transfusion, a further fetal blood sample is aspirated to determine the final hemoglobin concentration. Subsequent transfusions are given at 1–3-weekly intervals until 34–36 weeks, and their timing is based on the findings of non-invasive tests, such as Doppler studies, and the knowledge that, following a fetal blood transfusion, the mean rate of decrease in fetal hemoglobin is approximately 0.3 g/dl per day.

6. Doppler Studies

6.1 Uterine artery

In a longitudinal study of 12 fetuses, Copel et al. included the uterine artery pulsatility index (PI), together with the descending thoracic aortic peak velocity, in a multiple regression model to predict whether the fetal hematocrit was below or above 25% before the second fetal blood transfusion. The authors suggested that the significant contribution of uterine artery PI to the model could be explained by the effect of resolving placental edema after the correction of fetal anemia by the second transfusion. However, this is unlikely because there was no difference in uterine PI between hydropic and non-hydropic fetuses. Therefore; it is unlikely that fetal anemia alters the uteroplacental circulation.

6.2 Umbilical artery

Rightmire et al. found a significant inverse correlation between impedance to flow in the umbilical artery and fetal hematocrit. It was suggested that increased impedance to flow in the fetoplacental microcirculation may be due to hypoxemia-mediated capillary endothelial cell damage or clogging of the placental capillaries by the large fetal erythroblasts. In contrast, Warren et al. reported that impedance in the umbilical artery was not abnormal in red cell isoimmunized pregnancies with high amniotic fluid bilirubin concentration. Similarly, in a study of 95 affected pregnancies, umbilical artery PI, measured immediately before cordocentesis, was not increased and was not associated with fetal anemia.

6.3 Impedance to flow in fetal vessels

Vyas et al. measured the PI in the middle cerebral artery of 24 non-hydropic fetuses from red cell isoimmunized pregnancies; there were no significant associations between PI and either the degree of fetal anemia or the degree of deficit in oxygen content measured in samples obtained by cordocentesis. Furthermore, in a study of 95 fetuses undergoing cordocentesis for rhesus disease, the PI in both the middle cerebral artery and descending thoracic aorta was not significantly different from normal controls and there was no significant association between PI and fetal anemia. These findings indicate that impedance to flow is not affected by anemic hypoxia and by the alterations of blood constituents, such as hypoproteinemia, or red cell morphology, such as erythroblastemia, that accompany severe anemia.

6.4 Fetal cardiac Doppler studies

Meijboom et al. measured maximal and mean temporal velocity and early passive to late active ventricular filling phase (E/A) ratio on the atrioventricular orifices in 12 fetuses immediately before fetal blood transfusion. There was a non-significant increase in both maximal and mean temporal velocities. Furthermore, there was a significant reversal in the E/A ratio in the flow waveforms from the tricuspid valve. In normal fetuses, these two peaks present an ‘M’ shape, whereas in anemic fetuses the E peak is dominant, suggesting that, in fetal anemia, there is an increased pre-load in the right atrium. Copel et al. found that anemic fetuses before any intrauterine transfusion had significantly higher stroke volumes and ventricular outputs than normal controls. The increase was shared proportionately by both ventricles. Extremely compromised fetuses demonstrated diminished cardiac function as a terminal finding.

In an extended series of 95 previously untransfused fetuses undergoing cordocentesis for rhesus disease, there was a significant increase in aortic velocity with the degree of fetal anemia. Although, in some hydropic fetuses, aortic velocity was decreased, in the majority of cases the velocity was increased. In an additional series of 212 fetuses that had a transfusion 2–3 weeks previously, the relation between aortic velocity and anemia was weaker.

There was a significant association between the degree of fetal anemia and the increase in blood velocity. Some authors speculated that this increase in common carotid artery velocity reflected increased cardiac output associated with fetal anemia, rather than a chemoreceptor mediated redistribution in blood flow, as seen in hypoxemic growth-restricted fetuses.

Mari et al found a significant association between the peak systolic velocity in the middle cerebral artery and fetal hematocrit at cordocentesis. In a prospective study of 16 fetuses from isoimmunized pregnancies, they found that all the anemic fetuses had peak velocity values above the normal mean for gestation, whereas none of the fetuses with peak velocity below the normal mean was anemic. On the basis of these results, they suggested that, in the management of isoimmunized pregnancies, the indication for cordocentesis should be a peak systolic velocity above the normal mean for gestation. These results were confirmed in a multicenter study involving 111 fetuses from isoimmunized pregnancies; all moderately or severely anemic fetuses had increased peak velocity in the middle cerebral artery.

6.5 Blood Velocity in Fetal Veins

Rightmire et al. studied 21 previously transfused fetuses from red cell isoimmunized pregnancies, reported increased peak systolic and time averaged maximum velocities in the ductus venosus before intravascular fetal blood transfusion, which returned to normal values the following day.

It was suggested that the increase in ductus venosus blood flow in anemic fetuses reflects increased venous return and

therefore cardiac preload. Hecher et al. recorded flow velocity waveforms from the ductus venosus, right hepatic vein, inferior vena cava, middle cerebral artery and descending thoracic aorta from 38 red cell isoimmunized pregnancies and found that only the velocity in the thoracic aorta was significantly associated with the degree of fetal anemia. Furthermore, this study showed that heart failure is not the primary mechanism for the development of hydrops, but rather the end-stage of severe anemia, because the pulsatility of venous blood flow waveforms was not increased. Hydrops may be due to reduced colloid osmotic pressure, hypoxia-induced endothelial damage and increased permeability. Severe fetal anemia, with consequent cardiac failure, is associated with a reversed 'a' wave in the ductus venosus. Under these conditions, pulsations are also present in the venous portal system (which in normal fetuses is characterized by a continuous flow). The pulsatile pattern present in the venous system corresponds to findings in children with portal hypertension. Since, in fetal anemia, resistance to flow in the fetal circulation and placenta is unchanged, an increase of umbilical venous blood flow is in accordance with high cardiac output and elevated arterial velocities.

6.6 Hemodynamic changes following fetal blood transfusion

Warren et al. and Kirkinen et al. found that, immediately after a fetal intraperitoneal blood transfusion, there was a temporary increase in umbilical venous blood flow and subsequent gradual decrease from above to within the normal range. It was suggested that the gradual decrease in flow, coinciding with resolution of fetal ascites, was the result of absorption of the transfused blood and correction of the fetal anemia. Similarly, Mari et al. found that intrauterine transfusion is associated with a significant decrease in the peak velocity in the middle cerebral artery and this decrease is proportional to the increase in fetal hematocrit. These findings are likely to be the result of a decrease in cardiac output following the transfusion due to:

1) Increased blood hemoglobin concentration and viscosity, and consequent decrease in venous return;
2) Congestive heart failure due to overloading of the fetal circulation; or
3) Cardio-inhibition due to increased baroreceptor activity.

The most likely explanation for these findings is that transfusion results in temporary cardiovascular overload. Animal studies have also shown that the fetal heart has very limited reserve capacity to increase its output in response to acute overload, and that massive increases in fetal blood volume are associated with a decrease in cardiac output. After transfusion, there is a rapid rate of fluid loss and this explains the rapid recovery in cardiac output

6.7 The role of amniocentesis in management of Rh sensitized pregnancies

Bevis D.C.A in 1952 has 1st done the amniocentesis in the management of Rh disease of the newborn. Liley in 1961 assessed the progress of the disease by serial amniocentesis by using amniotic fluid billirubin levels detected by optic density at 450. A need for fetal transfusion was determined by plotting photo spectrometry values in a chart and the presence of early fetal ascitis. Several refinements of the Liley's chat has been published (Whifield 1970). Nevertheless the photo spectrometry billirubin levels seemed to be less reliable indirect predictors of fetal anemia especially before 28 weeks and in the presence of anti-kell antibodies. This has prompted some units to abandon the amniocentesis based diagnosis and rely exclusively on invasive and non invasive monitoring of fetal anemia. (Nicolaides at el. 1984).

7. Conclusion

Despite wide spread Rhesus prophylaxis still there are cases of isoimmunisation due to poor attention on Rh status of the mother. This needs further strengthening of our care at all levels in obtaining a proper clinical history and obtaining blood group and Rh status. USS has become one of the frontiers in the non invasive management of this condition with different variable with different merits. In the pathophysiology red cell isoimmunized pregnancies, placentation is normal and therefore indices of impedance to flow in the uterine and umbilical arteries are normal, irrespective of the severity of fetal anemia.

In red cell isoimmunized pregnancies, normal placental perfusion results in normal fetal blood pO2, pCO2 and pH and therefore there is no evidence of redistribution in the fetal circulation; the PI in the middle cerebral artery, thoracic aorta and renal arteries is normal.

In red cell isoimmunized pregnancies, the left and right cardiac outputs and blood velocity in the umbilical vein, middle cerebral artery, thoracic aorta, renal arteries and the fetal venous system are increased in proportion to the degree of fetal anemia.

The most likely mechanism for the hyperdynamic circulation of anemic fetuses is decreased blood viscosity, leading to increased venous return and cardiac preload.

In red cell isoimmunized pregnancies, fetal heart failure is not the primary mechanism for the development of hydrops. However, severe anemia with consequent end-stage cardiac failure may be associated with high pulsatility or even reversed 'a' wave in the ductus venosus and pulsations in portal sinus.

In red cell iso immunized pregnancies, intravascular fetal blood transfusion results in temporary cardiovascular overload with a temporary fall in both right and left cardiac outputs. The place for serial amniocentesis is limited in current practice due to its poor correlation with fetal anemia.

References

[1] Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan R, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunization. Lancet 1988;i:1073–6
[2] Nicolaides KH, Thilaganathan B, Rodeck CH, Mibashan RS. Erythroblastosis and reticulocytosis in anemic fetuses. Am J Obstet Gynecol 1988;159:1063–5
[3] Nicolaides KH, Snijders RJM, Thorpe-Beeston JG, Van den Hof MC, Gosden CM, Bellingham AJ. Mean red

cell volume in normal, small and anemic fetuses. Fetal Therapy 1989;4:1–13
[4] Nicolaides KH. Studies on fetal physiology and pathophysiology in rhesus disease. Semin Perinatol1989;13:328–37
[5] Soothill PW, Nicolaides KH, Rodeck CH, Bellingham AJ. The effect of replacing fetal with adult hemoglobin on the blood gas and acid–base parameters in human fetuses. Am J Obstet Gynecol 1988; 158:66–9
[6] Soothill PW, Lestas AN, Nicolaides KH, Rodeck CH, Bellingham AJ. 2,3-Diphosphoglycerate in normal, anaemic and transfused human fetuses. Clin Sci 1988;74:527–30
[7] Soothill PW, Nicolaides KH, Rodeck CH, Clewell WH, Lindridge J. Relationship of fetal hemoglobin and oxygen content to lactate concentration in Rh isoimmunized pregnancies. Obstet Gynecol 1987;69:268–71
[8] Nicolaides KH, Warenski JC, Rodeck CH. The relationship of fetal protein concentration and hemoglobin level to the development of hydrops in rhesus isoimmunization. Am J Obstet Gynecol 1985;152:341–4
[9] Nicolaides KH, Rodeck CH. Maternal serum anti-D concentration in the assessment of rhesus isoimmunisation. Br Med J 2000;in press
[10] Nicolaides KH, Sadovsky G, Cetin E. Fetal heart rate patterns in red blood cell isoimmunized pregnancies. Am J Obstet Gynecol 1989;161:351–6
[11] Nicolaides KH, Bilardo CM, Campbell S. Prediction of fetal anemia by measurement of the mean blood velocity in the fetal aorta. Am J Obstet Gynecol 1990;162:209–12
[12] Nicolaides KH, Soothill PW, Rodeck CH, Campbell S. Ultrasound guided sampling of umbilical cord and placental blood to assess fetal wellbeing. Lancet 1986;i:1065–7
[13] Nicolaides KH, Soothill PW, Rodeck CH, ClewellW. Rh disease: intravascular fetal blood transfusion by cordocentesis. Fetal Therapy 1986;1:185–92
[14] Copel JA, Grannum PA, Belanger K, Green J, Hobbins JC. Pulsed Doppler flow velocity waveforms before and after intrauterine intravascular transfusion for severe erythroblastosis fetalis. Am J Obstet Gynecol 1988;158:768–74
[15] Nicolaides KH, Kaminopetros P. Red-cell isoimmunization. In Pearce M, ed. Doppler Ultrasound in Perinatal Medicine. Oxford: Oxford University Press, 1992;244–57
[16] Rightmire DA, Nicolaides KH, Rodeck CH, Campbell S. Fetal blood velocities in Rh isoimmunization: relationship to gestational age and to fetal hematocrit. Obstet Gynecol 1986;68:233–6
[17] Warren PS, Gill RW, Fisher CC. Doppler blood flow studies in rhesus isoimmunization. Sem Perinatol 1987;11:375–8
[18] Meijboom EJ, De Smedt MCH, Visser GHA, Jager W, Nicolaides KH. Fetal cardiac output measurements by Doppler echocardiography. In Proceedings of the Sixth Annual Meeting of The Society of Perinatal Obstetricians. San Antonio, Texas, 1986: Abstract 17
[19] Copel JA, Grannum PA, Green JJ, Hobbins JC, Kleinman CS. Fetal cardiac output in the isoimmunized pregnancy: a pulsed Doppler echocardiographic study of patients undergoing intravascular intrauterine transfusion. Am J Obstet Gynecol 1989;161:361–4
[20] Barss VA, Doubilet PM, St.John-Sutton M, Cartier MS, Frigoletto FD. Cardiac output in a fetus with erythrobastosis fetalis: assessment using pulsed Doppler. Obstet Gynecol 1987;70:442–4
[21] Rizzo G, Nicolaides KH, Arduini D, Campbell S. Effects of intravascular fetal blood transfusion on fetal intracardiac Doppler velocity waveforms. Am J Obstet Gynecol 1990;163;569–71
[22] Lam YH, Tang MH, Lee CP, Tse HY Cardiac blood flow studies in fetuses with homozygous alpha-thalassemia-1 at 12–13 weeks of gestation. Ultrasound Obstet Gynecol 1999;13:48–51
[23] Huikeshoven FJ, Hope ID, Power GG, Gilbert RD, Longo LD. A comparison of sheep and human fetal oxygen delivery systems with use of a mathematical model. Am J Obstet Gynecol 1985;151: 449–55
[24] Oberhoffer R, Grab D, Keckstein J, Högel J, Terinde R, Lang D. Cardiac changes in fetusessecondary to immune hemolytic anemia and their relation to hemoglobin and catecholamine concentrations in fetal blood. Ultrasound Obstet Gynecol 1999;13:396–400
[25] Bilardo CM, Nicolaides KH, Campbell S. Doppler studies in red cell isoimmunization. Clin Obstet Gynecol 1989;32:719–27
[26] Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and utero-placental circulation: relationship with umbilical venous blood gases measured at cordocentesis. Am J Obstet Gynecol 1990;162:115–20.
[27] Mari G, Adrignolo A, Abuhamad AZ, Pirhonen J, Jones DC, Ludomirsky A, Copel JA. Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. Ultrasound Obstet Gynecol 1995;5:400–5
[28] Mari G. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. N Engl J Med 2000; 342: 9–14
[29] Steiner H, Schaffer H, Spitzer D, Batka M, Graf AH, Staudach A. The relationship between peak velocity in the fetal descending aorta and hematocrit in rhesus isoimmunization. Obstet Gynecol 1995;85:659–62
[30] Bahado-Singh R, Oz U, Deren O, Pirhonen J, Kovanci E, Copel J, Onderoglu L. A new splenic artery Doppler velocimetric index for prediction of severe fetal anemia associated with Rh alloimmunization. Am J Obstet Gynecol 1999;180:49–54
[31] Kirkinen P, Jouppila P, Eik-Nes S. Umbilical vein blood flow in rhesus isoimmunization. Br J Obstet Gynaecol 1983;90:640–3
[32] Iskaros J, Kingdom J, Morrison JJ, Rodeck C. Prospective non-invasive monitoring of pregnancies complicated by red cell alloimmunization. Ultrasound Obstet Gynecol 1998;11:432–7
[33] Oepkes D, Vandenbussche FP, van Bel F, Kanhai HHH. Fetal ductus venosus blood flow velocities before and after transfusion in red-cell alloimmunized pregnancies. Obstet Gynecol 1993;82;237–41
[34] Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, arterial, and intracardiac blood flows in red

blood cell isoimmunization. Obstet Gynecol 1995;85:122–8
[35] d'Ancona RL, Rahman F, Ozcan T, Copel JA, Mari G. The effect of intravascular blood transfusion on the flow velocity waveform of the portal venous system of the anemic fetus. Ultrasound Obstet Gynecol 1997; 10:333–7
[36] Weiner CP, Anderson TL. The acute effect of cordocentesis with or without fetal curarization and of intravascular transfusion upon umbilical artery waveform indices. Obstet Gynecol 1989;73: 219–24
[37] Hanretty KP, Whittle MJ, Gilmore DH, McNay MB, Howie CA, Rubin PC. The effect of intravascular transfusion for rhesus haemolytic disease on umbilical artery Doppler flow velocity waveforms. Br J Obstet Gynaecol 1989;96:960–3
[38] Weiner CP, Robillard GE. Effect of acute intravascular volume expansion on human fetal prostaglandin concentrations. Am J Obstet Gynecol 1989;161:1494–7
[39] Panos MZ, Nicolaides KH, Anderson JV, Economides DL, Rees L, Williams R. Plasma atrial natriuretic peptide: response to intravascular blood transfusion. Am J Obstet Gynecol 1989;161: 357–61
[40] Welch CR, Rodeck CH. The effect of intravascular transfusion for rhesus haemolytic disease on umbilical artery Doppler flow velocity waveforms. Br J Obstet Gynaecol 1990;97:865–6
[41] Mari G, Rahman F, Olofsson P, Ozcan T, Copel JA. Increase of fetal hematocrit decreases the middle cerebral artery peak systolic velocity in pregnancies complicated by rhesus alloimmunization. J Matern Fetal Med 1997;6:206–8
[42] Gillbert RD. Control of fetal cardiac output during changes in blood volume. Am J Physiol 1980;238:H80–6
[43] Mari G, Moise KJ, Russell LD, Kirshon B, Stefos T, Carpenter RJ. Flow velocity waveforms of the vascular system in the anemic fetus before and after intravascular transfusion for severe red blood cell alloimunization. Am J Obstet Gynecol 1990;162:1060–4
[44] Doppler in Obstetrics Copyright © 2002 by Kypros Nicolaides, Giuseppe Rizzo, Kurt Hecker and Renato Ximenes