

# Clinical Policy: Critical Issues in the Initial Evaluation and Management of Patients Presenting to the Emergency Department in Early Pregnancy

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This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Early Pregnancy. For a complete listing of subcommittee and committee members, please see page 131.

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## INTRODUCTION

In 1997, the American College of Emergency Physicians (ACEP) published a clinical policy that presented a general approach to all postmenarchal patients presenting with the chief complaint of vaginal bleeding.<sup>1</sup> The policy addressed serious but less acute causes of vaginal bleeding such as malignancy and infection, but the focus was on disorders with the greatest potential for acute morbidity and mortality, especially ectopic pregnancy. The policy format was based on collection of historical, physical examination, and diagnostic testing data with recommendations for actions based on these findings. Although the basic principles emphasized in the original policy have not changed, the broad-based, chief complaint–centered format did not permit detailed discussion of critical issues in evaluation and management of selected patients. This policy focuses on specific critical issues.

In the past decade, despite major changes in epidemiology, incidence, and demographics, ectopic pregnancy remains the most common cause of maternal death and serious morbidity in the first trimester of pregnancy. For this reason, critical issues selected for this policy revision are those primarily associated with initial evaluation and management of ectopic pregnancy and were not discussed with any specificity in the original policy. Those critical issues include: (1) interpretation of  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) assays, (2) use of Rh prophylaxis in the first trimester of pregnancy, and (3) outpatient management of ectopic pregnancy with cytotoxic agents.

In the United States, the incidence of ectopic pregnancy increased from 4.5 per 1,000 reported pregnancies in 1970 to 19.7 per 1,000 in 1992, accounting for 2% of reported pregnancies and 9% of pregnancy-related maternal deaths.<sup>2</sup> From 1970 to 1989, ectopic pregnancy incidence increased linearly, permitting extrapolation of case incidence up to 1992, the last year for official reporting in the United States.<sup>3,4</sup> The Scandinavian countries registered a similar incidence of ectopic pregnancy in the same years.<sup>5</sup> In the next 5 years, occurrence rates for ectopic pregnancy declined in Finland and Sweden, but no current registration method captured the number of cases in the United States during this same time period. It has been postulated that the same factors leading to the increase and decrease of Scandinavian rates may be operative in the United States.<sup>6</sup>

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Ectopic pregnancy after natural ovulation and fertilization is most associated with risk factors leading to tubal damage and altered embryo transport. History of tubal surgery, including sterilization, carries the highest risk. Salpingitis with resulting tubal occlusion doubles the likelihood of ectopic pregnancy with each recurrent episode.

Previous ectopic pregnancy results in a significant risk increase as a result of surgical management or persistence of risk factors associated with the original ectopic pregnancy.<sup>7,8</sup>

In the past decade, several factors may have reduced the true incidence of ectopic pregnancy and altered the relative importance of risk factors. Earlier diagnosis of infection and more effective antibiotic therapy could be expected to reduce tubal damage.<sup>9,10</sup> More early ectopic pregnancies are being managed medically rather than surgically, with the hope of less tubal damage. At the same time, although in vitro fertilization and induced ovulation are more commonly practiced and have become important risk factors, it must be emphasized that tubal factors (eg, previous salpingitis, tubal surgery, ectopic pregnancy) have been found to be the most important risk factors for ectopic pregnancy after in vitro fertilization.<sup>11-14</sup> No relationship has been found between spontaneous versus stimulated ovulation, type of ovarian stimulation, or number of implanted embryos and ectopic pregnancy, but heterotopic (includes both intrauterine and ectopic) pregnancy does appear to increase with increased number of implanted embryos and ovarian stimulation.<sup>10-13,15</sup>

Regardless of changes in incidence and risk factors, true or apparent, it remains essential for the emergency physician to understand the advances in diagnostic tests that permit earlier differentiation between ectopic pregnancy and intrauterine pregnancy. With earlier diagnosis comes increased consideration of first trimester anti-D prophylaxis for Rh incompatibility and increased medical outpatient management with methotrexate. The emergency physician needs to be aware of the indications and complications of using methotrexate for ectopic pregnancy.

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The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.<sup>16</sup> This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, members of the ACEP Section of Emergency Ultrasound, and physicians from specialty societies, including members of the American Academy of Family Physicians and members of the American College of Obstetricians and Gynecologists' (ACOG) Committee on Gynecologic Practice. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

This policy revision presents evidence for answering important questions about these critical diagnostic and management issues. Recommendations in this policy are not intended to represent the only diagnostic and management options that the emergency physician can consider. ACEP clearly recognizes the importance of the individual clinician's judgment. Rather, they define for the clinician those strategies for which medical literature exists to provide strong support for answers to the critical questions addressed in this policy.

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## METHODOLOGY

This clinical policy was created after careful review and critical analysis of the peer-reviewed literature.

Independent literature searches were conducted for each of the questions. Searches were limited in all areas to English-language, human studies, and included articles from bibliographies of selected papers and personal knowledge base.

For the introduction, a MEDLINE search for articles published between 1980 and 2000 was performed using the key words: ectopic pregnancy, epidemiology, and risk factors; pregnancy rates, assisted reproduction, in

vitro fertilization; embryo transfer, with a yield of 31 pertinent articles for review, of which 16 were used in the final document.

For the area on the use of serum hCG levels, a MEDLINE search for articles published between 1985 and 2000 was performed using the key words: pregnancy, ectopic; serum hCG; diagnostic ultrasonography, transvaginal, with a yield of 18 pertinent articles for review, of which 11 were used in the final document.

For the section on methotrexate use in ectopic pregnancy, a MEDLINE search for articles published between 1980 and 2000 was performed using the key words: methotrexate, ectopic pregnancy, side effects, drug interactions, with a yield of 68 pertinent articles for review, of which 15 were used in the final document.

For the section on use of Rh prophylaxis in first trimester pregnancy, a MEDLINE search for articles published between 1960 and 2000 was performed using the key words: Rh immunization, anti-D immunoglobulin, Rh sensitization, Rh-negative pregnancy complications, with a yield of 35 pertinent articles for review, of which 24 were used in the final document.

Abstracts and articles were reviewed by subcommittee members, and pertinent articles were selected. These were evaluated, and articles addressing the questions considered in this document were chosen. Subcommittee members also supplied references from bibliographies of initially selected articles or from their own knowledge base.

All publications were graded by at least 2 of the subcommittee members into 1 of 3 categories of strength of evidence. Some articles were downgraded 1 or more levels on the basis of a standardized formula that considers the size of study population, methodology, validity of conclusions, and potential sources of bias.

During the review process, all articles were given a baseline “strength of evidence” by the subcommittee members according to the following criteria:

**Strength of evidence Class I**—Interventional studies including clinical trials, observational studies including prospective cohort studies, aggregate studies including meta-analyses of randomized clinical trials only.

**Strength of evidence Class II**—Observational studies including retrospective cohort studies, case-controlled studies, aggregate studies including other meta-analyses.

**Strength of evidence Class III**—Descriptive cross-sectional studies; observational reports including case series and case reports; consensus studies including published panel consensus by acknowledged groups of experts.

Strength of evidence Class I and II articles were then rated on elements the committee believed were most important in creating a quality work. Class I and II articles with significant flaws or design bias were downgraded from 1 to 3 levels on the basis of a set formula. Strength of Evidence Class III articles were downgraded 1 level if they demonstrated significant flaws or bias. Articles downgraded below Class III strength of evidence were given an “X” rating and were not used in formulating this policy.

Recommendations regarding patient management were then made according to the following criteria:

**Level A recommendations.** Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on “strength of evidence Class I” or overwhelming evidence from “strength of evidence Class II” studies that directly address all the issues.)

**Level B recommendations.** Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on “strength of evidence Class II” studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of “strength of evidence Class III” studies).

**Level C recommendations.** Other strategies for patient management based on preliminary, inconclusive, or conflicting evidence, or, in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among

others, might lead to such a downgrading of recommendations.

### Scope of Application

This guideline is intended for physicians working in hospital-based emergency departments.

## CRITICAL QUESTIONS

### Interpretation of Serum hCG Levels

#### I. Is transvaginal ultrasound useful in detecting intrauterine pregnancy when the serum hCG level is less than 1,000 mIU/mL?

In 1988, Bernaschek et al<sup>17</sup> followed up 52 pregnant women in a fertility clinic with serial hCG determinations and transvaginal ultrasounds. The lowest hCG level associated with a correctly diagnosed intrauterine pregnancy was 141 mIU/mL. Between hCG levels of 50 mIU/mL and 280 mIU/mL, 2 (25%) out of 8 intrauterine pregnancies were correctly identified. All 9 pregnancies associated with hCG levels between 300 mIU/mL and 1,000 mIU/mL were correctly identified by transvaginal ultrasound.

Similarly, Kadar et al<sup>18</sup> followed up 52 women with singleton pregnancies in a fertility clinic. Below an hCG level of 1,000 mIU/mL, 2 (40%) of 5 intrauterine pregnancies were correctly diagnosed by transvaginal ultrasound, and the lowest hCG level associated with an accurately diagnosed pregnancy was 800 mIU/mL. Nyberg et al<sup>19</sup> followed up 27 women with intrauterine pregnancy. Below an hCG level of 500 mIU/mL, 1 (20%) of 5 intrauterine pregnancies were accurately diagnosed by transvaginal ultrasound, and between 500 mIU/mL and 1,000 mIU/mL, 4 (80%) of 5 intrauterine pregnancies were identified. Shapiro et al<sup>20</sup> followed up 31 women with normal intrauterine pregnancies and found that the lowest hCG level associated with an accurately diagnosed intrauterine pregnancy was 912 mIU/mL.

### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** None specified.

**Level C recommendations.** Consider transvaginal ultrasound because it may detect intrauterine pregnancy when the serum hCG level is below 1,000 mIU/mL.

#### II. Is transvaginal ultrasound useful in detecting ectopic pregnancy when the serum hCG level is less than 1,000 mIU/mL?

Kaplan et al<sup>21</sup> prospectively studied 439 pregnant women with first trimester abdominal pain and/or vaginal bleeding. Fifty-six patients had a final diagnosis of ectopic pregnancy, of whom 21 had an initial serum hCG level of less than 1,000 mIU/mL. Thirty-four patients had diagnostic evidence of ectopic pregnancy on initial transvaginal ultrasound, with 33 of these having a final diagnosis of ectopic pregnancy. Four of the patients with initial transvaginal ultrasound diagnostic of ectopic pregnancy had serum hCG levels less than 1,000 mIU/mL. Specificity of initial transvaginal ultrasound in diagnosing ectopic pregnancy in patients with serum hCG levels less than 1,000 mIU/mL was 100% and sensitivity was 19% in this study.

Dart et al<sup>22</sup> did a retrospective chart review of 111 pregnant patients with initial serum hCG levels less than 1,000 mIU/mL, presenting to the ED for abdominal pain and/or vaginal bleeding. Twenty-three of these patients had a final diagnosis of ectopic pregnancy. Of these, 9 (39%) had an initial transvaginal ultrasound diagnostic of ectopic pregnancy, 5 of whom had serum hCG levels less than 500 mIU/mL.

### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** None specified.

**Level C recommendations.** Consider transvaginal ultrasound because it may detect ectopic pregnancy when the serum hCG level is below 1,000 mIU/mL.

#### III. What is the role of serial quantitative hCG determinations in either diagnosing or excluding ectopic pregnancy?

Mol et al<sup>23</sup> followed up 134 pregnant women with risk factors for ectopic pregnancy. Serum hCG determinations were done on days 2 and 4 after the initial presentation. On day 2 of this study, a decline in hCG level excluded the possibility of a viable intrauterine pregnancy.

Shepherd et al<sup>24</sup> followed up 49 patients with positive hCGs and risk factors for ectopic pregnancy. Serial hCG determinations were done at 2- to 5-day intervals. Fourteen of 49 patients had ectopic pregnancy. By using percent increase as an end point, serial hCG determinations had a sensitivity of 36%, specificity of 63%, positive predictive value of 63%, and a negative predictive value of 29% in detecting ectopic pregnancy.

In a retrospective study, Romero et al<sup>25</sup> identified 74 women with ectopic pregnancy and matched them to 24 patients with normal intrauterine pregnancies. Measuring the change in slope of serum hCG, there was a 90% sensitivity to detect ectopic pregnancy. However, 12.5% of patients with normal intrauterine pregnancies were diagnosed as having ectopic pregnancies using this method. These findings were similar to those of Kadar et al.<sup>26</sup> In this small retrospective study, 15% of normal intrauterine pregnancies were diagnosed as ectopic pregnancy, and 13% of patients with ectopic pregnancy had delayed diagnoses.

#### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** Obtain a repeat serum hCG determination at least 2 days after the initial presentation because it is useful in characterizing the risk of ectopic pregnancy and the probability of a viable intrauterine pregnancy.

**Level C recommendations.** None specified.

**IV. Above what serum hCG level is the absence of intrauterine pregnancy by transvaginal ultrasound presumptive evidence of ectopic pregnancy?** In a prospective study of 354 pregnant women with ectopic pregnancy clinically suspected by presence of abdominal pain, vaginal bleeding, risk factors, or nondiagnostic transvaginal ultrasound, Mol et al<sup>23</sup> found that a cut off level for serum hCG as presumptive evidence of ectopic pregnancy, was dependent on presence of the sonographic abnormalities of fluid in the pouch of Douglas or an ectopic mass. In patients with these sonographic abnormalities, a serum hCG level greater than 1,500 mIU/mL indicated ectopic pregnancy with virtual certainty. For patients without these sono-

graphic abnormalities, a serum hCG level greater than 2,000 mIU/mL increased the likelihood of ectopic pregnancy and excluded viable intrauterine pregnancy.

In smaller, prospective, observational studies, Goldstein et al<sup>27</sup> identified all viable intrauterine pregnancies in patients with serum hCG levels above 1,025 mIU/mL, and Nyberg et al<sup>19</sup> identified all viable intrauterine pregnancies above hCG levels of 1,000 mIU/mL. In a study of 52 pregnant women, Bernaschek et al<sup>17</sup> identified all viable intrauterine pregnancies with hCG levels above 750 mIU/mL.

#### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** Arrange follow-up for patients with a nondiagnostic transvaginal ultrasound and a serum hCG level above 2,000 mIU/mL because they have an increased likelihood of ectopic pregnancy.

**Level C recommendations.** None specified.

#### METHOTREXATE IN ECTOPIC PREGNANCY

The emergency physician must be aware of potential side effects, complications, and drug interactions of methotrexate. Methotrexate is a cytotoxic agent that acts by inhibiting dihydrofolate reductase. It is a potent folate antagonist that blocks DNA synthesis before cell division. Rapidly dividing cells, such as trophoblastic tissue, are unable to divide and replicate. Methotrexate's side effects are directly related to its mechanism of action. Because of action on rapidly dividing cells, bone marrow suppression and gastrointestinal toxicity are possible. Possible complications include stomatitis, nausea, vomiting, diarrhea, and abdominal cramping.<sup>28-30</sup> Another potential side effect, hepatotoxicity, has been shown after prolonged methotrexate use and is not relevant in the short-term dosing used for ectopic pregnancy. Patients may experience acute pulmonary symptoms such as cough, dyspnea, and chest pain. These symptoms usually resolve with discontinuation of methotrexate and rarely occur with brief use.

Several drugs need to be carefully monitored during methotrexate use. Folic acid, found in many prenatal



vitamins, should be avoided because it may directly counteract methotrexate's primary action as a folate antagonist. Because of potentially lethal interactions of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) with methotrexate, it may be advisable for patients to avoid using these drugs concurrently with methotrexate until further research in this specific use is available.

The ACOG 1998 Practice Bulletin<sup>31</sup> recommended, after review of literature from 1985 to 1998, that methotrexate be used only in patients with an hCG level between 6,000 and 15,000 mIU/mL. They recommend a single dose of methotrexate (50 mg/m<sup>2</sup>). A second similar dose may be required during follow-up to increase success.<sup>32</sup> Some investigators have used an injection of 1 mg/kg directly into the ectopic sac, which appears to be as effective as intramuscular injections and causes fewer side effects, but is more invasive.<sup>29,33-35</sup> A 5-day regimen of methotrexate administered orally was not shown to be more effective than placebo.<sup>36</sup>

**V. What is the frequency of treatment failure in methotrexate therapy for ectopic pregnancy and its implication for ED management?** A review of the literature shows that selected patients with close follow-up have been safely treated with methotrexate, with success rates ranging from 64% to 94%.<sup>29,30,37-40</sup>

In 1993, Stovall and Ling<sup>32</sup> followed up 120 women diagnosed with ectopic pregnancy and treated with methotrexate by using a combination of hCG titers, serum progesterone levels, transvaginal ultrasonography, and curettage. Successful outcomes correlated with patients meeting the following criteria: an unruptured ectopic mass less than 3.5 cm in size, hemodynamic stability, and absence of active bleeding or signs of hemoperitoneum. All patients were required to be willing and able to return for follow-up care. Treatment was successful for 94% of the patients. Of these patients, 3.3% required a second intramuscular injection for successful treatment.

In 1996, Stitka et al<sup>28</sup> reviewed the cases of 50 women with ectopic pregnancy treated with methotrexate ad-

ministered intramuscularly. The success rate was 65% with the first injection. The success rate increased to 78% with a second injection. In 1998, Lipscomb et al<sup>37</sup> reviewed the cases of 315 women with ectopic pregnancy treated with methotrexate. Overall success rate of resolution without surgery was 90.1%, with 82.5% requiring only 1 injection. In 1999, Lipscomb et al<sup>41</sup> reviewed cases of 350 women with ectopic pregnancy treated with methotrexate. Overall success rate without surgery was 91%. More than 1 dose was given to 20% of the patients. The most important factor associated with single dose methotrexate failure was an elevated hCG level greater than 10,000 mIU/mL.<sup>28,41,42</sup> Stitka et al and Lipscomb et al both showed increased success when no fetal cardiac activity was detected. Stitka et al also noted that gastrointestinal side effects of methotrexate therapy are similar to symptoms of ruptured ectopic pregnancy.<sup>28</sup>

#### **Patient Management Recommendations**

**Level A recommendations.** None specified.

**Level B recommendations.** None specified.

**Level C recommendations.** Because the symptoms associated with gastrointestinal side effects of methotrexate therapy may mimic an acute ectopic rupture, rule out ectopic rupture resulting from treatment failure before attributing gastrointestinal symptoms to methotrexate toxicity. Treatment failure with single dose methotrexate for ectopic pregnancy can occur in up to 36% of patients.

#### **RH SEROCONVERSION AND INDICATIONS FOR ANTI-D IMMUNOGLOBULIN**

**VI. Is the administration of anti-D immunoglobulin indicated among Rh-negative women during the first trimester of pregnancy with threatened abortion, complete abortion, ectopic pregnancy, or minor abdominal trauma?** Data are limited, and the conclusion is based on a rational theoretical construct and limited observational studies rather than on prospective or experimental studies. The strength of that conclusion also varies somewhat with the individual entity being considered.

A series of studies builds the foundation for concern about potential first trimester alloimmunization:

1. The RhD antigen has been detected in a 38-day-old fetus<sup>43</sup> and is well developed by 6 weeks' gestation.<sup>44,45</sup>

2. Fetal red cells are found in the circulation of 50% of all postpartum patients regardless of Rh compatibility with the fetus, with estimates of fetomaternal hemorrhage ranging from 0.004 mL to more than 80 mL. The volume of measured fetomaternal hemorrhage is not always reflected in proportional fetal anemia, suggesting early, recurrent fetomaternal hemorrhage for which the fetus has compensated with prenatal blood production. Although nearly 90% of cases of fetomaternal hemorrhage and alloimmunization are believed to occur at delivery, fetal cells are found in maternal circulation in 7% of all pregnancies in the first trimester, 16% in the second trimester, and 29% in the third trimester.<sup>46</sup>

3. Injection of Rh antigen and antibody-negative volunteers with Rh-positive red cells demonstrated that alloimmunization occurred with as little as 0.1 mL injected cells. Only 60% of injected volunteers developed antibodies. Nonresponders did not become alloimmunized even when given subsequent repeated small doses.<sup>47,48</sup> This contrasts with a 90% alloimmunization rate in Rh-negative patients receiving a full unit transfusion of Rh incompatible blood.<sup>49</sup>

4. It is accepted that only 17% of Rh-negative women who do not receive anti-D immunoglobulin will become Rh immunized after pregnancy with an ABO-compatible, Rh-positive infant; however, actual immunization rates are probably greater because antibody levels may be insufficient to detect until the early anamnestic response in a second Rh-positive pregnancy.<sup>49</sup> This theory is reinforced by the 60% response rate in experimental exposures (see No. 3).

5. Fetal cells have been detected in maternal circulation after a variety of obstetric procedures such as amniocentesis, chorionic villous sampling, and external cephalic version. The value of administration of anti-D immunoglobulin attendant to such procedures is well accepted.<sup>50</sup>

6. Fetomaternal hemorrhage with theoretical risk of alloimmunization has been demonstrated after ruptured

ectopic pregnancy,<sup>51</sup> spontaneous abortion,<sup>52</sup> therapeutic abortion,<sup>53</sup> and minor trauma.<sup>54</sup>

7. Other patients may be at risk as a result of failure to recognize events resulting in fetomaternal hemorrhage. Hughes et al<sup>55</sup> reported 2 cases of alloimmunization with the only identified event being first trimester vaginal bleeding. McSweeney et al<sup>56</sup> reported 39 cases of alloimmunization involving only early spontaneous abortion, 2 cases involving unruptured ectopic pregnancy, and 67 cases in which there was no identified precipitating event.

Is there evidence that anti-D immunoglobulin prevents seroconversion in Rh-negative patients? The straightforward answer is that no randomized clinical trials to answer that question have been done on pregnant Rh-negative women. Rh-negative male volunteers were injected with Rh-positive blood, which resulted in 50% immunization. A second group received Rh-positive cells coated in vitro with Rh antibody, with no resulting immunization.<sup>47</sup> There is a large volume of circumstantial evidence based on observation of reduced alloimmunization after institution of routine use of anti-D immunoglobulin. In a Canadian study<sup>57</sup> of 1,216 Rh-negative patients delivering Rh-positive infants, testing negative for presence of Rh antibody at time of delivery, and receiving anti-D immunoglobulin, there were no cases of immunization at 6 months postpartum. This is compared with a 7.3% immunization rate in patients refusing treatment.<sup>57</sup> In a combined trial of patients in Liverpool, England, and Baltimore, MD,<sup>58</sup> 50% of patients were treated with anti-D immunoglobulin immediately postpartum and 50% were not. Untreated patients either refused or presented on weekends when the trial was not conducted. The treated patients had a 90% decrease in alloimmunization in comparison with the untreated patients when tested at 6 months postpartum. The introduction of a postpartum rhesus prevention program in the United Kingdom in 1969 reduced fetal mortality from Rh hemolytic disease from 120 per 100,000 live births to 1.5 per 100,000 by 1989.<sup>59</sup> Introduction of antenatal prophylaxis at 28 and/or 34 weeks' gestation reduced the immunization rate another 90%.<sup>44,50,60</sup> The positive effects continued

into a second Rh incompatible pregnancy.<sup>60</sup> There is no controversy in the health care systems of the United Kingdom, Canada, or the United States regarding the efficacy of late prenatal and early postnatal treatment of susceptible patients with anti-D immunoglobulin in prevention of Rh hemolytic disease of the newborn, and the practice has become routine.

There is a residual problem of Rh immunization even when the aforementioned practice standards are rigorously applied. This is assumed to result from failure to follow recommended treatment schedules, or from failure to recognize events other than delivery that put a patient at risk.<sup>55,61</sup> It has been shown that administration of anti-D immunoglobulin is ineffective once antibody formation has occurred.<sup>62,63</sup> It has also been shown in several studies<sup>51-54</sup> that significant fetomaternal hemorrhage with potential for Rh immunization occurs in threatened abortion, ectopic pregnancy, minor trauma, and elective abortion. The logical assumption is that early fetomaternal hemorrhage carries the same risk of alloimmunization as late fetomaternal hemorrhage. In a study of 1,027 Rh-negative women undergoing elective abortion at 12 weeks' or less gestation, a procedure with known risk of significant fetomaternal hemorrhage, administration of a 50- $\mu$ g dose of anti-D immunoglobulin resulted in no cases of sensitization. More research may be indicated for strict evidence-based recommendations, but the ethics of any prospective randomized trial in the face of the devastating effects on fetuses of sensitized mothers and available circumstantial evidence would be difficult to approve; furthermore, few investigators would be willing to participate in such studies.

#### THREATENED OR COMPLETE ABORTION OR ECTOPIC PREGNANCY

The risk of sensitization with threatened abortion in the first trimester is unknown, and there have been no randomized trials. One study of patients with threatened abortion in the first trimester measured fetal cells in the maternal circulation by the Kleihauer-Betke acid elution assay. Results were compared with case-matched patients presenting at the same gestational stage for

elective abortion. Patients with any history of antepartum bleeding were excluded. Eleven percent of the study population had a positive result compared with 4% in the control group.<sup>64</sup> Litwak et al<sup>52</sup> reported 32% overall rate of fetomaternal hemorrhage in patients undergoing spontaneous abortion. Individual rates were 48% in threatened abortion, 36% in complete abortion, and 22% for incomplete abortion. Uterine curettage for incomplete abortion further increased the rate of fetomaternal hemorrhage, with higher risk for primagravidas who required greater cervical dilation for the procedure. Four cases of alloimmunization believed to be the result of threatened abortions were reported by McSweeney et al.<sup>56</sup> Rh immunization as a result of first trimester threatened abortion was reported as "exceedingly rare" by ACOG.<sup>61</sup> The opinion from British authorities is that anti-D immunoglobulin may be unnecessary with a threatened abortion and viable fetus before 12 weeks' gestation. This recommendation was based on the theory that most vaginal bleeding before 12 weeks' gestation, when the pregnancy continues, is not from fetal vessels in chorionic villi but from maternal vessels in the decidua or cervix.<sup>65</sup> However, the same group suggests it may be prudent to administer anti-D immunoglobulin when there is "heavy" bleeding or associated abdominal pain, or when the event occurs near 12 weeks' gestation. Essentially identical recommendations arise from ACOG, although they state simply that there is no evidence-based recommendation and that many physicians do not treat when there is a live embryo or fetus.<sup>61</sup> The need for prophylaxis in a complete spontaneous abortion is not questioned by any of the reviewed authorities and is a Level A recommendation by ACOG. However, there is no class I evidence of this according to ACEP's methodology; thus, it is presented as a Level B recommendation (see Patient Management Recommendations). Because the volume of fetal cells potentially involved in the fetomaternal hemorrhage is small, the recommended dose of anti-D immunoglobulin is 50  $\mu$ g.<sup>61</sup>

The background discussion for spontaneous abortion also applies here, but the recommendations are unequivocally stronger, based on the fact that the proba-



bility of significant fetomaternal hemorrhage is substantially greater, especially in cases involving rupture of a tubal pregnancy. Katz and Marcus<sup>51</sup> reported significant fetomaternal hemorrhage in 24% of patients with ruptured ectopic pregnancy. Ectopic pregnancy was noted as the probable immunizing event in 2 patients, neither of whom received anti-D immunoglobulin.<sup>56</sup> In a case study of an Rh-negative primigravida who did not receive anti-D immunoglobulin after an ectopic pregnancy, the patient was found to have high anti-Rh titers in a second pregnancy and subsequently delivered a nonviable hydropic fetus.<sup>66</sup> Although the risk factors for Rh immunization after ectopic pregnancy “are not easily ascertained ... it would seem prudent to administer at least the standard 50 microgram dose.”<sup>45</sup> ACOG does not treat the management of ectopic pregnancies separately from other first trimester terminations for which the consensus opinion unequivocally recommends treatment with 50 µg of anti-D immunoglobulin.<sup>61</sup>

#### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** Administer 50 µg of anti-D immunoglobulin to Rh-negative women in all cases of documented first trimester loss of established pregnancy.

**Level C recommendations.** None specified.

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#### MINOR ABDOMINAL TRAUMA

In one study of pregnant patients suffering minor trauma after which they were all stable, required no surgery or admission, and suffered only contusions or superficial lacerations, 28% of patients had fetomaternal hemorrhage. The type of trauma included falls, minor moving vehicle accidents, and direct blows to the abdomen (ie, assaults).<sup>54</sup> There are equivocal recommendations from ACOG<sup>61</sup> to consider the possibility of alloimmunization and the use of anti-D immunoglobulin in trauma, and there are no direct data on the risk in the first trimester. There is insufficient evidence to establish clear guidelines on administration of anti-D immunoglobulin in cases of blunt abdominal trauma in pregnant patients.

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#### Patient Management Recommendations

**Level A recommendations.** None specified.

**Level B recommendations.** None specified.

**Level C recommendations.** Consider administration of anti-D immunoglobulin in cases of minor trauma in Rh-negative patients.

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This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Early Pregnancy.

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