Blood pressure regulation in third-trimester pregnant women receiving tocolytic terbutaline infusion

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Summary

Terbutaline (20 μg/min) was infused during 30 min in 17 women in whom a manual external manipulation of a breech presentation was going to be attempted. A significant increase in systolic (P = 0.003) and a decrease in diastolic blood pressure (P = 0.04) was noted at the end of the infusion but no change in mean arterial blood pressure was obtained. At the same time aldosterone serum levels had dropped significantly (P = 0.009) and plasma angiotensin II showed a marked increase (P < 0.001) which continued during the next 30 min. All changes were normalized after the infusion. The angiotensin-converting enzyme activity remained unchanged, as did vasopressin plasma levels. The combined results of terbutaline provocation have been interpreted to mean that blood pressure regulation in third-trimester pregnant women is similar to that in nonpregnant individuals. The increase in dehydroepiandrosterone sulphate (P < 0.05) noted at the end of infusion was suggested to be related to the blood pressure changes and was unrelated to fluctuations in serum cortisol. The latter steroid increased between 30 and 60 min, e.g. during the manual external manipulation, and was interpreted as being due to maternal stress.

Human third trimester pregnancy; Adrenergic β-receptor agonist; Terbutaline; Blood pressure; Aldosterone; Angiotensin II; Angiotensin-converting enzyme; Vasopressin; DHEA-Sulphate; Cortisol

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Introduction

Bricanyl® (terbutaline) has gained acceptance as a suitable drug to prevent premature labour [10,13]. However, some cardiovascular complications have been noted [2], and most adrenergic receptor agonists have been reported to increase blood pressure and pulse rate in pregnant women [15,18,20]. A terbutaline effect on blood pressure was suspected since we and others have reported that terbutaline caused marked changes in serum potassium in late pregnancy [4,7,17]. The present study deals with the question of how blood pressure changes following short term infusion of terbutaline may be regulated.

Materials and methods

Seventeen healthy women with otherwise uncomplicated pregnancies participated in the investigation and gave their consent to blood sampling. The study was approved by the Regional Ethical Committee. The patients were given terbutaline (Bricanyl®, Draco, Lund, Sweden) because a manual external manipulation of a breech position was going to be attempted [9]. The supine patients resting on their left side received terbutaline infusion with 100 ml glucose (0.1 g/ml) and 2 mg of Bricanyl® for 30 min at a rate of 1 ml/min. Thereafter a manual external manipulation was attempted under ultrasound control. This intervention was successful in 35% of the patients. Clinical data on the women and the newborn infants are given in Table I. As shown in the table, all women except two were nulliparae. All except one were delivered on term, but three children were small for date or slightly small for date. All children in breech presentation were delivered by cesarean section but one. One of the women in whom the manual external manipulation was successful was delivered by cesarean section because of asphyxia during labour.

Indwelling catheters were placed in each brachial vein, and the women underwent cardio-tocographic recording for 15 min before the infusion was started. Blood samples (10 ml each) were collected immediately before onset of β-receptor agonist infusion and at 30, 60, 90, 120 and 240 min into the experiments. After centrifugation, serum and heparin plasma were collected and stored at −20°C until used for analysis. All samples from each women were analyzed in the same assay. Maternal blood pressure and pulse rate were registered twice at the same time as the blood sampling. The blood pressure was measured in the left arm with a calibrated air-cuffed manometer and a mercury sphygmomanometer. Pulse rates were determined by palpation.

Chemical determinations

Blood hormone levels were determined by radioimmunoassay kits from Bühlman Laboratories, CH-4024 Basel, Switzerland (angiotensin II, vasopressin), Diagnostic Products Corporation, Los Angeles, CA, USA (aldosterone, cortisol), and BioMérieux, Marcy-l’Etoile, Charbonnieres-les-Bains, France (dehydroepiandrosterone sulphate, DHEA-SO₄) according to the instructions of the respective manufacturer. Except for the DHEA-SO₄ assay, which showed an approximate 80%
TABLE I
Clinical data on mothers and infants
MEM, manual external manipulation of breech position; PN, partus normalis; CS, cesarean section; 
SFD, small for date; SSFD, slightly small for date.

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crossreaction with dehydroepiandrosterone, and the angiotensin II assay, which was 
equally sensitive to angiotensin III, the other assays did not show significant 
crossreactions with related compounds. Intraassay coefficient of variation and 
interassay coefficient of variation for all assays were below 10 and 20%, respectively. 
These calculations were based on results obtained by analysing a pregnancy serum 
or plasma pool ten times in duplicate in one assay. This was repeated at least seven 
times to allow calculation of interassay coefficient of variation in the determination 
of each compound.

Statistical evaluation

Student's t-statistics were used to test correlation coefficients and differences 
between means. Correlation coefficients (Pearson) were used to compare relationships between variables over time.

Results

With the comparatively high dose of terbutaline used (i.e. 20 µg/min), a 
significant (P = 0.003; t = -3.60) increase in systolic blood pressure was registered 
30 min into therapy. A simultaneous decrease (P = 0.04; t = 2.23) in diastolic blood 
pressure was found (Fig. 1). These pressure changes returned to the pretreatment 
values 90 min after withdrawal of the infusion, e.g. 120 min into the experiment 
(Fig. 1). However, mean arterial blood pressure did not change significantly during
the whole experimental period (range from start to end of experiment: 81–92 mmHg). The pulse rate was increased ($P < 0.001$) during the first 30 min of infusion and an elevated pulse rate was maintained throughout the experimental period (cf. Bremme et al. [5]). There was also a concominant 25% decrease ($P < 0.001$) in serum potassium concentration with a mean nadir (2.7 nmol/l) at 60 min. At the end of the terbutaline treatment, e.g. 30 min into the experiment, serum aldosterone concentrations had dropped significantly ($P = 0.009; t = 2.98$) but were back at basal levels 120 min into the experiment (Fig. 2). Angiotensin II showed a marked
increase ($P < 0.001; t = -4.96$) which continued between 30 and 60 min into the experiment. A sustained elevation of angiotensin II levels was still observed at 120 min but at 240 min basal levels were approached (Fig. 2). Angiotensin-converting enzyme activity remained unchanged throughout the experiment. Thus the initial mean value before treatment was $24.6 \pm 3.8$ units ACE/min/l. The corresponding
values at 30, 60, 120 and 240 min were $30.3 \pm 6.1$, $29.0 \pm 3.5$ and $30.0 \pm 4.1$ units, respectively.

In half of the patients plasma vasopressin was determined. The mean value at the onset of terbutaline infusion was 5.5 pg/ml (range 3.4–8.7; $n = 7$) and blood samples from the different times of terbutaline infusion did not contain concentrations of vasopressin that were significantly different from the initial values.

Fig. 3. Changes in serum concentrations of cortisol and dehydroepiandrosterone sulphate after terbutaline infusion (20 µg/min) for 30 min. Values are means ± SE. Asterisks denote significance of changes from basal value: * $P < 0.05$. 
Dehydroepiandrosterone sulphate in serum increased during the treatment period and then remained unchanged \((P < 0.05; \text{Wilcoxon matched pairs signed rank test})\) (Fig. 3). Serum cortisol, on the other hand, showed an increase right after the interruption of the infusion \((P < 0.05)\) (Fig. 3), which coincided with the attempts to correct the breech position. The elevated cortisol concentrations then returned to baseline levels (Fig. 3).

**Discussion**

In accordance with previous reports \([6,18]\) on terbutaline in pregnant women the systolic blood pressure increased and the diastolic pressure decreased without a change in mean arterial pressure during the entire experimental period. Since the pulse rate was accelerated \([5]\) the mean cardiac output must have increased, possibly to the benefit of the fetus. Mean arterial blood pressure does not appear to be the factor triggering the change in serum aldosterone and angiotensin II levels. Since adrenaline stimulates plasma renin activity and hence formation of angiotensin I and II \([8]\) stimulation of aldosterone secretion takes place. Terbutaline seems to mimic this adrenaline effect, since angiotensin II increased after the infusion. The angiotensin II assay is equally sensitive to angiotensin III but not to angiotensin I. Thus, the measurement still estimates the formation of angiotensin II. Since the angiotensin-converting enzyme activity remained unchanged the likely explanation for the angiotensin II increase is an enhanced plasma renin activity \([8]\). Thus, these blood pressure regulating compounds in the third trimester of pregnancy seem to operate as in nonpregnant women. An impaired function of the renin-aldosterone system in pregnancy has been claimed \([19]\) and contradicted \([1]\). However, as most recently pointed out by Karlberg and co-workers \([11]\), the mismatch between serum aldosterone turnover rates, plasma renin activity and blood pressure in pregnancy remains unexplained. It may, however, be suggested that aldosterone binding to serum proteins is increased \([14]\) and that cellular receptivity to aldosterone is decreased \([12]\).

The lowering of serum magnesium previously noted \([5]\) 90 min after interrupting the terbutaline infusion, i.e. 120 min into the experiment, may be a delayed reaction secondary to the initial aldosterone drop \([8]\). Alternatively, an enhanced renin release may indicate an increased PTH activity which in turn might affect serum magnesium \([8]\). However, whether or not \(\beta\)-adrenergic agonists cause an enhanced PTH release is not known.

Whether a stress-induced endogenous release of catecholamines took place during the terbutaline infusion cannot be decided, but the changes we observed in cortisol were likely related to stress experienced by the women who underwent manual external manipulation of a breech presentation. The increase in dehydroepiandrosterone sulphate at the end of infusion when the systolic blood pressure was at its peak level is interesting, since elevated blood levels of this steroid have been reported in hypertensive states \([16]\). The possibility that the increase in DHEA-SO\(_{4}\) reflected fetal distress seems less likely, since we have previously shown that terbutaline therapy does not change maternal serum levels of estriol \([3]\).
Acknowledgements

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References

17 Smythe AR, Sakakini J. Maternal metabolic alterations secondary to terbutaline therapy for prema-