Recurrent pregnancy loss: Evaluation

Authors: Togas Tulandi, MD, MHCM, FRCSC, FACOG, FCAHS, Haya M Al-Fozan, MD
Section Editor: Charles J Lockwood, MD, MHCM
Deputy Editor: Kristen Eckler, MD, FACOG

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INTRODUCTION

Couples with recurrent pregnancy loss (RPL) require empathy and understanding as early pregnancy loss is an emotionally traumatic experience, similar to that associated with stillbirth or neonatal death. In addition, evaluation can be frustrating and difficult because the etiology of their RPL may not be determined and there are few evidence-based diagnostic and treatment strategies. This topic reviews the evaluation of RPL.

Information on related topics may be found elsewhere:

- (See "Recurrent pregnancy loss: Definition and etiology".)
- (See "Recurrent pregnancy loss: Management".)
- (See "Pregnancy loss (miscarriage): Terminology, risk factors, and etiology".)
- (See "Pregnancy loss (miscarriage): Clinical presentations, diagnosis, and initial evaluation".)

In this topic, when discussing study results, we will use the terms "woman/en" or "patient(s)" as they are used in the studies presented. However, we encourage the reader to consider the specific counseling and treatment needs of transgender and gender diverse individuals.

CANDIDATES FOR EVALUATION

The definition of RPL varies, which makes studying the phenomenon, and determining which couples to counsel or treat, more challenging. As examples, varying definitions have included:

- Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination [1,2].
- Three consecutive pregnancy losses, which are not required to be intrauterine [3,4].

In our practice, we start investigating after two failed clinical pregnancies, including biochemical pregnancies for women undergoing in vitro fertilization. The various definitions and rationale behind them is discussed in detail separately. (See "Recurrent pregnancy loss: Definition and etiology".)

There is a general consensus that healthy women should not undergo extensive evaluation after a single first trimester or early second trimester spontaneous miscarriage (up to 20 weeks), given these are relatively common, sporadic events: miscarriage occurs in approximately 10 to 15 percent of clinically recognized pregnancies under 20 weeks of gestation. In prospective studies, the overall risk of miscarriage in the next pregnancy remains at approximately 15 percent after one miscarriage, but rises to 17 to 31 percent after two consecutive miscarriages and to 25 to 46 percent after three or more miscarriages. Based on these and similar data, most experts initiate evaluation and treatment of RPL after two consecutive miscarriages [5,6].

It is important to remember that most women with RPL have a good prognosis for eventually having a successful pregnancy, even when a definitive diagnosis is not made and no treatment initiated. In one representative study, the overall live birth rates after normal and abnormal diagnostic evaluations for RPL were 77 and 71 percent, respectively [7].

HISTORY AND PHYSICAL EXAMINATION

The minimum diagnostic work-up of couples with RPL consists of a complete medical, surgical, genetic, and family history and a physical examination.

History — The history should include a description of the gestational age and characteristics (eg, anembryonic pregnancy, live embryo) of all previous pregnancies. Gestational age is important because RPL typically occurs at a similar gestational age in consecutive pregnancies and the most common causes of RPL vary by trimester. As an example, miscarriage related to chromosomal and endocrine defects tends to occur earlier in gestation than losses due to anatomic or immunological abnormalities; however, there is significant overlap.

Additional information to consider:

- Has there been uterine instrumentation, which may have caused intrauterine adhesions? (See "Intrauterine adhesions: Clinical manifestation and diagnosis".)
- Are the menstrual cycles normal? Abnormalities in cycle length may be due to endocrine dysfunction. Is there galactorrhea, which also suggests endocrine dysfunction (hyperprolactinemia)?
- Is there a history of congenital abnormalities or karyotypic abnormalities, which may be heritable? Was embryonic/fetal cardiac activity ever detected? RPL prior to detection of embryonic cardiac activity also suggests a chromosomal abnormality. Does the family history display patterns of disease consistent with a strong genetic influence? Is consanguinity present?
- Is there exposure to environmental toxins, which may be lethal to developing embryos?
- Is there a history of venous or arterial thrombosis suggestive of antiphospholipid syndrome?
- What information is available from previous laboratory, pathology, and imaging studies?

Physical examination — Physical examination should include a general physical assessment with attention to signs of endocrinopathy (eg, hirsutism, galactorrhea) and pelvic organ abnormalities (eg, uterine malformation, cervical laceration).

Mental health evaluation — RPL is a source of great stress for couples. One study of 301 women with RPL reported fourfold higher rates of depression (8.6 versus 2 percent) and

doubling of severe stress (41 versus 23 percent) for the women with versus without RPL [8]. This study highlights the importance of mental health evaluation, including screening for depression, as part of the RPL work-up. (See "Screening for depression in adults", section on 'Screening options'.)

EVALUATION

We take a step-wise approach to the evaluation of individuals with RPL [9].

Most useful tests

Karyotype — Karyotyping of couples is part of the evaluation of RPL, despite the low yield of abnormality, cost, and limited prognostic value [5,10]. The purpose is to detect balanced reciprocal or Robertsonian translocations or mosaicism that could be passed to the fetus unbalanced.

Because of the low likelihood of an abnormal karyotype in couples with RPL, this is the last test we obtain and only if the preceding work-up yielded negative results. A review of cytogenetic findings in 79 published surveys of couples with two or more pregnancy losses (n = 8208 women and 7834 men) observed the overall prevalence of major chromosome abnormalities was 2.9 percent, which is five to six times higher than that of the general adult population [11]. Approximately one-half of the abnormalities were balanced reciprocal translocations, one-quarter were Robertsonian translocations, and one-tenth were sex chromosome mosaicisms in females; the rest consisted of inversions and other sporadic abnormalities. A large database subsequently reported similar findings: 4.7 percent of couples with two or more spontaneous abortions included one carrier of a structural chromosomal abnormality, usually a translocation or inversion [12].

Chromosomal abnormalities detectable in parental peripheral blood preparations are an indirect and limited indicator of fetal karyotype [13]. Therefore, many experts also recommend karyotype of the abortus or products of conception. A normal karyotype suggests (but does not prove) a maternal environmental factor is the cause of pregnancy loss, while an abnormal karyotype (aneuploidy) is usually a sufficient explanation for a nonviable pregnancy. In some cases, karyotype analysis of the abortus indicates a normal chromosomal pattern, but more detailed array comparative genomic hybridization demonstrates major abnormalities [14]. Structural chromosomal rearrangements in the

abortus may be inherited or sporadic, and are an indication for parental karyotype analysis if not already done.

If the abortus specimen does not grow in culture, a conventional karyotype cannot be determined. Cells from chromosomally abnormal abortuses, especially trisomy 7 and triploidies, are less likely to grow in culture, thereby skewing the results of cohort studies of the frequency of aneuploidy in products of conception from spontaneously aborted pregnancies [15]. Array comparative genomic hybridization does not require dividing cells, and therefore can be useful in fetal demise with culture failure [2,16]. For this reason, at least one society advises array comparative genomic hybridization over karyotype [2].

Uterine assessment — Anatomic causes of RPL are typically diagnosed using hysterosalpingography (HSG) or sonohysterography. We prefer the latter because it is more accurate than HSG and gives more information than sonography alone [17]. Hysteroscopy, laparoscopy, or magnetic resonance imaging (MRI) can also be performed, as needed, but are more expensive and (except for MRI) more invasive than sonohysterography. Therefore, they are used as second-line tests when additional information is required to determine a diagnosis. Ultrasonography is particularly useful in pregnant women, in whom the other tests are relatively or absolutely contraindicated. (See "Congenital uterine anomalies: Clinical manifestations and diagnosis".)

Methods of imaging

- **Sonohysterography** – Sonohysterography delineates the internal contours of the uterine cavity and provides concomitant sonographic visualization of the outer surface and wall of the uterus. It provides information on tubal patency and can distinguish between the septate and bicornuate uterus. In comparative studies, sonohysterography was more accurate than HSG and provided more information about uterine abnormalities [17]. (See "Saline infusion sonohysterography".)

- **Hysterosalpingogram** – HSG provides some of the same information as sonohysterography. It provides more information about tubal anatomy and patency; however, it does not evaluate the outer contour of the uterus, therefore it cannot reliably differentiate between a septate and a bicornuate uterus unless a laparoscopy to view the uterine fundus is also performed [18]. (See "Hysterosalpingography".)

- **Hysteroscopy** – Hysteroscopy is considered the standard for diagnosis of intrauterine abnormalities [18]. In addition, treatment of many intrauterine lesions can be performed during the procedure. However, it also cannot reliably differentiate between a septate and a bicornuate uterus unless a laparoscopy to view the uterine fundus is also performed. Because of its cost and invasiveness, hysteroscopic uterine assessment is usually reserved for patients who have had a nondiagnostic evaluation of RPL or those in whom intrauterine pathology is suspected and operative hysteroscopy may be necessary. (See "Overview of hysteroscopy".)

- **Ultrasound** – Transvaginal ultrasound (TVS) and transabdominal ultrasound are useful for making the diagnosis of a septate uterus and renal abnormalities, and provide information about the presence and location of uterine myomas [18]. TVS also provides information about the presence and location of uterine myomas and, in pregnancy, the possibility of cervical insufficiency and assessment of fetal viability.

  Three-dimensional ultrasound, where available, is accurate in diagnosing uterine anomalies [19]. In contrast to two-dimensional ultrasound, but similar to magnetic resonance imaging, it allows visualization of both the uterine cavity and the external contour of the uterus [20].

- **Magnetic resonance imaging** – MRI is useful for distinguishing between a septate and bicornuate uterus suspected on ultrasonography or HSG. It is less invasive and less costly than laparoscopy for this purpose. As an example, a study of 26 women comparing MRI (n = 26), TVS (n = 14), and HSG (n = 20) for classification of müllerian duct anomalies reported that MRI diagnosed 24 of 24 cases correctly, TVS was correct in 11 of 12 cases, and HSG was correct in only four cases [21]. For diagnosis of septate uterus, MRI performed better than two-dimensional TVS (sensitivity and specificity of 100 percent for MRI versus 100 and 80 percent, respectively, for TVS). Three-dimensional ultrasound is also reliable, but simpler than MRI for distinguishing septate from bicornuate uteri.

Anatomic evaluation — For individuals with recurrent pregnancy loss, imaging of the uterus is performed to identify uterine anomalies, fibroids (leiomyoma), adenomyosis, and intrauterine adhesions [22,23]. However, these anatomic abnormalities are not clearly associated with increased risk of pregnancy loss, and the impact of treatment is less well

understood. Challenges include the varied definitions of recurrent pregnancy loss and inclusion of mixed populations (general obstetric patients versus those with identified recurrent pregnancy loss). The impact of each is discussed in detail in related content. (See "Recurrent pregnancy loss: Definition and etiology", section on 'Uterine factors'.)

Antiphospholipid syndrome — The minimum immunology work-up for women with RPL is measurement of anticardiolipin antibody (IgG and IgM) and lupus anticoagulant. Diagnosis of antiphospholipid antibody syndrome includes testing for anti-beta2 glycoprotein I antibodies as well as anticardiolipin antibody and lupus anticoagulant [24]. These tests should be done twice, at least 12 weeks apart, because a low- to mid-positive level can be due to viral illness and revert to normal. The anticardiolipin antibody titer is considered elevated if medium or high titers of both IgG and IgM isotypes are present in blood [25]. The detection of the lupus anticoagulant is generally based upon an activated partial thromboplastin time, kaolin plasma clotting time, or dilute Russell viper venom test time [26]. Full criteria for the diagnosis of antiphospholipid antibody syndrome are available in the table (table 1) and discussed in detail in related content. (See "Diagnosis of antiphospholipid syndrome".)

Thyroid function — Thyroid function should be assessed in women with clinical manifestations or a personal history of thyroid disease. Screening asymptomatic women for subclinical thyroid dysfunction is controversial. We feel screening is reasonable since there is evidence of an increased risk of miscarriage in women with subclinical hypothyroidism [27] and in euthyroid women with thyroid peroxidase (TPO) antibodies [28-30].

Meta-analyses of case-control and cohort studies have found that the presence of TPO autoantibodies in euthyroid women is associated with an increased risk of spontaneous miscarriage that is two to three times higher than in women without these antibodies [28,29]. In addition, meta-analysis of two randomized trials of the effect of thyroid replacement in these women found treatment was associated with a significant reduction in risk of miscarriage (relative risk 0.48, 95% CI 0.25-0.92) [29]; however, there were methodological limitations to these trials. (See "Overview of thyroid disease and pregnancy", section on 'Thyroid peroxidase antibodies in euthyroid women'.)

Less useful tests

Evaluation of ovarian reserve — Ovarian reserve can be evaluated by measurement of

antral follicle count (AFC), basal serum follicle stimulating hormone (FSH), anti-müllerian hormone (AMH), or inhibin-B. Evaluation of ovarian reserve using a day 3 FSH concentration can be considered in the evaluation of RPL in women of any age. If measurement of FSH levels was limited to women over 34 years of age, one quarter of those with elevated values would be missed [31]. (See "Recurrent pregnancy loss: Definition and etiology", section on 'Diminished ovarian reserve'.)

Adequate ovarian reserve is established using either a cycle day 3 FSH concentration less than 15 mIU/mL or a clomiphene challenge test (ie, clomiphene citrate 100 mg daily is administered on cycle days 5 to 9. An FSH level less than 15 mIU/mL on both days 3 and 10 is normal). High day 3 serum estradiol concentrations of over 80 pg/mL are also associated with reduced oocyte numbers. In one study, FSH or estradiol levels, or both, were elevated in 58 percent of women with unexplained RPL, but also in 19 percent of controls with a known cause for their RPL [31].

- (See "In vitro fertilization: Procedure", section on 'Assessment of ovarian reserve'.)
- (See "Evaluation and management of infertility in females of advancing age", section on 'Diminished ovarian reserve'.)

Medical work-up — Additional laboratory tests may be indicated in women with clinical manifestations suggestive of a medical disorder. However, there are many such medical disorders and testing for all of these disorders should not be a part of the routine evaluation of otherwise asymptomatic women with RPL. (See "Recurrent pregnancy loss: Definition and etiology".)

Hypercoagulable state — There is a large and contradictory literature on the association between maternal inherited thrombophilia and recurrent spontaneous abortion occurring in the first trimester. Evaluation for an inherited thrombophilia can be considered in rare cases of recurrent, unexplained late fetal loss (after nine weeks of gestation) associated with evidence of placental ischemia and infarction and maternal vessel thrombosis. Women with confirmed thrombophilia can be started on an anticoagulant immediately after conception. (See "Inherited thrombophilias in pregnancy".)

Culture and serology — Routine cervical cultures for Chlamydia species or Mycoplasma species, vaginal evaluation for bacterial vaginosis, and toxoplasmosis serology are not

useful in the evaluation of RPL among otherwise healthy women [5].

Autoantibodies and immune function — Many studies have reported the presence of autoantibodies in women with RPL [32]. Only anticardiolipin antibody and lupus anticoagulant have been clearly associated with pregnancy loss (see 'Antiphospholipid syndrome' above). The pregnancy outcome of women with and without antinuclear antibody (ANA) is the same [33]; available data do **not** support testing women with RPL for ANA. With the exception of anticardiolipin antibody and lupus anticoagulant, we recommend not testing women with known autoimmune diseases or unexplained RPL for autoantibodies for the purpose of attempting to predict their risk of pregnancy loss.

Selection of appropriate tests for diagnosis of immune-based RPL also requires further investigation and validation. Results from HLA typing, mixed lymphocytotoxic antibody tests and mixed lymphocyte culture reactions are not predictive of pregnancy outcome [34]. The role of differences in the CD56+ population of cells and alterations in cytokines produced by monocytes, CD4+ cells, and endometrium remains investigational [35,36]. (See "Immunology of the maternal-fetal interface".)

Screening for diabetes — Screening for diabetes mellitus should be limited to women with clinical manifestations of the disease. Only poorly controlled diabetes is associated with miscarriage. (See "Pregestational (preexisting) diabetes: Preconception counseling, evaluation, and management".)

Progesterone level — Single or multiple serum progesterone levels are not predictive of future pregnancy outcome.

Endometrial biopsy — Diagnosis of a luteal phase defect had been based upon results of endometrial biopsy. However, high quality data show that this test is not predictive of fertility status in the general population; therefore, it is no longer recommended. In the in vitro fertilization population, chronic endometritis has been associated with recurrent implantation failure in at least one study [37]. (See "Evaluation of female infertility", section on 'Endometrial biopsy'.)

MALE CONTRIBUTION TO RECURRENT PREGNANCY LOSS

Male contribution to RPL is still unclear. Sperm DNA fragmentation has been associated

with miscarriage [38]. However, with the exception of the karyotype analysis, no other testing is recommended for the male partner of a woman with RPL [39].

MANAGEMENT

The management of individuals with recurrent pregnancy loss is presented in detail in related content. (See "Recurrent pregnancy loss: Management".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Recurrent pregnancy loss" and "Society guideline links: Thyroid disease and pregnancy".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Repeat pregnancy loss (The Basics)" and "Patient education: Coping after pregnancy loss (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Candidates for evaluation** – Evaluation of recurrent pregnancy loss (RPL) is indicated after two or three consecutive miscarriages. (See 'Candidates for evaluation' above.)

- **Diagnostic evaluation** – The minimum diagnostic work-up of couples with RPL consists of a complete medical, surgical, genetic, and family history and a physical examination. (See 'History and physical examination' above.)

  - **History** – The history should include a description of the gestational age and characteristics (eg, anembryonic pregnancy, live embryo) of all previous pregnancies. Gestational age is important because RPL typically occurs at a similar gestational age in consecutive pregnancies and the most common causes of RPL vary by trimester.

  - **Physical examination** – Physical examination should include a general physical assessment with attention to signs of endocrinopathy (eg, hirsutism, galactorrhea) and pelvic organ abnormalities (eg, uterine malformation, cervical laceration).

  - **Laboratory and imaging tests** – We suggest the following tests for the initial evaluation of women with RPL:

    - Sonohysterography for assessment of uterine abnormalities. (See 'Uterine assessment' above.)

    - Anticardiolipin antibody (IgG and IgM) titer and lupus anticoagulant performed twice, 12 weeks apart. The rationale for repeat testing is that a low- to mid-positive level can be due to viral illness and revert to normal. The diagnosis of antiphospholipid syndrome requires testing for anti-beta2 glycoprotein I antibodies as well. (See 'Antiphospholipid syndrome' above.)

    - Thyroid-stimulating hormone (TSH) and thyroid peroxidase antibodies. (See 'Thyroid function' above.)

    - Parental karyotype and karyotype of the abortus if the above examinations are normal. Given the low likelihood of an abnormal karyotype in couples with RPL, this is the last test we obtain and is performed only if the preceding work-up yields negative results. However, we recognize that the full

evaluation may not be complete when the decision to perform a karyotype must be made and defer to the clinical scenario. (See 'Karyotype' above.)

- **Additional testing** – Additional testing depends upon the diagnosis suggested by the history, physical examination, and laboratory results. (See 'Less useful tests' above.)

- **Contribution of male partner** – Male contribution to RPL is unclear. (See 'Male contribution to recurrent pregnancy loss' above.)

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GRAPHICS

Revised classification criteria for antiphospholipid syndrome

Antiphospholipid syndrome is present if at least 1 of the clinical criteria and 1 of the laboratory criteria that follow are met*
Clinical criteria
1. Vascular thrombosis[¶] One or more clinical episodes[Δ] of arterial, venous, or small vessel thrombosis[◇], in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10^{th} week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b. One or more premature births of a morphologically normal neonate before the 34^{th} week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency[§]; or c. Three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria[¥]
1. LA present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or >the 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-beta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on 2 or more occasions, at least 12 weeks apart,

measured by a standardized ELISA, according to recommended procedures.

LA: lupus anticoagulant; aCL: anticardiolipin antibody; Ig: immunoglobulin; ELISA: enzyme-linked immunosorbent assay; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GFR: glomerular filtration rate.

* Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

¶ Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, 2 subgroups of APS patients should be recognized, according to: (a) the presence; and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) cases include: age (>55 in men and >65 in women) and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg m^{-2}, microalbuminuria, estimated GFR <60 mL $minute^{-1}$), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.

Δ A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

◇ Superficial venous thrombosis is not included in the clinical criteria.

§ Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), eg, a non-reactive non-stress test, suggestive of fetal hypoxemia; (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, eg, absent end-diastolic flow in the umbilical artery; (iii) oligohydramnios, eg, an amniotic fluid index of 5 cm or less; or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

¥ Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than 1 laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-beta2 glycoprotein I antibody present alone.

Graphic 104569 Version 4.0

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