Nitroglycerin as a uterine relaxant: a systematic review
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Authors’ objectives
To evaluate the effectiveness of nitroglycerin as a uterine relaxant.

Searching
The authors searched PubMed (from 1966 to 2001), the Cochrane Controlled Trials Register, the International Journal of Obstetric Anesthesia, and the reference lists of identified articles. They also searched abstracts from major scientific meetings, the American Society of Anesthesiologists, Canadian Anesthesiologists' Society, Society for Obstetric Anesthesia and Perinatology, Society of Obstetricians and Gynaecologists of Canada, and the American College of Obstetrics and Gynecology, for 3 years prior to the review for additional publications. The authors reported the search terms for the databases. Only published studies were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for the review. Two of the included studies used a crossover design.

Specific interventions included in the review
Studies using nitroglycerin as a uterine relaxant were potentially eligible. In the included studies, nitroglycerin was used in obstetrics and gynaecology for induction, version, foetal extraction, pre-eclampsia, tocolysis, cervical dilation, embryo transfer and dysmenorrhea. The dose and application (intravenous, vaginal or skin patch) of nitroglycerin varied in the included studies. The comparators were placebo, ritodrine, magnesium sulphate and prostaglandin.

Participants included in the review
The participants were obstetrics or gynaecology patients.

Outcomes assessed in the review
The primary outcome was the efficacy of the treatment with nitroglycerin, as defined in the individual studies. The reported occurrence of headaches, cardiovascular occurrences, and differences in blood-pressure or shortness of breath were extracted as secondary outcomes for each study. Other outcomes reported by the individual studies have also been noted.

How were decisions on the relevance of primary studies made?
The three authors specified that they all searched PubMed independently and that two authors each searched the Cochrane Controlled Trials Register and the International Journal of Obstetric Anesthesia. Details of how the studies were selected were not reported.

Assessment of study quality
The trials were assessed using the Jadad scale, which looks at randomisation, blinding and the description of withdrawals. Studies were included if they scored 2 or more out of a possible 5. All three authors independently assessed the studies, which were masked for the title, the author and the journal. Any disagreements were resolved by consensus.

Data extraction
The authors did not state exactly how the data were extracted for the review, or how many reviewers performed the data extraction, although it appeared to involve masking of the titles, authors and journal names.
Methods of synthesis
How were the studies combined?
The results of the studies were displayed graphically as L’Abbe plots of the proportion of patients improved in the treatment group against the proportion improved in the control group. Separate plots were used for studies of obstetric indications and gynaecologic purposes. The individual findings were summarised narratively and in tabular format.

How were differences between studies investigated?
In the narrative synthesis, the studies were grouped according to the indication for use of nitroglycerin: cervical ripening, acute tocolysis, ease of foetal extraction, success of external version, embryo transfer, development of pre-eclampsia and primary dysmenorrhoea.

The results of the individual studies were presented within topic groups.

Results of the review
Eleven RCTs, providing data from 945 patients, were included in the review.

Cervical ripening: for pregnancy terminations in the first trimester, less force was required to dilate the cervix when treated with nitroglycerin in comparison with no treatment (1 trial, n=24). Nitroglycerin was less effective than prostaglandin E2 for labour induction and was associated with more minor side-effects (1 trial, n=110).

Acute tocolysis: nitroglycerin given to arrest pre-term labour was more effective than a placebo (1 trial, n=33), but not more effective when compared with ritodrine (1 trial, n=133) or magnesium sulphate (1 trial, n=30). Headache was more common with nitroglycerin in these trials.

Ease of foetal extraction: nitroglycerin was not better than a placebo for uterine relaxation for foetal extraction at Caesarean section or for external version (1 trial, n=97). Maternal hypotension was more common with nitroglycerin.

Success of external version: nitroglycerin was not statistically significantly better than a placebo in the facilitation of external cephalic version, (1 trial, n=57). Adverse events were not reported.

Embryo transfer: a nitroglycerin spray did not ease embryo transfers in comparison with a placebo (1 trial, n=120). Unspecified adverse events were reported to be more common in the nitroglycerin group.

Development of pre-eclampsia: there were no differences in a small trial (n=40) comparing nitroglycerin and placebo patches that measured gestational age at development of pre-eclampsia, foetal growth restriction or pre-term delivery. When summarising these outcomes, more women receiving nitroglycerin had normal pregnancies, with a hazard reduction of 73%. There were no differences in adverse events.

Primary dysmenorrhoea: the application of nitroglycerin patches decrease pain in women with primary dysmenorrhoea in 2 crossover trials (n1=74, n2=14). The nitroglycerin-treated group reported more headaches.

Quality assessment: 9 of 11 assessed studies had a quality score of at least 3 (maximum 5).

Authors' conclusions
The authors concluded that although nitroglycerin is widely used, its superiority over currently used tocolytic agents is unproven. However, it decreases pain associated with dysmenorrhoea.

CRD commentary
The review involved a well-conducted search for evidence of the highest quality of study design (RCTs) for the effects of nitroglycerin. Care had been taken in the selection of studies, with independent raters going through databases, but other details of the search and decisions on which studies to include in the review were not reported. The review was restricted to published studies, which can introduce publication bias, potentially overestimating the positive effects of nitroglycerin. Several of the included studies had only a few participants and they might not have had sufficient power
to show significant treatment effects.

The decision not to pool the data statistically was justified given the differences in comparators and outcome measures between the studies. The narrative synthesis was less structured for secondary outcomes and was descriptive, rather than attempting to explain similarities and differences in the results of individual studies. Due to the disparate evidence base for the topic, the number of categories (7) was high in comparison with the number of studies (11). The validity of the studies was assessed in the review, but the assessment was not very detailed and important features of study conduct (e.g. allocation concealment) were missing. While small in number, the studies were not discussed with reference to study quality. The conclusions were graded into a class C recommendation (superiority unproven) and a class A recommendation (pain reduction), but the link to the quality of the evidence was unclear. The conclusion about pain relief for dysmenorrhea was based on two studies, one with only 14 patients, with low and moderate quality scores, and the quality assessment did not address the crossover design of these trials. The general conclusion that the superiority of nitroglycerin is unproven seems to be justified.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that further work is needed to elucidate the efficacy of nitroglycerin in the obstetric population.

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