Anti-D prophylaxis for rhesus D (RhD)-negative women having an abortion of a pregnancy up to 13^{+6} weeks' gestation: a systematic review and new NICE consensus guidelines

Mia Schmidt-Hansen ,[1] Jonathan Lord ,[2] James Hawkins,[1] Sharon Cameron,[3] Anuja Pandey,[1] Elise Hasler,[1] Fiona Regan[4]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjsrh-2019-200536).

[1]National Guideline Alliance, Royal College of Obstetricians & Gynaecologists, London, UK
[2]Department of Obstetrics & Gynaecology, Royal Cornwall Hospitals NHS Trust, Truro, UK
[3]Sexual and Reproductive Health Services, NHS Lothian, Edinburgh, UK
[4]Department of Haematology, Imperial College Healthcare NHS Trust and NHS Blood & Transplant, London, UK

Correspondence to
Dr Mia Schmidt-Hansen, National Guideline Alliance, Royal College of Obstetricians & Gynaecologists, London SE1 1SZ, UK; MSchmidt-Hansen@rcog.org.uk

Received 18 November 2019
Revised 17 December 2019
Accepted 25 December 2019
Published Online First 20 January 2020

To cite: Schmidt-Hansen M, Lord J, Hawkins J, *et al*. *BMJ Sex Reprod Health* 2021;**47**:84–89.

ABSTRACT

Background In order to develop the 2019 National Institute for Health and Care Excellence (NICE) national guideline on abortion care for the National Health Service[1] we undertook a systematic review comparing anti-D prophylaxis to no prophylaxis in rhesus D (RhD)-negative women undergoing medical or surgical abortion of pregnancy at ≤13^{+6} weeks' gestation

Methods We searched Embase, Medline and the Cochrane Library on 19 October 2018. We also consulted experts and checked reference lists for any missed trials. Eligible studies were randomised controlled trials and non-randomised comparative studies, published in English from 1985 onwards, comparing anti-D prophylaxis to no anti-D prophylaxis in RhD-negative women undergoing medical or surgical abortion at ≤13^{+6} weeks' gestation, and reporting subsequent anti-D isoimmunisation/sensitisation or subsequent affected pregnancy. These outcomes were to be analysed as risk ratios in Review Manager 5.3 using the Mantel-Haenszel statistical method and a fixed or random effect model. The overall quality of the evidence was planned to be assessed using GRADE.

Results The search identified 426 potentially relevant studies of which none met the inclusion criteria. Recommendations for practice were therefore based on the clinical expertise of the guideline committee.

Conclusions (1) Offer anti-D prophylaxis to women who are Rhesus D negative who are having an abortion after 10^{+0} weeks' gestation. (2) Do not offer anti-D prophylaxis to women who are having a medical abortion up to and including 10^{+0} weeks' gestation. (3) Consider anti-D prophylaxis for women who are rhesus D negative and are having a surgical abortion up to and including 10^{+0} weeks' gestation.

Key messages

- The role of anti-D was systematically reviewed for the 2019 National Institute for Health and Care Excellence (NICE) guideline on abortion care.
- The new guidance represent a significant change in practice by not recommending anti-D to all rhesus D (RhD)-negative women having an abortion.
- Instead the guidance recommends anti-D to RhD-negative women having an abortion at >10 weeks' gestation and to consider it for surgical procedures at ≤10 weeks' gestation.

BACKGROUND

The use of anti-D to prevent isoimmunisation and subsequent haemolytic disease of the newborn (HDN) in future pregnancies has been one of the major successes in public health since the 1960s, with a significant reduction in the associated neonatal mortality rate.[2] Despite a comprehensive programme to prevent sensitisation, in England and Wales it is estimated fetal anaemia and HDN lead to 37 neonatal deaths a year and eight children born with major developmental problems.[3] However, there is no evidence of benefit from the use of anti-D in the

first trimester. For women attending for an abortion, the testing of their rhesus D (RhD) group, and the subsequent procurement and administration of anti-D, can introduce significant delays in their care and even require return to a remote hospital while recovering from an abortion. This is especially disruptive now that 70% of abortion procedures are managed as outpatients by an early medical abortion at home.[4] Furthermore, there have been some shortages of anti-D,[5] and both testing for RhD group and administering anti-D are costly.

The role of anti-D was identified as being an important topic for review by stakeholders in the scoping phase of the development of the abortion care clinical guideline by the National Institute for Health and Care Excellence (NICE). NICE provides guidance and advice to the National Health Service (NHS) in England on effective, good value healthcare. It is established in primary legislation in England, being a non-departmental public body (NDPB) accountable to the English Government's Department of Health and Social Care. NICE guidance and other recommendations are made by independent committees who are operationally independent of government. NICE has gained a reputation for rigour, independence and objectivity through the use of its transparent, best practice methodology of systematic review and guideline development. This work forms part of the 2019 NICE abortion care clinical guideline.[1] Specifically, the objective of this systematic review was to determine whether women who are RhD (or D) negative and having a surgical (using vacuum aspiration) or medical (using mifepristone and misoprostol) abortion of a pregnancy up to 13^{+6} weeks' gestation should receive anti-D prophylaxis.

METHODS

Search strategy and selection criteria

Studies eligible for this systematic review were randomised controlled trials and non-randomised comparative studies, published in English from 1985 onwards, comparing intramuscular anti-D prophylaxis (minimum dose of 250 IU/50 μg within 72 hours of the abortion) to no anti-D prophylaxis in women who are RhD (or D) negative and undergoing either medical abortion with mifepristone and misoprostol or surgical abortion using vacuum aspiration of a pregnancy up to 13^{+6} weeks' gestation. To be eligible, the studies also had to report at least one of the following outcomes: subsequent anti-D isoimmunisation/sensitisation, subsequent affected pregnancy, allergic reaction (anaphylaxis) to anti-D prophylaxis, infection from anti-D prophylaxis, and patient satisfaction.

On 19 October 2018, one author (EH) searched Embase Classic and Embase from 1947 to 18 October 2018; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) from 1946 to 18 October 2018; and the Cochrane Library via Wiley Online using the search strategies detailed in online supplementary appendix 1. Once this search had been performed we imposed a date limit on the records, with only records published from 1985 included. We also consulted experts in this field for any ongoing or missed trials and checked reference lists of systematic and narrative reviews.

One author (MSH) screened the results of the computerised search, classifying the records into 'potentially relevant' and 'definitely not relevant' based on the titles and abstracts. The full-texts of the potentially relevant studies were examined and these studies were classified into 'include' and 'exclude'. The full-text classification list was checked by three of the other authors (SC, JL, FR), and the final list of included studies was confirmed by consensus between these four authors.

Data analysis

Had there been any included studies, one of the authors (MSH) would have extracted the following data from each of the included studies: country, dates, aim, inclusion and exclusion criteria, number of patients, baseline characteristics (eg, age, parity, gravidity, and gestational age), medical/surgical abortion details, intervention details, and outcome data for each of the intervention groups (individual patient data would not have been sought). The same author would also have assessed the risk of bias in each of the studies using the Cochrane Collaboration quality checklist for randomised controlled trials[6] and the Newcastle-Ottawa Scale for non-randomised studies.[7] Selection bias and outcome reporting bias would have been assessed at study-level whereas performance bias, detection bias and attrition bias would have been assessed at outcome-level.

We had planned to analyse all dichotomous outcomes as risk ratios (RRs) and any continuous outcomes as mean differences (MDs) or standardised mean differences (SMDs), and to undertake meta-analyses in Review Manager 5.3[8] using the Mantel-Haenszel statistical method for RRs and the inverse variance statistical method for MDs and SMDs. Moreover, if the I^2 was below 50% we planned to use a fixed effect model whereas if I^2 was 50%–80% then we would have used a random effects model, and if the I^2 was above 80% we would not have pooled the studies, but rather reported the results individually for each study. Moreover, we had aimed to undertake subgroup analyses based on complex pre-existing medical conditions (none vs present), type of abortion (medical vs surgical) and gestational age ($\leq 8^{+0}$ weeks vs 8^{+1} to 10^{+0} weeks vs 10^{+1} to 13^{+6} weeks), but given the absence of any included studies we were unable to perform these analyses.

We planned to use the GRADE system to rate the quality of the evidence for each outcome using the

GRADE profiler Guideline Development Tool software,[9] and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[6]

The GRADE approach has five domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome, and uses the following criteria for assigning grade of evidence:

- High: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We had also aimed to include 'Summary of findings' tables to present the main findings in a transparent and simple tabular format. In particular, we planned to include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all the outcomes of interest listed above. The reason for any decrease in quality rating would also have been justified in footnotes of the Summary of Findings tables. The systematic review protocol is available online[10].

Patient and public involvement

Patients were involved in the design and conduct of this research, which was undertaken as part of the 2019 NICE guideline on abortion care.[1] The abortion care guideline was developed by a technical team based at the National Guideline Alliance (NGA) and a guideline committee recruited specifically for this purpose. The guideline committee consisted of a mix of clinical experts, commissioners and patient members, who collaboratively decided on the focus and specific parameters of the clinical question under consideration, including agreeing the actual research question, the interventions under comparison, and the outcomes. The patient members were also involved in agreeing the recommendations for practice and research that came out of this systematic review and are presented in the Discussion. The results of this research (the recommendations) have been disseminated through press statements and resultant mainstream press coverage, in addition to more abortion-community-specific dissemination through events run for abortion providers launching the NICE guideline on abortion care and through the Royal College of Obstetricians & Gynaecologists.

RESULTS

The search of all the databases identified 426 possibly relevant papers of which 417 papers were excluded based on title/abstract and nine papers were obtained for full-text review. All nine of these papers were excluded as they did not meet the inclusion criteria (figure 1; see also online supplementary appendix 2 for detailed exclusion reasons). Consequently, we found no studies for inclusion in this systematic review.

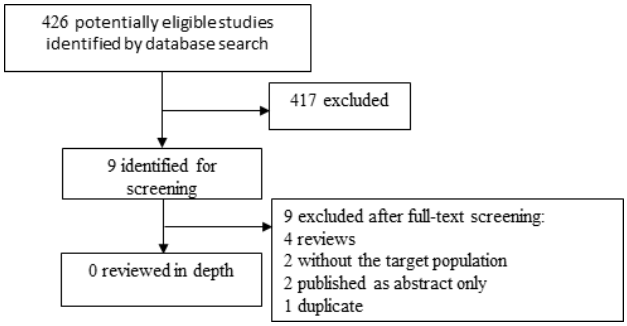

Figure 1 Flow chart illustrating study selection.

DISCUSSION

We found no evidence on the use of anti-D prophylaxis for women having an abortion of pregnancy up to 13^{+6} weeks' gestation despite undertaking a comprehensive systematic search. The committee recruited to develop the 2019 NICE guideline on abortion care[1] noted that there was significant variation between different international and national guidelines in this area, with most Scandinavian countries not recommending anti-D for medical abortion until 8–12 weeks' gestation but with other countries recommending its use in all abortions.[11–17] Epidemiological data comparing isoimmunisation rates in the Netherlands, where anti-D is not given to miscarriages under 10 weeks or abortions under 7 weeks, with Canada where anti-D is routinely administered showed that the prevalence of clinically significant antibodies was lower in the Netherlands.[18] The American National Abortion Federation has recently recommended not testing or administering anti-D for any abortion under 8 weeks, and to consider not doing so for medical abortions under 10 weeks.[19]

Current practice in the UK NHS is to give anti-D to all women who are having an abortion and are RhD-negative. However, testing for RhD status and then administering anti-D can result in significant delays for women. They may need to visit the service more than once to receive anti-D, and this can be a particular problem for women who are travelling a long way or who find it difficult to afford travel. The cost of testing for RhD status and giving anti-D also needs to be considered. With these points in mind, the NICE guideline committee made recommendations based on their knowledge and experience. The committee discussed the fact that the benefits of anti-D at under 10 weeks' gestation have not been demonstrated, accepting that there is a lack of published studies, and agreed that for women before 10^{+0} weeks' gestation the volume of fetal blood cells transmitted to the

mother is unlikely to cause maternal sensitisation, therefore any risks in not giving anti-D are unlikely to be significant. Many of the previous studies which had identified fetomaternal haemorrhage of sufficient volumes to cause maternal sensitisation in early pregnancy were undertaken in the 1970s using Kleihauer tests, which could not differentiate fetal red cells from maternal F cells and when gestations were calculated from last menstrual period rather than dating scans.[20] The committee were reassured by recent work using flow cytometry, using a method able to differentiate between fetal red cells and maternal F cells, which showed that fetal red cells were at a level well below the threshold for sensitisation following surgical evacuation at up to 12 weeks' gestation (personal communication S Hovarth 2019). Some fetal cells are present in the maternal circulation when no procedure is performed, and analysis in 110 patients with a mean gestational age of 18 weeks showed that the magnitude of exposure was similar following invasive procedures compared with measurements prior to these procedures.[21] The realisation that silent fetomaternal haemorrhage is common, yet sensitisation is rare, would infer that the prevention of sensitisation by using anti-D may be less important than has been previously assumed.

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.[22] Therefore, recommending a gestation cut-off of 10 weeks seemed reasonable, especially given the findings in Evidence Report G of the 2019 NICE guideline on abortion care[1] that this represented a reasonable upper limit for routine consideration of early medical abortion at home. This is also in line with the recommendation of not offering anti-D prophylaxis to women undergoing medical abortion for ectopic pregnancy and miscarriage in the NICE Guideline on ectopic pregnancy and miscarriage (recommendation 1.7.2),[22] and the risks and benefits of anti-D prophylaxis are likely to be similar for women undergoing medical abortion.

The situation for surgical procedures is less clear as there are theoretical concerns that greater fetomaternal haemorrhage could be possible in surgical procedures, although this may be less relevant with modern techniques using suction aspiration as opposed to sharp curettage. Because of this, anti-D prophylaxis before 10^{+0} weeks may be beneficial for this group, and there will be little impact on continuing to test and use anti-D for surgical procedures where these are not same-day, but providers should ensure their systems for doing so do not deter them from offering efficient pathways. However, in the absence of evidence, the precise benefits and risks of anti-D prophylaxis are unclear, and the uncertainty is highest for women having a surgical abortion before 10^{+0} weeks' gestation, so research is needed that examines whether women should have anti-D prophylaxis if they are having a surgical abortion up to and including 10^{+0} weeks' gestation and are RhD (or D) negative.

In the independent sector in the UK, point-of-care testing is used and anti-D is provided immediately. In contrast, NHS transfusion laboratories usually follow the same testing processes for managing anti-D as they do for managing transfusion of blood components. This is unnecessary and introduces delays, and means that women may have to choose between declining testing and prophylaxis or returning to the service after the abortion to receive this. On the basis of these considerations, the committee recruited to develop the 2019 NICE guideline on abortion care[1] therefore made the following recommendations for practice:

- Offer anti-D prophylaxis to women who are rhesus D negative who are having an abortion after 10^{+0} weeks' gestation.
- Do not offer anti-D prophylaxis to women who are having a medical abortion up to and including 10^{+0} weeks' gestation.
- Consider anti-D prophylaxis for women who are rhesus D negative and are having a surgical abortion up to and including 10^{+0} weeks' gestation.
- Providers should ensure that:
  - rhesus status testing and anti-D prophylaxis supply does not cause any delays to women having an abortion.
  - anti-D prophylaxis is available at the time of the abortion.

In addition to reducing overtreatment, an added benefit of these recommendations involves health resource use. Anti-D is sourced from commercial suppliers, 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[4] indicate that in 2017, 145 766 women had an abortion at under 10 weeks' gestation, of whom 116 135 (80%) had an early medical abortion. Given a prevalence of RhD-negative individuals of 15%, 21 865 women were RhD-negative, of whom 17 420 had an early medical abortion. The current cost of the available anti-D is £46.50,[23] meaning the savings to the NHS from not giving anti-D to all women under 10 weeks' gestation would be £1.02 million, or £0.81 million if restricted only to the medical abortion group. Savings of this magnitude are significant for any healthcare system, and could be especially valuable to women's health if they could be reinvested to deliver better contraceptive and sexual health provision within the abortion service. In healthcare systems where women bear the costs of abortion the impact on individuals can be significant.[24] Removing the need for testing and administering anti-D could at least reduce some of this burden. The World Health Organization (WHO)[25] observes that anti-D for RhD-negative

women having a medical abortion is recommended. While it notes that it is not a prerequisite, any savings made in resource-poor healthcare settings would be especially valuable. In addition to the drug costs, there would also be savings from not testing for RhD group and its associated staff time. Moreover, in addition to offering better women-centred care through reducing delay in care or the number of appointments, the adoption of point-of-care testing (instead of laboratory test-and-treat systems) would also result in cost savings as these systems are also significantly cheaper. Removing the need for testing and procuring anti-D would also facilitate improved woman-centred care pathways, for example in removing barriers to delivery in primary care, by pharmacists or through remote prescribing.

To adopt point-of-care testing, it would be necessary to: (1) use a CE marked system, to comply with the European Union In-Vitro Diagnostics Regulation and assure the test is fit for purpose; (2) agree a local standard operating procedure (SOP) with the organisation's point-of-care testing group, to include regular Internal Control and External Quality Assessment testing; and (3) if a point-of-care 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.

Finally, individualising care based on an individual woman's risk benefit profile and taking note of women's preferences are 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 the woman's 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. It is therefore 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, it was not possible to make a definitive recommendation in this specific area.

Additional Educational Resources

- We conducted this systematic review because there is a real paucity of evidence in this area (including no Cochrane reviews), which our review also confirmed. We feel it is inappropriate to include references in this section that relate to anti-D prophylaxis in other clinical scenarios, such as pregnancy, childbirth or miscarriage, and are therefore at a loss as to which resources to list here other than the British Pregnancy Advisory Service (BPAS) website: https://www.bpas.org

Acknowledgements The authors would like to thank the National Institute for Health and Care Excellence (NICE), the National Guideline Alliance (NGA) and the Guideline Committee for the 'Abortion Care' NICE Guideline (2019).

Contributors FR, JL, SC, EH and MSH conceived and designed the review and wrote the protocol. EH devised and undertook the search strategy. MSH screened the search results. JH performed the economic analyses. FR, JL, MSH, AP, JH, SC and EH wrote the first draft of different sections of the full review. All the authors critically revised the first draft of the review and approved the final version of the review. MSH is the guarantor.

Funding This article presents a systematic review undertaken as part of the 2019 NICE guideline on abortion care. This work was undertaken by the National Guideline Alliance (NGA) at the Royal College of Obstetricians & Gynaecologists (RCOG), which received funding from the National Institute for Health and Care Excellence (NICE). The funding body (NICE) did not play any direct role in the study design; the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The views expressed in this publication are those of the authors and not necessarily those of the NGA, RCOG or NICE. All researchers involved in this work were independent from the funding body at the time of completing this work. The authors would like to thank NICE, the National Guideline Alliance and the Guideline Committee for the 'Abortion Care' NICE Guideline (2019).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Mia Schmidt-Hansen http://orcid.org/0000-0002-4503-6870
Jonathan Lord http://orcid.org/0000-0003-2819-5973

REFERENCES

1 National Institute for Health and Care Excellence (NICE). Abortion care, 2019. Available: https://www.nice.org.uk/guidance/NG140 [Accessed 17 Oct 2019].
2 Manfroi S, Calisesi C, Fagiani P, *et al*. Prenatal non-invasive foetal RhD genotyping: diagnostic accuracy of a test as a guide for appropriate administration of antenatal anti-D immunoprophylaxis. *Blood Transfus* 2018;16:514–24.
3 National Institute for Health and Care Excellence (NICE). *Routine antenatal anti-D prophylaxis for women who are rhesus D negative (Report No. TA156)*. London, UK: NICE, 2008.
4 Department of Health and Social Care. *Abortion statistics, England and Wales: 2018*. London, UK: Department of Health and Social Care, 2019.
5 Dean M. Wanted: Rh D negative donors. *Aust Prescr* 2000;23:36–8.
6 Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. handbook.cochrane.org
7 Wells GA, Shea B, O'Connell. Newcastel-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available: www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 20 Jun 2018].

8 The Nordic Cochrane Centre. *Review Manager (RevMan) [Computer program]. Version 5.3*. Copenhagen, Denmark: The Cochrane Collaboration, 2014.
9 GRADEpro Guideline Development Tool [Software] [Computer program]. McMaster University, 2015 (developed by Evidence Prime, Inc.), 2015. Available: www.gradepro.org
10 National Institute for Health and Care Excellence, 2019. Available: https://www.nice.org.uk/guidance/ng140/evidence/c-antid-prophylaxis-for-women-up-to-136-weeks-gestation-pdf-6905052975 [Accessed 13 Jan 2020].
11 Swedish Society of Obstetrics and Gynecology. *Inducerad abort (Report No. 78)*. Stockholm, Sweden: Svensk förening för Obstetrik & Gynekologi, 2018.
12 Bjørge L, Løkeland M, Oppegaard K. *Provosert abort [Induced abortion]*. Oslo, Norway: Norsk gynekologisk forening, 2017.
13 Sundhedsstyrelsen. *Anbefalinger For Svangreomsorgen [Recommendations For Prenatal Care] (Report No. 9.2.3 - Indications for treatment with anti-D immunoglobulin for non-immunized RhD negative pregnant)*. Copenhagen, Denmark: Sundhedsstyrelsen [Danish National Board of Health], 2013.
14 American College of Obstetricians and Gynecologists. Prevention of Rh D alloimmunization (practice Bulletin 181), 2017. Available: https://www.hypermunes.com/documents/31474919/31475109/2017_ACOG_+RhD_Guidelines.pdf/bdc6b897-9412-4a28-995c-2c0c706ac5dc [Accessed 17 Oct 2019].
15 Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). *Guidelines for the use of Rh(D) immunoglobulin (anti-D) in obstetrics in Australia*. East Melbourne, Australia: RANZCOG, 2015.
16 New Zealand Blood Service. Use of Rh D immunoglobulin during pregnancy and the post-partum period (Id: 111G130); 2013. https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/USE-OF-RH-D-IMMUNOGLOBULIN-DURING-PREGNANCY-AND-THE-POST-PARTUM-PERIOD-111G130.pdf
17 Cortey A, Brossard Y. [Prevention of fetomaternal rhesus-D allo-immunization. Practical aspects]. *J Gynecol Obstet Biol Reprod* 2006;35:1S123–30.
18 Wiebe ER, Campbell M, Aiken ARA, *et al*. Can we safely stop testing for Rh status and immunizing Rh-negative women having early abortions? A comparison of Rh alloimmunization in Canada and the Netherlands. *Contraception* 2019;1:100001.
19 Mark A, Foster AM, Grossman D, *et al*. Foregoing Rh testing and anti-D immunoglobulin for women presenting for early abortion: a recommendation from the National Abortion Federation's Clinical Policies Committee. *Contraception* 2019;99:265–6.
20 Jabara S, Barnhart KT. Is Rh immune globulin needed in early first-trimester abortion? A review. *Am J Obstet Gynecol* 2003;188:623–7.
21 Hollenbach SJ, Cochran M, Harrington A. "Provoked" feto-maternal hemorrhage may represent insensible cell exchange in pregnancies from 6 to 22 weeks gestational age. *Contraception* 2019;100:142–6.
22 National Institute for Health and Care Excellence (NICE). Ectopic pregnancy and miscarriage: diagnosis and initial management, 2012. Available: https://www.nice.org.uk/Guidance/CG154 [Accessed 20 Jun 2019].
23 British National Formulary (BNF). Anti-D (RH0) immunoglobulin. Available: https://bnf.nice.org.uk/medicinal-forms/anti-d-rh0-immunoglobulin.html [Accessed 18 Feb 2019].
24 Coast E, Lattof SR, van der Meulen Rodgers Y, *et al*. Economics of abortion: a scoping review protocol. *BMJ Open* 2019;9:e029939.
25 World Health Organization (WHO). *Safe abortion: technical and policy guidance for health systems*. 2nd edn. Geneva, Switzerland: WHO, 2012. ISBN: 978 92 4 154843 4.

Appendix 1

Search strategy for Medline & Embase (Multifile)

#	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.
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
	General exclusions filter was applied

Search strategy for Cochrane Library via Wiley Online

#	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 2

Excluded studies

Study	Reason for Exclusion
Anonymous, Anti-D human immunoglobulin: new preparation. Important in young Rh D (-) women. *Prescrire Int.* 2001;**10**:4-7	Narrative review
Anonymous, Anti-D human immunoglobulin: new preparation. Important in young Rh D (-) women. *Prescrire Int.* 2001;**10**:4-7	Duplicate
Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, et al. A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus-negative. *Health Technol Assess* 2003;**7**:iii-62	Population not in PICO: Pregnant women not undergoing abortion
Fiala C, Fux M, Gemzell Danielsson K. Rh-prophylaxis in early abortion, *Acta Obstet Gynecol Scand* 2003;**82**:892-903	Narrative review; included studies checked for relevance, none found.
Fung Kee Fung K, Eason E, Crane J, Armson A, De La Ronde S, Farine D, et al. Prevention of Rh alloimmunization. *J Obstet Gynaecol Can.* 2003;**25**:765-773	Guideline/(systematic?) review; included studies checked for relevance, none found
Jabara S, Barnhart KT. Is Rh immune globulin needed in early first-trimester abortion? A review. *Am J Obstet Gynecol* 2003;**188**:623-627	Narrative (or semi-systematic review) review; included studies checked for relevance, none found.
Lobato,G., Soncini,C.S., RhD prophylaxis failure in Rio de Janeiro, Brazil. *Int J Gynaecol Obstet* 2008;100:276-277	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, *J Matern Fetal Neonatal Med* 2010: **Proccedings from European Congress of Perinatal Medicine**: 593	Published as abstract only. Not enough information to ascertain relevance.
Sainio S. Anti-D propylaxis in early pregnancy and abortion - What is the evidence? *Acta Obstet Gynecol Scand* 2012;91:54	Published as abstract only. Not enough information to ascertain relevance.