Efficacy of intravaginal misoprostol in second-trimester pregnancy termination: a randomized controlled trial.

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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
Misoprostol, a synthetic prostaglandin, structurally related to prostaglandin E1, used as an abortifacient agent for medical pregnancy interruption in the second trimester. The drug was administered vaginally at a dose of 200 mcg every 6 hours for a maximum period of 48 hours. Those undelivered after 48 hours received an extra-amniotic PGF2alpha infusion.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Women with fetal death in utero, severe fetal anomaly, or psychosocial pregnancy termination between 14 and 28 weeks gestation.

Setting
Hospital. The economic analysis was carried out in Australia.

Dates to which data relate
Effectiveness and resource use data were derived from patients recruited to the study from July 1996 through February 1997. The price year was not explicitly specified.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was performed on the same patient sample as that used in the effectiveness analysis. The costing (based only on the number of pessaries) appears to have been conducted prospectively.

Study sample
Power calculations were used to determine the sample size: a sample size of 100 women was calculated to demonstrate that misoprostol was as effective as gemeprost in achieving delivery within 24 hours, (alpha = 0.1, 80% power). In total, 100 patients were randomly assigned to either the gemeprost group (n=47, median age 29 years (range: 25 - 34)) or to the misoprostol group (n=53, median age 29 years (range: 24 - 35)). The median gestational age at recruitment was 19
weeks for women in both groups.

**Study design**
This was a randomised, double-blind, controlled trial, carried out in a single centre. The duration of the follow-up appears to have been until discharge. Loss to follow-up appears to have been zero in this study. A series of prepared opaque envelopes was employed for randomisation using random number tables. The women, the attending medical staff, and the research team were blinded to the agent received. Only the nursing staff administering the prostaglandin were aware of the treatment allocation. After 100 patients had been enrolled, an interim analysis was planned with two stopping rules: if the observed difference between the two rates was more than twice the clinically relevant difference, misoprostol would be declared clinically ineffective, or if the observed difference was less than 2%, misoprostol would be declared to be as clinically effective as gemeprost.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness appears to have been intention to treat. The health outcomes were the rate of delivery within 24 hours, the median time from prostaglandin commencement to delivery, median time to discharge, incidence of maternal adverse events, pain scores, and analgesic usage. A visual analogue scale assessment of pain was performed at 3-hourly intervals. The study groups were comparable in terms of the indication for pregnancy interruption, maternal age, race, parity, and median gestational age at recruitment. The effect of covariates on the time to delivery or discharge was analysed using Kaplan-Meier survival functions with log rank tests.

**Effectiveness results**
Delivery within 24 hours occurred in 75.1% of women receiving gemeprost and 74.9% receiving misoprostol, (p=1.0). The median time from prostaglandin commencement to delivery was similar: gemeprost 13.7 hours (interquartile range: 9.0 - 23.5 hours) versus misoprostol 16.9 hours (interquartile range: 10.3 - 23.5 hours), (p=0.769). The median time to discharge was 30.2 (IQ range: 25.2 - 50.7) hours in the gemeprost group versus 32.8 (IQ range: 25 - 48) hours, (p=0.885). A significant reduction in the incidence of vomiting in the misoprostol group occurred: 34% versus 13.2%, (p=0.017). There was no significant difference in the incidence of maternal fever greater than 37.5 degree C, nausea, diarrhoea, or placental retention. Pain scores and analgesic usage were not significantly different between the two groups.

**Clinical conclusions**
This study demonstrated that the vaginal administration of misoprostol at a dose of 200 mcg every 6 hours is an effective method for producing pregnancy interruption in the second trimester. In addition, misoprostol was as efficient as the study institution's traditional abortifacient, gemeprost, in achieving pregnancy expulsion in 24 hours.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only individual clinical outcomes were reported.

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Only quantities of median requirement of gemeprost pessaries and misoprostol tablets per termination were reported separately from the costs. The prices of gemeprost pessaries and misoprostol tablets were reported separately. Cost analysis covered only the costs of gemeprost pessaries and misoprostol tablets per termination. The perspective adopted in the cost analysis was not explicitly specified. The price year was not specified.

**Indirect Costs**
Indirect costs were not included.
Currency
Australian dollars (Aus$).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
With a median requirement of 5 gemeprost pessaries and 3 misoprostol tablets per termination, the prostaglandin cost comparison was Aus$402.4 for a pregnancy interruption using gemeprost compared with Aus$1.20 for misoprostol.

Synthesis of costs and benefits
Costs and benefits were not combined, as the intervention (the use of intravaginal misoprostol) was the (weakly) dominant strategy (better or equal clinical outcomes with significantly superior pharmaceutical cost advantage).

Authors’ conclusions
Intravaginal misoprostol performs as effectively as gemeprost in achieving delivery in the second trimester without increase in adverse effects and displaying a significant cost advantage.

CRD COMMENTARY - Selection of comparators
The strategy of using gemeprost, as the standard prostaglandin used in the study institution in the decade preceding the study, was regarded as the comparator. You, as a database user, should consider whether this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high due to the double-blind, randomised nature of the study design. The study groups were comparable in terms of indication for pregnancy interruption, maternal age, race, parity, and median gestational age at recruitment. The effect of covariates on the time to delivery or discharge was analysed using Kaplan-Meier survival functions with log rank tests. The study sample appears to have been representative of the study population: women admitted to a hospital for second-trimester pregnancy interruption.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was therefore of cost-consequences design.

Validity of estimate of costs
Only quantities of median requirement of gemeprost pessaries and misoprostol tablets per termination were reported separately from the costs. Adequate details of the methods of cost estimation were not given and the price year and perspective adopted in the cost analysis were not reported. All potentially relevant cost components do not appear to have been included in the cost analysis. For example, the costs associated with maternal side effects, or storage requirements of the study drugs were not presented. The effects of alternative procedures on indirect costs were not addressed. Statistical analyses were not performed on cost data or resource consumption. The cost results may not be generalisable to other countries.
Other issues
The authors’ conclusions appear to be justified given the uncertainties in the data. The issue of generalisability to other settings was not addressed although some comparisons were made with other studies. The degree to which the study sample was representative of the study population was partially addressed in that the majority of fetuses in this study were alive at the time termination of pregnancy commenced.

Implications of the study
Ongoing studies are in place to further refine the dose and dosing interval of misoprostol. The effectiveness, lower side-effect profile, reduced cost, and less rigid storage requirements of intravaginal misoprostol compared with gemeprost render this prostaglandin analogue the preferred agent for medical pregnancy interruption in the second trimester.

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