National Institute for Health and Care Excellence

Draft for consultation

Termination of pregnancy

[C] Anti-D prophylaxis for women up to 13+6 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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Anti-D prophylaxis for women up to 13^{+6} weeks' gestation

Review question

Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

Introduction

The aim of this review is to determine whether women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation should receive anti-D prophylaxis.

PICO table

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 RhD (or D) negative and having a medical (using mifepristone + misoprostol) or surgical (using vacuum aspiration) termination of a pregnancy up to 13^{+6} weeks' gestation
Intervention	Anti-D prophylaxis (minimum dose of 250 international units/50 micrograms, intra-muscularly) within 72 hours of the termination
Comparison	No anti-D prophylaxis
Outcome	**Critical outcomes:** • Subsequent anti-D isoimmunisation/sensitisation • Subsequent affected pregnancy • Allergic reaction (anaphylaxis) to anti-D prophylaxis in woman **Important outcomes:** • Infection from anti-D prophylaxis (as fractionated human blood product) • Patient satisfaction

RhD: Rhesus D

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 date limit was applied to the search.

See the literature search strategy in appendix B and the 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.

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

The committee agreed that the primary reason anti D prophylaxis is administered, is for the prevention of sensitisation to RhD antigen which could result in haemolytic disease of the new born in any subsequent pregnancies. Hence, anti-D isoimmunisation/sensitisation was considered as a critical outcome for this review. Being one of the most important and serious consequences of sensitisation, subsequent affected pregnancy was also considered as a critical outcome. The committee also considered potential harms of the administration of anti D prophylaxis. The risk of allergic reaction (anaphylaxis) to anti-D prophylaxis, although low, can be potentially serious and hence, it was included as a critical outcome.

The committee noted that Anti-D is a blood product and therefore has theoretical risk of transmission of infective agents. Hence, infection from anti-D prophylaxis (as fractionated human blood product) was included as an important outcome. Finally, patient satisfaction was selected as an important outcome as it is likely to be one of the important considerations for decision making.

The quality of the evidence

No evidence was identified about the administration of anti-D prophylaxis for termination of a pregnancy up to 13^{+6} weeks' gestation.

Benefits and harms

There was no evidence available on the use of anti-D prophylaxis for women having a termination of pregnancy up to 13^{+6} weeks' gestation. The committee noted that there was significant variation between different international and national guidelines in this area (The American College of Obstetricians and Gynaecologists, 2017; Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2015). The committee discussed that the benefits of anti-D at under 10 weeks have not been demonstrated, and any risks in not giving it are unlikely to be significant. In contrast, the benefits of not testing and administering anti-D are significant to women and providers, and there is precedent in other guidelines for not recommending its use in medical procedures at under 10 weeks (New Zealand Blood Service 111G130, 2013). Therefore, recommending a gestation cut-off of 10 weeks seemed reasonable, especially given the findings in Evidence Report G that this represented a reasonable upper limit for routine consideration of early medical abortion at home. The committee were aware of the recommendation of not offering anti-D rhesus prophylaxis to women undergoing medical termination of pregnancy for ectopic pregnancy and miscarriage in the NICE Guideline: Ectopic pregnancy and miscarriage: diagnosis and initial management [Recommendation 1.7.2, CG154]. The committee discussed that the risks and benefits of anti-D prophylaxis would be similar for women undergoing medical termination of pregnancy for other reasons.

The committee discussed that the situation for surgical procedures is less clear as there are theoretical concerns that greater feto-maternal haemorrhage could be possible in surgical procedures. The committee agreed that there would be little impact on continuing to test and use anti-D for surgical procedures where these are not same-day, but that providers should ensure their systems for doing so do not deter them from offering efficient pathways.

In the absence of evidence, for RhD (or D) negative women having a surgical termination before 10^{+0} weeks' gestation, the committee could only make a weak recommendation to consider anti-D prophylaxis based on historical practice and theoretical concerns that there may be greater feto-maternal haemorrhage with surgical compared with medical terminations. The committee agreed that further research in this area may allow for a stronger recommendation in future guidance. Hence, they made a research recommendation (see Appendix L).

Cost effectiveness and resource use

Anti-D is sourced from commercial suppliers using non-UK donors owing to concerns about the theoretical risk of contracting Creutzfeldt–Jacob disease. There have been shortages of it, and currently the lower doses that would normally be used in first trimester management are not marketed.

The national abortion statistics for England and Wales (Department of Health 2018) indicate that in 2017, 145,766 women had an abortion at under 10 weeks, of whom

116,135 had an early medical termination. Given a prevalence of RD negative of 15%, this means that 21,865 women were RhD negative, of whom 17,420 had an early medical termination. The current cost of the available anti-D is £46.50 (BNF), meaning the savings to the NHS from not giving anti-D to all women under 10 weeks' gestation would be £1.02m, or £0.81m if restricted only to the medical termination group. In addition to the drug costs, there would also be savings from not testing and its associated staff time.

The committee noted that one of the significant concerns raised by stakeholders was over the delay in care resulting from systems to check and treat women. They noted that practices were different between NHS and charitable providers with the latter using point of care (POC) testing which offered better woman-centred care. These systems are also significantly cheaper. To translate this into the NHS sector, they noted that it would be necessary to:

Use a CE marked system, to comply with EU In Vitro Diagnostics Regulation and assure the test is fit for purpose;

Agree a local SOP (Standard Operating Procedure) with the Trust's point of care (POC) Testing Group, to include regular Internal Control and External Quality Assessment testing;

If a POC result is inconclusive, treat the woman as RhD negative, unless time permits a sample to be tested in the Transfusion Laboratory, to resolve her RhD status.

Other considerations

The committee discussed that individualising care based on an individual woman's risk benefit profile and taking note of women's preferences were important considerations while making decisions regarding administering anti D prophylaxis. For example, anti-D is more likely to be beneficial in later gestations, in young women who are likely to desire pregnancies in the future and where there would be no delay to their care by testing. In contrast, for same-day procedures where aspiration is used, especially at earlier gestations and where the woman considers her family complete, an assessment may conclude that anti-D is not warranted. The committee thought that it is not helpful to have rigid guidance for this group and the current requirements of reporting all cases of "non-compliance" removes the autonomy of the woman to make an informed choice and of the clinician in advising her. However, due to the lack of evidence, the committee could not make a recommendation in this area.

References

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

American College of Obstetricians and Gynaecologists 2017

Prevention of Rh D alloimmunization. American College of Obstetricians and Gynaecologists. Practice Bulletin 181, August 2017.

British National Formulary

BNF. Anti-d (rh0) immunoglobulin. Available from https://bnf.nice.org.uk/medicinal-forms/anti-d-rh0-immunoglobulin.html [Accessed 18/02/2019]

Department of Health & Social Care 2018

Department of Health & Social Care. Abortion Statistics, England and Wales: 2017.

Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2015

Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Guidelines for the use of Rh(D) immunoglobulin (Anti-D) in obstetrics in Australia. East Melbourne: RANZCOG; 2015.

New Zealand Blood Service 2013

Use of Rh D immunoglobulin during pregnancy and the post-partum period 111G130. New Zealand Blood Service, 2013.

Appendices

Appendix A – Review protocols

Review protocol for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

Field (based on PRISMA-P	Content
Review question in SCOPE	Should women who are Rhesus negative and having termination of a first trimester pregnancy receive Rhesus prophylaxis?
Review question in guideline	Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?
Type of review question	Intervention
Objective of the review	To determine whether women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation should receive anti-D prophylaxis.
Eligibility criteria – population	Women who are RhD (or D) negative and having a medical (using mifepristone + misoprostol) or surgical (using vacuum aspiration) termination of a pregnancy up to 13^{+6} weeks' gestation Exclusions: - Studies with >10% of an indirect population
Eligibility criteria – intervention(s)	Anti-D prophylaxis (minimum dose of 250 international units/50 micrograms, intra-muscularly) within 72 hours of the termination
Eligibility criteria – comparator(s)/control	No anti-D prophylaxis
Outcomes and prioritisation	**Critical outcomes:** • Subsequent anti-D isoimmunisation/ sensitisation (as defined by anti-D in blood test; which is not due to anti-D prophylaxis. Anti-D prophylaxis is identified as the cause if anti-D was given in the previous 12 weeks, and immediately beforehand, her antibody screen was negative for anti-D: or if 12 weeks after anti-D prophylaxis was given, her antibody screen becomes negative for anti-D.) • Subsequent affected pregnancy (i.e., baby has D-antigen, which can lead to haemolytic disease of the new born/fetus; indicated by jaundice & anaemia in the new born; fetal need for intrauterine transfusion; or death due to hydrops fetalis, due to severe anaemia) • Allergic reaction (anaphylaxis) to anti-D prophylaxis in woman **Important outcomes:** • Infection from anti-D prophylaxis, as fractionated human blood product

Field (based on PRISMA-P	Content
	• Patient satisfaction
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs - If insufficient RCTs: comparative prospective cohort studies with n≥100 per arm - If insufficient comparative prospective cohort studies: comparative retrospective cohort studies with n≥100 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: Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Gestation: - ≤8+0 weeks - 8+1 - 10+0 weeks - 10+1 - 13+6 weeks Type of abortion: - Medical - Surgical
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 for medical termination and 1990 for surgical termination Only studies conducted from 1985 onwards will be considered for medical terminations included in 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. Studies conducted from 1990 onwards will be considered for surgical terminations included in this

Field (based on PRISMA-P	Content
	review question, as prior to this timeframe surgical techniques used in termination of pregnancy were different.
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
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 other 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 Minimum important differences: For subsequent anti-D isoimmunisation/ sensitisation, subsequent affected pregnancy and allergic reaction to anti-D prophylaxis in woman, statistical significance will be used as an MID. Important outcomes: For infection from anti-D prophylaxis and patient satisfaction 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

Field (based on PRISMA-P	Content
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 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; MID: minimally important difference; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RhD: Rhesus D; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategy for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

The search for this topic was last run on 19th October 2018. It was agreed to be unnecessary to undertake a re-run for this topic in November 2018 given that the original search was from only a month earlier.

Database: Medline & Embase (Multifile)

Last searched on **Embase Classic+Embase** 1947 to 2018 October 18, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to October 18, 2018

Date of last search: 19th October 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$).tw.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).tw.
12	((f?etal$ or f?etus$) adj loss$).tw.
13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).tw.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Rh-Hr Blood-Group System/ use ppez
17	Rh Isoimmunization/ use ppez
18	"Rho(D) Immune Globulin"/ use ppez
19	(blood group rhesus system/ or blood group, Rh/) use emczd
20	(Rh Isoimmunization/ or rhesus isoimmunization/ or rhesus immunization/) use emczd
21	(rhesus D antibody/ or rhesus antibody/ or rhesus antigen/) use emczd
22	((Rhesus$ or Rh$) adj3 (antibod$ or anti-bod$ or prophylax$ or immunoprophylax$ or isoimmuni?ation or immuni?ation or sensiti?ation)).mp.
23	(anti-D adj3 (antibod$ or anti-bod$ or prophylax$ or immunoprophylax$ or isoimmuni?ation or immuni?ation or sensiti?ation or serum$)).mp.
24	((Rh$ or anti-D) adj immune$ globulin$).mp.
25	((Rh$ or anti-D) adj immunoglobulin$).mp.
26	RhIG$.mp.

#	Searches
27	(Rhesus$ adj (negativ$ or factor$ or status$)).mp.
28	(Rh adj (factor$ or status$)).mp.
29	(Rh$ adj negativ$).mp.
30	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	15 and 30
32	limit 31 to english language
33	remove duplicates from 32
34	letter/
35	editorial/
36	news/
37	exp historical article/
38	Anecdotes as Topic/
39	comment/
40	case report/
41	(letter or comment*).ti.
42	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	randomized controlled trial/ or random*.ti,ab.
44	42 not 43
45	animals/ not humans/
46	exp Animals, Laboratory/
47	exp Animal Experimentation/
48	exp Models, Animal/
49	exp Rodentia/
50	(rat or rats or mouse or mice).ti.
51	44 or 45 or 46 or 47 or 48 or 49 or 50
52	letter.pt. or letter/
53	note.pt.
54	editorial.pt.
55	case report/ or case study/
56	(letter or comment*).ti.
57	52 or 53 or 54 or 55 or 56
58	randomized controlled trial/ or random*.ti,ab.
59	57 not 58
60	animal/ not human/
61	nonhuman/
62	exp Animal Experiment/
63	exp Experimental Animal/
64	animal model/
65	exp Rodent/
66	(rat or rats or mouse or mice).ti.
67	59 or 60 or 61 or 62 or 63 or 64 or 65 or 66
68	51 use ppez
69	67 use emczd
70	68 or 69
71	33 and 70

#	Searches
72	33 not 71

Database: Cochrane Library via Wiley Online

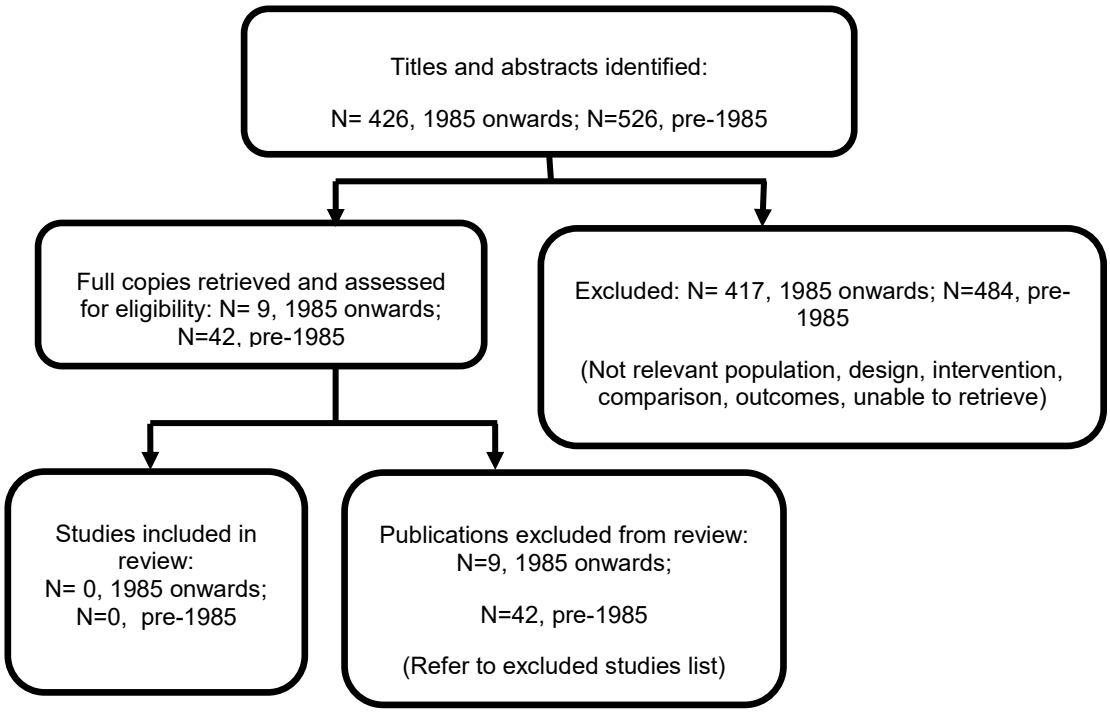
Date of last search: 19th October 2018

#	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: [Rh-Hr Blood-Group System] explode all trees
#14	MeSH descriptor: [Rh Isoimmunization] explode all trees
#15	MeSH descriptor: [Rho(D) Immune Globulin] explode all trees
#16	(((Rhesus* or Rh*) NEAR/3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmunisation or immunisation or sensitisation or isoimmunization or immunization or sensitization))):ti,ab,kw
#17	((((anti-D) NEAR/3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmunisation or immunisation or sensitisation or isoimmunization or immunization or sensitization or serum*)))):ti,ab,kw
#18	(((Rh* or anti-D) NEXT immune* globulin*)):ti,ab,kw
#19	(((Rh* or anti-D) NEXT immunoglobulin*)):ti,ab,kw
#20	(RhIG*):ti,ab,kw
#21	((Rhesus* NEXT (negativ* or factor* or status*))):ti,ab,kw
#22	((Rh NEXT (factor* or status*))):ti,ab,kw
#23	((Rh* NEXT negativ*)):ti,ab,kw
#24	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#12 AND #24

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

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

Appendix E – Forest plots

Forest plots for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

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

Appendix F – GRADE tables

GRADE tables for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

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

Appendix G – Economic evidence study selection

Economic evidence for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

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

Appendix H – Economic evidence tables

Economic evidence tables for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

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

Appendix J –Economic analysis

Economic analysis for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

Clinical studies

Study	Reason for Exclusion
Anonymous,, Abortion sequel--Rh problems, Northwest medicine, 70, 29, 1971	Letter to the editor (no relevant data)
Anonymous, Latent morbidity after abortion, British Medical Journal, 1, 506, 1973	Letter/editorial (no relevant data)
Anonymous,, Anti-D human immunoglobulin: new preparation. Important in young Rh D (-) women, Prescrire International, 10, 4-7, 2001	Narrative review
Anonymous, Anti-D human immunoglobulin. Important in young RH D (-) women, Prescrire International, 10, 4-7, 2001	Duplicate
Ascari, W. Q., Abortion and maternal Rh immunization, Clinical Obstetrics and Gynecology, 14, 625-634, 1971	Narrative review
Barron,S.L., Rh iso-immunization following abortion, Journal of Reproduction and Fertility, 27, 157-, 1971	Non-comparative study
Bliss, R. T., Schwartz, G. A., No significant risk of Rh sensitization in induced abortions, Journal of Abdominal Surgery, 19, 157-158, 1977	Non-comparative study (no treatment given)
Bliss,R.T., Schwartz,G.A., Minimal risk of Rh sensitization in induced abortions, Abdominal Surgery, 20, 35-36, 1978	Full-text unavailable.
Bowman,J.M., Rh sensitization following abortion, Canadian Medical Association Journal, 111, 1182-, 1974	Letter to the editor (no relevant data)
Brewer,C., Ball,E.W., Beard,R., Gittins,P., Comparative risks of rhesus autoimmunisation in two different methods of mid-trimester abortion, British Medical Journal Clinical Research Ed., 282, 1929-1930, 1981	Comparison not in PICO (no women received anti-D)
Chilcott, J., Lloyd Jones, M., Wight, J., Forman, K., Wray, J., Beverley, C., Tappenden, P., A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus-negative, Health Technology Assessment (Winchester, England), 7, iii-62, 2003	Population not in PICO: Pregnant women not undergoing termination of pregnancy
Clarke, C. A., Prevention of rhesus isoimmunization, Clinical Genetics, 1, 183-215, 1970	Narrative review
Clarke,C.A., Sheppard,P.M., Rhesus sensitization and abortion, BMJ, 4, 743-744, 1969	Letter to the editor (no relevant data)
Conti,M., Early legal abortion and Rh isoimmunization, Clinical and Experimental Obstetrics and Gynecology, 7, 168-172, 1980	Not in PICO (survey of students who were not pregnant)
Damstra-Wijmenga, S. M., Induced abortion and Rh-isoimmunisation, Lancet, 1, 1159-1160, 1969	Letter to the editor (no relevant data)
Davey, M. G., Prevention of rhesus immunization in Australia: the first seven years, Medical Journal of Australia, 2, 263-267, 1975	Comparisons not in PICO
Edwards, R. F., The place for anti d gamma globulin in abortion, Aust.N.Zj.Obstet.Gynaec, 10, 96-98, 1970	Comparison not in PICO (no women received anti-D)

Study	Reason for Exclusion
Fiala, C., Fux, M., Gemzell Danielsson, K., Rh-prophylaxis in early abortion, Acta obstetricia ET gynecologica scandinavica, 82, 892-903, 2003	Narrative review; included studies checked for relevance, none found.
Freda, V. J., Prevention of Rh disease, Haematologia, 6, 149-163, 1972	Narrative review
Freda,V.J., Gorman,J.G., Galen,R.S., Treacy,N., The threat of Rh immunisation from abortion, Lancet, 2, 147-148, 1970	Letter to the editor (no relevant data)
Fung Kee Fung, K., Eason, E., Crane, J., Armson, A., De La Ronde, S., Farine, D., Keenan-Lindsay, L., Leduc, L., Reid, G. J., Aerde, J. V., Wilson, R. D., Davies, G., Desilets, V. A., Summers, A., Wyatt, P., Young, D. C., Prevention of Rh alloimmunization, Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 25, 765-773, 2003	Guideline/(systematic?) review; included studies checked for relevance, none found
Gavin,P.S., Rhesus sensitization in abortion, Obstetrics and Gynecology, 39, 37-40, 1972	Non-randomised study; n=57 of whom n=24 had a spontaneous abortion with or without D
Gellen,J., Kovacs,Z., Szontagh,F.E., Boda,D., Surgical termination of pregnancy as a cause of rhesus sensitization, BMJ, 2, 1471-1472, 1965	Comparison not in PICO (no anti-D/treatment given)
Ghosh,S.C., Induced abortion and Rh-isoimmunisation, Lancet, 1, 1021-, 1969	Letter to the editor (no relevant data)
Glass, B., The relation of Rh incompatibility to abortion, American Journal of Obstetrics and Gynecology, 57, 323-332, 1949	Comparison not in PICO (no treatment given)
GLASS,B., Genetic research on the Rh blood types and the relation of Rh incompatibility to abortion, Bulletin of the School of Medicine (Baltimore, Md.), 33, 55-, 1948	Comparison (and probably also population) not in PICO (no treatment given)
Goldman, J. A., Eckerling, B., Prevention of Rh immunization following abortion, Harefuah, 83, 100-101+142, 1972	Not published in English; but appears to be the same data as those in Goldman
Goldman, J. A., Eckerling, B., Prevention of Rh immunization after abortion with Anti-Rh (D)-immunoglobulin, Obstetrics and Gynecology, 40, 366-370, 1972	Non-randomised study, n=88 (58 first trimester, 30 second trimester); no details of which kind of abortion they underwent although it may be curettage
Haymond, J. L., Giordano, A. S., Practical application of the Rh factor in congenital hemolytic anemia of the newborn (erythroblastosis fetalis), habitual abortion, and blood transfusions, The Journal of the Indiana State Medical Association, 39, 429-435, 1946	Full-text unavailable
Hensleigh, P. A., Leslie, W., Dixon, E., Reduced dose of Rh(o)(D) immune globulin following induced first-trimester abortion, American Journal of Obstetrics and Gynecology, 129, 413-416, 1977	Comparison not in PICO (no women received no treatment)
Hollan,S.R., Szelenyi,J.G., Soter,V.N., Hasitz,M., Therapeutic abortion as a possible source of Rh immunization, Acta Medica Academiae Scientiarum Hungaricae, 27, 337-340, 1970	Comparison not in PICO (no treatment given)
Hunt, A. B., The Rh factor in abortion, American Journal of Obstetrics and Gynecology, 53, 467-473, 1947	Comparison not in PICO (no treatment given)
Jabara, S., Barnhart, K. T., Is Rh immune globulin needed in early first-trimester abortion? A review, American journal of obstetrics and gynecology, 188, 623-627, 2003	Narrative (or semi-systematic review) review; included studies checked for relevance, none found.

Study	Reason for Exclusion
Jones,P., Rhesus sensitization and abortion, BMJ, 4, 496-, 1969	Letter to the editor (no relevant data)
Jorgensen,J., Rhesus-antibody development after abortion, Lancet, 2, 1253-1254, 1969	Letter to the editor (no relevant data)
Judelsohn, R. G., Berger, G. S., Wallace, R. B., Tiller, M. J., Rh immune globulin in induced abortion: Utilization in a high risk population, American journal of obstetrics and gynecology (Print), 114, 1031-1034, 1972	Non-comparative study/outcomes not in PICO
Katz, J., Marcus, R., The incidence of Rh iso-immunization in termination of early pregnancy, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 46, 843-844, 1972	Comparison not in PICO (no treatment given)
Katz,J., Marcus,R.G., Incidence of Rh immunization following abortion: possible detection of lymphocyte priming to Rh antigen, American Journal of Obstetrics and Gynecology, 117, 261-267, 1973	Comparison not in PICO (no treatment given)
Lobato,G., Soncini,C.S., RhD prophylaxis failure in Rio de Janeiro, Brazil, International Journal of Gynaecology and Obstetrics, 100, 276-277, 2008	Population not in PICO (severely RhD-alloimmunized pregnant women)
Lubusky,M., Prochazka,M., Simetka,O., Holuskova,I., Guideline for prevention of rhd alloimmunization in rhd negative women, Journal of Maternal-Fetal and Neonatal Medicine, 22nd European Congress of Perinatal Medicine,;#2010 Granada Spain. Conference Start, 593-Fetal, 2010	Published as abstract only. Not enough information to ascertain relevance.
Matthews,C.D., Matthews,A.E., Gilbey,B.E., Antibody development in rhesus-negative patients following abortion, Lancet, 2, 318-319, 1969	Letter to the editor (no relevant data)
Murray,S., Barron,S.L., Rhesus isoimmunization after abortion, British Medical Journal, 3, 90-92, 1971	Comparison not in PICO (no treatment given)
Normington,E.A., Jennison,R.F., Rhesus sensitization and abortion, BMJ, 4, 495-496, 1969	Letter to the editor (no relevant data)
Queenan, J. T., Role of Rho(D) immune globulin in induced abortions, Modern treatment, 8, 159-168, 1971	Narrative review
Queenan,J.T., Role of Rh o (D) immune globulin in induced abortions, Clinical Obstetrics and Gynecology, 14, 235-244, 1971	Narrative review
Sainio,S., Anti-D propylaxis in early pregnancy and abortion - What is the evidence?, Acta Obstetricia et Gynecologica Scandinavica, 91, 54-, 2012	Published as abstract only. Not enough information to ascertain relevance.
Simonovits, I., Efficiency of anti-D IgG prevention after induced abortion, Vox Sanguinis, 26, 361-367, 1974	Non-comparative study
Simonovits,I., Bajtai,G., Kellner,R., Kerenyl,M., Rucz,L., Szilvas,R., Takacs,S., Immunization of RhO(D)-negative secundigravidae whose first pregnancy was terminated by induced abortion, Haematologia, 8, 291-298, 1974	Observational study; population were women pregnant for the second time who had their first pregnancy medically terminated during first trimester before 1973 of whom 96 had received 50 mcg anti-D IgG and 301 had not been given anti-D IgG after their termination. No details presented about the characteristics of the women, the sampling method, or the method of medical termination.

Study	Reason for Exclusion
Sprague,C., The role of RhoGAM in therapeutic and spontaneous abortion, Hawaii Medical Journal, 29, 450-451, 1970	Non-comparative study
Stewart,F.H., Burnhill,M.S., Bozorgi,N., Reduced dose of Rh immunoglobulin following first trimester pregnancy termination, Obstetrics and Gynecology, 51, 318-322, 1978	Comparison not in PICO (no women received no treatment)
Whitehouse,W.L., Rhesus isoimmunization and therapeutic abortion, BMJ, 2, 759-760, 1969	Letter to the editor (no relevant data)

RhD: Rhesus D; PICO: population, intervention, comparison and outcome

Economic studies

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

Appendix L – Research recommendations

Research recommendations for review question: Should women who are RhD (or D) negative and having a termination of a pregnancy up to 13^{+6} weeks' gestation receive anti-D prophylaxis?

Should women have anti-D prophylaxis if they are having a surgical termination of pregnancy before 10^{+0} weeks' gestation and are RhD (or D) negative?

Why this is important?

When the scope of this guideline was being developed, the use of anti-D was identified by stakeholders as being one of the key issues. There is variation among international and national guidelines as to whether anti-D prophylaxis should be used in the first trimester, and if so whether this is in all treatments or just for surgical procedures, and at what gestations. Current practice in the NHS has been to administer anti-D prophylaxis routinely in all cases of termination of pregnancy where the woman is RhD negative. However, whilst this has little impact on traditional care pathways where women would return for a procedure at an interval, with modern, streamlined one-stop pathways the need to test RhD group and then to administer anti-D prophylaxis can introduce significant delays for the woman, or require her to return to the unit for an additional visit. This additional burden affects vulnerable groups most (e.g. those who find travelling difficult). The testing of RhD group and use of anti-D prophylaxis has a resource implication for the providers and wider NHS which must also be evaluated.

The national abortion statistics for England and Wales indicate that in 2017, 145,766 women had a termination of pregnancy before 10 weeks, of whom 29,631 had a surgical termination. Given a prevalence of RhD negative of 15%, this means that about 4400 women were RhD negative. The current cost of anti-D prophylaxis is £46.50, meaning the savings to the NHS from not giving anti-D to women having a surgical termination before 10 weeks' gestation would be over £200k. In addition to the drug costs, there would also be savings from not testing RhD status and staff time required to do this, and barriers to introducing cost-effective surgical pathways (e.g. same day surgical procedures using local anaesthesia) would be reduced.

Table 2: Research recommendation rationale

Research question	Should women have anti-D prophylaxis if they are having a surgical termination of pregnancy before 10^{+0} weeks' gestation and are RhD (or D) negative?
Importance to 'patients' or the population	If the use of anti-D prophylaxis is not necessary to prevent isoimmunisation for RhD (or D) negative women having a surgical termination before 10^{+0} weeks' gestation, testing and administering anti-D immunoglobulin would not be undertaken for this population. Women would need fewer tests, not require an injectable blood product, and there may be fewer delays. However, if surgical procedures do put the woman at risk of isoimmunisation, effective prevention of this would result in reduced morbidity and mortality in the neonate of any subsequent pregnancy.
Relevance to NICE guidance	For RhD (or D) negative women having a surgical termination before 10^{+0} weeks' gestation, the committee could only make a weak recommendation to consider anti-D prophylaxis based on historical practice and theoretical concerns that there may be greater feto-maternal haemorrhage with surgical compared with medical terminations. Further research in this area may allow for a stronger recommendation in future guidance.
Relevance to the NHS	The current practice of requiring testing and dispensing of anti-D prophylaxis can act as a barrier to the introduction of efficient woman-centred one-stop care pathways. If anti-D prophylaxis is not required for RhD (or D) negative

Research question	Should women have anti-D prophylaxis if they are having a surgical termination of pregnancy before 10^{+0} weeks' gestation and are RhD (or D) negative?
	women having a surgical termination before 10^{+0} weeks' gestation, the NHS would save in excess of £200k per year.
National priorities	The effective use of anti-D prophylaxis, when required, reduces stillbirth and neonatal morbidity which are national health priorities. However, identifying populations that do not require, and will not benefit from treatment, is a NHS priority.
Current evidence base	No evidence was identified to inform the use of anti-D prophylaxis for women having a termination of a pregnancy up to 13^{+6} weeks' gestation. Current practice, of giving anti-D to all women who are having a termination and are RhD (or D) negative, is based on observational trials largely conducted in the 1970s, when surgical techniques were different and before the routine use of ultrasound to date pregnancy, making their interpretation difficult. Feto-maternal haemorrhage was assessed using the Kleihauer test, but its accuracy in diagnosing feto-maternal haemorrhage is known to be limited by false positives arising from hereditary persistence of fetal haemoglobin (HPFH) in maternal red blood cells. Recent laboratory work with flow cytometry infers that much of what had been reported as feto-maternal haemorrhage in the first trimester may be due to maternal HPFH that are common in pregnancy. Therefore, it is unclear if there is greater feto-maternal haemorrhage with surgical compared with medical terminations and if, therefore, anti-D prophylaxis is required for RhD (or D) negative women having a surgical termination before 10^{+0} weeks' gestation.
Equality	Whilst this applies to all RhD (or D) negative women, delays caused by testing RhD status and administering anti-D prophylaxis may have the greatest effect on vulnerable women and/or women who find it difficult to travel.

RhD: Rhesus D; HPFH: hereditary persistence of fetal haemoglobin; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

Table 3: Research recommendation modified PICO table

Criterion	Explanation
Population	RhD (or D) negative women having a surgical termination of pregnancy before 10^{+0} weeks' gestation
Intervention	Anti-D prophylaxis
Comparator	No anti-D prophylaxis
Outcome	• Presence of fetal red blood cells in maternal serum identified by flow cytometry or other high-accuracy test after procedure • Calculation of volume of feto-maternal transfusion and extrapolation as to whether, and if so what dose of, anti-D would be sufficient to neutralise this • Anti-D isoimmunisation/sensitisation (defined by presence of anti-D in blood test that is not due to anti-D prophylaxis) • Patient satisfaction with RhD status testing and anti-D prophylaxis administration
Study design	Randomised controlled trial
Timeframe	2 years
Additional information	A parallel observational study using Rhesus positive women as an additional arm to the RCT could be a valid addition to record the first two outcomes. This could serve as an initial pilot to validate measurement techniques and to offer reassurance that the event rate of significant feto-maternal haemorrhage is low. That data should

Criterion	Explanation
	improve recruitment to the RCT by reassuring women that any risks are defined and quantified. An observational arm would also serve to deliver large numbers quickly to improve the overall power of detecting significant feto-maternal haemorrhage even at very low event rates. If events are detected, it could define what risk factors (e.g. in surgical technique or gestation) are associated. It could also extend to recruit women from later gestations as a potential pilot for future studies to determine at what gestation anti-D is needed.

RCT: randomized controlled trial