(1970) reported a series of six patients with angiographically-verified major pulmonary emboli treated with streptokinase. The two that died were distinguished from the survivors by a poor peripheral perfusion of the lungs. Our study supports this finding: six out of 10 patients with perfusion indices of 10 or more failed to complete the allocated trial therapy (fig. 3b). Cullum *et al.* (1972) found a broad relationship between the systemic systolic blood pressure and the angiographic index of severity. We also have found a tendency for hypotension and a high angiographic score to occur together. In this series a systemic systolic blood pressure of 100 mm Hg or less with an angiographic score of 24 or more was associated with a 70% chance of death or the need for pulmonary embolectomy (fig. 3). It is unfortunate, however, that by chance six of the seven patients within these limits had received heparin, and whether or not the outcome might have been different had streptokinase been used remains to be seen.

Paraskos *et al.* (1973) investigated the resolution of pulmonary emboli seven years after the initial episode. Of 43 subjects followed up by lung scan or at necropsy 28 showed complete resolution. The question still remains as to whether the initial accelerated thrombolysis by streptokinase is of value in terms of long-term resolution and survival. In our limited six-month follow-up study the five patients from the streptokinase group had lower scores than the two from the heparin group, but these numbers are too small for definitive answers.

Side effects of treatment with streptokinase were no more severe than those of heparin. This agrees with previous experience (Miller *et al.*, 1971). Though the trial protocol allowed for adjustment of the streptokinase dose if the fibrinogen titre fell to below 1 in 4 (in saline) this was never done. In our experience bleeding during streptokinase treatment tends to occur if the fibrinogen titre is very low in association with high levels of serum fibrin-fibrinogen related antigen. An indication of the latter can be obtained by repeating the fibrinogen titre estimation in the presence of protamine sulphate.

We believe that the current treatment of choice for most cases of acute life-threatening pulmonary embolism is streptokinase. However, the problem that faces every clinician in individual patients is that of selection for emergency embolectomy. It becomes increasingly difficult technically once anticoagulation, and more particularly thrombolytic therapy, has been initiated

and found to fail. The early allocation of cases for pulmonary embolectomy has obvious therapeutic advantages. We suggest that if the initial pulmonary angiographic score is 24 or more and the systemic systolic arterial blood pressure 100 mm Hg or less, then pulmonary embolectomy is probably the treatment of choice. A larger series would be needed to verify this statistically.

We would like to thank all of the staff in the participating hospitals who were involved in this study, particularly the numerous medical and technical staff of the cardiac laboratories. We thank all the physicians and surgeons who referred patients to us and Kabi Pharmaceuticals Limited for financial support and for supplying the streptokinase.

References

- Allington, M. J. (1971). *Scandinavian Journal of Haematology*, Suppl. No. 13, p. 389.
- Barritt, D. W., and Jordan, S. G. (1960). *Lancet*, 1, 1309.
- Chait, A., Summers, D., Krasnov, N., and Wechsler, B. M. (1967). *American Journal of Roentgenology*, 100, 364.
- Cross, F. S., and Mowlem, A. (1967). *Circulation*, 35, Suppl. No. 1, p. 86.
- Cullum, P. A., Kakkar, V. V., Macarthur, A. M., Oram, S., and Raftery, E. B. (1972). *Thrombo-embolism: Diagnosis and Treatment*, p. 212. Edinburgh, Churchill Livingstone.
- Dalen, J. E., *et al.* (1969). *New England Journal of Medicine*, 280, 1194.
- Fred, H. L., Lewis, M. J., and Alexander, J. K. (1966). *Journal of the American Medical Association*, 196, 1137.
- Gurewich, V., Thomas, D., Stein, M., and Wessler, S. (1963). *Circulation*, 27, 339.
- Hirsh, J., Hale, G. S., McDonald, I. G., McCarthy, R. A., and Pitt, A. (1968). *British Medical Journal*, 4, 729.
- Hirsh, J., McDonald, I. G., Hale, G. S., O'Sullivan, G. S., and Jelinek, V. M. (1970). *Cardiovascular Research, VI World Congress of Cardiology, Abstract of Papers*, p. 166. London, B.M.A.
- Hirsh, J., McDonald, I. G., Hale, G. A., O'Sullivan, E. F., and Jelinek, V. M. (1971). *Canadian Medical Journal*, 104, 488.
- Kakkar, V. V., and Raftery, E. B. (1970). *Lancet*, 2, 237.
- Miller, G. A. H. (1972). *British Journal of Surgery*, 59, 837.
- Miller, G. A. H., Sutton, G. C., Kerr, I. H., Gibson, R. V., and Honey, M. (1971). *British Medical Journal*, 2, 681.
- Paraskos, J. A., *et al.* (1973). *New England Journal of Medicine*, 289, 55.
- Robertson, J. D., and Reid, D. (1952). *Lancet*, 1, 940.
- Rosenberg, D. M. L., Pearle, C., and McNulty, J. (1964). *Journal of Thoracic and Cardiovascular Surgery*, 47, 1.
- Sharp, A. A., and Eggleston, M. J. (1963). *Journal of Clinical Pathology*, 16, 551.
- Thomas, D. P., Gurewich V., and Ashford, T. P. (1966). *New England Journal of Medicine*, 274, 953.
- Turnier, E., Kerth, W. J., and Gertode, F. (1973). *American Journal of Surgery*, 125, 611.
- Wilcox, W. C., *et al.* (1970). *Cardiovascular Research, VI World Congress of Cardiology, Abstracts of Papers*, p. 325. London, B.M.A.

Placental Lactogen Levels in Rhesus Isoimmunization

R. H. T. WARD, A. T. LETCHWORTH, P. A. R. NIVEN, T. CHARD

British Medical Journal, 1974, 1, 347-349

Summary

A prospective study of the plasma levels of human placental lactogen (HPL) in pregnancies complicated by rhesus isoimmunization showed that in mild and moder-

ately affected cases the levels were normal, while in severely affected cases they were raised. Serial levels of HPL before the 26th week provide a valuable indication of fetal outcome, and we suggest that this estimation should be used routinely as an adjunct to other tests in the management of rhesus isoimmunization.

Introduction

Attempts to determine the prognosis for the fetus in cases of rhesus isoimmunization rely heavily on serial determinations of bilirubin in the liquor amnii. Occasionally, however, incorrect predictions are made (Pridmore *et al.*, 1972) and an additional prognostic indicator would be desirable. The traditional endocrine tests of fetoplacental function, including determination of maternal urinary output of oestriol, pregnanediol, and chorionic gonadotrophin, are of little value (Fairweather *et al.*, 1972).

Department of Obstetrics and Gynaecology, University College Hospital Medical School, London WC1E 6JJ

R. H. T. WARD, M.R.C.O.G., Senior Lecturer

Department of Obstetrics and Gynaecology, St. Bartholomew's Hospital Medical College, London EC1A 7BE

A. T. LETCHWORTH, M.D., M.R.C.O.G., Lecturer

P. A. R. NIVEN, F.R.C.S., M.R.C.O.G., Senior Registrar

T. CHARD, M.D., M.R.C.O.G., Senior Lecturer

Results of Previous Studies on HPL Levels in Pregnancy complicated by Rhesus Isoimmunization

	HPL Levels	No. of Patients
Samaan <i>et al.</i> (1969)	Low or normal	20
Josimovich <i>et al.</i> (1969)	Normal or high	5
Genazzani <i>et al.</i> (1969)	High	1
Spellacy <i>et al.</i> (1970)	Normal	3
Singer <i>et al.</i> (1970)	High or normal	14
Josimovich <i>et al.</i> (1970)	Normal	26
Spellacy <i>et al.</i> (1971)	High	57
Genazzani <i>et al.</i> (1971)	High, normal, or low	14
Haour <i>et al.</i> (1971)	High, normal, or low	11
Varma <i>et al.</i> (1971)	High or normal	5

Several workers (see table) have studied blood concentrations of human placental lactogen (HPL) in rhesus isoimmunization; the consensus of opinion is that HPL levels are of little practical significance in this condition but the conclusions tend to be based on a few samples from a small number of patients. The present study was based on a large number of serial samples from 74 isoimmunized patients whose infants showed disease of varying severity.

Methods and Cases

A total of 303 maternal blood samples were obtained from 74 patients between the 21st and 37th weeks of pregnancy. Only the results from samples obtained before fetal death were included in the statistical analysis.

The 74 cases were divided into the following three groups: (a) 17 infants with mild disease—Coombs test result positive but exchange transfusions not needed (92 estimations); (b) 18 infants with moderate disease—Coombs test result positive and exchange transfusions required but criteria for severe disease not satisfied (57 estimations; there were two neonatal deaths in this group); and (c) 39 infants with severe disease (154 estimations), 22 of whom were delivered alive with a cord haemoglobin of less than 9 g/100 ml or a cord bilirubin of over 7 mg/100 ml, and 17 of whom were stillborn. Of the 22 infants alive at delivery in this last group eight died during the neonatal period. Also in this group intrauterine fetal transfusion was performed on one or more occasions in 24 pregnancies.

Blood HPL levels were estimated using a semiautomated radioimmunoassay (Letchworth *et al.*, 1971). The significance of the difference between means was assessed by Student's *t* test.

Results

In the mild and moderate groups the mean HPL levels did not differ from those of the normal pregnant population. In the severe group the levels were significantly raised ($P > 0.001$) (fig. 1), the highest levels being found in those pregnancies ending in perinatal death (fig. 2).

In 67% of the severe cases one or more levels were above the normal range—that is, more than 2 S.D.s above the normal mean—in contrast to 29% of the mild and moderate cases. Before 26 weeks this difference was even more striking; in 59% of the severe cases levels were above the normal, as against 10% of the mild and moderate cases. This difference is further emphasized when the results are analysed in relation to fetal survival. Of those cases with a favourable outcome in only 8% were the levels above the normal range before 26 weeks, as against 69% of those with an unfavourable outcome.

Discussion

This study was undertaken to answer three questions: (1) Do HPL levels in rhesus isoimmunization differ from those in normal pregnancy? (2) Do HPL levels relate to fetal outcome in those pregnancies in which the infant is severely affected? (3) Could HPL levels be used to identify at an early stage

FIG. 1—Mean HPL levels in pregnancies complicated by rhesus isoimmunization. Solid lines indicate normal range ± 2 S.D. ooooo Mildly affected cases. xxxxxx Moderately affected cases. — · — · Severely affected cases.

FIG. 2—Mean HPL levels in pregnancies complicated by severe rhesus isoimmunization. Solid lines indicate normal range ± 2 S.D. ooooo Cases in which the fetus survived. — · — · Cases in which fetus did not survive.

those patients in whom specialized treatment—for example, intrauterine transfusion—will be needed to prevent intrauterine death?

With respect to the first question, the results of this study showed high levels in severe cases, while those in the moderate and mild groups did not differ from those in the normal population. This finding agrees with some but not all of the previously published studies. As with diabetes (see Ursell *et al.*, 1973) raised levels in severe cases can probably be attributed to the enlarged placenta associated with rhesus isoimmunization. When the severe group was considered as a whole there was a difference between cases with a favourable outcome and those with an unfavourable one. In individual subjects, though, there was considerable overlap, and any prediction based solely on HPL levels is far from absolute.

The third question was answered in the affirmative. This is particularly important, since before the 26th week other values such as the liquor bilirubin level may be unreliable. On the basis of the present results a patient with isoimmunization who presents before the 26th week with a raised HPL level on one or

more occasions has a 9 in 10 chance of being delivered of a severely affected infant. At the same time it should be noted that about one-third of severe cases will be missed, so that HPL levels cannot be relied on as the sole diagnostic criterion. Nevertheless, when the simplicity and low cost of this test is taken into account there can be little doubt that serial levels of HPL are a valuable adjunct to other methods of diagnosis in rhesus isoimmunization.

The assays were supported by grants from the Medical Research Council and the Board of Governors of St. Bartholomew's Hospital and were performed by Miss Linda Howard. We are grateful to the medical and nursing staff of University College Hospital and St. Bartholomew's Hospital for their co-operation in this study, and to Professor D. V. I. Fairweather for his encouragement and advice.

References

Fairweather, D. V. I., Billewicz, W., Loraine, J. A., and Bell, E. T. (1972). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 79, 97.

Genazzani, A. R., Aubert, M. L., Casoli, M., Fioretti, P., and Felber, J. P. (1969). *Lancet*, 2, 1385.
 Genazzani, A. R., et al. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78, 577.
 Haour, F., Cohen, M., and Bertrand, J. (1971). *Revue Européenne d'Études Cliniques et Biologiques*, 16, 124.
 Josimovich, J. B., Kosor, B., and Mintz, D. H. (1969). *Foetal Autonomy*, ed. G. E. W. Wolstenholme and M. O'Connor. p. 117. London, Churchill.
 Josimovich, J. B., Kosor, B., Boccia, L., Mintz, D. H., and Hutchinson, D. L. (1970). *Obstetrics and Gynecology*, 36, 244.
 Letchworth, A. T., Boardman, R. J., Bristow, C., Landon, J., and Chard, T. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78, 542.
 Pridmore, B. R., Robertson, E. G., and Walker, W. (1972). *British Medical Journal*, 3, 136.
 Samaan, N. A., Bradbury, J. T., and Goplerud, C. P. (1969). *American Journal of Obstetrics and Gynecology*, 104, 781.
 Singer, W., Desjardins, P., and Friesen, H. G. (1970). *Obstetrics and Gynecology*, 36, 222.
 Spellacy, W. N., Teoh, E. S., and Bui, W. C. (1970). *Obstetrics and Gynecology*, 35, 685.
 Spellacy, W. N., Teoh, E. S., Bui, W. C., Birk, S. A., and McReady, S. A. (1971). *American Journal of Obstetrics and Gynaecology*, 109, 588.
 Ursell, W., Brudenell, M., and Chard, T. (1973). *British Medical Journal*, 2, 80.
 Varma, K., Driscoll, G. S., Emerson, K., and Selenkow, H. A. (1971). *American Journal of Obstetrics and Gynecology*, 38, 487.

Plasma Testosterone and Testosterone Binding Affinities in Men with Impotence, Oligospermia, Azoospermia, and Hypogonadism

DAPHNE M. LAWRENCE, G. I. M. SWYER

British Medical Journal, 1974, 1, 349-351

Summary

Mean plasma testosterone levels ($\pm$ S.D.), using Sephadex LH-20 and competitive protein binding, were 629 ± 160 ng/100 ml for a group of 27 normal adult men, 650 ± 205 ng/100 ml for 27 impotent men with normal secondary sex characteristics, 644 ± 178 ng/100 ml for 20 men with oligospermia, and 563 ± 125 ng/100 ml for 16 azoospermic men. None of these values differ significantly. For 21 men with clinical evidence of hypogonadism the mean plasma testosterone ($\pm$ S.D.), at 177 ± 122 ng/100 ml, differed significantly ($P < 0.001$) from that of the normal men.

The mean testosterone binding affinities (as measured by the reciprocal of the quantity of plasma needed to bind 50% of ^3H -testosterone tracer) were similar for normal, impotent, and oligospermic men. Though lower for azoospermic men the difference was not significant ($P > 0.1$). For 12 of the 16 hypogonadal males the testosterone binding affinity was normal, but raised binding affinities, similar to those found in normal adult females or prepubertal boys (about twice normal adult male levels), were found in four cases of delayed puberty. These findings help to explain why androgen therapy is usually useless in the treatment of impotence.

Introduction

It is common clinical practice to treat impotent men with androgen preparations either orally, by injection, or by implan-

tation but usually without noticeable clinical improvement. There appear to be few published data on plasma testosterone levels in impotent males, though there are reports that these men have a lower urinary testosterone excretion. Thus Ismail *et al.* (1970) compared 28 impotent men with 14 normal sexually active males and found the overall mean urinary testosterone excretion of the former to be significantly lower than that of the normal group ($P < 0.001$). Cooper *et al.* (1970) classified their impotent patients into predominantly psychogenic or predominantly constitutional groups and found the mean urinary testosterone of the latter group to be significantly lower ($P < 0.005$). Rosen and Weintraub (1971) reported on serum testosterone and luteinizing hormone concentration in idiopathic oligospermia and found a mean serum testosterone value of 560 ng/100 ml for 17 idiopathic oligospermic or azoospermic men aged 18 to 36. This was lower than the mean for normal men, 620 ng/100 ml, but the difference was not statistically significant ($P > 0.1$). The luteinizing hormone concentration was similar in both groups.

We have investigated the plasma testosterone concentration in normal and impotent men and in men with oligospermia and azoospermia, as well as in a group of men with clinical evidence of hypogonadism. We have also evaluated testosterone binding affinities in most of the subjects.

Subjects

The 27 normal men were hospital personnel aged 20 to 63 (mean 37 years), sexually active, and normospermic. Details of the 27 men with impotence aged 21 to 62 (mean 43 years) are given in the table.

The 20 men with oligospermia (sperm counts persistently less than 20 million/ml) aged 22 to 44 (mean 30 years) and the 18 men with azoospermia aged 25 to 34 (mean 29 years) had normal external genitalia and secondary sex characteristics on clinical examination. They were attending the fertility or endocrine clinics at University College Hospital. The group

Department of Obstetrics and Gynaecology, University College Hospital Medical School, London WC1E 6HX

DAPHNE M. LAWRENCE, B.Sc., PH.D., Senior Biochemist
 G. I. M. SWYER, D.M., F.R.C.P., Consultant Endocrinologist