Hyaline Membrane Disease

INCIDENCE IN CAPE TOWN, 1974

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SUMMARY

The incidence of hyaline membrane disease in three Cape Town hospitals during 1972 and 1973 was analysed, and compared with the incidence revealed in a similar survey in 1966. Striking and significant differences were found.

The over-all incidence of hyaline membrane disease has fallen from 12,6% to 5,0%. The altered incidence is due to a much lower incidence in the Coloured and Black groups. The incidence for the White group has remained at 12,8%. Other changes were a higher incidence associated with antepartum haemorrhage, and a protecting influence in toxaemia. Maternal diabetes did not carry the increased risk shown previously.

Several findings of the 1966 study were confirmed. They were the good correlation of hyaline membrane disease with immaturity, the male preponderance, and the increased incidence after delivery by Caesarean section.

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Despite advances in the knowledge of fetal physiology, hyaline membrane disease (HMD) remains a major problem in perinatal medicine. The incidence of HMD in Cape Town in 1966 corresponded to that found in the literature, namely 12,6% for infants born before 38 weeks' gestation.[1] Since that time, however, the practice of obstetrics has altered, in that newer techniques such as amniocentesis and fetal monitoring are used as a routine. The impression was that HMD had become less common.

To investigate this possibility, the more recent incidence of HMD was determined and statistically compared with the 1966 survey, and the influence of race, gestation, sex and certain maternal factors was again evaluated.

PATIENTS AND METHODS

The study included all live births during 1972 and 1973 in the Peninsula Maternity Service of the University of Cape Town teaching units at Groote Schuur Maternity, Mowbray Maternity and Peninsula Maternity Hospitals. During the 24 months there was a total of 19 769 live births among the three ethnic groups, as follows: Whites 3 341, Cape Coloureds 13 655, and Blacks 2 773.

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Details of pregnancy, labour, delivery and neonatal course were coded as a routine for each mother and infant, and stored on computer tapes. HMD was diagnosed on the standard criteria used previously.[1] Gestational age in preterm infants was assessed by the Dubowitz system.[2] The data were analysed by computer, using the chi-square test for two-by-two contingency tables with Yates's correction.

RESULTS

There are significant differences in the percentage of low birthweight infants in the three racial groups (Table I) as was noted previously.[1,3] Weight correlates poorly with gestational age, and is influenced by many other factors. To obtain a true comparison the gestational age was used for all further analysis.

TABLE I. DISTRIBUTION OF LIVE BIRTHS ACCORDING TO BIRTHWEIGHT AND RACIAL GROUP

Birthweight	Whites	Coloureds	Blacks
<2 500 g	201 (6%)	2 425 (18%)	357 (15%)
⩾2 500 g	3 140	11 230	2 416

Significance of difference in racial groups $P<0,001$.

Maturity

The effect of maturity is clearly demonstrated in Table II. Apart from the small step-up at 29 - 33 weeks in the Coloured and Black patients, the incidence of HMD decreases with increasing gestation—as had been found previously.[1] Of particular interest and importance is the sharp drop in incidence at 34 - 36 weeks. HMD is extremely rare after 38 weeks, and was ignored in the other analyses and comparisons. Tables III - VII therefore only refer to infants born at or before 38 weeks.

The over-all incidence of HMD in gestations up to and including 38 weeks was 5%. The corresponding figure in 1966 was 12,6%. There is thus a marked change, which is further explored in Table III.

Racial Incidence

Table II shows a striking difference in the racial incidence viz. 12,8% in White, 4,1% in Coloured and 6,1% in Black infants. The lower incidence in the Coloured and Black groups, as opposed to the Whites, is significant: the difference between the Coloured and Black groups is

TABLE II. INCIDENCE OF HMD ACCORDING TO MATURITY AND RACIAL GROUP

	Whites			Coloureds			Blacks			Total		
Gestation (wks)	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%
<29	6	8	42,9	15	66	18,5	2	11	15,4	23	85	21,3
29 - 33	12	25	32,4	68	237	22,3	20	38	34,5	100	300	25,0
34 - 36	9	47	16,1	48	810	5,6	6	121	4,7	63	978	6,0
37 - 38	16	213	7,0	8	2 118	0,38	1	271	0,37	25	2 602	0,95
>38	1	2 911	0,03	4	10 090	0,04	0	2 260	0,00	5	15 261	0,03
Total ⩽38*	43	293	12,8	139	3 231	4,1	29	441	6,1	211	3 965	5,0

* Significance of difference in racial incidence $P<0,001$.

TABLE III. COMPARISON OF THE INCIDENCE OF HMD BETWEEN THE TWO STUDIES

	Whites			Coloureds			Blacks			Total		
	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%
1966	23	152	13,1	28	204	12,1	4	26	13,3	55	382	12,6
1974	43	293	12,8	139	3 231	4,1	29	441	6,1	211	3 965	5,0
Significance of difference 1966 *v.* 1974	NS*			$P<0,001$			$P<0,05$			$P<0,001$		

* NS = not significant.

TABLE IV. INCIDENCE OF HMD ACCORDING TO SEX AND RACE

	Whites			Coloureds			Blacks			Total 1974			Total 1966		
	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%
Male	31	149	17,2	87	1 644	5,0	17	207	7,6	135	1 865	6,8	35	178	16,4
Female	12	144	7,7	52	1 587	3,2	12	234	4,9	76	1 889	3,9	20	204	9,0
Ratio male/female ...	2,58			1,67			1,41			1,77			1,75		
Significance of male preponderance	$P<0,01$			$P<0,01$			NS*			$P<0,001$			$P<0,05$		

* NS = not significant.

not significant. In 1966 no difference was found in the incidence of HMD among the racial groups.

Table III confirms that the over-all change now recorded is due mainly to a decreased incidence in the Coloured group, while the White group retained its 13% incidence. The change in Blacks is also significant, but the small numbers for 1966 make a comparison difficult.

Sex Incidence (Table IV)

The expected male preponderance in HMD was again confirmed—the ratio of 1,77 males for every female being virtually identical with that found in 1966. Note that the highest ratio was found in the White group. There is no explanation for the non-significant comparison in the Black group. The difference in the total figures is highly significant.

Caesarean Section

The influence of delivery by Caesarean section is shown in Table V. Elective Caesarean section refers to those cases where labour had not yet commenced. There is a significant increase in the incidence of HMD after Caesarean section compared with vaginal delivery—7,7% *v.* 4,6%. This was also shown in 1966, but the present figure is much lower than the 20% found previously (Table VI). Analysis showed that the rate of Caesarean section had not changed from 1966 to the time of the present study. The incidence of HMD after vaginal delivery is also reduced in the 1974 figures.

TABLE V. INFLUENCE OF CAESAREAN SECTION ON THE INCIDENCE OF HMD

	HMD	No HMD	%	Significance of difference
Elective CS*	24	248	8,8	NS†
CS in labour	24	328	6,8	
All CS	48	576	7,7	$P<0,01$
Vaginal delivery	163	3 388	4,6	

* CS = Caesarean section.
† NS = not significant.

TABLE VI. INCIDENCE OF HMD RELATED TO MODE OF DELIVERY IN THE TWO STUDIES

	% 1966	% 1974	Significance of difference 1966 *v.* 1974
Caesarean section	20,0	7,7	$P<0,001$
Vaginal delivery	11,2	4,6	$P<0,001$

Although this factor was not examined in 1966, there was no significant difference between the incidence of HMD according to whether Caesarean section was elective or performed during labour.

Antepartum Haemorrhage

Antepartum haemorrhage (APH) included all bleeding prior to delivery, whether it was due to accidental haemorrhage or placenta praevia, or whether it was of unknown aetiology. Table VII demonstrates that APH did not affect the incidence of HMD when an operation was done before the onset of labour. Once labour had commenced, APH significantly increased the risk of HMD in vaginal deliveries, and especially when Caesarean section had to be performed. In 1966 no such correlation could be demonstrated for vaginal deliveries, while Caesarean sections were excluded.

Toxaemia

Toxaemia was defined as maternal hypertension (blood pressure exceeding 140/90 mmHg at rest, with the patient lying down) with or without albuminuria. The results (Table VIII) show that toxaemia significantly lowers the incidence of HMD. In 1966 there were only 2 infants with HMD associated with toxaemia, and the numbers could not be analysed statistically.

TABLE VIII. INFLUENCE OF TOXAEMIA ON THE INCIDENCE OF HMD

	HMD	No HMD	% HMD
Toxaemia	31	845	3,5
No toxaemia	180	3 120	5,5

Significance of difference between toxaemia and no toxaemia $P<0,05$.

Maternal Diabetes

Of 178 infants born to mothers with diabetes, only 1 developed HMD. The 1966 figures, although small, suggested a correlation between the two conditions which was not substantiated in the present study.

DISCUSSION

The results of this analysis allow four main points to be made: (*i*) HMD has become less common in Cape Town owing to the decreased incidence among the Coloured and Black ethnic groups; (*ii*) Caesarean section increases the risk of HMD, but the size of this risk has decreased since 1966; (*iii*) antepartum haemorrhage increases the incidence of HMD, except when delivery is by elective Caesarean section; and (*iv*) toxaemia diminishes the risk of HMD.

It should be pointed out that the present study has several advantages over the 1966 survey, in that more than 10 times the number of case histories were analysed. The records also contained details, such as onset of labour, which had not been available previously. We furthermore believe that the scored gestational age is more reliable than the calculated age used in the first study. A full review of the literature was given in 1966.[1]

Decreased Incidence in Non-White Groups

The cause of the over-all decrease in the incidence of HMD in the Coloured and Black groups to a level which is significantly below that suffered by the White group, is a matter for speculation. Obstetric practice has changed

TABLE VII. EFFECT OF ANTEPARTUM HAEMORRHAGE ON THE INCIDENCE OF HMD

	Elective Caesarean section			Caesarean section in labour			Vaginal delivery			Total		
	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%	HMD	No HMD	%
APH	9	61	12,9	12	57	17,4	25	228	9,9	46	392	11,7
No APH	15	189	7,4	12	272	4,2	138	3 163	4,2	165	3 789	4,4
Significance of difference APH *v.* no APH		NS*			$P<0,001$			$P<0,01$			$P<0,001$	

NS = not significant.

dramatically since 1966, and in a way which might be expected to have contributed to the fall in the incidence of HMD. HMD is a condition of the immature neonate, and its principal determinant is therefore preterm delivery. Early delivery can be prevented, or at least delayed, to the benefit of the fetus, by β-adrenergic agents.[4] It is suggested that this change in obstetric practice is responsible, at least in part, for the decreased incidence of HMD. It does not explain why the non-White neonate should have a lower incidence than the White, because both reaped the benefit of the obstetric advance. Steroids[5] were only used towards the end of the period under study, but, again, were available to all mothers.

The results suggest that the Coloured and Black fetuses are better adapted than their White contemporaries, for extra-uterine life. The reasons for this are a matter for further investigation. It has been observed that fetal malnutrition protects against HMD.[6] Is it possible that the over-all lower socio-economic status of the non-White mothers increases the relative malnutrition of their fetuses, and thereby increases their protection against HMD? Against this theory is the 1967 finding that the percentage of fetal malnutrition was the same for all three racial groups[3], and that conditions in general have improved for the Coloured and Black groups. Prolonged rupture of the membranes is known to result in a lower incidence of HMD.[7] Amnionitis is common among the Coloureds and Blacks.[8] Perhaps this is another reason for the lower incidence of HMD in these two groups.

Increased Incidence with Caesarean Section

While obstetric measures might reduce the incidence of preterm labour, these measures cannot be said to have reduced the incidence of HMD associated with Caesarean section. There are two possibilities for the reduction of HMD in association with Caesarean section: (*i*) Caesarean sections might be performed less frequently; and (*ii*) they might be performed only when there is evidence of fetal pulmonary maturity. Firstly, intensive monitoring of the fetal heart rate and pH during labour has provided a more enlightened approach to 'fetal distress'. This has resulted in fewer sections for this reason. An analysis, however, shows that the Caesarean section rate was no different in 1974 compared with 1966. In the second place, it has become possible to predict accurately from a simple analysis of the liquor that a fetus will not develop HMD.[9] No obstetrician in 1973 would contemplate an elective Caesarean section unless he could be sure of fetal pulmonary maturity whatever the supposed gestational age, provided of course that there were no other considerations. The latter approach would certainly have contributed to the reduction of HMD.

Increased Risk with Antepartum Haemorrhage

It is striking that APH increases the incidence of HMD, except when the fetus is delivered by elective Caesarean section. This group of APH would be expected to be made up mostly of cases of placenta praevia, which do not, therefore, increase the incidence of HMD. When delivery was achieved vaginally or when vaginal delivery was anticipated but section became necessary during labour, accidental haemorrhage and haemorrhage of unknown origin were the more likely causes of APH. Two possible mechanisms arise to account for the increased incidence of HMD. In the first place, haemorrhage of unknown origin is known to be associated with preterm labour. It is possible that in this case labour would continue, while the other aspects of fetal physiology are still underdeveloped. Secondly, partial placental separation is associated with fetal hypoxia, and severe hypoxia causes circulatory changes resulting in underperfusion of the fetal lungs.[10] The fetal lungs can be so damaged by tissue hypoxia that they are incapable of maintaining the production of surfactant, and HMD occurs. It is suggested that this explains the high incidence of HMD in infants delivered by Caesarean section for APH during labour.

A very interesting observation is that when APH is excluded, the incidence of HMD is identical, both after Caesarean section in labour, and in vaginal delivery. Both are significantly lower than the incidence after vaginal delivery associated with APH. Further analysis of the indications for Caesarean section during labour without APH, compared with those for Caesarean section with APH, would be informative as to whether hypoxia was the determining factor in the generation of HMD, as suggested above.

Decreased Incidence with Toxaemia

Maternal toxaemia affords the fetus relative protection from HMD. Provided that the factors known to be associated with HMD were distributed equally between the two groups, and there is no reason to suppose that they were not, the protection afforded by toxaemia is a real phenomenon. In fact, there is good reason to suppose that Caesarean section and APH would be more likely to be associated with the toxaemic patients, and even so toxaemia appears to be protective. Toxaemia is associated with placental insufficiency which, if it operates at a low level over a long period, increases the fetal production of pulmonary surfactant. This may well be the mechanism of protection.

Maternal Diabetes

The extremely low incidence of HMD in maternal diabetes is contrary to previous experience. This may be due to improved medical control of diabetes and delivery nearer term, since amniocentesis is notoriously unreliable in diabetes mellitus. Since 1971 no diabetic mother has been delivered by 'cold' Caesarean section at Groote Schuur Hospital (excluding emergencies) until an attempt has been made to stimulate labour by means of stripping and rupture of membranes. We believe that this prepares the fetus, still growing normally, for delivery and extra-uterine adaptation.

CONCLUSION

The prevention of HMD rests with the obstetrician. He can do much to prevent or delay a preterm delivery

by the use of β-adrenergic agents. An elective Caesarean section before term in an uncomplicated pregnancy need never be associated with HMD if the simple precaution of looking for pulmonary surfactant in the liquor is carried out. Caesarean section should always be performed for good reason and, when performed in a labour not associated with APH, carries no greater risk of HMD than vaginal delivery. The general practitioner who is unable to test for surfactant in the liquor, should therefore rather wait until labour has commenced and not be tempted to do elective sections. The patient with an APH in labour continues to present a challenge to obstetric management.

REFERENCES

1. Malan, A. F., Evans, A. and Heese, H. de V. (1966): S. Afr. J. Obstet. Gynaec., **4**, 13.
2. Dubowitz, L. M. S., Dubowitz, V. and Goldberg, C. (1970): J. Pediat., **77**, 1.
3. Malan, A. F., Evans, A., Smit, W. B. de V. and Heese, H. de V. (1967): S. Afr. Med. J., **41**, 698.
4. Edelstein, H. and Baillie, P. (1972): Med. Proc., **18**, 92.
5. Liggins, G. C. and Howie, R. N. (1972): Pediatrics, **50**, 515.
6. Usher, R. H. (1970): Pediat. Clin. N. Amer., **17**, 169.
7. Bauer, C. R., Stern, L. and Colle, E. (1974): Pediatrics, **53**, 7.
8. Hartley, P. W. (1974): Personal communication.
9. Edwards, J. and Baillie, P. (1973): S. Afr. Med. J., **47**, 2070.
10. Chu, J., Clements, J. A., Cotton, E., Klaus, M. H., Sweet, A. Y., Thomas, M. A. and Tooley, W. H. (1965): Pediatrics, **35**, 733.