Thai Journal of Obstetrics and Gynaecology
September 2001, Vol. 13, pp. 135-145

OBSTETRICS

Assessment of Fetal Haemolytic Anaemia by Ultrasonography and Anti-D Levels

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ABSTRACTS

Objective To assess the value of ultrasonographic parameters including the measurements of fetal liver length, spleen perimeter and umbilical vein maximum flow velocity (UVV max), and anti-D levels in the prediction of fetal anaemia and delaying timing of the first invasive test.

Method One-hundred and thirty-two patients with Rhesus-alloimmunisation were seen between January 1995 and June 2000. Only patients with Rhesus (D) antibodies were included in this study (n=82). The following characteristics including age, parity, previuos obstetrics history, anti-D quantifications, the measurements of ultrasonographic parameters, the first invasive precedures performed (FBS and amniocentesis for amniotic delta OD 450), the timing and the results were reviewed. Postnatal delivery outcomes were recorded if there was no invasive procedure performed during pregnancy.

Results In patients with severe history, fetal anaemia tended to be higher and occur at an earlier gestation than those with none or mild history. The first invasive test can be deferred when multiple parameters of non-invasive assessment were used. Fetal blood sampling was mostly performed in patients with severe history at an early gestation while amniocentesis for amniotic delta OD 450 was mostly performed in those with none or mild history after 27 weeks. Anti-D levels in subsequent pregnancies or in patients with severe history were much higher and could not be used as the only indicator to predict fetal anaemia. However, serial measurements of anti-D levels can be used to defer the first invasive tests and when combined with UVV max measurement, the accuracy was higher in the prediction of fetal anaemia regardless of patient history. The measurement of only fetal liver length or fetal spleen perimeter can not be used to predict fetal anaemia. High UVV max measurement ($\geq 95^{th}$ percentile) prior to delivery indicated a risk of neonatal anaemia and postneonatal exchange transfusion.

Conclusions The number of invasive tests should be kept to a minimum and the combination of many ultrasonographic parameters including the measurements of fetal liver length, spleen perimeter and umbilical vein maximum flow velocity (UVV max), and the measurement of anti-D levels can be firstly used to predict fetal anaemia.

Key words: **fetal haemolytic anaemia, ultrasonography, anti-D levels**

Fetal haemolytic anaemia is caused by red cell-alloimmunisation. The incidence of fetal haemolytic anaemia has been dramatically reduced due to widespread use of prophylactic anti-D immunoglobulin.[1] If immunoprophylaxis fails, or who become sensitized, the fetus will develop severe erythroblastosis fetalis. Intrauterine management can prolong life in utero. The introduction of high-resolution real time ultrasound and the development of in utero fetal blood transfusion have influenced both assessment and therapy and have given rise to the improvement in pregnancy outcome.

Ultrasound is the most useful tool with which to diagnose the affected fetus in utero. The severely affected fetus may show signs of hydrops fetalis including ascites, pericardial and pleural effusion, subcutaneous oedema, polyhydramnios and placentomegaly. Marked erythroid hyperplasia of the bone marrow is stimulated by the prolonged and excessive haemolysis which give rise to the large areas of extramedullary haematopoiesis[2] especially in the liver and spleen. Measurement of fetal liver length and spleen perimeter appear to show potential in evaluating fetal anaemia, enlargement of these dimensions reflecting the increased extramedullary erythropoietic mass.[3-5] The use of fetal Doppler ultrasound in the evaluation of severe alloimmunisation is appealing in view of the correlation between fetal anaemia and elevated cardiac output and increased blood velocity measurements from fetal vessels.[6-9]

Currently many ultrasonographic parameters such as fetal liver length,[4,10] fetal spleen size[5] and Doppler measurements of flow velocities in the umbilical vein[11] have been present to have efficient values in the management of the fetuses. All studies have shown significant correlations between ultrasonographic Doppler results and fetal anaemia with high false negative rate.

It is known that Rhesus antibodies may develop during a first pregnancy, most frequently after 28th week of gestation.[12] Routine antibody testing is by indirect Coombs method. The trend of a sudden rise in antibodies is more significant than the absolute value. A sudden rise in antibody levels often indicates worsening disease which may require intervention. Nicolaides and Rodeck[13] have reported that invasive testing should be performed in the pregnancies with antibody levels above 15 IU/ml.

The principle aims of this study are to assess the value of ultrasonography and Doppler to predict fetal haemolytic anaemia, to assess the combination of the above parameters in combination with anti-D levels in predicting the severity of fetal haemolytic anaemia and to assess the use of non-invasive assessments of fetal anaemia in delaying the timing of the first invasive test.

Materials and methods

A total of 132 women with rhesus alloimmunisation were referred to the Fetal Medicine Unit at University College, London, between January 1995 and June 2000. Only rhesus (D) alloimmunisation was studied. The following characteristics were recorded. Those included maternal age, parity, medical and pregnancy histories, the type of rhesus antigens, ultrasound findings including fetal liver length, fetal spleen perimeter and umbilical vein maximum flow velocity (UVV max) which had been performed before any invasive procedures and at each visit and the timing and results of the first invasive procedures performed which include amniocentesis for amniotic delta OD 450 and FBS. If there was no invasive procedure performed during pregnancy, the haematocrit (Hct) and haemoglobin (Hb) at postnatal delivery will be recorded.

The patients were grouped according to history as follows: none (no history of abnormal baby or delivery), mild (term delivery with phototherapy), moderate (previous neonatal exchange transfusion following delivery at term) and severe (previous fetal transfusion, fetal death due to hydrops or neonatal exchange transfusion at < 34 weeks).

The fetal spleen perimeter, fetal liver length and UVV max were measured as described by Oepkes et al.[5,14] UVV max was recorded in a cross-section of the fetal abdomen during apnoea with an angle of insonation of < 30° as shown in Figure 1.

Maximum fetal liver length was measured in a

parasagittal scan of the fetal abdomen from the diaphragm to the lower edge of right lobe of liver[5,15] (Figure 2).

The fetal spleen perimeter was measured by the trace method in the same cross-sectional plane as used for the fetal stomach[5] (Figure 3).

These three measurements were plotted on a graphical data sheet with the reference ranges of Oepkes et al.[5] (Figure 4). Measurements above the 95th percentile were regarded as abnormal.

Indications to perform invasive procedures including amniocentesis for amniotic delta OD 450 and FBS were recorded. Fetal blood sampling was performed under ultrasound guidance with the use of a 20-guage spinal needle and free-hand technique.[2]

The outcome of measurements to detect fetal anaemia by using non-invasive assessments is the fetal Hb and Hct after the first FBS, the results of amniotic delta OD 450 from the first amniocentesis and neonatal Hb and Hct at postnatal delivery following only non-invasive assessment during pregnancy. Non-hydropic fetuses and severe hydropic signs of the fetuses which were present on ultrasound were excluded from this study.

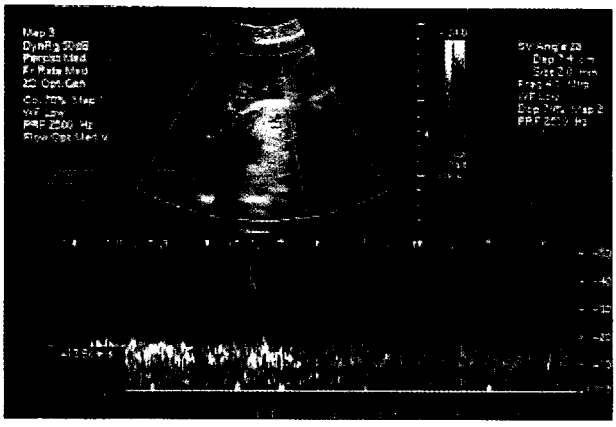

Fig. 1. The umbilical vein maximum flow velocity (UVV max) was recorded in a cross-section of the fetal abdomen during apnoea with an angle of insonation < 30°.

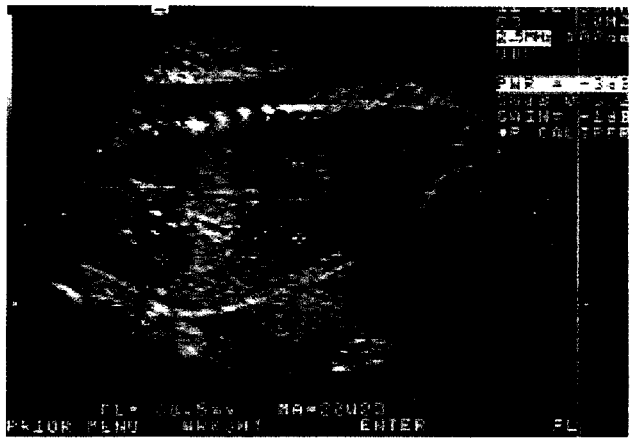

Fig. 2. Fetal liver length was measured in a parasagittal scan view of the fetal abdomen from the diaphragm to the lower edge of right lobe of liver.

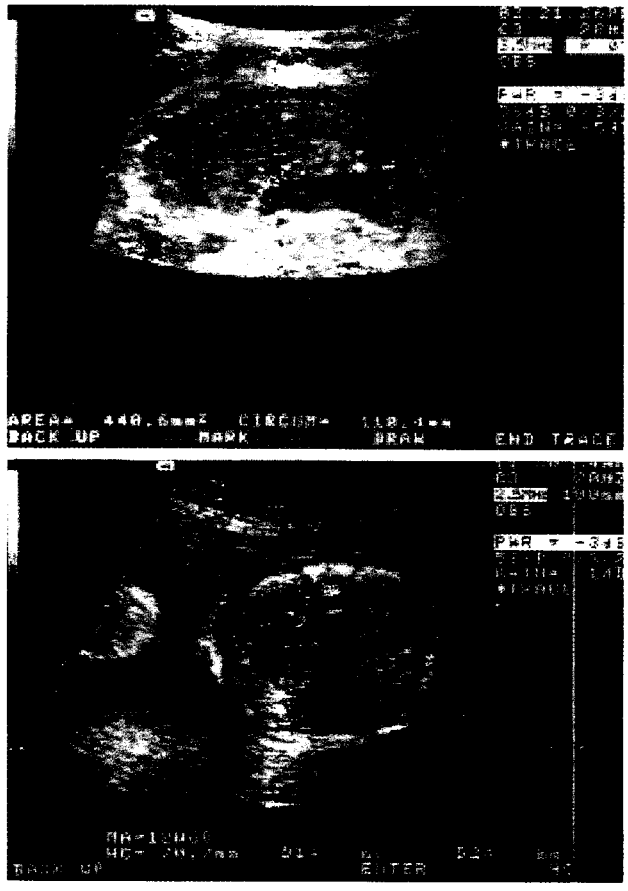

Fig. 3. Fetal spleen perimeter was measured by the trace method in the same cross-sectional plane as used for the fetal stomach.

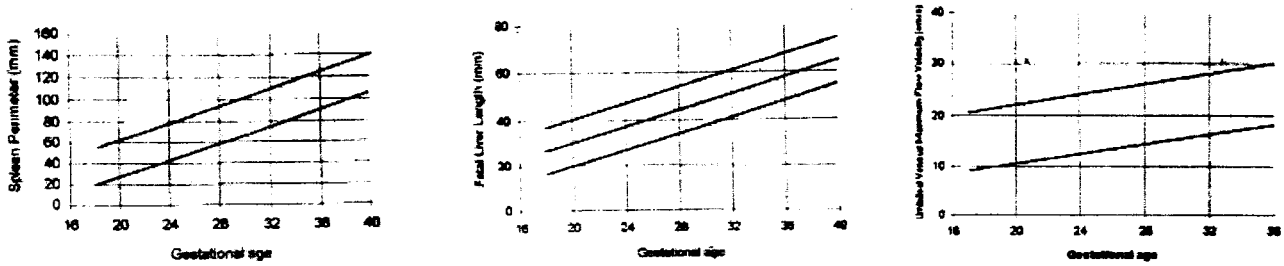

Fig. 4. The graphical data sheet with the reference ranges of Oepkes et al (1993b) was used to plot the fetal liver length, the fetal spleen perimeter and UVV max. Measurements above 95th percentile were regarded as abnormal.

Results

From 132 patients, 82 cases had antibodies to antigen D, 18 to Kell, 3 to e, 3 to anti-Fy and others as in Table 1. Only the patients with antibodies to D were studied.

Table 1. The type of antigens, number of the patients and mean of the parity in each type are present. Ranges of the parity are shown in parentheses

Antigen types	Number of the patients	Mean of the parity (range)
D	59	1.9 (0.5)
D, c	19	2.3 (0-4)
D, e	2	2.5 (2-3)
D, c, e	2	2.5 (2-3)
c	17	2.4 (0-6)
c, e	4	3.3 (2-5)
c, Anti-Le	1	0
e	2	2.7 (1-4)
e, Kp(a)	1	2
Kell	15	1.9 (0-5)
Kell, c, e	1	2
Kell, e	1	0
Kell, Fy	1	2
Fy	3	0.3 (0-1)
Le (a)	1	0
Anti J-Ka	1	1
Anti-u	1	4
Non-specific type	1	0
Total	132	1.7 (0-6)

Table 2. Anti-D quantification at the first examination according to history and subsequent first invasive tests with the mean gestational age are shown. Mean values are shown, with ranges in parentheses

	History		
	None or mild	**Moderate**	**Severe**
Number	55	9	18
Gestational age (weeks)	22(6-36)	22(13-35)	20(8-32)
At first examination			
First antibody concentration	18.1	41.4	70.5
(IU/ml)	(0.4-55)	(0.3-150)	(0.5-491.6)
Invasive procedures (n)	16	3	18
-First amniocentesis (n)	6	0	3
gestational age	31.4	-	28.6
(weeks)	(24.6-36.3)		(26.4-30.5)
-First FBS (n)	10	3	15
gestational age	28.5	29	24.1
(weeks)	(24-31.2)	(27-30.5)	(18-28.4)
No invasive procedure	39	6	0

The mean of first antibody concentration in the patients with severe history was the highest (70.5 IU/ml). The difference between the first fetal blood sampling (FBS) in the patients with none or mild history and those in severe history was found to be significance. (Chi-square test, $P < 0.05$) (Table 2)

Table 3. Reasons for the first invasive procedures according to the patient history with number of the patients in parentheses are shown

Reasons for the first	**Patient history**		
invasive procedures	**None or mild**	**Moderate**	**Severe**
High antibody levels (8)	3	-	5
Rapid rising antibody levels (5)	2	-	3
Abnormal delta OD 450 (3)	3	-	-
Rising of UVV max (1)	-	1	-
Rising of antibody and UVV max (13)	5	1	7
Rising of antibody, liver and UVV max (1)	-	-	1
Rising of antibody, spleen, liver and UVV max (2)	-	-	2
Rising of antibody, delta OD 450, spleen and UVV max (1)	-	1	-
Rising of delta OD 450 and UVV max (2)	2	-	-
Rising of liver, spleen and UVV max (1)	1	-	-
Total	16	3	18

None of the patient with severe history has the reason for the first invasive procedure of abnormal delta OD 450, rising of UVV max, rising of antibody, delta OD 450, spleen and UVV max, rising of delta OD 450 and UVV max, and rising of liver, spleen and UVV max. (Table 3)

Table 4. Mean haematocrit and haemoglobin (with ranges in parentheses) at the first invasive procedures performed including first FBS and first amniocentesis for amniotic delta OD 450 in Rh (D) alloimmunisation are shown

	Invasive procedures		No invasive procedure
	First FBS	First amniocentesis	
Gestational age (weeks)	24.6 (18-31.2)	30.3 (24.6-36.3)	-
Number of the patients	28	9	45
Mean haematocrit (%)	20.9	-	-
Mean haemoglobin (g/dl)	7.3	-	-
Mean delta OD 450	-	1.08/0.07 Mild/unaffected	-

From 82 cases of Rh-D alloimmunisation, the first fetal blood sampling was performed in 28 cases at the mean gestational age of 24.6 weeks (18-31.2), the first amniocentesis for amniotic delta OD 450 was performed in 9 cases at the mean gestational age of 30.3 weeks (24.6-36.3) and no invasive procedure was performed in 45 cases. Mean haematocrit and haemoglobin at the first fetal blood sampling were 20.9% and 7.3 g/dl respectively. Among 28 cases of the first fetal blood sampling, there was one fetal death during blood transfusion at 21.4 weeks in a patient with severe history and one intrauterine fetal death which was detected at 21.6 weeks due to chromosomal abnormality (balance translocation between chromosomes 1 and 11) (Table 4) The difference between gestational age of the first fetal blood sampling and those of the first amniocentesis was found to be significance. (Chi-square with Yates correction, $P < 0.05$) (Table 4)

Table 5. Number of the patients and procedures performed in each anti-D level are shown

Anti-D level (IU/ml)	Number of patients	No procedure performed	Fetal blood sampling		Amniocentesis
			without IUT	with IUT	
< 15	50	43	2	1	4
15-<20	6	2	1	3	-
20-<25	7	-	2	4	1
25-<30	3	-	-	2	1
30-<35	4	-	-	3	1
≥35	12	-	-	10	2
Total	82	45	5	23	9

The difference between number of the patients with no procedure performed in the group of anti-D level < 15 IU/ml and those in the group of anti-D level > 15 IU/ml was found to be significance. (Chi-square test, $P<0.005$) (Table 5)

Table 6. Mean gestational age and number of the patients with anti-D levels> 15 IU/ml at the first presentation and at the first invasive procedures performed are shown. The ranges are present in parentheses

The patients with anti-D levels > 15 IU/ml	Mean gestational age (weeks)	Number of the patients
At the first presentation	19.4 (8.5-33.3)	32
At the first invasive procedures performed	25 (18-35.4)	30
-At the first FBS	24 (18-31.2)	25
-At the first amniocentesis for amniotic Delta OD 450	29.5 (24.6-35.4)	5
No invasive procedure performed	-	2

The difference between mean gestational age of the patients with anti-D levels > 15 IU/ml at the first presentation and those of the patients with anti-D levels > 15 IU/ml at the first invasive procedures performed was found to be significance. (Chi-square test, $P<0.05$) (Table 6)

Table 7. Indications for the first fetal blood sampling, number of the patients, mean Hct and Hb and patient history are shown

Indications for fetal blood sampling	Number of the patients	Mean Hct (%) and Hb(g/dl)	Patient history
High antibody level	8	19.7(6.6)	severe5, none or mild3
Rapid rising of antibody lev	3	18.6(6.3)	severe3
Abnormal delta OD 450	3	29.7(9.4)	none or mild 3
Rising of UVV max	1	28.4(9.6)	moderate 1
Rising of antibody and UVV max	7	24.2(8.1)	severe 4, moderate 1, none or mild 2
Rising of antibody, liver and UVV max	1	13.0(4.4)	severe 1
Rising of antibody, liver, spleen and UVV max	2	25.1(8.1)	severe 2
Rising of antibody, delta OD 450, Spleen and UVV max	1	32.1(11.2)	moderate 1
Rising of delta OD 450 and UVV max	2	34.2(11.7)	none or mild 2
Total	28	25(8.37)	severe15, moderate3, none or mild 10

The most indication for fetal blood sampling was high antibody level with number of the patients of 8 which was second to the indication of rising of antibody and UVV max (n=7). (Table 7)

Table 8. Indications for the first amniocentesis, number of the patients, results of amniotic delta OD 450 and patient history are shown

Indications for amniocentesis	Number of the patients	Results of amniotic delta OD 450	Patient history
Rising of antibody level	2	mild to unaffected(n=2)	none(n=2)
Rising of antibody and UVV max	6	mild to unaffected(n=3) severe to moderate(n=3)	none(n=3) severe(n=3)
Rising of liver, spleen and UVV max	1	mild to unaffected(n=1)	none(n=1)
Total	9	-	severe3,none6

The patients with severe history (n=3) were found to have rising of antibody and UVV max as the only indication for amniocentesis. (Table 6)

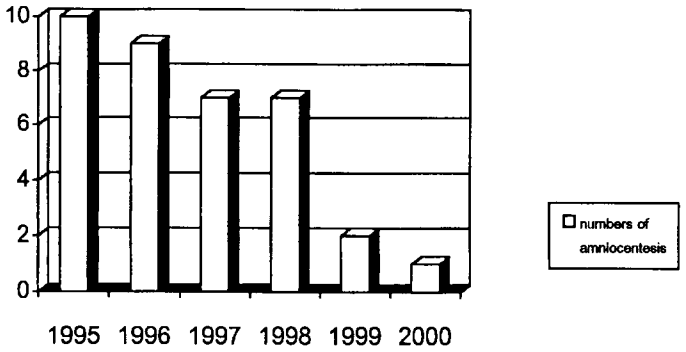

Fig. 5. The numbers of amniocentesis for amniotic delta OD 450 (including the first and subsequent amniocenteses) in each year (from January 1995 to March 2000) are shown.

Table 9. Mean haematocrit and haemoglobin of the babies after delivery of the patients with only non-invasive assessments performed and the patient history (born in both UCLH and other hospitals) are shown

			Number of the babies	Patient history
Mean neonatal Haematocrit and Haemoglobin	<30% or <10g/dl	22.2(25.1-28.3) 8.8 (7.8-9.6)	5	none or mild(n=2) moderate(n=3)
	> 30% or >10g/dl	42.1 (31.1-63) 14.3 (10.4-22.2)	34	none or mild(n=34)
		Total	39	none or mild(n=36) moderate(n=3)

Fourty-five from 82 cases of Rhesus-D alloimmunisation patients had only non-invasive assessments. Twenty-seven from 45 cases of the babies born in UCLH and the remaining 18 cases born other hospitals. Twelve from 18 cases of the babies who born at other hospitals can be followed up while 6 cases were loss. A total number of 39 cases from 45 cases can be determined. From 39 cases with only non-invasive assessments, 34 babies had mean haematocrit and haemoglobin of 42.1% and 14.3 g/dl, respectively. The difference between number of the babies in the group of mean neonatal haematocrit and haemoglobin < 30% or < 10g/dl and those in the group of mean neonatal haematocrit and haemoglobin > 30% or > 10 g/dl was found to be significance. (Chi-square test with Yate correction, $P<0.05$) (Table 9)

Table 10. Mean haematocrit and haemoglobin, mean gestational age at delivery and neonatal exchange transfusion according to each method of the measurement of non-invasive assessments during pregnancy are shown

	The methods of measurement	
	Anti-D and UVV max (n=17)	**Anti-D, UVV max, fetal liver length and spleen perimeter (n=22)**
Hct < 30%(n=5) (or Hb<10g/dl)	26.3(8.7)(n=3/17)	25.2(8.5)(n=2/22)
Mean gestational age at delivery	37.1 weeks (36-40)	35.7 weeks (33.1-38.2)
Neonatal exchange transfusion	1/3	1/2
Hct ≥ 30%(n=34) (or Hb ≥ 10g/dl)	38.9 (13.3)(n=14/17)	42.2(14.5)(n=20/22)
Mean gestational age at delivery	37.3 weeks (35-40)	37.8 weeks (35-40)
Nonatal exchange transfusion	1/14	2/20

Non-invasive assessments were classified into 2 types of the methods including the measurements of anti-D levels and UVV max and the measurements of anti-D levels, UVV max, fetal liver length and fetal spleen perimeter. The difference between each method of measurement of non-invasive assessments during pregnancy was found to be non-significance. (Fisher's exact test, $P>0.05$) (Table 10)

Table 11. Number of the babies in the group of mean Hct>30% (or Hb>10g/dl) and the UVV max measurements prior toodelivery are shown

Mean neonatal Hct and Hb	**UVV max measurements**	
	Normal	**≥95th percentile**
Hct<30%(or Hb<10g/dl)(n=5)	2	3
Hct>30%(or Hb>10g/dl)(n=34)	34	-
Total(n=39)	36	3

In the group of the patients with anaemic babies (n=5) (mean neonatal haematocrit < 30% or haemoglobin <10 g/dl), 2 from 5 cases had normal UVV max measurements and the remaining 3 cases had high UVV max measurements (>95th percentile) prior to delivery. In the group of the patients with non-anaemic babies (n=34) (mean neonatal haematocrit >30% or haemoglobin >10 g/dl) had normal UVV max measurements prior to delivery. The difference between number of the babies with normal UVV max measurements in the group of mean haematocrit > 30% (or haemoglobin > 10g/dl) and those in the group of mean haematocrit < 30% (or haemoglobin < 10 g/dl) was found to be significance. (Fisher's exact test, P<0.05) (Table 11)

Discussion

Fetal anaemia will lead to extramedullary haematopoiesis where liver and spleen play roles and can be studied in the prediction of fetal anaemia. Vintzileos et al[3] have found that fetal liver length can be used to predict fetal anaemia in Rhesus alloimmunised pregnancy. Oepkes et al[5] then have identified that fetal spleen perimeter can be used to predict fetal anaemia in pregnancies affected by Rhesus alloimmunisation. All non-hydropic fetuses had increased spleen perimeter (>95th percentile for gestational age) even though this was not consistent in hydropic fetuses. Another line of investigation for the non-invasive prediction of fetal anaemia is based on animal data indicating that fetal blood velocities in venous circulating beds increase secondary to elevated cardiac output and decreased in blood viscosity. Iskaros et al[11] have found that serial antibody quantification and Doppler monitoring of UVV max can be used to predict fetal anaemia in cases with mild or no history of fetal haemolytic pregnancies.

From this study, previous history can indicate the onset and severity of fetal anaemia which is very useful and important for the management of Rhesus (D) alloimmunised pregnancies. In the patients with a moderate or severe history and subsequent pregnancy, the tendency of fetal anaemia was higher and likely to occur at an early gestation unless the patient has had adequate and appropriate treatment prior to this subsequent pregnancy. Mean gestational age at the first examination of the patients with severe history was earlier than those of the patient with moderate and none or mild history with a statistically significant difference. This is not surprising as patients with severe history were more likely to have an early assessment due to their awareness of the disease.

The failure of immunoprophylaxis may result from the administration of an insufficient dose of anti-D, the late administration of anti-D and failure to give anti-D after potentially sensitising events, i.e. after an operation or blood transfusion as in this study. From this study, the combination of anti-D levels and other ultrasonographic parameters including UVV max, fetal liver length and fetal spleen perimeter can be used to defer the first invasive procedure performed. Anti-D quantification > 30 IU/ml indicated that fetus was prone to be anaemic and intrauterine blood transfusion was mostly needed in this study. The combination of rapid rising anti-D levels with UVV max was very useful to predict fetal anaemia in pregnancies affected by Rhesus (D) alloimmunisation regardless of the patient's history.

From this study, only the measurement of fetal liver length or spleen perimeter could not be use to predict fetal anaemia. The combination of fetal liver length, spleen perimeter and UVV max as well as anti-D levels had been shown to be correlate with fetal anaemia in the patients with severe history, but not in those with none or mild history.

The combination of UVV max measurements and anti-D levels was very useful to predict fetal and neonatal anaemia in either the patients with none or mild or severe histories. Moreover, the high UVV max (>95th percentile) with progressive fetal anaemia prior to delivery tended to occur before the rising of either fetal liver length or fetal spleen perimeter as the result in this study. The high UVV max (>95th percentile) prior to delivery indicated the tendency of neonatal anaemia and the risk of postnatal exchange transfusion even though the measurements of fetal liver length and fetal

spleen perimeter were normal prior to delivery. This may be a useful information for early neonatal care after delivery. A well-trained ultrasonographer to assess Doppler flow measurement and a good quality ultrasound machine are needed in the management of pregnancies affected by Rhesus (D) alloimmunisation. However, the management of the patients does not rely only on the UVV max measurement. The past history and anti-D quantification are important factors in the management of those patients.

From this study, in patients with none or mild history, non-invasive assessments were preferred to perform than invasive assessments. Amniocentesis for amniotic delta OD 450 was the first choice of invasive assessments which tended to occur in later gestation of the patient with none or mild history and fetal blood sampling (FBS) tended to be performed at an early gestation in the patients with severe history.

Most of the patients with none or mild history have normal non-invasive assessments which make the patients feel they do not take any risk during pregnancy and prefer to deliver the babies at their local hospitals regardless of the later complications. Six patients were lost to follow up in this study due to their deliveries at other hospitals. Good counseling should be given to Rhesus alloimmunised pregnancies for making a decision to deliver the babies in the tertiary centres in order to reduce the morbidity and mortality rates of both babies and mothers.

The clinician at primary and secondary centres should be aware of the importance of immunoprophylaxis to all unsensitised women. This can help to reduce the affected cases in subsequent pregnancy. The good outcome of the babies will be increased because the complications during pregnancy and after delivery is reduced.

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