Recurrent Pregnancy Loss

Evaluation and Treatment

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KEYWORDS

- Recurrent pregnancy loss • Recurrent miscarriage • Recurrent fetal loss
- Recurrent embryonic loss

KEY POINTS

- Evaluation for women with recurrent pregnancy loss includes checking for uterine anomalies and parental chromosomal rearrangements and testing for antiphospholipid antibodies.
- Fifty percent of patients will have no definite cause for recurrent pregnancy loss after a thorough evaluation.
- The prognosis for a live birth in women with unexplained recurrent pregnancy loss is 50% to 80% without intervention with evidence-based treatments and supportive care.
- More than half of first-trimester miscarriages tested will have sporadic numeric chromosomal abnormalities.
- Chromosomal screening of embryos after in vitro fertilization has been proposed as a treatment option to reduced aneuploidy conceptions, but it has not been evaluated in randomized controlled studies.

BACKGROUND AND DEFINITIONS

The definitions of miscarriage and recurrent pregnancy loss (RPL) are important to review because they vary within the literature and clinical teaching. Classically, RPL is defined as 3 pregnancy losses before the twentieth week of gestation and excludes ectopic, molar, and biochemical pregnancies. The American Society of Reproductive Medicine (ASRM) states that, for the purposes of determining whether an evaluation for RPL is appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination and that a clinical evaluation may proceed following 2 first-trimester pregnancy losses.[1] ASRM

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maintains that a threshold of 3 or more pregnancy losses should be used for epidemiologic studies.[1]

RPL may be considered a primary or secondary condition. Primary RPL refers to multiple pregnancy losses in which a patient has never had a live birth, and secondary RPL refers to multiple pregnancy losses in a patient who has had a live birth previously.[2] Definitions are provided in **Table 1**.

INCIDENCE

Clinically recognized pregnancy loss occurs in approximately 15% to 25% of all pregnancies.[1] If preclinical losses are included, pregnancy loss is estimated to be as high as 57%.[3–5] It is estimated that less than 5% of women will experience 2 consecutive pregnancy losses and that only 1% of women will experience 3 or more.[3] The incidence of miscarriage increases with age of the woman such that women less than 35 years old have a 9% to 12% risk of spontaneous loss in the first trimester,[4,5] but this risk increases to 50% in women aged 40 years and older.[5–7]

EVALUATION AND TREATMENT BY CAUSE

RPL has been associated with factors related to genetics, age, antiphospholipid syndrome, uterine anomalies, thrombophilias, hormonal or metabolic disorders, infection, autoimmunity, sperm parameters, and lifestyle issues. With a thorough evaluation, a definitive diagnosis for RPL will be made in only 50% of patients. The following review of causes includes the evidence-based evaluation for RPL associated with each cause.

ANATOMIC CAUSES

Congenital and acquired uterine anomalies are found in 10% to 15% of women with RPL compared with 7% of all reproductive-aged women.[8,9] A uterine evaluation is widely considered an important part of the evaluation for patients with RPL and may include a hysterosalpingogram (HSG), saline infusion sonogram (SIS), 3-dimensional (3D) ultrasound, diagnostic hysteroscopy, or MRI.

Congenital uterine anomalies are associated with second-trimester losses and other obstetric complications, such as preterm labor, fetal malpresentation, and a higher rate of delivery by cesarean section. Although the role of uterine anomalies in

Table 1
Definitions of pregnancy and RPL

Pregnancy	Clinical pregnancy documented by ultrasonography or histopathologic examination
Clinical miscarriage	Pregnancy loss before the twentieth week of gestation
Biochemical pregnancy	Beta Human Chorionic Gonadotropin hormone detected in urine or blood stream, but pregnancy loss occurs before it could be clinically documented
RPL: classic definition	Three pregnancy losses before the twentieth week of gestation and excludes ectopic, molar, and biochemical pregnancies
RPL: evaluation indicated according to ASRM	Clinical evaluation may proceed following 2 first-trimester pregnancy losses
Primary RPL	RPL in a patient who has never had a live birth
Secondary RPL	RPL in a patient who has had at least one live birth

first-trimester losses is debated, uterine cavity evaluation is widely considered a part of the evaluation for RPL.[10–15] Mullerian tract anomalies include unicornuate, didelphic, bicornuate, septate, or arcuate uteri. A review of several studies found that congenital uterine anomalies are present in 4.3% (range 2.75%–16.7%) of the general population of fertile women and in 12.6% (range 1.5%–37.6%) of patients with RPL defined as 2 or more losses.[16] A high rate of miscarriage occurred in patients with septate (n = 499, 44.3% loss), bicornuate (n = 627, 36.0% loss), and arcuate (n = 241, 25.7% loss) uteri. Surgical resection of uterine septums showed beneficial effects (n = 366, live birth rate 83.2%, range 77.4%–90.9%). All data came from retrospective reviews or observational studies.

The clinical management of patients with RPL with acquired uterine abnormalities, such as adhesions, polyps, retained products of conception, and fibroids, is debated. Submucosal fibroids may impede implantation because of the position, poor endometrial receptivity, or degeneration leading to increased cytokine production.[17] Intrauterine adhesions may lead to an increased risk of miscarriage because there is insufficient endometrium to support a developing pregnancy.[18] There is likely less biological plausibility to argue how endometrial polyps may impact implantation. There are no randomized controlled trials showing that surgical intervention decreases the subsequent miscarriage rate; however, the general consensus is that hysteroscopic correction of these defects should be considered[1] because of the potential impact on subsequent fertility, miscarriage, and pregnancy outcomes.

The options for uterine evaluation include HSG, hysteroscopy, SIS, and overall anatomy with 3D ultrasound or MRI. The selection depends on the availability and access for each provider and patient. The gold standard for uterine cavity evaluation is a diagnostic hysteroscopy; however, this is more invasive than an HSG or SIS. A SIS may be more accessible to some providers and patients, allows for the view of the ovaries and intramural uterine lesions, and avoids radiation. A uterine evaluation for RPL may stop with a normal cavity evaluation with HSG, SIS, or diagnostic hysteroscopy. However, if a congenital anomaly is suspected, additional imaging is needed. A congenital anomaly will be more fully characterized by 3D ultrasound or MRI because a full view of the uterus is needed to differentiate some anomalies (especially septate vs bicornuate). If a uterine anomaly is detected, one should consider evaluating the renal system because renal and uterine anomalies are often associated.[19]

ANTIPHOSPHOLIPID SYNDROME

The antiphospholipid syndrome (APS) is associated with RPL. Diagnostic criteria are outlined in **Box 1**.[20,21] Consensus statements agree that approximately 5% to 20% of patients with RPL will test positive for antiphospholipid antibodies (aPLs), although some report an incidence as high as 42%.[21,22] Laboratory assays have not been standardized,[20] which leads to high variability between laboratories and assays. The most widely accepted tests are lupus anticoagulant, anticardiolipin antibody, and anti-B2 glycoprotein I.[23] These antibodies have several detrimental effects on the developing trophoblast, including inhibition of villous cytotrophoblast differentiation and extravillous cytotrophoblast invasion into the decidua,[24–28] induction of syncytiotrophoblast apoptosis,[29] and initiation of maternal inflammatory pathways on the syncytiotrophoblast surface.[30–33]

The identification of aPLs and subsequent treatment of patients with RPL with these antibodies is highly debated. The aPLs are highly diverse among patients and results vary. With the exception of lupus anticoagulant, anticardiolipin, anti-B2-glycoprotein,

Box 1
International consensus classification criteria for APS

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 caused by eclampsia, severe preeclampsia, 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 2 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 (1 GPL unit is microgram of IgG antibody) or MPL (1 MPL unit is 1 microgram of 1gM antibody) or >99th percentile) on 2 or more occasions at least 12 weeks apart or
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile) present on 2 or more occasions at least 12 weeks apart

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M.
Data from American College of Obstetricians Gynecologists, Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin No. 132: antiphospholipid syndrome. Obstet Gynecol 2012;120:1514–21; and Yetman DL, Kutteh SR. Antiphospholipid antibody panels and recurrent pregnancy loss: prevalence of anticardiolipin antibodies compared with other antiphospholipid antibodies. Fertil Steril 1996;55:540–6.

and antiphosphatidylserine, clinical assays for aPLs are not standard; routine screening is not warranted.[1] Testing for additional aPLs will increase the statistical probability of finding a positive test and possibly lead to unnecessary intervention.

The authors of the international consensus statement provide recommendations for several clinical events that should trigger testing for aPLs (see **Box 1**).[20] That group recommends testing patients with 3 or more unexplained spontaneous abortions before the 10th week of gestation. Unexplained spontaneous loss requires excluding maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes. The group recommended screening for aPLs in the setting of a single unexplained loss of a morphologically normal fetus at or beyond 10 weeks' gestation.[20] In many cases, a miscarriage is diagnosed weeks after the pregnancy has stopped developing. A situation whereby a miscarriage is diagnosed after 10 weeks' gestation but ultrasound evidence is available that shows a pregnancy stopped developing earlier than 10 weeks would not warrant aPLs testing. An association between APS and preeclampsia has been suggested; in a combined analysis of 9 studies (n = 741), 17.9% of patients with severe preeclampsia had moderate to high levels of aPLs.[34–42] Thus, consider screening patients for aPLs who have a history of delivering a morphologically normal fetus before 34 weeks in the setting of severe preeclampsia or placental insufficiency (intrauterine growth restriction).[1]

The treatment of documented APS consists of low-dose aspirin (usually 81 mg daily) and heparin (usually 5000 units by subcutaneous injection twice a day) beginning with a positive pregnancy test.[43,44] The strongest evidence for treating APS is a live birth rate of 74.3% in patients treated (n = 70) with both aspirin and heparin compared with 42.9% (n = 70) with aspirin alone.[45,46] Low-molecular-weight heparin has not been established as an effective alternative.[47,48] Administration of prednisone does not improve outcomes and may be associated with an increased risk of gestational hypertension and gestational diabetes.[48] Multiple large randomized trials examining the use of heparin and/or aspirin in women with RPL not meeting strict criteria for APS have shown no difference in clinical outcomes.[43,44] Therefore, the use of heparin and aspirin should be limited to only women who have met both the clinical and laboratory criteria for APS.

THYROID FUNCTION

Thyroid dysfunction can be associated with poor obstetric outcomes.[49] Untreated overt maternal hypothyroidism (elevated thyroid-stimulating hormone [TSH] associated with decreased T4 levels) is associated with poor obstetric outcomes, including miscarriage, premature birth, low birth weight, and gestational hypertension.[50–55] Subclinical hypothyroidism (serum TSH elevated but normal serum free T4 levels) has been associated with preterm deliveries, increased neonatal intensive care unit admissions, and neonatal distress after delivery.[56] Some studies found that euthyroid patients with autoimmune thyroid disease (positive thyroid antibodies in the setting of normal TSH and T4 levels) have a higher risk of miscarriage and recurrent pregnancy loss.[57–59] Other retrospective studies failed to show a higher miscarriage rate in women with positive thyroid antibodies compared with those without these antibodies.[60] Inadequately treated maternal hyperthyroidism has been associated with preterm delivery, intrauterine growth restriction, preeclampsia, congestive heart failure, and fetal death but not specifically associated with RPL.[61]

Universal screening of healthy women for thyroid dysfunction before pregnancy is not currently recommended.[49] However, providers may screen patients who are considered high risk for thyroid dysfunction, including women with a history of miscarriage. Recommendations for targeted thyroid screening when planning pregnancy or in early pregnancy are summarized at the following link: http://dx.doi.org/10.1210/jc.2011-2803.

Screening for patients with RPL may include TSH and thyroid peroxidase antibodies.[49] A randomized prospective study found higher pregnancy complications in women with TSH levels greater than 2.5 mIU/mL in the first trimester with and without the presence of thyroid antibodies.[62] Retrospective data support these findings,[63] and correction of hypothyroidism before pregnancy restores pregnancy outcomes to the rate seen in euthyroid women.[64,65] Some studies contradict these findings.[55,66]

Although the evidence varies, consensus by the Endocrine Society in the 2012 practice guidelines for the "Management of Thyroid Dysfunction during Pregnancy and Postpartum"[49] recommends the following:

1. Screen all at-risk women either before pregnancy or when newly pregnant when risk factors for thyroid dysfunction present (http://dx.doi.org/10.1210/jc.2011-2803).
2. Repeat the test to confirm the assay result if the prenatal TSH level is greater than 2.5 mIU/L.
3. Administer T4 replacement to achieve a prepregnancy TSH level less than 2.5 mIU/L.

4. If the TSH is 2.0 to 10.0 mIU/L, a starting dosage of T4 at 50 mcg daily or more is recommended.
5. T3 replacement is not recommended.
6. Monitor TSH levels approximately every 4 to 6 weeks with adjustments in doses or, at a minimum, once a trimester.
7. For patients who are taking levothyroxine before conception, increase replacement by 30% to meet the demands of the fetus by taking 2 extra doses per week.
8. Most women will return to their prepregnancy dose of T4 replacement after delivery.

The ASRM's guidelines for the treatment of RPL states that, although TSH values of 4.0 to 5.0 mIU/L were once considered normal, a consensus is emerging that TSH values greater than 2.5 mIU/L are outside the normal range and should be addressed in patients with RPL.[1]

OTHER HORMONAL CONDITIONS

Poorly controlled diabetes is associated with pregnancy loss.[67] High hemoglobin A1C levels (especially greater than 8%) have been associated with an increased risk of miscarriage and congenital malformations.[68–70] The increased risk in poorly controlled patients is likely associated with hyperglycemia, maternal vascular disease, and possibly immunologic factors. Well-controlled diabetes is not associated with an increased risk of miscarriage.[71]

Elevated levels of prolactin (hyperprolactinemia) have been associated with an increased risk of miscarriage.[1] Theories of this association involve prolactin's ability to alter the hypothalamic-pituitary-ovarian axis resulting in impaired folliculogenesis and oocyte maturation and/or its involvement in implantation in the luteal phase. Using a dopamine agonist (bromocriptine) to normalize prolactin levels before pregnancy in patients with a history of RPL (2 or more losses) improved pregnancy outcomes in one randomized trial (live birth rate 85.7% in the treated group compared with 52.4% in the untreated group).[72]

Progesterone in the luteal phase is essential for implantation and early pregnancy development. Defects in ovarian progesterone production are likely to impact the early success of a pregnancy. A shortened luteal phase has been associated with pregnancy loss in the past, but assessment and interpretation of an inadequate luteal phase is problematic.[73] The use of histologic and/or biochemical testing for diagnosis is unreliable and not reproducible.[74] Routine endometrial biopsy for luteal-phase dating is not recommended.[75] Some newer markers for endometrial receptivity are currently being investigated but cannot be considered part of a standard RPL evaluation until further evidence emerges.

Serum progesterone concentrations are not reflective of endometrial tissue levels of progesterone and are not predictive of pregnancy outcome.[76] Supplementing progesterone with exogenous progesterone does not decrease the risk of sporadic miscarriage.[77,78] However, in patients with 3 or more consecutive miscarriages, empirical progesterone administration may have some benefit.[72,79,80] The types of progesterone supplements vary; but in general, intramuscular injections and vaginal suppositories are the most widely used. Oral progesterone is ineffective at increasing uterine progesterone levels. Recommendations differ on the timing of empirical progesterone supplement. Traditionally, progesterone administration was given after ovulation in the luteal phase. Starting progesterone supplements after a positive pregnancy test may provide adequate pregnancy support and reduce costs, side effects, and the emotional toll of a delayed menses and negative pregnancy test.

INHERITED THROMBOPHILIAS

Thrombosis of spiral arteries within the placenta may affect perfusion and lead to late fetal loss, intrauterine growth restriction, placental abruption, or preeclampsia. Inherited thrombophilia disorders including factor V Leiden, prothrombin gene mutation, and deficiencies in protein C, protein S, and antithrombin may put a patient at an increased risk for late (second and third trimester) losses but have not been associated with recurrent first-trimester losses.[81,82]

Screening for inherited thrombophilias may be justified in patients with a personal history of thrombosis in a nonrisk setting (ie, not associated with surgery) or a first-degree relative with a known or suspected high risk of a thrombophilia.[1] Routine testing of women with RPL for inherited thrombophilia is not currently recommended.[21,83]

INFECTION

Some pathogens have been found more frequently in vaginal and cervical cultures of women with sporadic miscarriages. These pathogens include *Mycoplasma hominis*, chlamydia, *Listeria monocytogenes*, *Ureaplasma urealyticum*, Toxoplasma gondii, rubella, cytomegalovirus, herpes virus, and others.[84] No pathogens have been proven to cause RPL, and routine screening for infectious agents in patients with RPL is not recommended.[1,85] The use of empirical antibiotics in patients with asymptomatic RPL is not supported by randomized prospective studies.[1]

MALE FACTOR

The male contribution to miscarriage and RPL is highly debated. Some studies find a trend toward abnormal sperm morphology and RPL,[86–88] whereas other data do not support an association between any standard sperm parameters and RPL.[89] Sperm aneuploidy and DNA fragmentation have been studied in couples with RPL, but no strong association has been determined.[90] A single randomized controlled trial showed improved subsequent live birth rates after varicocelectomy in couples with RPL when the male partner has a significant varicocele.[91] A semen analysis and/or referral to a urologist may be informative in couples taking longer than expected to conceive, but no sperm testing should be considered a routine evaluation for a couple with RPL.[1]

ALLOIMMUNE FACTORS

Studies investigating the association of RPL with HLA typing, embryotoxic factors, HLA-G polymorphisms, antipaternal antibodies, decidual cytokine profiles, and natural killer cells have been inconsistent and nonreproducible.[1] Immunomodulation treatments designed to address these issues have not been proven to be effective.[1]

Treatments designed to develop immune tolerance, such as paternal white blood cell immunization (also known as lymphocyte immunization therapy), have not been shown to be effective at decreasing the risk of miscarriage.[92] Immunosuppressive treatment with intravenous immunoglobulin has also been proposed as a treatment of RPL but has been shown to be ineffective in randomized controlled trials.[93,94]

ENVIRONMENTAL AND PSYCHOLOGICAL FACTORS

Several environmental exposures are can be linked to the risk of sporadic miscarriage and, therefore, should be minimized in all couples considering pregnancy, particularly

women with a history of miscarriage. Examples of these exposures are tobacco, caffeine, and alcohol. Although tobacco exposure has not specifically been linked to RPL, it is associated with adverse trophoblastic function, increased risk of sporadic miscarriage, and other poor obstetric outcomes.[95] Other exposures, including alcohol (3–5 drinks per week), cocaine, and caffeine (>3 cups of coffee per day), have been associated with an increased risk of miscarriage.[95–97] Obesity is linked to poor obstetric outcomes, including miscarriage[98] and RPL.[99] Obesity is an important risk factor to discuss because it is not only linked to the risk of euploid pregnancy loss but also to a higher recurrence risk in the setting of RPL compared with women of normal weight.[100]

RPL is extraordinarily impactful on a patient's emotional well-being, and awareness of the psychological needs of these patients is important. The grief and sense of loss for these couples can manifest itself in all aspects of personal and work life and may impact success with future pregnancies. Some small prospective studies have shown a positive influence in patients with RPL with the use of tender loving care (TLC) defined as psychological support with weekly medical and ultrasonographic examinations.[101,102]

GENETIC ABNORMALITIES IN RECURRENT PREGNANCY LOSS

Parental Balanced Translocations

Parental karyotype will identify chromosomal rearrangements that place couples at an increased risk of miscarriage. Parental balanced translocations affect 3% to 4% of couples with RPL. The most common types of balanced translocations are reciprocal translocations, which involve the exchanged of genetic material from one chromosome to another, and robertsonian translocations, whereby the long arms of 2 acrocentric chromosomes erroneously share a centrosome. Carriers of balanced translocations are typically asymptomatic, as they have the normal quantity of genetic material at all loci. However, during gametogenesis, the segregation of chromosomes may result in unbalanced gametes, which can lead to an increased miscarriage rate or ongoing conception with congenital anomalies. Although parental carriers of structural rearrangements have increased reproductive loss rates, similarly to patients with unexplained RPL, most carriers of parental translocation will succeed in having successful pregnancies without intervention.[103]

Preimplantation genetic chromosome screening (PCS) of embryos is one proposed therapy for carriers of parental translocations; however, well-designed prospective trials comparing expectant management with in vitro fertilization–preimplantation genetic diagnosis (IVF-PGD) or preimplantation genetic screening (PGS) have not been performed. Proponents have published several case series suggesting benefits, including fewer miscarriages, less emotional distress, and shorter time to successful pregnancy. However, these studies do not take into account the emotional and financial cost of a failed cycle or the time it takes to prepare for a PGS cycle in carriers of translocation. Fischer and colleagues[104] wrote one of the largest case series published to date on this subject. They reported on 192 couples with a history of 3 or more miscarriages undergoing IVF-PGD for either reciprocal or robertsonian translocations. Overall 35% of cycles had no suitable embryos for transfer, and the pregnancy rate per embryo biopsy cycle was 25%. The overall pregnancy loss rate in this cohort was 13%, and the live birth rate per cycle was 22%. Several smaller studies and reports either looked at individually or in summary do not show significantly different outcomes when day 3 biopsy and fluorescence in situ hybridization (FISH) is used.[104–107]

Scriven and colleagues[107] performed the only large intent-to-treat study in a population of carriers of translocations. They followed 59 couples with reciprocal translocations undergoing 1 to 3 cycles of PGS using cleavage stage embryo biopsy and FISH for their translocation. Only 110 of the 132 cycles started (83%) reached the biopsy stage, and 26% of cycles resulted in no eligible embryos for transfer. The overall live birth rate per initiated cycle was 20%. The investigators calculated that, based on their data, couples would have to undergo 3 cycles to achieve a 50% live birth rate. This study is particularly important because it calculates outcomes by intent to treat. This method showed that 40% of initiated cycles reach the embryo transfer. Their conclusion was that patients with a high risk of unbalanced viable offspring benefit from PGS, but that couples with lower-risk translocations may conceive more quickly without PCS and have a high rate of healthy offspring with spontaneous conception. They defined high risk of unbalanced offspring by personal or family history of an unbalanced live birth with congenital anomalies. Couples with balanced translocations benefit from genetic counseling to better understand their individual risk.

Very little data currently exist for the use of 24 chromosome screening of translocation carriers done after blastocyst biopsy. These data will be very helpful to couples with translocations. As we improve technology in this area, the live birth rate per transfer may increase. However, we must keep in mind that with extended culture and genetic screening there will be a higher rate of patients not reaching transfer. Patients willing to accept the risk and cost of PCS will likely see a significant reduction in miscarriage and reduction in the risk of unbalanced offspring. However, given the current literature, the chances of a healthy live birth per attempt are still low. Additionally, unbalanced live offspring are rare for most chromosomal rearrangements.

Aneuploidy and Miscarriage

Approximately half of couples with RPL will not have an identifiable cause for their losses.[12,13] The documented high incidence of chromosomal errors in first-trimester miscarriages has led to the theory that screening embryos before implantation for these errors may decrease the risk of a subsequent loss.

Most sporadic pregnancy losses in the first trimester result from random numeric chromosomal errors, specifically, trisomy, monosomy, and polyploidy.[6] Extensive research shows a consistently high rate of aneuploidy in analysis of pregnancy losses.[12,108–112] Approximately 60% of first-trimester pregnancy losses are associated with sporadic chromosomal anomalies.[6,113] Up to 90% of chromosomally abnormal pregnancies abort spontaneously,[6] but only 7% of chromosomally normal pregnancies abort spontaneously.[114] Miscarriage associated with chromosomal abnormalities increases with age.[115,116]

Analysis of pregnancy losses also shows a high rate of aneuploidy in some patients with RPL. The risk of aneuploidy increases with age such that up to 80% of miscarriages in patients with RPL who are older than 35 years.[116] The rate of aneuploidy in miscarriages increases with increasing maternal age. This association is seen in women with sporadic and recurrent miscarriages is not significantly different in women with RPL compared with women of similar in ages with sporadic miscarriage.[113] The type and frequency of chromosomal error is similar in patients with RPL to patients with advanced reproductive age.[117] The risk of aneuploidy in ongoing pregnancies may also increase with the number of previous miscarriages.[118]

Preimplantation Genetic Screening in Patients with Recurrent Pregnancy Loss

The evidence showing a high rate of aneuploidy found in sporadic miscarriages, and an increased rate of aneuploidy in patients with RPL, has provided a basis for suggesting

embryo selection with PGS. PGS is a possible treatment option to decrease the risk of miscarriage in patients with unexplained RPL. The ability to provide genetic screening of embryos to patients with an increased risk of aneuploidy has been rapidly adopted in assisted reproductive technology, but the evidence remains limited.

Early investigations showed a higher rate of aneuploidy in the embryos from patients with RPL compared with controls using PGS for other reasons, such as X-linked disease.[119–121] One group using day 3 embryo biopsy and FISH for chromosome analysis showed a 70.7% aneuploidy rate in tested embryos from 71 couples with RPL (defined as 2 or more miscarriages) to a 45.1% aneuploidy rate in embryos from a control group of 28 couples doing PGS for sex-linked diseases ($P<.0001$). This group published a summary of their work in 2005 with 71 couples with RPL defined as 2 or more miscarriages compared with 28 couples undergoing PGD for sex-linked diseases.[122]

Munne and colleagues[123] compared the rate of miscarriage after IVF-PGS for patients with a history of 3 or more previous losses to their own expected loss rate based on age and number of previous miscarriages. A total of 58 patients with RPL (average age of 37.0 years) underwent IVF with day 3 embryo biopsy and FISH analysis for chromosomes 13, 15, 16, 17, 18, 21, 22, X, and Y. Patients with RPL experienced an average of 3.9 pregnancies before the intervention, of which 87% resulted in miscarriage. After IVF-PGS, 15.7% of pregnancies were lost ($P<.001$). The investigators also calculated the expected loss rate for each patient based on prediction parameters by Brigham and colleagues,[124] which uses a formula predicting the probability of successful pregnancy outcome based on the patient's age and pregnancy history. The expected miscarriage rate for 58 couples in the study was 36.5% based on Brigham's formula; however, the observed loss rate was 16.7% ($P = .028$). For patients 35 years old or older (37 patients), the expected loss rate was 44.5%; but the observed loss rate after IVF-PGS was 12% ($P = .007$). For patients with RPL who were less than 35 years old (21 patients), there were no differences between the expected and observed loss rate (29% vs 23%). The live birth rate per embryo biopsy was 40% for patients less than 35 years old and 34% for patients aged 35 years and older. This study suggested that women older than 35 years were more likely to benefit from PGS then younger women, which is consistent with studies that show patients with RPL who are younger than 35 years miscarry a higher percentage of euploid pregnancies than women older than 35 years.

Hodes-Wertz and colleagues[125] published a case series report on 287 IVF cycles from couples with unexplained RPL, defined as 2 or more losses, with PGS on cleavage stage biopsy (193 cycles), PCS on blastocyst biopsy (94 cycles), and chromosome analysis with array comparative genomic hybridization. The miscarriage rate from these IVF-PGS cycles were compared with the expected miscarriage rate determined by (1) predictive parameters determined by Brigham and colleagues and (2) expected miscarriage rate in a control infertile population as reported in the United States to the Society of Assisted Reproduction Technology (SART). The overall aneuploidy rate for all 2282 embryos analyzed was 64.8%: 68.8% for cleavage stage embryos (1710 total) and 53% for blastocyst embryos (572 total). The average age of patients overall was 36.7 years $\pm$ 4.2 (36.5 $\pm$ 4.2 for cleavage stage biopsy and 36.9 $\pm$ 4.0 for blastocyst biopsy). The overall clinical pregnancy rate per embryo transfer was 55.2%, with a significantly higher pregnancy rate for blastocyst biopsy compared with cleavage stage biopsy (63.6% vs 50.4%, $P<.001$). There were 7 miscarriages overall (6.9%), which is less than the expected rate of miscarriage by Brigham and colleagues (33.5%) and SART (23.7%). There was a trend toward a higher miscarriage rate in cleavage stage biopsy compared with blastocyst biopsy (8.5% vs 4.7%), but this was not statistically significant.

The results of Hodes-Wertz and colleagues[125] look promising for the new technology; however, the data require careful interpretation. There were a total of 287 IVF cycles in couples with RPL, but the conclusions drawn are limited to certain groups. When reporting on pregnancy outcomes, only cycles with embryo transfers and pregnancy data are included (181 total); when reporting on miscarriage, only cycles with implantation are included (102 total). By excluding cycles that started but had no embryo transfer and cycles that were canceled before biopsy, intention to treat is lost, which overestimates the success rate of the PGS.

The technology has advanced rapidly in assisted reproductive technology and PGS. Early studies tested 1 to 2 cells from a day 3 or cleavage stage embryo and used FISH to test for euploidy; however, FISH allows for the diagnosis of only a few chromosomes. PGS is moving toward testing 4 to 5 cells from a blastocyst, which decreases the risk error because of mosaicism; 24 chromosome testing increases the detection of chromosomal abnormalities associated with miscarriage. The advances in technology seem promising. However, the costs, success rates, and number needed to treat with the use of PGS for individual patient groups have yet to be clarified.

Future research should be held to a high standard in order to provide the strongest evidence. First, miscarriage should be defined as a clinical loss by ultrasound evidence of histopathologic evidence because medical records could verify only 71% of reported miscarriages.[14] Second, although defining RPL as 2 or more losses may be beneficial clinically in order to identify treatable causes in women to prevent a third miscarriage, maintaining a distinction of 3 or more losses for inclusion criteria in research design would provide stronger evidence.[126] Third, intention-to-treat analysis must be used so that results are reported on all patients doing IVF with the intention of genetic screening of the embryos, not just the patients who have embryos suitable for transfer. Finally, the most challenging part of designing a compelling clinical study for patients with RPL will be finding an appropriate comparison group. The best evidence would be a randomized controlled trial of patients with RPL in which half of the patients had the intervention of IVF-PCS and the other half had no intervention beyond expectant management. With the possibility of a benefit of any intervention, finding a control group willing to forgo such treatment will be extremely difficult.

Furthermore, it must be stated that for any intervention in patients with RPL to be recommended, it must be shown to provide a higher chance of live birth beyond no intervention. IVF with PGS has medical risks and financial burdens to patients that must be justified before widespread use of this technology is offered as standard care. Given the current state of the literature, a provider must provide balanced and evidence-based counseling to patients with RPL. On one hand, IVF-PGS seems to decrease the miscarriage risk compared with natural conception; however, the live birth rate per started cycle is variable. Given this, the emotional and financial burden of IVF and PGS must be weighed against the estimated chances of live birth and the risk of subsequent miscarriage without this treatment. Patient preference for intervention, financial means, and social support will be important determinants of a patient's choice for or against treatment. The journey of RPL is challenging, and provider support throughout the process is essential regardless of a patient's choice for treatment.

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