Plasma oxytocin during the first and second stages of spontaneous human labour

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A technique for complete oxytocinase inhibition has been combined with a rapid serial sampling strategy to determine plasma oxytocin concentrations in twelve women during the early and late first stage and in eight women throughout the second stage of labour. The progress of labour is not related to an increase in oxytocin concentration, uterine contractions are not associated with changes in plasma oxytocin concentration and hypocontractile labour does not appear to be the result of a deficit of oxytocin. The majority of patients do not demonstrate an increase in plasma oxytocin concentration during the second stage of labour; however, a minority produce a large surge immediately before delivery. The results do not support a role for oxytocin during spontaneous labour unless uterine activity is controlled by extremely low plasma hormone concentrations or the uterus becomes sensitive to a constant oxytocin concentration.

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The physiological mechanisms underlying the onset and progress of spontaneous labour remain obscure. Oxytocin is considered to be important, however, because exogenous administration results in uterine contractions which are clinically indistinguishable from those of spontaneous labour (1). Alcohol infusion may reduce both the frequency of contractions (2) and the plasma oxytocin concentration (3), and an increase in plasma hormone concentration has been reported from cross-sectional studies during labour (3-4). Nevertheless, the progress of spontaneous labour may not be related to changes in plasma oxytocin because not all studies have demonstrated an increase in its plasma concentrations (5-7) and labour progresses normally in patients with diabetes insipidus, although the complete absence of oxytocin in this condition has not been confirmed.

During the first stage of labour, determination of plasma oxytocin has produced widely differing results, usually attributed to the pulsatile release of the hormone (4-6, 8-10), similar to that documented during labour in animal studies (11). Many studies in human subjects, however, neglected to measure oxytocin serially throughout labour, which is mandatory if fluctuations are to be accurately documented. Most studies failed to document oxytocin fluctuations (7, 10, 12) although two (4, 13) have demonstrated increases in oxytocin concentration with individual contractions in some women.

During the second stage of labour, uterine contractions often increase in frequency and intensity, possibly due to an increase in plasma oxytocin resulting from the Ferguson reflex, whereby vaginal distension causes oxytocin release from the posterior pituitary. Determination of plasma oxytocin concentration in the second stage of labour has also produced conflicting results. Some authors report an increase (3, 7, 14-15), whereas others have failed to demonstrate a change (5-6, 16-18).

In addition to the inadequate sampling strategies used in many studies, another major methodological flaw has been the failure to recognize the significance of oxytocinase, a human placental cysteine aminopeptidase which rapidly degrades oxytocin in blood samples. Immediate oxytocinase inhibition at the time of venepuncture is crucial to prevent hormone loss and must be followed by extraction to prevent degradation of the components of the radioimmunoassay (RIA).

We have developed a rapid serial sampling strategy (19) which has been combined with complete oxytocinase inhibition, immediate sample extraction and a solid-phase RIA. The aim of the present study was to determine plasma oxytocin concentration in the same women in the early and late first stage of labour and in a separate group of women throughout the active second stage of labour.

Patients and methods

Twelve patients (age range 22-35 years) in the first stage and eight different patients (age range 25-32 years) in the second stage of labour were studied. All had an uneventful singleton pregnancy followed by the
spontaneous onset of labour at term. Labour was defined as regular palpable contractions at least every 5 min associated with cervical dilation.

Fetal heart rate was continuously monitored by ultrasound or a scalp electrode (Rolon, Watford, UK) and uterine contractions by an external pressure transducer (Sonicaid M3R, Sussex, UK).

Patients were recruited during pregnancy and included if the study criteria were met on admission to delivery suite. All gave informed consent and ethical approval was granted by Newcastle Health Authority. A 19 gauge indwelling intravenous cannula (Venflon, BOC, Helsingborg, Sweden) was inserted into a forearm vein 10 min prior to the studies, during which blood sampling was undertaken every minute. During the first stage study, samples (4 ml) were collected for 15 min at < 5 cm cervical dilation and again for 15 min at > 5 cm cervical dilation. A minority of patients (5/12) developed hypocontractile labour (and required exogenous oxytocin) after 5 cm cervical dilation in the first stage of labour. Samples were then taken during oxytocin infusion for the latter part of the first stage. During the second stage labour study, samples were collected from the onset of maternal effort until fetal delivery.

In order to prevent oxytocin degradation, each sample was taken into a chilled syringe containing 40 µl of the oxytocinase inhibitors 1,10 phenanthroline (125 mmol/l) and ethylenediaminetetra-acetic acid (EDTA: 1 mol/l). Plasma was separated in a pre-cooled (4°C) centrifuge at 2,800 g and extracted within an hour by a Florisil-acetone technique (13). Extracts were stored at −20°C prior to solid phase RIA within two weeks. The reference preparation was the 4th International Standard (79/575) from the National Institute for Biological Standards and Control, London. Each sample was assayed in triplicate and all samples from the same patient were measured in a single assay. The detection limit was 1.4 pmol/l, intra-assay coefficient of variation 9% and interassay coefficient of variation 14.8% at 10 pmol/l. Recovery of oxytocin from spiked plasma was 77% (N = 14) and 76% (N = 20) at 2 and 10 pmol/l respectively. No correction was made for extraction losses. Full details of the RIA of oxytocin and its characteristics have been reported elsewhere (20).

Statistics
In accordance with previous publications (21) samples containing undetectable concentrations of oxytocin (< 1.4 pmol/l) were assigned the value of 1.4 pmol/l. This represents the upper limit of the concentration of oxytocin which may be present since the true concentration is between 0 and 1.4 pmol/l. Consequently the calculated mean may be slightly higher than the true mean and is referred to as "the upper limit of the mean." Significance testing is inappropriate. For comparison with previous studies 2 pmol/l can be taken as 1 µU/ml oxytocin.

Results
Patient details are shown in Table 1. Of the blood samples taken, 68% in the first stage and 62% in the second stage had undetectable concentrations of oxytocin.

First stage of labour
Five of the 12 patients studied in the first stage required oxytocin augmentation for hypocontractile labour prior to the second series of samples. All five had clinically adequate uterine contractions during the early first stage and were not augmented until after 5 cm cervical dilation. Intravenous oxytocin was commenced at 4 mIU/min and increased at 15 min intervals until adequate uterine activity was achieved.

Individual contractions were not associated with fluctuations in plasma oxytocin concentration. Since there were no large fluctuations, results are shown as the upper limit of the mean for all patients who did and did not subsequently require augmentation. Plasma concentrations were remarkably similar during the early first stage but were greater during infusion during the late first stage in patients with hypocontractile labour (Fig. 1). In patients who did not require augmentation, the range of plasma concentrations was undetectable — 6.2 pmol/l and undetectable — 4.8 pmol/l, whereas the range in those who did require augmentation was undetectable — 4.6 pmol/l and undetectable — 10.0 pmol/l in the early and late first stage of labour, respectively.

Second stage of labour
Of the eight patients studied, six failed to demonstrate an increase in plasma oxytocin concentration. The profile from a single patient who failed to demonstrate an increase (in whom most of the samples contained more than 1.4 pmol/l) is shown in Fig. 2. The remaining two patients had a large increase in endogenous oxytocin.

The profile from one of these two patients is shown in Fig. 3. The duration of sampling was different in each patient, so it is inappropriate to show the upper limit of the mean for each time point. None of the patients studied during the second stage of labour required oxytocin augmentation.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>First stage (N = 12)</th>
<th>Second stage (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.9</td>
<td>28.9</td>
</tr>
<tr>
<td>Parity (range)</td>
<td>0–2</td>
<td>1–5</td>
</tr>
<tr>
<td>Weight at booking (kg)</td>
<td>69.8 ± 5.9</td>
<td>75.2 ± 9.2</td>
</tr>
<tr>
<td>Method of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal delivery</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Forceps</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Oxytocin during labour

The results of this study demonstrate that individual contractions do not coincide with fluctuations in plasma oxytocin concentration. Indeed, frequent contractions (sometimes each minute) during the late first or during the second stage are unlikely to be caused by rapid fluctuations in hormone concentration, since the half-life of oxytocin (22) (4.5 mins) would not permit removal of one surge of oxytocin before the next was released. Furthermore, the initiation of frequent contractions by oxytocin release from the posterior pituitary is theoretically unlikely because of the time taken for oxytocin to reach the uterus and its dilution in the circulation. Hypocontractile labour may be associated with a reduction in plasma oxytocin concentration (10). However, the similarity of the upper limit of the mean in augmented and spontaneous labour (Fig. 1) during the early first stage does not support this hypothesis. The upper limit of the mean was markedly higher in the late first stage during augmentation. This is surprising since, if hypocontractile labour is the result of a reduction in plasma oxytocin concentration, infusion would be expected to replace the deficit of hormone leading to

Discussion

Fig. 1. Plasma oxytocin concentration during the early (< 5 cm) and late (> 5 cm) first stage of labour. Open squares, no augmentation (N = 7); filled circles, augmented with exogenous oxytocin after 5 cm cervical dilation (N = 5). LD, limit of detection.

Fig. 2. Plasma oxytocin concentration during the second stage of labour in one woman who did not demonstrate an increase in concentration. LD, limit of detection.
normal concentrations. The high concentrations could be due to overstimulation of the uterus although uterine activity is reported to be normal in augmented labour (1). The increased plasma oxytocin concentrations during augmented labour may be required if hypoxic contractile labour is associated with fewer receptors for oxytocin.

A previous study (21), using identical methodology, demonstrated that 74% of samples taken at term (in patients who were not in labour) contained undetectable concentrations of oxytocin. The present results do not, therefore, support a role for oxytocin during the first stage of labour unless uterine activity is controlled by plasma concentrations below 1.4 pmol/l. This is most improbable since the physiological concentrations during the third stage of labour are much higher than the detection limit of this assay (20) and induction or augmentation of labour at term requires concentrations in excess of 1.4 pmol/l (23-24). Nevertheless, changes in oxytocin receptor number could modify uterine activity without an associated change in plasma hormone concentration. Indeed, an increase in receptor concentration has been documented during pregnancy and labour (25), the significance of which is controversial (26).

Many of the samples contained undetectable concentrations of oxytocin (<1.4 pmol/l). It is extremely unlikely that oxytocinase degradation of oxytocin occurred since all samples were collected into chilled syringes containing high concentrations of inhibitors and were extracted within 1 h. These techniques have been fully validated for oxytocin measurement in human pregnancy (13). Although 60% of samples (N = 59) from non-pregnant patients contained undetectable concentrations (range undetectable – 7.0 pmol/l) we have demonstrated increased plasma oxytocin concentrations in a proportion of patients during the third stage of labour (mean ± SD peak concentration 11.6 ± 1.5 pmol/l) (27) and during breast feeding (peak concentration 16.3 pmol/l) (unpublished observations). The methodology has thus been adequately validated and is sufficiently sensitive to identify increases in plasma oxytocin when there are high concentrations of plasma oxytocinase.

A marked increase in plasma oxytocin concentration during the second stage of labour only occurred in two of the eight patients studied, even though all eight had a normal delivery, implying that the increase is not a prerequisite for the normal progression of the second stage. The reason why only two patients demonstrated an increase is unclear, although it may represent an early increase in endogenous oxytocin which is known to occur in the third stage of labour in a proportion of patients (27). The source of any increase in oxytocin during the second stage cannot be determined but since it coincides with the time of maximal vaginal distension, it may be due to release from the posterior pituitary via the Ferguson reflex. Nevertheless, the majority of patients did not demonstrate an increase in plasma oxytocin. This suggests that the Ferguson reflex is not prominent during human labour.

Since our results demonstrate that the progress of labour is not related to changes in plasma oxytocin concentration, the function of oxytocin during labour must be questioned. There is no doubt that exogenous oxytocin causes contraction of the pregnant uterus yet contractions during spontaneous labour are not controlled by an increase in plasma oxytocin. The role of the oxytocin surge at the end of the second stage in some patients is also unclear, but it may cause a sustained uterine contraction following delivery in order to ensure haemostasis.

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References


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