National Institute for Health and Care Excellence

Draft for consultation

Termination of pregnancy

[L] Medical termination of pregnancy after 24 weeks' gestation

NICE guideline <TBC>

Evidence reviews

April 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Medical termination of pregnancy after 24 weeks' gestation

Review question

What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

Introduction

The aim of this review is to determine the optimal regimen and route of administration for misoprostol (after mifepristone) after 24^{+0} weeks' gestation for women having a medical termination of pregnancy.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women who are having a medical termination of pregnancy after 24^{+0} weeks' gestation and received both mifepristone and misoprostol
Intervention	Route of misoprostol administration: • Vaginal • Sublingual • Buccal Dose of misoprostol • 100 micrograms (mcg) • 200 mcg • 400 mcg • 600 mcg • 800 mcg Dose interval (both interval between mifepristone and misoprostol [simultaneous, delayed] and interval between subsequent doses of misoprostol)
Comparison	All routes of administration, doses, number of doses, and dosing intervals listed above will be compared.
Outcome	**Critical outcomes:** • Failure to pass any products of conception • Uterine rupture • Incomplete abortion with the need for surgical intervention **Important outcomes:** • Time to expulsion (induction-to-abortion interval) • Diarrhoea • Haemorrhage requiring transfusion or ≥500 ml of blood loss

- Infection reported within 1 month of termination

mcg: micrograms

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

A systematic review of the clinical literature was conducted but no studies were identified which were applicable to this review question. This was also the case when no limit was applied to the minimum number of women in each intervention group.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

No studies were identified which were applicable to this review question (and so there are no evidence tables in Appendix D). No meta-analysis was undertaken for this review (and so there are no forest plots in Appendix E).

Quality assessment of clinical studies included in the evidence review

No studies were identified which were applicable to this review question.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Resource impact

Table 2: Units costs associated with medical termination of pregnancy

Resource	Unit costs	Source
Repeat misoprostol 7 microgram per 1 hour	£93.00 per unit	BNF 75

Evidence statements

No evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

One of the aims of medical termination of pregnancy is to pass the products of conception, and hence failure to pass any products of conception was considered as a critical outcome. The committee discussed that although uterine rupture is rare, it has very serious implications for the woman, hence it was considered as one of the critical outcomes. Incomplete abortion leading to the need for a surgical intervention can have implications for the woman and resources, hence it was included as a critical outcome.

Time to expulsion (induction-to-abortion interval) may differ with different regimens and can affect the acceptability of the regimen; hence it was included as an important outcome. Haemorrhage requiring transfusion or ≥500 ml of blood loss can be a serious complication of termination of pregnancy, and was therefore listed as one of the important outcomes. Diarrhoea during the procedure and infection within 1 month of the procedure are adverse events which may differ with different regimens, and hence were included as important outcomes. Patient satisfaction, although an outcome of interest for this group was not included in the review as other outcomes were prioritised, which were considered to be more relevant to this review question.

The quality of the evidence

No evidence was identified about the optimal regimen for medical termination of pregnancy after 24 weeks' gestation.

Benefits and harms

The committee noted, based on their knowledge and clinical experience, that there is concern of increased uterine rupture in women having a medical termination of pregnancy after a previous caesarean section. Also that there can be spontaneous uterine rupture resulting from the use of prostaglandins after 24 weeks' gestation. As a consequence, a more cautious approach towards medical termination after 24 weeks' gestation is often used, with a lower dose of prostaglandin being given. However the committee were aware that there is no evidence that lowering the dose of misoprostol is safer and that doing so may prolong the procedure for the woman and increase the failure rate.

The committee considered that when recommending the dose of misoprostol to use, it was important to get a balance between a dose which was too high, and therefore had the potential to cause uterine rupture, and a dose which was too low and would result in the

procedure lasting longer and possibly failing. They agreed that in the absence of any direct evidence it would be appropriate to base the dose on evidence for the optimal regimen for medical termination up to 24 weeks' gestation for women between 24^{+0} and 25^{+0} weeks' gestation. Using clinical experience and expertise, the committee agreed that the uterus is more sensitive to misoprostol with gestational age, and hence the initial loading dose of misoprostol used in the regimen for medical termination up to 24 weeks' gestation would not be needed for the regimen for women between $24+^{0}$ to and $25+^{0}$ weeks'.

Based on their knowledge and expertise, the committee agreed that the uterus becomes more sensitive to misoprostol with gestational age, and hence a lower dose misoprostol regimen would be needed for women with a gestational age beyond 24 weeks. The committee also noted that the recommended dose reductions in misoprostol would be in line with the international guidance from FIGO for this group (Morris 2017).

Based on their knowledge and experience, the committee agreed that women with a history of previous caesarean section or uterine surgery may be at higher risk of uterine rupture with increased doses of misoprostol as the uterus becomes more sensitive to misoprostol as gestation advances. Hence they agreed that further research regarding the efficacy of drug regimens for this subgroup will be beneficial to inform future practice. Therefore the committee made a research recommendation for efficacy of drug regimens for medical termination of pregnancy in this group (see Appendix L). The committee noted that a subgroup of the women with a history of previous caesarean section or uterine surgery needed to be prioritised for research considering the higher risk for this group, and hence instead of recommending research for the whole group, focussed on them.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question and no economic analysis was conducted. Whilst the recommendations are likely to result in a standardised dose of misoprostol being used for medical terminations of pregnancy after 24 weeks, this is not likely to have a significant resource impact because of the small number of women having this procedure. Any net effect is likely to be cost saving with effective standardised drug regimens needing fewer surgical interventions.

Other considerations

The committee were aware of guidelines from the Royal College of Obstetricians and Gynaecologists that recommend feticide is used for medical termination of pregnancy after 21^{+6} weeks' gestation, unless the termination is being conducted for lethal fetal anomaly or the woman does not wish feticide (RCOG 2010).

The evidence considered for this review question covered the gestational age range after 24^{+0} weeks' gestation. However, recommendations were made for women after 23^{+6} weeks' gestation to be consistent with the requirements of the 1967 Abortion Act.

References

No evidence was identified which was applicable to this review question.

Morris 2017

Morris, J. L., Winikoff. B., Dabash, R., Weeks, A., Faundes, A., Gemzell-Danielsson, K., Kapp, N., Castleman, L., Kim, C., Chung Ho, P., Visser, G. H. A. (2017). FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Gynecology & Obstetrics, 138, 363-366.

RCOG 2010

Royal College of Obstetricians and Gynaecologists (2010). Termination of pregnancy for fetal abnormality in England, Scotland and Wales: Report of a Working Party.

Appendices

Appendix A - Review protocol

Review protocol for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the optimal regimen for termination of pregnancy after 24 weeks, for example, for fetal anomaly?
Review question in guideline	What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?
Type of review question	Intervention
Objective of the review	To determine the optimal regimen and route of administration for misoprostol (after mifepristone) after 24+0 weeks' gestation
Eligibility criteria – population	Women who are having a medical termination of pregnancy after 24+0 weeks' gestation and received both mifepristone and misoprostol Exclusions: - Any studies with an indirect population
Eligibility criteria – intervention(s)	Route of misoprostol administration: • Vaginal • Sublingual • Buccal Dose of misoprostol: • 100 mcg • 200 mcg • 400 mcg • 600 mcg • 800 mcg Dose interval (both interval between mifepristone and misoprostol [simultaneous, delayed] and interval between subsequent doses of misoprostol)
Eligibility criteria – comparator(s)/control	1. All routes of administration, doses, number of doses, and dosing intervals listed above will be compared.
Outcomes and prioritisation	**Critical outcomes:** • Failure to pass any products of conception • Uterine rupture • Incomplete abortion with the need for surgical intervention **Important outcomes:** • Time to expulsion (Induction to abortion interval) • Diarrhoea • Haemorrhage requiring transfusion or ≥500ml of blood loss • Infection reported within 1 month of termination

Field (based on PRISMA-P	Content
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs - If insufficient RCTs: comparative prospective cohort studies with n≥50 per arm - If insufficient comparative prospective cohort studies: comparative retrospective cohort studies with n≥50 per arm
Other inclusion exclusion criteria	Inclusion: - English-language
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Caesarean section or hysterotomy: - Previous caesarean section and/or hysterotomy - No previous caesarean section or hysterotomy Feticide: - Feticide administered - No feticide administered
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Dates: from 1985 Only studies conducted from 1985 onwards will be considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991.
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual

Field (based on PRISMA-P	Content
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs • Newcastle-Ottawa scale for non-randomised studies The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: • 'Haemorrhage requiring transfusion or >500 loss': Statistical significance • 'Uterine rupture': Statistical significance • 'Failure ((i.e. failure to pass any products)': Statistical significance All other outcomes default values will be used of: 0.8 and 1.25 for relative risks which will be calculated for all dichotomous outcomes; 0.5 times SD (of the control group) for continuous outcomes
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National

Field (based on PRISMA-P	Content
	Guideline Alliance and chaired by Professor Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; mcg: micrograms; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B - Literature search strategies

Literature search strategy for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

The search for this topic was last run on 3rd May 2018. It was decided not to undertake a re-run for this topic in November 2018 as this is not a fast moving evidence base and there were unlikely to be any new studies published which would affect the recommendations.

Database: Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2018 May 02, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
Date of last search: 3rd May 2018

#	Searches
1	exp abortion/ use emczd
2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
4	Abortion Applicants/ use ppez
5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort$ or postabort$ or preabort$).mp.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).mp.
12	((f?etal$ or f?etus$) adj loss$).mp.
13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).mp.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).mp.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Mifepristone/ use ppez
17	mifepristone/ use emczd
18	(mifepriston$ or mifeprex$ or mifegyn$ or ru-486$ or ru486$ or ru-38486$ or ru38486$).mp.
19	16 or 17 or 18
20	Misoprostol/ use ppez
21	misoprostol/ use emczd
22	(misoprostol$ or cytotec$ or arthrotec$ or oxaprost$ or cyprostol$ or mibetec$ or prostokos$ or misotrol$).mp.
23	20 or 21 or 22
24	15 and 19 and 23
25	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.

#	Searches
26	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
27	meta-analysis/
28	meta-analysis as topic/
29	systematic review/
30	meta-analysis/
31	(meta analy* or metanaly* or metaanaly*).ti,ab.
32	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
33	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
34	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36	(search* adj4 literature).ab.
37	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38	cochrane.jw.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	letter/
41	editorial/
42	news/
43	exp historical article/
44	Anecdotes as Topic/
45	comment/
46	case report/
47	(letter or comment*).ti.
48	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49	randomized controlled trial/ or random*.ti,ab.
50	48 not 49
51	animals/ not humans/
52	exp Animals, Laboratory/
53	exp Animal Experimentation/
54	exp Models, Animal/
55	exp Rodentia/
56	(rat or rats or mouse or mice).ti.
57	50 or 51 or 52 or 53 or 54 or 55 or 56
58	letter.pt. or letter/
59	note.pt.
60	editorial.pt.
61	case report/ or case study/
62	(letter or comment*).ti.
63	58 or 59 or 60 or 61 or 62
64	randomized controlled trial/ or random*.ti,ab.
65	63 not 64

#	Searches
66	animal/ not human/
67	nonhuman/
68	exp Animal Experiment/
69	exp Experimental Animal/
70	animal model/
71	exp Rodent/
72	(rat or rats or mouse or mice).ti.
73	65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74	57 use ppez
75	73 use emczd
76	74 or 75
77	25 use ppez
78	26 use emczd
79	77 or 78
80	(or/27-28,31,33-38) use ppez
81	(or/29-32,34-39) use emczd
82	80 or 81
83	24 and 76
84	24 not 83
85	limit 84 to english language
86	limit 85 to yr="1985 -Current"
87	remove duplicates from 86

Database: Cochrane Library via Wiley Online
Date of last search: 3rd May 2018

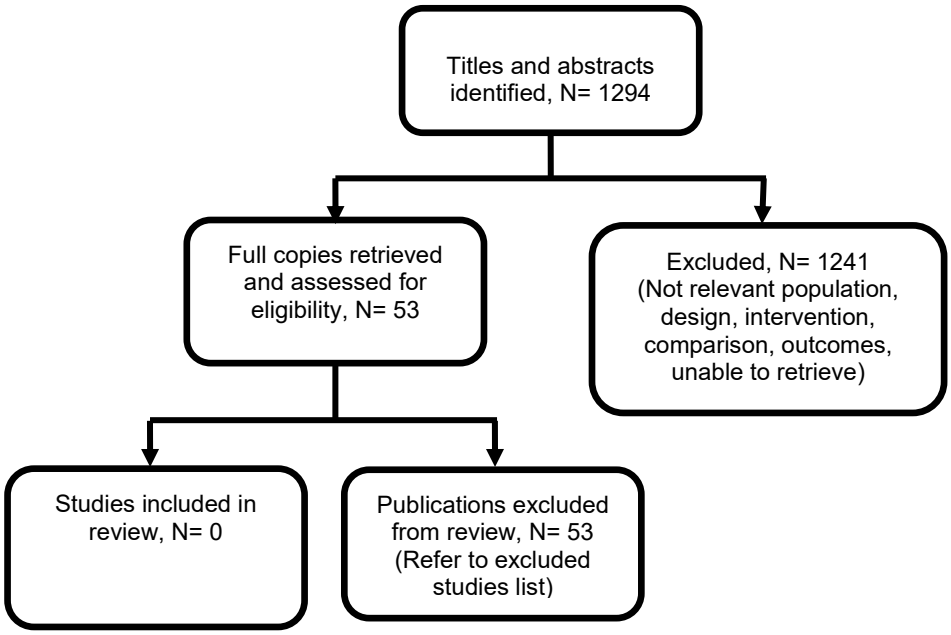
#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	(((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Mifepristone] this term only
#14	(mifepriston* or mifeprex* or mifegyn* or ru-486* or ru486* or ru-38486* or ru38486*):ti,ab,kw (Word variations have been searched)

#	Searches
#15	#13 or #14
#16	MeSH descriptor: [Misoprostol] this term only
#17	(misoprostol* or cytotec* or arthrotec* or oxaprost* or cyprostol* or mibetec* or prostokos* or misotrol*):ti,ab,kw (Word variations have been searched)
#18	#16 or #17
#19	#12 and #15 and #18 Publication Year from 1985 to 2018

Appendix C - Clinical evidence study selection

Clinical study selection for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

Figure 1: Study selection flow chart



Appendix D - Clinical evidence tables

Clinical evidence tables for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No evidence was identified which was applicable to this review question.

Appendix E - Forest plots

Forest plots for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No evidence was identified which was applicable to this review question.

Appendix F - GRADE tables

GRADE tables for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No evidence was identified which was applicable to this review question.

Appendix G - Economic evidence study selection

Economic evidence study selection for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No economic evidence was identified which was applicable to this review question.

Appendix H - Economic evidence tables

Economic evidence tables for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No economic evidence was identified which was applicable to this review question.

Appendix I - Economic evidence profiles

Economic evidence profiles for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No economic evidence was identified which was applicable to this review question.

Appendix J - Economic analysis

Economic analysis for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

No economic analysis was conducted for this review question.

Appendix K - Excluded studies

Excluded studies for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

Clinical studies

Study	Reason for Exclusion
Abbas, D. F., Blum, J., Ngoc, N. T. N., Nga, N. T. B., Chi, H. T. K., Martin, R., Winikoff, B., Simultaneous Administration Compared with a 24-Hour Mifepristone-Misoprostol Interval in Second-Trimester Abortion, Obstetrics and Gynecology, 128, 1077-1083, 2016	Population not in PICO: 13 to 22 weeks of gestation
Chaudhuri, P., Mandal, A., Das, C., Mazumdar, A., Dosing interval of 24 hours versus 48 hours between mifepristone and misoprostol administration for mid-trimester termination of pregnancy, 124, 134-138, 2014	Population not in PICO: 13 to 20 weeks of gestation
Constant, D., Harries, J., Malaba, T., Myer, L., Patel, M., Petro, G., Grossman, D., Clinical outcomes and women's experiences before and after the introduction of mifepristone into second-trimester medical abortion services in South Africa, PLoS ONE, 11 (9) (no pagination), 2016	Population not in PICO: 12 to 20 weeks of gestation
Dickinson, J. E., Doherty, D. A., Mifepristone-misoprostol second trimester medical termination in women with previous cesarean delivery, American journal of obstetrics and gynecology, 216 (1 Supplement 1), S495, 2017	Published as abstract only. Not enough information available to ascertain relevance
El-Refaey, H., Templeton, A., Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: A randomized comparison between two misoprostol regimens, 10, 475-478, 1995	Population not in PICO: 13-20 weeks of gestation
Esteve, J. L. C., Gallego, F. G., Llorente, M. P., Bermudez, S. B., Sala, E. S., Gonzalez, L. V., Texido, C. S., Late second-trimester abortions induced with mifepristone, misoprostol and oxytocin: a report of 428 consecutive cases, Contraception, 78, 52-60, 2008	Population not in PICO: Mean (SD) weeks of gestation = 21.8 (1.5)
Fairley, T. E., Mackenzie, M., Owen, P., Mackenzie, F., Management of late intrauterine death using a combination of mifepristone and misoprostol - Experience of two regimens, European journal of obstetrics gynecology and reproductive biology, 118, 28-31, 2005	Comparison not in PICO: Oral mifepristone vaginal misoprostol oral misoprostol versus oral mifepristone vaginal misoprostol (also, non-randomised study with n=29 and 20 in the two groups, respectively)
Garg, G., Takkar, N., Sehgal, A., Buccal Versus Vaginal Misoprostol Administration for the Induction of First and Second Trimester Abortions, 65, 111-116, 2015	Population not in PICO: 14 to 20 weeks of gestation
Gomperts, R., Kleiverda, G., Gemzell, K., The effectiveness of home medical abortions provided through telemedicine, International Journal of Gynecology and Obstetrics, 5), E299-E300, 2015	Published as abstract only. Not enough information available to ascertain relevance
Gomperts, R., Van Der Vleuten, K., Jelinska, K., Da Costa, C. V., Gemzell-Danielsson, K., Kleiverda, G., Provision of medical	Population not in PICO: N = 29 had a gestational age of 13 weeks or more

Study	Reason for Exclusion
abortion using telemedicine in Brazil, Contraception, 89, 129-133, 2014	
Haimov-Kochman,R., Arbel,R., Sciaky-Tamir,Y., Brzezinski,A., Laufer,N., Yagel,S., Risk factors for unsuccessful medical abortion with mifepristone and misoprostol, Acta Obstetricia et Gynecologica Scandinavica, 86, 462-466, 2007	Population not in PICO: Gestational age 34 to 57 days
Hajri, S., Blum, J., Gueddana, N., Saadi, H., Maazoun, L., Chelli, H., Dabash, R., Winikoff, B., Expanding medical abortion in Tunisia: Women's experiences from a multi-site expansion study, Contraception, 70, 487-491, 2004	Population not in PICO: Gestational age <56 days
Haque, L., Fatima, F., Mathur, M., Ashok, P., Medical management of late intrauterine death using a combination of mifepristone and misoprostol, International Journal of Gynecology and Obstetrics, 3), S810, 2012	Published as abstract only. Not enough information available to ascertain relevance
Hedley, A., Trussell, J., Turner, A. N., Coyaji, K., Ngoc, N. T., Winikoff, B., Ellertson, C., Differences in efficacy, differences in providers: results from a hazard analysis of medical abortion, Contraception, 69, 157-63, 2004	Population not in PICO: Gestational age 63 days or less
Heikinheimo, O., Suhonen, S., Haukkamaa, M., One- and 2-day mifepristone-misoprostal intervals are both effective in medical termination of second-trimester pregnancy, Reproductive BioMedicine Online, 8, 236-239, 2004	Population not in PICO: Gestation < 24 weeks
Hinshaw, K., El-Refaey, H., Rispin, R., Templeton, A., Mid-trimester termination for fetal abnormality: Advantages of a new regimen using mifepristone and misoprostol, British Journal of Obstetrics and Gynaecology, 102, 559-560, 1995	Population not in PICO: Gestation 13 to 22 weeks
Ho, P. C., Ngai, S. W., Liu, K. L., Wong, G. C. Y., Lee, S. W. H., Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy, 90, 735-738, 1997	Population not in PICO: Gestation 14 to 20 weeks
Hoopmann, M., Hirneth, J., Pauluschke-Frohlich, J., Yazdi, B., Abele, H., Wallwiener, D., Kagan, K. O., Influence of mifepristone in induction time for terminations in the second and third trimester, Geburtshilfe und Frauenheilkunde, 74, 350-354, 2014	Comparison/analyses not in PICO
Jannet,D., Aflak,N., Abankwa,A., Carbonne,B., Marpeau,L., Milliez,J., Termination of 2nd and 3rd trimester pregnancies with mifepristone and misoprostol, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 70, 159-163, 1996	Non-comparative study (intervention) / analyses not in PICO
Jyothi, S, Pallavi, Mnv, Medical abortion by mifepristone with oral versus vaginal misoprostol, 56, 529-531, 2006	Population not in PICO: Gestation < 9 weeks
Kahn,J.G., Becker,B.J., MacIsaa,L., Amory,J.K., Neuhaus,J., Olkin,I., Creinin,M.D., The efficacy of medical abortion: A meta-analysis, Contraception, 61, 29-40, 2000	Population not in PICO: Gestation up to 63 days
Kizer Ores, A., Rodriguez Perez, M. A., Prats Rodriguez, P., Comas Gabriel, C., Protocol of pregnancy termination. Our experience at Institute Dexeus, Journal of Maternal-Fetal and Neonatal Medicine, 1), 337, 2010	Published as abstract only. Not enough information available to ascertain relevance
Kopp Kallner, H., Gemzell Danielsson, K., Gomperts, R., The efficacy, safety, and acceptability of medical abortion provided by nurse midwives or physicians-a randomized controlled equivalence trial, European Journal of Contraception and Reproductive Health Care, 18, S77, 2013	Published as abstract only. Not enough information available to ascertain relevance

Study	Reason for Exclusion
Mark, A. G., Edelman, A., Borgatta, L., Second-trimester postabortion care for ruptured membranes, fetal demise, and incomplete abortion, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 129, 98-103, 2015	Comparison not in PICO: Misoprostol /- mifepristone
Mazouni, C., Vejux, N., Menard, J. P., Bruno, A., Boubli, L., d'Ercole, C., Bretelle, F., Cervical preparation with laminaria tents improves induction-to-delivery interval in second- and third-trimester medical termination of pregnancy, Contraception, 80, 101-104, 2009	Comparison/analyses not in PICO
Mazouni,C., Provensal,M., Porcu,G., Guidicelli,B., Heckenroth,H., Gamerre,M., Bretelle,F., Termination of pregnancy in patients with previous cesarean section, Contraception, 73, 244-248, 2006	Comparison/analyses not in PICO
Meena, S. R., Comparative Study of Mifepristone with Vaginal Misoprostol for First Trimester Termination of Pregnancy at Different Gestational Ages, Journal of Obstetrics and Gynecology of India, 66, 426-430, 2016	Population not in PICO: Gestation up to 63 days
Mentula, M., Heikinheimo, O., Risk factors of surgical evacuation following second trimester medical termination of pregnancy, Reproductive Sciences, 1), 235A, 2012	Population not in PICO: Gestation 13 to 24 weeks
Mentula, M., Kalso, E., Heikinheimo, O., Same-day and delayed reports of pain intensity in second-trimester medical termination of pregnancy: A brief report, 90, 609-611, 2014	Population not in PICO: Gestation 14 to18 weeks
Mentula,M., Heikinheimo,O., Risk factors of surgical evacuation following second-trimester medical termination of pregnancy, Contraception, 86, 141-146, 2012	Population not in PICO: Gestation 13 to 24 weeks
Ngai, S. W., Tang, O. S., Ho, P. C., Randomized comparison of vaginal (200 mug every 3 h) and oral (400 mug every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy, Human Reproduction, 15, 2205-2208, 2000	Population not in PICO: Gestation 14 to 20 weeks
Ngo, T. D., Park, M. H., Shakur, H., Free, C., Comparative effectiveness, safety and acceptability of medical abortion at home and in a clinic: a systematic review, Bulletin of the world health organization, 89, 360-70, 2011	Population not in PICO: Gestation up to 56 days
Ngoc,N., Blum,J., Nga,N., Raghavan,S., Winikoff,B., Medical abortion with misoprostol only versus mifepristone plus misoprostol: Results from a randomized controlled trial, International Journal of Gynecology and Obstetrics, #19th FIGO World Congress of Gynecology and Obstetrics Cape Town South Africa. Conference Start, S286-, 2009	Comparison not in PICO: Misoprostol alone versus mifepristone misoprostol
Nigam, A., Singh, V. K., Prakash, A., Vaginal vs. oral misoprostol for mid-trimester abortion, International Journal of Gynecology and Obstetrics, 92, 270-271, 2006	Population not in PICO: Gestation 12 to 20 weeks
Niinimaki, M., Suhonen, S., Mentula, M., Hemminki, E., Heikinheimo, O., Gissler, M., Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: Population register based study, BMJ, 342 (7804) (no pagination), 2011	Population not in PICO: Gestation up to 20 weeks
Nisand, I., Bettahar, K., Medical termination of pregnancy. Observational study in France, the aMaYa study, European Journal of Contraception and Reproductive Health Care, 18, S200, 2013	Published as abstract only. Not enough information available to ascertain relevance

Study	Reason for Exclusion
Perritt, J. B., Burke, A., Edelman, A. B., Interruption of nonviable pregnancies of 24-28 weeks' gestation using medical methods: release date June 2013 SFP guideline #20133, Contraception, 88, 341-9, 2013	(Systematic/narrative) review. Included studies checked for relevance.
Perritt, J. B., Edelman, A. B., Burke, A. E., Controversies in family planning: Management of lethal fetal anomalies in the third trimester, Contraception, 86, 93-95, 2012	Narrative review
Prine,L., Shannon,C., Gillespie,G., Crowden,W.A., Fortin,J., Howe,M., Dzuba,I., Medical abortion: Outcomes in a family medicine setting, Journal of the American Board of Family Medicine, 23, 509-513, 2010	Population not in PICO: Gestation up to 63 days
Puri, M., Tamang, A., Shrestha, P., Joshi, D., The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal, Reproductive health matters, Part S1. 22, 94-103, 2015	Population not in PICO: Gestation up to 9 weeks
Raghavan, S., Ngoc, N. T. N., Shochet, T., Winikoff, B., Clinic-level introduction of medical abortion in Vietnam, International Journal of Gynecology and Obstetrics, 119, 39-43, 2012	Population not in PICO: Gestation up to 56 days
Rose,S.B., Shand,C., Simmons,A., Mifepristone- and misoprostol-induced mid-trimester termination of pregnancy: a review of 272 cases, Australian and New Zealand Journal of Obstetrics and Gynaecology, 46, 479-485, 2006	Population not in PICO: Gestation 14 to 22 weeks
Ross, S., Sadler, L., Jackson, B., Stone, P., Time taken for completion of medical termination of pregnancy in the second trimester, Australian and New Zealand Journal of Obstetrics and Gynaecology, 56 (Supplement 1), 54, 2016	Published as abstract only. Not enough information available to ascertain relevance
Saokaew, S., Suan-Ek, P., Khusawangsri, C., Rattanangamkul, T., Netthip, J., Hongsamsibjet, S., Kengkla, K., Comparative effectiveness and safety of medical abortion for second-trimester pregnancy termination: A systematic review and network meta-analysis, 20 (9), A684, 2017	Published as abstract only. Not enough information available to ascertain relevance
Saurel-Cubizolles, M. J., Opatowski, M., David, P., Bardy, F., Dunbavand, A., Pain during medical abortion: A multicenter study in France, European journal of obstetrics gynecology and reproductive biology, 194, 212-217, 2015	Population not in PICO: Gestation up to 12 weeks
Shannon, C. S., Winikoff, B., Hausknecht, R., Schaff, E., Blumenthal, P. D., Oyer, D., Sankey, H., Wolff, J., Goldberg, R., Multicenter trial of a simplified mifepristone medical abortion regimen, Obstetrics and Gynecology, 105, 345-351, 2005	Population not in PICO: Gestation up to 50 days
Sharp, A., Navaratnam, K., Abreu, P., Alfirevic, Z., Short versus Standard Mifepristone and Misoprostol Regimen for Second- and Third-Trimester Termination of Pregnancy for Fetal Anomaly, Fetal Diagnosis and Therapy, 39, 140-146, 2016	Mixed population: Does not present subgroup analyses for the target population for the current review (non-randomised study with n=119; includes gestations from 13 weeks upwards; the median (range) gestation for the population is 22 (16.4 to 35.1) weeks).
Smith, A., Chebsey, C., Deneraz, A., Draycott, T., Siassakos, D., Intrauterine death and late termination of pregnancy: Method of delivery, complications and post-delivery support, BJOG: An	Published as abstract only. Not enough information available to ascertain relevance

Study	Reason for Exclusion
International Journal of Obstetrics and Gynaecology, 120, 462, 2013	
Vincienne, M., Anselem, O., Cordier, A. G., Le Ray, C., Tsatsaris, V., Benachi, A., Goffinet, F., Comparison of the induction-to-delivery interval in terminations of pregnancy with or without Dilapan-S, Fetal diagnosis and therapy, 43, 61-67, 2018	Comparison not in PICO
Wagaarachchi, P. T., Ashok, P. W., Narvekar, N. N., Smith, N. C., Templeton, A., Medical management of late intrauterine death using a combination of mifepristone and misoprostol, BJOG: An International Journal of Obstetrics & Gynaecology, 109, 443-7, 2002	Non-comparative study
Wildschut, Hajo, Both, Marieke I, Medema, Suzanne, Thomee, Eeke, Wildhagen, Mark F, Kapp, Nathalie, Medical methods for mid-trimester termination of pregnancy, Cochrane Database of Systematic Reviews, 2011	Systematic review. Included studies checked for relevance.
Wong, H. S., Comparison of regimes for second trimester medical abortion for fetal abnormality, 1), 38, 2014	Published as abstract only. Not enough information available to ascertain relevance
Wong, H. S., To compare the methods of pregnancy termination for fetal abnormality in the first and second trimesters, ISRN Obstetrics and Gynecology, (no pagination), 2012	(Narrative) review. Included studies checked for relevance.

PICO: population, intervention, comparison and outcomes

Economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix L - Research recommendations

Research recommendations for review question: What is the optimal regimen for medical termination of pregnancy after 24 weeks' gestation?

What is the effectiveness and safety of regimens using mifepristone and misoprostol for women who are having medical termination of pregnancy after 23^{+6} weeks' gestation and have had a previous caesarean section or uterine surgery?

Why this is important?

There is lack of evidence regarding the optimal regimen for women undergoing medical termination of pregnancy after 24 weeks' gestation. Optimal regimens for women with a history of previous caesarean section or uterine surgery are of particular interest as they may be at higher risk of uterine rupture with increased doses of misoprostol as the uterus becomes more sensitive to misoprostol as gestation advances. Further research regarding the efficacy of drug regimens for this subgroup is needed to address the clinical uncertainty around the risks and inform future practice.

Table 3: Research recommendation rationale

Research question	What is the effectiveness and safety of regimens using mifepristone and misoprostol for women who are having havingmedical termination of pregnancy after 23^{+6} weeks' gestation and have had previous caesarean section or uterine surgery?
Importance to 'patients' or the population	A safe and effective regimen for termination of pregnancy will reduce failure rates, increase patient acceptability and reduce complication rates
Relevance to NICE guidance	To address clinical uncertainty around the risks of medical termination of pregnancy using mifepristone and misoprostol after 24 weeks' gestation in women with history of prior caesarean section or uterine surgery
Relevance to the NHS	To determine the effectiveness and safety of current regimes for medical termination of pregnancy using mifepristone and misoprostol for medical termination of pregnancy after 24 weeks' gestation in women with history of prior caesarean section or uterine surgery
National priorities	A safe and effective regimen for termination of pregnancy in women with a history of prior caesarean section or uterine surgery will reduce uterine rupture, failure and haemorrhage, thus reducing morbidity among women undergoing medical termination of pregnancy after 24 weeks' gestation
Current evidence base	The relevant research has not been done
Equality	Applies to all women with a history of prior caesarean section or uterine surgery undergoing medical termination of pregnancy after 24 weeks' gestation

NHS: National Health Service; NICE: National Institute for Health and Care Excellence

Table 4: Research recommendation modified PICO table

Criterion	Explanation
Population	Women undergoing medical termination of pregnancy (TOP) after 24 weeks' gestation with history of prior caesarean section or uterine surgery.

Criterion	Explanation
Intervention	Medical termination of pregnancy with mifepristone or misoprostol (irrespective of dosage regime)
Comparator	None
Outcome	• Failure rate (failure to pass products of conception) as determined at 24 and 48 hours after starting misoprostol • Uterine rupture • Haemorrhage • Acceptability
Study design	Prospective cohort study
Timeframe	12 months
Additional information	None

TOP: termination of pregnancy