4 Recurrent pregnancy loss

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INTRODUCTION

Recurrent pregnancy loss (RPL) can be devastating to families involved. It is defined as three or more spontaneous or two or more consecutive losses prior to 20 weeks of gestation. It can be subdivided into preclinical losses at less than 6 weeks or clinical losses at greater than or equal to 6 weeks of gestation. Clinical losses can be further subclassified as embryonic (crown–rump length is at least 5 mm with no cardiac activity) or fetal (10–20 weeks without cardiac activity). Other experts have instead subdivided the losses into early (prior to 12 weeks of gestation) or late (between 12 and 20 weeks). Primary RPL exists if a couple has never carried a pregnancy to viability, whereas secondary loss is present if at least one viable term pregnancy has been achieved.

In considering the incidence of this disorder, one must keep in mind the baseline risk of miscarriage: fetal viability is achieved in only 30% of all conceptions and at least 50% of pregnancies are lost before a missed period (1). Among clinically recognized pregnancies, 10% to 15% still undergo sporadic loss during the first or early second trimester (2). RPL occurs in 1% to 4% of couples, with a definite cause identified in no more than 40%. Risk of subsequent loss, stratified by the number of prior losses, is detailed in Table 1.

It follows that the workup of couples with recurrent loss can justifiably be undertaken after two or more consecutive losses as the risk of recurrence is similar to that after three losses (2). Furthermore, the frequency of identifiable causative factors is similar after two or three losses. Other experts have suggested proceeding with workup for couples only after three consecutive losses at less than 10 weeks, unless the couple has had a previous euploid loss or experiences concomitant infertility or advanced maternal age (3). This latter approach can be justified by the fact that 25% of women aged 30 or less will have a subsequent loss whereas 50% to 60% of women at or beyond age 40 will experience a repeated loss (4,5).

PRECONCEPTION EVALUATION

Upon presentation to the clinic, it is imperative to have an organized diagnostic approach in order to avoid overwhelming either the affected couple or the provider. We recommend evaluation after a second consecutive loss without prior live-born child, a third loss if the couple has had a prior live-born child, or after two losses in the presence of infertility or advanced maternal age.

History should include age; past medical history and medications; characteristics, pattern, and gestational age of prior losses; exposure to toxins or recent travel; previous gynecologic or obstetrical infections; previous workup; family history [cycle regularity, spontaneous losses, diethylstilbestrol (DES) exposure, genetic syndromes, and thromboses]; and a thorough review of systems (e.g., rheumatic diseases). Karyotypes of prior losses

should be recorded if available. A general overall physical examination should then be performed including a pelvic examination.

Testing can then be offered. Keep in mind when ordering tests that nocturnal gonadotropin-releasing hormone pulses do not resume until 4 weeks postpartum, so some endocrine evaluations [prolactin (PRL), follicle-stimulating hormone (FSH), if indicated] should not be pursued until at least one month after a loss. Anticardiolipin antibodies, homocysteine, and protein S levels are altered by pregnancy and may not return to baseline until 6 to 12 weeks postpartum, further supporting a slight delay before initiating the workup (Table 2).

As a final note on the general evaluation, it is important that prenatal vitamin supplementation is recommended to all preconceptional patients. Poor dietary intake of vitamins has been associated with spontaneous pregnancy loss. For example, a folate level of 2.2 ng/mL (4.9 mmol/L) is associated with an increased rate of sporadic loss with an odds ratio of 1.47 (95% CI 1.01–2.14) (6). A recent Cochrane review of randomized trials, however, showed that vitamin supplementation does not prevent miscarriage or stillbirth. They do, however, lessen the likelihood of developing pre-eclampsia and have been shown to increase the likelihood of multiple gestations (7). Other benefits include lesser likelihood of neural tube defects, anemia, or other vitamin-associated deficiencies that may be common in pregnancy.

The remainder of this chapter will focus on the evidence supporting or refuting various proposed etiologies for RPL and their respective evidence-based management strategies.

ETIOLOGY AND MANAGEMENT

Uterine Abnormalities

With the exception of the septate uterus and possible acquired anomalies, uterine abnormalities are more commonly associated with second rather than first-trimester losses. These abnormalities include congenital anomalies of fusion or resorption, fibroids and polyps, synechiae or Asherman syndrome, and DES exposure. The diagnostic modalities for appropriate diagnosis include hysterosalpingogram (HSG), hysteroscopy, sonohysterography, laparoscopy, MRI, or three-dimensional ultrasonography. Each modality has advantages and disadvantages. For example, the sensitivity and specificity of standard two-dimensional transvaginal ultrasonography in diagnosing a uterine septum are 100% and 80%, respectively, while sensitivity and specificity using MRI are both 100% (8). Three-dimensional ultrasonography can be added after an abnormal two-dimensional ultrasound to improve the aforementioned specificity. Three-dimensional sonography is preferred over hysterosalpingography as the former test is less expensive and less invasive and allows for improved visualization of the endometrial cavity and myometrium. Three-dimensional ultrasonography can reliably delineate between septate and bicornuate uteri (9,10).

Anomalies

Overall, the presence of a congenital uterine anomaly appears to almost double the risk of RPL: anomalies have been identified in 6.3% of recurrent loss patients versus 3.8% of fertile women ($p < 0.05$). In one investigation, the breakdown of specific anomalies among RPL patients was 1.9% bicornuate (vs. 0.4% among fertile women, $p < 0.01$), 2% septate, and 1% arcuate uteri, with latter two not holding a statistically significant difference when compared with fertile women (Table 3) (11).

One common current theory holds that the causative factor for loss in patients with a septate uterus is implantation on the septum itself. This is thought to result in inadequate placentation secondary to poor septal vascularity and resultant early demise. This theory is supported by the timing of losses: early first trimester with septate uteri versus second-trimester losses or preterm deliveries with bicornuate and unicornuate uteri (13). In addition, although the vascular density of septa is similar to normal myometrium (14), a study of 12 pregnancies in women with septate uteri revealed that the only four successful pregnancies were those that had implanted away from the septum (15). Furthermore, several uncontrolled studies have shown that septum resection leads to an improved rate of successful subsequent pregnancy. A retrospective case series showed that 70% to 85% of RPL patients who underwent surgical correction of bicornuate and septate uteri delivered viable infants in the next pregnancy (16). Hysteroscopic resection of uterine septa

leads to comparable subsequent pregnancy rates with those seen after metroplasty (16), leading the American College of Obstetricians and Gynecologists (ACOG) to make a compendium recommendation supporting hysteroscopic resection. No prospective controlled studies have been undertaken. Extensive surgical procedures, such as Strassman unification, are rarely undertaken.

The contribution of the arcuate uterus to RPL is more controversial. One study of 61 RPL patients identified an arcuate uterus in 15% via three-dimensional ultrasound and hysteroscopy versus 3% of 1000 general gynecologic patients (17,18). Others, however, have argued against the presence of an association (19,20).

Leiomyomata and Polyps

Theories concerning the contribution of leiomyomata or endometrial polyps as an etiology of RPL have centered on their disruption of endometrial vasculature, the intrauterine cavity, or tubal patency. Either polyps or fibroids may act as foreign bodies, similar to intrauterine devices, and thus disrupt pregnancy. The direct association between submucosal fibroids and RPL has had some controversy in the past although uncontrolled studies do reveal an association. Intramural fibroids have been proven to interfere with implantation of in vitro fertilization pregnancies, though little data are available relative to intramural fibroids and RPL. The rate of spontaneous loss decreases after removal of fibroids over 5 cm in diameter, regardless of their location (21) and, therefore, resection is recommended. Hysteroscopic approaches for fibroid removal are preferred when possible.

Synechiae

Uterine synechiae may occur after uterine infection, intrauterine curettage, or other uterine instrumentation. Synechiae have been found in 5% of patients with RPL. Hysteroscopy is typically recommended to lyse these adhesions, although strong data to support this treatment are lacking.

Table 1 Risk of Subsequent Pregnancy Loss	
After one successful pregnancy	12%
After two consecutive losses	24–26%
After three consecutive losses	
With at least one previous live birth	30%
Without previous live birth	32–45%
After four consecutive losses	40–50%

Table 2 Diagnostic Evaluation	
Anatomic	Sonohysterogram or hysteroscopy MRI if indicated
Genetic	Parental karyotype and conceptus cytogenetic results Genetic counseling if indicated
Thrombophilias	(Consider full testing if >10-week loss, history of VTE, family history of thrombosis, or non-Caucasian) All patients: factor V Leiden, PT G20210A mutations, homocysteine level APC resistance Consider AT III, PC, and PS deficiency testing in all Asian patients
Immunologic	(Low or unsustained, moderately positive values are not clinically significant) Russel’s viper venom time (RVVT) (=lupus anticoagulant) Anticardiolipin antibodies (IgG or IgM) Anti-β2 glycoprotein I antibodies (IgG and IgM) Consider antithyroid antibodies
Endocrine	Luteal phase duration (positive ovulation kit test till day 1 menses; <13 days indicative of deficiency) Day 3 FSH (for ovarian reserve), TSH, PRL (if menses irregular or with galactorrhea) If menses irregular with signs of PCOS, consider androgens, SHBG, 17OHP, and insulin sensitivity testing
Abbreviations: MRI, magnetic resonance imagine; VTE, venous thromboembolism; FMH, family medical history; FVL, Factor V Leiden; PT, prothrombin; APC, activated protein C—15% of activated protein C resistance is not due to FVL; AT, antithrombin; PC, protein C; PS, protein S; Ig, immunoglobulin; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; PRL, prolactin; PCOS, polycystic ovarian syndrome; SHBG, sex hormone–binding globulin; 17OHP, 17-hydroxyprogesterone.	

DES Exposure

While isolated spontaneous loss is more common with a history of DES exposure (22), little data exist regarding its relation to RPL. No approach to the correction of anatomic abnormalities related to DES exposure has been successful. It does, however, seem warranted to seek this history, as the implications go beyond maintenance of pregnancy.

Cervical Incompetence

A Cochrane review of six trials, including 2175 women, found there to be no benefit for either prophylactic or therapeutic cervical cerclage among patients with presumed cervical incompetence and any adverse pregnancy outcomes (including RPL). For prophylactic cerclage, no reduction was seen in overall pregnancy loss and preterm delivery rates in the overall analysis, although a small decrease in births prior to 33 weeks was reported in one of the included trials (RR 0.75, 95% CI 0.58–0.98). Additionally, the use of therapeutic cerclage upon ultrasound findings of decreased cervical length failed to positively alter total pregnancy loss, early pregnancy loss, or preterm delivery rates (23).

Genetic Factors

Parental chromosomal anomalies are identified in 4% of couples with RPL versus 0.2% of couples in the general population. Maternal anomalies are identified in a 3:1 ratio relative to paternal anomalies. Of spontaneous abortions, 60% to 75% have an abnormal fetal karyotype (24). These fetal chromosomal abnormalities have a more prominent role in single losses than recurrent losses. In fact, as the number of pregnancy losses increases for any given couple, the risk of fetal chromosomal aberrations decreases. In other words, loss of a chromosomally abnormal fetus carries a higher chance of subsequent live birth than loss of a euploid embryo (25,26). To this point, if the karyotype of the first abortus is aneuploid, then the karyotype of the second successive loss is abnormal in 50% to 70%; if the first is chromosomally normal, then the incidence of a karyotypic abnormality in the second loss is decreased to 20% (27,28).

At least half of clinically recognized, isolated spontaneous abortions have a chromosomal anomaly. Of these, 56% are trisomic, 20% are polyploid, 18% exhibit monosomy X, and 4% carry unbalanced translocations (29). For comparison, 70% of preclinical spontaneous losses are chromosomally abnormal whereas only 5.6% of second- and third-trimester losses carry these abnormalities (30,31). It has been suggested that the majority of these losses may be secondary to maternal

aging rather than nonrandom events (32,33). Preimplantation genetic diagnosis (PGD) studies have irrefutably demonstrated that 50% of embryos from RPL couples have aneuploidy (34,35).

The ACOG recommends karyotype screening of all RPL couples. This recommendation is based (i) on the couple's desire to identify a cause, (ii) on the fact that the couple may benefit from prenatal genetic testing if a balanced chromosomal abnormality is identified, and (iii) on the fact that normal appearing offspring may carry the abnormality and thus have potential reproductive complications of their own (2).

Aneuploidy

One aneuploid loss increases the risk of a subsequent aneuploid loss (36). Trisomies are the most common anomaly as a group, led by trisomy 16. Still, the single most common aneuploidy found in first-trimester pregnancy loss specimens is 45 X,0. Some experts therefore suggest that it would be prudent to perform cytogenetic analysis of second and subsequent losses, understanding that a trisomic loss does not increase the risk of recurrent loss (33). In fact, recurrent aneuploidy or polyploidy, though seen with sporadic loss, has not been proven to be associated with recurrent loss when stratified for age (37). If the karyotype of an abortus is found to be aneuploid, a maternal cause for loss can be effectively excluded. The discovery of a legitimate cause for the loss may also be a source of comfort for the grieving family.

A recent study examined 420 losses from 285 couples and compared the frequency of chromosomal anomalies among recurrent loss patients with the frequency among patients without such a history. Significant differences were found between the two groups in the distribution of cytogenetic abnormalities, but the difference dissipated after stratification for maternal age. In younger women (i.e., less than 36 years of age), more spontaneous losses were euploid (37), suggesting other etiologies for RPL.

It is important to note that generalized screening for aneuploidy (as opposed to screening for a specific genetic abnormality using PGD) among embryos from chromosomally normal couples with a history of RPL is not currently recommended. Once considered promising, a recent review article concluded that preimplantation genetic screening (PGS) does not increase pregnancy rates in patients at risk of aneuploidy, including couples experiencing RPL (38). This is not surprising, however, given the current limitations on the numbers of chromosomes that can be screened using PGS. The outcomes of this intervention among recurrent loss patients should, therefore, be revisited when techniques for simultaneously screening all 23 chromosomes, such as complete genomic hybridization, become widely available.

Chromosomal Rearrangements

Overall, 2% to 4% of RPL couples have a partner with a chromosomal rearrangement (2). This is less common if there is no history of prior stillbirth or anomalous infant: 2.4% of females and 1.6% of males with no such history versus 4.6% of females and 1.7% of males with the aforementioned history (39). In these situations, family history may be telling as the translocation may have been in the lineage for multiple generations prior to detection. Although the carrier parents

Table 3 Reproductive Performance with Different Uterine Malformations

	Spontaneous abortion (%)	Preterm delivery (%)	Live birth (%)
Didelphys	20	53.3 ^{b,c}	40 ^f
Unicornuate	37.5 ^b	25 ^b	43.7 ^f
Bicornuate	25	25 ^b	62.5 ^e
Septate	25.5	14.5 ^{b,d}	62 ^e
Arcuate	12.7 ^a	4.5 ^a	82.7 ^e

Note: Statistical significance by column: ^{a/b} $p < 0.05$; ^{c/d} $p < 0.01$; ^{e/f} $p < 0.001$. Source: Adapted from Ref. 11,12.

Table 4 Thrombophilias and Recurrent Pregnancy Loss

Study	Associations supported	Associations refuted
Rey 2003 (meta-analysis of 31 studies)	RPL <13 weeks associated with FVL (G1691A), Activated protein C resistance, PT gene mutation (20210A), and PS deficiency	MTHFR, PC deficiency, and ATIII deficiency were not associated
Kovalesky 2004 (meta-analysis of 16 studies)	RPL (two or more first- or second-trimester losses) associated with FVL and PT gene mutation	
Krabbendam 2005 (review of 69 studies)	Hyperhomocysteinemia, antiphospholipid antibodies, FVL, and activated protein C resistance are associated with early RPL	

Abbreviations: RPL, recurrent pregnancy loss; FVL, Factor V Leiden; MTHFR, methyltetrahydrofolate reductase; PC, protein C; ATIII, antithrombin III deficiency; PT, prothrombin; PS, protein S.

are balanced in their chromosomal content, segregation during meiosis results in duplication or deficiency in the chromosomal constitution of some of the gametes. The incidence of de novo translocations is 1/2000 for reciprocal translocations (which makes up 60% of anomalies and yields normal gametes one-half of the time) and 1/9000 for Robertsonian translocations (40% of anomalies and yields normal gametes one-third of the time) (40). A natural selection of sorts appears to occur among sperm from men with balanced translocations, explaining why female carriers generally have a 10% risk of a subsequent abnormal live birth whereas the risk for male carriers is only 1%.

Therapy for the couples with RPL and balanced translocations relies on genetic counseling and discussion of options for prenatal diagnosis, donor gametes for the affected partner, or PGD with implantation of unaffected embryos. For fully evaluated RPL couples in whom one partner carries a structural chromosomal rearrangement, the subsequent live-birth rate is greater than 70% after evidence-based treatment, close monitoring, and supportive care (41).

Other

Other chromosomal anomalies associated with pregnancy loss tend to involve the X-chromosome. Women with Turner mosaicism who become pregnant are more susceptible to spontaneous loss. Of 160 pregnancies in these mosaic patients, 29% ended in spontaneous loss, 20% delivered children with malformations, and 7% resulted in perinatal death (42). Additionally, highly skewed X-chromosome inactivation may be responsible for otherwise unexplained recurrent losses (43). However, as commercial tests are generally unavailable for X-inactivation and other rare genetic abnormalities, testing is generally not available, performed, or recommended.

Thrombophilias

Thrombophilias include a diffuse group of inherited hypercoagulable states. The most often discussed include Factor V Leiden (FVL), prothrombin (PT) G20210A promoter mutation, deficiencies of proteins C and S (PC and PS, respectively), antithrombin III deficiency (ATIII), and hyperhomocysteinemia [including abnormalities in methyltetrahydrofolate reductase (MTHFR)] function. The antiphospholipid syndrome (APS) is another hypercoagulable state associated with RPL, but it is acquired and will be discussed separately under the Immunology section. It has been suggested that patients to be tested for

familial hypercoagulability should include those with unexplained fetal death beyond 10 weeks, personal history of venous thromboembolism, a suggestive family history, and those with at least three first-trimester losses.

The presence of two or more heritable thrombophilic defects has been associated with adverse outcomes, including pre-eclampsia, thrombosis, intrauterine growth restriction (IUGR), and even fetal death (44). The association between RPL and hypercoagulable states continues to be somewhat controversial with some research supporting (45–48) and other reports refuting (49–53) an association. The results of two recent meta-analyses and one review have been summarized in Table 4. Since controversy continues, it is useful to discuss the individual defects separately.

First, consider FVL and the PT promoter gene mutation. These mutations are common and carry low thrombotic risk in the heterozygotic state. They are reported to be present in approximately 9% and 3% of Caucasian women in the United States, respectively. These two thrombophilias have been associated with 25% of isolated thromboses and 50% of familial thromboses. Among RPL patients (with at least three losses and no successful pregnancies), the prevalence of FVL is 9% (OR 2.6, 95% CI 1–6.7, $p = 0.048$) (48). Furthermore, a prospective case-control study of FVL patients has shown lower pregnancy success rate among women with FVL who were not treated with anticoagulants (54).

The autosomal-dominant deficiencies in ATIII, PC, and PS are much less common in Caucasians, but carry a significantly greater thrombotic risk. These three mutations double the relative risk of abortion and stillbirth in carriers when compared with women who test negative (RR 2, 95% CI 1.2–3.3) (55). Diagnosis, however, can be affected by many factors. Oral contraceptive pills increase levels of both PC and PS while decreasing ATIII. Cigarette smoking decreases levels of PC and PS, while pregnancy decreases only the level of PS. Protein C and S testing can evaluate protein function or antigen levels. Protein S functional screening is non-diagnostic if less than 60% and antigenic levels should be performed.

Hyperhomocysteinemia may be caused by MTHFR mutation (heritable) and/or low levels of vitamin B6 or B12, or folate (acquired). Random homocysteine levels are considered mildly elevated at 16 to 24 $\mu\text{mol/L}$, moderately elevated at 25 to 100 $\mu\text{mol/L}$, and severely elevated at $>100 \mu\text{mol/L}$. Dietary supplementation with vitamins B₆, B₁₂, and folate can

Table 5 Diagnostic Criteria for Antiphospholipid Syndrome

Patients should have at least one clinical and one laboratory criteria

Clinical criteria

- ≥ 1 clinical episodes of arterial, venous, or small-vessel thrombosis
- ≥ 1 unexplained pregnancy loss of a morphologically normal fetus of at least 10 weeks of gestation
- ≥ 1 preterm births of a morphologically normal newborn at <34 weeks of gestation due to severe pre-eclampsia or placental insufficiency
- ≥ 3 unexplained consecutive spontaneous abortions before 10 weeks of gestation, with anatomic, hormonal, and parental structural genetic factors excluded

Laboratory criteria: the same antibody must be present on two separate occasions ≥ 12 weeks apart

- Anticardiolipin IgG and/or IgM, present in medium or high titers (>40 GPL or MPL)
- Anti β_2 -glycoprotein-1 IgG and/or IgM, present in titers >99 th percentile
- Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Hemostasis

Source: Adapted from Ref. 65.

normalize homocysteine levels, but has not yet been shown to decrease thrombotic risk (56).

To summarize, evidence is mounting that supports the association between heritable and acquired thrombophilias and RPL as well as other adverse pregnancy outcomes. Our best data to date are from Caucasian populations and support to testing for FVL, PT promoter gene mutations, activated protein C resistance, homocysteine elevations, and the APS (dealt with in more detail in the next section). In non-Caucasian patients, the data are more limited and additional testing may be prudent. For instance, protein C, protein S, and ATIII deficiencies are significantly more common among patients of Asian descent than among Caucasian patients.

Ideal treatment for patients with heritable thrombophilias and RPL remains to be determined. A recent Cochrane review of anticoagulants for the treatment of RPL in the absence of APS noted that when 20 females with fetal loss after the 20th week and a thrombophilic defect were randomized to enoxaparin or aspirin, enoxaparin increased the live-birth rate (RR 10, 95% CI 1.56–64.2). Live-birth rates were unchanged, however, in controlled studies of aspirin versus placebo. The review's summary recommendation was that "data are too limited to recommend use of anticoagulants" in the setting of two or more spontaneous losses or one late intrauterine fetal death without apparent causes other than inherited thrombophilias except for anticardiolipin antibodies (57). The formal ACOG statement agrees that "whether antithrombotic treatment improves subsequent pregnancy outcome is uncertain" (2). Further trials are therefore needed.

Immunologic

APS

APS or Hughes syndrome is present in and felt to be responsible for 5% of RPL. In this syndrome, losses more commonly occur beyond 10 weeks of gestation, generally during the second or even early third trimesters (58,59). The mechanisms for APS-related losses are thought to be related to impaired vascular flow to the fetus. Since blood flow in placental vessels is not established until at least 9 to 10 weeks of gestation, losses at less than 10 weeks of gestation may be the result of impaired gestational nutrition, which occurs via diffusion prior to the establishment of intervillous blood flow. Thereafter, theories propose that thrombosis and vasoconstriction may occur due to antiphospholipid antibody binding to platelets and vascular endothelial membranes (60).

Other researchers purport that the antibodies in APS cause inhibition of cytotrophoblastic fusion, invasion, and differentiation and that this inhibition in turn leads to recurrent pre-embryonic or embryonic pregnancy loss (61–63).

Diagnosis of APS is based on an international consensus that was most recently updated in their criteria in 2006 (Table 5). The syndrome may be subdivided into primary (no other related disease present) or secondary (systemic lupus erythematosus (SLE), valvular heart disease, or other rheumatic diseases coexist). ACOG recommends testing all RPL patients for APS laboratory criteria as outlined in Table 5. Although there exists evidence linking antiphosphatidylserine antibody positivity to early RPL, its role in diagnosis, treatment, and prognosis remains controversial (64,65).

Numerous interventional studies have been performed in patients with RPL. The most promising approaches involve various regimens of aspirin and heparin. In controlled studies, combinations of aspirin, low molecular-weight heparin (LMWH), and human chorionic gonadotropin (hCG) as well as unfractionated heparin and aspirin led to 70% to 75% successful pregnancy outcome versus 50% in untreated controls (66,67). Heparin clearly lends benefit, as shown in Empson's study, where addition of heparin to aspirin when compared with aspirin alone resulted in a 54% decreased rate of pregnancy loss (RR 0.46, CI 0.29–0.71) (68). Heparin also proved more effective than intravenous immunoglobulin (IVIG) in randomized trials (69). A low-dose aspirin versus placebo study is currently underway. LMWH has also been suggested as an effective alternative to unfractionated heparin (67,70–72) although not all investigators agree. Steroids should not be given if no other clinical indication is present, as they have been shown to decrease the live-birth rate and increase the rate of fetal and maternal complications (73,74).

Current recommendations for the treatment of patients with APS and RPL (but no prior thrombotic episode) support initiation of heparin at the time of a positive pregnancy test. If given LMWH, these patients are maintained on prophylactic doses through approximately 36 weeks of gestation when it is recommended to convert to unfractionated heparin to decrease the risk of hematoma with epidural placement or hemorrhage at the time of delivery. Anticoagulation prior to conception is discouraged due to the risk of hemorrhage with ovulation. Therapeutic rather than prophylactic doses of LMWH or unfractionated heparin should be used if a history of thrombosis is present. Close maternal and fetal surveillance

should be performed instituted in all patients with a history of APS due to the increased risk of significant perinatal morbidity including pre-eclampsia, IUGR, and preterm labor. Finally, since the risk of thrombosis continues to be increased during the first 6 weeks postpartum, anticoagulation should be continued after delivery bridge this time period.

Thyroid Antibodies

Associations have been made between the presence of thyroid antibodies and spontaneous abortion. An increased rate of spontaneous pregnancy loss is seen with autoantibodies to thyroglobulin or thyroid peroxidase (TPO) if identified in early pregnancy or immediately before conception (75,76). In other studies, the presence of antithyroperoxidase antibodies increased the risk of spontaneous loss from 23% to 50% (77). A meta-analysis published in 2004 found the odds ratio for spontaneous miscarriage in the presence of thyroid antibodies to be 2.73 (95% CI 2.2–3.4) using 8 case-control studies and 2.3 (95% CI 1.8–2.95) using 10 longitudinal studies (78).

Antimicrosomal and antithyroglobulin antibodies have been identified with increased frequency among females experiencing RPL. An investigation of RPL patients in 2000, however, concluded that if the patient is euthyroid, the presence of antithyroid antibodies does not affect pregnancy outcomes (Rushworth 2000). Nevertheless, much additional work has been done since 2000 that suggests otherwise and, although not specific to the recurrent loss population, is worthy of discussion. Studies have shown that patients with subclinical hypothyroidism (antibody status not delineated) do experience significantly increased rates of adverse obstetric events (Abalovich 2002, Casey 2005). A more recent study prospectively divided 984 euthyroid pregnant women into three groups: those with positive TPO antibodies to whom they gave levothyroxine (group A), those with antibodies that did not receive levothyroxine (group B), and controls who were negative for antibodies and untreated (group C). These researchers found a similar miscarriage rates for groups A and C (3.5 and 2.4%, respectively), but both A and C had significantly lower miscarriage rates than women in group B at 13.4% [$p < 0.05$, RR 1.72 (95% CI 1.13–2.25) and $p < 0.01$, RR 4.95 (95% CI 2.59–9.48), respectively]. Additionally, untreated antibody-positive women (group B) had a higher preterm delivery rate (22.4%) than women in group A (7%) ($p < 0.05$, RR 1.66 (95% CI 1.18–2.34)) or group C (8.2%) ($p < 0.01$, RR 12.18 (95% CI 7.93–18.7)) (79). These data support treatment of euthyroid pregnant women who test positive for TPO antibodies with levothyroxine to decrease the rates of both spontaneous abortion and preterm delivery. Further study in patients with a history of RPL is certainly warranted. It is, however, important to note that in the presence of anti-TPO antibodies, the risk of developing hypothyroidism during pregnancy or the postpartum period is increased. Therefore, it is recommended that the thyroid-stimulating hormone be checked during each trimester and after delivery in antibody positive women (80,81).

Antinuclear Antibodies

It has been reported that 7.5% of RPL females, compared with less than 2% of controls, test positive for antinuclear antibodies (ANA) (82). Still, testing for ANA among RPL patients does not appear to be helpful in the absence of

co-existent rheumatic autoimmune disorders. Subsequent pregnancy outcomes among RPL patients with an untreated, isolated, positive ANA is no different from those who test negative. In a randomized trial, patients with positive autoantibodies (including ANA) had no difference in outcomes when treated with prednisone and aspirin versus placebo (74). Data, therefore, do not support testing for ANA or treating positive results.

SLE

Patients with SLE have increased rates of both spontaneous and recurrent pregnancy loss in all trimesters. Not surprisingly, the most sensitive marker for poor pregnancy outcome among this group is the presence of antiphospholipid antibodies, which are seen in 37% of SLE patients (83,84). Additional predictors of poor prognosis include preexisting renal disease and the number and severity of pre-pregnancy lupus flares (85,86). Patients who meet the criteria for the APS should be treated with heparin and low-dose aspirin (see above).

Alloimmune Disorders

Alloimmune disorders are purported to cause pregnancy loss via an abnormal cell-mediated maternal immune response to placental or fetal antigens. One hypothesis for alloimmune RPL holds that in normal pregnancies, maternal production of a blocking factor prevents rejection of the fetus and that these factors are missing in women experiencing RPL (87). Evidence used to support this theory includes (i) the tendency for RPL partners to share human leukocyte antigens, (ii) the fact that females experiencing RPL often do not produce purported serum blocking factors, and (iii) the fact that women with a history of RPL commonly produce anti-leukocytotoxic antibodies against paternal leukocytes (2). The blocking factor hypothesis has been widely studied, but is poorly supported.

Among RPL patients, there is a proposed dysregulation of normal immune mechanisms at the maternal-fetal interface. Theories suggest that a T helper cell type 2 (Th-2) cytokine predominance is necessary for successful pregnancy and that T helper cell type 1 (Th-1) cytokines (IFN- λ and TNF- α) negatively affect embryo and trophoblast viability (88–90). One investigator demonstrated that production of an embryotoxic factor (possibly like IFN- λ) from RPL patient leukocytes cocultured with placental extracts predicted subsequent pregnancy failure (88). These findings have not been successfully reproduced in other studies (91). Testing for embryotoxic factor and treatment based on such testing is not currently recommended.

Decidual NK-like cells that secrete transforming growth factor may also be required for successful pregnancy (92). Studies show both increased (93) and decreased (92,94) NK-like cell number in luteal phase endometrial biopsies from recurrent loss patients. Subsequent pregnancy outcomes may be worse with increased decidual NK cell numbers (95). Furthermore, higher levels of circulating NK cells have also been shown to predict poor outcome with the next pregnancy (96,97). The relationship of peripheral NK cell numbers and activity of the NK-like cells present at the site of implantation is unclear.

To date, no specific testing regimens or treatments for abnormal alloimmune responses among RPL patients have been definitively shown to predict future pregnancy outcomes (3,98,99). Flow cytometric assays to document maternal antibodies to paternal leukocytes have been proposed and do offer biologic plausibility. However, investigations into the role of these allo-antibodies have lacked controls and no efficacious therapies have resulted. Randomized controlled trials of mononuclear cell immunization for patients with a history of RPL have yielded conflicting results. Although initial investigations appeared promising (100), further studies have concluded that immunotherapy to stimulate tolerance is not effective. Rather, alloimmune mononuclear cell immunization increases the rate of pregnancy loss when compared with placebo while carrying the infectious disease and allergic risks of transfusions with several other blood products (101). Trials using IVIG in patients with RPL have been fairly extensive with five randomized trials demonstrating a benefit with intervention (102) while other investigations and two meta-analyses have shown no benefit (103–107). A recent Cochrane review of this topic concluded that “paternal cell immunization, third party donor leukocytes, trophoblast membranes, and IVIG provide no significant benefit over placebo in improving the live birth rate” (108). In light of this body of evidence, a recent ACOG practice bulletin stated that HLA typing, measurement of maternal anti-leukocyte antibodies against paternal leukocytes, and measurement of maternal serum blocking factors do not predict the outcome of subsequent pregnancies. Furthermore, luteal phase biopsy for the presence of decidual NK cells, testing for percentage of NK cells in maternal peripheral blood, and testing for embryotoxic factor are not indicated in patients with a history of RPL. In short, alloimmune testing is not indicated and no beneficial immunologic treatment options are currently available.

Maternal Infection

Although no single infectious agent has been clearly linked as causative in recurrent loss, several infectious agents have been linked to sporadic losses. These include vaginal and cervical culture-proven infections with *Toxoplasma gondii*, rubella, herpes simplex virus, measles, cytomegalovirus, coxsackievirus, *Listeria monocytogenes*, *Chlamydia trachomatis*, and *Mycoplasma hominis*. RPL patients do exhibit increased rates of endometrial colonization with *Ureaplasma urealyticum* (109). In light of the large number of possible infectious agents, it could be cost-effective to treat each partner empirically with azithromycin 1 g or doxycycline 100 mg twice daily for 10 days rather than performing multiple repeat cultures. The risks associated with this approach are low. It is also reasonable to completely omit diagnostic testing and treatment for infectious etiologies in RPL as ACOG recommends that tests for these agents are generally not useful and empiric antibiotics not warranted.

Endocrine

Before considering individual endocrine abnormalities that have been associated with RPL, it is important to highlight that no current evidence exists to support that any asymptomatic endocrine or metabolic diseases directly cause RPL.

Luteal Phase Defect

Luteal phase defect (LPD) is one of the most scrutinized of the proposed endocrine causes of RPL. It is hypothesized that with LPD, a defective corpus luteum produces insufficient amounts of progesterone, preventing implantation or impairing pregnancy maintenance. It is also hypothesized that poor follicular-phase oocyte development often precedes and causes LPD due to disordered estrogen secretion and dysfunction of the corpus luteum. This may also lead to increased luteinizing hormone levels and a hyperandrogenic decidual environment.

The diagnostic criteria for LPD require a histologic lag of more than 2 days between dating of an endometrial specimen and the documented day of the menstrual cycle. This lag must be documented in two cycles. This definition introduces the first line of criticism concerning the relationship of LPD with RPL: there is considerable inter-observer (110–112) and intra-observer (113,114) variations in histologic interpretation of the endometrial biopsy. It has been estimated that had a different pathologist read an individual biopsy, the “in-phase” or “out-of-phase” classifications would change in 20% to 40% of cases (112,115). Although LPD has been more often associated with RPL than with subfertility, the utility of the test is called into question by the fact that no histologic differences can be documented in the biopsy specimens from fertile and infertile women (116). Furthermore, LPD is common in all women tested. Females without a history of pregnancy loss show histologic LPD in up to 50% of single biopsies and 25% of sequential cycles (117).

Proposed treatments for LPD in patients with RPL have included artificial insemination, ovarian stimulation with clomiphene citrate or gonadotropins, administration of hCG, and progesterone supplementation. Administration of hCG to support the corpus luteum was tested in an international, multicentered randomized trial of 75 women. In this trial, injection of 10,000 IU of hCG at the diagnosis of pregnancy followed by 5000 IU weekly was compared with injection of placebo. No significant differences were noted in pregnancy outcomes (118). Abnormal expression of endometrial progesterone receptors or endometrial adhesion molecules during the window of implantation have been detected in women with impaired fertility and/or pregnancy outcomes and these can sometimes be reversed using supplemental progesterone or clomid (119). This restoration of endometrial protein expression may be a biomarker for resumption of normal endometrial function. Further support for the use of progesterone in the treatment of patients with RPL can be found in a recent Cochrane review. This meta-analysis of 15 trials including 2118 women showed no statistically significant difference when progesterone was used for the prevention of isolated spontaneous miscarriage (OR 0.98, 95% CI 0.78–1.24). By contrast, among women with three or more consecutive pregnancy losses, a benefit of progesterone supplementation was noted (OR 0.38, 95% CI 0.2–0.7), regardless of the route of administration and with no adverse effects for mother or baby (120). Although the utility of progesterone supplementation in women with otherwise unexplained RPL is clear, it remains unclear whether the mechanism of progesterone action is through correction of LPD, through immune modulation, or through alternative or additional activities.

Thyroid Disease

While inadequately treated hyper-, hypo-, and subclinical hypothyroidism have been associated with an increased rate of isolated spontaneous pregnancy loss and preterm delivery, no causal relationship has been established with RPL (121). Clinical thyroid dysfunction has also been linked with pregnancy complications such as low birth weight, placental abruption, reduced childhood intelligence quotients, and fetal death (122). Due to these associations, it is recommended that patients receive treatment for thyroid disorders and become euthyroid prior to attempting pregnancy. For additional discussion of this topic, please refer to the previous section on thyroid auto-antibodies and RPL.

Diabetes Mellitus, Insulin Resistance, and Polycystic Ovarian Syndrome

Diabetes mellitus is a risk factor for many adverse pregnancy outcomes. It is well established that poor diabetes control leads to an increased rate of spontaneous loss, while improved glucose control using insulin leads to decreased loss rates (123–125). Tight preconceptional glucose control is essential among RPL patients with diabetes mellitus.

The prevalence of insulin resistance is also higher among RPL patients than controls (27% compared with 9.5%; OR 3.55, 95% CI 1.4–9.01) (126). This may indicate causality. In fact, results from small retrospective studies support this in that treatment of insulin-resistant RPL patients with insulin-sensitizing agents appears to improve pregnancy outcomes (127–129).

Obesity itself has also been proven to carry an increased risk for pregnancy loss. A body mass index of over 30 kg/m² is associated with a 1.2 odds ratio of first-trimester loss (95% CI 1.01–1.46) and a 3.5 odds ratio for RPL (95% CI 1.03–12.01) (130).

Among patients with RPL, ultrasonographic evidence of polycystic-appearing ovaries has been found more commonly than in the general population (131–134). The presence of polycystic ovaries itself did not predict worse outcomes than the finding of normal ovaries (131–134), although among women with polycystic ovarian syndrome, those who suffer pregnancy loss tend to have higher levels of circulating androgens than those who have successful pregnancies (134).

In summary, while no single treatment has definitively proven to improve pregnancy outcomes among patients with disorders of glucose metabolism, evidence is mounting that weight loss and improved glucose control using insulin sensitizers or optimized insulin regimens will probably increase pregnancy maintenance.

Decreased Ovarian Reserve

The prevalence of elevated FSH levels among RPL patients is similar to that of an infertility population (135). Women with unexplained RPL, however, have a greater incidence of elevated day 3 FSH levels than RPL patients with an identified etiology. Among 57 women with three or more spontaneous pregnancy losses, 31% of those with unexplained losses (n = 36) had day 3 FSH levels greater than 10 mIU/mL compared with only 5% of women with explained losses (136). Testing for ovarian reserve among older RPL patients may help to determine the level of urgency in diagnostic testing and interventions.

Table 6 Nonsteroidal Anti-inflammatory Drug Use and Risk of Pregnancy Loss

	Hazard ratio (95% CI)
Users overall	1.8 (1.0–3.2)
Gestational age at first use:	
At conception	5.6 (2.3–13.7)
After conception	1.2 (0.5–2.6)
Duration of use:	
≤1 week	1.3 (0.7–2.6)
>1 week	8.1 (2.8–23.4)
Abbreviation: CI, confidence interval. Source: Adapted from Ref. 138.	

Hyperprolactinemia

Elevated levels of PRL induce LPDs and may decrease progesterone production by the corpus luteum. Hyperprolactinemia is also thought to interact with the hypothalamic–pituitary–ovarian axis to cause inadequate follicular development and oocyte maturation. After evaluation for intracranial lesions, treatment of elevated serum PRL levels in women experiencing RPL can be safely undertaken with bromocriptine or cabergoline. Pharmacologic normalization of the PRL levels has been proven to improve pregnancy success rates among RPL patients (137).

Environmental/Occupational Factors and Habits

No associations have been clearly established between RPL and environmental factors, occupational exposures, or work itself. Furthermore, exercise has not been proven to increase the rate of sporadic loss, though no studies have been conducted involving recurrent loss patients.

It is important to recognize, however, that some environmental exposures lead to a slight, but statistically significant, increase in the rate of isolated spontaneous pregnancy losses including nonsteroidal anti-inflammatory drugs (Table 6), tobacco, alcohol, and heavy caffeine use. These may act in a dose-dependent fashion or synergistically. Their discussion with RPL patients must be carefully approached to avoid generating guilt. It may be useful to discuss these factors as methods to maximize desirable pregnancy outcomes.

Tobacco Abuse

Smokers incur a 1.4- to 1.8-fold increase in their risk of pregnancy loss (139,140), and secondhand smoke leads to a 1.52- to 2.18-fold increase in the risk (141). It remains important to encourage both partners to attempt smoking cessation.

Alcohol

Drinking more than one alcoholic beverage per day carries an adjusted odds ratio for spontaneous pregnancy loss of 4.84 (95% CI 2.87–8.16) (142). Additionally, the average number of daily drinks is directly proportional to the risk of second-trimester pregnancy loss, irrespective of age, parity, race, marital status, smoking, or the number of previous spontaneous losses or induced abortions (143) (Table 7).

Coffee and Caffeine

Excessive caffeine intake has an established link to an increase in the risk of isolated spontaneous pregnancy loss of fetuses with normal karyotypes among nonsmokers (144).

Table 7 Alcohol Use and Age-Adjusted Relative Risk of Pregnancy Loss

Average no. of drinks	First-trimester loss rate	Second-trimester loss rate
<1/day	1.12 (ns)	1.03 (ns)
1–2/day	1.15 (ns)	1.98 ($p < 0.01$)
≥3/day	1.15 (ns)	3.53 ($p < 0.01$)

Abbreviation: ns, non-significant p value. Source: Adapted from Ref. 143.

Table 8 Caffeine Intake and Risk of Pregnancy Loss

Caffeine intake	Pregnancy loss risk
100–299 mg/d	RR 1.3 (95% CI 0.9–1.8)
300–499 mg/d	RR 1.4 (95% CI 0.9–2)
≥500 mg/d	RR 2.2 (95% CI 2.3–3.8)
≥375 mg/d	Adjusted OR 2.21 (95% CI 1.53–3.18) (142)

Abbreviations: RR, relative risk; OR, odds ratio.

Table 9 Etiology-Specific Interventions for Patients with Recurrent Pregnancy Loss

Disorder	Intervention
Anatomic	
Müllerian anomalies	• Hysteroscopic resection of septa, adhesions, submucosal fibroids, and polyps
Intrauterine synechiae	• Myomectomy for intramural and subserosal fibroids >5 cm
Asherman's Syndrome	
Leiomyomata	
Endometrial polyps	
Genetic	
Parental balanced translocations	• Genetic counseling
	• IVF with pre-implantation genetic diagnosis
	• Donor gametes
Thrombophilic (heritable)	
	• Combined thrombophilic defects—therapeutic anticoagulation
	• Isolated defect and no personal or strong family history of thrombotic complications—prophylactic anticoagulation
	• Hyperhomocysteinemia—supplemental folic acid (0.4–1.0 mg/day), vitamin B ₆ (6 mg/day), and possibly vitamin B ₁₂ (0.025 mg/day)
Immunologic	
Antiphospholipid antibody syndrome	• Low-dose aspirin plus prophylactic heparin in women without a history of a systemic autoimmune disease like SLE or a history of thrombosis
	• Full anticoagulation if history of thrombosis or systemic autoimmune disease
Endocrine	
PCOS	• Metformin
Hypothyroidism	• Thyroid-hormone replacement
Luteal phase defect/unexplained	• Progesterone supplementation
Diabetes mellitus	• Appropriate management of diabetes, insulin if indicated
Other	
Environmental exposures	• Limit exposures to maximize pregnancy outcomes (e.g., tobacco, alcohol, caffeine)
All patients/unexplained	• Progesterone supplementation
	• Daily aspirin (81–100 mg), if losses at greater than 13 weeks of gestation

Abbreviations: IVF, in vitro fertilization; LMWH, low molecular-weight heparin; SLE, systemic lupus erythematosus; PCOS, polycystic ovarian syndrome.

The half-life of caffeine is halved in smokers and is doubled in users of oral contraceptives. See Table 8 for the caffeine dose-related increases in the risk of spontaneous pregnancy loss.

Irradiation

The incidence of chromosomal anomalies among spontaneously expelled ova is higher among couples in which either the female or the male was exposed to irradiation prior to conception (145). These data provide validity to the generally accepted recommendation that both partners avoid irradiation when attempting pregnancy.

Environmental Toxins

Anesthetic gases, tetrachloroethylene (a dry-cleaning chemical), lead, mercury, and isotretinoin (Accutane) have all been associated with an increased rate of spontaneous pregnancy loss. Organic solvents have rarely been linked to sporadic loss.

Unexplained

Much research has been devoted to possible therapeutic options for couples with unexplained RPL. Two recent studies have evaluated the role of preimplantation genetic screening for couples with idiopathic RPL. They have yielded conflicting results. Munne et al. studied 58 couples with unexplained RPL among whom the female partner was 35 years of age and older. The authors performed PGS for chromosomes X, Y, 13, 15, 16, 17, 18, 21, and 22 and transferred up to four embryos (euploid for these particular chromosomes). The subsequent miscarriage rate after identification of a gestational sac was 15.7%, which was lower than expected. They also found the “take-home” baby rate per retrieval to be 36% (146). Work by Platteau and colleagues (147) included 49 women with idiopathic RPL in a prospective cohort study. Their embryos were tested for abnormalities in chromosomes X, Y, 13, 16, 18, 21, and 22. For women less than age 37, the pregnancy rate per cycle initiated was 23%, whereas for women at or beyond

37 years of age, the rate dropped drastically to 3%, with 44% and 67% aneuploidy rates, respectively. Like Shahine and colleagues (38), these researchers concluded that no therapeutic evidence currently exists to support the use of in vitro fertilization with or without PGS for idiopathic RPL patients. Oocyte donation may be effective (148). Randomized controlled trials are needed.

Other studies have supported or refuted the benefit of various other treatment options. In considering the following, keep in mind that a meta-analysis from 1995 (149) concluded that 60% to 70% of unexplained RPL couples will have success with the next pregnancy in the absence of intervention; this provides both a frame of reference for evaluation of treatment success and an encouraging fact with which to counsel patients. After negative testing with karyotyping, HSG or hysteroscopy, and antiphospholipid antibodies for second-trimester losses, patients with recurrent loss beyond 13 weeks had an improved live-birth rate with daily low-dose aspirin (OR 1.88; 95% CI 1.04–3.37) (150). Providing supportive care to idiopathic first-trimester RPL couples is perhaps one of the best interventions, leading to a live-birth rate near 75% (vs. 50% of those not attending an early pregnancy clinic; $p = 0.002$) (4). Appropriately timed intercourse may also improve outcomes as intercourse remote from ovulation has been associated with an increase spontaneous loss rate due to chromosomal anomalies (145,151). Requiring bed rest for RPL patients during pregnancy is not supported by evidence (RR 1.54, 95% CI 0.92–2.58), although bed rest alone did perform better when compared with supplemental hCG without bed rest in a Cochrane review (RR 2.5, 95% CI 1.22–5.11) (152). An additional Cochrane review has been performed to evaluate the utility of hCG administration to treat women with a history of unexplained RPL. Randomized trials comparing the use of hCG in early pregnancy versus placebo or no treatment for women with two or more miscarriages ($n = 180$) showed a decreased risk of pregnancy loss among hCG-treated patients (OR 0.26, 95% CI 0.14–0.52) (153). Readers are encouraged by the authors of this study to interpret the data cautiously due to a large influence on the data by the two weakest studies. These authors therefore conclude that “there is not enough evidence to evaluate the use of hCG during pregnancy to prevent miscarriage” in patients with unexplained RPL (153).

It has been shown in meta-analyses that treatment of unexplained RPL with progesterone supplementation is useful (see above). We recommend the use of vaginal progesterone, typically 100 mg twice daily, starting 3 days after ovulation during cycles in which the couple is attempting conception. Progesterone supplementation is thought to have implications in treating both immune and luteal phase aberrancies though specific mechanisms are unclear.

POSTCONCEPTION EVALUATION

Close monitoring of subsequent pregnancies leads to an increased pregnancy success rate among patients with a history of RPL (154). These couples are prone to heightened senses of anger, depression, anxiety, and even psychoses. Careful evaluation for signs and symptoms of these disorders is warranted. The availability of counseling services, with or

without the use of support groups and/or a reproductive psychiatrist, is strongly encouraged.

SUMMARY

The assessment and management of patients with RPL continue to be somewhat controversial and both are likely to remain so. The disorder itself is multifactorial and the baseline rate of isolated pregnancy losses secondary to spontaneous fetal aneuploidy is high. The prognosis for most patients, even in the absence of a defined etiology, is remarkably good, making assessment of the utility of a given diagnostic test or intervention difficult in the absence of very large trials.

Evidence does exist for etiologies that should be excluded and effective treatment regimes for most diagnosed etiologies are available. After a thorough evaluation, if the resulting diagnosis is unexplained RPL, interventions such as progesterone supplementation, aspirin therapy (in selected patients), conception timing, and close clinical follow-up during early pregnancy have merit. Table 2 lists our recommendations for useful diagnostic testing in patients with a history of RPL. Table 9 lists etiology-specific interventions.

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