

# Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy

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*Spontaneous pregnancy loss is a surprisingly common occurrence, with approximately 15% of all clinically recognized pregnancies resulting in pregnancy failure. Recurrent pregnancy loss (RPL) has been inconsistently defined. When defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period, it affects approximately 1% to 2% of women. This review highlights the current understanding of the various etiologies implicated in RPL, including factors known to be causative, as well as those implicated as possible causative agents. The appropriate diagnostic evaluation, therapy, and prognosis are also addressed.*

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**Key words:** Recurrent pregnancy loss • Spontaneous abortion • Habitual abortion

Spontaneous pregnancy loss is a surprisingly common occurrence. Whereas approximately 15% of all clinically recognized pregnancies result in spontaneous loss, there are many more pregnancies that fail prior to being clinically recognized. Only 30% of all conceptions result in a live birth.<sup>1</sup>

Spontaneous pregnancy loss can be physically and emotionally taxing for couples, especially when faced with recurrent losses. Recurrent pregnancy loss (RPL), also referred to as *recurrent miscarriage* or *habitual abortion*, is historically defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period. Based on the incidence of sporadic pregnancy loss, the incidence of recurrent pregnancy loss should be approximately 1 in 300 pregnancies. However,

epidemiologic studies have revealed that 1% to 2% of women experience recurrent pregnancy loss.<sup>2</sup> Defining RPL as a clinical entity requiring diagnostic testing and therapeutic intervention rests on knowledge of the elevation of risk for subsequent fetal loss and the probability of finding a treatable etiology for the disorder. Although no reliable published data have estimated the probability of finding an etiology for RPL in a population with 2 versus 3 or more miscarriages, the best available data suggest that the risk of miscarriage in subsequent pregnancies is 30% after 2 losses, compared with 33% after 3 losses among patients without a history of a live birth.<sup>3</sup> This strongly suggests a role for evaluation after just 2 losses in patients with no prior live births. An earlier evaluation may be further indicated if fetal cardiac activity was identified prior to a loss, the woman is older than 35 years, or the couple has had difficulty in conceiving.

The high baseline rate of spontaneous isolated and recurrent pregnancy losses in the general population, the lack of consistent definition for RPL, limited access to tissues allowing study of the disorder, and the remarkably good prognosis for live birth among patients with RPL combine to frustrate aims at diagnostic and therapeutic recommendations. At present, there exist a small number of accepted etiologies for RPL (Figure 1). These include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, and antiphospholipid antibody syndrome (APS). Other probable or possible etiologies include additional endocrine disorders, heritable and/or acquired thrombophilias, immunologic abnormalities, infections, and environmental factors. After evaluation for these causes (Table 1), approximately half of all cases will remain unexplained.

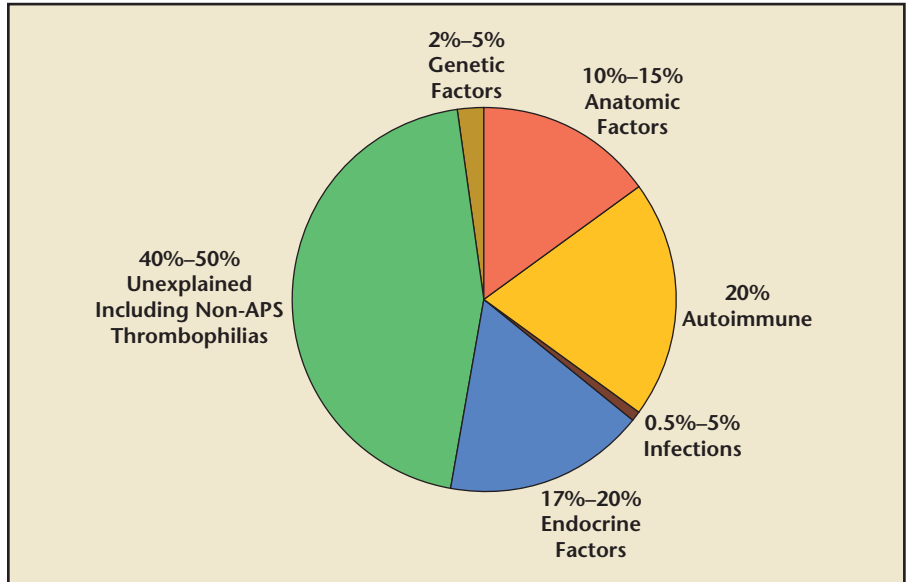


Figure 1. Etiology of recurrent pregnancy loss. APS, antiphospholipid antibody syndrome.

**Table 1**  
Suggested Diagnostic Evaluation of Recurrent Pregnancy Loss Based on Etiology

Etiology	Suggested Diagnostic Evaluation
Genetic	Parental karyotype
Anatomic	HSG or office hysteroscopy 2D or 3D ultrasound Saline-infusion sonohysterography
Endocrine	TSH Possible testing for insulin resistance, serum prolactin level, ovarian reserve testing, antithyroid antibodies
Infectious	No evaluation recommended unless patient has evidence of chronic endometritis/cervicitis on examination, or is immunocompromised
Autoimmune	Anticardiolipin antibody levels (IgG and IgM) Lupus anticoagulant
Non-APS thrombophilias	Homocysteine, factor V Leiden, prothrombin promoter mutation, activated protein C resistance

APS, antiphospholipid antibody syndrome; HSG, hysterosalpingography; IgG, immunoglobulin G; IgM, immunoglobulin M; TSH, thyroid-stimulating hormone.

**Genetic Etiologies**

Approximately 2% to 4% of RPL is associated with a parental balanced structural chromosome rearrangement, most commonly balanced reciprocal or

Robertsonian translocations. Additional structural abnormalities associated with RPL include chromosomal inversions, insertions, and mosaicism. Single gene defects, such as those

associated with cystic fibrosis or sickle cell anemia, are seldom associated with RPL.

Appropriate evaluation of RPL should include parental karyotyping. Genetic counseling is indicated in all cases of RPL associated with parental

ing RPL is unclear. The presence of intrauterine adhesions, sometimes associated with Asherman syndrome, may significantly impact placentation and result in early pregnancy loss. Intramural fibroids larger than 5 cm, as well as submucosal fibroids of any

endocrinologic disorders implicated in approximately 17% to 20% of RPL.<sup>2,8</sup>

Traditionally, LPD has been proposed to result from inadequate production of progesterone by the corpus luteum and endometrial maturation insufficient for proper placentation. It is diagnosed when there is a persistent lag of longer than 2 days in the histologic development of the endometrium compared with the day of the menstrual cycle. Today, the true role of LPD in RPL is controversial and endometrial biopsies for LPD diagnosis are rarely indicated. Some studies have noted abnormal elevations in luteinizing hormone or in androgens (both features associated with PCOS) among patients experiencing RPL, suggesting that these abnormalities may result in premature aging of the oocyte and/or dyssynchronous maturation of the endometrium.<sup>9,10</sup> This hypothesis is not without question. Studies have found evidence of PCOS in at least 40% of women with RPL.<sup>11</sup> Insulin resistance and the resultant hyperinsulinemia that is often present in cases of PCOS (as well as type II diabetes mellitus) may also play a role in RPL, as evidenced by the decreased rate of spontaneous

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chromosomal abnormalities. Depending on the particular diagnosis, directed therapy may include in vitro fertilization with preimplantation genetic diagnosis. The use of donor gametes may be suggested in cases involving genetic anomalies that always result in embryonic aneuploidy (ie, Robertsonian translocations involving homologous chromosomes).

### Anatomic Etiologies

Anatomic abnormalities account for 10% to 15% of cases of RPL and are generally thought to cause miscarriage by interrupting the vasculature of the endometrium, prompting abnormal and inadequate placentation. Thus, those abnormalities that might interrupt the vascular supply of the endometrium are thought to be potential causes of RPL. These include congenital uterine anomalies, intrauterine adhesions, and uterine fibroids or polyps. Although more readily associated with second trimester losses or preterm labor, congenital uterine anomalies also play a part in RPL. The uterine septum is the congenital uterine anomaly most closely linked to RPL, with as much as a 76% risk of spontaneous pregnancy loss among affected patients.<sup>4</sup> Other Müllerian anomalies, including unicornuate, didelphic, and bicornuate uteri have been associated with smaller increases in the risk for RPL.<sup>4,5</sup> The role of the arcuate uterus in caus-

size, can cause RPL.<sup>6</sup> Although congenital anomalies caused by prenatal exposure to diethylstilbestrol are clearly linked to RPL, this is becoming less clinically relevant as most affected patients move beyond their reproductive years.

Diagnostic evaluation for uterine anatomic anomalies should include office hysteroscopy or hysterosalpingography (HSG). Hysteroscopic resection of intrauterine adhesions and intrauterine septa are indicated if these abnormalities are identified. Patients undergoing successful hysteroscopic septum resection seem to enjoy near normal pregnancy outcomes, with term delivery rates of approximately 75% and live birth rates approximating 85%.<sup>7</sup> Myomectomy should be

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considered in cases of submucosal fibroids or any type fibroids larger than 5 cm. Resection has been shown to significantly improve live birth rates from 57% to 93%.<sup>6</sup> Myomectomy can be performed via open laparotomy, laparoscopy, or hysteroscopy.

### Endocrine Etiologies

Luteal phase defect (LPD), polycystic ovarian syndrome (PCOS), diabetes mellitus, thyroid disease, and hyperprolactinemia are among the en-

pregnancy loss when patients undergo therapy with the insulin-sensitizing drug, metformin.<sup>12</sup> Poorly controlled type 1 diabetes mellitus is also associated with an increased risk of spontaneous abortion.<sup>13</sup> Although untreated hypothyroidism is clearly associated with spontaneous miscarriage and RPL,<sup>14</sup> the connection between antithyroid antibodies and RPL in euthyroid patients is currently under great debate.<sup>15,16</sup> There are data to suggest that euthyroid women with

antithyroid antibodies, especially those undergoing fertility therapy, are likely to become clinically hypothyroid very soon after the onset of pregnancy.<sup>17</sup> Because pregnancy outcomes in these women may improve with early (possibly prenatal) thyroid hormone replacement,<sup>18</sup> similar approaches are presently being studied among women with RPL.

Evaluation of endocrine disorders should include measurement of the thyroid-stimulating hormone (TSH)

### *Therapy with insulin-sensitizing agents for the treatment of RPL that occurs in the presence of polycystic ovarian syndrome has recently gained popularity.*

level. Other testing that might be indicated based on the patient's presentation include insulin resistance testing, ovarian reserve testing, serum prolactin in the presence of irregular menses, antithyroid antibody testing, and, very rarely, luteal phase endometrial biopsies. Therapy with insulin-sensitizing agents for the treatment of RPL that occurs in the presence of PCOS has recently gained popularity.

### **Infectious Etiologies**

Certain infections, including *Listeria monocytogenes*, *Toxoplasma gondii*, rubella, herpes simplex virus (HSV), measles, cytomegalovirus, and coxsackieviruses, are known or suspected to play a role in sporadic spontaneous pregnancy loss. However, the role of infectious agents in recurrent loss is less clear, with a proposed incidence of 0.5%<sup>2</sup> to 5%.<sup>8</sup> The proposed mechanisms for infectious causes of pregnancy loss include: (1) direct infection of the uterus, fetus, or placenta, (2) placental insufficiency, (3) chronic endometritis or endocervicitis, (4) amnionitis, or (5) infected intrauterine device. Because most of these are isolated events, it appears that there is a limited role for infections as a

causative factor in RPL. Those particular infections speculated to play a role in RPL include mycoplasma, ureaplasma, *Chlamydia trachomatis*, *Listeria monocytogenes*, and HSV.<sup>19</sup> The most pertinent risk for RPL secondary to infection is chronic infection in an immunocompromised patient.

Evaluation and therapy should be tailored to individual cases. If a patient with RPL has a condition that leaves her immunocompromised or a history suggestive of sexually trans-

mitted diseases, evaluation for chronic infections may be warranted. There is no evidence that routine infectious evaluation is appropriate or productive.

### **Immunologic Etiologies**

Because a fetus is not genetically identical to its mother, it is reasonable to infer that there are immunologic events that must occur to allow the mother to carry the fetus throughout gestation without rejection. In fact, there have been at least 10 such mechanisms proposed.<sup>20</sup> It therefore follows that there may be abnormalities within these immunologic mechanisms that could lead to both sporadic and recurrent pregnancy loss. Despite the intense interest in this potential etiology for RPL, there is no consensus on appropriate diagnostic workup or therapy. Therapies such as paternal leukocyte immunization, intravenous immune globulin, third-party donor cell immunization, and trophoblast membrane infusions have been shown to provide no significant improvement in live birth rates, and are only available for use in approved studies.<sup>3,21</sup>

One specific autoimmune disorder, APS, requires particular attention as it

has been clearly linked with many poor obstetric outcomes, including RPL. The discussion of APS could also appear within the context of thrombophilias, given that it is the most frequently acquired risk factor for thrombophilia, with a prevalence of 3% to 5% in the general population. APS is characterized by the presence of at least 1 clinical and 1 laboratory criterion<sup>22</sup>:

- Clinical
  - 1 or more confirmed episodes of vascular thrombosis (venous, arterial, or small vessel)
  - Pregnancy complications including either 3 or more consecutive pregnancy losses at less than 10 weeks of gestation, 1 or more fetal deaths at greater than 10 weeks of gestation, or at least 1 preterm birth (< 34 weeks) due to severe preeclampsia or placental insufficiency
- Laboratory (repeated at least 2 times, more than 12 weeks apart)
  - Positive plasma levels of the anti-cardiolipin antibodies (IgG or IgM) at medium to high levels
  - Positive plasma levels of the lupus anticoagulant

The mechanisms by which APS results in RPL are incompletely understood. A complete evaluation for RPL should include testing for anticardiolipin antibodies and lupus anticoagulant. Once diagnosed, treatment recommendations include low-dose aspirin (LDA, 81-100 mg/d) plus prophylactic low-molecular-weight heparin in otherwise healthy women (ie, absence of a systemic autoimmune disease such as systemic lupus erythematosus, or a history of thrombosis). LDA should be started before conception or with a positive pregnancy test. Heparin should be started with a positive pregnancy test.<sup>22</sup> Heparin is a large complex of molecules that do not cross the placenta and, as such, is regarded as safe during pregnancy.

### Thrombotic Etiologies

Both inherited and combined inherited/acquired thrombophilias are common, with more than 15% of the white population carrying an inherited thrombophilic mutation.<sup>23</sup> The most common of these are the factor V Leiden mutation, mutation in the promoter region of the prothrombin gene, and mutations in the gene encoding methylene tetrahydrofolate reductase (MTHFR). These common mutations are associated with mild thrombotic risks, and it remains controversial whether homozygous MTHFR mutations are associated with vascular disease at all.<sup>24</sup> In contrast, more severe thrombophilic deficiencies, such as those of antithrombin and protein S, are much less common in the general population.

The potential association between RPL and heritable thrombophilias is based on the theory that impaired placental development and function secondary to venous and/or arterial thrombosis could lead to miscarriage. Based on studies that have shown maternal blood to begin flowing within the intervillous spaces of the placenta at approximately 10 weeks of gestation, the link between thrombophilias and pregnancy losses at greater than 10 weeks of gestation is more widely accepted than a link to those that occur prior to 10 weeks of gestation. However, evidence that the transfer of nutrition from the maternal blood to the fetal tissues depends on uterine blood flow, and thus may be affected by thrombotic events occurring there, suggests a role for thrombophilias in pregnancy losses regardless of gestational age.<sup>25</sup>

The heritable thrombophilias most often linked to RPL include hyperhomocysteinemia resulting from MTHFR mutations, activated protein C resistance associated with factor V Leiden mutations, protein C and protein S deficiencies, prothrombin promoter

mutations, and antithrombin mutations. Acquired thrombophilias associated with RPL include hyperhomocysteinemia and activated protein C resistance. Although definite causative links between these heritable and acquired conditions have yet to be solidified, the best available data suggest testing for factor V Leiden mutation, protein S levels, prothrombin promoter mutations, homocysteine levels, and global activated protein C resistance, at least in white women.<sup>26-28</sup>

Appropriate therapy for heritable or acquired thrombophilias should be initiated once the disorder is diagnosed. Therapy is disorder specific and includes (1) supplemental folic acid for those patients with hyperhomocysteinemia, (2) prophylactic anticoagulation in cases of isolated defects with no personal or family history of thrombotic complications, and (3) therapeutic anticoagulation in cases of combined thrombophilic defects. Homocysteine levels should be retested after initial treatment, and prophylactic anticoagulation considered when hyperhomocysteinemia is refractory to dietary intervention.<sup>29</sup>

### Environmental Etiologies

Because of its propensity to result in feelings of responsibility and guilt, patients are often particularly concerned about the possibility that envi-

to be retrospective and confounded by alternative or additional environmental exposures.<sup>3,8</sup>

Three particular exposures—smoking, alcohol, and caffeine—have gained particular attention, and merit special consideration given their widespread use and modifiable nature. Although maternal alcoholism (or frequent consumption of intoxicating amounts of alcohol) is consistently associated with higher rates of spontaneous pregnancy loss, a connection with more moderate ingestion remains tenuous.<sup>30</sup> Studies linking moderate alcohol intake with pregnancy loss have shown an increase in risk when more than 3 drinks per week are consumed during the first trimester (odds ratio [OR] 2.3)<sup>31</sup> or more than 5 drinks per week are consumed throughout pregnancy (OR 4.8).<sup>32</sup> It seems logical that cigarette smoking could increase the risk of spontaneous abortion based on the ingestion of nicotine, a strong vasoconstrictor that is known to reduce uterine and placental blood flow. However, the link between smoking and pregnancy loss remains controversial, as some, but not all, studies have found an association.<sup>32-34</sup> Although still not undisputed,<sup>35</sup> there appears some evidence that caffeine, even in amounts as low as 3 to 5 cups of coffee per day, may increase the risk of spontaneous pregnancy loss

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*Patients are often particularly concerned about the possibility that environmental exposures may have caused their pregnancy losses.*

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ronmental exposures may have caused their pregnancy losses. Links between sporadic and/or RPL and occupational and environmental exposures to organic solvents, medications, ionizing radiation, and toxins have been suggested, although the studies performed are difficult to draw strong conclusions from because they tend

with a dose-dependent response.<sup>32,36,37</sup> The association of caffeine, alcohol, and nicotine intake with recurrent pregnancy loss is even weaker than their associations with sporadic loss.

### Unexplained Etiologies

Directed interventions for patients with RPL are outlined in Table 2.

**Table 2**  
**Therapeutic Interventions for Recurrent Pregnancy Loss Based on Etiology**

Disorder	Therapy
<b>Genetic</b> Balanced translocations	Genetic counseling IVF with preimplantation genetic diagnosis Donor gametes
<b>Anatomic</b> Müllerian anomalies Asherman syndrome Leiomyomas	Hysteroscopic resection of septa, adhesions, and submucosal fibroids Myomectomy for those intramural and subserosal fibroids >5 cm
<b>Endocrine</b> PCOS Hypothyroidism Luteal phase defect/unexplained Diabetes mellitus	Metformin Thyroid hormone replacement Progesterone supplementation Appropriate management of diabetes, insulin if indicated
<b>Infectious</b>	Antibiotics for endometritis or underlying infection
<b>Autoimmune</b> APS	Low-dose aspirin plus prophylactic LMWH in women without a history of a systemic autoimmune disease such as SLE, or a history of thrombosis
<b>Other</b> Non-APS thrombophilias Environmental exposures	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/d), vitamin B <sub>6</sub> (6 mg/d), and possibly vitamin B <sub>12</sub> (0.025 mg/d) Consider prophylactic anticoagulation if hyperhomocysteinemia refractory to dietary intervention Limit exposures that could be factors (eg, tobacco, alcohol, caffeine)

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

However, when all known and potential causes for RPL are accounted for, almost half of patients will remain without a definitive diagnosis. The optimal management of these patients is often as unclear as the etiology of their

only been proven to increase live birth rates among those women with previous miscarriages beyond 13 weeks of gestation.<sup>39,40</sup> In fact, the most effective therapy for patients with unexplained RPL is often the most simple:

*The most effective therapy for patients with unexplained RPL is often the most simple: antenatal counseling and psychological support.*

RPL. Progesterone has been shown to be beneficial in decreasing the miscarriage rate among women who have experienced at least 3 losses.<sup>38</sup> LDA has also been investigated as a potential therapy for unexplained RPL. Its use prior to and during pregnancy has

antenatal counseling and psychological support. These measures have been shown to have subsequent pregnancy success rates of 86% when compared with success rates of 33% in women provided with no additional antenatal care.<sup>41</sup>

### Prognosis

Although the diagnosis of RPL can be quite devastating, it can be helpful for the physician and patient to keep in mind the relatively high likelihood that the next pregnancy will be successful. A particular individual's prognosis will depend on both the underlying cause for pregnancy losses and the number of prior losses. Correction of endocrine disorders, APA, and anatomic anomalies enjoy the highest success rates, approximately 60% to 90%. Patients with a cytogenetic basis for loss experience a wide range of success (20%-80%) that depends on the type of abnormality present.<sup>42,43</sup> Overall, the prognosis for

RPL is encouraging. Even with the diagnosis of RPL and as many as 4 to 5 prior losses, a patient is more likely to carry her next pregnancy to term than to have another loss.<sup>44</sup> ■

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## Main Points

- Spontaneous pregnancy loss is common, with approximately 15% of all clinically recognized pregnancies resulting in miscarriage.
- When recurrent pregnancy loss (RPL) is defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period, 1% to 2% of women will be affected.
- Because the risk of subsequent miscarriages is similar among women that have had 2 versus 3 miscarriages, and the probability of finding a treatable etiology is similar among the 2 groups, most experts agree that there is a role for evaluation after 2 losses.
- Accepted etiologies for RPL include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, and the antiphospholipid antibody syndrome (APS). Other probable or possible etiologies include additional endocrine disorders, heritable and/or acquired thrombophilias, immunologic abnormalities, and environmental causes. After evaluation for these causes, more than 33% of all cases will remain unexplained.
- Diagnostic evaluation should include maternal and paternal karyotypes, assessment of the uterine anatomy, and evaluation for thyroid dysfunction, APS, and selected thrombophilias. In some women, evaluation for insulin resistance, ovarian reserve, antithyroid antibodies, and prolactin disorders may be indicated.
- Therapy should be directed toward any treatable etiology, and may include in vitro fertilization with preimplantation genetic diagnosis, use of donor gametes, surgical correction of anatomic abnormalities, correction of endocrine disorders, and anticoagulation or folic acid supplementation.
- In cases of unexplained RPL, progesterone has been shown to be beneficial in decreasing the miscarriage rate in women who had experienced at least 3 losses. Low-dose aspirin benefits those with a history of losses at more than 13 weeks of gestation.
- Antenatal counseling and psychological support should be offered to all couples experiencing RPL, as these measures have been shown to increase pregnancy success rates.
- Prognosis will depend on the underlying cause for pregnancy loss and the number of prior losses. Patients and physicians can be encouraged by the overall good prognosis, as even after 4 consecutive losses a patient has a greater than 60% to 65% chance of carrying her next pregnancy to term.

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