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Doppler ultrasound assessment of fetal anaemia in an alloimmunised pregnancy

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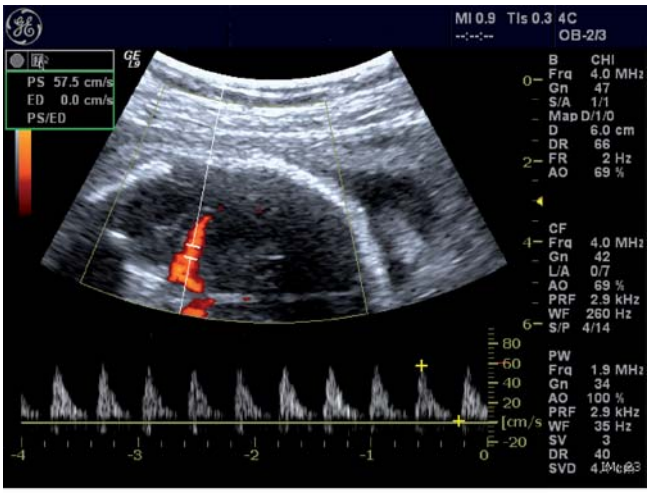

Fig. 1: Initial presentation. MCA PSV at 29 weeks and 1 day.

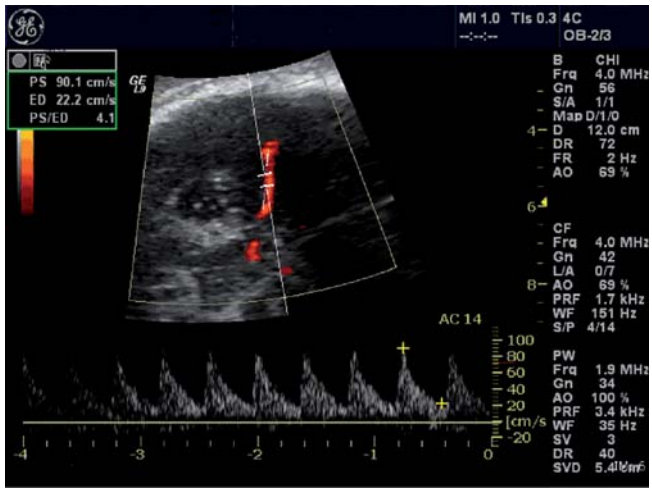

Fig. 2: Pre delivery at 34 weeks: MCA PSV of 90.1 cm/s or 1.7-2 MOM.

Introduction

While the use of elevated middle cerebral artery peak systolic velocity (MCA PSV) in assessing fetal anaemia is well known, its occurrence is uncommon due to the current practice of giving prophylactic doses of ultrafiltered Rh (D) immunoglobulin (anti-D) in Rh (D) negative women. In mothers who do not receive prophylaxis with Rh immunoglobulin, the overall risk of immunisation for an Rh-positive ABO-compatible infant with an Rh-negative mother is about 16%[1]. With appropriate use of anti-D the incidence of fetal anaemia is approximately 0.1% of pregnancies in Rh (D) negative women[2]. Despite this, maternal Rh alloimmunisation has not been eliminated with subsequent erythroblastosis fetalis and haemolytic disease still occasionally occurring. This article illustrates a case where MCA PSV successfully identified a fetus with anaemia allowing appropriate intervention and a good outcome.

Case history

Pregnancy in this 37-year-old G5 P3 T1 female was not diagnosed until 25 weeks gestation, due to the patient being ammenorrheic from the presence of a Mirena (Bayer Healthcare, Pymble, NSW, Australia) intrauterine system. She was first seen at our institution at 28 weeks and 2 days, and her booking bloods showed a blood group of O Rh (D) negative with an Anti D antibody titre of 1:512. Quantitation of her anti-D measured 1175 IU/mL. Identification of her fetal DNA (ffDNA) in maternal serum indicated that the fetus was most likely RH (D) positive. How this patient became isoimmunised is unknown. It is believed that isoimmunisation occurred during the second pregnancy as the first reports of antibodies occurred during the third pregnancy. This pregnancy (and a previous termination) was with a new partner who was Rh (D) positive.

Ultrasound findings

On the initial ultrasound at 29 weeks and 1 day there was no overt evidence of fetal anaemia and the fetal MCA PSV measured 58 cm/s (Fig. 1). A follow-up ultrasound was organised for a weeks time. Ultrasound scan performed at 30 weeks and 2 days demonstrated a symmetrically grown fetus lying on the 85th percentile for gestational age. The fetus appeared morphologically and biophysically well. There was no evidence of fetal hydrops. The liver had a length of 4.8 cm, which was around the 90th percentile. The middle cerebral artery peak systolic velocity measured 65 cm/sec or just above 1.5 multiples of the median (MOM). The patient continued to be monitored with weekly MCA PSVs. At 31 weeks and 2 days, the MCA PSV measured 70 cm/s and the fetus remained biophysically well.

Management

Due to the persistently raised MCA PSV, the fetus was steroid loaded and underwent *inutero* fetal blood transfusion at 32 weeks gestation. The fetal Hb prior to IUT was 70 and increased to 140 post transfusion. MCA PSV levels returned to the normal range until 34 weeks, when they started to increase dramatically (MCA PSV max 90 cm/s Fig. 2), at which stage a decision was made to deliver the fetus. Elective caesarean section was performed at 35 weeks gestation as the patient had had three previous lower uterine segment caesarean sections (LUSCS).

Surgical/pathological findings

Histopathology: Deep to the membranes on the fetal surface there were two areas of haemorrhage. These were surrounded by a green-yellow bilious tinge. The cotyledons on the maternal surface were also disrupted and frayed across the whole placenta. The cord contained three vessels (Fig. 3).

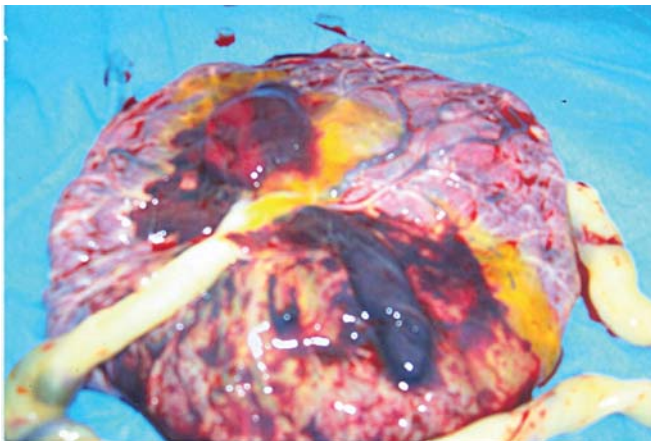

Fig. 3: Placenta demonstrating hyperbillirubinaemia.

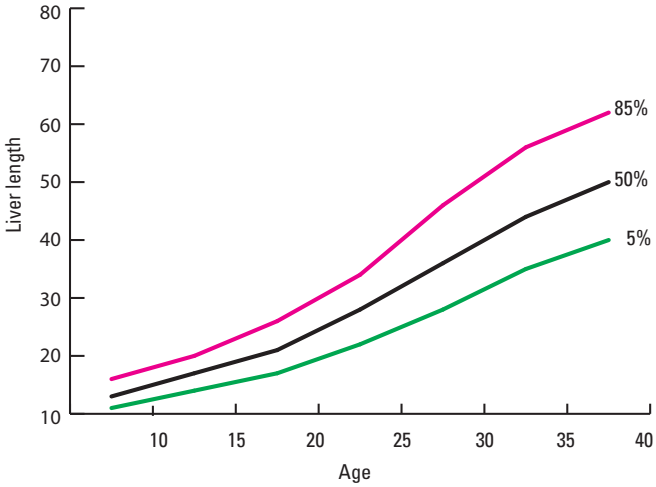

Fig. 4: Relationship between fetal liver length (mm) and gestational age (weeks)[14].

Table 1: Causes of transplacental fetomaternal haemorrhage.

Causes of transplacental fetomaternal haemorrhage [3]
• Delivery • Spontaneous / threatened / induced abortion • Ectopic pregnancy • Partial Molar Pregnancy • Invasive procedures: CVS / amniocentesis (2% risk of sensitisation) / Cordocentesis • External Cephalic Version • Antenatal haemorrhage: Abruptio placenta or placenta previa • Fetal death • Maternal abdominal trauma • Spontaneous

Neonatal outcome

The baby was born at 35 weeks and 2 days by elective caesarean section. No resuscitation was required as Apgars were 9 at 1 minute and 9 at 5 minutes. Birth weight was 2732 g. The Hb level in the neonate measured 98 g/L on Day 1. Due to prematurity, mild jaundice, hyperbilirubinaemia and rhesus isommunisation, the baby was transferred to the special care nursery. Blood group was O Rh (D) positive, direct Coombes positive and Anti D negative. Jaundice was managed by SBR monitoring (max 212 on Day 2) and one week of phototherapy. Some respiratory distress was experienced on Day 2 requiring nasal oxygen for one hour, at which time a stat dose of prophylactic triple antibiotics was given. The rhesus isominusation was managed by FBC and SBR monitoring, with blood transfusions required on Day 8 and Day 23. Discharge occurred on Day 25, with a discharge weight of 3186 g. A subsequent transfusion was required at five weeks of age. On subsequent follow-up baby was doing well.

Discussion

Pathogenesis

Red blood cell isoimmunisation develops after an initial exposure of "foreign" red blood cells to the mother's immune system. Such sensitisation events include:

- Transplacental fetomaternal haemorrhage during pregnancy. This is the most common cause with frequency and volume increasing with gestational age (Table 1)
- Inadvertent transfusion or injection with a needle contaminated with Rh(D) positive blood
- D-mismatched allogenic haemopoietic stem cell transplantation[3].

Further antigenic exposure during subsequent pregnancies in a sensitised mother results in a significant increase in maternal IgG antibody titre. The maternal antibodies cross the placenta and target the fetal red blood cells causing haemolysis. In severe cases of anaemia, oxygen delivery becomes impaired; this results in a compensatory increase in cardiac output which in turn may lead to increased cerebral arterial flow, heart failure and fluid collection in various body cavities. If left untreated, hydrops fetalis will eventually lead to death[3]. Extensive liver erythropoiesis may also occur, disrupting the normal hepatic architecture and function. This leads to decreased protein production, portal hypertension, hepatomegaly and ascites[1].

Diagnosis

The diagnosis of Rh (D) alloimmunisation is by detection of anti-Rh (D) antibodies in maternal serum. Screening by the way of Rh (D) typing and antibody screen is performed at the first antenatal visit. This is repeated at 28 and 36 weeks prior to administration of prophylactic anti-D). This test is safe, accurate and inexpensive. Following delivery of a Rh positive baby, antibody testing and quantification of fetal RBC in maternal circulation (Kleihauer-Betke test) is performed, and an appropriate amount of anti-D is given[3].

Imaging features

Ultrasound easily detects evidence of fetal hydrops. Features include serious cavity effusions (peritoneal, scrotal, pleural or pericardial effusion), polyhydramnios, placental, skin and subcutaneous oedema, hepatosplenomegaly, cardiomegaly and alterations in fetal and umbilical vessel size and flow[4].

Overt evidence of fetal hydrops on ultrasound, however, is an end-stage sign of severe anaemia. It does not present until the haemolytic disease is quite severe and fetal haemoglobin is one-third of normal or less[5]. As such, fetal surveillance is required to identify the anaemic fetus prior to the onset of hydrops.

The gold standard for fetal anaemia assessment is fetal blood sampling. Unfortunately this is the most invasive method and hence carries the highest risk. Under direct ultrasound guidance a needle is placed through the maternal abdomen into a fetal/cord vessel (usually at the level of

Table 2: Reference values of peak systolic velocity of middle cerebral artery[13].

Gestational age (weeks)	Peak systolic velocity of middle cerebral artery Multiples of the median			
	1	1.5	1.7	2.0
15	20	30	34	40
16	21	32	36	42
17	22	33	37	44
18	23	35	39	46
19	24	36	41	48
20	25	38	43	50
21	26	39	44	52
22	28	42	48	56
23	29	44	49	58
24	30	45	51	60
25	32	48	54	64
26	33	50	56	66
27	35	53	60	70
28	37	56	63	74
28	38	57	65	76
30	40	60	68	80
31	42	63	71	84
32	44	66	75	88
33	46	69	78	92
34	48	72	82	96
35	50	75	85	100
36	53	80	90	106
37	55	83	94	110
38	58	87	99	116
39	61	92	104	122
40	63	95	107	126

cord insertion into the placenta[4] and 1–2 mL of fetal blood is obtained)[3].

In the past, assessment of fetal anaemia was carried out by serial amniocentesis. The degree of fetal haemolysis was indicated by measuring the level of bilirubin by using spectral analysis of the amniotic fluid at 450 nm (delta OD_{450}) and plotting the result on a Lilly or Queenan Curve[3].

More recently surveillance has been carried out by serial Doppler ultrasounds. This is due to the noninvasive nature of Doppler ultrasound and its increased accuracy (85%) over the Liley (76%) and Queenan (81%) Curves[6]. The MCA PSV is measured in the MCA closest to the maternal skin, with the fetal head in the transverse position. With the assistance of colour or power Doppler the pulsed gate is placed over the vessel just as it bifurcates from the carotid siphon and the minimal angle of insonation is applied (< 15°). This is important as velocity measurements are angle dependent. Measurements should be taken during a period of apnoea or no fetal movement, to reduce the chance of compensatory fetal heart rate acceleration causing a false elevation in the peak velocity. Measurements from a more peripheral portion of the MCA may result in falsely low peak values. Multiple measurements should be recorded with the highest MCA PSV being reported as a function of gestational age or Multiples of the median (MOM) (Table 2). Serial scans should be performed weekly with the trend of the MCA PSV having greater clinical significance for intervening than a single value[7].

MCA PSV measurements may be carried out from 16–18 weeks gestation. After 35 weeks the false-positive rate for predicting fetal anaemia increases, as such amniocentesis and delta OD_{450} or delivery of at risk fetuses may be indicated[3]. Likewise amniocentesis may also have a limited role in centres where training in MCA Doppler and a good level of sonographic expertise is not available.

While MCA PSV has proved effective in the assessment of fetal anaemia before the first transfusion, the data do not seem to support its use in predicting the need for subsequent transfusions[8]. Current studies indicate that accuracy becomes less with each transfusion. This is believed to be due to the increase in donor red blood cells within the fetal circulation. This shift from principally fetal haemoglobin to adult haemoglobin results in an increased viscosity of the whole blood (decreased fetal haemocrit and increased RBC rigidity), which in turn results in decreased velocity of blood through the fetal circulation. In addition the adult haemoglobin has a poorer capacity to deliver oxygen to the tissues than fetal haemoglobin, which results in a compensatory increase in flow.

Other parameters for assessment of fetal anaemia, such as cardio-femoral index, liver length and spleen perimeter

have not proven to provide much additional benefit[9]. The use of liver length however is commonly used, and has its role as a supportive tool. The fetal liver is measured in the longitudinal plane at the maximum length of the right lobe (from the dome of the right diaphragm to the tip of the right lobe). Measurements obtained are plotted on a nomogram indicating gestational age adjusted percentiles (Fig. 4).

Other uses of MCA PSV are currently being investigated. These include applications in intrauterine growth retardation (IUGR), parvovirus, twin-to-twin transfusion, fetomaternal haemorrhage, alphathalassemia and Kell alloimmunisation[6]. Of particular interest is its use in IUGR.

IUGR due to placental insufficiency is associated with chronic hypoxia, triggering a blood flow centralisation process in order to maintain blood flow to key organs such as the brain, chest and adrenal glands. Traditionally, this centralisation process has been identified as a reduction in the pulsatillity index in the middle cerebral artery (MCA PI)[10]. The main benefit in using this measurement is that it is not angle dependent and thus is easy to obtain.

Recent studies, however, have suggested that MCA PSV may be more clinically useful as an indicator of IUGR than MCA PI. This is due to research in fetal haemodynamic adaptation and regional haemodynamic redistribution.

While MCA PI is initially reduced in IUGR, with progression of the process, fetal haemodynamic adaptation may occur resulting in plateauing and then an actual increase in MCA PI, returning the value to within the normal range preceding fetal demise or delivery. Hence it is difficult to quantify the severity or progression of IUGR based on MCA PI alone. In fact at the fetuses most compromised state it may have a normal MCA PI. MCA PSV on the other hand, exhibits a well defined pattern, progressively increasing with advanced gestation and progression of IUGR, and only slightly decreases (but remains well above normal) prior to fetal demise or delivery[11,12].

The pulsatility index of the posterior cerebral artery (PCA PI) has also been postulated as an alternative. Initial research implies that regional haemodynamic redistribution results in a regional hierarchy of brain deterioration, which is reflected by different cerebral arteries displaying a change in PI at different stages of progression. It has been reported that PCA and ACA respond earlier than MCA and that the PCA PI remains reduced throughout progression of the process[12].

With all of this in mind, one should reiterate the importance of performing and interpreting measurements within the clinical context, and that the use of multiple measurement types and assessment of the trend provides more information than does any single measurement alone.

Therapeutic options

Severe fetal anaemia is treated in the antenatal period via intrauterine transfusion (IUT). The umbilical cord is cannulated under direct ultrasound guidance. Several transfusions may be performed over the course of the pregnancy to keep the fetus within the normal target range. Complications of IUT include infection, fetomaternal haemorrhage, cord haematoma, rupture of membranes, premature labour, cardiac overload, fetal bradycardia and fetal loss[4]. Survival rates for transfused fetuses are approximately 92% for nonhydropic fetuses and 70% for hydropic fetuses. Neurologically, 90% of all transfused fetuses (hydropic and non-hydropic) have a normal outcome[8].

Conclusion

This case demonstrates the usefulness of MCA PSV in identifying and monitoring fetuses at risk of fetal anaemia and in turn allowing appropriate intervention (in the form of IUT) and improving fetal and in turn neonatal outcomes.

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