# Plasma oxytocin during third stage of labour: comparison of natural and active management

S Thornton, J M Davison, P H Baylis

## Abstract

**The incidences of postpartum haemorrhage and retained placenta have decreased with the use of synthetic oxytocin and controlled cord traction. Whether such treatment is valuable is open to question because of the lack of clinical and physiological studies. The physiological effects of synthetic oxytocin on plasma concentrations of oxytocin and events during delivery were assessed. Plasma oxytocin concentration was determined in serial samples during the late second stage and throughout the third stage of labour in 25 women. Ten women received combined ergotamine and synthetic oxytocin intramuscularly and 15 were not treated. The geometric mean plasma oxytocin concentration significantly increased in the women given oxytocin when measured before and after delivery of the fetal anterior shoulder (3·1 (SD 2·0) pmol/l before and 15·9 (2·7) pmol/l after). Six of the women who did not receive treatment showed a significant increase in geometric mean plasma oxytocin concentration before and after delivery of the fetal shoulder (3·2 (2·0) pmol/l before and 6·4 (2·0) pmol/l after) and nine did not show an increase (geometric mean 2·4 (3·1) pmol/l before and 2·2 (2·2) pmol/l after). Of these nine women, two had an abnormal third stage of delivery; one woman had a postpartum haemorrhage and one required manual removal of the placenta.**

**As it is impossible to predict which women will show a rise in the plasma concentration of endogenous oxytocin, intramuscular oxytocin should be given routinely.**

## Introduction

Postpartum haemorrhage and retained placenta are the most common serious abnormalities encountered during the third stage of labour. The reduction in their incidence has been attributed to active management, consisting of routine administration of an oxytocic and controlled cord traction.[1] These techniques have, however, been criticised for two reasons: the regimens were introduced without proper clinical or physiological validation[2] and the incidence of problems during the third stage of labour decreased further after routine administration of an oxytocic became widespread. Inch argued that, rather than active management being a logical progression, each intervention procedure represents a cascade of interventions leading to unforeseen effects that require further changes in management.[3,4]

The present conflict can be resolved only by undertaking both large prospective clinical trials of management and smaller studies aimed at elucidating the underlying physiological mechanisms of placental separation and delivery, in particular the role of endogenous oxytocin and the effect of an exogenous oxytocic.[5] The oxytocic is usually a combination of 500 μg ergometrine and 5 IU synthetic oxytocin (Syntometrine).[6] Although clinical trials are well under way,[2] reliable studies of the role of oxytocin in pregnancy have been few because of difficulties in measuring the hormone. Even with the development of a specific radioimmunoassay[7,8] studies have failed to provide information because oxytocin has been degraded by the enzyme oxytocinase before assay[9] and the pulsatile release of oxytocin that has been identified in animals[10,11] has not been fully investigated in humans.[12]

We have combined a technique of rapid serial sampling and immediate inhibition of oxytocinase activity[13] with a specific assay system to measure plasma oxytocin concentrations in women managed with and without combined ergometrine and synthetic oxytocin during the late second stage and throughout the third stage of labour. We report our results.

## Patients and methods

Approval was granted by the ethical committee of Newcastle Health Authority. Sixty five women who had an uncomplicated pregnancy were recruited from the antenatal clinic at 32-36 weeks' gestation and allocated alternately to one of the two management regimens. Of these 65 women, 25 ultimately met the criteria for inclusion in the study—that is, spontaneous onset of labour at term without subsequent augmentation followed by a normal delivery.

Ten women received intramuscular oxytocin on delivery of the fetal anterior shoulder and 15 did not. In all 25 women the umbilical cord was clamped immediately, and when possible the placenta was delivered by controlled cord traction (modified Brandt-Andrews technique).[4,14,15] Women managed by routine active methods could thus be compared with those in whom oxytocin was not given.

A 19 gauge indwelling intravenous cannula was inserted into a forearm vein before delivery, and samples of blood (4 ml) were collected every 30 seconds for 15 minutes, starting at crowning of the fetal head. The sampling strategy was designed to permit determination of rapid fluctuations in plasma oxytocin concentration in addition to meeting technical and ethical demands.[16] Each sample was taken into a chilled syringe containing 40 μl of the oxytocinase inhibitors 1,10-phenanthrolene (125 mmol/l) and edetic acid (1 mol/l)[16] and then immediately transferred to a chilled tube containing lithium heparin. Samples were stored on ice and extracted within one hour after collection. Plasma (2 ml) was extracted by an activated magnesium silicate acetone technique[16-18] and stored at −20°C before measurement of oxytocin by solid phase radioimmunoassay within four weeks after collection. All samples from each woman were assayed in triplicate in the same assay. Details of the radioimmunoassay of oxytocin and its characteristics (which are not influenced by ergometrine) have been reported elsewhere.[16,19]

Unless otherwise stated, results are expressed as the geometric mean (SD) plasma oxytocin concentration. Results were analysed by Student's unpaired or paired *t* test. The data were logarithmically transformed because the standard deviation increased with the mean plasma oxytocin concentration.

## Results

The women managed with and without synthetic oxytocin were comparable with respect to age, parity, length of gestation at delivery, length of labour, number of vaginal examinations during labour, and analgesia received (table). The mean plasma oxytocin concentration before delivery of the fetal anterior

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shoulder was not significantly different between the two groups (3·1 (2·0) *v* 2·7 (2·0) pmol/l, unpaired *t* test, 23 df, mean ratio 1·1; 95% confidence interval for mean ratio 0·6 to 2·4).

*Characteristics of women in study*

| | Women not given oxytocin (n=15) | Women given oxytocin (n=10) |
|---|---|---|
| Mean age (range) (years) | 30·6 (25-39) | 30·7 (19-39) |
| Range of parity | 0-4 | 0-5 |
| Mean (SD) length of gestation (days)* | 283 (7·0) | 282 (6·3) |
| Mean (SD) length of first stage of labour (h) | 5·4 (2·0) | 5·5 (2·3) |

*After last menstrual period.

WOMEN MANAGED WITH OXYTOCIN

All 10 women managed with oxytocin delivered the placenta during the 15 minute sampling period and showed a rapid increase in plasma oxytocin concentration after delivery of the fetal anterior shoulder, from 3·1 (2·0) pmol/l before to 15·9 (2·7) pmol/l (paired *t* test, 9 df, p<0·001, mean ratio 5·2; 95% confidence interval for mean ratio 2·6 to 10·2). The increase consistently occurred after delivery of the anterior shoulder and before delivery of the placenta. The mean peak plasma oxytocin concentration was 30·5 (2·5) pmol/l. Figure 1 shows the profile of the plasma oxytocin concentration in one of the women.

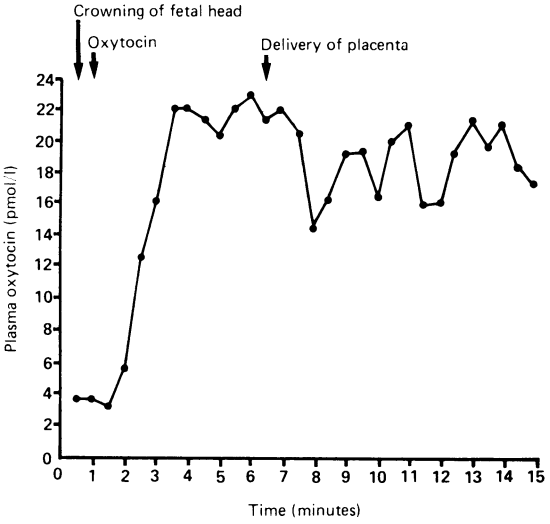


FIG 1—*Plasma oxytocin concentration during third stage of labour in one woman after intramuscular administration of synthetic oxytocin when fetal anterior shoulder delivered*

WOMEN MANAGED WITHOUT OXYTOCIN

Of the 15 women managed without oxytocin, nine delivered the placenta during the sampling time and four did not, although the placenta was delivered at the end of the study period after administration of oxytocin. The two remaining women had an abnormal third stage of labour; in one the placenta was removed manually and in the other a postpartum haemorrhage of 1200 ml occurred. Six of the women showed increased plasma concentrations of endogenous oxytocin. Figure 2 shows the concentration throughout the third stage of labour in one woman.

The plasma oxytocin concentration increased after delivery of the anterior shoulder, from 3·2 (2·0) pmol/l before to 6·4 (2·0) pmol/l (paired *t* test, 5 df, p<0·01, mean ratio 2·0; 95% confidence interval for mean ratio 1·4 to 2·8). The mean peak plasma oxytocin concentration was 11·6 (1·5) pmol/l. In nine women, including the two who had an abnormal third stage of

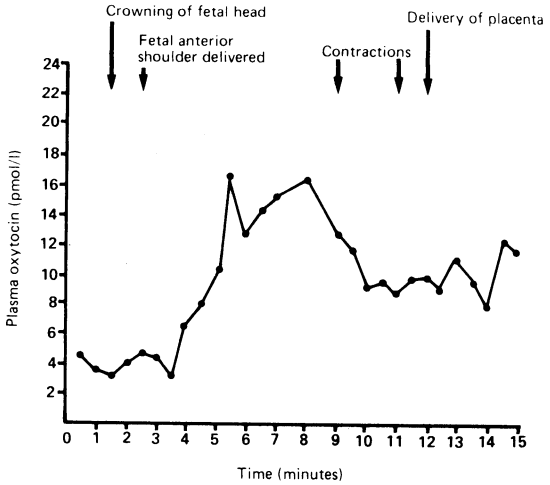


FIG 2—*Plasma oxytocin concentration during third stage of labour in one woman not given synthetic oxytocin*

labour, the plasma oxytocin concentration did not increase (mean concentration 2·4 (3·1) pmol/l before and 2·2 (2·2) pmol/l after delivery of the anterior shoulder).

The women whose plasma oxytocin concentration increased were similar to those in whom it did not with respect to age (30·3 (3·5) *v* 30·9 (4·2) years), parity, length of gestation at delivery (282 (8·0) *v* 283 (6·6) days), length of the first stage of labour (5·8 (3·4) *v* 5·1 (2·4) hours), and number of vaginal examinations during labour (2·0 (1·1) *v* 1·7 (0·5)) respectively.

## Discussion

The rate of attrition after allocation to the management regimen was high for various obstetric, personal, and technical reasons. Nevertheless, it is most unlikely that bias was introduced into the study. The profile of plasma oxytocin concentration in women given intramuscular oxytocin was remarkably similar to that observed in some of the untreated women, whose plasma concentrations of endogenous oxytocin increased. This was especially remarkable as the routine administration of oxytocin was introduced without adequate physiological validation. Indeed, if the observed increase is required to ensure a normal third stage of delivery it could be argued that a good physiological reason now exists for giving oxytocin routinely because it is not possible to predict which women will show a rise in the plasma concentration of endogenous oxytocin.

The results for the untreated women provide some evidence that a rise in plasma oxytocin concentration is required for a normal third stage of delivery: delivery of the placenta within the sampling time was more common in women whose plasma oxytocin concentration increased, and women who had an abnormal third stage did not show an increase in plasma oxytocin concentration.

It is reasonable to presume that the function of oxytocin in the third stage of delivery is to cause uterine contraction. Failure of the uterus to contract can have life threatening consequences, and such an important event is likely to have several mechanisms of control. This may explain why some women had a normal third stage without an increase in the plasma concentration of endogenous oxytocin.

The origin of the fluctuations in endogenous oxytocin cannot be determined from this study, but several observations suggest that the increase is due to increased release of oxytocin by the mother. Fetal oxytocin may contribute to the circulating maternal concentrations during the first and second stages of

labour[20] but is unlikely to cause a rapid increase in the third stage because the increase was delayed in some patients until after the umbilical cord had been clamped and cut. If the increase in oxytocin is maternal in origin it may be due to increased release from the posterior pituitary or a sudden reduction in metabolism. Suddenly reduced metabolism is perhaps unlikely because the placenta (the main source of oxytocinase) was removed after the increase in oxytocin concentration. The posterior pituitary is thus the likely source of the endogenous oxytocin; it is tempting to suggest that vaginal distension during delivery could cause the release of oxytocin as a result of the Ferguson reflex.[21]

In conclusion, in 40% of the women who did not receive oxytocin treatment plasma concentrations of endogenous oxytocin increased. The increase was similar to that that always occurs after intramuscular administration of synthetic oxytocin. As yet we cannot predict in which women the increase will occur; therefore, assuming that the increase is important in the natural third stage of delivery we advise that oxytocin should be given routinely.

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# Flosequinan in heart failure: acute haemodynamic and longer term symptomatic effects

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## Abstract

**There is no single, simple test with which to evaluate new treatments for heart failure. Various methods need to be used, and a study of both the acute haemodynamic and longer term symptomatic effects of flosequinan, a new direct acting arteriolar and venous vasodilator, was therefore carried out in patients with heart failure. In one group of patients flosequinan increased cardiac output and caused a fall in pulmonary capillary wedge pressure, both effects lasting for 24 hours. In a double blind, placebo controlled study in another group flosequinan improved mean exercise tolerance from 9·9 to 12·7 minutes after four weeks of treatment. The drug also reduced perceived exertion during submaximal exercise and increased calf and therefore skeletal muscle blood flow. It reduced plasma renin activity and noradrenaline concentrations.**

**Flosequinan possesses all the important properties of a drug likely to be of value in the treatment of heart failure.**

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## Introduction

Adding vasodilators to diuretics is now standard practice in the management of patients with severe heart failure in whom no surgically remediable cause is present. Not all vasodilators are effective, however, and the reason is not clear.

In acute heart failure vasodilators may increase cardiac output and reduce high pulmonary capillary wedge pressures, but in chronic heart failure these changes do not correlate with patients' symptoms.[1] In chronic heart failure exercise tolerance is related to limb and therefore skeletal muscle blood flow and vasodilators may be more important in improving skeletal muscle blood flow than in changing central haemodynamics.[2]

In chronic heart failure the renin-angiotensin and sympathetic nervous systems are often activated and both may further be activated by diuretics; this may limit the efficacy of these agents.[3] The angiotensin converting enzyme inhibitors partially reverse these neurohumoral changes, which may explain their long term symptomatic benefit.[4,5] Conversely, other vasodilators that stimulate the renin-angiotensin and sympathetic nervous systems may not produce long term benefit.[6]

Though angiotensin converting enzyme inhibitors are used routinely for treating severe heart failure, they are not ideal; some patients fail to respond and others develop undesirable side effects. New vasodilators are clearly needed but there is no simple way of evaluating them. Apart from vasodilator activity they must be