

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

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The majority of miscarriages are sporadic and most result from genetic causes that are greatly influenced by maternal age. Recurrent pregnancy loss (RPL) is defined by two or more failed clinical pregnancies, and up to 50% of cases of RPL will not have a clearly defined etiology. (Fertil Steril® 2012; ■:■-■. ©2012 by American Society for Reproductive Medicine.)

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Clinically recognized pregnancy loss is common, occurring in approximately 15–25% of pregnancies. The majority of sporadic losses before 10 weeks' gestation result from random numeric chromosome errors, specifically, trisomy, monosomy, and polyploidy (1). In contrast, recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies (2). It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more (3).

WHO TO EVALUATE

The challenge for clinicians is to differentiate sporadic miscarriage from RPL. Self-reported losses by patients may not be accurate. In one study, only 71% of self-reported clinical pregnancy losses could be verified in hospital records (4). For the purposes of determining whether evaluation for RPL is appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination. Ideally, a threshold of three or more losses should be used for epidemiological studies while clinical

evaluation may proceed following two first-trimester pregnancy losses.

ETIOLOGY OF RECURRENT PREGNANCY LOSS

Studies that focus on RPL have examined factors related to genetics, age, antiphospholipid syndrome, uterine anomalies, thrombophilias, hormonal or metabolic disorders, infection, autoimmunity, sperm quality, and lifestyle issues (Table 1). Several recommendations have been published (5, 6) regarding the evaluation and management of RPL. These publications do not support definitive conclusions about the causes of RPL because most studies of pregnancy loss have focused on sporadic miscarriage and not RPL. A putative diagnosis will be made and treated in approximately 50% of patients with RPL (7, 8). The following overview acknowledges that our understanding of this field is in flux.

Cytogenetic Abnormalities in Pregnancy Loss

Virtually every published set of recommendations and reviews on this topic

agrees that genetic causes should be evaluated and appropriate treatments considered (4–6, 9). Unfortunately, clinical genetic testing remains rudimentary and rarely includes molecular studies which show promise in helping to elucidate mechanisms for RPL. There is a very high frequency of sporadic karyotypic abnormalities in products of conception while the incidence of karyotypic abnormalities in the parents is low.

Of the examined products of conception, approximately 60% of early pregnancy losses are associated with sporadic chromosomal anomalies, primarily trisomies that are, in part, age related (1, 10, 11). In those losses with a normal karyotype, gross morphological abnormalities in the fetus diagnosed by transcervical embryoscopy have been described in 18% of patients (12). The risk of sporadic miscarriage between 6 and 12 weeks of gestation in women less than 35 years of age is 9% to 12% (13, 14). The risk increases in women over 35 years of age due to the markedly increased incidence of trisomic pregnancies (10). In women older than 40 years of age, the sporadic miscarriage rate approaches 50% (1, 14, 15) (Fig. 1). The risk of aneuploidy at each age is lower in women with RPL than in those who undergo sporadic miscarriages (11).

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TABLE 1

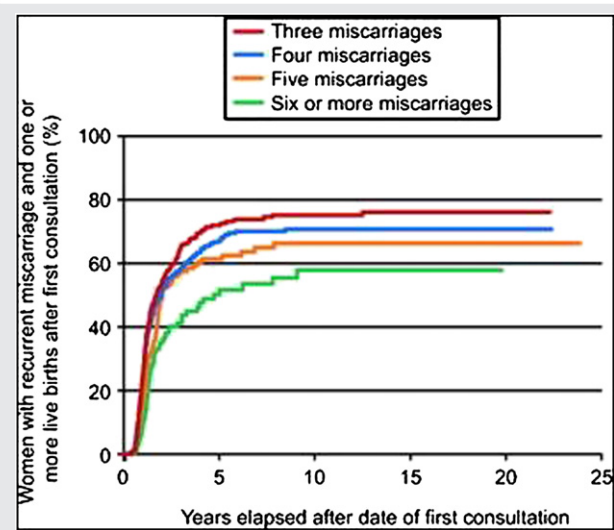
Suspected causes of recurrent pregnancy loss.

Cause	Contribution to RPL (%)	Recommended screening	Supportive scientific evidence	Controversial scientific evidence	Not recommended
Cytogenetic	2–5	Balanced reciprocal translocations			
aPL syndrome	8–42 (mean, 15)	Lupus anticoagulant, anticardiolipin IgG or IgM antibody, anti- β_2 glycoprotein I	IgG and IgM antibodies, aPL testing for other phospholipids and β_2 glycoprotein I	IgG or IgM anti-annexin A5, anti-factor XII, anti-prothrombin, IgA aPLs	ANA, antithyroid antibodies
Anatomic	1.8–37.6 (mean, 12.6)	Hysterosalpingography Sonohysterography	Congenital uterine abnormalities	Uterine fibroids, polyps	Cervical incompetence
Hormonal or metabolic		Prolactin TSH Hemoglobin A1c	Uncontrolled diabetes or thyroid disease, prolactin	Polycystic ovary syndrome and insulin resistance, luteal phase progesterone	
Infectious		None		Bacterial vaginosis, endocervical infections	
Male factors		None		Abnormal sperm DNA	
Psychological		None		Psychological effects on uterine receptivity	
Alloimmune		None		Mucosal CD16– NK cells, embryotoxic factor, cytokine profiles, blocking antibodies, HLA typing, anti-paternal leukocyte antibodies, circulating CD16– NK cells	Circulating CD16– NK cells
Environmental, occupational, or personal habits		History			Not related to recurrent pregnancy loss

Note: ANA = antinuclear antibodies; aPL = antiphospholipid.

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FIGURE 1



Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation by number of miscarriages before first consultation. (Lund et al. Recurrent miscarriage and prognosis for live birth. *Obstet Gynecol* 2012.)

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In the evaluation of RPL, parents should undergo peripheral karyotyping in order to detect any balanced structural chromosomal abnormalities. Balanced reciprocal translocations and Robertsonian translocations (6) are observed in about 2%–5% of couples with recurrent miscarriage.

Genetic counseling is important when a structural genetic factor is identified. The likelihood of a subsequent healthy live birth depends on the chromosome(s) involved and the type of rearrangement. When one of the partners has a structural genetic abnormality, preimplantation genetic testing (PGT), amniocentesis, or chorionic villus sampling are options to detect the genetic abnormality in the offspring. Treatment options include preimplantation genetic diagnosis (PGD) for specific translocations, with transfer of unaffected embryos, or the use of donor gametes. While data are limited comparing in vitro fertilization (IVF)/PGD versus medical management (defined as natural conception and observation) for couples with RPL carrying a structural genetic abnormality, two systematic reviews have summarized the success rates from the literature (16, 17). In these reviews, live birth rates were estimated to be between 31%–35% per cycle for IVF/PGD and cumulative live birth rates were 55%–74% for natural conception/medical management. Therefore, there are insufficient data demonstrating that IVF/PGD improves live birth rate in couples with RPL and a structural genetic abnormality. Based on limited cytogenetic data, 36%–39% of miscarriages in couples with recurrent pregnancy loss associated with a structural genetic factor have an unbalanced structural rearrangement (18, 19). Treatment options should be based on whether repeated miscarriages are euploid, aneuploid, or due to an unbalanced structural rearrangement and not exclusively on the parental

carrier status. Currently, routine preimplantation embryo aneuploidy screening is not justified (20, 21).

If the evaluation of RPL identifies a remediable cause, cytogenetic analysis of subsequent losses can be employed to evaluate whether the event was random and not a treatment failure *per se*. Testing of the products of conception may also be of psychological value to the couple (6). There are pitfalls to this approach, however, including: the possibility of maternal tissue contamination of the specimen; failure to seek other causes of RPL if cytogenetic assessment reveals an abnormal karyotype; and the occurrence of non-cytogenetic embryonic abnormalities (e.g., dimorphic fetal development has been documented via hysteroscopy prior to dilatation and evacuation in the setting of normal fetal karyotype) (12). In the event that cytogenetic analysis of the products of conception reveals a 46,XX karyotype, reflex DNA extraction and analysis of a sample of maternal blood by means of microsatellite analysis can permit differentiation between a fetal source vs. maternal contamination (22).

Antiphospholipid Syndrome

The antiphospholipid syndrome is associated with recurrent pregnancy loss. The diagnostic criteria are outlined in Table 2 (23, 24). Although it is generally agreed that between 5% and 20% of patients with recurrent pregnancy loss will test positive for antiphospholipid antibodies (aPLs), the actual reported range varies between 8% and 42% (24, 25). Several groups of investigators have characterized these antibodies in laboratory-specific assays that have not been standardized (23). The most widely accepted tests are for lupus

TABLE 2

International Consensus Classification criteria for the antiphospholipid syndrome (APS) (23, 24).

APS is present if one of the following clinical criteria and one of the laboratory criteria are met.

Clinical criteria

1. Vascular thrombosis
2. Pregnancy morbidity
 - a. One or more unexplained deaths of morphologically normal fetuses after the 10th week of gestation by ultrasound or direct examination of the fetus.
 - b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia or recognized features of placental insufficiency.
 - c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, or
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer (>40 GPL or MPL or > 99th percentile), on two or more occasions at least 12 weeks apart, or
3. Anti- β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions at least 12 weeks apart.

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TABLE 3

Antiphospholipid antibodies (aPLs).

Test	Result	Specificity
Lupus anticoagulant	In vitro assays in which aPLs prevent the initiation of clotting.	A mixture of aPLs that act in concert to bind phospholipids or phospholipid-binding proteins or both. Both activated partial thromboplastin time and dilute Russell's viper venom time are suitable screening tests.
Serologic test for syphilis	Recurrent false-positive test.	Related to aPLs against cardiolipin, which is used in most screening tests for syphilis.
ELISAs for IgG, IgM, or IgA antibodies	Highly specific and sensitive assays using purified antigens.	Individual tests available for: Phospholipids: Cardiolipin (CL) Phosphatidylserine (PS) Phosphatidylethanolamine (PE) Phosphatidylinositol (PI) Phosphatidylglycerol (PG) Phosphatidylcholine (PC) Phosphatidic acid (PA) Phospholipid-binding proteins: β 2-glycoprotein I (β 2-GPI) Activated protein C Annexin A5 Clotting factors Xa, XII, and Va Protein S Prothrombin Thrombomodulin Low and high molecular weight kininogens

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anticoagulant (LA), anticardiolipin antibody (aCL), and anti- β 2 glycoprotein I (26) (see Table 3).

Antiphospholipid antibodies have a variety of effects on the trophoblast, including inhibition of villous cytotrophoblast differentiation and extravillous cytotrophoblast invasion into the decidua (27–31), induction of syncytiotrophoblast apoptosis (32), and initiation of maternal inflammatory pathways on the syncytiotrophoblast surface (33–36).

The identification of relevant antiphospholipid antibodies (aPLs) is one of the most contentious elements in the evaluation of autoimmune pregnancy loss. The aPLs are highly diverse and variable from patient to patient and are specific for a variety of cellular phospholipids and phospholipid-binding proteins. The aPLs may react directly with phospholipids, the protein co-factors bound to plastic (i.e., ELISA plates), or only when the co-factors are bound to phospholipids. Individual aPLs may be monospecific (reacting against only one antigen) or have varying degrees of cross-reactivity (reacting against multiple antigens).

With the exception of anticardiolipin, lupus anticoagulant, anti- β 2-glycoprotein I, and antiphosphatidylserine, clinical assays for antiphospholipid antibodies are not standardized and the level of evidence does not warrant routine screening. If screening for these additional aPLs is pursued, the statistical probability of finding a positive test will increase and will likely not reflect a true cause for RPL.

The most recent recommendations from the antiphospholipid consensus group list several clinical events that should trigger testing for aPLs (Table 2) (23). That group concluded that testing for aPLs is indicated in the setting of three or more unexplained spontaneous abortions before the 10th week of gestation when maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal

causes have been excluded. A single unexplained loss of a morphologically normal fetus at or beyond 10 weeks of gestation also is considered to warrant testing for aPLs.

The standard treatment for documented antiphospholipid syndrome consists of low-dose aspirin and heparin (70 patients, 74.3% live-born rate) which was superior to treatment with aspirin alone (70 patients, 42.9% live-born rate) (37, 38). The combination of twice daily unfractionated heparin and low-dose aspirin appears to confer a significant benefit in pregnancies with aPLs and otherwise unexplained recurrent pregnancy loss; comparable efficacy of low molecular weight heparin has not been established (38, 39). Administration of prednisone does not improve pregnancy rates and may be associated with an increased risk of gestational hypertension and gestational diabetes (40).

In an analysis of 9 studies (n = 741) in which patients were initially selected because of preeclampsia, 17.9% of the patients with severe preeclampsia had moderate to high levels of aPLs (41–49). Thus, a history of a morphologically normal fetus delivered before 34 weeks because of severe preeclampsia/eclampsia or placental insufficiency warrants testing for aPLs.

Anatomic Factors

Congenital uterine abnormalities are associated with second trimester pregnancy loss in addition to other complications, including preterm labor, fetal malpresentation, and increased rates of cesarean delivery. Although the role of uterine malformations in first-trimester RPL is debatable, assessment of uterine anatomy is widely recommended (4–6, 9). Potentially relevant congenital Müllerian tract anomalies include unicornuate, didelphic, bicornuate, septate, or arcuate uteri. These anomalies are often detected at the

time of hysterosalpingography, and can be more fully characterized by either MRI or 3-D ultrasound imaging. A septate uterus is amenable to hysteroscopic surgical correction; there are no surgically corrective options for the unicornuate or didelphic uterus.

A review of a large number of studies concluded that congenital uterine anomalies were present in 4.3% (range from 2.7% to 16.7%) of the general population of fertile women and in 12.6% (range from 1.8% to 37.6%) of patients with recurrent pregnancy loss (2 or more consecutive losses) (50). A high incidence of pregnancy loss occurred in patients with septate ($n = 499$, 44.3% loss), bicornuate ($n = 627$, 36.0% loss), and arcuate ($n = 241$, 25.7% loss) uteri. Correction of septate defects in particular may have beneficial effects ($n = 366$, live birth rate 83.2%, range from 77.4% to 90.9%) and should be considered in women with RPL. The primary limitation of these data is the lack of randomized, controlled therapeutic trials.

The clinical management of pregnancy-loss patients with Asherman syndrome/intrauterine synechiae, uterine fibroids, and uterine polyps is also controversial, and there is no conclusive evidence that surgical treatment reduces the risk of pregnancy loss. Because randomized trials in this area are lacking and difficult to conduct, the general consensus is that surgical correction of significant uterine cavity defects should be considered. In the event of irreparable anatomic uterine abnormalities and RPL, IVF with transfer of embryos to an appropriately selected gestational carrier also may be a clinical consideration.

Inherited Thrombophilias

Screening for inherited thrombophilias (specifically, factor V Leiden and the prothrombin gene mutations, protein C, protein S, and antithrombin deficiencies) may be clinically justified when a patient has a personal history of venous thromboembolism in the setting of a non-recurrent risk factor (such as surgery) or a first-degree relative with a known or suspected high-risk thrombophilia. Although an association between hereditary thrombophilias and fetal loss has been suggested (51, 52), prospective cohort studies have failed to confirm this (53, 54). Routine testing of women with RPL for inherited thrombophilias is not currently recommended (24, 55).

Hormonal and Metabolic Factors

It is generally agreed that maternal endocrine disorders (e.g., diabetes, thyroid dysfunction) should be evaluated and treated (56–59). As long as thyroid-stimulating hormone (TSH) levels are in the normal range, there is insufficient evidence to recommend routine thyroxine (T_4) testing or screening for anti-thyroid antibodies (60). However, this is problematic given the lack of consensus regarding the definition of a normal upper limit of TSH. Whereas TSH values of 4.0–5.0 mIU/L were once considered normal, a consensus is emerging that TSH values above 2.5 mIU/L are outside the normal range. Well-controlled diabetes is not a risk factor for RPL. However, uncontrolled diabetes is associated with increased pregnancy loss (61).

Prolactin is commonly measured because elevated prolactin levels are associated with ovulatory dysfunction. Hyperprolactinemia may be associated with recurrent pregnancy loss through alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation, and/or a short luteal phase. Normalization of prolactin levels with a dopamine agonist improved subsequent pregnancy outcomes in patients with recurrent pregnancy loss (62). Patients ($n = 64$) with 2 or more pregnancy losses and hyperprolactinemia were treated with bromocriptine in their next pregnancy (62). Treatment resulted in an 85.7% live-born rate, whereas the untreated cohort had a 52.4% live-born outcome.

The role of other hormonal abnormalities remains controversial. Conceptually, delayed or late implantation may increase pregnancy losses (63). A shortened luteal phase has been associated with pregnancy loss but the assessment and interpretation of a putative luteal phase defect is problematic (64). The use of histologic and biochemical endpoints as diagnostic criteria for endometrial dating are unreliable and not reproducible utilizing the traditional histological criteria or other biochemical approaches (65). Therefore, routine endometrial biopsy for dating is not recommended, although continued research on the emerging molecular markers of endometrial development should be encouraged (66).

Administration of progesterone to women with sporadic miscarriages is ineffective (67, 68). However, in patients with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration may be of some potential benefit (62, 69, 70).

Infection

Ureaplasma urealyticum, *Mycoplasma hominus*, chlamydia, *Listeria monocytogenes*, *Toxoplasma gondii*, rubella, cytomegalovirus, herpes virus, and other less frequent pathogens have been identified more frequently in vaginal and cervical cultures and serum from women with sporadic miscarriages (71). There are no convincing data that infections cause recurrent pregnancy loss. Therefore, there are no clear indications for routinely testing for these organisms in the RPL evaluation. Given the lack of prospective studies linking any infectious agent to recurrent early pregnancy loss, any use of antibiotics is not supported by the evidence.

Male Factors

Standard semen parameters, including sperm morphology, do not appear to be predictive of recurrent pregnancy loss (72).

Sperm aneuploidy and DNA fragmentation have been studied in couples with recurrent pregnancy loss (73). Abnormal DNA fragmentation may be seen in the setting of advanced paternal age or may result from correctable environmental factors, such as exogenous heat, toxic exposures, varicoceles, or increased reactive oxygen species in semen. Currently, there are contradictory data regarding a causal effect between pregnancy loss and fragmentation of sperm DNA in IVF cycles (74).

Although increased rates of sex chromosome disomy have been demonstrated in sperm from the male partner in couples with recurrent miscarriage, cytogenetic analysis of the products of conception from couples with RPL does not reveal an increased rate of sex chromosome aneuploidy, thus suggesting that such cytogenetically abnormal sperm may be selected against during fertilization (11, 75). Therefore, routine testing for sperm ploidy (e.g., fluorescence in situ hybridization [FISH]) or DNA fragmentation is not recommended.

Psychological Factors

It is clear that pregnancy loss exacts an immense psychological toll on affected couples and that an increased sensitivity to that effect is necessary throughout follow-up evaluations and during ensuing pregnancies (76, 77). The observed psychological response falls well within the normal bounds of a “grief response”. Recurrent pregnancy loss patients are prone to heightened anger, depression, anxiety, and feelings of grief and guilt.

A possible psychological etiology for recurrent pregnancy loss was suggested by a published trial with expanded data in a later publication (78, 79). A cohort of 158 couples with ≥ 3 consecutive pregnancy losses and no otherwise identifiable etiology were divided into 2 groups, one receiving routine obstetrical care during the next pregnancy ($n = 42$) and the other additionally receiving tender-loving care (TLC) ($n = 116$). TLC was defined as psychological support with weekly medical and ultrasonographic examinations and instructions to avoid heavy work, travel, and sexual activity. The difference in live births was significant: 36% in the control group and 85% in the TLC group. These results should be interpreted with caution, however, as the groups were not randomized. Inclusion into the TLC or control group was based on residence; only those living “within a reasonable distance” of the hospital were offered TLC. The resultant differences in lifestyle, social support, and other psychological variables were unknown.

A psychological component in pregnancy loss was also suggested by a small prospective study of 45 pregnancies in patients with histories of 2 consecutive first-trimester miscarriages, with other causes eliminated (80). The patients completed a group of self-report questionnaires and interviews before their next pregnancy. Ten of the pregnancies (22.2%) resulted in a miscarriage, which was significantly predicted by the degree of baseline depressive symptoms.

Although the data to support a psychological role in the etiology of recurrent pregnancy loss are inconclusive, it is clearly advisable to offer these patients psychological support and counseling. Two non-randomized studies have shown significant improvement of subsequent pregnancy outcomes with close monitoring and support at a dedicated recurrent pregnancy loss clinic (81, 82).

Alloimmune Factors

Studies of human leukocyte antigen (HLA) typing, embryotoxic factors, decidual cytokine profiles, blocking or anti-

paternal antibody levels, HLA-G polymorphism, and other immunologic traits and factors have produced inconsistent data that generally have not been reproduced in more than one laboratory. Proposed immunomodulatory treatments for RPL in the setting of one or more of these findings have not been proven effective.

A meta-analysis of trials on paternal white blood cell immunization concluded that it had no beneficial effect (83). Treatment with intravenous immunoglobulin (IVIG) has also been proposed for unexplained pregnancy loss. However, several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss (84–88); thus, this treatment is not recommended.

Lifestyle, Environmental, Occupational Factors

Cigarette smoking has been suggested to have an adverse effect on trophoblastic function and is linked to an increased risk of sporadic pregnancy loss (89). Obesity has also been shown to be associated with an increased risk of RPL in women who conceive naturally (90). Other lifestyle habits such as cocaine use (91), alcohol consumption (3 to 5 drinks per week), and increased caffeine consumption (>3 cups of coffee, [92]) have been associated with risk of miscarriage.

Unexplained Recurrent Pregnancy Loss

No apparent causative factor is identified in 50% to 75% of couples with RPL. It is important to emphasize to patients with unexplained RPL that the chance for a future successful pregnancy can exceed 50%–60% depending on maternal age and parity (93, 94) (see Fig. 1).

SUMMARY

- The majority of miscarriages are sporadic and are thought to result from genetic causes that are greatly influenced by maternal age.
- Recurrent pregnancy loss is defined by two or more failed clinical pregnancies.
- Up to 50% of cases of RPL will not have a clearly defined etiology.

CONCLUSIONS

- Evaluation of RPL can proceed after two consecutive clinical pregnancy losses.
- Assessment of RPL focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anatomy, hormonal and metabolic factors, and lifestyle variables. These may include:
 - Peripheral karyotypic analysis of the parents
 - Screening for lupus anticoagulant, anticardiolipin antibodies, and anti- β_2 glycoprotein I
 - Sonohysterogram, hysterosalpingogram, and/or hysteroscopy
 - Screening for thyroid or prolactin abnormalities

- Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for RPL.
- Women with persistent, moderate-to-high titers of circulating antiphospholipid antibodies can be treated with a combination of prophylactic doses of unfractionated heparin and low-dose aspirin.
- Psychological counseling and support should be offered to couples with RPL.

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