varicose veins in seven. Most patients had relatively normal-looking legs apart from some swelling. It must be emphasized that the primary purpose in the treatment of these patients is to relieve pain. The appearance of the leg is of secondary importance. Successful operative relief of venous obstruction results in the relief of "venous claudication" (Cockett, 1967), and, though swelling of the leg is usually little if at all affected, patients are well satisfied to be rid of the intractable and incapacitating pain.

The mechanism of "venous claudication" remains obscure. The results of these investigations do not indicate distension of the vein wall as a likely cause, nor does ischaemia of the calf muscle seem responsible. Other possible underlying causes for the pain are that it is either the result of increased pressure or that it results from the accumulation of tissue metabolites in the presence of venous obstruction. No investigation of these possibilities has so far been undertaken.

Though the mechanism by which calf pain is produced remains unknown, the present study shows that this pain is confined to patients in whom post-thrombotic damage to the veins of the lower limb has resulted in occlusion or stenosis sufficient to cause functional obstruction to venous return. Those patients whose post-thrombotic damage consisted only of incompetence of the peripheral deep veins did not experience this severe and incapacitating pain.

Summary

The clinical features of 27 patients with post-thrombotic obstruction to the iliac veins or inferior vena cava, compared with those of 17 patients with post-thrombotic incompetence of the peripheral deep veins alone, have shown that the chief dis-

tinguishing feature is calf pain on exercise, which occurs in patients with iliac venous obstruction.

The pain, "venous claudication," is usually severe enough to interfere with work and leisure activities, and usually constitutes a greater disability than varices, swelling, or ulceration.

The mechanism of pain production is obscure. There is no evidence that venous distension or muscle ischaemia is responsible.

A patient with the "post-phlebotic syndrome" who can mark time briskly for five minutes is unlikely to have significant obstruction to venous return.

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Preliminary Communications

Urinary Oestriol after Intra-amniotic Injection of Oestriol Sulphate

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It is now agreed that the foetus, as well as the placenta, plays a part in the biogenesis of the large amounts of oestriol excreted in the mother's urine during pregnancy. In the foetal circulation and liquor amnii the oestriol is largely present as oestriol sulphate (Diczfalusy *et al.*, 1961a, 1961b, 1961c). In the placenta and maternal urine, on the other hand, the main conjugates are oestriol glucosiduronates. It is likely that desulphurylation and rejugation as glucosiduronate are involved in the process whereby oestriol finds its way from the foetal compartment to the maternal urine. Studies of placental enzymology show it is probable that a considerable part of this takes place in the placenta.

We have been exploring the possibility that a sudden load on this transfer system in late pregnancy may constitute a useful test of placental function. To this end, doses of 100 mg. of oestriol sulphate have been injected direct into the liquor amnii and the output of oestriol in the maternal urine examined. To our knowledge such pharmacological doses of oestriol have not been used before; the metabolic studies having been done in early pregnancy with tracer amounts of radioactive steroids. The experiments to determine the normal turnover of oestriol sulphate are still in progress, but the initial results appear to be of sufficient interest to warrant a preliminary communication.

PATIENTS

The study was carried out on five volunteers, all of whom were within a week on either side of their expected date of delivery. Four were multiparae, of whom two had a mild essential hypertension. The only primigravida and the remaining two multiparae were normal in all respects. All patients subsequently gave birth to normal live babies.

EXPERIMENTAL DESIGN AND METHODS

All the patients were admitted to a metabolic research unit and given a high fluid intake. Urine collections, in periods of four hours, were made for 40 to 48 hours before injection. The overnight collection periods were increased to eight hours. Duplicate oestriol assays were done on each four-hour specimen, the method of Klopper and Wilson (1962) being used. This made it possible to calculate the mean four-hourly oestriol output before injection. Uterine contractions, measured by external tocograph, were recorded at intervals, particularly in the last two to four hours before oestriol injection. A trans-abdominal amniocentesis was then done, and 100 mg. of oestriol sulphate dissolved in 10 ml. of sterile neutral distilled water was injected direct into the liquor amnii. After injection further recordings of uterine contractions were made, and the urine collections, in four-hour periods with eight-hour overnight collections, continued for a further 36 hours. The recovery of injected oestriol during any period was calculated by subtracting the mean preinjection value of the patient from the amount of urinary oestriol found in that period.

Effect of Intra-amniotic Oestriol Sulphate on Urinary Oestriol Excretion

Case No.	Mean $\pm$ S.D. Oestriol before Injection mg/4 Hours	Oestriol Excretion after Injection mg/4 Hours									Percentage of Injected Dose Recovered		
		0-4 Hours	4-8 Hours	8-12 Hours	12-16 Hours	16-20 Hours	20-24 Hours	24-28 Hours	28-32 Hours	32-36 Hours	In 12 Hours	In 24 Hours	In 36 Hours
1	8.91 $\pm$ 2.06	12.24	17.36	14.85	12.65	12.65	15.60	11.40	9.61	—	23.9%	43.2%	—
2	8.13 $\pm$ 1.57	9.48	12.30	11.79	9.55	9.55	9.64	10.46	11.82	15.61	12.4%	18.3%	36.6%
3	7.92 $\pm$ 1.48	10.04	10.84	8.28	10.40	10.40	14.22	9.60	7.26	9.92	8.0%	25.1%	27.5%
4	6.10 $\pm$ 1.33	8.91	11.50	14.15	14.15	7.40	8.14	8.81	8.70	7.8	21.9%	37.3%	46.9%
5	3.18 $\pm$ 0.95	8.69	5.53	7.23	7.23	6.72	5.80	3.96	3.23	3.68	16.1%	25.5%	31.7%

RESULTS

The findings are summarized in the Table. In the first 12 hours the recovery of administered steroid as urinary metabolite averaged 16.5% over all five patients. By 24 hours the average recovery rose to 29.9% and by 36 hours to 35.7%.

The pattern of urinary oestriol excretion after injection is shown in the Chart, which is a histogram of the average percentage of the total recovery at each period after injection. In every case the oestriol output rose above baseline levels in the first four hours after injection. On the average, 11.3% of the total recovery was excreted during this period. The peak excretion occurred at four to eight hours after injection, when 15.9% of the total recovery was excreted. Thereafter it fell away, but it rose again in the last four hours (32-36 hours) to 11.1% of the total recovery. No attempt was made to distinguish between various urinary oestriol conjugates, but it is tempting to suppose that the initial compound recovered was mainly oestriol-16-glucosiduronate and that the late rise was due to oestriol-3-sulphate, which is known to be more slowly excreted (Goebelsmann *et al.*, 1965).

Distribution in time of urinary oestriol recovered after intra-amniotic injection.

A change in uterine contractions after intra-amniotic injection of oestriol sulphate was noted. In every case increased activity was evident clinically some four to six hours after the injection, during the time of peak excretion. These observations were confirmed by the tocograph recording.

DISCUSSION

These findings show that when oestriol sulphate is injected into the liquor amnii a substantial part of the oestriol finds its way into the mother's urine within a short while. It may be that the rate of transmission, the proportion transmitted, or the nature of the compounds which appear in the urine will be affected by the state of the foeto-placental unit. We propose to test this hypothesis by examining the transmission in a large group of normal subjects and comparing these findings with

those in patients suffering from obstetric disease affecting the foeto-placental unit. The apparent association between oestriol administration and increased uterine activity was not altogether unexpected. The relation between urinary oestriol levels and the onset of labour first noted by Klopper and Billewicz (1963) has since been confirmed (Turnbull *et al.*, 1967).

In a recent experiment we gave repeated injections of oestriol sulphate into the liquor amnii and were able to effect delivery without any other form of uterine stimulation. In women at term rapid changes in myometrial activity are to be expected, and these experiments do not prove that the oestriol was the cause of the increased myometrial activity. This hypothesis will have to be tested in a trial specifically designed for the purpose. It would be a therapeutic advance if the onset of labour could be influenced by the administration of such a physiological compound. In our previous trial (Klopper and Dennis, 1962), we were concerned with the effect of oral administration of free oestriol on the onset of labour. It may be that the failure of oestriol to have any effect on that occasion was due to the fact that insufficient steroid or an inactive combination reached the myometrium and that manipulations of the endocrine environment of the myometrium from within the uterus may be more successful in imitating the natural course of events.

SUMMARY

The excretion of oestriol in the mother's urine after intra-amniotic injection of oestriol sulphate was determined. Some steroid finds its way into the urine within four hours of injection. The excretion reaches a peak by four to eight hours, and after 36 hours an average of 35.7% of the administered oestriol has been excreted. It was noted that myometrial activity increased after injection of the hormone.

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A. I. KLOPPER, M.D., PH.D., F.R.C.O.G.

K. J. DENNIS, F.R.C.S.ED., M.R.C.O.G.

V. FARR, M.D., D.C.H.

Clinical Research Unit, Department of Obstetrics and Gynaecology, University of Aberdeen.

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