SOME CLINICAL ASPECTS OF RHESUS SENSITIZATION IN PREGNANCY

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Once Rhesus (Rh) sensitization occurs in pregnancy, the perinatal mortality and neonatal morbidity rises steeply above the national average.

At the Queen Victoria Hospital[6] it was the third commonest cause of macerated stillbirths, accounting for 12·8% of this complication of pregnancy. About 3·1% of fresh stillbirths and 5% of neonatal deaths are caused by Rh sensitization. But survival or death are not the only facets to this problem; one need only recollect the very specialized neonatal paediatric care these cases need until they are eventually discharged. Tragic indeed is the survival of the kernicterus spastic child, completely dependent for the rest of its life. Rh sensitization in pregnancy is unpredictable—the grande multipara with 10 normal children, the para 1 with a severely affected second child—so many factors are unknown.

I wish to present 3 cases of severe Rh sensitization where a maternal syndrome could be recognized. Unduly hesitant action, to obtain a more mature foetus, resulted in depressing perinatal mortality and morbidity. Antenatal antibody-titre values gave very little guidance on the ultimate obstetric management of these cases. In one of them a baby with hydrops foetalis survived—a tribute to the neonatal exchange transfusion and paediatric care.

Case 1

Mrs. B.T., aged 31. Para. 2 (6 and 3 years previously); both these pregnancies and deliveries were normal, and neither child was affected by haemolytic disease. Maternal blood group: A-group, Rh-negative. Husband's blood group: A-group Rh-positive; heterozygous. The sensitizing factor was an emergency blood transfusion with Rh-positive blood for a secondary haemorrhage after trachelorrhaphy.

The patient was first seen in consultation at 30 weeks' gestation. The blood pressure (BP) was 130/80 mm.Hg, the weight 170 lb., and the abdominal girth 34 inches. There was oedema of the feet. She was allowed home in the country on bed rest, salt-free diet, and diuretics. Antibodies were present in the maternal serum.

At 34 weeks BP was 140/80, weight 174½ lb., and girth 38 inches. The antibody reactions had not changed significantly and the serologist advised induction at 38 weeks. Arrangements were made to induce labour at 37 weeks.

At 35 weeks the patient noticed that (1) the abdomen had suddenly increased enormously in size, (2) that foetal movements were diminished, and (3) that her feet and abdomen were swollen. She consulted her house doctor, who assured her that the foetal heart was normal. BP 160/100 mm.Hg. She had gained 8 lb. in 14 days and there was oedema of the lower half of the body. The abdomen was grossly enlarged and the foetus difficult to palpate and almost impossible to identify. A twin pregnancy was suspected. The potent antibody reactions were slightly more intense.

The patient was admitted for medical induction—now at 36 weeks. A live female with hydrops foetalis was born, weighing 6 lb. 1 oz., oedematous and pale but not jaundiced. The placenta weighed 2 lb. 14 oz. and was large and pale. The report on the cord blood was as follows: Group-O Rh-positive. Haemoglobin 7 G. per 100 ml. Total bilirubin 10·3 mg. per 100 ml.

An exchange transfusion of 500 ml. of concentrated group-O Rh-negative blood was carried out. After 24 hours the haemoglobin was 13·5 G. and the total bilirubin 9·4 mg. Another 500 ml. of the same blood was transfused by the

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exchange method. The next day the bilirubin was 9·5 mg. and 24 hours later it was 8 mg.

The baby also received the following medical treatment: (1) Incubation. (2) Intramuscular digoxin, 0·125 mg., repeated in 12 hours and thereafter daily. (3) Intramuscular 'cortogen', 25 mg., repeated 8-hourly for 3 doses, and reduced step by step afterwards. (4) 'Neptal', 1/8th ml. on the first day. (5) Penicillin, 200,000 u. daily. (6) Packed cells, 400 ml. on the 17th day, for anaemia. (7) Feeding with mother's milk, 1 dr. 8-hourly after 48 hours; gradually increased in amount and fortified with 'casec'.

After all the oedema had disappeared, the weight had dropped from 6 lb. 1 oz. to 3 lb. 10 oz.

Further 'milestones': (i) Weight 6 lb. after 1 month. (ii) Smiled at 2 months and laughed at 4 months. (iii) At 4 months the neck was held stiff and she followed objects with the eyes. (iv) At 5 months she grasped objects with the left hand, but not the right. (v) At 7 months she blew bubbles. (vi) Sat straight up at 8 months. (vii) At 17 months she crept around and could walk by holding with her hand, and had a vocabulary of 30 words.

Clinically there is now slight spasticity of the right arm and leg, with increased reflexes, and we have a child with normal mental development but slight hemiparesis on the right side.

Case 2

Mrs. M.J., aged 42. This was her first pregnancy. Blood group-O and Rh-negative with antibodies to the titre of 1/16. The finding of antibodies was unusual in a first pregnancy. The patient had never had a blood transfusion or intramuscular injection of blood.

At 28 weeks her BP was 135/80 mm.Hg, and she had gained 4 lb. in 4 weeks. There was no oedema. At 30 weeks the BP was 140/80, with no oedema or gain in weight. At 32 weeks her BP was 140/80, and she had gained 5 lb. in 2 weeks. The foetal lie was rather difficult to make out, which at that stage was attributed to the tense musculature of the elderly primipara.

At 33½ weeks her BP was 140 mm.Hg. There was oedema of the lower half of the body and the legs, and a sudden gain in weight of 9 lb. in 9 days, which could not be accounted for by the amount of oedema. The foetal lie could not be made out. The abdomen had increased considerably in girth and had a peculiar doughy feel. The foetal heart could be heard and was normal. The antibody reactions had increased since the previous investigation.

Arrangements were made for medical induction, but that night the patient went into spontaneous labour and she was delivered, as a breech, of a stillborn hydropic male child of 4 lb. 11 oz. The placenta was large and pale and weighed 2 lb. 4 oz.

Case 3

Mrs. G.M., aged 33. Para 2: both children unaffected by haemolytic disease. Maternal blood group: B-group, Rh-negative. Husband's blood: A-group, Rh-positive; heterozygous. The sensitizing factor was probably the previous pregnancy 4½ years ago. She had had a blood transfusion 17 years ago after an appendicectomy, but not since the last pregnancy.

The patient was seen at 35 weeks' gestation. The antibody titre was not high or rising; mainly of the saline agglutination type. Induction was suggested at 37 weeks. The following danger signs were noted: (i) BP 150/80 mm.Hg. (ii) Mild hydramnios—girth 37 inches. (iii) Slight oedema of the feet. (iv) Weight 140 lb. The patient was not prepared to be admitted and was allowed home to her country farm on rest and sedation.

By 37 weeks the whole picture had changed. She had a grossly enlarged abdomen (girth 43 inches). The foetus was difficult to palpate and the foetal heart difficult to hear. She had gained 8 lb. in 2 weeks. The BP was normal, but there was oedema of the feet and lower abdomen. Severe haemolytic disease of the foetus was suspected, and the patient was admitted for medical induction.

She went into spontaneous labour, had a concealed accidental haemorrhage in the late first stage of labour, the foetus died, and delivery was obstructed by the swollen abdomen of a hydropic foetus weighing 8 lb. 14 oz. A postpartum haemorrhage of 24 oz. occurred. The placenta weighed 4 lb. and was large, pale and oedematous, with retroplacental blood clot. 1,000 ml. of whole blood was transfused.

A MATERNAL SYNDROME

Once Rh sensitization has occurred, selective premature induction of labour offers some hope by removing the foetus from the unfavourable surroundings of antigen-antibody reaction. The problem is akin to premature induction of labour in toxaemia of pregnancy. Antibody-titre values are disappointing with regard to foetal prognosis. It is accepted that a rise in Rh antibodies cannot be used as an accurate guide for the gynaecologist whether or when to induce labour in the Rh-sensitized patient. We think here in particular of the anamnestic reaction in cases with a Rh-negative foetus, where the antibodies may rise to high levels. Too much reliance has been placed on antibody titre as an aid to foetal prognosis. It was thought to offer a quantitative calculable estimation of the degree of affection. Application of this knowledge of rising titre has brought us to a certain level of success. Success, however, even after full application of this scientific knowledge, is frequently a matter of trial and error.

Each case must be considered as an individual problem. A close liaison should exist between gynaecologist, antenatal serologist, and paediatrician, if the perinatal mortality is to be improved. The gynaecologist is the key person in this picture. He should offer a clinical plan of action in cases that require selective premature induction of labour to avert erythroblastosis foetalis.

The main thesis of this communication is to draw attention to a maternal syndrome that can be recognized in cases of severe Rh sensitization in pregnancy.

Most of these symptoms and signs, and their importance, occur at a stage where selective premature induction of labour offers some hope of survival of the baby, even if it is very premature. In such cases the following individual symptoms and signs, or a combination of them, must thus be carefully looked for and their significance realized:

1. *Oedema.* Severe sudden oedema of the legs and lower half of the body without hypertension and albuminuria.[3,1] The incidence of oedema in normal pregnancy is about 5%, but in cases of Rh sensitization oedema of increasing degree with increasing severity of affection occurs in 33%.[4] The condition is characteristic, and one can be sure that if the mother is not a cardiac or nephritic, and if the BP and urine are normal, the mother is carrying an infant severely affected with haemolytic disease.[3] If there is superimposed pre-eclampsia, the BP may be raised, with albuminuria. The mother to some extent mirrors the infant, owing to (?) an allergic or toxic reaction from the placenta. The oedema tends to occur rapidly, with excessive gain in weight, oedema of the ankles, legs and lower abdomen, and hydramnios.

2. *Excess weight gain.* Even if oedema is not marked sudden excessive gain in weight indicates the combined effect of hydramnios, hydropic changes in the foetus and placenta, and the enlarged liver and spleen of the foetus. This excess gain in weight is usually out of proportion if compared with the weight gain of toxaemia. Excess weight gain is of more importance if unassociated with oedema.

3. *Rapid increase of abdominal girth.* This is the result of oedema of the abdominal wall, hydramnios, and the oedematous placenta.

4. *Toxaemia of pregnancy.* The occurrence of signs of toxaemia in a Rh-sensitized patient carries a grave prognosis for the foetus. A toxaemia incidence of 50 - 70% in cases of severe Rh sensitization with hydrops foetalis is given in the literature.[4] There is convincing evidence of an association between Rh sensitization and toxaemia, and the risk of sensitization rises with increasing severity of the toxaemia. The mechanism is probably through placental abnormalities resulting in foetal-maternal transfusion. These abnormalities may be noticeable after delivery. If this association between toxaemia and Rh sensitization is causal, then a close study of sensitizing pregnancies may solve many problems of the disease.[4]

5. *Difficulty in palpating the foetus.* Sudden doubt about the foetal lie and position in a case where previously it was easily recognized should arouse suspicion of a foetus severely affected by haemolytic disease. The abdomen is bigger and more indefinite to palpate, with a soft, doughy feel, and a twin pregnancy may be suspected. This is the combined effect of hydramnios, enlarged hydropic foetus and placenta.

6. *Reduced foetal movements.* This subjective observation must be treated with great respect, in spite of the hearing of a normal foetal heart. It may be explained by the hydramnios and the drowsiness of the jaundiced, anaemic foetus, and by the filling of most of the uterus by the enlarged hydropic placenta.

It is important to realize that most, if not all, of the components of this maternal syndrome appear 2 - 3 weeks before intra-uterine death of the foetus. Even reduced foetal movements may occur 7 - 10 days before intra-uterine death.

How can the maternal syndrome be utilized in the decision to carry out selective premature induction of labour in cases of severe Rh sensitization?

From the clinical point of view, the mortality risk for foetal survival and well-being can be divided into four stages (O, I, II and III):

Stage-O risk: 34 per 1,000 (normal perinatal mortality risk) Rh-negative mother with a Rh-positive husband. If antibodies do not develop, the risk is no higher than in normal pregnancy.

Stage-I risk: 70 per 1,000[5]
(i) If Rh antibodies develop for the first time.
(ii) If a previous immunized pregnancy resulted in a mildly affected infant (not transfused).

Stage-II risk: 170 per 1,000[5]
Where a previous immunized pregnancy resulted in an affected infant that survived, after exchange transfusion.

Stage-III risk: 540 per 1,000[5]
(i) Where a previous stillbirth or neonatal death was the direct result of erythoblastosis foetalis.
(ii) Where Rh antibodies are produced by a previous transfusion with Rh-positive blood.

The total perinatal mortality in cases of Rh sensitization in pregnancy (the risk in stages I, II and III) is 260 per 1,000, as compared with the normal perinatal risk of 34 per 1,000, a figure arrived at by the Perinatal Mortality Survey of the National Birthday Trust Fund in England. The risk in cases of Rh sensitization is thus 8 times as great as the total risk in all pregnancies.

According to the stage of risk the maternal syndrome serves as a guide in the following way:

1. *Cases at stage-O and stage-I risk.* Should any of the symptoms or signs of the maternal syndrome develop, the patients should be admitted for daily assessment. Severe sudden iso-immunization may occur, even in stage-O risk cases, especially if there is toxaemia with placental damage.

2. *Cases at stage-II and stage-III risk.* These may have to be admitted at the stage of foetal viability—say 30 weeks' gestational age—for daily observation of symptoms and signs of the maternal syndrome. These cases cannot be observed adequately as outpatients, because oedema, toxaemia, rapid increase in abdominal girth, and other components of the maternal syndrome, may develop suddenly. Graphic charting of maternal weight should be used as an ancillary record in the daily assessment of these cases.

SUMMARY

Three cases of severe Rh sensitization are presented, in which a maternal syndrome can be recognized. In one case the premature baby survived after exchange transfusion and elaborate paediatric care, and in the other two a hydropic foetus was delivered stillborn. Stress is laid on the danger of undue hesitancy in induction.

The maternal syndrome is described, and also its utilization in the decision to carry out selective premature induction according to the degree of the mortality risk to which the foetus is exposed.

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45th SOUTH AFRICAN MEDICAL CONGRESS (M.A.S.A.) : 45ste SUID-AFRIKAANSE MEDIESE KONGRES (M.V.S.A.)

GENERAL INFORMATION

The 45th South African Medical Congress will be held in Port Elizabeth from 27 June to 3 July 1965. In accordance with the trend at most Congresses today, the Committee have decided to have a central theme: this will be 'Disease and Race'. This will not necessarily eliminate papers on specific subjects unrelated to the central theme.

The Congress will be preceded by a public lecture on the evening of 27 June. Registration will commence on the afternoon of 27 June. The central hall will be the Feathermarket Hall, where the various exhibitions will be staged and where teas will be served. The Assembly Rooms and St. Augustine's School, both of which are within 30 yards of the Feathermarket Hall, will be the venue for the delivery of papers.

It is proposed to hold a competition for amateur films of medical interest in conjunction with the Congress.

Further information about the programme, and intention forms, will be published shortly.