intervals as necessary. A second indication of Rh I G that is often overlooked is blunt trauma to the maternal abdomen, particularly at the time of a motor vehicle accident. Finally, if micro g of Rh I G are given late in gestation for external cephalic version or third-trimester amniocentesis for fetal lung maturity, a repeat dose is unnecessary if delivery occurs within 3 weeks, assuming there is no feto-maternal hemorrhage by maternal testing. Clinical Management of Isoimmunized Patient: This is most useful for the atypical antigens because isoimmunization is often secondary to a transfusion. If the father of the fetus does not possess the antigen, the fetus is not at risk. Maternal serum antibody titers can be measured by a variety of techniques. Agglutination of erythrocytes in saline measures maternal IgM antibody, and this is too large a molecule to cross the placenta. Albumin is a more viscous medium; therefore, the smaller IgG molecules are capable of agglutinating erythrocytes, but the contribution by IgM is not eliminated. The most sensitive and accurate barometer for clinical practice is the indirect Coombs test. In , once the molecular basis of the Rh D negative blood group became known, prenatal diagnosis of fetal RHD genotype evolved from serologic diagnosis of fetal erythrocytes obtained at cordocentesis to genotypic diagnosis of cells obtained by amniocentesis, a more widely available procedure with a reduced risk of miscarriage. Subsequently, with the demonstration that maternal plasma and serum contain large quantities of cell-free fetal DNA, it became possible to determine fetal RHD genotype non-invasively. This is due to fact that most Rh D negative pregnant women have a deletion of the sequence on both copies of their chromosome 1. Advances in both our understanding of the RHD locus and its variants, as well as technical improvements in the extraction and amplification of cell-free fetal DNA in maternal plasma, have led to incorporation of non-invasive diagnosis of RHD genotype into routine prenatal care in the United Kingdom, France, and the Netherlands 6. An antibody titer should be determined at the first prenatal visit, 20 weeks of gestation, and approximately every 4 weeks thereafter. Once the maternal antibody screen

returns positive for anti-D, a titer should be ordered. The titer is considered critical if it has been linked to an increased risk of fetal hydrops for a particular institution. An anti-D titer of 1: However, one should be cautious in interpreting antibody titers; they are only crude estimates of the amount of circulating antibody. When the antibody titer is 1: A change of more than one dilution i. If a patient has had a prior affected pregnancy neonatal exchange transfusion, early delivery, or intrauterine transfusion , antibody titers are not necessary because amniocentesis or percutaneous umbilical cord blood sampling will be required. It has become the cornerstone of fetal therapy for hemolytic disease of the fetus and newborn. One of the most significant breakthroughs in recent years has been research that validates the peak systolic MCA Doppler velocity as a reliable screening tool to detect fetal anemia. The vessel can be easily visualized with color flow Doppler. Pulsed Doppler is then used to measure the peak systolic velocity of the MCA just distal to its bifurcation from the internal carotid artery. Enhanced fetal cardiac output and a decrease in blood viscosity contribute to an increased blood flow velocity in fetal anemia. Since the general trend is for the MCA velocity to increase with advancing gestational age, results are reported in multiples of the median MOMs much like serum alpha fetoprotein 7. Many centers have yet to adopt serial MCA Dopplers. Amniotic fluid bilirubin is most likely derived from fetal tracheal and pulmonary secretions. It can be quantitated by spectrophotometrically measuring absorbance at the nm wavelength in a specimen of amniotic fluid that has been shielded from light. Contamination of amniotic fluid by meconium and by erythrocytes and their porphyrin breakdown products can significantly alter spectrophotometric analysis of nm, but these problems can be largely overcome by chloroform extraction of the amniotic fluid. Heme pigmentation will also generate a peak at the nm wavelength, and in the absence of blood contamination this may be indicative of severe hemolysis. The recent modification by Queenan and coworkers may be more useful due to its accuracy at gestational ages of less than 27 weeks 8. A rise or plateauing trend into the Rh-positive affected zone warrants more invasive testing through cordocentesis. Amniocentesis for lung maturity is widely accepted. Tests for fetal lung maturity such as phosphatidyl-glycerol quantitation, lamellar body count, or the lecithin-sphingomyelin ratio should be employed in cases of rhesus disease as these assays are not affected by excess bilirubin. It was introduced in the mids; direct access to the umbilical cord vessels by ultrasound guided needle puncture allows clinicians to measure fetal hematocrit, reticulocyte count, bilirubin level, and direct Coombs. Today, cordocentesis is reserved as a second-line diagnostic tool once amniocentesis or MCA Doppler suggests fetal anemia. Once a critical value usually 1: This will accelerate fetal hepatic maturity and allow for more efficient neonatal conjugation of bilirubin 9. In these cases, a unit of packed RBC cross-matched to the pregnant patient should be prepared prior to delivery so that it is available if the pediatrician must do an emergency neonatal transfusion. For a previously affected fetus of infant that has had a transfusion -- maternal titers are not helpful in predicting the onset of fetal anemia after the first affected gestation. If an Rh D-negative fetus is found and paternity is certain, no further testing is needed. Repeat at 1 to 2 week intervals. Absorption was slower if hydrops was already evident. Because of erratic absorption, especially in hydropic fetuses intravascular fetal transfusion has largely replaced the intraperitoneal technique. As experience with cordocentesis accumulated, the direct intravascular transfusion IVT of donor red cells into the fetal umbilical vein at its placental insertion became the most common method of intrauterine transfusion in the United States. Some US centers combine intravascular transfusion with the original intraperitoneal method in an effort to prolong the intervals between procedures. This step allows a minimal blood volume to be administered to the fetus during transfusion. The blood is then leuko-reduced with a special filter and irradiated with 25 Gy to prevent graft-vs-host reaction. Data on the neuro-development of neonates transfused by intravascular transfusion are limited. Hydrops fetalis does not seem to affect this outcome. Sensineural hearing loss may be slightly increased due to prolonged exposure of the fetus to high levels of bilirubin. A hearing screen should be performed during the early neonatal course and repeated by two years of life. Encouraging is the improved outcome for hydropic fetuses, although these results are promising, there are complications with any invasive procedure. Additional significant morbidity has included prolonged fetal heart rate decelerations that required emergency cesarean section and increases in maternal antibody titer, presumably secondary to fetal-maternal hemorrhage. When weighing the procedure-related risks against those

for the neonate in the nursery, one should seriously consider delivery rather than performing an intravascular transfusion after 34 completed weeks of pregnancy. Economic analysis of anti-D immune globulin prophylaxis is based on the cost of anti-D immune globulin and the number of alloimmunizations that would be prevented. In summary, the cost-effectiveness of antenatal Rh D immune globulin to all Rh D-negative pregnant women and in all circumstances wherein fetomaternal hemorrhage might occur has not been proven. Available data support that third-trimester antenatal prophylaxis is cost-effective in primigravidas. As long as the supply of anti-D immune globulin is adequate and data do not exist to support other recommendations, most experts believe that it is unethical to withhold anti-D immune globulin from any patient at risk of Rh D alloimmunization The risk of excessive fetomaternal hemorrhage exceeding 30 mL the amount covered by the standard micro g dose of anti-D immune globulin at the time of delivery is approximately 1 in 1, Pregnancies designated as high risk should be screened for excessive fetomaternal hemorrhage, including cases of abdominal trauma, abruptio placentae, placenta previa, intrauterine manipulation, multiple gestation, or manual removal of placenta. Based on this finding, the American Association of Blood Banks has recommended that all Rh D-negative women who deliver Rh D-positive infants be screened using the Kleihauer-Betke or rosette test Autism risk with anti-D Rh immunoglobulin exposure: Until , anti-D IgG contained thimerosal in a concentration of 0. This compound has been present in a number of vaccines given to infants and young children and has been studied as a possible causal factor in the development of autism spectrum disorders. To date, most studies have eliminated this possibility and the findings of the current study appear to concur with previous findings The authors conducted a case-control study examining prenatal, perinatal, and neonatal risk factors for autism spectrum disorders. They identified children with at least one diagnosis of autism spectrum disorders born between and who were monitored for at least 2 years after birth. Each child was matched with five controls without autism spectrum disorders for sex, year of birth, and hospital. The authors gathered information on maternal Rh status and anti-D immunoglobulin G IgG exposure during pregnancy and determined whether the mother had received and influenza vaccination during pregnancy. The proportion of Rh-negative mothers did not differ between patients and controls No association between maternal Rh status and risk of autism spectrum disorders was observed for subgroups of children defined by sex, plurality, autism severity, birth order, or number of affected children within siblings. The number of total anti-D IgG injections received was similar for affected mothers and control mothers. The authors concluded that there was no association between maternal Rh status, prenatal anti-D IgG exposure, and autism spectrum disorders. The authors attempted to find a second source of mercury in these children by determining if the mother had received an influenza vaccine containing thimerosal as a preservative, but they did not investigate other sources of mercury exposure, such as fish consumed by mothers or dental amalgam in teeth fillings.

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3: Rh disease - Wikipedia

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During this and subsequent pregnancies the IgG is able to pass through the placenta into the fetus and if the level of it is sufficient, it will cause destruction of rhesus D positive fetal red blood cells leading to the development of Rh disease. It may thus be regarded as insufficient immune tolerance in pregnancy. Generally rhesus disease becomes worse with each additional rhesus incompatible pregnancy. However, in many cases there was no apparent sensitizing event. The incidence of Rh disease in a population depends on the proportion that are rhesus negative. Many non-Caucasian people have a very low proportion who are rhesus negative, so the incidence of Rh disease is very low in these populations. In Caucasian populations about 1 in 10 of all pregnancies are of a rhesus negative woman with a rhesus positive baby. It is very rare for the first rhesus positive baby of a rhesus negative woman to be affected by Rh disease. The first pregnancy with a rhesus positive baby is significant for a rhesus negative woman because she can be sensitized to the Rh positive antigen. Many babies who managed to survive would be severely ill. Even higher disease rates would occur in the third and subsequent rhesus positive infants of rhesus negative women. By using anti-RhD immunoglobulin Rho D immune globulin the incidence is massively reduced. Rh disease sensitization is about 10 times more likely to occur if the fetus is ABO compatible with the mother than if the mother and fetus are ABO incompatible. Diagnosis[edit] Maternal blood The Kleihauerâ€”Betke test or flow cytometry on a postnatal maternal blood sample can confirm that fetal blood has passed into the maternal circulation and can also be used to estimate the amount of fetal blood that has passed into the maternal circulation. The indirect Coombs test is used to screen blood from antenatal women for IgG antibodies that may pass through the placenta and cause hemolytic disease of the newborn. Free Cell DNA can be run on certain antigens. This blood test is non-invasive to the fetus and is an easy way of checking antigen status and risk of HDN. For US patients, blood may be sent to either of the labs. Sequenome does not accept insurance in the US, but US and Canadian patients have had insurance cover the testing done overseas. Paternal Blood Blood is generally drawn from the father to help determine fetal antigen status. With RhD, the test is called the RhD genotype. With RhCE, and Kell antigen it is called an antigen phenotype. Full blood count â€”the hemoglobin level and platelet count are important Bilirubin total and indirect In some cases, the direct coombs will be negative but severe, even fatal HDN can occur. Anti-M also recommends antigen testing to rule out the presence of HDN. It is recommended to wait and retest 10â€”12 months after last transfusion. In some cases, DNA testing from saliva can be used to rule out certain conditions. Prevention[edit] Most Rh disease can be prevented by treating the mother during pregnancy or promptly within 72 hours after childbirth. The mother has an intramuscular injection of anti-Rh antibodies Rho D immune globulin. This is done so that the fetal rhesus D positive erythrocytes are destroyed before the immune system of the mother can discover them and become sensitized. This is passive immunity and the effect of the immunity will wear off after about 4 to 6 weeks or longer depending on injected dose as the anti-Rh antibodies gradually decline to zero in the maternal blood. It is part of modern antenatal care to give all rhesus D negative pregnant women an anti-RhD IgG immunoglobulin injection at about 28 weeks gestation with or without a booster at 34 weeks gestation. This reduces the effect of the vast majority of sensitizing events which mostly occur after 28 weeks gestation. Giving Anti-D to all Rhesus negative pregnant women can mean giving it to mothers who do not need it because her baby is Rhesus negative or their blood did not mix. In other countries, stocks of Anti-D can run short or even run out. The discovery of cell-free DNA in the maternal plasma has allowed for the non-invasive determination of the fetal RHD genotype. In May , the Society for Obstetrics and Gynecology of Canada is now recommending that the optimal management of the D-negative pregnant woman is based on the prediction of the fetal D-blood group by cell-free DNA in maternal plasma with targeted antenatal anti-D prophylaxis. It is no longer considered appropriate to treat all D-negative pregnant women with human plasma derivatives when there are no benefits to her or to the fetus in a substantial percentage of cases. Management[

edit] Antenatal Serial Ultrasound and Doppler examinationsâ€”to detect signs of fetal anemia such as increased blood flow velocities and monitor hydrops fetalis Quantitative analysis of maternal anti-RhD antibodiesâ€”an increasing level is a sign of fetal Rh disease Intrauterine blood transfusion Intraperitoneal transfusionâ€”blood transfused into fetal abdomen Intravascular transfusionâ€”blood transfused into fetal umbilical vein â€”This is the method of choice since the late s, and more effective than intraperitoneal transfusion. A sample of fetal blood can be taken from the umbilical vein prior to the transfusion. Early delivery usually after about 36 weeks gestation Postnatal Phototherapy for neonatal jaundice in mild disease Exchange transfusion if the neonate has moderate or severe disease the blood for transfusion must be less than a week old, Rh negative, ABO compatible with both the fetus and the mother, and be cross matched against the mothers serum IVIG has been used to successfully treat many cases of HDN. It has been used not only on anti-D, but on anti-E as well. If necessary, this dose can be repeated in 12 hours evidence quality B: Wiener , [19] who listed it in and alongside their tables for blood-typing and cross-matching. In Philip Levine and Rufus E. Stetson [20] published their findings about a family who had a stillborn baby who died of hemolytic disease of the newborn. They investigated this transfusion reaction. They did not name this blood group antigen, but it was subsequently found to be the rhesus factor. In , Group O: Paul in Irvington, NJ, delivered a normal infant in [22]: The second pregnancy April, resulted in an infant suffering icterus gravis. That procedure was further refined by Harry Wallerstein, [25] a transfusionist. Although the most effective method of treating the problem at the time, it was only partially ameliorative in cases where damage to the neonate had already been done. However, it is estimated that in the two decades it was used approximately , lives were saved, and the great majority were not brain damaged. It led him to propose that the disease might be prevented by injecting the at-risk mother with an antibody against fetal red blood cells. He proposed this for the first time to the public on February 18, A few months later, he proposed at a meeting of the British Genetical Society that the antibody be anti-RhD. Animal studies had previously been conducted by William Pollack, using a rabbit model of Rh. One of the needs was a dosing experiment that could be used to determine the level of circulating Rh-positive cells in an Rh-negative pregnant female derived from her Rh-positive fetus. Sir William Liley performed the first successful intrauterine transfusion in Clinical trials set up by Pollack in 42 clinical centers in the US, Great Britain, Germany, Sweden, Italy, and Australia confirmed their hypothesis, and the vaccine was finally approved in England and the United States in There being no known harm done by delaying the dosage for a week or more after birth, Ortho asked the FDA to grant permission for it to be given without a postpartum time restriction. In addition, John M. Bowman, one of the researchers at the University of Manitoba, and Freda pushed to allow antepartum use. All of this was subsequently granted. Within a year or so, the antibody had been injected with great success into more than , women. Time magazine picked it as one of the top ten medical achievements of the s. The use of Rh immune globulin to prevent the disease in babies of Rh negative mothers has become standard practice, and the disease, which used to claim the lives of 10, babies each year in the US alone, has been virtually eradicated in the developed world. The total cost of the effort was only a couple of million dollars, which is about the cost of the life-time care of a half-dozen irreparably brain-damaged children. Friesen, PhD, licensed a version of the vaccine, known as WinRho, in Chown is honored by the Canadian Medical Hall of Fame for his lifelong work with erythroblastosis fetalis. He has made over donations throughout his lifetime, and these donations are estimated to have saved over two million unborn babies from the condition. Up to , every batch of anti-D in Australia was made from his blood.

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However, in the case of a large antenatal fetomaternal hemorrhage or a fetomaternal hemorrhage at delivery, maternal B lymphocyte clones that recognize the RhD.

Advanced Search Abstract Rhesus Rh D alloimmunization may cause haemolytic disease of the fetus and newborn if the fetal Rh blood type is positive. Although the incidence of severe RhD alloimmunization has decreased with prophylactic anti-D immunoglobulin administration during and after pregnancy, sensitization still occurs in a small group of women. In such women, Rh disease will continue to be significant problem and for their babies who may be affected. Preimplantation genetic diagnosis PGD may be utilized to avoid materno-fetal blood group incompatibility in an RhD-sensitized woman. Biopsy of a single cell from early cleavage-stage embryos screening for RhD-negative embryos allows the transfer of only RhD-negative embryo s into the uterus. This avoids any complications related to haemolytic disease of the fetus and newborn. This article describes the first reported case of an unaffected pregnancy using PGD for Rh disease. IVF and embryo transfer resulted in a clinical pregnancy and the birth of a healthy girl confirmed to be blood type RhD negative. PGD in couples with a heterozygous RhD-positive male partner provides an option for avoiding haemolytic disease of the newborn in RhD alloimmunized mothers. An RhD-negative woman may develop anti-D antibodies when exposed to an RhD-positive fetus during or after pregnancy. Although various red cell antigens have been implicated in haemolytic disease of the newborn, RhD antigen is the most common and immunogenic NHMRC, ; Avent and Reid, As a result of red blood cell destruction, the fetus develops haemolytic anaemia, which, when severe, leads to hydrops fetalis, intrauterine fetal demise or both. D antigen expression is by the RhD protein while the RhCE protein expresses either C or c antigens together with E or e antigens on the same protein Mouro et al. The two genes are each composed of 10 exons that in tandem encompass 69 kilobases of DNA Avent and Reid, The gene that encodes the D polypeptide is present in Rh-positive persons and is absent in Rh-negative subjects Colin et al. Should a woman become sensitized in her first pregnancy, all subsequent RhD-positive babies will be at risk of haemolytic disease of the fetus and newborn. In the latter case the fetus will avoid any potential adverse sequelae from maternal RhD alloimmunization. Severe RhD alloimmunization is uncommonly encountered today largely due to the development of anti-D immunoglobulin and its utilization in clinical practice. In these sensitized women, Rh haemolytic disease will continue to be a significant problem and for their babies who are affected. In women who have suffered repeated pregnancy losses, invasive interventions such as serial intrauterine blood transfusions or an affected fetus or neonate, the prospect of having another affected pregnancy with all its complications may seem too great. In such women, rather than risk having another baby with haemolytic disease of the newborn, they may opt to avoid further pregnancies. Even with close monitoring of sensitized pregnant women for the early detection of fetal anaemia and the instituting of intrauterine transfusion at the appropriate time, there is a significant degree of fetal mortality Abdalla et al. Although the risk of fetal death from cordocentesis is relatively low, procedure-related fetal loss has been documented Daffos et al. The procedures are also associated with the risk of potentially increasing maternal RhD antibody production through secondary feto-maternal haemorrhage Nicolini et al. PGD was designed for the prevention of genetic disorders in the offspring of couples at increased risk. The ethics of such use is beyond the scope of this paper and will not be discussed. After IVF, the early embryo is screened for the disorder before the corresponding embryo is transferred into the uterus of the mother. In Rh disease this allows the transfer of Rh-negative embryos back into the RhD-alloimmunized mother, avoiding the potential complications and morbidity of haemolytic disease of the fetus and newborn. Although the use of PGD in the management of Rh disease has been previously published, clinical pregnancy has not to date been achieved Avner et al. However, PGD for the Kell genotype has been performed successfully to prevent severe alloimmunization occurring in an at-risk couple Verlinsky et al. We discuss the role of PGD in the management of RhD alloimmunization in selected couples where the sensitized woman and her RhD heterozygous partner can avoid the potential morbidity and mortality associated with an RhD-positive fetus. Case report A 27 year old married woman sensitized with

RhD antibodies sought preconception counselling regarding her options in attempting a future pregnancy. She and her husband had had two children, the second of which was affected by haemolytic disease of the newborn. Both of these pregnancies had proceeded to term and delivered vaginally. The second child developed hyperbilirubinaemia and neonatal jaundice requiring phototherapy as well as significant haemolytic anaemia that did not require transfusion. He was genotyped and found to be RhD heterozygote positive. The pertinent issues regarding RhD alloimmunization and future potentially more severely affected pregnancies were discussed with the couple. The couple were counselled that RhD screening prior to implantation using PGD could allow the selective transfer of only RhD-negative embryos and thereby avoid any possibility of materno-fetal blood incompatibility in that pregnancy. The couple agreed to assisted reproduction and PGD for transfer of an RhD-negative embryo to the uterus. The woman underwent routine ovarian stimulation and ICSI fertilization. Nineteen oocytes were aspirated and 17 were suitable for ICSI. On day 1, 12 were observed as fertilized. Day 3 biopsy, PCR amplification and analysis revealed nine RhD-positive embryos, two RhD-negative embryos and one with a uni-parental amplification profile. Two embryos a cell embryo and a compacting morula were transferred on day 5. This resulted in a clinical pregnancy. A total of 12 different primer pairs targeting different regions of the alignment that would result in amplification product differing in size between RHCE and RHD genes were designed Primer Express; Applied Biosystems, Australia. After testing, three pairs of primers gave both reliable amplification and distinguishable amplicon differences and were suitable for further use. Amplification was performed in a two-step PCR: The RhD genotypes of 12 embryos were determined. Regular ultrasound examination of the fetus throughout the pregnancy failed to show any evidence of fetal anaemia or hydrops fetalis. The maternal anti-D antibody level was also monitored regularly and remained stable, although significantly raised, throughout the duration of the pregnancy range Labour was induced at 39 weeks gestation. There were no complications noted in the immediate neonatal period or thereafter. Discussion The incidence of RhD alloimmunization has decreased since the introduction of anti-D prophylaxis during and after pregnancy Bowman, ; Bowman and Pollock, ; Crowther and Middleton, Nevertheless severe RhD alloimmunization still occurs and can have serious implications in a pregnancy with haemolytic anaemia, which, when extreme, causes fetal morbidity, stillbirth or perinatal mortality. After having experienced a significantly affected pregnancy, couples in whom RhD alloimmunization is present are often faced with the dilemma of whether to attempt further pregnancies and potential adverse sequelae. The tendency for Rh disease to worsen with each subsequent Rh-incompatible pregnancy in a sensitized woman also plays a major part in the decision-making process. In the case presented above, such a scenario existed. In such couples, the use of PGD for RhD typing allows the selective transfer of only RhD-negative embryo s , thereby avoiding any complications due to materno-fetal incompatibility. The case presented is, to our knowledge, the only PGD cycle resulting in a successful pregnancy. PGD was introduced in with the first established pregnancies in two couples known to be at risk of transmitting recessive X-linked diseases Handyside et al. Since then it has been usually offered for three major categories of disease: PGD allows at-risk couples to avoid potential complications or another unfortunate experience in future pregnancies. PGD necessarily involves assisted reproductive techniques where ovarian stimulation and IVF are required to produce in vitro several embryos in order to select unaffected ones for transfer. This means that even couples that are fertile must undergo the processes of assisted reproduction. However, the economic cost for follow-up and treatment of a typical pregnancy and newborn affected by severe RhD is not inconsiderable together with the psychological and physical burden van den Veyver et al. This case demonstrates that PGD can be used to determine the RhD status of early cleavage-stage embryos by single cell analysis. This permits selective transfer of only RhD-negative embryos, avoiding the development of haemolytic disease in the fetus. Although at-risk pregnancies detected by prenatal diagnosis may be treated by intrauterine transfusion, potential complications including fetal death cannot always be completely prevented even after this procedure. Pregnancy termination may also be unacceptable to the couple. PGD may be seen as a preventative treatment measure in couples affected by RhD alloimmunization and a male Rh-positive heterozygote. PGD was designed for detecting genetic defects, but, as this case demonstrates, may be used for couples at risk with RhD alloimmunization. This provides an approach for selected couples to avoid the risk of having babies

affected by haemolytic disease of the fetus and newborn. View large Download slide Electropherogram demonstrating in: D represents RHD gene productd. Amplicon identifications as seen in Table 1 are indicated in each panel. Paired primers for the Rhesus genes and short tandem repeats Locus.

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5: Maternal Alloimmunization (Rh-isoimmunization) - Dayton

The management of rhesus D alloimmunization in pregnancy continues to evolve to now include fetal genotyping and middle cerebral artery Doppler detection of fetal anemia. Division of Maternal-Fetal Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

The method used should be stated as the titer will vary according to the method. An albumin titer of 1: It is possible to encounter women with titers as high as with fetuses that are negative for the antigen to which the antibody is directed. Postpartum if the antibody screen is negative a second dose of RhIgG is given if the infant is Rh-positive or Du-positive. Rh-immune globulin must be given before the mother begins to produce her own antibody to the Rh factor. Antibody Sensitized Patient In general the priniciples used in the management of the Rh-D negative sensitized patient and the management of the patient with atypical blood antibodies do not differ. However, the management of the Kell-sensitized pregnancy may require more intensive surveillance, since maternal titers and amniotic fluid bilirubin levels do not necessarily correlate with disease severity. May involve marrow suppression. First Sensitized Pregnancy no prior severely affected pregnancy. If the father is Rh negative or negative for the atypical antigen then no further testing is necessary. Fetal DNA testing is available for: If the fetus is antigen positive then the pregnancy is followed with serial titers and ultrasound as long as titers remain below the "critical" value. Previously Affected Pregnancy For patients with a previously affected pregnancy, the timing of the initial procedure is determined by past clinical history. It is usually performed at least weeks earlier than the prior gestational age at which significant morbidity occurred. Surveillance Serial Amniocentesis Fetuses affected by hemolytic disease secrete abnormally high levels of bilirubin into the amniotic fluid. The amount of bilirubin can be quantitated by spectrophotometrically measuring absorbance at the nm wavelength in a specimen of amniotic fluid that has been shielded from light. Alternatively, percutaneous umbilical blood sampling PUBS may be used to determine all blood parameters directly. If amniocentesis is used to monitor the fetus, the results delta are plotted on a "Liley" curve. The Liley Curve The Liley curve is divided into three zones. A result in Zone I indicates mild or no disease. Fetuses in zone I are usually followed with amniocentesis every 3 weeks. A result in zone II indicates intermediate disease. Fetuses in low Zone II are usually followed by amniocentesis every weeks. A result above the middle of Zone II may require transfusion or delivery. In most cases, patients in the middle of zone II can progress to weeks of gestation. Depending on gestational age, patients in zone III should either be delivered or should receive intrauterine fetal transfusion. Although serial determinations of Delta optical density at nm and PUBs are the most common methods for the evaluation of fetal status, Doppler ultrasonography of the middle cerebral artery has also been used to identify fetuses at risk for moderate to severe hemolytic disease. Specific contraindications to intravenous immunoglobulin use include a previous episode of intravenous immunoglobulin-induced anaphylaxis rare and selective IgA deficiency. American College of Obstetricians and Gynecologists. Blood Special Issue No 2 ;3: J Clin Invest Lacey PA et al. Fatal hemolytic disease of the newborn due to anti-D in anRH positive Du variant mother. Maternal Alloimmunization and Fetal Hemolytic Disease. Bergstrom H et al. Demonstration of Rh antigens in a day-old fetus. Am J Obstet Gynecol Management of Blood Group Isoimmunization. Related Articles Percutaneous umbilical blood sampling in the management of Kell isoimmunization. N Engl J Med. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. Ultrasound Obstet Gynecol ;5: Liquor amnii analysis in management of pregnancy complicated by rhesus immunization. Am J Obstet Gynecol ; High-dose intravenous IgG for the treatment of severe rhesus alloimmunization.

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