Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour (Review)

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[Intervention Review]

Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour

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ABSTRACT

Background

Slow progress in the first stage of spontaneous labour is associated with an increased caesarean section rate and fetal and maternal morbidity. Oxytocin has long been advocated as a treatment for slow progress in labour but it is unclear to what extent it improves the outcomes for that labour and whether it actually reduces the caesarean section rate or maternal and fetal morbidity. This review will address the use of oxytocin and whether it improves the outcomes for women who are progressing slowly in labour compared to situations where it is not used or where its administration is delayed.

Objectives

To determine if the use of oxytocin for the treatment of slow progress in the first stage of spontaneous labour is associated with a reduction in the incidence of caesarean sections, or maternal and fetal morbidity compared to situations where it is not used or where its administration is delayed.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2011) and bibliographies of relevant papers.

Selection criteria

Randomised controlled trials which compared oxytocin with either placebo, no treatment or delayed oxytocin in the active stage of spontaneous labour in low-risk women at term.

Data collection and analysis

Two authors independently assessed studies for inclusion, assessed risk of bias and extracted data. We sought additional information from trial authors.

Main results

We included eight studies in the review involving a total of 1338 low-risk women in the first stage of spontaneous labour at term. Two comparisons were made; 1) the use of oxytocin versus placebo or no treatment (three trials); 2) the early use of oxytocin versus its delayed use (five trials). There were no significant differences in the rates of caesarean section or instrumental vaginal delivery in either comparison. Early use of oxytocin resulted in an increase in uterine hyperstimulation associated with fetal heart changes. However, the early use of oxytocin versus its delayed use resulted in no significant differences in a range of neonatal and maternal outcomes. Use of early oxytocin resulted in a statistically significant reduction in the mean duration in labour of approximately two hours but did not increase the normal delivery rate. There was significant heterogeneity for this analysis and we carried out a random-effects meta-analysis; however, all of the trials are strongly in the same direction so it is reasonable to conclude that this is the true effect. We also performed a random-effects meta-analysis for the four other analyses which showed substantial heterogeneity in the review.

Authors' conclusions

For women making slow progress in spontaneous labour, treatment with oxytocin as compared with no treatment or delayed oxytocin treatment did not result in any discernable difference in the number of caesarean sections performed. In addition there were no detectable adverse effects for mother or baby. The use of oxytocin was associated with a reduction in the time to delivery of approximately two hours which might be important to some women. However, if the primary goal of this treatment is to reduce caesarean section rates, then doctors and midwives may have to look for alternative options.

PLAIN LANGUAGE SUMMARY

The effect/use of the drug oxytocin as a treatment for slow progress in labour

Slow progress in the first stage of spontaneous labour may be caused by weak contractions of the womb. Doctors and midwives commonly give a drug called oxytocin with the aim of strengthening contractions and speeding up labour to avoid harm to both the mother and the newborn infant. The belief is that managing the labour in this way will enable progression to a normal vaginal delivery and reduce the need for caesarean section. However, others have been fearful that it has no effect on the type of delivery a woman might have and in other ways may do more harm than good. This review of eight studies, involving 1338 low-risk women in the first stage of spontaneous labour at term, showed that oxytocin did not reduce the need for caesarean sections. Neither did it reduce the need for forceps deliveries or increase the number of normal deliveries when compared with no treatment or delayed oxytocin treatment. Oxytocin seemed to shorten labour by nearly two hours on average. The uptake of epidurals was no different. It does not seem to cause harm to the mother or baby, but the sample size was too small to determine if its use has an effect on the death rates of babies. The decision whether to undergo this treatment is one that can reasonably be left to women to decide in the context of a reduction in the length of labour. The included trials used different doses of oxytocin, and different criteria for starting treatment in the delayed oxytocin arm.

BACKGROUND

Description of the condition

Slow progress in labour is commonly diagnosed by observing the rate of cervical dilatation once a woman has been confirmed to be in the first stage of active labour. A woman's labour progress can be pictorially represented on a partograms and alert lines can be used to highlight a woman who is progressing slowly (Lavender 2008). The actual definition, however, remains controversial. Initially O'Driscoll 1969 suggested that any nulliparous woman with a rate of cervical dilatation less than 1cm/hr should required treatment for slow progress. However, more recently a rate below 0.5 cm/hr is now taken as the threshold for treatment (NICE 2008). Studies to establish normal ranges for progress in natural labour (Albers 1999) are difficult to perform in modern practice because women agreeing to undergo natural labour are rarely representative of the population, and the labours of other women are frequently augmented or cut short by operative delivery. Occasionally, the

maternal pelvis is absolutely too small to allow the passage of the fetus, or the fetus is too big or in such a position that it cannot negotiate the pelvis. Such absolute disproportion is rare. More commonly, the cause is a mixture of moderate disproportion and poor uterine contractions (Gibb 1993).

Description of the intervention

Slow progress is commonly treated with an intravenous oxytocin infusion to increase the frequency, duration and strength of uterine contractions. This use of oxytocin for the augmentation of labour in nulliparous women was first popularised over 40 years ago as part of a package of care termed 'active management of labour' (O'Driscoll 1969; Sadler 2000).Various infusion protocols have been advocated and indeed a variety of such regimens are used by the trials in this review (Characteristics of included studies). However, all have the common feature of titrating the dose of oxytocin against uterine activity or labour progress.

How the intervention might work

Intravenous oxytocin infusions are used to augment uterine contractions in the belief that this will enable labour to progress to a normal vaginal delivery (Bugg 2006a). When given in low-dose intravenous infusions, oxytocin induces rhythmic uterine contractions which are indistinguishable in frequency, duration and strength from contractions observed during spontaneous labour (Fraser 1988; Phaneuf 2000). However it is important to remember that, at higher doses, oxytocin is capable of causing sustained tetanic uterine contractions, which would result in fetal death (Bremme 1980; Chia 1993; Liston 2002; Majoko 2001; Mathur 1968).

Why it is important to do this review

Slow progress in labour is associated with both maternal and fetal morbidity (Giles 1970; Hall 2001). In 2001, failure to progress, as a primary indication, contributed to 20% of the overall caesarean rate of 21% in England and Wales, and it was the primary indication for caesarean section in 35% of women with term cephalic pregnancies and no uterine scar (Thomas 2001). Improvements in the management of labours with slow progress might thus have an important impact on the overall number of caesarean sections performed. The use of oxytocin as part of packages of care to reduce operative delivery in those with slow progress in labour has been questioned (Thornton 1994). It does not seem to have the desired effect of normalising a woman's chance of having a normal delivery if she is progressing slowly in an otherwise uncomplicated labour (Bugg 2006a). Randomised trials are needed because many confounding variables associated with longer labours such as narcotic analgesia, ambulation, electronic fetal monitoring, advanced maternal age, nutrition, appropriate pain management, and one-to-one midwifery care complicate observational studies in this area (Fenwick 1987; Gagnon 1997; Scheepers 1998). Perhaps unsurprisingly, expert guidelines have given conflicting advice. In 2001, the authors of the National Sentinel Caesarean Section Audit suggested that all nulliparous women who have a caesarean section for failure to progress should have had a trial of oxytocin first (Thomas 2001). In 2004, the National Collaborating Centre for Women's and Children's Health clinical guideline on caesarean section recommended that augmentation with oxytocin should not be offered for slow progress because of lack of evidence of effectiveness (Nice 2004).

OBJECTIVES

To determine if the use of oxytocin for the treatment of slow progress in the first stage of spontaneous labour is associated with a reduction in the incidence of caesarean sections, or maternal and fetal morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials.

Types of participants

Low-risk pregnant women with slow progress in the first stage of spontaneous labour at term (37 to 42 weeks) and a singleton fetus presenting by the vertex. We included only women in trials which used oxytocin to augment labour, i.e. women who commenced oxytocin for poor progress in the active stage of labour. We excluded women being induced with oxytocin from the outset and women who had a previous caesarean section.

Types of interventions

The meta-analysis compared women treated with oxytocin with women who received placebo or no treatment with oxytocin or in whom the treatment with oxytocin was delayed.

Primary comparisons

1. Intravenous oxytocin versus placebo
2. Intravenous oxytocin versus no treatment
3. Early use of intravenous oxytocin versus delayed use

We included studies in the 'early versus delayed' comparison if the aim was to delay use by one hour or more.

We have not included studies comparing low-dose with high-dose oxytocin. This is the topic of a separate Cochrane protocol (Mori 2008).

Types of outcome measures

Primary outcomes

We chose four primary outcomes as being most representative of the clinically important measures of effectiveness and complications. Subgroup analyses were limited to these:

(a) uterine hyperstimulation with fetal heart rate (FHR) changes necessitating intervention (such as fetal blood sampling, stopping the oxytocin infusion or emergency operative delivery);

(b) caesarean section;

(c) serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood);

(d) serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicaemia).

Secondary outcomes

Secondary outcomes relate to measures of effectiveness, complications and satisfaction.

Complications

(e) Uterine hyperstimulation without FHR changes;

(f) uterine rupture;

(g) epidural analgesia;

(h) instrumental vaginal delivery;

(i) Apgar score less than seven at five minutes;

(j) neonatal intensive care unit admission;

(k) neonatal encephalopathy;(l) perinatal death;

(m) maternal side effects (all);

(n) postpartum haemorrhage (as defined by the trial authors);

(o) serious maternal complications (e.g. intensive care unit admission or septicaemia, but excluding uterine rupture);(p) maternal death.

Measures of satisfaction and need for pain relief

(q) Woman not satisfied;

(r) caregiver not satisfied.

Non-prespecified outcomes

In addition to the specified outcomes above we also decided to included outcomes which were not previously specified in the protocol but which we felt were important and they are reported separately in the results section.

(s) Normal vaginal delivery;

(t) emergency caesarean section for fetal distress;

(u) time from randomisation until delivery;

(v) women undelivered after 12 hours from randomisation.

While all the above outcomes were sought, only those with data appear in the analysis tables.We included outcomes in the analysis if reasonable measures were taken to minimise observer bias; missing data were insufficient to materially influence conclusions; and data were available for analysis according to the original allocation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 April 2011).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched bibliographies of relevant papers.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

The review authors (George Bugg (GJB) and Farah Siddiqui (FS) independently assessed for inclusion all the potential studies which were identified as a result of the search strategy. We resolved any disagreements through discussion or, if required, in consultation with the third review author (Jim Thornton (JGT)).

Data extraction and management

We designed a form to extract data. For eligible studies, GJB and FS extracted the data using the agreed form. We resolved any discrepancies through discussion or, if required, we consulted JGT. We entered the data into Review Manager software (RevMan 2011) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

GJB and FS independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or by involving JGT.

(1) Random sequence generation (checking for possible selection bias)

We describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We describe for each included study the method used to conceal allocation to interventions prior to assignment and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding of participants, personnel and outcome assessors (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We consider studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or was supplied by the trial authors, we re-included missing data in the analyses which we undertook.
We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We describe for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials. In future updates of this review, if we identify cluster-randomised trials we will include them in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there had been 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) using funnel plots. We planned to assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we planned to use the test proposed by Egger 1997, and for dichotomous outcomes we planned to use the test proposed by Harbord 2006. If we had detected asymmetry in any of these tests or by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detected substantial statistical

heterogeneity, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we did not combine trials. If we used random-effects analyses, we presented the results were presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we planned to investigate it using subgroup analyses. However, we will restrict further analyses to the review's primary outcomes. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

In total we considered 36 trials for inclusion. Of these we excluded 28, leaving eight studies involving a total of 1338 women with a low-risk singleton pregnancies at term. All these women were in the active stage of spontaneous labour at term, with a vertex presentation. Of these women, all were nulliparous apart from a total of 39 multiparous women described in the studies by Blanch 1998 (n = 11), Hemminki 1985 (n = 24) and Read 1981 (n = 4). For further details of trial the characteristics please refer to the Characteristics of included studies.

We excluded trials for a variety of reasons. For example Hunter 1991, Pattinson 2003 and Shennan 1995 randomised women in normal labour who were not necessarily progressing slowly. We excluded Breart 1992, Cammu 1996, Rogers 1997, Sadler 2000 because the main intervention they studied was not oxytocin; it was other interventions of active labour management such as artificial rupture of membranes. We also excluded studies because they compared the use of oxytocin with other interventions such as nipple stimulation (Curtis 1999; Stein 1990; Van Lier 1987), labouring in water (Cluett 2001; Cluett 2004) or Chinese herbal remedies (Qui 1999; Zhang 1994). For further details of other trials, please refer to the Characteristics of excluded studies.

Risk of bias in included studies

The two multicentred trials included in this review (Dencker 2009; Hinshaw 2008) were considered high quality according to the review criteria. Both trials employed a blinded method of randomisation according to a computer-generated randomisation schedule using pre-numbered envelopes held remote from the recruiting sites. Two further studies (Bidgood 1987; Blanch 1998) had evidence of sequence generation and allocation concealment, although this was via sealed envelopes. In the remaining four trials (Cheewawattana 1991; Hemminki 1985; Illia 1996; Read 1981) it was unclear whether allocation concealment was adequate. Only in Cheewawattana 1991 and Illia 1996 were participants or the caregivers blinded to study groups the other trials were therefore susceptible to ascertainment and co-intervention bias. None of the studies used quasi-random methods of allocating participants to different interventions. None of the included studies had registered their trial protocols prior to commencement of the trials therefore it was unclear whether they were free from selective reporting. Incomplete outcome data were only adequately addressed in three studies (Dencker 2009; Hinshaw 2008; Read 1981).

Effects of interventions

We analysed eight studies in this review examining a total of 1338 women. The exact number of trials and participants varied for each outcome. We have reported only outcomes where data were available for each comparison.

Intravenous oxytocin versus placebo or no treatment (three trials; 138 women)

Primary outcomes

Cheewawattana 1991 and Illia 1996 are both examples of double blinded randomised studies comparing the use of oxytocin with placebo. Read 1981 was a small unblinded randomised study comparing standard administration of oxytocin with ambulation. Overall, eight caesarean sections were performed in the intervention group and 10 caesarean sections in the control group (risk ratio (RR) 0.84; 95% confidence Interval (CI) 0.36 to 1.96) (Analysis 1.1).

Secondary outcomes

All three trials reported on instrumental vaginal deliveries and found no differences between the two groups (RR 1.04; 95% CI 0.45 to 2.41) (Analysis 1.2). Cheewawattana 1991 reported that no neonates had Apgar scores under seven at five minutes in either group.

Non-prespecified outcomes

All three trials reported on normal vaginal deliveries and found no differences between the two groups (RR 1.02; 95% CI 0.84 to 1.25) (Analysis 1.4). Cheewawattana 1991 reported that no neonates had Apgar scores under seven at five minutes in either group.

Early use of intravenous oxytocin versus delayed use (five trials; 1200 women)

Primary outcomes

Uterine hyperstimulation with FHR changes necessitating intervention was reported in two studies involving 472 women (Bidgood 1987; Hinshaw 2008), and a significant increase in the experimental group was noted (RR 2.51; 95% CI 1.04 to 6.05) (Analysis 2.1). All five studies reported on caesarean sections; there was no significant difference between the number of women requiring caesarean section in the experimental group and the control group (RR 0.88; 95% CI 0.66 to 1.19) (Analysis 2.2). A single perinatal death, unrelated to delivery, was reported in each arm by Hinshaw 2008. The only other study to report on perinatal deaths was Hemminki 1985, where there were no deaths in either group (Analysis 2.3).

Secondary outcomes

Bidgood 1987 reported six cases of uterine hyperstimulation without FHR changes in the oxytocin group but none in the control group; however, this difference was not significant (RR 6.66; 95% CI 0.39 to 112.60) (Analysis 2.4). Three studies (Blanch 1998; Dencker 2009; Hinshaw 2008) reported on the uptake of epidurals amongst women; no significant difference were found between the oxytocin group and the control group (RR 0.95; 95% CI 0.76 to 1.06) (Analysis 2.5). This analysis showed substantial heterogeneity, prompting the use of a random-effects meta-analysis ($Tau^2 = 0.01$; $I^2 = 52\%$). The heterogeneity appears to be almost entirely due to the anomalous result of one small study (Blanch 1998). Five studies (1200 women) (Bidgood 1987; Blanch 1998; Dencker 2009; Hinshaw 2008; Hemminki 1985) reported on instrumental vaginal delivery; there was no significant difference in the percentage of women having an instrumental vaginal delivery in the experimental group as compared to the control group (RR 1.17; 95% CI 0.72 to 1.88). However, there is also substantial heterogeneity in this analysis, prompting the use of a random-effects meta-analysis ($Tau^2 = 0.17$; $I^2 = 68\%$). The trials in this analysis have effects in both directions, so although there is close to zero effect on average, in different situations oxytocin might increase or decrease the proportion of women having instrumental delivery (Analysis 2.6). There was no significant difference in the number of babies having Apgar scores less than seven at five minutes between the oxytocin group and the control group (RR 1.09; 95% CI 0.46 to 2.28) (Analysis 2.7).

Four studies (Blanch 1998; Dencker 2009; Hemminki 1985; Hinshaw 2008) reported on neonatal intensive care unit admissions; there was no significant difference between the two groups (RR 0.95; 95% CI 0.60 to 1.50) (Analysis 2.8). Three studies (Dencker 2009; Hemminki 1985; Hinshaw 2008) reported on postpartum haemorrhage; no significant differences were noted between the oxytocin group and the control group (RR 0.83; 95% CI 0.59 to 1.15) (Analysis 2.9). Hinshaw 2008 also studied the labour agency scores, a measure of satisfaction, with a higher score suggesting higher rates of satisfaction. Higher scores were observed in the intervention group as opposed to the controls, but this was not significant (mean difference 3.00; 95% CI -3.33 to 9.33) (Analysis 2.10).

Non-prespecified outcomes

Four studies, involving 1143 women (Bidgood 1987; Blanch 1998; Dencker 2009; Hinshaw 2008) reported on normal delivery rates; there was no significant difference between the percentage of normal deliveries in the oxytocin group (66.7%) and the control group (70%) (RR 1.02; 95% CI 0.88 to 1.19). We used a random-effects meta-analysis for this analysis because there is substantial heterogeneity ($Tau^2 = 0.01$; $I^2 = 46\%$) in that the trials in this analysis have effects in both directions (Analysis 2.11). Three studies (909 women) (Blanch 1998; Dencker 2009; Hinshaw 2008) reported on cases where it was necessary to perform an emergency caesarean section for fetal distress and found no significant differences between the two groups (RR 1.08; 95% CI 0.59 to 2.00) (Analysis 2.12).

Three studies (Blanch 1998; Dencker 2009; Hinshaw 2008) studied the time from randomisation to delivery. The overall mean difference was just over two hours. The intervention group was significantly shorter -2.20 hours (95% CI -3.29 to -1.10; 1083 women). This analysis had substantial heterogeneity prompting the use of a random-effects analysis ($Tau^2 = 0.69$; $I^2 = 80\%$) (Analysis 2.13). Two studies (Dencker 2009; Hinshaw 2008) reported on the number of women undelivered after 12 hours from randomisation; there were fewer women undelivered in the oxytocin group (19.2%) as compared with the control group (39.8%). However, this was not significant (RR 0.32; 95% CI 0.07 to 1.42) and the heterogeneity was also very high ($Tau^2 = 1.11$; $I^2 = 95\%$), suggesting that the results of this meta-analysis should be treated with caution even though a random-effects analysis was used (Analysis 2.14).

DISCUSSION

The review looked at two comparisons: first, the intravenous use of oxytocin versus placebo or no treatment; and second the early

use of intravenous oxytocin versus its delayed use. The first comparison only reported results for one of the primary outcomes, caesarean section rates, for which there was no difference. This comparison contained only three small trials and therefore was clearly underpowered to make any firm conclusions.The second comparison, however (early use of oxytocin as opposed to its delayed use), was much larger and also showed no effect on caesarean section rates. The review had sufficient power for a reasonable precise estimate of effect for this outcome and therefore the trials at least clearly ruled out a 30% increase or reduction in caesarean sections.

The early use of oxytocin did significantly increase uterine hyperstimulation with fetal heart rate changes; however, this did not translate into serious neonatal morbidity or perinatal death. We included a non-prespecified outcome at this stage to determine if this had an effect of the emergency caesarean section rates, and found that it did not. The comparison, oxytocin treatment as opposed placebo or no oxytocin treatment, involved fewer women but also showed no difference in the caesarean section rates. An examination of the secondary outcomes for both comparisons showed no benefits for the use of oxytocin in terms of instrumental vaginal delivery rates, and indeed no benefit or harm on a range of measures of maternal and fetal outcomes.

We decided to include non-prespecified outcomes in the review to highlight the potential benefits from the use of early oxytocin as opposed to its delayed use to treat slow labour. The early use of oxytocin, as opposed to its delayed use, did significantly shorten the time to delivery by approximately two hours. This meta-analysis did show substantial heterogeneity; however all of the trials were strongly in the same direction, so it is reasonable to conclude that the true effect is in this direction. The random-effects analysis assumes that the treatment effect varies between trials, so in different situations the effects might be greater or less than 2.2.hours. However this result did not translate into an increase in normal vaginal delivery rates. Frigoletto 1995 also described a similar finding of an approximate two-hour reduction in the length of labour in a large randomised controlled trial looking at the effect of a package of care which also included the use of oxytocin in the treatment of women progressing slowly in labour. However this did not result did not translate into an increase in normal vaginal delivery rates.

The strength of the above conclusions depends on the rigor of the systematic review methodology and the quality of the included primary studies, which was generally good. However, a number of weaknesses remain. First, for all important fetal outcomes the trials were underpowered. In particular, the clinically important effects on perinatal death have not been reliably excluded. However, we have excluded large effects on the surrogate outcomes of low Apgar score and admission to neonatal intensive care, which makes a large effect on these substantive outcomes less plausible. Second, the entry criteria and comparison groups for the included studies varied and trials used different doses, and different criteria for starting treatment in the delay arm as described in the Characteristics of included studies. It is most likely for these reasons that significant statistical heterogeneity was observed for the secondary outcomes of instrumental vaginal delivery and epidural analgesia and the non-prespecified outcomes of time from randomisation to delivery and women undelivered after 12 hours. However, there was little statistical heterogeneity for the primary outcomes and therefore we did not explore the heterogeneity through subgroup analysis. Third, neither obstetricians nor participants were blinded to the treatment group in seven of the studies. This is perhaps hardly surprising, since double blind trials of oxytocin are difficult, though not impossible, as exemplified by the small studies (Cheewawattana 1991; Illia 1996). However, the decision to perform caesarean section and instrumental delivery is rarely an absolute one. It is likely that some decisions were altered by knowledge of the treatment arm, although it is impossible to know the direction of this effect. For example, on the one hand knowing that a patient had failed to progress after a period of oxytocin might precipitate a caesarean section. On the other hand, knowing that a patient with an episode of fetal distress was receiving oxytocin might encourage the obstetrician to be conservative while stopping the infusion. Finally, multiparous women were also included in the review and difficult to exclude from the analysis, although the numbers were small. Notwithstanding these limitations, this review represents the best synthesis of currently available evidence, and allows clinicians to begin to counsel women as regards the benefits of oxytocin use in labour.

AUTHORS' CONCLUSIONS

Implications for practice

Oxytocin is a drug commonly administered to pregnant women whose labours are progressing slowly, in the hope that the progress of labour can be improved and the need for caesarean section reduced. It is unlikely that the early oxytocin use as compared to its delayed use substantially reduces the need for caesarean section or indeed instrumental vaginal delivery rate. However, neither is it likely to cause harm to mother or baby, and clinicians with some degree of confidence can suggest that early administration of oxytocin will reduce the time to delivery. The dilemma for obstetricians and midwives on labour wards is that a drug they have used for over 40 years to reduce the need for operative delivery has still not been proven to be effective in its original primary role.

Implications for research

The increase in the rate of caesarean sections remain of significant concern in the UK and indeed worldwide. Slow progress in labour is a common indication for caesarean section and oxytocin has been the mainstay of its treatment. The role of oxytocin, however,

has once again been questioned in this review; the early use of oxytocin does not contribute to a reduction in operative delivery. Early oxytocin does however, have some effect: it does shorten labour. Possibly there is a subgroup of women, progressing slowly in the first stage of labour, in whom this effect will translate into a reduced rate of operative delivery. Future research into how better to define these groups might be worthwhile.

A buildup of myometrial lactic acid (Quenby 2004), hypoxia (Bugg 2006b) and superoxide anions (Bugg 2006c) have all been shown to affect myometrial contractility. Therefore, it is not surprising that rest, food intake (Dencker 2010) and adequate hydration (Garite 2000) have all been associated with improved progress in labour. These factors could be candidates for future research into alternate treatment options for slow progress in labour.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bidgood 1987

Methods	RCT.
Participants	60 nulliparous women were recruited to the study. All the women were spontaneous labour, with vertex presenting and within 3 weeks of term. The diagnosis of labour was established by full effacement of the cervix and a dilatation of at least 3 cm, regular contractions with a frequency of at least 1 every 5 min and partographic evidence of cervical progress. All women had ruptured membranes prior to randomisation. Slow progress in labour was diagnosed if the rate of cervical dilatation was less than 0.5 cm/hour
Interventions	There were 3 management groups: 1) the expectant management group (n = 20) where oxytocin was deferred for 8 hours and given at the discretion of the supervising clinician; 2) a low-dose oxytocin group (n = 20) where the oxytocin was infused at an initial rate of 2 mU/min and increased by 2 mU/min every 15 minutes until stable contractions; and 3) a high-dose oxytocin intervention group (n = 20) where the oxytocin infusion was started at 7 mU/min and increased by 7 mU/min every 15 min, limited by a frequency of 7 contractions in 15 minutes
Outcomes	• Mode of delivery • Hyperstimulation • Rate of cervical dilation • Admission to delivery time • Randomisation to delivery interval • Duration of second stage • Cord pH artery at delivery • Apgar score < 7 at 5 mins
Notes	For the purposes of this review the 2 oxytocin groups were combined to form the experimental group (n = 40) and were compared with the expectant management group acting as the control group (n = 20)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	150 envelopes were "shuffled at the beginning of the study".
Allocation concealment (selection bias)	Low risk	Sealed envelopes kept in a location apart from the delivery suite
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	High risk	

Bidgood 1987 (*Continued*)

Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	High risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	High risk	
Blinding (performance bias and detection bias) Caesarean section rate	High risk	
Blinding (performance bias and detection bias) Hyperstimation rates	High risk	
Blinding (performance bias and detection bias) Delay delivery interval	High risk	
Blinding (performance bias and detection bias) Length of second stage	High risk	
Blinding (performance bias and detection bias) Analgesia requirements	High risk	
Blinding (performance bias and detection bias) Arterial cord gas	High risk	
Blinding (performance bias and detection bias) Apgar scores	High risk	
Blinding (performance bias and detection bias) Admission to NNU	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was no trial flow diagram. There was no mention of missing envelopes
Selective reporting (reporting bias)	Unclear risk	The trial had been approved by an ethics committee but the protocol had not been otherwise registered

Bidgood 1987 (*Continued*)

Other bias	High risk	The original plan was to recruit 50 participants per group giving a total of 150. In fact only 60 were recruited due to 'limitations of time'

Blanch 1998

Methods	RCT.
Participants	61 women (both primiparous and multiparous women) making slow progress in the active phase of spontaneous labour with intact membranes were randomised. Inclusion criteria were singleton fetus; cephalic presentation; gestation greater than 37 weeks; full cervical effacement; cervical dilatation greater than 3 cm dilation, with at least 1 contraction in every 5 mins. Slow progress in labour was diagnosed by using a partogram with an alert line representing cervical dilatation of 1 cm per hour and an action line drawn 3 hours to the right of the action line
Interventions	In the amniotomy and oxytocin group (n = 21) the infusion was started immediately after amniotomy. In the amniotomy alone group (n = 20) and the expectant management group (n = 20), if progress was still slow after 4 hours management of labour was shifted to the standard labour ward protocol which included the use of oxytocin. The oxytocin infusion started with 2 mU/min and doubled every 30 minutes
Outcomes	• Cervical dilatation rate • Before randomisation • After randomisation during first 4 hours • After randomisation until delivery • Randomisation - delivery interval (mins) • Epidural analgesia • Caesarean section • Failure to progress • Fetal distress • Instrumental delivery • Cord pH • Apgar < 7 at 5 mins • Admission to NNU
Notes	In order to only study the effects of intravenous oxytocin on labour, we compared the amniotomy and oxytocin group with the amniotomy alone group. Women in the expectant management group were not included in the review. Nulliparous women represented 76% of the experimental group and 70% of the control group. Although nulliparous and multiparous women were randomised separately they have been analysed together. For this review 30 primiparous women and 11 multiparous women were included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Blanch 1998 (*Continued*)

Random sequence generation (selection bias)	Low risk	The allocation sequence was determined using a table of random numbers
Allocation concealment (selection bias)	Low risk	Consecutively numbered sealed opaque envelopes were used.
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	High risk	
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	High risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	High risk	
Blinding (performance bias and detection bias) Caesarean section rate	High risk	
Blinding (performance bias and detection bias) Hyperstimation rates	High risk	
Blinding (performance bias and detection bias) Delay delivery interval	High risk	
Blinding (performance bias and detection bias) Length of second stage	High risk	
Blinding (performance bias and detection bias) Analgesia requirements	High risk	
Blinding (performance bias and detection bias) Arterial cord gas	High risk	
Blinding (performance bias and detection bias) Apgar scores	High risk	

Blanch 1998 (*Continued*)

Blinding (performance bias and detection bias) Admission to NNU	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was no trial flow diagram. Missing data was recorded for cord pH (7 cases) and base excess (12 cases) but not for the pre-specified outcomes in the review
Selective reporting (reporting bias)	Unclear risk	The trial was not registered.
Other bias	Unclear risk	The intended sample size was 'at least' 120 in 3 groups. However, the achieved sample size was 60 in 3 groups. 1 participant was randomised in error because of a breech presentation and excluded from analysis

Cheewawattana 1991

Methods	Double blinded RCT.
Participants	The trial included 87 nulliparous women in the active phase of labour diagnosed as cervical dilatation equal to 4 cm. Slow progress in labour was diagnosed when uterine contractions were less than 3 times in 10 minutes
Interventions	The women either received an Intravenous infusion of 5% dextrose saline including oxytocin 10 units/litre (n = 45) or a placebo infusion of 5% dextrose saline (n = 42) .The initial infusion rate was started at 5 drops per minute and increased by 2 drops per minute until contractions were sufficient or up to a maximal dose of 40 drops per minute
Outcomes	• The successful rate of delivery after augmentation (%) • Mode of delivery (normal delivery, caesarean section, instrumental vaginal delivery) • Obstetrics complications • Indication of obstetrics operation • Analgesic drug used • Deterioration in the fetal heart rate • Apgar score at 1 and 5 mins
Notes	The paper needed to be translated from Thai to English

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details were given. The method described was 'drawing lots'
Allocation concealment (selection bias)	Unclear risk	No details were given. The method described was 'drawing lots'

Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	Unclear risk	No details were given. The method was 'drawing lots'.
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	Low risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	Low risk	
Blinding (performance bias and detection bias) Caesarean section rate	Low risk	
Blinding (performance bias and detection bias) Hyperstimation rates	Low risk	
Blinding (performance bias and detection bias) Delay delivery interval	Low risk	
Blinding (performance bias and detection bias) Length of second stage	Low risk	
Blinding (performance bias and detection bias) Analgesia requirements	Low risk	
Blinding (performance bias and detection bias) Arterial cord gas	Low risk	
Blinding (performance bias and detection bias) Apgar scores	Low risk	
Blinding (performance bias and detection bias) Admission to NNU	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All the outcomes were reported for caesarean section and instrumental vaginal delivery. Missing data were not clearly re-

Cheewawattana 1991 (*Continued*)

		ported for other outcomes
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not registered.
Other bias	Unclear risk	Data was extracted from a partial translation from Thai to English

Dencker 2009

Methods	RCT.
Participants	630 nulliparous women with primary dysfunctional spontaneous labour were included in the study. All women had low-risk pregnancies and were at greater than 37 weeks but less than 42 weeks of gestation. Active labour was defined when the cervical dilatation was greater than 4 cm. Slow progress in labour was defined when the rate of cervical dilatation was less than 1 cm over 3 hours or there was no cervical dilatation over 2 hours
Interventions	Women were either randomised into the intervention group (n = 314) where an oxytocin infusion was started within 20 mins of randomisation or the control group (n = 316) where oxytocin was withheld for a period of 3 hours. Oxytocin was infused at a rate of 3.3 mU/min and raised by 3.3 mU/mins every 30 minutes until efficient contractions were achieved
Outcomes	• Mode of delivery • Instrumental deliveries (for either failure to progress or non-reassuring CTG) • LSCS (failure to progress, failed instrumental, non reassuring CTG, non reassuring CTG abnormal scalp pH) • Spontaenous vaginal delivery • Duration of labour • Randomisation to delivery interval • Haemorrhage • Haemorrhage > 1000 ml • Sphincter laceration • Epidural analgesia • Birthweight • Head circumference • Apgar score < 7 at 5 mins • Arterial pH in umbilical artery • Arterial pH < 7 and BE <-12 • Transferred to NICU • Days in NICU • Phototherapy treatment • Visual analogue scale assessment of pain
Notes	36 cases did not meet the randomisation criteria; however, these were subsequently added to the 593 giving a total no of 630. Within the experimental group there were 16 such cases; 11 were randomised at a cervical dilatation of 10 cm, 1 at 3 cm of cervical dilatation, 1 at 42 weeks of gestation and 3 before amniotomy. Within the control group 21 women were randomised in error, 9 were randomised at a cervical dilatation of 10

	cm, 5 at 3 cm of cervical dilatation, 3 at 42 weeks of gestation and 4 before amniotomy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed in blocks of 10 using a computer randomisation sequence generation program
Allocation concealment (selection bias)	Low risk	Opaque sealed serially numbered [envelopes] were placed in another department
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	Low risk	
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	High risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	High risk	
Blinding (performance bias and detection bias) Caesarean section rate	High risk	
Blinding (performance bias and detection bias) Hyperstimation rates	High risk	
Blinding (performance bias and detection bias) Delay delivery interval	High risk	
Blinding (performance bias and detection bias) Length of second stage	High risk	
Blinding (performance bias and detection bias) Analgesia requirements	High risk	
Blinding (performance bias and detection bias) Arterial cord gas	High risk	

Dencker 2009 (*Continued*)

Blinding (performance bias and detection bias) Apgar scores	High risk	
Blinding (performance bias and detection bias) Admission to NNU	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	The trial was not registered. Although the data collection was completed in 2003 the trial was not reported until 2008
Other bias	Low risk	A sample of 247 per group was estimated to have 80% power (alpha 0.05) to show an increase in spontaneous vaginal delivery from 81.2% to 90%. The intended sample size was increased by 20% to 296 per group to allow for protocol violations. The achieved sample size was 314 and 316 per group respectively

Hemminki 1985

Methods	RCT.
Participants	57 women with singleton pregnancies in active but protracted labour were randomised in this study. 24 multiparous women were included in this study. Active labour defined as regular contractions (more than 2 contractions in 10 mins) with dilatation of the cervix. Slow progress in labour was determined by the doctors in charge. The study protocol gave an advisory definition: no progress in the cervical dilatation or with no descent of the fetus as shown by 2 examinations 2 hours apart. If the membranes were still intact at the time protracted labour was diagnosed, amniotomy was performed. At least 2 hours were then allowed to elapse to see whether labour began to progress
Interventions	Women randomised to oxytocin group (n = 27) received the standard treatment of the hospital; oxytocin was given by intravenous drip and controlled by hand according to the clinical response. The control group (n = 30) consisted of ambulant women; ambulation was considered to have failed if: 1) 4 hours had elapsed since randomisation without any progress; 2) 8 hours had elapsed from randomisation and the child's birth was not expected within a short period of time (about 1 hour). When the treatment was judged to have failed, the women were given oxytocin or other appropriate treatment
Outcomes	• Randomisation-delivery interval (mins) • Epidural analgesia • Caesarean section • Failure to progress • Fetal distress • Instrumental delivery • Blood loss

Hemminki 1985 (*Continued*)

	• Apgar < 7 at 5 mins • Admission to NNU • Women's experiences of labour
Notes	For the purposes of this review ambulation was not considered to be an active intervention. Women in the ambulant group were given delayed oxytocin if they failed to progress after a prescribed time interval. Nulliparous women represented 56% of the experimental group and 60% of the control group. Although nulliparous and multiparous women were randomised separately, they have been analysed together

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not properly reported, women were just described as being 'randomly allocated'
Allocation concealment (selection bias)	Low risk	Sealed envelopes were reportedly used.
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	High risk	
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	High risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	High risk	
Blinding (performance bias and detection bias) Caesarean section rate	High risk	
Blinding (performance bias and detection bias) Hyperstimation rates	High risk	
Blinding (performance bias and detection bias) Delay delivery interval	High risk	
Blinding (performance bias and detection bias) Length of second stage	High risk	

Hemminki 1985 (*Continued*)

Blinding (performance bias and detection bias) Analgesia requirements	High risk	
Blinding (performance bias and detection bias) Arterial cord gas	High risk	
Blinding (performance bias and detection bias) Apgar scores	High risk	
Blinding (performance bias and detection bias) Admission to NNU	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with valid outcomes was not reported. Outcome data were reported as percentages or as means with standard deviations
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not registered.
Other bias	Unclear risk	No pre-determined sample size estimate or power calculation was reported

Hinshaw 2008

Methods	RCT.
Participants	412 low-risk nulliparous women at term (37 to 42 weeks) were randomised to this study. All the women had a low-risk pregnancy with a singleton fetus presenting by the vertex. Slow progress in labour was defined as when the cervical dilatation had progressed by 2 cm or less over 4 hours from an initial dilatation of between 3 cm and 6 cm. As a result women with secondary arrest of labour were excluded from the study
Interventions	All participating women underwent amniotomy if the membranes were intact prior to randomisation. Women randomised to active management (n = 208) commenced an oxytocin infusion within an intended 20 mins of randomisation. If the participant was randomised to conservative management (n = 204), oxytocin was withheld for a period of 8 hours unless intervention became clinically indicated. The oxytocin was infused at a rate of 2 mU/min, increasing every 30 minutes until 4 contractions were achieved in 5 minutes or a maximum infusion rate of 32 mU/min
Outcomes	• Rate of cervical dilatation after randomisation • Incidence of hyperstimulation • Randomisation to delivery interval • Length of second stage • Analgesic requirements

	• Instrumental deliveries (for either failure to progress or non reassuring CTG) • LSCS (failure to progress, failed instrumental, non reassuring CTG, non reassuring CTG abnormal scalp pH) • Maternal psychological well being at 48 hrs and 2 weeks (Edingburgh Post Natal Scale; Labour agency Scale, McGill Pain Questionaire, Attitudes towards Pregnancy and the Baby Scales) • Postnatal maternal infection • Arterial cord pH • Apgar scores • Intubation • Admission to NNU • Serious perineal sequelae
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer generated randomisation sequence was stratified by the unit
Allocation concealment (selection bias)	Low risk	Numbered, sealed, opaque envelopes were kept on a gynaecology ward
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	Low risk	
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	High risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	High risk	
Blinding (performance bias and detection bias) Caesarean section rate	High risk	
Blinding (performance bias and detection bias) Hyperstimation rates	High risk	
Blinding (performance bias and detection bias)	High risk	

Hinshaw 2008 (*Continued*)

Delay delivery interval		
Blinding (performance bias and detection bias) Length of second stage	High risk	
Blinding (performance bias and detection bias) Analgesia requirements	High risk	
Blinding (performance bias and detection bias) Arterial cord gas	High risk	
Blinding (performance bias and detection bias) Apgar scores	High risk	
Blinding (performance bias and detection bias) Admission to NNU	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not registered. Recruitment ended in 2001; however, the trial was not published until 2008
Other bias	Low risk	

Illia 1996

Methods	Double blind RCT.
Participants	37 nulliparous women were randomised. All pregnancies were low risk with a gestational age greater than or equal to 38 weeks. All women were in active labour, defined as a cervical dilatation greater than 4 centimetres, 50% of cervical effacement and with at least 2 uterine contraction in 10 minutes. Slow progress in labour was defined as cervical dilatation less than 2 centimetres over 4 hours
Interventions	This was a double blinded study; both the experimental (n = 14) and control group (n = 23) received an identical infusion of saline, only the experimental group's infusion contained oxytocin (10 units/litre)
Outcomes	• Rate of cervical dilatation before randomisation • Rate of cervical dilatation after randomisation • Delay - delivery interval • Length of second stage • Instrumental deliveries

Illia 1996 (*Continued*)

	• Caesarean section • Arterial cord pH • Apgar scores
Notes	The authors state that the difference in the size of the groups was due to the randomisation. The original paper was in Spanish and was translated to English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated.
Allocation concealment (selection bias)	Low risk	Method not reported.
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	Low risk	Double blind.
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	Low risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	Low risk	
Blinding (performance bias and detection bias) Caesarean section rate	Low risk	
Blinding (performance bias and detection bias) Hyperstimation rates	Low risk	
Blinding (performance bias and detection bias) Delay delivery interval	Low risk	
Blinding (performance bias and detection bias) Length of second stage	Low risk	
Blinding (performance bias and detection bias) Analgesia requirements	Low risk	

Illia 1996 (*Continued*)

Blinding (performance bias and detection bias) Arterial cord gas	Low risk	
Blinding (performance bias and detection bias) Apgar scores	Low risk	
Blinding (performance bias and detection bias) Admission to NNU	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reason given for disparity in group sizes; the authors state that the difference in the size of the groups was due to the randomisation but this is very unlikely
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not published.
Other bias	Unclear risk	There was no predetermined sample size.

Read 1981

Methods	RCT.
Participants	14 women were randomised to his study, 10 of these women were nulliparous, 4 were multiparous. All women had ruptured membranes, were thought to have failure to progress in labour over 1 to 2 hours, had inadequate contractions and were deemed by the attending clinician to need augmentation. The average gestation of the women was 40 weeks
Interventions	Women randomised to the experimental group received oxytocin infusions (n = 6) and those in the ambulatory group (n = 8) remained out of bed, walking, standing and sitting. Oxytocin was infused at a rate of 0.2 mU/min and increased every 15 minutes until a contraction occurred every 2-3 minutes
Outcomes	• Normal spontaneous vaginal delivery • Forceps • Caesarean section • Apgar score at 1 min • Apgar score at 5 mins
Notes	This was a pilot study. For the purposes of this review ambulation was not considered to be an active intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Read 1981 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding (performance bias and detection bias) Rate of cervical dilatation prior to randomisation	Unclear risk	This was not reported.
Blinding (performance bias and detection bias) Rate of cervical dilation post randomisation	High risk	
Blinding (performance bias and detection bias) Operative vaginal delivery rates	High risk	
Blinding (performance bias and detection bias) Caesarean section rate	High risk	
Blinding (performance bias and detection bias) Hyperstimation rates	High risk	
Blinding (performance bias and detection bias) Delay delivery interval	High risk	
Blinding (performance bias and detection bias) Length of second stage	High risk	
Blinding (performance bias and detection bias) Analgesia requirements	High risk	
Blinding (performance bias and detection bias) Arterial cord gas	High risk	
Blinding (performance bias and detection bias) Apgar scores	High risk	

Read 1981 (*Continued*)

Blinding (performance bias and detection bias) Admission to NNU	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	The trial protocol was not registered.
Other bias	High risk	There was no predetermined sample size. The study was reported as a 'pilot' but no definitive trial has subsequently appeared

CTG: cardiotocograph
mins: minutes
NICU: neonatal intensive care unit
NNU: neonatal unit

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arraztoa 1994	This is a study of augmentation after caesarean section and previous caesarean section is one of the exclusion criteria for this review
Arulkumaran 1989a	This is a trial of monitoring the strength of the uterine contractions and did not report on any of the primary and secondary outcomes listed in the methods
Breart 1992	This study was a randomised controlled study of amniotomy and oxytocin with existing protocols. Only a proportion of women in the experimental group received oxytocin and it was not clear whether any effect was due to amniotomy or oxytocin or both
Cammu 1996	This study was a randomised controlled study comparing a package of active management with existing protocols. Only 53% of women in the active arm received oxytocin, and all received other co-interventions
Cardozo 1990	This was a randomised controlled study of oxytocin versus saline, the subjects were crossed over from active treatment to saline after 6 hours in primigravida and 3 hours in multigravidas. The patients who were not responding the oxytocin were also crossed over to the saline treatment at the same time. There was also loss to follow-up of a large proportion of randomised women. It was not possible to extract outcome data by initial allocation group
Chalk 1969	This study investigated the effects of buccal oxytocin in women whose labour had been failed to be induced by artificial membrane rupture alone

(*Continued*)

Cluett 2001	This pilot study compared labouring in water versus augmentation with oxytocin. Only 4 women were recruited to each arm. The group felt that labouring in water was an active intervention
Cluett 2004	The studied compared labouring in water with augmentation with oxytocin. The group felt that labouring in water was an active intervention
Compitak 2002	The randomised controlled study compared 2 different regimes of oxytocin administration for the induction of labour at term
Curtis 1999	This study compared the effect of nipple stimulation with oxytocin in prolonged active labour. The group felt that nipple stimulation was an active intervention
Daniel-Spiegel 2001	This randomised controlled study studied the effects of continuing oxytocin into the 2nd stage of labour. The study was excluded as it was not designed to study the effects on a prolonged active first stage
Fraser 1988	This was a meta-analysis of 12 studies comparing a policy of early labour with amniotomy and oxytocin
Grubb 1996	This was a study of the effects of the active management of latent labour with an unknown uterine scar. As the study was primarily on patients who had had a previous caesarean section the study was excluded
Hunter 1991	Healthy nulliparous women were randomised to either aggressive or expectant management protocols based on 2 different definitions of slow progress, a 'tight' definition and a 'less tight' definition. All women were in normal spontaneous active labour at randomisation. Only women who ultimately had slow progress in labour after randomisation would receive oxytocin. Only 51.6% and 40.5% actually received oxytocin in either group respectively and this is the reason for this study's exclusion
Kececi 1994	Abstract of a randomised controlled trial investigating the effects of oxytocin on the rate of operative delivery and maternal morbidity. Unfortuantely the method of randomisation was not described and no analytical data were presented in the abstract
Labrecque 1994	This was a study of the effects of oxytocin on the latent phase of labour
Majoko 2001	This study compared high-dose oxytocin protocols to low dose and was therefore excluded from the review
Pattinson 2003	Healthy nulliparous women were randomised to either aggressive or expectant management protocols based on the use of different alert lines on partograms and which included the use of oxytocin. All women were in normal spontaneous active labour at randomisation. Only women who ultimately had slow progress in labour after randomisation received oxytocin and this is the reason for this studies exclusion
Pickrell 1989	This study was excluded as it was designed to study the effects of augmentation in the second stage in women who had an epidural
Qui 1999	This study examined the use of a Chinese herbal medicine (Chanlibao) in 2nd stage of labour
Rogers 1997	This study compared active management with usual care protocols. Only 56% of women in the active management group were commenced on oxytocin and they also received many other co-interventions

(*Continued*)

Rouse 1994	This studied compared oxytocin augmentation with intact membranes against oxytocin augmentation with the membranes absent
Sadler 2000	This study compared active management with routine care. Only 53% of the women in the active management group were commenced on oxytocin and they also received many other co-interventions
Setchik 1982	This study determine the effectiveness of a specific oxytocin dose on uterine contractility
Shennan 1995	Women having an epidural, not necessarily in primary dysfunctional labour, were randomised into having a oxytocin infusion or placebo
Stein 1990	This was a randomised controlled study comparing nipple stimulation with augmentation with oxytocin. Nipple stimulation was considered to be an active intervention
Van Lier 1987	This was a randomised controlled study comparing nipple stimulation with augmentation with oxytocin. Nipple stimulation was considered to be an active intervention
Zhang 1994	The women in this study were randomised to receive either oxytocin or chanliboa, a herbal Chinese medicine which strengthens uterine contractions