National Institute for Health and Care Excellence

Ectopic pregnancy and miscarriage

[E] Evidence review for anti-D immunoglobulin prophylaxis

NICE guideline NG126

Evidence underpinning recommendations 1.7.1 to 1.7.3 and research recommendations

February 2026

Draft for consultation

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ISBN: [XXX]

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Anti-D immunoglobulin for immunoprophylaxis

1.1 Review question

This evidence review summarises the evidence for: Should anti-D immunoglobulin for immunoprophylaxis be given to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?

We are updating this question from the Ectopic pregnancy and miscarriage NICE guideline (NG126). The update was prompted by an update to the NICE abortion care guideline (NG140)[6] recommendations on anti-D prophylaxis in 2025. The abortion care recommendations refer to the WHO Abortion care guideline[11] and recommend against using anti-D prophylaxis before 11+6 weeks' gestation. The current ectopic pregnancy and miscarriage guideline recommendations differentiate between surgical management versus medical management, whereas the abortion care recommendations do not. The 2012 recommendations were based on committee consensus. The guideline committee from the old guideline felt that due to the lack of evidence it was not appropriate to recommend that women with a miscarriage or ectopic pregnancy that resolves spontaneously, without intervention, routinely receive anti-D immunoglobulin immunoprophylaxis. This was based on the possibility that the risk of mixing of maternal and fetal blood was less likely in those medically managed. It was thought that treatments such as misoprostol or methotrexate are more likely to mimic the physiological changes during a spontaneously completing miscarriage, and therefore presenting less risk. For your information, please see the current recommendations below.

The original ectopic pregnancy and miscarriage recommendations are:

Offer anti-D immunoglobulin prophylaxis at a dose of 250 IU (50 micrograms) to all rhesus-negative women who have a surgical procedure to manage an ectopic pregnancy or a miscarriage. [2012]

Do not offer anti D immunoglobulin prophylaxis to women who:

- receive solely medical management for an ectopic pregnancy or miscarriage or
- have a threatened miscarriage or
- have a complete miscarriage or
- have a pregnancy of unknown location. [2012]

The abortion care guideline recommendations, updated in 2025 are:

1.3.1 For people who are rhesus D negative and having a medical or surgical abortion up to and including 11+6 weeks' gestation, follow the recommendation against the use of anti-D prophylaxis in section 3.3.3 of the World Health Organization abortion care guideline. [2025]

1.3.2 Providers should ensure that for people who are rhesus D negative and are having an abortion at 12 weeks or over:

- 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. [2019, amended 2025]

The WHO guideline[12] recommendation 3.3.3 Rh isoimmunisation:

For both medical and surgical abortion at < 12 weeks: Recommend against anti-D immunoglobulin administration.

1.1.1 Summary of the protocol

Table 1: Summary of the protocol (PICOS)

Population	Rhesus negative pregnant women who have a threatened miscarriage, miscarriage or ectopic pregnancy before 12 weeks gestation
Interventions	Anti-D immunoglobulin prophylaxis at 12 weeks or less gestation.
Comparator	Placebo or no anti-D immunoglobulin prophylaxis at 12 weeks or less gestation.
Outcomes	Incidence of sensitisation

Study type	Recommendations from an external guideline will be included if it meets the protocol and is judged to be of high quality.
	Include published full-text papers:
	• Systematic reviews of RCTs
	• RCTs
	• If insufficient RCTs:
	  ○ Quasi-randomised controlled trials
	  ○ Non-randomised controlled trials/prospective cohort studies
	  ○ Retrospective cohort studies
	• Historically controlled studies

Abbreviations: RCTs: randomised controlled trials; anti-D: rhesus D immunoglobulin; PICOS: population, intervention(s), comparator(s), outcome(s) and study type(s).

The full protocol has been published on PROSPERO (The International Prospective Register of Systematic Reviews). Registration number CRD420251102207.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol and in section 1.1.2.3 below. General methods and search strategy are described in the Appendices document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.2.1 Search methods

Searches for effectiveness evidence were run on 10th July 2025. The following databases were searched: Medline (OVID), Embase (OVID), Cochrane Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley). Limits were applied to remove letters and editorials and conference abstracts. A date limit of 2012 onwards was applied.

The searches for the cost effectiveness evidence were run on 16th July 2025. The following databases were searched: Econlit (OVID), Embase (OVID), International HTA database (INAHTA) and Medline (OVID). Limits were applied to remove conferences and to limit the date from January 2012 onwards. A broad economic search filter was used on Medline and Embase.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in Appendix B.

1.1.2.2 Protocol deviations

There were no protocol deviations.

1.1.2.3 Methods specific to this review

This was an update of one question, focusing on whether the use of anti-D immunoglobulin for immunoprophylaxis should be provided to people with miscarriage, threatened miscarriage or ectopic pregnancy, to prevent sensitisation to the D antigen following a potentially sensitising event. A short scope and protocol were created for this updated question in the guideline. A guideline search and scoping search were conducted to search for evidence to focus the protocol. Following creation of the protocol a full search was conducted for the question. As no evidence was found that matched the protocol, studies identified in our search relating to the topic, the previous guideline or the abortion guideline were described narratively as supporting information to aid the GC discussion. An expert witness in transfusion

medicine provided a presentation to the GC. This included details on the D antigen and anti-D immunoglobulin immunoprophylaxis, SHOT data, guidelines which included anti-D immunoglobulin, the complexity of conflicting guidance, ensuring consent and shared decision-making, and the practical considerations of anti-D such as availability and dosing.

1.1.3 Effectiveness evidence

1.1.3.1 Included studies

Study selection

A systematic search was carried out to identify potentially relevant studies as detailed in **appendix J** in the technical appendices document. See **appendix B** in the technical appendices document for the literature search strategy. The study selection process is presented as a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram in **appendix C** in the technical appendices document.

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

1.1.3.2 Excluded studies

Details of studies excluded at full text, along with the primary reason for exclusion, are given in **appendix I** in the technical appendices document.

1.1.4 Summary of studies included in the effectiveness evidence

Although no new studies were identified which met the protocol we have included supporting evidence for background information. The previous ectopic pregnancy and miscarriage guideline included studies published between 1970-1980. No newer evidence was found relating to miscarriage or ectopic pregnancy, which met the protocol. The previous guideline included only 3 comparative studies (Visscher 1972[10]; Gavin 1972[2] and Simonovits 1974[9]). Visscher 1972[10] had a gestational age of 8-24 weeks (with most 8-16 weeks); Simonovitis 1974[9] included women who were sensitised after an induced abortion, and Gavin 1972[2], was an RCT which included 22.8% with a gestational age of over 13 weeks, albeit they state that the sensitisations were not in this group, 33/57 had a therapeutic abortion. None of these studies found a significant difference between those who received anti-D immunoglobulin and those who did not. The other 5 studies were non-comparative. None of these studies matched the protocol and so were not included in this review.

The NICE Abortion care guideline (2025)[6] refers to the WHO guideline on abortion care[12] for their recommendation on anti-D immunoglobulin. The rationale behind the WHO recommendation was based on their systematic review which assessed the effect of routine anti-D immunoglobulin administration among unsensitized Rh-negative individuals undergoing an abortion. Only two studies were found for their systematic review, both from 1972 (Goldman 1972[3] and Gavin 1972[2]), which were included in a systematic review by Chan (2022)[1]. These studies suggested that anti-D immunoglobulin administration reduced the likelihood of antibody development following a first pregnancy, with no adverse effects. An additional supporting study included in the WHO guideline was a comparative study (Wiebe 2019)[11] examined Rh D alloimmunisation rates in Canada and Netherlands and found no increase in the risk of sensitisation among D negative individuals with spontaneous abortion before 10 weeks of gestation who did not receive anti D immunoglobulin; and a theoretical study. The WHO expert panel considered multiple factors, including

resource allocation, cost-effectiveness, and feasibility of administering anti-D, alongside the very low certainty of the evidence. They concluded that the overall evidence did not strongly support routine anti-D administration, and they recommended against its use for gestational ages under 12 weeks, modifying the previous guidance from 2012, which had set the threshold at 9 weeks.

A study found in our search, Horvath (2023)[4], included participants that had either a medical or surgical abortion and examined the levels of fetal red blood cells in the maternal circulation before and after first trimester abortion. No one in the study showed a new rise in fetal red blood cells (fRBCs) above the sensitisation threshold (125 fRBCs/5 million RBCs). One participant with AB+ blood type who had a medical abortion had an elevated fRBC above the threshold of sensitisation following abortion. However, the participant had elevated fRBCs above the threshold prior to the procedure, and they had reported prior bleeding in the pregnancy. They concluded that induced first trimester abortion is not a risk factor for Rh sensitisation and therefore anti-D prophylaxis is not required in the first 12 weeks gestation. This study was also excluded from this review as it included abortion rather than miscarriage or ectopic pregnancy. An earlier study by Horvath (2020)[5] had included data from women with miscarriage which found no evidence of elevated fetal red blood cells following uterine evacuation, although the numbers were small. UK data from Serious Hazards of Transfusion (SHOT)[8] had not detected any increase in sensitisation events since the change was made to the NICE abortion care guideline in 2019, which limited anti-D immunoglobulin to D negative individuals in the first trimester to those having surgical abortions but not medical abortions. Although cases would only be detected if there was a subsequent pregnancy.

1.1.5 Summary of effectiveness evidence

No studies identified that match the protocol.

1.1.6 Economic evidence

1.1.6.1 Included studies

A search was performed to identify published economic evaluations of relevance to this review question. See the literature search strategy in **appendix B** in the technical appendices document.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in **appendix G** in the technical appendices document).

1.1.6.2 Excluded studies

See **appendix I** in the technical appendices document for a list of excluded economic studies, with reason for exclusion.

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1.1.7 Economic model

No original economic modelling was completed for this review question.

1.1.8 Unit costs

Table 2: Unit Costs - NHS drug tariff (October 2025)

Medicine	Pack size	Cost	Dose
Anti-D (Rh0) immunoglobulin	1-Vial	£54.00	500 unit
Anti-D (Rh0) immunoglobulin	1-pre-filled disposable injection	£76.50	1,500 units

1.1.9 Committee discussion and interpretation of the evidence

1.1.9.1 What are the key issues and priorities relating to this question?

In people who are pregnant who do not have the D antigen (D negative) who are carrying a D positive fetus, the fetal cells could pass into the bloodstream of the mother and cause sensitisation. There are a variety of potentially sensitising events including ectopic pregnancy and miscarriage. Sensitisation could lead to haemolytic disease of the foetus and newborn (HDFN) in subsequent pregnancies, which in severe cases can be life-threatening to the fetus. Anti-D immunoglobulin can be given within 72 hours of sensitisation to counteract this. The GC discussed that there was variation in practice when it came to the provision of anti-D immunolgobulin prophylaxis for those with bleeding and pain in the first trimester of pregnancy, and whether these were significant enough to warrant anti-D prophylaxis. A key issue was whether there was a difference in medical or surgical management of miscarriage and ectopic pregnancy within those first 12 weeks, and whether sensitisation from miscarriage would differ from sensitisation in abortion in that time period.

1.1.9.2 Certainty of evidence and the balance of effects

No evidence was found that relates specifically to people with threatened miscarriage, miscarriage or ectopic pregnancy, which met the protocol. Evidence found when searching provided important supporting information on the topic to present narritively to the committee. The recommendations were based on the expert view of the committee, expert testimony and discussion of the supporting information. The previous ectopic pregnancy and miscarriage NICE guideline review included evidence from the 1970s, and included people having an abortion, and/or were not 12 weeks or less when they received anti-D prophylaxis. The evidence did not show significant difference in rates of sensitisation, was low quality and so the last guideline's recommendations were based on the committee's consensus. No further evidence was found which met the protocol, however one abortion study (Horvath 2023)[4] was discussed by the expert witness and included narratively here as supporting evidence because the committee felt that there was the potential for surgical management of miscarriage or ectopic pregnancy to have different potentially sensitising effects. Horvath[4] used flow cytometry which is a more accurate measure of true fetal cell volume in the maternal

circulation; earlier studies relied on Kleihauer tests which reports signficant false positive from higher levels of maternally derived fetal haemoglobin (HbF) that is raised in certain groups, including the first trimester of pregnancy. The evidence did not show abortions of either type lead to sensitisation, however three people were already shown to have raised fRBC levels prior to the abortion. One of the three had bleeding prior to the procedure however they were AB+ so anti-D would not have been necessary in this case. The other two people did not have bleeding, and the levels of fRBC post procedure were below the threshold for sensitisation. Furthermore Wiebe 2019[9] was an observational study that was discussed as background context because it included two different healthcare systems (Netherlands and Canada). Policy in the Netherlands is to offer anti-D to D negative women with spontaneous abortions over 10+0 weeks gestation and induced abortions over 7+0 weeks. In Canada, it is recommended to offer anti-D prophylaxis to all D negative women, when they have an induced or spontaneous abortion. No significant difference was found between the two settings in sensitisation rates in simulated data. Recommendations from other guidelines were presented by the expert witness including the British Society of Haematology (BSH) and the Australian National Blood Authority guidelines. Similarly, they were not based on evidence from ectopic pregnancy, miscarriage or threatened miscarriage studies. The GC considered that there was a lack of evidence to show a benefit of providing anti-D prophylaxis to people less than 12+0 weeks of pregnancy, and no evidence that there was a difference between medical and surgical management of miscarriage orectopic pregnancy; therefore they used committee consensus to arrive at the updated recommendations. This does not change the second part of the recommendation which did not recommend anti-D immunoglobulin prophylaxis to those undergoing medical management under 12+0 weeks, however the recommendation regarding those with surgical management of miscarriage in that initial 12+0 week period was changed on the basis of committee consensus using the supporting information.

The recommendation to not offer anti-D immunoglobulin prophylaxis to people who are D negative and are less than 12+0 completed weeks of pregnancy

was made as there is no evidence of the benefit of using anti-D prior to 12+0 weeks gestation, and to align with the WHO and NICE abortion care guidelines[6,12]; and evidence tends to make the distinction at 12+0 weeks.

The GC thought that any risk from anti-D immunoglobulin prophylaxis was low and it would be useful to discuss this with patients. They considered the side effects were generally rare and mild, however they noted that very occasionally there could be a severe hypersensitivity reaction including anaphylaxis. They discussed that generally anti-D immunoglobulin is considered a safe product. The risk of viral transmission is low due to screening of pooled plasma and to viral inactivation. Health care practitioners should make patients aware of this.

Further new recommendations were made for provision of anti-D immunoglobulin to those between 12+0 to 12+6 completed weeks of pregnancy who are D negative and undergoing medical management or a surgical procedure to manage ectopic pregnancy or miscarriage. This covers the guideline population.

The committee also opted to make a consider recommendation for anti-D immunoglobulin at a dose of 250 IU (50 micrograms) for a threatened miscarriage with heavy or recurrent bleeding. This was based solely on the expert witness' presentation which had featured the difficulty of not always knowing when sensitisation occurs and the views of the committee.

The GC decided that the previous recommendation to not use a Kleihauer test for quantifying feto-maternal haemorrhage was still relevant and so has been retained in its entirety.

1.1.9.3 Resources and cost-effectiveness

The committee noted that because there is very limited evidence on clinical effectiveness, the cost-effectiveness of anti-D immunoglobulin prophylaxis for women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester could not be assessed quantitatively. Therefore, the

committee made a qualitative judgement about cost-effectiveness when developing its recommendations.

They considered the unit costs of anti-D immunoglobulin (see Table 2) and the fact that it is in short supply. Given the lack of evidence of clinical benefit and the opportunity costs of anti-D immunoglobulin prophylaxis at less than 12+0 weeks of pregnancy, the committee agreed that there was a case for reserving its use for populations where there is stronger evidence of benefit. They also noted that the opportunity costs of funding anti-D immunoglobulin in this population may not be offset by any measurable benefits.

On this basis, the committee concluded that anti-D immunoglobulin for ectopic pregnancy or miscarriage at less than 12+0 weeks of pregnancy was not cost-effective. Given there is no evidence that the risk of sensitisation differs between medical and surgical management, the recommendation to offer anti-D immunoglobulin for surgical management under 12 weeks was removed. The committee recognised that this change in NHS practice, in the absence of any increase in haemolytic disease of the newborn, would result in cost savings.

However, the committee considered that anti-D immunoglobulin prophylaxis could be cost-effective at 12+0 to 12+6 completed weeks of pregnancy. Guidance was amended to reflect this, partly to align with international recommendations and partly because physiological changes at this stage make clinical and cost-effectiveness more likely. The committee acknowledged that this represents a change in practice with resource implications for the NHS but noted that the population affected is relatively small and that any increase in costs is likely to be offset by reductions in use for women at less than 12 weeks.

1.1.9.4 Equity

The GC included an additional patient-centred recommendation regarding provision of information on anti-D prophylaxis. The GC discussed whether certain groups of people would not want to take anti-D prophylaxis due to personal reasons. The final recommendation reflects this, to ensure that

health care practitioners discuss the use of anti-D immunoglobulin with those requiring it, explaining that the protein is from blood plasma, rather than containing blood cells.

1.1.9.5 Acceptability and values

The committee were confident in the value of anti-D prophylaxis in prevention of haemolytic disease of the newborn in later pregnancy (NICE TA156)[7], and of the seriousness of haemolytic disease, which could be life-threatening. The uncertainty is in whether it is required in the first trimester for miscarriage, threatened miscarriage, ectopic pregnancy and bleeding. The GC discussed that anti-D immunoglobulin is a blood product and that this may be a consideration for individuals when seeking their informed consent. The GC expressed that the explanation of anti-D prophylaxis should be accurate in the recommendation and so worded as 'protein obtained from blood plasma,' and clarified that it does not include blood cells and that these products were filtered and treated blood products which reduces any risk of contamination.

1.1.9.6 Feasibility

The Guideline Committee discussed that one issue of feasibility of giving anti-D immunoglobulin prophylaxis at 12+0 weeks or more and not to those under 12+0 weeks could be the accuracy of dating the pregnancy, particularly so early in pregnancy. They could be reliant on self-report of date of last menstrual period, which may be less reliable than scan results. However it is routine practice for women presenting to early pregnancy units to have a scan.

1.1.9.7 Other considerations

In the abortion care guideline it was noted that a requirement to test for maternal blood group and antibody screen to determine or confirm the D antigen group and check for the presence of immune anti-D impacted on the development of NHS community-delivered services as access to laboratory services was limited. This meant that women may have to return for an additional appointment, or have their access to local care restricted. Although

most early pregnancy services operate from acute hospital Trusts, future quality improvements could include provision of services within community settings such as women's health hubs. If these service provision changes occur, the need to routinely test for RhD status, if this were not evidence-based, could be a barrier. It was also noted for some people blood testing is unpleasant, and if it is not necessary then it would improve the patient experience.

1.1.9.8 Strength of the recommendations

The first recommendation is a 'do not offer' which is justified given the lack of evidence and the committee consensus for provision of anti-D immunoglobulin prophylaxis in the first 12+0 weeks of pregnancy. The second recommendation to 'offer' anti-D immunoglobulin prophylaxis at 12+0 to 12 +6 weeks aligns with the abortion care guideline and with changes that occur clinically after 12+0 weeks. The third recommendation was to consider anti-D immunoglobulin prophylaxis at 12+0 to 12+6 weeks for those with threatened miscarriage, which similarly was not based on any evidence but aligns with the abortion care guideline. It was agreed that 'consider' would be appropriate because there is more uncertainty about sensitisation occuring with threatened miscarriage and there are challenges about identifying when it occurs. The fourth recommendation was about discussing with the patient about anti-D immunoglobulin being a blood plasma product which does not contain blood cells, which is not based on evidence and is not a strong recommendation, but was agreed to be a useful discussion to have given its status as a blood product.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1 to 1.7.5.

1.1.11 References

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1.1.11.1 Effectiveness evidence

No evidence was found that met the protocol.