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Decrease of serum oestriol during intravenous hexoprenaline or salbutamol treatment

M. HAUKKAMAA *The State Maternity Hospital, SF-00610 Helsinki 61, and Steroid Research Laboratory, Department of Medical Chemistry, University of Helsinki, SF-00170 Helsinki 17*
M. GUMMERUS *The State Maternity Hospital, SF-00610 Helsinki 61, Finland*

Summary. Patients with premature labour were treated with intravenous hexoprenaline (18 patients) or salbutamol (10 patients) infusion between 26 and 36 weeks gestation. After at least 12 h infusion, oral therapy was started. Serum total oestriol was determined by radioimmunoassay every 6 h during intravenous treatment, and then every day after stopping the infusion, for 4 days. The mean serum total oestriol concentration decreased significantly during the intravenous β-mimetic infusion ($P<0.005$). One day after stopping intravenous treatment, serum oestriol returned to pretreatment levels. The results show that fetal monitoring by maternal oestriol determinations is not reliable during intravenous β-adrenoceptor agonist therapy.

Treatment of premature uterine contractions by intravenous β-adrenoceptor agonist infusion is widely accepted in obstetric practice. Determination of plasma oestriol or urinary oestriol excretion still has its position in the assessment of fetoplacental function, although the importance of cardiotocography is increasing. It has previously been shown that urinary oestrogen excretion decreases during β-mimetic treatment (Jütting *et al.* 1975). The concentration of plasma oestradiol also decreases during such treatment (Turnbull 1977; Bibby *et al.* 1978; Ylikorkala *et al.* 1978; Schreyer *et al.* 1981). Previous studies of plasma oestriol and intravenous β-mimetic infusion have shown both significant (Schreyer *et al.* 1981) and non-significant (Ylikorkala *et al.* 1978) decreases of plasma oestriol levels. In a third report of only eight patients and a short 2-h infusion of isoxsuprine or terbutaline, no changes in serum free or total oestriol were observed (Bremme & Eneroth 1981).

The present study was designed to find out if fetal monitoring by maternal serum total oestriol determinations can be used reliably during and after intravenous hexoprenaline of salbutamol treatment, routinely used for the prevention of premature labour.

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Patients and methods

Patients

The patients included in the study were admitted to hospital at between 26 and 36 weeks gestation because of premature uterine contractions (Table 1); all had intact fetal membranes. The diagnosis of regular premature uterine contractions was confirmed by 30–60 min of external cardiotocography. An intravenous infusion of hexoprenaline

Table 1. Study patients. Results are means±SD

	Hexoprenaline (n=18)	Salbutamol (n=10)
Age (years)	30±6	27±4
Duration of pregnancy (weeks)	32·2±2·9	32·7±2·6
Infusion time (h)	15·5±8·8	15·6±6·2

(18 patients) or salbutamol (10 patients) was given to stop uterine activity. The patients did not receive corticosteroids. The dose of salbutamol varied between 6 and 42 μg/min and that of hexoprenaline between 0·10 and 0·35 μg/min. The infusion was continued for at least 12 h or until contractions stopped, after which oral therapy by tablets was started. The oral dose of salbutamol was 4 mg six times per day and that of hexoprenaline 0·5 mg six times per day. Intravenous treatment was begun at the time of admission to the hospital (Table 2).

Table 2. Time of admission to the hospital and beginning of β-mimetic infusion.

Time (hours)	No. of patients
24.00–04.00	8
04.00–08.00	0
08.00–12.00	4
12.00–16.00	4
16.00–20.00	5
20.00–24.00	7

Sample collection

Venous blood samples were collected before initiation of therapy and every 6 h until the infusion was stopped at 12 h or later, when the last sample during therapy was taken. The next samples were taken 1, 2, 3 and 4 days after stopping intravenous therapy, during oral therapy. The concentration of serum total oestriol was determined by radioimmunoassay (RIA) (Total oestriol E_3I^{125} radioimmunoassay kit, Farmos Diagnostica, Farmos Oy, PO Box 425, SF-20101 Turku 10, Finland).

The method includes hydrolysis of oestriol conjugates by β-D-glucuronide glucuronohydrolase and aryl-sulphate sulphohydrolase at 37°C for 2 h. Duplicate aliquots of the hydrolysed samples are analysed by RIA using ^{125}I-labelled oestriol as tracer. Bound and free steroids are separated by centrifugation at 2000 *g* for 15 min after addition of polyethylene glycol. The antiserum against oestriol has been produced by immunizing rabbits with a conjugate of oestriol-6-(O-carboxymethyl)-oxime and bovine serum albumin. The cross-reactivity of the antiserum with other oestrogens is negligible.

To control the effect of the intravenous infusion on the RIA method, five samples were taken from both the right and left antecubital veins of one patient. Serum oestriol concentrations were not affected by the arm used. The β-mimetics had no effect on the RIA when the drugs were added to analysed samples *in vitro*. The significance of the results was calculated by Student's *t*-test.

Results

The mean concentration of total serum oestriol decreased significantly during the intravenous β-adrenoceptor agonist treatment (Fig. 1). If the mean pretreatment value is taken as 100%, the mean levels during treatment were 75–80% ($P<0·005$). One day after stopping the infusion, serum oestriol had already increased to pretreatment levels and it stayed at the same level, 90–108%, for the next 3 days. However,

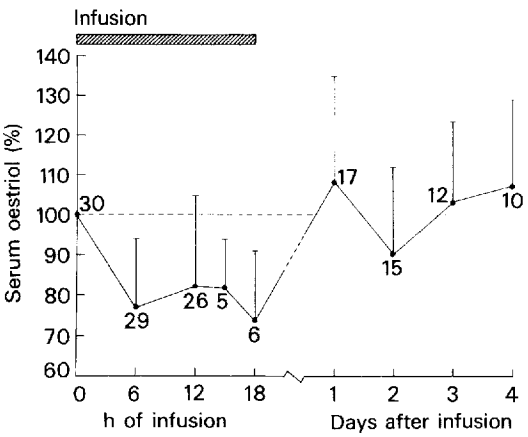

Fig. 1. Relative concentration of serum total oestriol during intravenous hexoprenaline and salbutamol infusion. The differences in concentration had the following significances: 0–6, 0–12, 0–15 and 0–18 h, $P<0·005$; 6–1, 6–3 and 6 h–4 days, $P<0·005$. Numbers refer to the number of samples analysed. Two patients were treated twice by intravenous β-mimetics during the same pregnancy.

individual variation was great and the serum total oestriol decrease was not significant in all subjects. The pattern of serum oestriol in one patient on salbutamol treatment is shown in Fig. 2. In this patient serum oestriol decreased by as much as 50–60% during the first 18 h intravenous treatment. Thereafter a slight increase was seen, even during intravenous therapy.

From these results, fetal monitoring by serum oestriol determination is not reliable during intravenous β-mimetic treatment but it can be used 1 day after cessation of treatment. The effects of hexoprenaline and salbutamol were

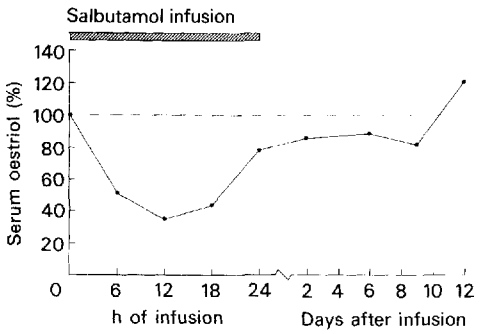

Fig. 2. Relative concentration of serum total oestriol of a patient with premature labour in the 33rd week of pregnancy. The dose of intravenous salbutamol was 12–30 μg/min. A female infant weighing 3270 g with an Apgar score of 9 was born in the 39th week.

similar and no clear-cut differences could be seen. The delivery of 24 (86%) patients was postponed by ⩾7 days and 19 (68%) of the 28 patients were delivered after the 37th completed week of pregnancy.

Discussion

Determination of maternal serum oestriol is a rapid and simple method of fetal monitoring and it has displaced the more laborious urinary oestriol methods in many hospitals. It is important to know if the concentration of serum oestriol is affected by the β-mimetic treatment of patients with premature labour. Ylikorkala *et al.* (1978) reported a non-significant decrease of plasma free oestriol during a 6-h infusion of ritodrine of isoxsuprine, but the doses of isoxsuprine (150–200 μg/min) and ritodrine (100–150 μg/min) were low when compared with the therapeutically efficient doses used for prevention of premature labour in our hospital (Gummerus 1977); isoxsuprine 150–400 μg/min and ritodrine 100–450 μg/min. The equipotent doses of salbutamol (6–24 μg/min) and hexoprenaline (0·10–0·35 μg/min) used in the present study are efficient at stopping premature uterine contractions. Sixty one per cent of patients on such treatment were delivered after the 37th week of pregnancy (Gummerus 1981). In another report plasma oestriol concentrations decreased significantly during intravenous ritodrine infusion at a dose of 200 μg/min for 3 h (Schreyer *et al.* 1981). Contradictory results have also been presented (Bremme & Eneroth 1981). The discrepancy in results might be because depression of maternal plasma oestriol may be seen only in cases where high doses of intravenous β-mimetics are given for periods of several hours, as is often done in clinical situations when preterm delivery is imminent.

The reason for the oestriol decrease is unknown. It cannot be explained by decreased activity of 16α-hydroxylase because both oestradiol (Turnbull 1977; Bibby *et al.* 1978; Ylikorkala *et al.* 1978; Schreyer *et al.* 1981) and oestriol were depressed. It might be explained by decreased placental aromatization of oestrogen precursors. The placenta is rich in β-adrenoceptors (Schocken *et al.* 1980) and many enzyme effects caused by β-adrenoceptor agonists are possible.

Information concerning a possible diurnal rhythm of plasma oestriol during pregnancy is contradictory. According to Patrick *et al.* (1979, 1980), a diurnal rhythm exists, whereas Wisser *et al.* (1979) hold that plasma oestriol samples can be taken at any time of day. The blood samples in the present study were taken randomly during both day and night. Thus it is obvious that the decrease of oestriol found does not reflect a diurnal rhythm. For ethical reasons all patients with premature labour were treated with β-mimetics without placebo controls.

We conclude that serum total oestriol concentrations were significantly depressed during intravenous β-adrenoceptor agonist therapy of premature uterine contractions. The decrease was reversible and 1 day after stopping intravenous infusion, during oral treatment, serum oestriol could be used for fetal monitoring.

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