Diagnostic procedures for assessing the severity of alloimmune fetal anemia

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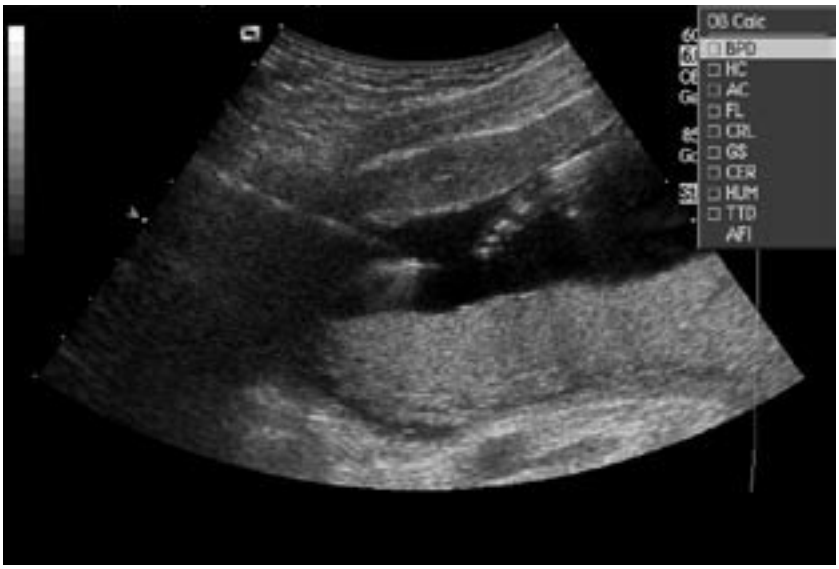
Part 1: Chemical approach



Diagnostic accuracy of Δ OD 450 measurements and middle cerebral artery peak systolic velocity in the prediction of severe fetal alloimmune anemia: a literature review

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Introduction

The severity of fetal alloimmune anemia can be diagnosed biochemically or sonographically. The biochemical method is based on the fact that hemolysis results in increased bilirubin concentrations in fetal blood and in amniotic fluid.[1] Already in 1956, Bevis found that bilirubin concentrations in amniotic fluid are indicative of the severity of the hemolytic process in fetuses of alloimmunized mothers.[2] In 1961, Liley proposed amniotic fluid sampling to measure deviation of optical density at 450 nm (Δ OD 450) to predict life-threatening fetal anemia in the third trimester.[3]
The American College of Obstetricians and Gynecologists (ACOG) still recommends serial amniocentesis in pregnancies at risk, followed by intrauterine transfusion (IUT) or early delivery when Δ OD 450 values are in Liley zone 3 or in the upper third of Liley zone 2 and rising.[4] Amniotic fluid Δ OD 450 can also be plotted in other charts (Queenan, extended Liley) or be used as Ovenstone factor, or transmutance ratio.[5-8]

The invasive nature of amniocentesis remains a disadvantage, however. With each procedure, there is a risk of iatrogenic rupture of the fetal membranes or infection, both of which can lead to fetal loss. There is also the risk of increasing severity of sensitization by either boosting of antibody titer or formation of additional antibodies.[9] Since the introduction of non-invasive methods to diagnose fetal anemia, the evaluation of the diagnostic performance of invasive Δ OD 450 measurement is now warranted.[10;11]

Sonographic prediction of severe anemia is easy when the fetus is hydropic. However, treatment results are definitely worse in hydropic than in non-hydropic fetuses.[12] Therefore, severe fetal anemia should preferably be diagnosed and treated before hydrops develops. During the last decade, different methods for this purpose have been proposed: sonographic liver[13;14] and spleen[15] measurements, Doppler measurements of the middle cerebral artery[10], intrahepatic umbilical vein[16;17], descending aorta[18], splenic artery[19] or combined measurements.[11;20] Of these methods, measurement of Middle cerebral artery (MCA) peak systolic velocity is the most widely used. An increased peak systolic velocity in the MCA as

predictor of severe fetal anemia was first described by Mari et al. [21] It is thought that this increase in systolic velocity is caused by a hyperdynamic circulation with increased contractility of the heart and decreased viscosity of the blood.[18] In a prospective series, Mari et al., established the normal median for MCA peak systolic velocity throughout gestation and drew the demarcation line between moderate and severe anemia around 1.5 MoM.[10]

We aimed to compare the accuracy of amniotic fluid Δ OD 450 with the accuracy of the more recent non-invasive Doppler measurement of MCA peak systolic velocity. Therefore we performed a literature review on the accuracy of, first, Δ OD 450 and, second, MCA peak systolic velocity. We calculated the sensitivities and specificities for the different cut-offs used in each study.

Methods

Δ OD 450

English language journals indexed in Medline between 1961 and 2003 were searched for articles addressing amniotic fluid bilirubin levels in the management of red cell alloimmunization. Search terms included "rhesus", "Liley", "Queenan", "OD 450", "amniotic bilirubin", and "amniotic optical density". Selected abstracts were reviewed for relevant information on the test characteristics of amniotic fluid Δ OD 450 to predict fetal anemia. The references of retrieved articles were reviewed for additional articles not identified through the database search. Data on hydropic fetuses were excluded. Two groups were recognized. The first group describes test characteristics of amniotic fluid Δ OD 450 in the prediction of fetal anemia at fetal blood sampling. The second group describes test characteristics of amniotic fluid Δ OD 450 in the prediction of fetal anemia at birth. Sensitivity, specificity, and overall accuracy (combined rate of true-positive and true-negative results) were calculated for different Δ OD 450 cut-offs in the prediction of anemia by two of the authors (ES and FV).

MCA peak systolic velocity

We also searched English language journals indexed in Medline between 1995 and 2005 addressing MCA peak systolic velocity in predicting fetal anemia. The following search term was used: "middle cerebral artery and fetal anemia". Selected abstracts were reviewed for relevant information on the test characteristics of MCA peak systolic velocity to predict fetal anemia. The references of retrieved articles were reviewed for additional articles not identified through the database search. Sensitivity and specificity were calculated for different MCA cut-offs in the prediction of anemia by two of the authors (ES and FV).

Simultaneous Δ OD 450 and MCA peak velocity

In addition, the search consisted of English language journals indexed in Medline between 1995 and 2005 addressing both Δ OD 450 and MCA peak systolic velocity in predicting fetal anemia. The following search term was used: "amniocentesis and middle cerebral artery". Selected abstracts were reviewed for relevant information on the test characteristics of both Δ OD 450 and MCA peak systolic velocity to predict fetal anemia in the same patient population. The references of retrieved articles were reviewed for additional articles not identified through the database search. Sensitivity, specificity, and overall accuracy (combined rate of true-positive and true-negative results) were calculated by two of the authors (ES and FV).

Results

Studies with test characteristics of Δ OD 450

The literature search resulted in 73 abstracts. In 28 papers, test characteristics were mentioned and these papers were read in detail. Twelve additional papers were found by checking the references of these papers. Finally, five papers compared Δ OD 450 with hemoglobin concentration obtained by fetal blood sampling and gave sufficient data to calculate test characteristics.[22-26] All patients in these studies were rhesus-D immunized. These papers are listed in Table I. Sensitivities of Liley's zone III and Queenan's zone 4 in the prediction of severe anemia (not uniformaly

Table 1 - Test characteristics of amniotic fluidΔ OD 450 in the prediction of fetal anti-rhesus D alloimmune anemia at fetal blood sampling (non-hydropic fetuses)

First author, year	*Number of patients*	*Number of amnio centeses*	*Range of gestational age (weeks)*	*Test*	*Cut-off*	*Definition of*	*Sensitivity (%)*	*Specificity (%)*	*Accuracy (%)*
Nicolaides,[23] 1986	45	45	< 26	Extrapolated Liley	Zone III	Hb < 6 g/dl	47	82	69
				Zone IIB			94	43	62
					Zone III	Hb < 9.7 g/dl	38	92	53
					Zone IIB		84	62	78
MacKenzie,[22] 1988	36	63	17 - 35	Extrapolated Liley	Zone III	Ht < 25 (17-25 weeks) Ht < 30 (25-35 weeks)	--	--	79
Rahman,[24] 1998	43	43	< 27	Queenan	Zone 4	Ht < 15 %	33	36	35
					Zone 3		80	7	33
					Zone 4	Ht < 30 %	44	22	40
					Zone 3		88	11	72
Scott,[25] 1998	35	72	16 - 38	Queenan	Zone 4	Hb-deficit > 7 g/dl	100	79	81
					Zone 3		100	38	42
					Zone 4	Hb-deficit > 2 g/dl	88	95	93
					Zone 3		100	47	60
	--	36	27 - 38	Liley	Zone III	Hb-deficit > 7 g/dl	--	92	92
					Zone III	Hb-deficit > 2 g/dl	100	97	97
Sikkel,[26] 2002	79	79	20 - 35	Extrapolated Liley	Zone III	Hb-deficit > 5 g/dl	79	50	75
				Zone IIc			97	25	86
	24	24	< 27		Zone III		74	100	79
					Zone IIc		95	60	88
	55	55	≥ 27	Liley	Zone III		81	14	73
					Zone IIc		98	0	85

Hb: Hemoglobin concentration, Ht: Hematocrit, --: not given

Hb-deficit: Difference between actual Hb and mean Hb for corresponding gestational age

defined) ranged from 33% to 100%. Sensitivities of the upper half of Liley's zone II (IIB) or Queenan's zone 3 ranged from 80% to 100%. Table 2 lists another 12 studies, where Δ OD 450 was compared with the severity of clinically defined fetal anemia or hemoglobin concentration at birth.[3;5-8;27-33] Although the majority of patients in these studies were rhesus-D immunized, other antibodies (including anti-Kell) may have played a role in some of the patients. In case of anti-Kell antibodies, anemia may be partially caused by erythroid precursor damage and not merely by hemolysis. Consequently, the haemolytic-induced rise in amniotic fluid bilirubin may be less pronounced in case of anti-Kell antibodies and severe anemia may remain undetected.[34-36]

Studies with test characteristics of MCA peak systolic velocity

This literature search resulted in 75 abstracts. In 32 papers, test characteristics were mentioned and these papers were read in detail. There were no additional papers found by checking the references of these papers. Finally, 14 papers compared MCA peak systolic velocity with fetal hemoglobin concentration at fetal blood sampling or at birth and gave sufficient data to calculate test characteristics.[10;20;37-48] These papers are listed in Table 3. Sensitivities of MCA peak systolic velocity in the prediction of severe anemia (according to different definitions) ranged from 31% to 100%.

Studies with test characteristics of both Δ OD 450 and MCA peak systolic velocity in the same fetuses

Our search resulted in 12 abstracts. In 3 papers, test characteristics were mentioned and these papers were read in detail. One additional paper was found by checking the references of these papers. Finally, three papers compared Δ OD 450 and MCA peak systolic velocity with hemoglobin concentration and gave sufficient data to calculate test characteristics.[49-51] These papers are listed in Table 4. Sensitivities of Δ OD 450 in the prediction of severe anemia (according to different definitions) ranged from 53% to 86%. Sensitivities of MCA peak systolic velocity in the prediction of severe anemia (according to different definitions) ranged from 64% to 100%.

Table 2 - Test characteristics of amniotic fluid Δ OD 450 in the prediction of neonatal anemia at birth.

First author, year	*Number of patients*	*Number of amnio centeses*	*Range of gestational age (weeks)*	*Test*	*cut-off*	*Definition of*	*Sensitivity (%)*	*Specificity (%)*	*Accuracy (%)*
Liley,[3] 1961	47	47	27 - 38	Liley		Zone III	Hb < 11 g/dl	76	89	79
						Zone IIc		87	67	83
Pridmore,[7] 1972	716	> 716	20 - 39	Transmittance ratio	> 1.06	or death	Hb < 7.5 g/dl	--	--	89
Bosch,[27] 1974	312	312			≥ 26	Liley	Zone III	Hb < 11 g/dl	80	98	91
Bowman,[5] 1975	928	2615	21 - 37	Extrapolated Liley		Zone III	hydrops fetalis or need for treatment		91	99	97
MacDougall,[30] 1975	173	173	--	Liley		Zone III	Hb < 10 g%		33	100	88
Fairweather,[29] 1976	141	468	21 - 39		Δ OD 450	<30 wks: >0.25 >30 wks: >0.15	Hb < 7.5 g/dl		72	91	85
Robertson,[31] 1976	288	920	28 - 35	Bilrubin ratio or stillbirth	> 1.1		Hb < 7.4 g/dl		69	86	82
Moore,[6] 1977	46	78	24 - 40	Liley		Zone III	death or multiple exchange transfusions		50	100	85
						Zone IIb			71	88	83
				Ovenstone factor	> 30				36	100	80
						> 20			64	100	89
Weiner,[33] 1981	56	158	--	Liley		Zone B''	fetal demise or need for neonatal transfusion		67	90	79
Skjaeraasen,[32] 1983	71	72	26 - 32		Δ OD 450	>0.3	intrauterine or neonatal death		86	71	79
Ananth,[28] 1989	32	41	16 - 20		Δ OD450	>0.15	fetal death or IUT or exchange transfusion		59	95	76
Queenan,[8] 1993	74	163	16 - 36	Queenan		Zone 4	"Potentially fatal"		100	100	100

Hb: Hemoglobin concentration, --: not given. IUT: Intrauterine transfusion

Table 3 - Test characteristics of MCA peak systolic velocity in the prediction of fetal anemia at fetal blood sampling or at birth.

First author year	*Number of measurements*	*Number of anemic fetuses*	*Number of hydropic fetuses*	*Test*	*cut-off*	*Definition of anemia*	*Sensitivity (%)*	*Specificity (%)*	*Study design*
Mari,[10] 2000	111	35	12	1.5 MoM	Hb < 0.65 MoM	100	88	retrospectively, cut-off drawn at 100 % sensitivity	
Teixera,[46] 2000	26	13	1	> 2 SD above the mean	z_Ht	< -4	67	90	prospective
Delle Chiaie,[39] 2001	140	108	1	1.29 MoM	Hb < 0.84 MoM	73	82	--	
Detti,[41] 2001	64	11	4	1.69 MoM	Hb < 0.55 MoM	100	94	cut-off drawn at 100 % sensitivity	
Sikkel,[20] 2001	42	38	0	1.5 MoM	Hb	≤ -5 SD	71	50	prospective
Deren,[40] 2002	103	53	0	1.35 MoM	Hb < 0.6 MoM	100	82	prospective	
Zimmerman,[48] 2002	125	15	3	1.5 MoM	Hb < 0.65 MoM	88	87	prospective, < 35 weeks	
Alshimmiri,[38] 2003	66	29	27	1.5 MoM	Hb < 0.65 MoM	31	97	prospective	
Duckler,[42] 2003	16	6	0	1.5 MoM	Hb deficit > 5 SD	100	100	prospective	
Sikkel,[45] 2003	60	46	12	1.5 MoM	z_Ht	≤ -5 SD	54	57	prospective
Mc Lean,[43] 2004	42	3	0	1.5 MoM	Hb < 0.65 MoM	100	90	retrospective	
Scheier,[44] 2004	58	23	9	1.5 MoM	Hb deficit > 6 SD	96	86	cross-sectional	
Ahmed,[37] 2005	65	4	0	1.5 MoM	--		50	97	prospective
v Dongen,[47] 2005	27	18	10	1.5 MoM	Hb deficit > 5 SD	89	89	prospective	

Hb: Hemoglobin concentration, Ht: Hematocrit, MCA: Middle cerebral artery, MoM: Multiples of the median value for gestational age in normal fetuses, SD: Standard deviation, --: not given

Table 4 - Test characteristics of Δ OD 450 and MCA peak systolic velocity in the prediction of fetal anemia in the same patients.

First author year	*Number of fetuses*	*Number severely anemic fetuses*	*Definition of anemia*	*Cut-off MCA*	*MCA sensitivity (%)*	*Cut-off specificity (%)*	*accuracy (%)*	*Δ OD 450*	*Δ OD 450 sensitivity (%)*	*specificity (%)*	*accuracy (%)*	*Study design*
Nishie,[51] 2003	28	7	Hb deficit > -5 SD	> 1.5 MoM	100	65	73	Bowman's curve zone 3	86	100	96	prospective
Pereira,[50] 2003	28	4	Hb < 0.55 MoM	> 1.5 MoM	100	88	89	Liley high zone 2 or zone 3	75	75	75	retrospective
Bullock,[49] 2005	38	22	Hb < 5th percentile	> 1.5 MoM	64	81	71	Liley curve "over the action line"	53	71	59	cross-sectional

Hb: Hemoglobin concentration, MCA: Middle cerebral artery, MoM: Multiples of the median value for gestational age in normal fetuses, SD: Standard deviation.

Discussion

This study shows that sensitivities to predict severe anemia at fetal blood sampling (Table1) were between 80 % and 100% for Δ OD 450 in the upper half of Liley's zone II (IIB) or Queenan's zone 3. These results are excellent, because the procedure-related risk of amniocentesis is low compared to the procedure-related risk of fetal blood sampling. The sensitivities of Δ OD 450 in the prediction of neonatal anemia at birth (Table 2) were much more variable. This is readily explained by the commonly longer time period between amniocentesis and birth. Also, it should be noted that different inclusion criteria and different definitions of severe anemia were used in the different studies.

The ACOG recommends diagnostic amniocentesis for red cell alloimmunization with high antibody titers from as early as 20 weeks gestation and therapeutic intervention when Δ OD 450 is in Liley's zone 3 or rising in the upper third of zone 2.[4] The results of our previous study support this guideline: a 95 % sensitivity for severe fetal anemia was found.[26] However, a specificity of 50% and the risk associated with repeated amniocentesis remain the major drawbacks of this approach. In addition, fetal and perinatal procedure-related loss rates are reported to be 0.25 to 1% per amniocentesis.[52;53] Further, false positive results of amniocentesis can lead to unnecessary IUTs with procedure-related fetal loss rates of 1 to 3%.[54] Finally, another drawback of amniocentesis or fetal blood sampling is the risk of feto-maternal hemorrhage that may increase the severity of alloimmunization. Feto-maternal hemorrhage occurs in 2.3% of cases after amniocentesis.[9] A significant increase in antibody titers and induction of additional antibodies occurs in respectively 50% and 26% of cases after IUT.[9;55;56] Thus, there is still a need for non-invasive tests that can predict fetal anemia with equal or higher accuracy.

Recent studies suggest that arterial and venous Doppler flow velocities in fetal vessels accurately predict anemia.[10;46;57;58] These studies report that Doppler measurements, when performed by experienced operators, have sensitivities between 67% and 100% and specificities between 70% and 100% in the prediction of severe fetal anemia.[10;46;57;58] However, there is a

tendency to be overly optimistic about early results with new techniques. In the present study, we also performed a literature review on the accuracy of Doppler measurements of MCA peak systolic velocity in the prediction of severe fetal anemia. The selected studies showed sensitivities and specificities that were comparable to those reported in the Δ OD 450 studies.

In three small studies, each with less than 40 patients, Doppler and Δ OD 450 were compared.[46-48] Two of these studies were retrospective, only one was prospective. In these studies, the accuracy of MCA peak systolic velocity was better than that of Δ OD 450.

From our literature review, we conclude that Δ OD 450 measurement predicts severe anemia with sensitivities ranging between 80 and 100 % in most studies. In recently published series on MCA Doppler velocimetry, sensitivities for the prediction of severe fetal anemia range between 54 and 100 %. It is still unknown which test, the traditional minimally invasive amniocentesis with Δ OD 450 measurements, or the more recent non-invasive MCA Doppler measurements, is the more accurate. Only a prospective trial, comparing the characteristics of the two tests (Δ OD 450 and MCA peak systolic velocity) simultaneously measured in the same patients, with the gold standard test (fetal hemoglobin concentration) can provide the answer. We have been engaged in such a trial, called the DIAMOND ("diagnostic amniocentesis or non-invasive Doppler") study and the results of this trial will become available soon.[59]

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