

Oral misoprostol for induction of labour at term: randomised controlled trial

Jodie M Dodd, Caroline A Crowther, Jeffrey S Robinson

Abstract

Objective To compare oral misoprostol solution with vaginal prostaglandin gel (dinoprostone) for induction of labour at term to determine whether misoprostol is superior.

Design Randomised double blind placebo controlled trial.

Setting Maternity departments in three hospitals in Australia.

Population Pregnant women with a singleton cephalic presentation at $\geq 36+6$ weeks' gestation, with an indication for prostaglandin induction of labour.

Interventions 20 μg oral misoprostol solution at two hourly intervals and placebo vaginal gel or vaginal dinoprostone gel at six hourly intervals and placebo oral solution.

Main outcome measures Vaginal birth within 24 hours; uterine hyperstimulation with associated changes in fetal heart rate; caesarean section (all); and caesarean section for fetal distress.

Results 741 women were randomised, 365 to the misoprostol group and 376 to the vaginal dinoprostone group. There were no significant differences between the two treatment groups in the primary outcomes: vaginal birth not achieved in 24 hours (misoprostol 168/365 (46.0%) *v* dinoprostone 155/376 (41.2%); relative risk 1.12, 95% confidence interval 0.95 to 1.32; $P=0.134$), caesarean section (83/365 (22.7%) *v* 100/376 (26.6%); 0.82, 0.64 to 1.06; $P=0.127$), caesarean section for fetal distress (32/365 (8.8%) *v* 35/376 (9.3%); 0.91, 0.57 to 1.44; $P=0.679$), or uterine hyperstimulation with changes in fetal heart rate (3/365 (0.8%) *v* 6/376 (1.6%); 0.55, 0.14 to 2.21; $P=0.401$). Although there were differences in the process of labour induction, there were no significant differences in adverse maternal or neonatal outcomes.

Conclusions This trial shows no evidence that oral misoprostol is superior to vaginal dinoprostone for induction of labour. However, it does not lead to poorer health outcomes for women or their infants, and oral treatment is preferred by women.

Trial registration National Health and Medical Research Council, Perinatal Trials, PT0361.

Introduction

Induction of labour is a common intervention.¹ In 2002 in Australia, nearly 27% of pregnant women had

their labour induced.² Prostaglandins to induce labour are used in about 23% of all confinements.³ Misoprostol, an oral prostaglandin compound, is being used increasingly in induction of labour, with vaginal⁴ and oral⁵ administration, although it is unlicensed for this indication. We conducted a randomised double blind trial to compare 20 μg oral misoprostol solution with vaginal prostaglandin gel (dinoprostone) for induction of labour at term.

Methods

The study took place at the Women's and Children's Hospital and Lyell McEwin Health Service (South Australia) and the Hervey Bay Hospital (Queensland) between April 2001 and December 2004.

Inclusion, exclusion, and randomisation

If the attending obstetrician decided to induce labour we approached any women with a singleton pregnancy at $\geq 36+6$ weeks' gestation. We then obtained written informed consent. We excluded women with a "favourable" cervix (defined as a modified Bishop score of ≥ 7), any contraindication to vaginal birth, previous uterine surgery (including caesarean section), or ruptured membranes. Participants were randomised in variable blocks and stratified for parity (0 and 1-4) and collaborating centre (see bmj.com for more details).

Treatment schedules

Women in the misoprostol group took 20 μg misoprostol solution every two hours (to a maximum of six doses in 12 hours). Women randomised to dinoprostone vaginal gel (2 mg for nulliparous women and 1 mg for multiparous women) received it every six hours (to a maximum of two doses in 12 hours). Six weeks after the birth we posted women a questionnaire relating to satisfaction with care.

Outcome measures

Our primary outcome measures were vaginal birth not achieved in 24 hours (including women who achieved vaginal birth after 24 hours and those women who had a caesarean section), caesarean section (all and for heart rate tracing indicating fetal distress), and uterine hyperstimulation with changes in fetal heart rate.⁶

Department of Obstetrics and Gynaecology, University of Adelaide, Women's and Children's Hospital, North Adelaide, SA 5006, Australia

Jodie M Dodd
maternal fetal
medicine specialist

Caroline A
Crowther
professor of obstetrics
and gynaecology

Jeffrey S Robinson
professor of obstetrics
and gynaecology

Correspondence to:
J Dodd
jodie.dodd@
adelaide.edu.au

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We defined uterine hyperstimulation as uterine tachysystole (with five or more contractions in a 10 minute period for two consecutive 10 minute periods) or uterine hypertonus (a uterine contraction lasting for more than two minutes).⁷ The changes in fetal heart rate that we considered abnormal included persistent decelerations (early, late, or variable decelerations), fetal tachycardia (fetal heart rate >160 beats per minute), fetal bradycardia (fetal heart rate <100 beats per minute), or reduced short term variability (<5 beats per minute).^{8,9} A single investigator blinded to the treatment allocated reviewed all fetal heart rate tracings from an induced labour to maintain consistency in interpretation.

For details of secondary outcome see bmj.com.

Data analysis

We analysed data on an intention to treat basis, blind to the allocated treatment. Before the analysis of any outcomes, we considered baseline characteristics and corrected those sufficiently imbalanced (more than 5% difference between treatment groups) using log binomial regression techniques. See bmj.com for more details.

Sample size

We calculated our sample size to detect clinically important differences in caesarean birth and vaginal birth not achieved within 24 hours. We were powered to detect a threefold difference in the less common outcome of uterine hyperstimulation with changes in fetal heart rate. For rare maternal and neonatal complications we were powered to detect only large differences (see bmj.com for details).

Results

Baseline characteristics at trial entry

Of 1319 eligible women approached, 939 (71.2%) provided written consent. Of these, 741 (78.8%) were admitted for induction of labour and randomised, 365 women to oral misoprostol, and 376 to vaginal dinoprostone. In total, 740 (99.9%) women received treatment as allocated. We had outcome data for all 741 women up to hospital discharge. Baseline characteristics were comparable except for initial Bishop score. We adjusted for this in the analyses and have presented adjusted results.

Outcomes

There were no significant differences between the two treatment groups for vaginal birth not achieved in 24 hours (misoprostol 46.0% *v* dinoprostone 41.2%), caesarean section (22.7% *v* 26.6%), caesarean section for fetal distress (8.8% *v* 9.3%), or uterine hyperstimulation with changes in fetal heart rate (0.8% *v* 1.6%). The table shows the relative risks and confidence intervals. Women randomised to misoprostol reported a more

What is already known on this topic

More than one in four pregnant women have induced labour

Prostaglandins are used to induce labour in more than one in five confinements, and misoprostol, a prostaglandin E₁ analogue, is being used increasingly

What this study adds

There was no significant difference between oral misoprostol and vaginal dinoprostone gel in the risk of not achieving vaginal birth in 24 hours, caesarean section, uterine hyperstimulation with changes in fetal heart rate, or adverse health outcomes for the woman and her infant

Women preferred the oral treatment

positive birth experience. For additional details of secondary outcome see bmj.com.

Discussion

Oral misoprostol was not associated with significant differences in the number of women who achieve vaginal birth within 24 hours after induction, caesarean section, or uterine hyperstimulation with changes in fetal heart rate, compared with vaginal dinoprostone gel.

Strengths and weaknesses

Our inclusion criteria represented the spectrum of indications for induction, and with over 70% of the women we approached agreeing to participate, our results have external validity and are applicable to the general obstetric population requiring induction of labour.

Our findings of reduced efficacy raise the possibility that our dosing regimen was too low. An incremental increase in dose to 40 µg after four hours in the absence of uterine activity, as described by Hofmeyr et al¹⁰ and later Dallenbach et al,¹¹ may be more appropriate, but difficult to achieve in our trial while maintaining blinding.

Unanswered questions and future research

The outcome of vaginal birth not achieved in 24 hours⁶ covers women who deliver by caesarean or who give birth vaginally after 24 hours. Vaginal birth achieved after 24 hours reflects a longer time from induction to birth and may reflect an inappropriately low dose of misoprostol. An increase in caesarean birth may reflect uterine hyperstimulation or worrying changes in fetal heart rate. For completeness and to ensure clarity of information, future trials should report both components of this composite outcome.

The extent of rare but potentially serious adverse complications such as uterine rupture, maternal or perinatal death, and neonatal acidaemia remains uncertain.

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Primary outcomes. Figures are numbers (percentages)

Outcome	Misoprostol (n=365)	Dinoprostone (n=376)	Relative risk (95% CI)*	P value
Vaginal birth not achieved in 24 hours	168 (46.0)	155 (41.2)	1.12 (0.95 to 1.32)	0.134
Uterine HSS with changes in FHR	3 (0.8)	6 (1.6)	0.55 (0.14 to 2.21)	0.401
Caesarean section:				
All	83 (22.7)	100 (26.6)	0.82 (0.64 to 1.06)	0.127
For fetal distress	32 (8.8)	35 (9.3)	0.91 (0.57 to 1.44)	0.679

HSS=hyperstimulation syndrome; FHR=fetal heart rate. *Adjusted for initial Bishop score at trial entry.

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Competing interests: None declared.

Ethical approval: Ethical approval was obtained from each institution.

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Opportunistic screening for alcohol use disorders in primary care: comparative study

Simon Coulton, Colin Drummond, Darren James, Christine Godfrey, J Martin Bland, Steve Parrott, Timothy Peters, on behalf of the Stepwice Research Team

Abstract

Objective To evaluate the efficacy and relative costs of different screening methods for the identification of alcohol use disorders in an opportunistic screening programme in primary care in the United Kingdom.

Design Comparative study.

Setting Six general practices in south Wales.

Participants 194 male primary care attendees aged 18 or over who completed an alcohol use disorders identification test (AUDIT) questionnaire.

Main outcome measures Scores on alcohol use disorders identification test and measures of γ -glutamyltransferase, aspartate aminotransferase, per cent carbohydrate deficient transferrin, and erythrocyte mean cell volume. Hazardous alcohol consumption, weekly binge consumption, and monthly binge consumption were ascertained using the time line follow back method over the previous 180 days. Alcohol dependence was determined using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. Unit costs were established from published resource references and from actual costs of analysing the biochemical tests.

Results A significant correlation was observed between alcohol consumption and score on the alcohol use disorders identification test (Pearson's correlation coefficient $r = 0.74$) and measures of γ -glutamyltransferase ($r = 0.20$) and per cent carbohydrate deficient transferrin ($r = 0.36$) but not aspartate aminotransferase ($r = 0.08$) or erythrocyte mean cell volume ($r = 0.02$). The alcohol use disorders identification test exhibited significantly higher sensitivity, specificity, and positive predictive value than all of the biochemical markers for hazardous consumption (69%, 98%, and 95%), weekly binge consumption (75%, 90%, and 71%), monthly binge consumption (66%, 97%, and 91%), and alcohol dependence (84%, 83%, and 41%). The questionnaire

was also more cost efficient, with a lower cost per true positive for all consumption outcomes.

Conclusion The alcohol use disorders identification test questionnaire is an efficient and cost efficient diagnostic tool for routine screening for alcohol use disorders in primary care.

Introduction

Primary care is viewed as the most promising location to offer brief interventions aimed at reducing excessive alcohol consumption,¹ yet to offer such interventions, general practitioners need access to screening instruments that are high in sensitivity and specificity, quick and easy to apply, and cost effective.

Several studies have questioned the value of measuring traditional biochemical markers of excessive alcohol consumption.^{2,3} The alcohol use disorders identification test (AUDIT) was developed as a short screening instrument for the identification of hazardous, harmful, or dependent alcohol users.^{4,5}

We evaluated the sensitivity, specificity, and positive predictive value of the test and biochemical markers in the context of an opportunistic screening programme in primary care. We also carried out an economic analysis to establish the relative costs per true positive for each of the screening methods.

Methods

Research nurses asked male attendees in primary care to complete an alcohol use disorders identification test questionnaire embedded within a general lifestyle questionnaire while awaiting appointments in six general practices in south west Wales.

All patients, irrespective of score, were invited to take part in a more detailed assessment. Those who

Department of Health Sciences, University of York, York YO10 5DD
Simon Coulton
senior research fellow
Christine Godfrey
professor
J Martin Bland
professor

Section of Addictive Behaviour, Division of Mental Health, St George's Hospital Medical School, University of London, London SW17 0RE
Colin Drummond
professor

Department of Clinical Psychology Training, Whitchurch Hospital, Cardiff CF14 7XB
Darren James
trainee clinical psychologist

Centre for Health Economics, Alcuin College, University of York
Steve Parrott
research fellow

Department of Biochemistry, King's College, University of London, London WC2R 2LS
Timothy Peters
professor

Correspondence to: S Coulton
sc21@york.ac.uk

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