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The diagnostic evaluation of iso-immunization due to the Rh factor

by

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The remarkable prophylactic successes obtained by means of IgG anti D in preventing immunization due to the Rh factor have recently resulted in a drastic reduction in the number of cases of Rh immunization. Further organizational progress and the formation of a more mature health knowledge at all levels leads one to think that cases of Rh iso-immunization will become still rarer.

Nevertheless, Rh iso-immunization cannot disappear altogether, and the obstetrician will still find himself in the position (even if very infrequently) of having to take decisions concerning a pathological condition of which everyday practice and his personal experience will more and more have lost sight.

We have therefore thought it worth while to collect together the results we have obtained in 4 years of studying the Rh problem, in order to define the limits of a grave diagnosis and the correctness of a therapeutic operation. This seems permissible statistically because of the large number of cases that we have observed, though what the future situation may be cannot be determined.

In assessing a case of iso-immunization due to the Rh factor, the obstetrician must establish whether the condition of the foetus is such as to allow the pregnancy to continue, or whether it justifies the induction of labour and possible

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Clinical Experimental Obst. & Gynecology
Vol. III, 1-4, 1976 pp. 29-41

caesarean section, in order to remove the foetus from threatened attack of the antibodies.

The parameters (which are closely correlated) involved in this decision have reference to:

- the nature of maternal iso-immunization;
- the nature of the antibody attack in relation to foetal anaemia;
- changes in the materno-foetal exchange, with a consequent chronic foetal condition and diminished foetal vitality;
- the degree of foetal maturity, in view of the expectation of delivery.

The diversity of factors that partecipate in the therapeutic decision explains the disparity and the number of biochemical tests necessary, especially in view of the familiar fact that many of these tests are only of indicative value.

For these manifold reasons we have felt that our experience could best be explained in terms of each biochemical test, considering separately for each parameter its validity in relation to the results obtained.

PROGNOSTIC VALUE OF THE ANTIBODY TITRE

Our observations have reference to 96 cases of iso-immunizing pregnancy, which we followed up carefully and repeatedly.

The results obtained are shown in Table 1, which compares the foetal situation at birth with the values of the last indirect Coombs' test carried out, in order

Table 1.

Iso-Immunization	Patient N.	Precedents	Patient N.		Antibody titre at delivery	Patient N.
Light	44	positive	9	(20%)	1/2	2
					1/4	10
					1/8	7
					1/16	17
		negative	35	(80%)	1/32	8
Middle serious	20	positive	5	(25%)	1/16	5
					1/32	11
					1/64	3
					1/128	–
		negative	15	(75%)	1/256	1
Serious	11	positive	7	(64%)	1/32	4
					1/64	6
					1/128	–
					1/256	–
		negative	4	(36%)	1/512	1
Highly serious	11	positive	7	(64%)	1/64	3
					1/128	5
					1/256	2
					1/512	–
		negative	4	(36%)	1/1024	1
Intra-uterine death	11	positive	6	(55%)	1/32	2
					1/64	4
					1/128	–
					1/256	2
		negative	5	(45%)	1/512	3

to see whether the maternal antibody titre is a true index of the foetal condition and to verify its reliability for prognostic purposes.

On examining the table we see that the antibody titre does not increase in parallel with the deterioration of the foetal condition, and this finding is in agreement with the observations made by most authors ([2, 6, 8, 10, 18, 23, 24, 25]). One interesting finding in our own results, however, is that with levels less than 1:32 there were no serious situations at birth.

This observation is confirmed by study of the long-term results in this disease; in Table 2 we see that for levels less than 1:32 there were no cases with lesions of the nervous system, neonatal deaths or intra-uterine deaths.

Table 2.

Antibody Titre	Total	Living Healthy	Living with lesions of the nervous system	Neonatal Deaths	Intra-Uterine Deaths
1/2	2	2(100%)	–	–	–
1/4	10	10(100%)	–	–	–
1/8	7	7(100%)	–	–	–
1/16	22	22(100%)	–	–	–
1/32	25	23(92%)(*)	–	–	2(8%)
1/64	16	7(43.75%)	2(12.5%)	3(18.75%)	4(25%)
1/128	5	–	–	5(100%)	–
1/256	5	1(20%)	–	2(40%)	2(40%)
1/512	4	–	1(25%)	–	3(75%)
1/1024	1	–	–	1(100%)	–

Not even study of the antibody curve provides definite prognostic significance in testing the individual case ([9]); in Table 3, in fact, we see how serious situations can arise with stationary curves, or with curves showing values that increase or diminish.

As a whole, therefore, the indirect Coombs' test, being an expression of the nature of maternal iso-immunization, is favourable when the level is less than 1:32, but otherwise it does not always express the true foetal situation. However, this test remains fundamental for general clinical evaluation, and is always supported by other parameters that more precisely express the foetal condition.

PROGNOSTIC VALUE OF OESTRIOLURIA

Our observations refer to the curves showing the oestrioluria values for 25 iso-immunized pregnant women. The prognostic value of the examination has been studied by relating the excretion curve of oestriol to the ΔOD and to the foetal situation at birth. The results obtained are reported in detail in Table 4.

Table 3.

Antibody Titre	Patient total	Living	Neonatal deaths	Intra-uterine deaths
Increase	48(50%)	34(70,83%)	8(16,67%)	6(12,50%)
Stationary	44(45.83%)	39(88.65%)	3(6,81%)	2(4,54%)
Diminish	4(4,17%)	1(25%)	–	3(75%)

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In Figs. 1, 2 and 3 we show, for greater lucidity, the oestrioluria curves, classified according to the gravity of the condition at birth, extracted from Table 4, and to the values for ΔOD in the amniotic fluid (Fig. 4).

The values obtained demonstrate that both the absolute value for oestrioluria, and the progress of the curve of the serial analyses, have no prognostic value in cases of slight or moderate gravity; only in the cases that were highly serious (case no. 21) did a rapid fall in oestrioluria indicate a terminal situation, in which the foetal anaemia had already seriously compromised its vitality.

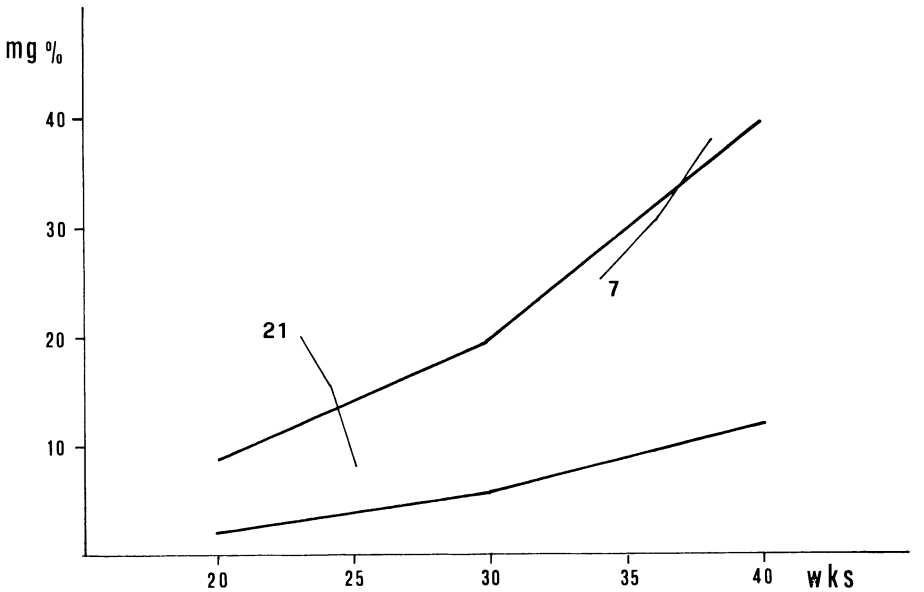

FIG. 1 - Oestrioluria Curves in Patients with severe Erithroblastosis.

On the whole, therefore, it seems that oestrioluria is useful from the prognostic aspect in order to indicate a serious situation, which will require immediate intervention; but there is no need to await a fall in oestriol before operating; it is necessary to act even earlier, basing the decision on more specific tests for Rh iso-immunization.

PROGNOSTIC VALUE OF COLPOCYTOLOGY

Our experience is limited to 25 cases, already reported in Table 4. Examining the results of colpocytology and comparing them with those from other parameters, we can see that, on the whole, colpocytological investigation can more or less be superimposed on the oestrioluria values, though the results appear less quickly, and may more often be falsified by vaginal inflammation and hormonal therapy.

This test, considering the low specificity and disadvantages as compared to oestrioluria, seems to be omitted from the diagnostic point of view, as regards Rh iso-immunization.

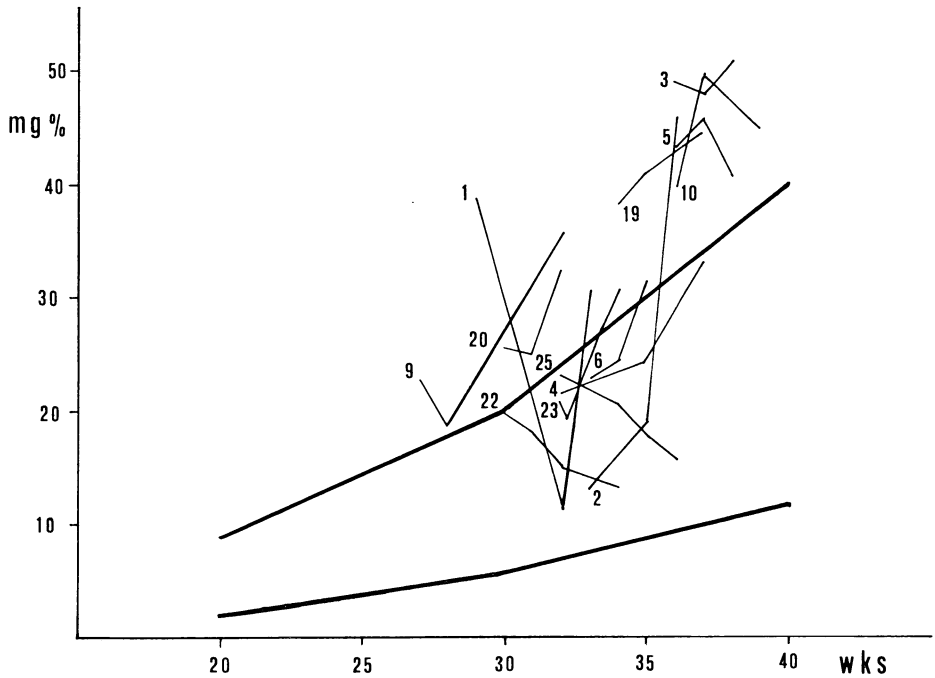

FIG. 2 - Oestrioluria Curves in Patients with middle serious Rh iso-immunization.

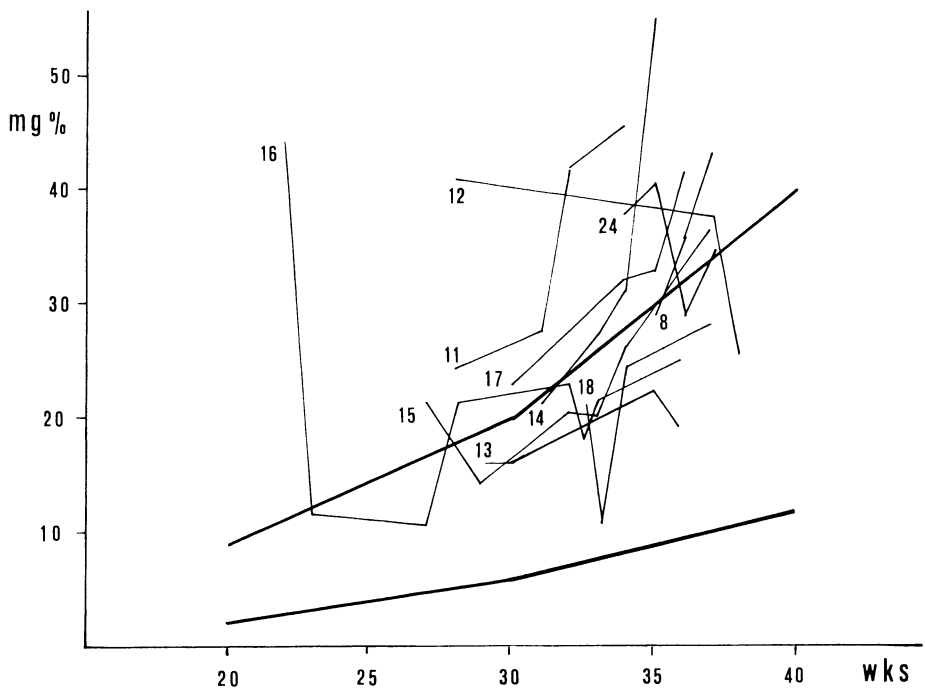

FIG. 3 - Oestrioluria Curves in Patients with light Rh iso-immunization.

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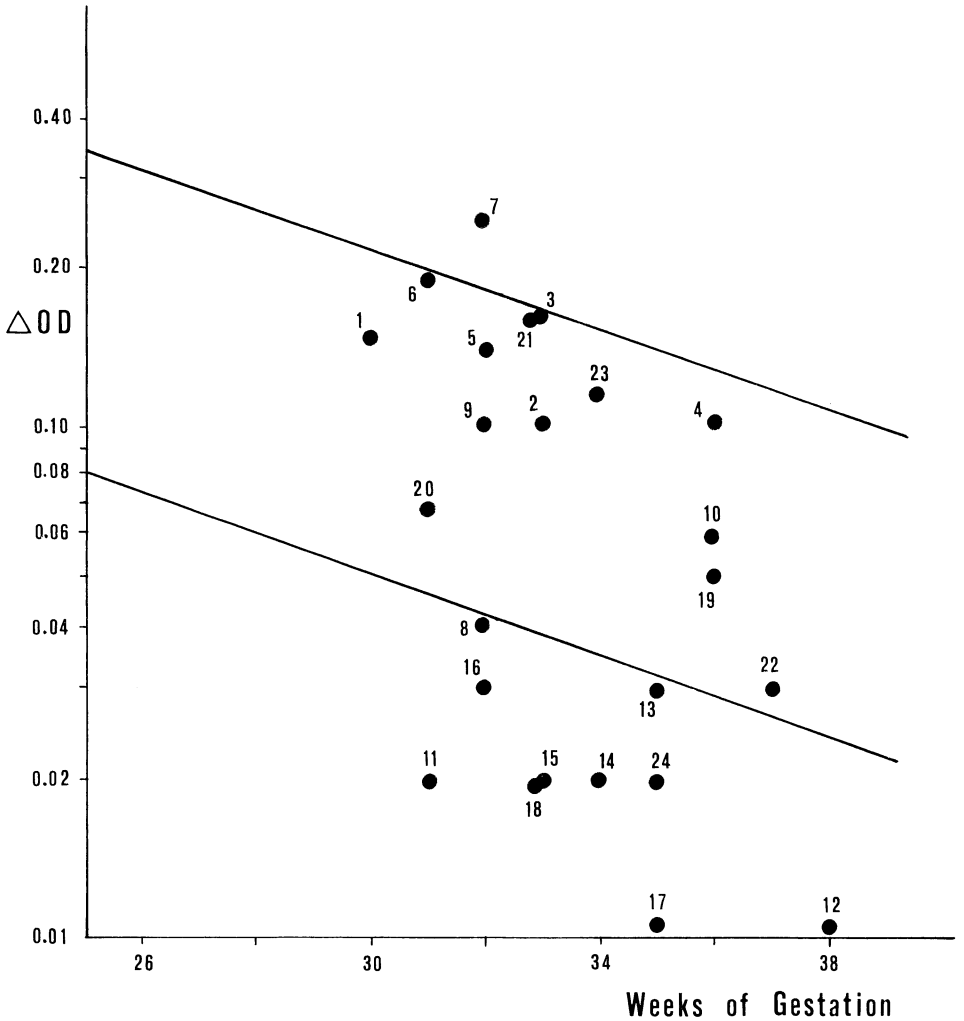

FIG. 4.

PROGNOSTIC VALUE OF HCG

The results are listed in Table 4. The values obtained seem to have little significance and no conclusions can be drawn from them.

PROGNOSTIC VALUE OF SPECTROPHOTOMETRY OF THE AMNIOTIC FLUID

We have had experience of 96 iso-immunized patients, who underwent amniocentesis once of twice: giving a total or 139 samples. The values for ΔOD in the last amniocentesis carried out are shown in Fig. 5.

The results obtained seem satisfactory; in all cases, the value given corresponded fairly exactly with the intra-uterine foetal condition. In no case were there

Table 4.

No.	Name	Weeks pregnant	Oestrioluria mg/100 ml	Hormonal colpocytology	Antibody Titre	Value of HCG	Weeks at delivery	Delivery	Weight at birth	Neonatal therapy
1	R.A.	29	29.09	Normal pregnancy pattern	1:128	1:2	34	T.C.	2.200	Exchange transfusion cure
		32	11.25	Pregnancy with slight progesterone deficiency pattern	1:128	1:2				
		33	30.55	Pregnancy with slight progesterone deficiency pattern	1:128	1:2				
2	P.J.	33	13.34	Normal pregnancy pattern	1:64	1:2	36	T.C.	—	Exchange transfusion cure
		35	18.09	Pregnancy with slight progesterone deficiency pattern	1:128	1:2				
		36	46.92	Pregnancy with slight progesterone deficiency pattern	1:512	1:2				
3	A.F.	36	48.51	Pregnancy with slight progesterone deficiency pattern	1:256	1:2	39	T.C.	3.150	Exchange transfusion cure
		37	47.80	Pregnancy with slight progesterone deficiency pattern	1:1024	1:2				
		39	50.31	Near term pregnancy pattern	1:1024	1:2				
4	F.J.	32	21.92	Pregnancy with slight progesterone deficiency pattern	1:16	1:2	38	Spont.	3.000	Exchange transfusion cure
		35	24.73	Pregnancy with slight progesterone deficiency pattern	1:16	1:2				
		37	32.22	At term pregnancy pattern	1:16	1:2				
5	T.V.	35	47.74	Pregnancy with medium progesterone deficiency pattern	1:16	1:2	38	Spont.	2.850	Exchange transfusion cure
		37	45.90	At term pregnancy pattern	1:16	1:2				
		38	40.56	At term pregnancy pattern	1:32	1:2				
6	T.L.	33	22.49	Normal pregnancy pattern	1:16	1:4	36	Spont.	2.600	Exchange transfusion cure
		34	24.18	Normal pregnancy pattern	1:16	1:4				
		35	31.56	Near term pregnancy pattern	1:64	1:4				
7	F.N.	34	25.15	Pregnancy with slight progesterone deficiency pattern	1:64	1:4	37	T.C.	1.760	Exchange transfusion cure
		36	31.29	Pregnancy with slight progesterone deficiency pattern	1:256	1:4				
		37	38.75	Pregnancy with medium progesterone deficiency pattern	1:256	1:4				

(zusätzl.)

No.	Name	Weeks pregnant	Oestrioluria mg/100 ml	Hormonal colpocytology	Antibody Titre	Value of HCG	Weeks at delivery	Delivery	Weight at birth	Neonatal therapy
8	M.B.	35	29.20	Normal pregnancy pattern	1:4	1:2	38	T.C.	2.150	Exchange transfusion cure
		36	35.80	Normal pregnancy pattern	1:16	1:2	38	Twin	2.350	
		37	43.47	At term pregnancy pattern	1:16	1:2				
9	G.A.	27	22.60	Normal pregnancy pattern	1:32	1:2	33	T.C.	2.900	Exchange transfusion cure
		28	18.30	Pregnancy with slight progesterone deficiency pattern	1:64	1:2				
		32	35.70	Pregnancy with slight progesterone deficiency pattern	1:64	1:2				
10	B.E.	36	39.47	Normal pregnancy pattern	1:128	1:2	39	Spont.	2.800	Exchange transfusion cure
		37	49.99	Normal pregnancy pattern	1:128	1:2				
		39	45.00	Near term pregnancy pattern	1:128	1:2				
11	C.A.	28	24.86	Normal pregnancy pattern	1:128	1:2	36	Spont.	2.650	Exchange transfusion cure
		31	27.36	Pregnancy with slight progesterone deficiency pattern	1:256	1:2				
		32	42.00	Normal pregnancy pattern	1:256	1:2				
		34	46.15	Normal pregnancy pattern	1:256	1:2				
12	D.T.S.	28	41.00	Normal pregnancy pattern	1:2	1:2	39	T.C.	2.370	Cure
		33	39.00	Normal pregnancy pattern	1:4	1:2				
		37	37.40	Not interpretable	1:16	1:2				
		38	26.74	Pregnancy with slight progesterone deficiency pattern	1:16	1:2				
13	B.F.	29	16.50	Not interpretable	1:64	1:2	37	T.C.	2.550	Exchange transfusion cure
		30	16.55	Pregnancy with medium progesterone deficiency pattern	1:64	1:2				
		35	22.45	Not interpretable	1:64	1:2				
		36	19.02	At term pregnancy pattern	1:64	1:2				
14	G.A.	31	21.00	Not interpretable	1:4	1:2	37	T.C.	3.020	Exchange transfusion cure
		33	27.60	Not interpretable	1:16	1:2				
		34	31.20	Not interpretable	1:16	1:2				
		35	55.70	Not interpretable	1:16	1:2				
15	B.O.	27	21.00	Normal pregnancy pattern	1:32	1:2	37	Spont.	2.700	Exchange transfusion cure
		29	14.50	Normal pregnancy pattern	1:32	1:2				
		32	20.34	Normal pregnancy pattern	1:64	1:2				
		33	20.00	Normal pregnancy pattern	1:64	1:2				
		34	26.60	Normal pregnancy pattern	1:64	1:2				
		37	37.40	Not interpretable	1:64	neg.				

(segue)

No.	Name	Weeks pregnant	Oestrioluria mg/100 ml	Hormonal colpocytology	Antibody Titre	Value of HCG	Weeks at delivery	Delivery	Weight at birth	Neonatal therapy
16	B.G.	22	44.00	Normal pregnancy pattern	1:64	1:2	36	Spont.	2.400	Exchange transfusion cure
		23	11.50	Pregnancy with slight progesterone deficiency pattern	1:64	1:2				
		27	10.30	Pregnancy with slight progesterone deficiency pattern	1:64	1:2				
		28	21.05	Pregnancy with slight progesterone deficiency pattern	1:64	1:2				
		32	23.00	Normal pregnancy pattern	1:64	1:4				
		32	18.36	Normal pregnancy pattern	1:64	1:4				
		33	20.87	Normal pregnancy pattern	1:64	1:4				
		36	25.70	Normal pregnancy pattern	1:64	1:4				
17	S.W.	30	22.75	Normal pregnancy pattern	1:16	1:16	37	Spont.	2.750	Exchange transfusion cure
		34	31.76	Not interpretable	1:32	1:16				
		35	32.68	Normal pregnancy pattern	1:32	1:16				
		37	42.00	Normal pregnancy pattern	1:32	1:16				
18	T.E.	33	21.66	Normal pregnancy pattern	1:8	1:2	37	T.C.	2.400	Exchange transfusion Dead after one month for
		33	10.33	Normal pregnancy pattern	1:8	1:2				
		34	24.30	Normal pregnancy pattern	1:8	1:2				
		37	28.80	Not interpretable	1:8	1:2				
19	B.M.	34	38.20	Normal pregnancy pattern	1:32	1:2	37	Spont.	3.150	Cure
		35	41.80	Normal pregnancy pattern	1:32	1:2				
		37	45.70	Normal pregnancy pattern	1:32	1:2				
20	A.G.P.	30	26.34	Normal pregnancy pattern	1:64	1:16	33	T.C.	2.400	Exchange transfusion cure
		31	25.40	Normal pregnancy pattern	1:64	1:16				
		32	32.56	Normal pregnancy pattern	1:64	1:16				
21	C.B.	23	20.00	Normal pregnancy pattern	1:256	1:2	27	Spont.	900	Still-born
		24	16.43	Normal pregnancy pattern	1:512	1:4				
		25	8.19	Pregnancy with medium progesterone deficiency pattern	1:512	1:8				
22	F.R.	20	20.00	Not interpretable	1:32	1:2	37	T.C.	2.900	Repeated exchange transfusion cure
		31	18.01	Not interpretable	1:128	1:2				
		32	15.20	Pregnancy with medium progesterone deficiency pattern	1:128	1:2				
		34	13.16	Pregnancy with medium progesterone deficiency pattern	1:512	1:4				

(segue)

No.	Name	Weeks pregnant	Oestrioluria mg/100 ml	Hormonal colpocytology	Antibody Titre	Value of HCG	Weeks at delivery	Delivery	Weight at birth	Neonatal therapy
23	B.G.	32	21.40	Normal pregnancy pattern	1:64	1:4	34,5	T.C.	2.600	Repeated exchange transfusion cure
		32	19.40	Normal pregnancy pattern	1:64	1:4				
		33	25.70	Normal pregnancy pattern	1:64	1:4				
		34	28.16	Normal pregnancy pattern	1:64	1:2				
24	D.G.	34	38.42	Normal pregnancy pattern	1:16	1:16	37	T.C.	2.640	Exchange transfusion cure
		35	41.68	Normal pregnancy pattern	1:16	1:8				
		36	28.61	Normal pregnancy pattern	1:16	1:8				
		37	34.70	Normal pregnancy pattern	1:16	1:8				
25	N.E.	32	22.85	Pregnancy with slight progesterone deficiency pattern	1:128	1:2	36	T.C.	2.350	Repeated exchange transfusion cure
		34	20.62	Normal pregnancy pattern	1:128	1:2				
		35	18.07	Near term pregnancy pattern	1:256	1:4				
		36	16.26	Near term pregnancy pattern	1:512	1:8				

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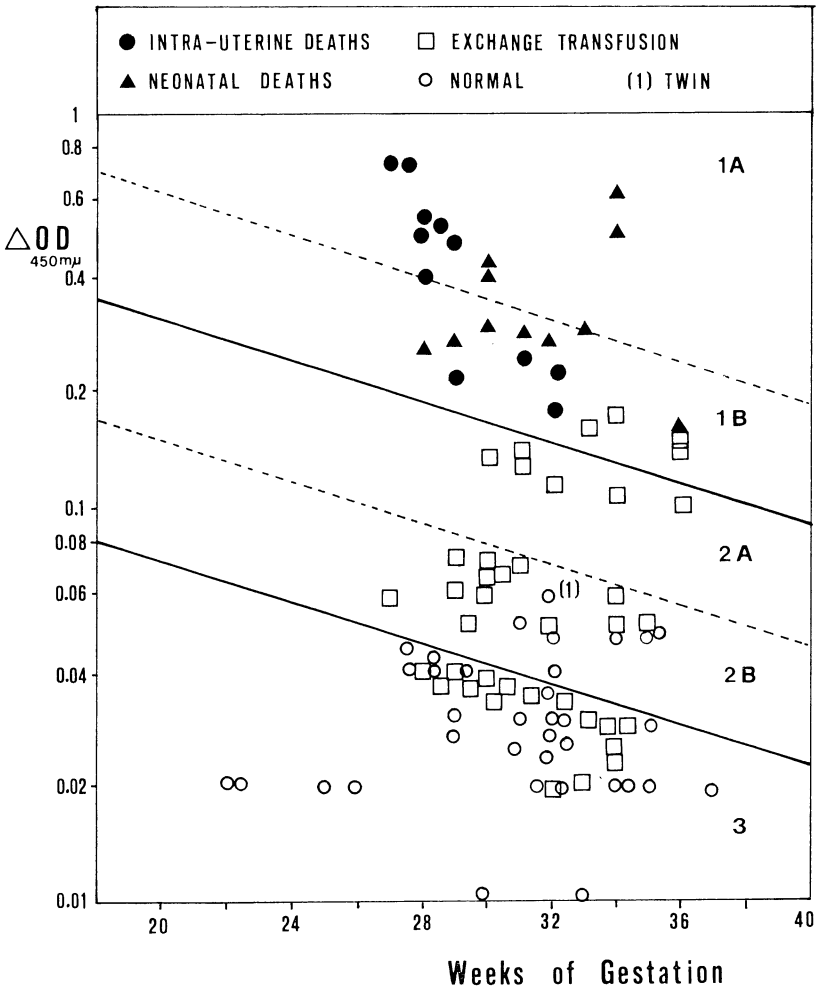

FIG. 5.

any undersired effects due to the trans-abdominal amniocentesis, and we therefore think that, when the indirect Coombs' test exceeds the value of 1:8, it is correct to carry out amniocentesis, taking as a basis the results of ΔOD at 450 mμ according to Liley in order to assess the nature of the Rh iso-immunization.

This finding, once verified by a second amniocentesis, will make it possible to decide whether it is advisable to induce delivery or caesarean section, so long as the foetal maturity tests enable one to assume that the foetus has attained an independent life.

CONCLUSIONS

The correct procedure to be followed in cases of Rh iso-immunization is first of all to assess the family history, taking into consideration parity ([3, 4, 19, 20, 26]), any

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previous abortions and incompatible haemotherapy. Once these parameters have been defined, it is useful to study the paternal genotype ([9,14]), any ABO incompatibility ([27,29]) and the nature of the maternal iso-immunization, expressed by the values for the inderect Coombs' test that have been carried out throughout pregnancy.

The scheme we have followed is:

1) determination of the Rh factor and the ABO group in all the pregnant women;

2) In the case of Rh negative patients, determination of the husband's Rh;

3) If the husband is Rh positive, investigate the homo- and hetero-zygotism;

4) in case of conjugal incompatibility, determine the indirect Coombs' test, by the following procedure:

– primiparae: at the third, sixth and eight month, and at term;

– multiparae with a negative history: at the third, sixth and eight month and at term;

– multiparae with a positive history: at the third and sixth month, and every 20 days until delivery.

In case of conjugal incompatibility to the ABO system with a positive history (newborn infants with serious icterus) investigate the potentially pathogenic immune antibodies at the sixth and eighth month and st the time of delivery.

5) Determination of the ABO group and Rh factor in the umbilical blood.

6) Direct Coombs' test in cases of Rh incompatibility.

7) In cases of iso-immunization, establish the gravity of the Rh iso-immunization by means of appropriate controls.

Whenever the indirect Coombs' test gives values greater than 1:8, we consider that the degree of iso-immunization is such as to compromise the state of the foetus, and an amniocentesis will therefore be required to determine the ΔOD at 450 mμ by Liley's method ([7,11,14,15,21]). Depending on the results obtained from spectrophotometric investigation of the amniotic fluid, we suggest the following procedure:

a) if the optic index is reassuring, repeat the amniocentesis after two or three weeks, and if the second value is satisfactory, the pregnancy may be allowed to proceed, with or without a third amniocentesis;

b) if the optic index gives cause for alarm, the amniocentesis must be repeated after 6-10 days in order to decide whether either of the following is necessary:

– premature delivery, if this can be done without too much risk;

– intra-uterine transfusion;

c) if the index is in the intermediate zone, the amniocentesis should be repeated after 10-15 days.

In all situations in which the all-round evaluation of the results of the investigations we carried out suggested the presence of an Rh iso-immunization of considerable gravity, and the laboratory results declared a condition of definite immaturity, we considered that an intra-uterine transfusion should be attempted, using Liley's technique ([12,13,22,28]).

We have also had good results in the past with the use of immunodepressors, with anti-folic acid substances at relatively low doses, and especially with antipurines, at doses of 50 - 100 - 200 mg per day, in relation to the individual tolerance and the antibody levels; these doses suitably controlled the maternal antibody response, keeping it within bounds or even reducing it, with an appreciable diminution of the antibody level. With this therapy, which we always initiated

after completion of the 4th month of pregnancy, we observed no injury either to the mother or the foetus ([17]).

However, when the foetus shows some degree of maturity, it is preferable to induce delivery ([1,5]).

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Morphological and histological changes in the intestinal mucosa after the urinary shunt operation in gynaecology

by

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Some interest seems to attach to the problem of the morphological and histological changes that may be induced on the intestinal wall due to more or less prolonged contact with the urine, following a permanent urinary shunt operation, especially in the light of many contradictory reports in the literature concerning the behaviour of the intestinal mucosa of the excluded and not completely excluded segments of the intestine ([1,3,4,5,7,9,10,11,12,13]).

Whenever it has been possible to examine the intestinal tract throughout its

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