Research questions

| Question number | 1  | Notes  |
| --- | --- | --- |
| Date of consideration  | 5 October 2017  |
| New Question (in full)  | In Rh D negative pregnant women with no preformed anti-D, does universal[[1]](#footnote-1) routine antenatal prophylaxis with Rh D immunoglobulin (1 or 2 doses) prevent Rh D alloimmunisation?  |
| Subquestions (in full)  | In Rh D negative pregnant women with no preformed anti-D, is universal routine antenatal prophylaxis with one dose of Rh D immunoglobulin as effective at preventing Rh D alloimmunisation as universal routine prophylaxis with two doses of Rh D immunoglobulin?  | The evidence for this question will come from the same evidence base as identified for the above question – so it is included as a subquestion rather than a separate question  |
| Question type  | Population  | Intervention  | Comparator  | Outcome  | Importance of outcome[[2]](#footnote-2)  |
| Main Question (Intervention)  | Rh D negative pregnant women with no preformed anti-D  | Routine antenatal prophylactic Rh D immunoglobulin Stratify by: * 1 or 2 doses
* 1 dose only
* 2 doses only
 | Placebo or no routine antenatal prophylactic Rh D immunoglobulin  | * incidence of Rh D alloimmunisation[[3]](#footnote-3)
* incidence of a positive test for feto-maternal haemorrhage[[4]](#footnote-4) (e.g. Kleihauer test, flow cytometry)
* adverse neonatal events (e.g. jaundice)
* adverse maternal events attributed to anti-D (e.g. allergic response, infection)
 | Critical Not Important If available[[5]](#footnote-5)If availablee  |
| Subquestion (Intervention)  | Rh D negative pregnant women with no preformed anti-D  | 1-dose routine antenatal prophylactic Rh D immunoglobulin  | 2-dose routine antenatal prophylactic Rh D immunoglobulin  | * incidence of Rh D alloimmunisation
* adverse neonatal events (e.g. jaundice)
* adverse maternal events (e.g. allergic response, infection)
 | Critical If availablee If availablee  |
| Additional information |
| Data to extract | Number of pregnancies | Product typeMode of administrationNumber of dosesDosageTiming | Subquestion onlyProduct typeMode of administrationDosageTiming | Rh D alloimmunisationTiming (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy)Kleihauer test / flow cytometryAt potentially sensitising events and postpartum [after birth of a Rh-positive infant])Adverse neonatal eventsTiming (current or subsequent pregnancy) and severityAdverse maternal eventsTiming and severity |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

| Question number  | 2  | Notes  |
| --- | --- | --- |
| Date of consideration  | 05 October 2017  |
| New Question (in full)  | In Rh D negative women with no preformed anti-D who have experienced one of the following first trimester[[6]](#footnote-6) sensitising events – abdominal trauma, molar pregnancy, ectopic pregnancy, spontaneous miscarriage, threatened miscarriage or medical termination of pregnancy (with/without a curette), does universal[[7]](#footnote-7) first-trimester sensitising event prophylaxis with Rh D immunoglobulin prevent Rh D alloimmunisation?  |
| Subquestions (in full) | -- |
| Question type | Population  | Intervention  | Comparator  | Outcome  | Importance of outcome[[8]](#footnote-8)  |
| Main Question (intervention) | Rh D negative women with no preformed anti-D with a first-trimester sensitising event, specifically: * abdominal trauma
* molar pregnancy
* ectopic pregnancy
* spontaneous miscarriage
* threatened miscarriage
* medical termination of pregnancy (with/without a curette)
 | First trimester sensitising event prophylactic Rh D immunoglobulin  | Placebo or no first trimester sensitising event prophylactic Rh D immunoglobulin  | * incidence of Rh D alloimmunisation[[9]](#footnote-9)
* incidence of a positive test for feto-maternal haemorrhage[[10]](#footnote-10) (e.g. (Kleihauer test, flow cytometry)
* adverse neonatal events (e.g. jaundice)
* adverse maternal events attributed to anti-D (e.g. allergic response, infection)
 | Critical Not important If available[[11]](#footnote-11) If availablek  |
| Additional information |
| Data to extract | Number of pregnancies Timing of sensitising event Nature of sensitising event Use of curette  | Product type Mode of administration Number of doses Dosage Timing  |   | Rh D alloimmunisation Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy) Kleihauer test / flow cytometryAt potentially sensitising events and postpartum [after birth of a Rh-positive infant]) Adverse neonatal events Timing (current or subsequent pregnancy) and severity Adverse maternal events Timing and severity |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

| Question number  | 3 | Notes  |
| --- | --- | --- |
| Date of consideration  | 05 October 2017  |
| New Question (in full)  | In Rh D negative pregnant women with no preformed anti-D, does targeted[[12]](#footnote-12) routine antenatal or sensitising event prophylaxis to women with a Rh D positive fetus increase the incidence of Rh D alloimmunisation compared with universal[[13]](#footnote-13) routine antenatal or sensitising event prophylaxis?  |
| Subquestions (in full)  | In Rh D negative pregnant women with no preformed anti-D, what is the diagnostic accuracy of noninvasive prenatal screening to identify fetal Rh D status?  |  |
| Question type | Population  | Intervention/Test  | Comparator and/or reference standard  | Outcome  | Importance of outcome[[14]](#footnote-14)  |
| Main Question (Screening)  | Rh D negative pregnant women with no preformed anti-D  | Targeted administration of prophylactic Rh D immunoglobulin (based on noninvasive prenatal screening) Stratify by: * any prophylaxis
* routine antenatal prophylaxis
* sensitising event antenatal prophylaxis
 | Universal administration of prophylactic Rh D immunoglobulin Stratify by: * any prophylaxis
* routine antenatal prophylaxis
* sensitising event antenatal prophylaxis
 | * incidence of Rh D alloimmunisation[[15]](#footnote-15)
* utilisation of anti-D
* incidence of a positive test for feto-maternal haemorrhage[[16]](#footnote-16) (e.g. Kleihauer test, flow cytometry)
* adverse neonatal events (e.g. jaundice)
* adverse maternal events attributed to anti-D (e.g. allergic response, infection)
 | Critical Resource use Not important If available[[17]](#footnote-17) If availablef  |
| Subquestion (Diagnostic)  | Rh D negative pregnant women with no preformed anti-D  | Noninvasive prenatal testing for fetal Rh D status  | Postnatal cord blood testing (or other neonatal sample) for fetal Rh D status Other noninvasive fetal RhD determination  | * sensitivity
* specificity
* false positives
* false negatives
* positive likelihood ratio
* negative likelihood ratio
 | Critical Critical Critical Critical ImportantImportant  |
| Additional information |
| Data to extract | Number of pregnancies BMI | Screening question Product type Number of doses Dosage Timing Testing methodology Timing Diagnostic question Testing methodology Timing  | Screening question Product type Number of doses Dosage Timing Diagnostic question Testing methodology Timing  | Rh D alloimmunisation Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant up to 12 months] and subsequent pregnancy) UtilisationRates Kleihauer test /flow cytometryAt potentially sensitising events and postpartum [after birth of a Rh-positive infant]) Adverse neonatal eventsTiming (current or subsequent pregnancy) and severityAdverse maternal events Timing and severityDiagnostic accuracy Timing of test  |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

| Question number  | 4 | Notes  |
| --- | --- | --- |
| Date of consideration  | 05 October 2017  |
| New Question (in full) | In Rh D negative pregnant or postpartum women with no preformed anti-D, does increasing BMI increase the risk of failure of anti-D administration? |
| Subquestions (in full) | -- |
| Question type  | Population  | Prognostic/Risk factor  | Outcome  | Importance of outcome[[18]](#footnote-18) |
| Main Question(prognostic) | Rh D negative pregnant or postpartum women with no preformed anti-D receiving prophylactic Rh D immunoglobulin Stratify by* pregnant women
* postpartum women
 | * BMI (dichotomous or continuous)
* weight
* any other weight-related factors examined
 | * incidence of Rh D alloimmunisation[[19]](#footnote-19)
* anti-D levels [[20]](#footnote-20)
* incidence of a positive test for feto-maternal haemorrhage (e.g. (Kleihauer test, flow cytometry)[[21]](#footnote-21)
* adverse neonatal events (e.g. jaundice)
* adverse maternal events (e.g. allergic response, infection)
 | Critical Critical (if data for Rh D alloimmunisation is not available) Not important If available If available (particularly if increased dose or different mode of administration/technique used) |
| Additional information  |
| Data to extract | Product type Mode of administration Number of doses/dosage Timing of administration Administration technique  | Specific details of weight-related risk factors  | Rh D alloimmunisation Timing (i.e., during pregnancy, postpartum [after birth of a Rh-positive infant] up to 12 months and subsequent pregnancy) Anti-D levels Timing Kleihauer test /flow cytometryAt potentially sensitising events and postpartum [after birth of a Rh-positive infant]) Adverse neonatal events Timing (current or subsequent pregnancy) and severity Adverse maternal events Timing and severity |  |

Source: Anti-D scoping report (Health Research Consulting, November 2017)

1. Includes all pregnant women who are Rh D negative with no preformed anti-D. [↑](#footnote-ref-1)
2. Critical, important or resource use. [↑](#footnote-ref-2)
3. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-3)
4. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full) the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-4)
5. Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted. [↑](#footnote-ref-5)
6. The definition of first trimester varies across countries and for this review will be defined by the literature. The definition used by each included study should be extracted. [↑](#footnote-ref-6)
7. Includes all pregnant women who are Rh D negative with no preformed anti-D. [↑](#footnote-ref-7)
8. Critical, important or resource use. [↑](#footnote-ref-8)
9. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-9)
10. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full) the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-10)
11. Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted. [↑](#footnote-ref-11)
12. Includes pregnant women who are Rh D negative with no preformed anti-D with a Rh D positive fetus identified via first trimester non-invasive prenatal screening. [↑](#footnote-ref-12)
13. Includes all pregnant women who are Rh D negative with no preformed anti-D. [↑](#footnote-ref-13)
14. Critical, important or resource use. [↑](#footnote-ref-14)
15. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-15)
16. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full), the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-16)
17. Data will be extracted for these outcomes if they are available in the studies included for the critical outcome – Rh D alloimmunisation. Additional searches to identify studies for these outcomes will not be conducted. [↑](#footnote-ref-17)
18. Critical, important or resource use. [↑](#footnote-ref-18)
19. Also known as Rh D sensitisation. Defined as the presence of antibody to D antigen in maternal serum detected during the current pregnancy, postpartum or a subsequent pregnancy. Measured as a dichotomous outcome (present or not present). [↑](#footnote-ref-19)
20. This is a surrogate outcome. Measured as a continuous outcome (actual anti-D level in maternal blood). If this is used instead of Rh D alloimmunisation will need background research to look for evidence of link between lower anti-D levels and alloimmunisation. [↑](#footnote-ref-20)
21. The ERG debated whether to include ‘incidence of a positive Kleihauer test’ as an outcome. Given its inclusion in the 2015 Cochrane review (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000020.pub3/full), the ERG agreed to include in this review, but have noted the outcome as not important. [↑](#footnote-ref-21)