

REVIEW ARTICLE

Obstetrics

Prevention of RhD alloimmunization in the first trimester of pregnancy: Clinical practice guidelines of the French College of Obstetricians and Gynecologists

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Abstract

The French College of Obstetricians and Gynecologists has decided to update its clinical practices guidelines for preventing RhD alloimmunization in the first trimester of pregnancy. The quality of evidence of the literature was assessed following the GRADE methodology with questions formulated in the Patients, Intervention, Comparison, Outcome (PICO) format and outcomes defined a priori and classified according to their importance. An extensive bibliographic search was performed using Pubmed, Cochrane, EMBASE, and Google Scholar databases. The quality of evidence was assessed (high, moderate, low, very low) and a recommendation was formulated: strong, weak, or no recommendation. The recommendations were reviewed in two rounds by members of the scientific board of the French College of Obstetricians and Gynecologists (Delphi survey) in order to select the consensus recommendations. The three recommendations from the PICO questions were agreed upon through the use of the Delphi method. It is not recommended to administer RhD immune globulin before 12 weeks of gestation to reduce the risk of alloimmunization in the event of induced or spontaneous abortion in RhD-negative patients when the progenitor is RhD-positive or unknown (weak recommendation, very low-quality evidence). It is not recommended to administer RhD immune globulin before 12 weeks of gestation to reduce the risk of alloimmunization in the event of bleeding (weak recommendation, very low-quality evidence). The quality and quantity of literature data are insufficient to determine whether injection of RhD immune globulin can reduce the risk of alloimmunization in ectopic pregnancy, so no recommendation could be made.

KEYWORDS

alloimmunization, bleeding, ectopic pregnancy, first trimester, guidelines, induced abortion, prevention, RhD, spontaneous abortion

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1 | INTRODUCTION

The theoretical risk of alloimmunization in the first trimester of pregnancy is challenging to quantify. RhD immunization occurs when the maternal immune system encounters the D antigen present on fetal red blood cells that have entered the maternal circulation. The D antigen is theorized to be present on fetal red blood cells from 7.5 weeks of gestation.¹ The gestational age at which fetal red blood cells can be identified in the mother's blood and are likely to elicit an immune response is currently unknown. This is due to the fact that the studies that have investigated this phenomenon are outdated, lacking a precise method for determining the gestational age, and based on tests with limited accuracy for quantifying the number of fetal red blood cells present in the mother's circulation.

In 2005, the French College of Obstetricians and Gynecologists (CNGOF) published recommendations pertaining to the prevention of RhD alloimmunization during pregnancy, including the first trimester. Situations involving induced or spontaneous abortion (with surgical or medical treatment), bleeding, or ectopic pregnancy were deemed to pose a moderate risk of fetal red blood cell passage during the first trimester.² This justified the prevention of RhD alloimmunization through the administration of anti-RhD immune globulin.

However, at the time these recommendations were established, there were few published studies that specifically evaluated the benefits and efficacy of preventing alloimmunization in the first trimester. Furthermore, the epidemiologic and theoretical data that informed these recommendations were heterogeneous and dated (while the techniques for quantifying fetal red blood cells in maternal blood have since evolved), and were subject to bias, resulting in a very low quality of evidence.

Moreover, in the meantime, a number of national and international learned societies, including the International Federation of Gynecology and Obstetrics (FIGO) have published guidelines recommending that alloimmunization should not be systematically prevented in the first trimester.³⁻¹⁵ Thus, while there is a broad consensus on the need to systematically prevent RhD alloimmunization during pregnancy at 28 weeks of gestation and during events at risk for fetomaternal hemorrhage in the second and third trimesters, the recommendations of the various learned societies on immunoprophylaxis are heterogeneous when it comes to events at risk during the first trimester (Table 1).

Finally, a recent prospective observational study of good methodological quality published in 2023¹⁶ examined the passage of fetal red blood cells during surgical or medical abortion, and concluded that these procedures do not increase the concentration of fetal red blood cells in the maternal blood and are therefore not associated with an additional risk of alloimmunization.

For these reasons, the CNGOF has decided to update its recommendations for preventing RhD alloimmunization in the first trimester of pregnancy. These recommendations are intended to assist health care professionals in their daily clinical practice when counseling or caring for patients in the first trimester of pregnancy who are considered, rightly or wrongly, to be at risk for alloimmunization. They

concern gynecologists and obstetricians, but also midwives and general practitioners. The topic of these Recommendations for Clinical Practice (RCPs) was proposed by the CNGOF Scientific Committee to the CNGOF Bureau and Board of Directors, which approved it.

2 | METHODS

As a first step, the workgroup coordinators defined the questions to be addressed and identified the workgroup members responsible for each question. The questions were formulated according to the Patients, Intervention, Comparison, Outcome (PICO) format. Thus, in a given population (P), the outcome of a treatment (I) is assessed in relation to a reference treatment (C), or even the absence of treatment, on the basis of an a priori assessment criteria (O), such as a clinical or paraclinical outcome. The formulation of a question in the PICO format implies a classification of the importance of the evaluation criteria: crucial, important, not very important. An extensive bibliographic search was performed using Medline, Cochrane, EMBASE and Google Scholar databases. To be included in the analysis, publications had to be considered important by the expert group and published in English or French.

The GRADE methodology was used to develop these recommendations. After analyzing the literature, this method makes it possible to determine the quality of the evidence and thus provide an estimate of the confidence we can have in the effect observed for a given intervention and, ultimately, in the strength of the recommendation. The quality of the evidence is classified into four categories:

- High: Future research is unlikely to change our confidence in the effect estimate.
- Moderate: Future research is likely to change the confidence in the effect estimate and may change the effect estimate itself.
- Low: Future research is very likely to affect confidence in the effect estimate and is likely to change the estimate of the effect itself.
- Very low: The estimate of the effect is very uncertain.

The quality of evidence is analyzed for each assessment criterion, and an overall quality of evidence is then defined based on the quality of evidence for the predefined criteria, with priority given to those that are most important. The final wording of recommendations, when the data in the literature allows, is always binary: either positive or negative and either strong or weak.

The strength of the recommendation is determined based on five key factors and validated by expert voting using the GRADE methodology:

- Estimation of effect.
- Overall quality of the evidence: the higher the quality, the stronger the recommendation. Sometimes the strength of the recommendation is not related to the quality of the evidence. In such cases, the working group would provide a rationale.

TABLE 1 Learned societies recommendations on first trimester RhD alloimmunization prevention.

American College of Obstetricians and Gynecologists (ACOG)–2024 ¹²	Not necessary for both medical and surgical treatment in case of induced or spontaneous abortion before 12 WG
Society of Obstetricians and Gynecologists of Canada–2024 ¹³	Not necessary for both medical and surgical treatment in case of induced abortion before 12 WG
National Abortion Federation–2024 ¹⁴	Not necessary for both medical and surgical treatment in case of induced abortion before 12 WG
Society for Maternal-Fetal Medicine (SMFM)–2024 ¹⁵	Necessary for both medical and surgical treatment in case of induced or spontaneous abortion regardless of gestational age
Royal College of Obstetricians and Gynecologists–2022 ⁵	Not necessary for both medical and surgical treatment in case of induced abortion before 12 WG
Society of Family Planning–2022 ⁴	Not necessary for both medical and surgical treatment in case of induced or spontaneous abortion before 12 WG
World Health Organization–2022 ³	Not necessary for both medical and surgical treatment in case of induced abortion before 12 WG
International Federation of Gynecology and Obstetrics and international Confederation of Midwives guidelines (FIGO/ICM)–2021 ⁶	Not necessary before 10 WG in case of induced or spontaneous abortion without surgical treatment Necessary in case of: • Induced or spontaneous abortion with surgical treatment • Molar pregnancy • Ectopic pregnancy • Chorionic villus biopsy
Royal Australian and New Zealand College of Obstetricians and Gynecologists–2021 ⁷	Not necessary in case of: • Bleeding before 12 WG • Induced abortion with medical treatment before 10 WG Necessary in case of: • Spontaneous abortion (regardless of treatment) • Induced abortion with medical treatment after 10 WG • Induced abortion with surgical treatment • Molar pregnancy • Ectopic pregnancy • Chorionic villus biopsy • Important or recurrent bleedings with pain • Abdominal trauma
National Institute for Clinical Excellence–2019 ^{8,9}	Not necessary before 14 WG in case of: • Spontaneous abortion with medical treatment or without any treatment • Ectopic pregnancy with medical treatment • Pregnancy of undetermined location • Risk of spontaneous abortion Necessary before 14 WG in case of spontaneous abortion or ectopic pregnancy with surgical treatment Necessary after 10 WG in case of induced abortion regardless of treatment Should be considered before 10 WG in case of induced abortion with surgical treatment
Dutch Association of Abortion Specialists–2018 ¹⁰	Not necessary before seven WG in case of induced abortion Not necessary before 10 WG in case of spontaneous abortion
British Society for Hematology–2013 ¹¹	Not necessary before 12 WG in case of: • Spontaneous abortion with complete expulsion • Moderate bleedings • Risk of spontaneous abortion if bleeding has stopped completely Necessary before 12 WG in case of: • Induced abortion • Ectopic pregnancy • Molar pregnancy
French College of Obstetricians and Gynecologists (CNGOF)–2005 ²	Necessary before 14 WG in case of: • Spontaneous abortion • Risk of spontaneous abortion • Ectopic pregnancy • Molar pregnancy • Bleedings • Chorionic villus biopsy • Embryonic reduction • Abdominal trauma • Cervical cerclage • Induced abortion

Abbreviation: WG, weeks of gestation.

- Balance between desirable and undesirable effects: the more favorable the balance, the stronger the recommendation.
- Values and preferences: the more uncertain or highly variable these are, the weaker the recommendation. These values and preferences should be obtained from the stakeholders (patient, physician, decision maker) as much as possible.
- Cost: the higher the cost or use of resources, the lower the recommendation.

The recommendations formulated by the working group, along with their rationale and tables, were sent to 24 obstetrician-gynecologists of the CNGOF Scientific Advisory Board, who rated each recommendation on a scale of 1 (strongly disagree) to 9 (strongly agree). Two rounds of Delphi were organized. Only experts who answered more than one question in the first round were invited to participate in the second round. Of the experts contacted, 20 (83.3%, 20/24) responded in the first round and all (100%, 20/20) responded in the second round.

A recommendation was considered validated if it received at least 75% of the responses in the same section, with a median greater than or equal to 7. The recommendation that did not meet the consensus of the reviewers in the first evaluation, together with the reason for the lack of consensus, was analyzed by the working group, then modified and returned to the same group of reviewers, together with a specific argument explaining the modification of the recommendation in question. At the time of this second evaluation, in order to validate the recommendation, at least 75% of the responses had to be in the same section, with a median greater than or equal to 7. If this was not the case, no recommendation would be made and the proposal would be considered rejected.

These RCPs were publicly presented at the CNGOF Annual Congress, Pari(s) Santé Femme, in Paris on June 13, 2024. They have already been published in French language.¹⁷

We decided to address the following three PICO questions with a five-person working group:

Question 1: In a patient who is RhD negative, when the progenitor is RhD positive or unknown, in case of induced or spontaneous abortion before 12 weeks of gestation, does the injection of RhD immune globulin reduce the risk of alloimmunization?

Question 2: In a patient who is RhD negative, when the progenitor is RhD positive or unknown, in case of bleeding in an ongoing pregnancy before 12 weeks of gestation, does the injection of RhD immune globulin reduce the risk of alloimmunization?

Question 3: In a patient who is RhD negative, when the progenitor is RhD positive or unknown, in case of ectopic pregnancy, does the injection of RhD immune globulin reduce the risk of alloimmunization?

3 | RECOMMENDATIONS

After summarizing the work of the experts and applying the GRADE methodology, three recommendations were formalized.

All recommendations were submitted to the expert group for evaluation using the GRADE method. After a first round of scoring, agreement was reached on 66.6% (2/3) of the recommendations. In the second round of scoring, agreement was reached on the third recommendation, which had been modified following comments made in the first round. For three questions, the quality of the evidence was rated as very low, and two weak recommendations were given. The quality and quantity of the data in the literature were considered insufficient to make a recommendation on the third question.

3.1 | Question 1

In a patient who is RhD negative, when the progenitor is RhD positive or unknown, in case of induced or spontaneous abortion before 12 weeks of gestation, does the injection of RhD immune globulin reduce the risk of alloimmunization? (Table S1).

R1—It is not recommended to administer RhD immune globulin before 12 weeks of gestation in order to reduce the risk of alloimmunization in the event of induced or spontaneous abortion in RhD-negative patients when the progenitor is RhD-positive or unknown

Weak recommendation
Very low-quality evidence

Delphi: $n=20$; median 8; 80.0% agreed at first round.

Argumentation

Benefit of RhD immune globulin

Few studies have evaluated the efficacy of RhD immune globulin in preventing alloimmunization in the first trimester. A single randomized controlled interventional trial published in 1972 compared administration of RhD immune globulin with no administration of RhD immune globulin.¹⁸ In this previous study of spontaneous abortions, a total of 19 patients (14 with surgical treatment) received prophylaxis (RhD immune globulin μg IM within 72 h) compared with 38 patients (34 with surgical treatment) in the control group. Gestational ages, which were not reported in detail, ranged from eight to 24 weeks of gestation. There were no cases of immunization in this study, but the number of patients involved was small and there was a potential lack of power. There are two other interventional studies, including spontaneous abortion with surgical treatment, that compared administration of RhD immune globulin with no administration.^{19,20} However, these studies contain numerous biases that severely limit the reliability of the results: recruitment bias (RHD phenotype of progenitor not systematically known), selection bias (lack of randomization or randomization not detailed), and detection bias (diagnostic method for alloimmunization not optimal).

Population-based study of the effect of prophylaxis

A population-based study published in 2018 compared the prevalence of alloimmunization among pregnant women in Canada and the Netherlands.²¹ These countries have different practices: systematic administration of RhD immune globulin in Canada for spontaneous or induced abortion versus no administration in the Netherlands for spontaneous abortion before 10 weeks of gestation (WG) or induced abortion before 7 WG. The study was based on public health data. The primary endpoint was the prevalence of immunization, that is, the presence of clinically significant perinatal antibodies at a significant titer (whatever the type of antibody) when screening for irregular antibodies at the beginning of pregnancy in the entire population of pregnant women. The calculated estimated prevalence was 4.21/1000 (95% CI: 4.12–4.30) in Canada and 4.03/1000 (95% CI: 3.93–4.12) in the Netherlands. A sensitivity analysis taking into account a compliance with the national health policy of 80% and 90%, respectively confirmed these results. This study is subject to several biases, in particular the fact that the populations of the two countries are not strictly comparable. In addition, this type of study cannot formally establish a causal relationship. However, this population-based study suggests that systematic prophylaxis does not influence the prevalence of alloimmunization.

Passage of fetal red blood cells into the maternal circulation before 12 WG

A recent multicenter prospective observational study, published in 2023, examined the passage of fetal red blood cells into the maternal circulation in patients who underwent medical or surgical abortion at multiple centers in the USA before 12 WG between 2019 and 2022.¹⁶ Fetal red blood cells (FRBC) were detected and quantified by flow cytometry before and after the procedure. Because the cytometry protocol was modified during the study, three groups were defined: a medical abortion group with a first cytometry protocol including 113 patients, a medical abortion group with a second cytometry protocol including 206 patients, and a surgical abortion group with the second protocol including 187 patients. Of the 506 women, three had preprocedure FRBC concentrations above the threshold of 125 FRBC/5 million adult red blood cells (ARBC), which is considered the risk threshold for immunization according to the literature.²² Only one of these three women (medical abortion group with first cytometry protocol) still had a high post-procedural FRBC level (0.2% [95% CI: 0%–0.93%]). None of the 506 women had an elevated post-procedural FRBC concentration if they did not have an elevated preprocedural FRBC concentration (0% [95% CI: 0%–0.59%]). The increase in post-procedural concentration was a median of 0 FRBC/5 million ARBC (maximum 35.6) for the entire population and a median of 0.5 FRBC/5 million ARBC (maximum 28.5) for the group using the first cytometry protocol.

The only factors significantly associated with the level of post-procedural concentration were the preprocedural concentration and the patient's blood group: taking patients with blood group O as a reference, having group AB was significantly associated with a higher post-procedural concentration of FRBC. This can be explained by the fact that in the case of group O, there is a greater clearance of FRBC. On the

other hand, group A or B were not significantly associated with a different concentration. Given that the majority of patients in the population were group O (54%), this may have minimized the results on the concentrations, but the extent of this bias appears to be limited, as group A or B patients (43%) had concentrations that were not significantly different from those of group O patients. No details were provided on the time at which the post-procedure samples were obtained, but the stability of repeat samples taken from six patients up to 72 h may suggest that this time did not really influence the results.

Thus, even if the threshold of FRBC at risk of immunization used in this study is controversial because it is not consensual or formally established, these results show that an abortion before 12 weeks' gestation, by medical or surgical method, does not increase the concentration of FRBC in the blood of the patients and is therefore not associated with an additional risk of alloimmunization compared to a normally progressing pregnancy in the first trimester. To be noted that only patients in whom a FRBC concentration above the risk threshold was found were the ones with already preprocedural elevated FRBC. This can probably be extrapolated to the situation of spontaneous abortion.

It should be noted that while these guidelines were being prepared for publication in French, the American Society for Maternal-Fetal Medicine (SMFM) issued a statement recommending administration of RhD immune globulin in the event of a spontaneous or induced abortion.¹⁴ The reasons given are that RhD alloimmunization is a particularly serious pathology and that there are insufficient data in the literature to show that prevention with RhD immune globulin is of no benefit. Indeed, there is no reliable evidence for the lack of benefit of prophylaxis in these circumstances, but on the other hand, there is no reliable evidence for the need to prevent alloimmunization in the first trimester either, and no evidence for an increased risk of alloimmunization during abortion. Therefore, it does not necessarily seem legitimate to expose a potentially large number of women to a blood-derived product for which there is no proven benefit. Regarding the interpretation of the observational study on the passage of fetal red blood cells during abortion,¹⁶ the authors, like us, point out that the risk threshold for alloimmunization is controversial, but this study shows anyway that the fact of having an abortion might not increase the concentration of fetal red blood cells in the blood of patients. During this period, two other additional recommendations were issued in which the administration of RhD immune globulin was not recommended for induced and spontaneous abortions before 12 WG.^{13,14} Recently, the American College of Obstetricians and Gynecologists suggested the possibility of not administering RhD immune globulin in these situations and, consequently, not testing for RhD.¹²

Risks associated with RhD immune globulin administration

The risks associated with RhD immune globulin are low (viral and prion risks associated with injection of a blood-derived product, hypersensitivity or allergies). It is a product of human origin, obtained primarily from healthy, hyperimmunized and compensated North American donors.²³ Since 2005, only Rhophylac has been marketed in France in two doses, 200 µg and 300 µg, depending on the indication. There is

a theoretical risk associated with prions, as well as a viral risk, which is low because of the treatments used to eliminate viruses, but the risk is not zero, particularly with regard to viruses that have not yet been identified.^{23,24} There is also a risk of allergy and hypersensitivity. A few cases of serious allergic reactions to other brands of RhD immune globulin have been reported in the literature.²⁵⁻²⁷ No allergic reactions have been reported in antenatal and postnatal efficacy studies of Rhophylac.²⁴ Therefore, the risks associated with RhD immune globulin are very low but potentially serious.

Population potentially concerned by RhD immune globulin administration

A total of 234253 induced abortions were performed in 2022 in France.²⁸ The exact number of spontaneous abortions in France in the first trimester is not known, but has been calculated at 176280.²⁹ The proportion of RhD-negative individuals in the French population is approximately 15%.³⁰ The administration of RhD immune globulin in France for these two indications therefore affects approximately 61580 patients per year.

Overall, there is no evidence in the literature that RhD immune globulin administration reduces the risk of alloimmunization in cases of spontaneous or induced abortion before 12 WG. A population-based study suggests that routine prophylaxis in the first trimester of pregnancy has no effect on the prevalence of alloimmunization in pregnant women.²¹ In addition, a prospective multicenter observational study published in 2023 showed that medical or surgical abortion before 12 WG does not appear to increase the concentration of fetal red blood cells in maternal blood and therefore would not be associated with an increased risk of alloimmunization.¹⁶ Finally, the risk of RhD immune globulin is not zero and the potentially affected population is large.

3.2 | Question 2

In a patient who is RhD negative, when the progenitor is RhD positive or unknown, in case of bleeding in an ongoing pregnancy before 12 WG, does the injection of RhD immune globulin reduce the risk of alloimmunization? (Table S2).

R2—It is not recommended to administer RhD immune globulin before 12 weeks of gestation in order to reduce the risk of alloimmunization in case of bleeding in an ongoing pregnancy in RhD-negative patients when the progenitor is RhD-positive or unknown

Weak recommendation
Very low-quality evidence

Delphi: $n=20$; median 8; 80.0% agreed at first round

Argumentation

Risk of alloimmunization and benefit of RhD immune globulin

There are very few studies in the literature evaluating the risk of alloimmunization and the benefit of RhD immune globulin in

case of first trimester bleeding. These studies provide a very low level of evidence because they are purely observational, reporting clinical cases or case series. Some studies have a case-control design, but sometimes the controls are not even pregnant women. For example, a 2003 study compared 24 cases (RhD negative pregnant women who were not immunized at the beginning of pregnancy and were immunized at the end) with 24 controls (RhD negative pregnant women who were not immunized at the end of pregnancy), all of whom had bleeding during pregnancy. This study showed that there was no association between alloimmunization and bleeding during pregnancy before the 20th week of pregnancy.³¹ In addition, these studies are old, the most recent being published 20 years ago, and methods for detecting alloimmunization have evolved since then. Finally, these studies focus on the risk factors for alloimmunization rather than the benefit of prophylaxis with RhD immune globulin injection and refer to highly heterogeneous patient populations, not only in the first trimester of pregnancy.³²

Passage of fetal red blood cells into the maternal circulation before 12 WG

A recent multicenter, prospective, observational study published in 2023 examined the passage of fetal red blood cells into the maternal circulation in patients who underwent medical or surgical abortion before 12 WG at multiple centers in the USA between 2019 and 2022.¹⁶ Fetal red blood cells were detected and quantified by flow cytometry before and after the procedure. Of the 506 women, three had a preabortion FRBC concentration above the threshold of 125 FRBC/5 million ARBC, which is considered the risk threshold for immunization according to literature data.²² None of the three women had a history of prior bleeding. In addition, the level of FRBC was not significantly increased after the procedure in cases of bleeding (RR 1.06 [95% CI: 0.84–1.36], $P=0.62$). It should be noted that no high FRBC concentration was found in any of the 506 women after the procedure when it was not present before the procedure (0% [95% CI: 0%–0.59%]). This study, focusing on the effect of abortion (medical or surgical) on FRBC passage in maternal blood, suggests that abortion before 12 WG is not associated with an increased risk of alloimmunization. This result is likely to be extrapolated to bleeding before 12 WG.

Risks associated with RhD immune globulin administration

The risks associated with RhD immune globulin are low (viral and prion risks associated with injection of a blood-derived product, hypersensitivity or allergies). It is a product of human origin, obtained primarily from healthy, hyperimmunized and compensated North American donors.²³ Since 2005, only Rhophylac has been marketed in France in two doses, 200 µg and 300 µg, depending on the indication. There is a theoretical risk associated with prions, as well as a viral risk, which is low because of the treatments used to eliminate viruses, but the risk is not zero, particularly with regard to viruses that have not yet been identified.^{23,24} There is also a risk of allergy and hypersensitivity. A few cases of serious allergic reactions to other brands

of RhD immune globulin have been reported in the literature.^{25–27} No allergic reactions have been reported in antenatal and postnatal efficacy studies of Rhophylac.²⁴ Therefore, the risks associated with RhD immune globulin are very low but potentially serious.

Population potentially concerned by RhD immune globulin administration

Approximately 20%–25% of pregnant women will experience bleeding in the first trimester and will go to their doctor or gynecologic emergency room for diagnosis and management.³⁴ The proportion of RhD negative individuals in the French population is approximately 15%.³⁰ The administration of RhD immune globulin for first-trimester bleeding therefore potentially affects approximately 30 000 women per year in France.

Overall, there is no evidence in the literature to support the efficacy of RhD immune globulin administration to prevent alloimmunization in the setting of first-trimester bleeding in an ongoing pregnancy. Moreover, a recent multicenter prospective observational study shows that the risk of alloimmunization is low in cases of abortion before 12 WG and that there is no association between bleeding and an increased risk of alloimmunization. Finally, the risk of RhD immune globulin is not zero and the potentially affected population is large.

3.3 | Question 3

In a patient who is RhD negative, when the progenitor is RhD positive or unknown, in case of ectopic pregnancy, does the injection of RhD immune globulin reduce the risk of alloimmunization? (Table S3).

R3—The current literature does not provide sufficient data to determine whether the administration of RhD immune globulin can effectively reduce the risk of alloimmunization in case of ectopic pregnancy

No recommendation
Very low-quality evidence

Delphi: $n=20$; median 7; 50.0% agreed at first round; $n=20$; median 8.5; 80.0% agreed at second round

Argumentation

Previous recommendations of the CNGOF

In 2005, the CNGOF published recommendations for the prevention of RhD alloimmunization during pregnancy including the first trimester.² The following circumstances were considered to be at moderate risk of fetal red blood cell passage in the first trimester: spontaneous or induced abortion, bleeding, and ectopic pregnancy.²⁹ This provided justification for the prevention of alloimmunization through the administration of RhD immune globulin injections.

However, at the time these recommendations were formulated, there were few studies in the existing literature specifically designed to evaluate the benefits and efficacy of preventing alloimmunization in the first trimester. Furthermore, the epidemiologic and theoretical data on which these recommendations were based were heterogeneous, outdated (whereas techniques for quantifying fetal red blood cells in maternal blood have since evolved), and subject to certain biases, resulting in a very low quality of evidence. In addition, none of the data specifically addressed the risk of alloimmunization in ectopic pregnancy.

Benefit of RhD immune globulin

The review of the literature reveals that no study has specifically evaluated the interest of RhD immune globulin in preventing alloimmunization in ectopic pregnancy.

Passage of fetal red blood cells into the maternal circulation in case of ectopic pregnancy

A single comparative study, published in 1972, examined the passage of fetal red blood cells into maternal blood in case of ectopic pregnancy.³³ This single-center South African study compared women who had undergone surgery for a ruptured tubal pregnancy with a control group of non-pregnant women. The primary endpoint was a Kleihauer test result of at least 5 FRBC/150 000 ARBC in the blood sample obtained within 24 h of surgery. This criterion was met in nine out of 38 (23.7%) patients in the operated group, but not in the control group (0 out of 40). The presence of intraperitoneal fetal red blood cells was a secondary criterion observed in 16 of the 21 cases of operated patients for whom this examination was available, representing a proportion of 76.2%. In the control group, 12.5% (5/40) of cases demonstrated the presence of 1 to 2 FRBC per 150 000 ARBC. The authors assumed two potential mechanisms by which fetal red blood cells may gain access to the maternal circulation: through the fallopian tube wall and by absorption through the peritoneum. This study was subject to a number of biases, including a lack of randomization, a control group of non-pregnant patients, and lack of information on the characteristics of the groups. Furthermore, the potential for false-positive results of the Kleihauer test due to hemoglobinopathy or the presence of F cells, which can be observed in early pregnancy,³⁴ was not considered. Therefore, the study does not provide sufficient evidence to determine the risk of alloimmunization in ectopic pregnancy. Moreover, a recent prospective observational study of good methodological quality, published in 2023,¹⁶ examined the passage of fetal red blood cells during surgical or medical abortion. The study concluded that these procedures did not increase the concentration of fetal red blood cells in the maternal blood and thus were not associated with an additional risk of alloimmunization. The results of this study call for a re-evaluation of the value of alloimmunization prophylaxis in the first trimester. However, it is not possible to extrapolate these results to ectopic pregnancy because the underlying pathophysiology is different

1. Bergström H, Nilsson L-Å, Nilsson L, Ryttinger L. Demonstration of Rh antigens in a 38-day-old fetus. *Am J Obstet Gynecol*. 1967;99:130-133. doi:[10.1016/S0002-9378\(16\)34502-1](https://doi.org/10.1016/S0002-9378(16)34502-1)
2. Collège National des Gynécologues et Obstétriciens Français. Recommendations for clinical practice. Prevention in maternal-fetal Rh immunization (December 2005). *Gynecol Obstet Fertil*. 2006;34(4):360-365. doi:[10.1016/j.gyobfe.2006.02.007](https://doi.org/10.1016/j.gyobfe.2006.02.007)
3. World Health Organization. Abortion care guideline 2022. Accessed October 3, 2024. <https://iris.who.int/bitstream/handle/10665/349316/9789240039483-eng.pdf?sequence=1>
4. Horvath S, Goyal V, Traxler S, Prager S. Society of Family Planning committee consensus on Rh testing in early pregnancy. *Contraception*. 2022;114:1-5. doi:[10.1016/j.contraception.2022.07.002](https://doi.org/10.1016/j.contraception.2022.07.002)
5. Royal College of Obstetricians and Gynaecologists. Best practice in abortion care. Making abortion safe. Accessed October 26, 2024. <https://www.rcog.org.uk/media/geify5bx/abortion-care-best-practice-paper-april-2022.pdf>
6. Visser GHA, Thommesen T, Di Renzo GC, et al. FIGO/ICM guidelines for preventing rhesus disease: a call to action. *Int J Gynaecol Obstet*. 2021;152(2):144-147. doi:[10.1002/ijgo.13459](https://doi.org/10.1002/ijgo.13459)
7. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Guideline for the prophylactic use of Rh D immunoglobulin in pregnancy care. 2021 Accessed October 5, 2023. <https://production.nba-old.doghouse.cloud/sites/default/files/Guideline%20for%20the%20prophylactic%20use%20of%20Rh%20D%20immunoglobulin%20in%20pregnancy%20care.pdf>
8. Recommendations|Ectopic pregnancy and miscarriage: diagnosis and initial management|Guidance|NICE 2019. Accessed October 5, 2023. <https://www.nice.org.uk/guidance/ng126/chapter/Recommendations>
9. Schmidt-Hansen M, Lord J, Hawkins J, et al. Anti-D prophylaxis for rhesus D (RhD)-negative women having an abortion of a pregnancy up to 13⁺ weeks' gestation: a systematic review and new NICE consensus guidelines. *BMJ Sex Reprod Health*. 2020;1-6. doi:[10.1136/bmjsex-2019-200536](https://doi.org/10.1136/bmjsex-2019-200536)
10. Dutch Association of Abortion Specialists (NGvA). Guideline for the treatment of women undergoing termination of pregnancy 2016. Accessed October 5, 2023. <https://fiapac.org/media/docs/Guideline-Treatment.pdf>
11. Qureshi H, Massey E, Kirwan D, et al. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. *Transfus Med*. 2014;24(1):8-20. doi:[10.1111/tme.12091](https://doi.org/10.1111/tme.12091)
12. Rh D immune globulin administration after abortion or pregnancy loss at less than 12 weeks of gestation. *Obstet Gynecol*. 2024;144(6):e140-e143. doi:[10.1097/AOG.0000000000005733](https://doi.org/10.1097/AOG.0000000000005733)

13. Fung-Kee-Fung K, Wong K, Walsh J, Hamel C, Clarke G. Guideline No. 448: prevention of Rh D alloimmunization. *J Obstet Gynaecol Can.* 2024;46(4):102449. doi:[10.1016/j.jogc.2024.102449](https://doi.org/10.1016/j.jogc.2024.102449)
14. National Abortion Federation. Clinical policy guidelines for abortion care 2024. Accessed October 26, 2024. <https://prochoice.org/providers/quality-standards/>
15. Society for Maternal-Fetal Medicine (SMFM), Prabhu M, Louis JM, Kuller JA, SMFM Publications Committee. Society for Maternal-Fetal Medicine Statement: RhD immune globulin after spontaneous or induced abortion at less than 12 weeks of gestation. *Am J Obstet Gynecol.* 2024;230(5):S0002-9378(24)00368-5. doi:[10.1016/j.ajog.2024.02.288](https://doi.org/10.1016/j.ajog.2024.02.288)
16. Horvath S, Huang Z-Y, Koelper NC, et al. Induced abortion and the risk of Rh sensitization. *JAMA.* 2023;330:1167-1174. doi:[10.1001/jama.2023.16953](https://doi.org/10.1001/jama.2023.16953)
17. Vigoureux S, Maurice P, Sibiude J, Garabedian C, Sananès N. Prevention of Rh D alloimmunization in the first trimester of the pregnancy: French College of Obstetricians and Gynecologists guidelines for clinical practice. *Gynecol Obstet Fertil Senol.* 2024;52:446-453. doi:[10.1016/j.gofs.2024.02.026](https://doi.org/10.1016/j.gofs.2024.02.026)
18. Visscher RD, Visscher HC. Do Rh-negative women with an early spontaneous abortion need Rh immune prophylaxis? *Am J Obstet Gynecol.* 1972;113:158-165. doi:[10.1016/0002-9378\(72\)90765-x](https://doi.org/10.1016/0002-9378(72)90765-x)
19. Goldman JA, Eckerling B. Prevention of Rh immunization after abortion with anti-Rh (D)-immunoglobulin. *Obstet Gynecol.* 1972;40:366-370.
20. Gavin PS. Rhesus sensitization in abortion. *Obstet Gynecol.* 1972;39:37-40.
21. Wiebe ER, Campbell M, Aiken ARA, Albert A. 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.
22. Zipursky A, Pollock J, Neelands P, Chown B, Israels LG. The transplacental passage of foetal red blood-cells and the pathogenesis of Rh immunisation during pregnancy. *Lancet.* 1963;2(7306):489-493. doi:[10.1016/s0140-6736\(63\)90228-9](https://doi.org/10.1016/s0140-6736(63)90228-9)
23. Circulaire DGS/SQ 4 no 98-231 du 9 avril 1998. Accessed October 5, 2023. <http://www.hemovigilance-cncrh.fr/www2/Textes/1998/09041998.HTM>
24. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish hepatology research group. *N Engl J Med.* 1999;340:1228-1233. doi:[10.1056/NEJM199904223401602](https://doi.org/10.1056/NEJM199904223401602)
25. Sulakvelidze I, Evans S, Switzer I, Underdown B, Greenbaum J, Dolovich J. Urticaria from allergy to a purified human anti-Rh antibody preparation. *Allergy.* 1995;50:981-983. doi:[10.1111/j.1398-9995.1995.tb02511.x](https://doi.org/10.1111/j.1398-9995.1995.tb02511.x)
26. Rutkowski K, Nasser SM. Management of hypersensitivity reactions to anti-D immunoglobulin preparations. *Allergy.* 2014;69:1560-1563. doi:[10.1111/all.12494](https://doi.org/10.1111/all.12494)
27. Jones BF, Trevillian PR, Nanra RS. Serum sickness due to Rh(anti-D) immunoglobulin. *Aust N Z J Obstet Gynaecol.* 1984;24:49-50. doi:[10.1111/j.1479-828x.1984.tb03322.x](https://doi.org/10.1111/j.1479-828x.1984.tb03322.x)
28. IVG. Accessed October 5, 2023. https://data.drees.solidarites-sante.gouv.fr/explore/dataset/3647_ivg/
29. Branger B, Winer N. Epidemiology of anti-D allo-immunization during pregnancy. *J Gynecol Obstet Biol Reprod (Paris).* 2006;35:1587-81592.
30. Lefrère J-J, Rouger P. 3—Immunologie transfusionnelle. *Transfus. Sang.* Elsevier Masson; 2015:89.
31. Hernández-Andrade E, Ahued-Ahued JR. Transvaginal bleeding in pregnancy, as risk factor of rhesus-D antigen isoimmunization. *Salud Publica Mex.* 2003;45:492-496.
32. Von Stein GA, Munsick RA, Stiver K, Ryder K. Fetomaternal hemorrhage in threatened abortion. *Obstet Gynecol.* 1992;79(3):383-386. doi:[10.1097/00006250-199203000-00011](https://doi.org/10.1097/00006250-199203000-00011)
33. Katz J, Marcus RG. The risk of Rh isoimmunization in ruptured tubal pregnancy. *Br Med J.* 1972;3:667-669. doi:[10.1136/bmj.3.5828.667](https://doi.org/10.1136/bmj.3.5828.667)
34. Pembrey ME, Weatherall DJ, Clegg JB. Maternal synthesis of haemoglobin F in pregnancy. *Lancet.* 1973;1(7816):1350-1354. doi:[10.1016/s0140-6736\(73\)91675-9](https://doi.org/10.1016/s0140-6736(73)91675-9)
35. Bouyer J. Epidemiology of ectopic pregnancy: incidence, risk factors and outcomes. *J Gynecol Obstet Biol Reprod (Paris).* 2003; 32:S8-S17.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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