Comparative efficacy and cost of the prostaglandin analogs dinoprostone and misoprostol as labor preinduction agents

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of prostaglandin (PG) analogues as labour preinduction agents. The three agents examined were:

misoprostol (Cytotec, PGE1), 50 microg intravaginally in the posterior fornix initially with one-time repeat dosing 6 hours later;

dinoprostone gel (Prepidil, PGE2), 0.5 mg administered intracervically initially, with one-time repeat dosing 6 hours later; and

dinoprostone insert (Cervidil, PGE2), 10 mg administered into the posterior fornix for a total of 12 hours.

After the preinduction interval, the women received a standard oxytocin (Pitocin) infusion according to labour patterns.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women with a medical or obstetric indication for labour induction. The inclusion criteria were an unfavourable cervical Bishop score of less than or equal to 5, a singleton pregnancy with vertex presentation and no contraindication to vaginal delivery, the absence of spontaneous uterine contractions, and a reactive nonstress test. Women were excluded if they had ruptured membranes, suspected chorioamnionitis, parity of greater than 5, or a known hypersensitivity to PGs. They were also excluded if they had had a Caesarean delivery, had a history of uterine surgical procedures, and had already attempted to induce labour for this pregnancy.

Setting
The setting was secondary care. The economic study was carried out at the Mayo Medical Center in Michigan, USA.

Dates to which data relate
The effectiveness and resource use data were gathered from April 1996 to August 1997. No price year was reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.
Link between effectiveness and cost data
The costing was carried out on the same sample of patients as that used in the effectiveness analysis.

Study sample
Power calculations were carried out in the preliminary phase of the study. These suggested that a sample of 45 women in each group was required to detect a 25% absolute difference in the main outcome measure, assuming a baseline rate of 60% for women who reached complete dilation within 24 hours of treatment initiation (alpha: 0.05; beta: 0.20). Recruitment was stopped before the desired sample size was reached, after three of the four recruitment strata were filled. A sample of 111 women was enrolled and allocated to the study groups. There were 35 women in the dinoprostone gel group, 38 women in the dinoprostone insert group and 38 women in the misoprostol group. The mean ages were 28 (+/- 4.4) years (dinoprostone gel), 26.7 (+/- 3.6) years (dinoprostone insert) and 27.9 (+/- 4.6) years (misoprostol), respectively. It was not stated whether some patients refused to participate, or were excluded from the initial study sample for any reason.

Study design
This was a prospective, phase-III, randomised, blinded clinical trial, which was carried out in a single centre (Mayo Medical Center, Ann Arbor, MI, USA). Randomisation was carried out independently through the central hospital pharmacy using dynamic allocation with stratification by parity and initial Bishop score. A physician who was blinded to the allocation of the patients assigned a cervical Bishop score on admission. A different physician administered the agents. No follow-up was performed and the patients were assessed until birth took place. No loss to follow-up occurred.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary outcome measure was the proportion of women who reached complete dilation within 24 hours of treatment initiation. The secondary outcome measures were:

Bishop score change over the initial 12-hour interval,
the time to active labour,
the time to complete dilation,
the time to delivery,
the time to vaginal delivery,
the total hours of oxytocin infusion,
the total amount of oxytocin,
adverse obstetric outcomes (Caesarean delivery, chorioamnionitis, meconium passage, postpartum haemorrhage, and hyperstimulation requiring terbutaline treatment), and
neonatal outcomes (birth weight, Apgar score, venous and arterial cord pH, supplemental oxygen and neonatal intensive care unit admission).

The study groups were comparable in terms of their maternal age, maternal body mass index, gestational age, initial Bishop score, parity, or indication for induction.

Effectiveness results
The proportion of women who reached complete dilation within 24 hours of treatment initiation was 68.4% in the
misoprostol group, 51.4% in the dinoprostone gel group, and 50% in the dinoprostone insert group. The difference was not statistically significant.

The change in Bishop score over the initial 12 hours was 2.2 (+/- 1.3) in the dinoprostone gel group, 3.2 (+/- 2.3) in the dinoprostone insert group, and 5.2 (+/- 3.1) in the misoprostol group. There was a statistically significant difference between the misoprostol and the dinoprostone gel and insert groups.

The time to active labour was 25.2 (+/- 12.6) hours in the dinoprostone gel group, 26.1 (+/- 13.3) hours in the dinoprostone insert group, and 19 (+/- 10.2) hours in the misoprostol group. There was a statistically significant difference between the misoprostol and the dinoprostone gel and insert groups.

The time to complete dilation was 28.9 (+/- 13.1) hours (dinoprostone gel), 30.3 (+/- 13.3) hours (dinoprostone insert), and 22.7 (+/- 10.9) hours (misoprostol), respectively. All differences were statistically significant.

The time to delivery was 31.6 (+/- 13.4) hours (dinoprostone gel), 32.2 (+/- 14.7) hours (dinoprostone insert), and 24 (+/- 10.8) hours (misoprostol), respectively. There were statistically significant differences between the misoprostol and the dinoprostone gel and insert groups.

The time to vaginal delivery was 31.1 (+/- 14.2) hours (dinoprostone gel), 31.5 (+/- 13.5) hours (dinoprostone insert), and 23.9 (+/- 11.1) hours (misoprostol), respectively. All differences were statistically significant.

The total hours of oxytocin infusion were 12.1 (+/- 5.1) for the dinoprostone gel group, 13.8 (+/- 9.1) for the dinoprostone insert group, and 7.6 (+/- 7.2) for the misoprostol group. There were statistically significant differences between the misoprostol and the dinoprostone gel and insert groups.

The total amount of oxytocin was 362 (+/- 218) mU (dinoprostone gel), 503 (+/- 415) mU (dinoprostone insert), and 237 (+/- 270) mU (misoprostol), respectively. All differences were statistically significant.

There were no statistically significant differences in adverse obstetric outcomes and neonatal outcomes.

Clinical conclusions
The effectiveness analysis showed that the change in the mean Bishop score was significantly higher in the misoprostol group than in both the dinoprostone groups, while the induction-to-delivery intervals were significantly shorter.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the change in the cervical Bishop score. This was derived directly from the effectiveness study.

Direct costs
Discounting was not relevant since the costs were incurred during a short time. The unit costs and the quantities of resources used were not presented separately and the cost items were not broken down. The health services included in the economic evaluation were drugs, oxytocin, labour and delivery suite/nursing. The cost/resource boundary of the study was likely to have been that of the hospital. The cost data were obtained from the institutional cost centre of the hospital where the study was carried out. Resource use was estimated using actual data coming from the sample of patients who were enrolled in the effectiveness study from April 1996 to August 1997. The price year was not given.

Statistical analysis of costs
The costs were presented as mean values and standard deviations. Statistical tests were carried out to test the statistical significance of the difference in total costs.

Indirect Costs
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were not conducted.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The average relative cost per patient per PG preinduction was $2.37 (+/- 0.65) with misoprostol, $68.23 with dinoprostone insert, and $203.43 (+/- 21.84) with dinoprostone gel, (p<0.0001).

The total cost per patient was $1,036 (+/- 475.15) in the misoprostol group, $1,565.72 (+/- 631.60) in the dinoprostone insert group, and $1,572.92 (+/- 567.12) in the dinoprostone gel group.

The difference between the misoprostol group and the dinoprostone groups (gel or insert) was statistically significant, (p<0.0001).

**Synthesis of costs and benefits**
An average cost-effectiveness ratio was calculated to combine the costs and benefits of the three alternative treatments.

The average cost per patient to achieve a 1-point change in the cervical Bishop score was $0.97 (+/- 0.80) in the misoprostol group, $90.39 (+/- 49.16) in the dinoprostone insert group, and $136 (+/- 63.6) in the dinoprostone gel group, (p<0.0001).

**Authors’ conclusions**
Misoprostol was more cost-effective than dinoprostone prostaglandin (PG) preparations as an adjuvant to labour induction in women with an unfavourable cervix.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators. Both dinoprostone gel and insert treatments were the only agents in the USA that the Food and Drug Administration had approved for cervical ripening. Misoprostol, on the other hand, was marketed in the USA for the prevention of gastric ulcers in patients at high risk of developing peptic ulcerative disease, but several trials had demonstrated that misoprostol increased cervical Bishop scores and reduced induction-to-delivery intervals. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used a prospective randomised trial, which was appropriate for the study question and ensured a high internal validity. The occurrence of selection bias and confounding factors was minimised. The sample size was determined in the preliminary phase of the study (although full recruitment was not carried out) and the study groups were comparable at baseline. The method of sample selection was described, but it was unclear whether some patients were excluded from the initial study sample. The method of randomisation was presented and details of the women enrolled in the study were provided. The study sample is likely to have been representative of the study population. The study was partially blinded and this reduced assessment bias. All of these factors enhance the internal validity.
validity of the analysis.

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the study intervention. It may be difficult to compare it with the benefits of other health care interventions.

**Validity of estimate of costs**
The authors did not explicitly report the perspective of the economic analysis and only limited details of the cost study were reported. A detailed breakdown of the cost items was not provided, and the unit costs were not presented separately from the quantities of resources used. The price year was also not reported. Therefore, replication and reflation exercises in other settings will be difficult. The source of the cost data was stated, as was the time during which resource consumption was estimated. Overall, the cost analysis was a secondary objective of the study, which focused mainly on the effectiveness side.

**Other issues**
The authors compared their findings with those from a large systematic review of the literature, which showed the safety profile and effectiveness of misoprostol for cervical ripening and labour induction when used at appropriate dosages. However, the issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. This reduced the external validity of the study. The authors enrolled women with unfavourable cervix and this was reflected in the conclusions of the analysis.

**Implications of the study**
The study results suggested that misoprostol is a safe, effective and efficient alternative treatment for pregnant women with unfavourable cervix. This conclusion supports earlier results, although caution is required when interpreting the conclusions of the study due to the limitation on the cost side of the analysis.

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**Other publications of related interest**

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