Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis

Zarko Alfirevic,[1]* Edna Keeney,[2] Therese Dowswell,[1] Nicky J Welton,[2] Nancy Medley,[1] Sofia Dias,[2] Leanne V Jones,[1] Gillian Gyte[1] and Deborah M Caldwell[2]

[1]Centre for Women's Health Research, University of Liverpool and Liverpool Women's Hospital, Liverpool, UK
[2]School of Social and Community Medicine, University of Bristol, Bristol, UK

*Corresponding author

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Scientific summary

Methods for the induction of labour

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Background

More than 150,000 pregnant women in England and Wales will have their labours induced each year. There are multiple pharmacological, non-pharmacological, mechanical and complementary methods available to induce labour. Different induction methods have advantages and disadvantages; they vary in effectiveness, safety and cost. We carried out a systematic review, network meta-analysis (NMA) and cost-effectiveness analysis to identify the best method for induction of labour. Findings have implications for women, clinicians and the UK NHS.

Objectives

To assess the effectiveness and safety of a range of induction methods to determine which method (or methods) achieves the best outcomes by providing a quantitative summary of the evidence on the relative effects of different methods; to develop a decision model to evaluate the cost-effectiveness of the different methods for induction; and if evidence is available, to explore effectiveness and cost-effectiveness in different clinical subgroups [with intact or ruptured membranes, at different gestational ages, in women following a previous caesarean section (CS) and with low (< 6) or higher Bishop scores].

Methods

We carried out a systematic review using Cochrane methods. The search was carried out by an information specialist using a predefined strategy. The final search date was March 2014. Two reviewers independently assessed all reports identified by the search for eligibility for inclusion. Studies were included if they were randomised controlled trials (RCTs) examining interventions to induce labour compared with placebo, no treatment or other interventions. Participants were women who were eligible for third-trimester induction of labour. We focused on key outcomes relating to efficacy, safety and acceptability of the method to women: vaginal delivery (VD) not achieved within 24 hours; uterine hyperstimulation with fetal heart rate (FHR) changes; CS; serious neonatal morbidity or death; serious maternal morbidity or death; instrumental delivery; maternal satisfaction with the method used; neonatal intensive care unit admission; Apgar score < 7 at 5 minutes.

We extracted data on the type of intervention and, when appropriate, dose and route of administration. We assessed risk of bias as high, low or unclear, based on the method used to conceal allocation. We noted whether or not the method was used in hospital (inpatient) or outpatient settings. We recorded information on characteristics of participants, including gestational age, parity, previous CS, state of amniotic membranes and Bishop score.

For key outcomes we carried out a NMA. The method uses all of the available evidence, both direct and indirect, to produce estimates of the relative effects of each treatment compared with every other in a network, even though some pairs may not have been directly compared. This method allows the relative effects of a range of treatments to be compared for the outcome of interest.

We developed a de novo decision tree model to estimate the cost-effectiveness of various methods for the induction of labour using the data obtained from the systematic review and NMA. We adapted the NMA to account for multiple outcomes to inform probabilities for all of the outcomes and interventions in the model. This was done using Bayesian Markov chain Monte Carlo simulation, so that all correlations and uncertainties were fully reflected in the estimates. The costs included in the economic analysis were the intervention costs, costs of method of delivery, and length of neonatal stay in level I, II or III units. The price year was 2012–13. We attributed a utility score to each of the outcomes in our model, which represents the strength of preferences for a set of health-related outcomes, where utility scores take values of between 0 and 1, with '1' representing perfect health. We reviewed the literature to identify preference-based utilities for the health-related outcomes in the model. We performed a probabilistic cost-effectiveness analysis, conceptualised as a hypothetical cohort of patients who vary in their probabilities, utilities and costs, and who experience the consequences of each induction strategy. Total utilities and costs are then averaged over this cohort to obtain the expected total utility and expected total cost for each induction strategy. We conducted a fully incremental analysis, reporting incremental cost-effectiveness ratios, interpreted as the additional expected cost per additional unit gain in utility for an intervention compared with the previous non-dominated intervention, and cost-efficiency frontiers, which plot expected cost against expected utility for each intervention. We report expected costs, expected utilities and expected net benefit (the difference between expected utilities and costs, for which utilities are monetaried by multiplying by the willingness-to-pay per unit increase in utility). We prefer the intervention that maximises expected net benefit. We represent uncertainty in the optimal intervention using cost-effectiveness acceptability curves and the cost-effectiveness plane.

Results

A total of 1508 reports corresponding to 1190 separate studies were identified.

Thirty-four active treatment types/regimens were included in our review, including different dose regimes and routes of administration. Overall, the search identified > 1000 studies and, after eligibility assessment using our PICO criteria (population, intervention and relevant comparators, outcomes), 579 studies were excluded and 611 trials were included in the review. Together, the included trials reported findings for > 100,000 women who were randomised to different methods for third-trimester induction of labour.

The active interventions most likely to achieve VD within 24 hours were intravenous (i.v.) oxytocin with amniotomy (mainly tested in trials recruiting women with favourable cervix), higher-dose ≥ 50 µg of vaginal misoprostol and vaginal prostaglandin E_2 (PGE_2; a type of prostaglandin used in the induction of labour) pessary (normal release). Titrated (low-dose) oral misoprostol solution and sustained-release misoprostol vaginal pessary also performed well; however, there was greater uncertainty around the effect of these interventions for this outcome.

Compared with placebo, several treatments showed statistically significant reduction in the odds of CS: titrated low-dose misoprostol, vaginal misoprostol at both ≥ 50 µg and < 50 µg, vaginal PGE_2 gel, intracervical PGE_2, oral misoprostol tablet (≥ 50 µg), Foley catheter, membrane sweeping and buccal/sublingual misoprostol. In this group, titrated oral misoprostol achieved the lowest odds of an eventual CS but there was still considerable uncertainty in this finding, as observed by the posterior mean rank order of sixth (out of 33) and 95% credible interval from second to thirteenth (out of 33). There was little to distinguish between the other interventions and, again, we observed considerable uncertainty in treatment rankings.

Uterine hyperstimulation with FHR changes was one of the key safety outcomes. Here, double-balloon catheter had the highest probability of being among the best three treatments, whereas vaginal misoprostol (≥ 50 µg), which was among the best treatments for efficacy, was most likely to increase the odds of excessive uterine activity.

For other safety outcomes there were insufficient data or there was too much uncertainty around estimates to identify which treatments performed 'best'.

Very few studies collected information on women's views. On the whole, women tended to have positive views, or at least accepted the induction process, but there was insufficient information to determine whether or not some methods were preferred over others.

There was considerable uncertainty of our cost-effectiveness estimates, with the majority of the interventions having very similar utility values, and mainly differing in total costs. The cost-effectiveness analysis suggested that all of the methods of induction were cost-saving compared with no treatment, and titrated (low-dose) misoprostol solution and buccal/sublingual misoprostol had the highest probability of being cost-effective, although this was very uncertain.

Only two subgroup analyses were possible with the data available, and these were based on a small number of studies and so should be interpreted as hypothesis generating. In the subgroup of women with intact membranes, and limiting to interventions feasible on the NHS, i.v. oxytocin with amniotomy was identified as the intervention most likely to be most cost-effective. In the subgroup of women with an unfavourable cervix, titrated low-dose oral misoprostol solution and buccal/sublingual misoprostol were found to be the interventions that were most likely to be most cost-effective.

Conclusions

Our NMA suggested that oxytocin with amniotomy and higher-dose (≥ 50 µg) vaginal misoprostol were more successful than other agents in achieving VD within 24 hours, although the former was tested in trials predominantly recruiting women with favourable cervix. The safety profile of different methods was less clear. The cost-effectiveness analysis suggested that titrated (low-dose) oral misoprostol solution is the intervention with the highest utility for mothers and babies, whereas buccal/sublingual misoprostol has the lowest cost to the NHS. Both of these interventions had the highest chance of being most cost-effective. However, the considerable uncertainty in our findings points the way for further research. When induction of labour is clinically indicated, placebo or no-intervention arms may not be feasible or even ethical. Therefore, rather than restrict RCTs to low-risk women, we suggest that titrated oral misoprostol solution should be used as a comparator, particularly in the NHS setting. Future RCTs should be powered to detect a method that is more cost-effective that misoprostol solution. We urge all triallists to report 11 outcomes included in this NMA in all future RCTs. There is also an urgent need to explore women's views of the process as part of any future trial, and measure utilities from the perspective of the mother and baby, preferably using the European Quality of Life-5 Dimensions instrument.

Study registration

This study is registered as PROSPERO CRD42013005116.

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