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Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD002857.

DOI: [10.1002/14651858.CD002857.pub2](https://doi.org/10.1002/14651858.CD002857.pub2).

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[Intervention Review]

Uterine muscle relaxant drugs for threatened miscarriage

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ABSTRACT

Background

Miscarriage is the spontaneous loss of a pregnancy before the fetus is viable. Uterine muscle relaxant drugs have been used for women at risk of miscarriage in the belief they relax uterine muscle, and hence reduce the risk of miscarriage.

Objectives

To assess the effects for the woman and her baby of uterine muscle relaxant drugs when used for threatened miscarriage.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (10 September 2009).

Selection criteria

Randomised trials were included, and quasi-randomised trials were excluded. The participants were women with a pregnancy of less than 20 weeks' gestation having a threatened miscarriage. The interventions were any uterine muscle relaxing drugs (including tocolytic and antispasmodic agents) compared with either placebo or no drug. Primary outcomes for the review were miscarriage: defined as spontaneous pregnancy loss before fetal viability, baby death (stillbirth or neonatal death) and maternal death.

Data collection and analysis

Both review authors independently assessed studies for eligibility and trial quality, and extracted data.

Main results

One poor quality trial (170 women) was included. This compared a beta-agonist with placebo. There was a lower risk of intrauterine death associated with the use of a beta-agonist (relative risk (RR) 0.25, 95% confidence interval (CI) 0.12 to 0.51). Preterm birth was the only other outcome reported (RR 1.67, 95% CI 0.63 to 4.38).

Authors' conclusions

There is insufficient evidence to support the use of uterine muscle relaxant drugs for women with threatened miscarriage. Any such use should be restricted to the context of randomised trials.

PLAIN LANGUAGE SUMMARY

Uterine muscle relaxant drugs for threatened miscarriage

Not enough evidence to say if drugs that relax the muscles of the uterus can prevent threatened miscarriage.

Miscarriage is the loss of a baby in the very early weeks of pregnancy (before 20 weeks), before the baby would be able to survive on its own. This can be a devastating loss to expectant parents. Threatened miscarriage is when there is vaginal bleeding, and sometimes pain, but when the cervix remains closed. The review of studies found just one small trial on uterine relaxant drugs to prevent miscarriage, but the study provided insufficient data to be able to assess its effect adequately. More research is needed.

BACKGROUND

Miscarriage is the spontaneous loss of a fetus before it is viable. Caregivers and society may sometimes not consider this to be as tragic a loss as fetal death later in pregnancy, but often it results in a similar degree of mental suffering and anguish for the woman and her partner. Bleeding during the first half of pregnancy is usually referred to as threatened miscarriage, and this may or may not be associated with pain. Once the cervix begins to dilate, miscarriage is inevitable. Threatened miscarriage may present with anything from barely perceptible blood loss to profound life-threatening shock (McBride 1991).

Miscarriage is common. In fact, it is the most frequent complication of pregnancy. A recent population-based study in Finland of a random sample of 3000 Finnish women showed that by the end of their reproductive lives about 15% of these women had had at least one miscarriage (Hemminki 1999). One in seven clinically recognised pregnancies will miscarry, usually during the first 14 weeks of pregnancy. Over half the babies who miscarry during this period have a chromosomal abnormality (Szabo 1996). Other factors which influence the risk of miscarriage include maternal age greater than 35 years, multiple pregnancy (particularly monozygous), uterine malformations, polycystic ovaries, autoimmune factors (such as phospholipid antibodies, lupus anticoagulant and anti-cardiolipin antibodies), genetic disorders, poorly controlled diabetes, and having had two or more previous miscarriages. For some women, the specific cause may never be identified.

Ultrasound has the ability to establish rapidly and accurately whether a fetus is alive or not, and to predict whether a pregnancy is likely to continue when there is bleeding. In settings where ultrasound is available, this ability has rationalised the care of women with threatened miscarriage in early pregnancy. Attempts to maintain the pregnancy are only likely to be successful if the fetus is viable, and does not have a chromosomal abnormality. This is one explanation of the high failure rate for many interventions.

Increased uterine activity is associated with threatened miscarriage, although whether as cause or effect is often unclear. In the nineteenth century morphine was introduced in the belief it would reduce uterine activity, and so prolong the pregnancy (Charpentier 1883). Morphine is no longer used for threatened miscarriage, having been replaced many years ago by two groups of drug thought to have a more specific effect in relaxing uterine smooth muscle. The first were antispasmodic drugs, such as hyoscine. Later, myometrial relaxants, often referred to as tocolytic agents, became popular. These included isoxsuprine, ritodrine, and salbutamol.

In the past, the use of both antispasmodic and tocolytic drugs was widely advocated. There are few reliable data on use, but these agents seem to have been particularly popular in Latin America where they were recommended in several influential textbooks (De Lee 1945; León 1967; Schwarcz 1986). There is little current information about use of either group of drugs, but anecdotally they are thought to be used rarely, if at all, in the UK or USA. However, in other parts of the world their use may be more widespread. For example, in 2001, in an informal survey of 34 obstetricians from seven countries in Latin America, half reported prescribing myometrial relaxants (fenoterol, isoxsuprine)

or antispasmodics (scopolamine butylbromide) for women with threatened miscarriage (Lede 2001).

Myometrial relaxants are beta2-adrenoreceptor stimulants (beta-agonists), and antispasmodics are atropine-like agents derived from belladonna. The hypothesis is that beta 2-adrenoreceptor stimulants decrease the intensity and frequency of uterine contractions, hence reducing the risk of miscarriage. As they also affect smooth muscle elsewhere in the body, side-effects include palpitations, increased heart rate, flushing, nausea and vomiting, low serum potassium, and an increase in blood glucose levels. There are case reports of rare but serious adverse effects of these drugs associated with intravenous or intramuscular use for prevention of preterm delivery. These include myocardial ischemia (Vermees 1997), neutropenia (Onoe 1995) and acute pulmonary edema (Coggiola 1982). The risk of these occurring following threatened miscarriage, where oral use is the norm, is unclear, but is likely to be low.

Antispasmodic agents are an old class of drug used to treat common clinical features, such as intestinal, renal or hepatobiliary colic. They should be used with caution during pregnancy, and have considerable side-effects including dry mouth, thirst, difficulty in swallowing, flushing and cardiac arrhythmias. These drugs also cross the placenta, and can produce a variety of secondary effects, such as increased fetal heart rate. Studies on atropine in mice do not show teratogenic effects (USP DI 1999), but there are few data and no well-controlled studies in humans.

The aim of this review is to summarise the evidence to date about the benefits and harms associated with the use of uterine muscle relaxing drugs when used for women with a threatened miscarriage.

OBJECTIVES

To assess the effects for the woman and her baby of uterine muscle relaxant drugs when used for threatened miscarriage, before 20 weeks' gestation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials were included. Quasi-randomised trials were excluded.

Types of participants

All women with a pregnancy of less than 20 weeks' gestation having a threatened miscarriage. Threatened miscarriage was defined whenever possible as vaginal bleeding, with or without lower abdominal pain, but with a closed cervix.

Types of interventions

Any uterine muscle relaxing drugs (including tocolytic and antispasmodic agents), regardless of dose or how administered, compared to either placebo or no drug for women with threatened miscarriage.

Types of outcome measures

Main outcomes

1. Miscarriage: defined as spontaneous pregnancy loss before fetal viability (for most trials, the lower limit of viability is likely to be defined somewhere between 20 and 24 weeks of gestational age).
2. Baby death: stillbirth and neonatal death.
3. Maternal death.

Other outcomes

1. Low birthweight: birthweight less than 2500 g or less than 1500 g, or however defined in the trials.
2. Preterm birth: born before 37 completed weeks, or before 33 completed weeks, or however defined in the trials.
3. Abnormal baby (chromosomal or genetic abnormality, or malformation).
4. Antenatal hospital admission.
5. Blood transfusion for the woman.
6. Side-effects:
7. for myometrial relaxants: cardiovascular events, nausea, vomiting;
8. for antispasmodics: blurred vision, urinary retention, mucosal dryness, flushing, arrhythmias;
9. any side-effects for liveborn babies;
10. rare serious adverse events such as neutropenia, acute pulmonary oedema.
11. Women's feelings about treatment.
12. Measures of growth and development in childhood.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (10 September 2009).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

See: [Appendix 1](#) for additional searching carried out for the previous version of this review.

Data collection and analysis

Two review authors independently reviewed all potentially eligible trials for eligibility and extracted relevant data from each publication. All discrepancies were resolved by discussion.

We evaluated trials for methodological quality using the standard Cochrane criteria ([Alderson 2004](#)) of adequacy of allocation concealment: adequate (A), unclear (B), inadequate (C). Quasi-random studies, such as those using alternate allocation or allocation by days of the week, were excluded.

In addition, quality scores for completeness of follow-up and blinding of the assessment of outcome were assigned to each reported outcome using the following criteria.

For completeness of follow up

(A) less than 3% of participants excluded.

(B) 3% to 9.9% of participants excluded.

(C) 10% to 19.9% of participants excluded.

Excluded: if it is not possible to enter data based on intention to treat, and/or 20% of participants were excluded from that outcome.

For blinding of assessment of outcome

(A) Double blind, neither investigator nor participant knew or were likely to guess the allocated treatment.

(B) Single blind, either the investigator or the participant knew the allocation. Or, the trial is described as double blind, but side-effects of one or other treatment mean that it is likely that for a significant proportion (greater than 20%) of participants the allocation could be correctly identified.

(C) No blinding, both investigator and participant knew (or were likely to guess) the allocated treatment. Or, blinding not mentioned.

The main comparison was of any uterine muscle relaxant regimens versus either placebo or no uterine muscle relaxant. This was regardless of dose and duration of therapy and of mode of administration, and irrespective of whether in combination with another agent. Summary relative risks were calculated using a fixed-effect model, provided there was no significant heterogeneity. If there was significant heterogeneity, a random-effects model was used.

Sensitivity and subgroup analyses

Future versions of this review may include sensitivity and subgroup analyses, should sufficient data become available. A sensitivity analysis will exclude studies in which non-viable pregnancies could not be excluded at trial entry. Subgroup analyses for the main outcomes will be by type of drug, and by dose and duration of therapy.

RESULTS

Description of studies

Six potentially eligible studies were identified. Of these, one is included and five are excluded from the review. These studies are described in detail in the [Characteristics of included studies](#) table, and the [Characteristics of excluded studies](#) table respectively.

The only included study reported data for 170 women with threatened miscarriage between 6 and 20 weeks' gestation. This study compared buphenine hydrochloride, a beta-agonist, with placebo ([Egypt 1986](#)).

Of the five excluded studies, three were excluded because they were not randomised trials. Two used a quasi-random design ([Bigby 1969](#); [Ruppin 1981](#)) the third does not give an adequate description of the methods, but is unlikely to have been randomised ([Souka 1980](#)). The fourth study was excluded as the intervention was not a uterine muscle relaxant drug ([Hirahara 1998](#)). The fifth was excluded because it was a quasi-randomised trial and the intervention was not a uterine muscle relaxant drug ([Goisis 1975](#)).

Risk of bias in included studies

The only included study did not report methods for generation of the randomisation sequence, or for concealment of allocation. The study is reported to have been double-blind. However, despite the use of placebo both participants and care givers were likely to have been able to guess the allocation, for at least some of the women. beta-agonists increase the heart rate, and cause palpitations. The trial report states women allocated buphenine had palpitations and those allocated placebo did not, although frequencies in the two groups are not given.

Effects of interventions

One trial (170 women) was included, which compared a beta-agonist with placebo. In this study, there was a lower risk of intrauterine death associated with the use of a beta-agonist (relative risk (RR) 0.25, 95% confidence interval (CI) 0.12 to 0.51). Preterm birth was the only other outcome reported (RR 1.67, 95% CI 0.63 to 4.38).

DISCUSSION

Studies evaluating uterine muscle relaxant drugs were conducted over 20 years ago. Results of the single small trial included in this review should be interpreted with considerable caution. As discussed above, the methodological quality of this study is unclear. Also, outcome after birth for the babies is not reported. Although the study reports a reduction in intrauterine death, this is difficult to interpret without any information about survival up to discharge from hospital, and beyond, and it requires confirmation in other studies. It is also important to have reassurance about any possible effects on neonatal morbidity, and on later growth and development for the child. This single study is insufficient evidence for any reliable conclusions about whether uterine muscle relaxants are worthwhile for women with threatened miscarriage.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of uterine muscle relaxant drugs for women with threatened miscarriage. Any such use should be restricted to the context of randomised trials.

Implications for research

Uterine muscle relaxants should only be used for women with threatened miscarriage within the context of randomised trials. Such trials should report measures of morbidity and mortality for the baby, both before and after discharge from hospital, as well as congenital malformations and side-effects of the specific agents.

ACKNOWLEDGEMENTS

Thanks to Ariel Karolinski for his contribution to developing the protocol for this review.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

REFERENCES

References to studies included in this review

Egypt 1986 {published data only}

Soltan MH. Buphenine and threatened abortion. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1986;**22**:319-24.

References to studies excluded from this review

Bigby 1969 {published data only}

Bigby MAM, Barnard EE, Chatterji S. A clinical trial of isoxsuprine in the treatment of threatened abortion. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1969;**76**:934-5.

Goisis 1975 {published data only}

Goisis M, Candotti G. Treatment of threatened abortion in a serotonin antagonist. Clinico-statistical data [Sul trattamento delle minacce d'interruzione di gravidanza con un antienteraminico. Rilievi clinico-statistici]. *Minerva Ginecologica* 1975;**27**:773-8.

Hirahara 1998 {published data only}

Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. *Fertility and Sterility* 1998;**70**(2):246-52.

Ruppin 1981 {published data only}

Ruppin E, Ruppin J, Chelius HH. A double blind study of the treatment of threatened abortion with fenoterol hydrobromide. *Geburtshilfe und Frauenheilkunde* 1981;**41**:218-21.

Souka 1980 {published data only}

Souka AR, Osman M, Sibaie F, Einem MA. Therapeutic value of indomethacin in threatened abortion. *Prostaglandins* 1980;**19**:457-60.

Additional references

Alderson 2004

Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Charpentier 1883

Charpentier, editor. *Traité pratique des accouchements*. Paris: Bailliers, 1883.

Coggiola 1982

Coggiola F, Scarrone G, Cabiati EG. 3 cases of acute pulmonary edema in pregnant women treated with tocolytics and betamethasone. *Minerva Ginecologica* 1982;**34**:191-4.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

De Lee 1945

De Lee-Greenhill, editor. *Principios y práctica de la obstetricia*. México: Hispano-Americana, 1945.

Hemminki 1999

Hemminki E, Forssas E. Epidemiology of miscarriage and its relation to other reproductive events in Finland. *American Journal of Obstetrics and Gynecology* 1999;**181**:396-401.

Lede 2001

Lede R. Personal communication 2001.

León 1967

León J, Corneli O, editors. *Manual de obstetricia*. Buenos Aires: El Ateneo, 1967.

McBride 1991

McBride WZ. Spontaneous abortion. *American Family Physician* 1991;**43**:175-82.

Onoe 1995

Onoe T, Takahashi Y, Noda Y. Ritrodine-induced neutropenia in two cases of threatened premature delivery. *Nippon Sanka Fujinka Gakkei Zasshi* 1995;**47**:283-6.

Schwarcz 1986

Schwarcz R, Duverges C, Diaz A, Fecsina R, editors. *Obstetricia*. Buenos Aires: El Ateneo, 1986.

Szabo 1996

Szabo I, Szilagyi A. Management of threatened abortion. *Early Pregnancy* 1996;**2**:233-40.

USP DI 1999

Drug Information for the Health Care Professional. United State Pharmacopeial Dispensing Information, 19th edition 1999; Vol. 1.

Vermes 1997

Vermes E, Leroy G, Halphen C, Guyon P, Labib M, Stolz JP, et al. Myocardial infarction in a pregnant woman during salbutamol therapy. *Archives des Maladies du Coeur et de Vaisseaux* 1997;**90**:1651-4.

References to other published versions of this review

Prendiville 1995

Prendiville WJ. Tocolytics/antispasmodics for threatened miscarriage. [revised 24 March 1993]. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.). *Pregnancy and Childbirth Module*. The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Egypt 1986

Methods	'Randomized double blind' but no further details. Exclusions: 8 women (4%), 4 in each group. with missed abortion or hydatidiform mole, diagnosed after randomisation.
Participants	178 women aged 17-43 years at 6-20 weeks' gestation with vaginal bleeding and cramps or labour-like pains.
Interventions	Exp: buphenine hydrochloride 6 mg x 3/day for 3 days, then 6 mg x 2/day for 2 days, then 6 mg/day for 2 days. Control: placebo tablets. Both groups: ultrasound after one week. Trial intervention repeated if further symptoms.
Outcomes	Women: none reported. Baby: intrauterine death (miscarriage or stillbirth), preterm birth (< 37 completed weeks).
Notes	If imminent miscarriage, women in both groups admitted for 2 hr iv infusion 5 mg buphenine hydrochloride in 500 ml 5% dextrose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ctrl: control
exp: experimental
hr: hour
iv: intravenous

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bigby 1969	Quasi-random design, using alternate allocation. Participants: 60 women at less than 28 weeks' gestation with a positive pregnancy test, lower abdominal pain, vaginal bleeding and a closed cervix. Interventions: isoxsuprine versus placebo. Outcomes: side-effects pre-eclampsia, antepartum haemorrhage, fetal death, birthweight < 2.5 kg, congenital abnormalities.
Goisis 1975	Quasi-random design, using alternate assignment. Intervention: it is not a uterine muscle relaxant drug. It was an antienteraminic (anti-serotonine drug, named 1-metil-carbobenzosi-diidrolisergamina) drug.
Hirahara 1998	Intervention not a uterine muscle relaxant, participants did not have threatened miscarriage. Study design: randomised trial. Participants: 48 women with history of recurrent miscarriage and hyperprolactinaemia. Intervention: bromocriptine versus no bromocriptine. Outcomes: conception, miscarriage, livebirth.
Ruppin 1981	Quasi-random design, using date of birth. Participants: 112 women with threatened miscarriage.

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Study	Reason for exclusion
	Interventions: fenoterol hydrobromide versus placebo. Outcomes: fetal death, gestation at birth.
Souka 1980	Methods not clearly described, but seems likely this was not a randomised trial. Described as "treatment randomly allocated to the patients on condition of equal sample size". Women who miscarried within 24 hours or recruitment were excluded, but nevertheless the four study groups are each reported as having 25 women. Participants: 100 women with threatened miscarriage at 6-20 weeks. Interventions: progesterone versus belladonna and phenobarbitone versus indomethacin versus placebo. Outcomes: miscarriage, side-effects.

DATA AND ANALYSES

Comparison 1. Uterine muscle relaxants versus placebo/no relaxants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intrauterine death (miscarriage or stillbirth)	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.12, 0.51]
1.1 Beta-agonists	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.12, 0.51]
2 Preterm birth	1	170	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.63, 4.38]
2.1 Beta-agonists	1	170	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.63, 4.38]

Analysis 1.1. Comparison 1 Uterine muscle relaxants versus placebo/no relaxants, Outcome 1 Intrauterine death (miscarriage or stillbirth).

Analysis 1.2. Comparison 1 Uterine muscle relaxants versus placebo/no relaxants, Outcome 2 Preterm birth.

APPENDICES

Appendix 1. CENTRAL search strategy

1. ABORTION-THREATENED*:ME
2. MISCARRIAGE*
3. (SPONTANEOUS near (PREGNANCY next LOSS))
4. (SPONTANEOUS* near ABORT*)
5. (ABORTION near THREAT*)
6. (((#1 or #2) or #3) or #4) or #5)
7. (MYOMET* near RELAXANT*)
8. (UTERINE near RELAXANT*)
9. PARASYMPATHOLYTICS*:ME
- 10.TOCOLYSIS*:ME
- 11.TOCOLYTIC-AGENTS*:ME
- 12.TOCOLY*
- 13.RITODRIN*
- 14.RITODRINE*:ME
- 15.SALBUTAMOL
- 16.TERBUTALIN*
- 17.TERBUTALINE*:ME
- 18.FENOTEROL
- 19.FENOTEROL*:ME
- 20.ISOXSUPRINE
- 21.ATROPIN*
- 22.ATROPINE*:ME
- 23.BELLADONNA
- 24.BELLADONNA*:ME
- 25.SCOPOLAMINE*:ME
- 26.SCOPOLAMINE*
- 27.((((((((((((((((#7 or #8) or #9) or #10) or #11) or #12) or #13) or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22) or #23) or #24) or #25) or #26)
- 28.(#27 and #6)

Authors ran this search in the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, 2004, Issue 2).

WHAT'S NEW

Date	Event	Description
10 September 2009	New search has been performed	Search updated. One new report added to Excluded studies (Goi-sis 1975) .

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 3, 2005

Date	Event	Description
20 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The protocol was written by Roberto Lede, Ariel Karolinski and Lelia Duley. For the review, Roberto Lede and Lelia Duley both assessed potentially eligible studies, and extracted data. Data were entered by Lelia Duley, and checked by Roberto Lede. Both review authors drafted the text of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Argentinian Institute for Evidence-Based Medicine, Argentina.
- University of Oxford, UK.

External sources

- Medical Research Council, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Threatened [*prevention & control]; Parasympatholytics [*therapeutic use]; Tocolytic Agents [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy