Reproductive Failure

A PRELIMINARY REPORT ON THE MANAGEMENT OF HIGH RISK PATIENTS *

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SUMMARY

The need for the establishment of a Reproductive Failure Clinic at Groote Schuur Hospital was considered long overdue, as it was felt that there were a number of high risk pregnancies continually being lost among the large volume of pregnant women attending the routine, busy and overcrowded antenatal clinics.

Various criteria for the referral of pregnant women to the clinic are outlined, together with a scheme of investigation and management.

Special investigations, other than routine antenatal tests, are presented and discussed with reference to their aetiological role in causing reproductive catastrophes.

The results of work performed at the clinic are presented.

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During the latter half of 1970, a Reproductive Failure Clinic was established at Groote Schuur Hospital with the view to the investigation and management of pregnant women who fail to reproduce satisfactorily. The need for the establishment of such a clinic was considered long overdue, as there are a large number of high risk pregnancies continually being lost among the large volume of pregnant women attending the routine antenatal clinics. It was considered that if these high risk pregnancies could be singled out to attend a separate special clinic, their underlying problem could become far more striking and apparent, additional investigations could be performed in order to detect a further threat to their pregnancy, and more personal care and antenatal supervision could be administered.

The criteria for selection of pregnant women to attend the special clinic are as follows:

1. Married women with a history of 2 or more spontaneous abortions.
2. One or more dysmature, or 2 or more premature infants in their past history.
3. A history of stillbirths or neonatal deaths, unrelated to rhesus or diabetic problems.
4. Evidence of foetal growth retardation in present pregnancy.
5. Pregnancy following induction of ovulation or treatment of infertility.

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Each patient referred to the clinic is carefully screened with regard to the fulfilment of these criteria, and only in special selected cases are unmarried pregnant women accepted. In this way only women with a past history of genuine spontaneous abortions are further investigated, and not the unmarried pregnant women, whose abortions are in most cases criminally induced.

Patients becoming pregnant following induction of ovulation or following the treatment of infertility attend the clinic, and in this way the importance of their pregnancy is not overlooked, as could possibly happen at the large routine antenatal clinic. These women are also fully investigated so as not to miss a further treatable condition, which could otherwise pose a threat to the continuation of their pregnancy.

Once selected to attend the clinic, the following scheme of management is adopted:

1. All patients are booked for hospital delivery.
2. Routine antenatal investigations are recorded.
3. Blood specimens are sent off for the following investigations: serum folates; toxoplasmosis; mycoplasma infection; protein-bound iodine estimations; and full blood count and peripheral smear.
4. Vaginal swabs and smears are taken for mycoplasma, trichomonal vaginitis and other infections; and vaginal cytology.
5. The cervix is checked for cervical incompetence.
6. Each patient has an appointment made for a glucose tolerance test and a leucocyte alkaline phosphatase estimation.

At the next and subsequent visits, each patient being seen either at weekly or at fortnightly intervals, all the results are collected, conditions where tests are positive are treated, close antenatal care is carried out and personal interest is taken by the staff. Great importance is attached to the latter two points. Unlike the overcrowded antenatal clinics, these patients see the same 2 or 3 doctors only, at each visit; both parties get to know each other well, and it is felt that this goes a long way towards the achievement of success at the clinic.

The role played by these lesser-known diseases in pregnancy will now be discussed in terms of their aetiology in reproductive failure.

SERUM FOLATES

It is well known that folic acid is essential for the synthesis of nucleic acids and hence for cellular reproduction.[1] There

is a great cellular proliferation during pregnancy, presenting an increased demand for nucleic acid, and therefore for folates. Complications of folate deficiency in pregnancy have been reported as being repeated abortions, defective placentation, abruptio placentae, impaired growth of the foetus, malformation and early death of the foetus.[2] It is not easy to diagnose marginal folic acid deficiency in pregnancy. At this clinic, use is made primarily of serum folate estimations and peripheral blood smears, and results will be shown.

TOXOPLASMOSIS

The role played by *Toxoplasma gondii* in abortions is not entirely clear. There is, however, no doubt that the parasite can cross to the foetus, causing congenital toxoplasmosis and even sporadic abortion.

In order to understand its effect in causing habitual abortions, one must appreciate the pathogenesis of the disease process. The organism enters into the host cell and reproduces rapidly until the invaded cell becomes packed with these intracellular parasites, and eventually ruptures. The released parasites attach themselves to further cells and the whole process is repeated.[3] In this way tissue death occurs, and abortion will ensue. However, with adequate antibody build-up, or with effective treatment, the extracellular parasites are eradicated, but the intracellular organisms, not being as susceptible to eradication, have their reproductive capacity reduced, and rendered towards cyst formation. With a subsequent pregnancy, some of these cysts with their intracellular parasites become ruptured with a release of these parasites, and the whole process of tissue destruction can re-occur. In this way, it is understood that toxoplasmosis can cause not only the congenital form of the disease, but also sporadic and habitual abortion, if in the latter case, with each successive pregnancy, cysts rupture; a pregnancy may even continue to term unaffected, if no further cysts become involved.

MYCOPLASMA

The *Mycoplasma hominis* organism has been isolated from the genital tract of pregnant and non-pregnant women, from the membranes of abortions and from the upper respiratory tract of premature and full-term infants. Steytler[4] found that there was a 5,5% incidence of mycoplasma infection in the cord blood of infants born alive and healthy at term. He found that the organism caused no ill-effect on the mother during pregnancy, nor on the course of the pregnancy itself, or on the developing foetus. However, in these infants who were found to have mycoplasma cultured at birth from their cord blood, he demonstrated a high incidence of hyaline membrane disease, upper respiratory tract infections and neonatal jaundice—all leading to an increase in the neonatal, perinatal and infantile morbidity and mortality rates. For this reason, it is advocated that if mycoplasma is isolated from the genital tract of pregnant women it should be treated, and the infants born to these mothers should have their upper respiratory tracts swabbed for identification of the organism.

PROTEIN-BOUND IODINE

The thyroid gland is known to play an important role in most of the phases of reproduction.[5] Underactivity of the gland in pregnancy can result in abortions, prematurity, stillbirths and abnormal neonates.

Function of the gland in pregnancy can be assessed by doing protein-bound iodine estimations.[6] Combined studies by several authors have shown that the protein-bound iodine estimation rises early in pregnancy and remains unaltered throughout pregnancy, returning to normal in the puerperium; and if the level of protein-bound iodine drops below 6,2 μg/100 ml, this constitutes a threat to the continuation of the pregnancy, and should be treated throughout the pregnancy.

FULL BLOOD COUNT AND PERIPHERAL SMEAR

One of the effects of the treatment of toxoplasmosis with the antimalarial compound pyrimethamine (Daraprim),[7] is to cause a thombocytopenia and megaloblastic anaemia. For this reason, all patients attending the clinic have a routine blood examination, and those on treatment for toxoplasmosis, have the blood tests repeated during and after a full course of therapy.

TRICHOMONAS VAGINALIS

This is a parasite of the genito-urinary tract. Many claims have been made that this organism is responsible for abortion and prematurity by setting up an inflammatory reaction in the foetal membranes. For this reason, if the *Trichomonas vaginalis* organism is isolated from the genital tract during pregnancy, this condition should be energetically treated.

CERVICAL INCOMPETENCE

Elaboration of cervical incompetence as a cause of abortions, is not necessary. At this clinic, Shirodkar sutures are inserted either electively on the past history of the previous abortions, or on the vaginal findings during the present pregnancy. When a suture is indicated it is put in as a matter of urgency, either the same day, or at the latest, the following day.

VAGINAL CYTOLOGY

Again, the use of vaginal cytology in assessing the well-being of early pregnancy needs no further elaboration. Apart from the use of progestogens administered where indicated, this clinic has, in selected cases, used human chorionic gonadotrophins.

GLUCOSE TOLERANCE TEST

Each patient has a glucose tolerance test as a routine, and, in a few cases, abnormal results have been obtained in patients not otherwise known to be diabetic.

LEUCOCYTE ALKALINE PHOSPHATASE

Placental dysfunction may be responsible for disturbances in foetal growth and for foetal loss. Clinical signs of placental dysfunction and hence foetal growth retardation, such as small amounts of liquor or 'small-for-dates' infants, are usually late signs of an affected pregnancy. Various laboratory tests of placental dysfunction are available. One of these, the leucocyte alkaline phosphatase estimation, can prove to be useful early in a pregnancy when assessing placental dysfunction.[8]

If peripheral smears of normal pregnant women are studied, it is noted that there is an increase in the immature granulocyte series, reaching a peak before term. Further studies indicate that there is a corresponding increase in the alkaline phosphatase as well, showing a similar distribution curve as the granulocytes, in that a peak is reached before term.[9] It is believed that the leucocyte alkaline phosphatase is under the influence of placental hormones. This suggests that leucocyte alkaline phosphatase actively reflects placental function, and therefore is of diagnostic value in predicting or assessing placental dysfunction and acting as a further yardstick in the monitoring of high risk pregnancies.

At the Reproductive Failure Clinic, the leucocyte alkaline phosphatase test is done as a 'booking investigation' only, and the relationship of leucocyte alkaline phosphatase levels at the time when the patient first booked at the clinic, and the outcome of the pregnancy, will be shown.

MATERIAL

All told, since the latter half of 1970 and until the end of 1971, 167 patients were referred. Of these 99 had delivered by the end of 1971, 43 were undelivered and 25 were referred, not pregnant. It is intended to discuss only the 99 high risk pregnancies who had delivered by the end of 1971 (Table I).

TABLE I. REPRODUCTIVE FAILURE CLINIC 1970 - 71

Total No. of patients referred	167
Delivered	99
Undelivered	43
Non-pregnant	25

Table II shows the analysis of this group. The late age of 29 years substantiates the desire of the group, with previous poor obstetrical history, for a successful outcome. Of the 102 live births delivered to these 99 women at the time of referral to the clinic, there were only 50 living children.

TABLE II. DELIVERED PATIENTS

Total	99
Mean age	29 years
Mean gestation referred	15 weeks
Past obstetrical history:	
Abortions	288
Stillbirths	22
Neonatal deaths	14
Delivered	102 (29 premature)
Alive at time of referral	50

RESULTS

Of the group of 99 pregnant women who booked at the clinic, 83% were delivered of live and healthy infants, and 17% were repeated reproductive failures. The mean birth weight of the successful pregnancies, which included 18 premature infants, was 3,09 kg.

TABLE III. +VE RESULTS IN GROUP OF 99 HIGH RISK PREGNANCIES

+ve Wassermann reaction	7
Marginal serum folate deficiency	20
+ve toxoplasmosis	27
Low PBI	8
+ve mycoplasma	17
+ve GTT	5
KPI >15%	5
Trichomonas + candida	15
Shirodkar sutures	32

Table III includes the positive investigations which were present in the group as a whole, i.e. the successes and the failures. It should be noted that positive results occurred more than once in a few patients.

The 17% of patients who were repeated reproductive failures, included 12 abortions, 3 neonatal deaths and 2 stillbirths.

TABLE IV. POSITIVE INVESTIGATIONS IN 12 ABORTIONS

+ve mycoplasma	2
+ve Wassermann reaction	2
Incompetent cervix	8
Low serum folates	3
↑ KPI	2
+ve toxoplasmosis	2
Severe trichomonas	1
Thyroid deficient	1

The positive investigations that occurred in the abortions are outlined in Table IV. Here again, it will be seen that double pathology existed in a few patients.

In the 3 neonatal deaths, 1 was a patient who delivered at 33 weeks' gestation, in spite of a Shirodkar suture; 1

delivered at 30 weeks' gestation, who had a Shirodkar suture and mycoplasma infection; the third patient delivered at 37 weeks' gestation. This infant, born to the last patient, developed hyaline membrane disease and shortly before death, mycoplasma organisms were cultured from the infant's upper respiratory tract.

The 2 stillbirths included 1 at 37 weeks' gestation, where the patient had been treated for a positive Wassermann reaction as well as a positive toxoplasmosis infection, and 1 at term, born with congenital abnormalities. This patient had been treated for positive toxoplasmosis, as well as for marginal serum folate deficiency.

It is interesting to note the results of the leucocyte alkaline phosphatase estimations. Fig. 1 includes only the leucocyte alkaline phosphatase values that fell below the lower line of normal. It will be seen that of these 4 low leucocyte alkaline phosphatase values, 1 continued to successful delivery, 1 aborted, 1 was a neonatal death and 1 a stillbirth. The stillbirth occurred in a patient who had a low alkaline phosphatase estimation when she booked at 24 weeks' gestation, and this was the stillbirth mentioned above, where the patient had a positive Wassermann reaction and a positive toxoplasmosis infection. The neonatal death was the one mentioned above, which occurred at 37 weeks' gestation; here the leucocyte alkaline phosphatase estimation was already abnormal when the patient booked at 17 weeks' gestation. The abortion occurred soon after 17 weeks' gestation, when the patient booked, and an abnormal leucocyte alkaline phosphatase score was found.

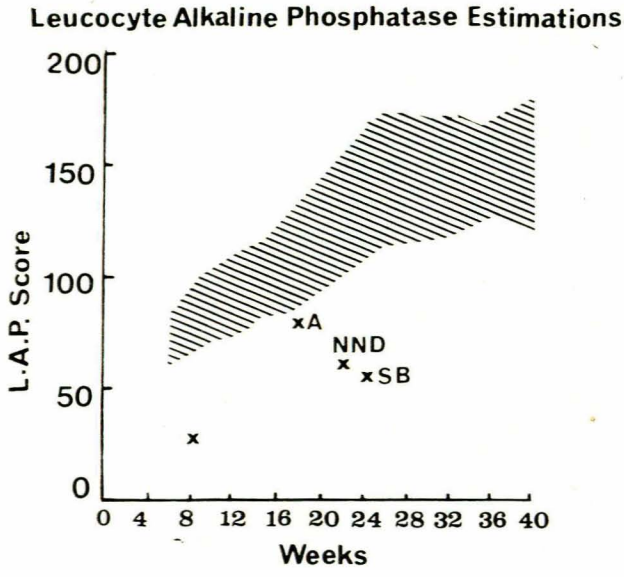

Fig. 1. Leucocyte alkaline phosphatase estimations.

It should be remembered that these leucocyte alkaline phosphatase estimations were done as booking tests only, but 3 out of the 4 abnormal tests at booking ended in reproductive failures, and 2 of these many weeks after the patients had booked at the clinic.

CONCLUSION

The Reproductive Failure Clinic sees 15 - 20 pregnant patients per week. These are women with poor past obstetrical histories who are desperately keen to achieve a successful outcome with their present pregnancies. The small number of women seen at the clinic, compared with the large routine antenatal clinics, enables one to work more closely with the patients and to do all these additional investigations. It is considered that the clinic is worth while, providing a platform for identifying diseases such as toxoplasmosis, mycoplasma and others, as aetiological factors in reproductive failure.

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REFERENCES

1. Chanarin, I., MacGibbon, B. M., O'Sullivan, W. J. and Mollin, D. L. (1959): Lancet, **2**, 634.
2. Hibbard, B. M. and Hibbard, E. D. (1963): *Ibid.*, **2**, 1430.
3. Te Groen, F. W. (1971): S. Afr. Med. J., **45**, 60.
4. Steytler, J. G. (1969): 'Mycoplasma in human umbilical cord blood: its isolation, identification, and characterization with reference to congenital mycoplasma infections', M.D. thesis, University of Stellenbosch.
5. Russel, K. P. (1953): Surg. Gynec. Obstet., **96**, 577.
6. Man, E. B., Heinemann, M., Johnson, C. E., Leary, D. C. and Peters, J. P. (1951): J. Clin. Invest., **30**, 137.
7. Wright, W. H. (1957): Amer. J. Clin. Path., **28**, 1.
8. Sadovsky, E., Diamant, Y. Z., Zuckerman, H., and Polishuk, W. Z. (1969): J. Obstet. Gynaec. Brit. Cwlth, **76**, 538.
9. Efrati, P., Presentey, B., Margalith, M. and Rozenzajn, L. (1964): Obstet. and Gynec., **23**, 429.