PAPERS AND ORIGINALS

Comparison by Controlled Clinical Trial of Streptokinase and Heparin in Treatment of Life-threatening Pulmonary Embolism

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Summary

Treatment with heparin or streptokinase was allocated randomly to 30 patients with life-threatening pulmonary embolism verified by angiography. Treatment was given for 72 hours and pulmonary angiography was repeated. There was significantly greater ($P < 0.001$) evidence of thrombolysis in those patients treated with streptokinase compared with those treated with heparin. The reduction of systolic and mean pulmonary arterial pressures was also significantly greater ($P < 0.05$ and $P < 0.02$ respectively) in the streptokinase group.

Seven patients failed to complete 72 hours of the trial treatment: five successfully underwent pulmonary embolectomy. Six of these "failures" had initial pulmonary angiographic scores of 24 or more and systemic systolic blood pressure recordings of 100 mm Hg or less. Patients with these features should probably be considered for pulmonary embolectomy as the initial treatment.

A febrile reaction commonly occurred in the streptokinase group; otherwise side effects were no more common than in the heparin group.

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Introduction

Though pulmonary embolism is very common most patients either recover spontaneously or die before treatment can be given. There is, however, a small proportion who develop severe symptoms and signs, and a number of reports claim that streptokinase is superior to heparin in this situation (Hirsh *et al.*, 1968, 1970; Wilcox *et al.*, 1970; Hirsh *et al.*, 1971; Miller *et al.*, 1971). Because these studies were uncontrolled it seemed important to assess further the role of streptokinase by a comparative randomized, controlled trial. This report concerns such a study in which streptokinase and heparin were allocated at random to a group of 30 patients with life-threatening pulmonary embolism.

Patients and Methods

Selection of Patients.—Any patient presenting with features of acute or progressive life-threatening pulmonary embolism was considered for the trial. The following categories could be excluded from the trial at the discretion of the physician in charge: recent surgery, gastrointestinal disease, malignant hypertension, a recent cerebrovascular episode, pregnancy, or recent delivery.

Pretreatment Assessment.—The history and clinical features were recorded by the assessors. A 12-lead electrocardiogram and chest *x*-ray picture were recorded. Venous blood was drawn for the following estimations: full blood count, plasma thrombin clotting time (0·2 ml thrombin 25 U/ml in 0·025 M Ca Cl_2 (Diagnostic Reagents Ltd.) added to 0·5 ml platelet-free citrated plasma), fibrinogen titre (Sharp and Eggleton, 1963), protamine-sulphate titration of heparin (Sharp and Eggleton, 1963), fibrin-fibrinogen related antigen (Allington, 1971), blood group and serum glutamic oxaloacetic and

glutamic pyruvate transaminase, lactic dehydrogenase, and bilirubin.

Pulmonary Angiography and Haemodynamics.—Assessment of the severity of the embolus and progress after treatment were based mainly on information gained from pulmonary angiography. Accumulation of other data was regarded as subordinate and was carried out before angiography only if the condition of the patient allowed and in the following order of importance: right atrial, right ventricular, and pulmonary arterial phasic and mean pressure measurements; arteriovenous oxygen difference, arterial oxygen saturation, cardiac index calculated by the Fick principle from measurement of, or assumed, oxygen consumption (Robertson and Reid, 1952); total pulmonary resistance and brachial arterial oxygen and carbon-dioxide tensions, pH and bicarbonate estimations. Right heart catheterization was carried out by the standard method using a catheter (N.I.H. or Eppendorf) of maximum possible size up to No. 8 French gauge. After pulmonary angiography the tip of the catheter was left in the main pulmonary artery for infusion of treatment solution.

TABLE I—*Pretreatment Clinical Data*

	Heparin	Streptokinase
No. of patients	17	13
Males:females	11:6	4:9
Mean age in years (range)	47 (25-63)	51 (29-71)
Mean bodyweight in kg (range)	70·7 (45-123)	71·8 (45-107)
Surgery or trauma (accidental) in preceding four weeks	11	7
Bed rest during preceding four weeks	14	10
Cardiopulmonary disease	3	1
Carcinoma	1	0
Oral contraception	0	2
Pregnancy	0	1 (18 weeks)
Symptoms:		
Period of unconsciousness	3	2
Faintness	8	8
Chest pain	14	11
Breathlessness	14	13
Haemoptysis	4	2
Mean heart rate/min (range)	118 (96-140)	122 (96-150)
Mean blood pressure (mm Hg):		
Systolic (range)	106 (65-175)	110 (90-140)
Diastolic (range)	63 (*-100)	70 (40-80)
Cardiac dysrhythmia	0	2†
Right heart gallop	11	9
Deep venous thrombosis (clinical)	7	5
Other features:	Right hemiparesis (10 weeks previously)	Peripheral neuropathy
	Ulcerative colitis and diabetes mellitus	Brain-stem "stroke" (one week previously)
Mean haemoglobin, g/100 ml (range)	12·1 (10·0-15·0)	13·2 (8·9-15·3)
Time lapse (hours) massive embolism and beginning of treatment:		
0-6	0	1
7-12	6	1
13-24	5	5
25-72	5	4
>72	1 (6 days)	2 (7 and 17 days)

*Unrecordable.
†Atrial fibrillation in both.

TABLE III—*Side Effects of Treatment*

	Treatment	
	Heparin (n = 12)	Streptokinase (n = 11)
Allergic reaction	0	2
Temperature rise >1°C	3	8
Bleeding:		
Cut down sites	0	1*
Operation sites	2*	0
Other sites	2	3
Hb fall >1 g/100 ml	8	9

*One in each group required blood transfusion.

Assessment of Treatment.—Clinical features and complications were noted as shown in tables I and III. Where possible a daily electrocardiogram and chest *x*-ray picture were recorded. Haematological and biochemical investigations as listed above were carried out daily. The angiographic and haemodynamic studies were repeated at 72 hours, after which the cardiac catheter was removed. Six months later patients were reassessed clinically and, if the patient agreed, further pulmonary angiographic and haemodynamic studies were performed. All pulmonary angiographs were subsequently reviewed by two independent radiologists (M.L.T. and E.W.L.F.) who had no knowledge of the clinical state of the patients or the response to treatment. The method devised by Miller *et al.* (1971) was used to grade the severity of the pulmonary arterial occlusion. This system provides a score from zero to 34, made up of a maximum of 16 for the thrombus itself and 18 for peripheral perfusion as assessed by opacification of the peripheral vessels by contrast medium (perfusion index) (fig. 1).

Treatment Regimens.—Treatment with heparin or streptokinase (Kabikinase) was allocated according to random lists, each centre using a separate list. Because the physical characteristics of streptokinase in solution are easily recognized it was not possible to use a double-blind technique. A loading dose of 100 ml of normal saline or 5% glucose containing 600,000 units of streptokinase or 5,000 units heparin, each with 100 mg of hydrocortisone added, was infused through the catheter in the pulmonary artery over 30 minutes. This was followed by an hourly infusion of either 100,000 units of

TABLE II—*Mean Angiographic Score and Haemodynamic Variables (±1S.D.) before and after 72 Hours' Treatment. Figures in Parentheses are Numbers of Patients*

	Heparin		Streptokinase		Difference between Means before and after Treatment		P
					Heparin	Streptokinase	
Angiographic score							
Before	(12)	18·6 ± 5·7	(11)	21·9 ± 6·1	−2·8 ± 4·3	−13·3 ± 7·0	<0·001
After		15·8 ± 7·0		8·6 ± 5·9			
Right ventricular end-diastolic pressure (mm Hg)							
Before	(9)	10·4 ± 6·0	(10)	7·7 ± 4·3	−3·9 ± 3·6	−2·7 ± 4·8	>0·05
After		6·6 ± 7·6		5·1 ± 3·7			
Pulmonary arterial systolic pressure (mm Hg)							
Before	(11)	46·9 ± 14·1	(10)	46·2 ± 10·9	−3·8 ± 9·6	−15·4 ± 11·7	<0·05
After		43·1 ± 15·4		30·8 ± 8·6			
Mean pulmonary arterial pressure (mm Hg)							
Before	(9)	34·3 ± 10·5	(8)	30·8 ± 6·4	−4·8 ± 5·4	−12·3 ± 5·7	<0·02
After		29·6 ± 12·4		18·5 ± 5·9			
Arteriovenous oxygen difference (ml/100 ml)							
Before	(7)	8·8 ± 2·6	(7)	6·8 ± 1·5	−2·9 ± 3·0	−1·0 ± 1·5	>0·05
After		5·9 ± 1·0		5·7 ± 1·9			
Systemic arterial oxygen saturation (%)							
Before	(5)	85·2 ± 7·6	(7)	86·1 ± 3·4	+3·8 ± 4·7	+6·7 ± 4·0	>0·05
After		89·0 ± 5·5		92·9 ± 4·1			
Total pulmonary resistance (units/m²)							
Before	(6)	22·6 ± 8·9	(6)	15·0 ± 8·2	−8·3 ± 1·0	−8·0 ± 1·0	>0·05
After		14·3 ± 9·1		7·0 ± 5·3			
Cardiac index (l/min/m²)							
Before	(7)	1·5 ± 0·5	(6)	2·5 ± 1·4	+0·7 ± 0·6	+0·1 ± 0·1	>0·05
After		2·2 ± 0·6		2·6 ± 0·9			

This table includes only those cases in which data was collected both before and after treatment.

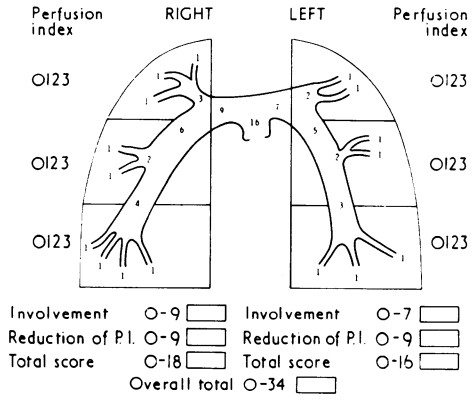

FIG. 1—Angiographic score chart: the right and left pulmonary arteries were regarded as having nine and seven major segmental branches respectively. Presence of a filling defect in any one of these branches scored one point. Presence of a filling defect proximal to segmental branches scored a value equal to number of segmental branches arising distally. Effect of embolism on opacification of peripheral vessels by contrast medium ("perfusion" index, P.I.) was scored for each of six lung zones: absent (3 points), severely reduced (2), mildly reduced (1), or normal (zero).

streptokinase or 2,500 units of heparin for 72 hours. At 60 hours from the start of the infusion warfarin was prescribed at an initial dose of 25 mg and continued with laboratory control for six months.

Control of Treatment.—Treatment was monitored by daily coagulation tests as follows: in patients treated with heparin if the protamine heparin titration exceeded 1·5 mg/100 ml the maintenance dose was reduced by 500 U/hr and the test repeated in six hours. In the streptokinase group if the observed fibrinogen titre (in saline) fell below 1 in 4 the dose of streptokinase could be increased by 50,000 U/hr and the test repeated in six hours. Subsequent oral anticoagulation was controlled by the one-stage prothrombin time, aiming for a prothrombin ratio (patient's time/control time) equivalent to 2·0-3·0 (British comparative ratio) using the British comparative thromboplastin.

Results

Thirty patients entered the trial, 21 at the Brompton Hospital (eight of these were from that part of an earlier trial (Miller *et al.*, 1971) conducted in the same way as the present one) and nine at the Radcliffe Infirmary. Twenty-three patients completed the 72 hours' trial regimen, 12 in the heparin group and 11 in the streptokinase group. The seven patients who failed to complete the trial regimen will be discussed below, but they have been excluded from the overall analysis of results. The ages and clinical features were similar in both treatment groups, but there were more men than women in the heparin group and more women than men in the streptokinase group (table I). The severity of illness, as judged by haemodynamic measurements and angiography, was similar in both groups (table II).

RESPONSE TO TREATMENT

The changes in the angiographic scores and haemodynamic measurements after 72 hours are shown in table II and fig. 2. Of the eight patients treated with heparin and who had an initial angiographic score of greater than 16, none had a score of less than 16 at 72 hours. In contrast, of the 10 patients in the streptokinase group with an initial score above 16, the score fell to below this figure in all except two. In addition, the angiographic appearances in four of the heparin-treated group showed no change or deteriorated. The mean angiographic score in the streptokinase-treated group fell by 61%, whereas the score in the heparin-treated group fell by only 15%.

Improvement during the 72 hours of treatment, assessed by the two group *t* test, was significantly greater in the streptokinase group for the angiographic score ($P < 0.001$), the pulmonary arterial systolic pressure ($P < 0.05$), and the mean pulmonary arterial pressure ($P < 0.02$) (fig. 2).

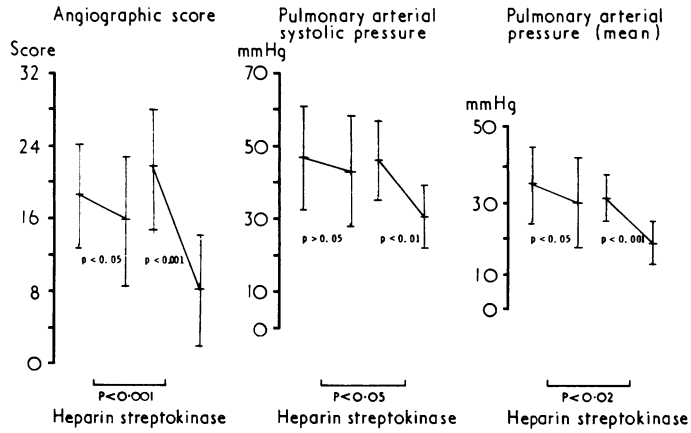

FIG. 2—Mean values (±1 S.D.) before and after 72 hours' treatment in respect of angiographic score, systolic, and mean pulmonary arterial pressures.

There appeared to be some improvement in all other haemodynamic measurements, but the changes in the two treatment groups were not significantly different. However, of the factors measured, only the angiographic data was collected in full in every case completing 72 hours of treatment. The haemodynamic measurements, especially at the initial assessment, tend to represent patients who were less ill and in whom it was thought safe to carry out the longer cardiac catherization procedure.

TRIAL FAILURES

Seven patients failed to complete 72 hours of the trial treatment. One patient having made satisfactory clinical progress suddenly died 18 hours after starting heparin treatment. The angiogram had shown complete occlusion of the right pulmonary artery. At necropsy there was fresh thrombus in the left pulmonary artery and it was concluded, therefore, that the patient had died from a second embolism. The clinical condition of the other six patients deteriorated, hypotension persisted, therefore they were withdrawn from the trial so that in accordance with the trial protocol alternative treatment could be in instituted. Pulmonary embolectomy, with cardiopulmonary bypass, was carried out on four patients (two from each group) and all made a satisfactory recovery. The treatment in two patients was changed from heparin to streptokinase: in one the angiographic score fell from 26·0 to 20·5 at 72 hours, but in the other the score rose from 24·0 to 27·0. This last patient subsequently underwent a successful pulmonary embolectomy. The main points of discrimination of these trial failures from the other patients were the high initial angiographic scores and the low systemic systolic blood pressures. All except one of the "failed" cases had an angiographic score of 24 or more and a systemic systolic blood pressure of 100 mm Hg or less. The relation between the initial angiographic scores and systemic systolic blood pressures of all patients entering the trial is shown in fig. 3. The dotted line separates all except one of the "failed" cases and only one of the successful group. There was a similar relation between the perfusion index and the systemic systolic blood pressure (fig. 3); the patients with poor opacification of

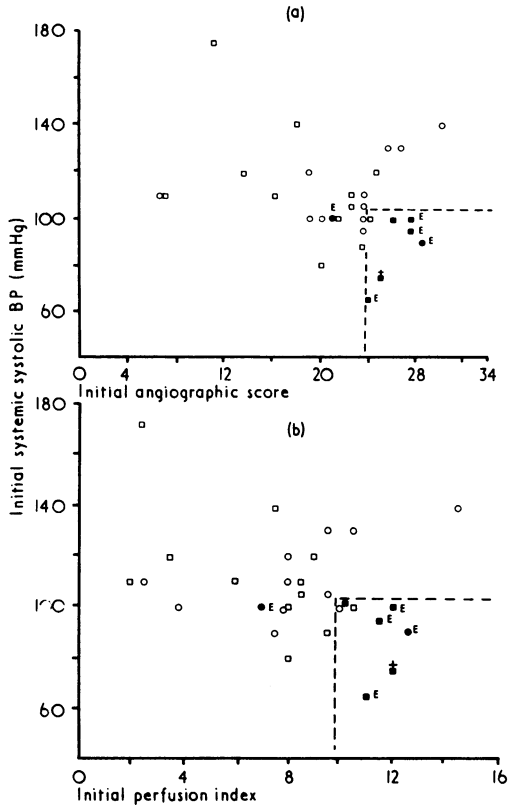

FIG. 3—Relation between initial systemic systolic blood pressure and angiographic scores. □ and ■ = heparin, O and ● = streptokinase, closed symbols represent patients failing to complete 72 hours' trial treatment. E = Underwent pulmonary embolectomy. + = Died. Dotted lines separate all cases with blood pressures of 100 mm Hg or less and angiographic scores of 24 or more, or a perfusion index of 10 or more.

peripheral vessels of the lungs had only a 40% chance of completing the trial schedule.

FOLLOW-UP AT SIX MONTHS

Eleven patients, four from the heparin group and seven from the streptokinase group, were followed up six months after treatment. Two patients, one from each treatment group, had dyspnoea on exertion but in both this was mild and in no way incapacitating. However, in one case pulmonary hypertension remained with a mean pulmonary arterial pressure of 40 mm Hg and an angiographic score of 16. A further patient from the streptokinase-treated group had a loud pulmonary valve closure sound. Seven patients agreed to have a third pulmonary angiogram carried out after the purpose of the study had been explained to them. Two had been treated with heparin and five with streptokinase. There was a tendency towards further improvement (fig. 4); unfortunately, the pulmonary arterial pressure data was not complete for all three examinations in each case.

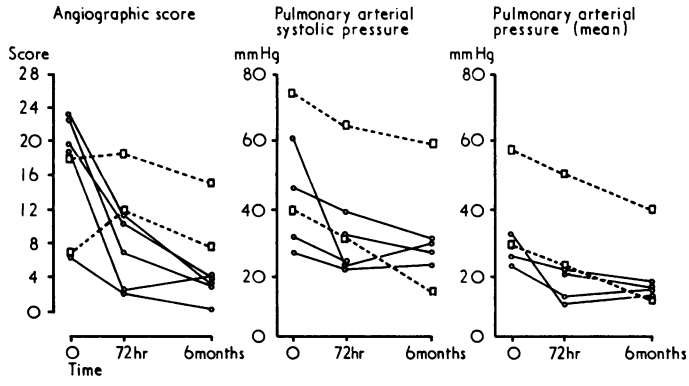

FIG. 4—Six-month follow-up studies. Angiographic scores and systolic and mean pulmonary arterial pressures. □ - - - □ Treated with heparin. O ——— O = Treated with streptokinase.

SIDE EFFECTS OF TREATMENT

Eighteen (78%) of the 23 patients completing 72 hours of the trial suffered one or more side effects (table III), 10 in the heparin group and eight in the streptokinase group. One patient became severely hypotensive with peripheral vasoconstriction during the loading dose of streptokinase; this responded well to additional intravenous hydrocortisone and chlorpheniramine. Another patient developed a widespread erythematous irritating rash on the third day of streptokinase treatment, which rapidly cleared within 48 hours. A rise in temperature was frequent in the streptokinase group. Bleeding was not a serious problem, though one patient in each group required blood transfusion.

Discussion

Treatment with heparin can be life-saving in acute massive pulmonary embolism (Barritt and Jordan, 1960) by preventing extension of thrombus and recurrent embolism and perhaps also by minimizing the release of vasoactive agents from platelets adhering to the embolus (Gurewich *et al.*, 1963; Thomas *et al.*, 1966). Complete resolution of pulmonary emboli has been shown to occur with and without routine anticoagulation (Fred *et al.*, 1966) though such resolution may take several weeks (Chait *et al.*, 1967; Dalen *et al.*, 1969). Therefore, in assessing the value of a thrombolytic agent a controlled trial with accurate diagnosis by pulmonary angiography is essential. The results of the trial presented in this paper provide clear evidence that streptokinase is superior to heparin in the early clearance of pulmonary emboli and in the reduction of the pulmonary hypertension.

Of the patients dying as a consequence of pulmonary embolism about 50% are dead within two hours (Rosenberg *et al.*, 1964; Turnier *et al.*, 1973). All except one of the patients in this trial began treatment more than six hours after the major episode. They were, therefore, not representative of all cases with acute massive pulmonary embolus as by surviving this long they had selected themselves into a group carrying a relatively better prognosis. A trial including much larger numbers of subjects would be needed to show a significant difference based solely on mortality between heparin and streptokinase treatment.

Clinical deterioration, as in the present study, often leads to surgical treatment. Pulmonary embolectomy with cardiopulmonary bypass still carries a significant mortality though this is gradually being reduced. Cross and Mowlem (1967) and Turnier *et al.* (1973) reported operative mortalities of 57% and 29% respectively. The operative mortality at the Brompton Hospital from 1968 to 1971 was 23% in patients undergoing pulmonary embolectomy as the initial treatment (Miller, 1972). A lytic agent that would reduce the need for pulmonary embolectomy would be of great value. Hirsh *et al.* (1968) reported on 18 patients who had major pulmonary embolism "severe enough to be considered for pulmonary embolectomy." All were treated with streptokinase and heparin combined and only two required pulmonary embolectomy. Miller *et al.* (1971) treated 11* similar patients with streptokinase and only one deteriorated so as to need surgical treatment. However, the selection of the patient for pulmonary embolectomy is rarely a simple matter. Kakkar and Raftery

*Excludes four cases incorporated into this series.

(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.

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Placental Lactogen Levels in Rhesus Isoimmunization

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Summary

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

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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).