Recurrent pregnancy loss: Management

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

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Feb 2021. | **This topic last updated:** Feb 18, 2021.

INTRODUCTION

High-quality data on management of recurrent pregnancy loss (RPL) are limited; therefore, therapeutic recommendations are largely based upon clinical experience and data from observational studies. Nevertheless, the prognosis for a successful future pregnancy is generally good: The overall live birth rates after normal and abnormal diagnostic evaluations for RPL are 77 and 71 percent, respectively [1].

Therapeutic intervention is guided by the underlying cause of RPL. In all cases, emotional support is important in caring for these often anxious couples, and may enhance therapeutic success [2].

Management of RPL will be discussed here. Causes and evaluation of RPL are reviewed separately. (See "Recurrent pregnancy loss: Definition and etiology" and "Recurrent pregnancy loss: Evaluation".)

PARENTAL KARYOTYPE ABNORMALITY

Couples in whom chromosomal abnormalities are discovered in one or both partners or the abortus are generally referred for genetic counseling [3]. They should receive information regarding the probability of having a chromosomally normal or abnormal conception in the future. In the latter case, the risk of miscarriage and bearing a chromosomally abnormal offspring who may be phenotypically normal or abnormal and a carrier of a chromosomal defect should be discussed. The magnitude of these risks varies according to the specific chromosomal abnormality and the sex of the carrier parent. (See "Chromosomal translocations, deletions, and inversions" and "Congenital cytogenetic abnormalities".)

Couples with karyotypic abnormalities may choose to undergo prenatal genetic studies, such as amniocentesis or chorionic villus sampling, to determine the fetal karyotype. Pregnancy termination is an option if the fetus is affected. In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) can be used to avoid transfer and implantation of an affected embryo [4,5]. PGD improves the pregnancy outcome of translocation carriers with a history of repeated pregnancy loss [6]. On the other hand, this procedure reduces the live birth rate after IVF if preimplantation testing is performed solely because of advanced maternal age [7]. (See "Preimplantation genetic testing".)

Gamete donation (egg or sperm), surrogacy, and adoption are methods of preventing conception of an affected embryo. The choice depends upon the specific abnormality and parental preference. (Refer to individual topic reviews on these topics).

UTERINE ABNORMALITIES

Uterine abnormalities are managed surgically if the defect is a surgically correctable cause of pregnancy loss, such as a uterine septum, intrauterine adhesions, or submucosal myoma. These conditions can be treated

hysteroscopically. (See "Congenital uterine anomalies: Surgical repair" and "Intrauterine adhesions: Clinical manifestation and diagnosis".)

There are no randomized trials evaluating pregnancy outcome after surgical correction of uterine anomalies. In a classic observational series, repair of bicornuate and septate uteri reduced the abortion rate from 84 percent (before surgery) to 12 percent (after surgery) [8]. The problem with this and similar studies is use of patients as their own controls [9]. However, studies using better control groups also support the efficacy of surgical correction of uterine defects, especially for uterine septum.

- In a prospective study, the probability of conception and live birth in women after hysteroscopic metroplasty was significantly higher than in women with unexplained infertility (live birth rate 34.1 versus 18.9 percent) [10].
- In another study, the effect of uterine septum on IVF outcome was investigated in 289 embryo transfers before and 538 embryo transfers after hysteroscopic resection of uterine septum and in a control group that underwent two consecutive embryo transfers [11]. For women with a large septum, the live birth rate was 2.7 percent before surgery and 15.6 percent after surgery versus 20.9 percent in the control group. For women with a small septum, the live birth rate was 2.8 percent before surgery and 18.6 percent after surgery versus 21.9 percent in the control group.

The value of prophylactic cervical cerclage in women with a uterine anomaly, but no history of second trimester pregnancy loss, is controversial [12]. We do not advocate prophylactic cervical cerclage in women with no history of cervical insufficiency. (See "Cervical insufficiency" and "Transvaginal cervical cerclage" and "Transabdominal and laparoscopic cervicoisthmic cerclage".)

A gestational carrier is an option for women with irreparable uterine defects. (See "Gestational carrier pregnancy".)

ANTIPHOSPHOLIPID SYNDROME

Drugs such as aspirin and heparin appear to improve pregnancy outcome in women with antiphospholipid syndrome who have recurrent fetal losses. In contrast, such therapy is not associated with improved outcomes in women without antiphospholipid antibody syndrome. (See "Antiphospholipid syndrome: Pregnancy implications and management in pregnant women" and 'Aspirin with or without heparin' below.)

SUSPECTED IMMUNOLOGIC DYSFUNCTION

Although no alloimmune mechanism has been proven to cause RPL, several immunologic treatments have been advocated to improve the live birth rate in women with previous unexplained RPL. None are effective, and some appear to be harmful [13-17]. (See 'Immune therapy with intravenous immunoglobulin' below and 'Glucocorticoids' below.)

THYROID DYSFUNCTION AND DIABETES MELLITUS

Women with overt thyroid disease or diabetes mellitus should be treated, as medically appropriate, since these disorders can result in serious sequelae. (See "Overview of general medical care in nonpregnant adults with diabetes mellitus" and "Graves' hyperthyroidism in nonpregnant adults: Overview of treatment" and "Treatment of primary hypothyroidism in adults" and "Subclinical hypothyroidism in nonpregnant adults".)

Women with elevated serum thyroid peroxidase antibody concentrations are at high risk of developing hypothyroidism in the first trimester and autoimmune thyroiditis postpartum, and should be followed appropriately [18]. Euthyroid women with high serum thyroid peroxidase antibody concentrations may benefit from treatment with thyroid hormone during pregnancy as this therapy may reduce the risk of miscarriage and preterm birth [19]. In

a randomized trial, administration of levothyroxine (median dose 50 mcg daily) to early pregnant euthyroid women with positive thyroid peroxidase antibodies decreased the miscarriage rate from 13.8 to 3.5 percent (relative risk [RR] 1.72, 95% CI 1.13-2.25) [20]. In addition, the incidence of premature deliveries in treated women was lower than in those who were not treated (7.0 versus 22.4 percent, RR 1.66, 95% CI 1.18-2.34). A limitation of this study is that the mean gestational age of starting therapy was 10 weeks, and all but one of the losses had occurred at less than 11 weeks. Further study is required to evaluate the efficacy of levothyroxine in women with RPL and positive thyroid peroxidase antibodies. (See "Overview of thyroid disease and pregnancy", section on 'Thyroid peroxidase antibodies in euthyroid women'.)

POLYCYSTIC OVARY SYNDROME

The miscarriage rate in women with polycystic ovary syndrome (PCOS) is 20 to 40 percent, higher than the baseline rate in the general obstetric population [21]. Metformin has been used in women with PCOS to decrease this risk, but the effectiveness of this approach is unproven. (See "Metformin for treatment of the polycystic ovary syndrome", section on 'Spontaneous abortion'.)

HYPERPROLACTINEMIA

Normal circulating levels of prolactin may play an important role in maintaining early pregnancy. A study of 64 hyperprolactinemic women with RPL randomly assigned to bromocriptine therapy or no bromocriptine found treatment was associated with a significantly higher rate of successful pregnancy (86 versus 52 percent) [22]. Prolactin levels during early pregnancy were significantly greater in women who miscarried. We suggest treatment of women with hyperprolactinemia and RPL, even in the absence of overt hypogonadism. (See "Management of hyperprolactinemia".)

THROMBOPHILIA

Anticoagulation of women with certain inherited thrombophilias may improve maternal outcome (eg, prevention of venous thromboembolism), but does not appear to prevent pregnancy loss. These issues are discussed separately. (See "Inherited thrombophilias in pregnancy".)

TREATMENT OPTIONS FOR UNEXPLAINED RECURRENT PREGNANCY LOSS

After evaluation, RPL remains unexplained in approximately one-half of couples. Nevertheless, the chance of a live birth is good (ie, over 50 percent with no intervention). This rate must be considered in evaluating therapies for unexplained RPL.

Although data may be lacking, treatments that may be offered to couples with unexplained RPL include the following:

Lifestyle modification — Epidemiological studies suggest that lifestyle modifications can increase fertility potential, although these have not been definitively tested in randomized trials. These modifications include eliminating use of tobacco products, alcohol, and caffeine and reduction in body mass index (for obese women). (See "Optimizing natural fertility in couples planning pregnancy".)

Progesterone — For women with RPL, we do not prescribe supplemental vaginal progesterone therapy once a pregnancy has been established because treatment does not appear to increase the live birth rate [23-26]. However, we recognize that there is not universal agreement for this approach [27]. Our rationale is informed by the following data:

- In the largest trial, which included over 800 women with RPL randomly assigned to first-trimester vaginal progesterone therapy or placebo, approximately two-thirds of women in each group delivered a live infant after 24 weeks of gestation (progesterone and placebo birth rates: 66 versus 63 percent) [28]. Furthermore, there were no differences between the groups in the rates of clinical pregnancy at 6 to 8 weeks, ongoing pregnancy at 12 weeks, ectopic pregnancy, miscarriage, or stillbirth. There were also no differences in neonatal outcomes. For this study, RPL was defined as three or more first-trimester pregnancy losses.

- A subgroup analysis of a subsequent trial reported, for women with three or more prior pregnancy losses, an increased live birth rate following vaginal progesterone treatment compared with placebo (72 versus 57 percent, relative rate 1.28, 95% CI 1.08-1.51), but the results were based on a prespecified study subgroup limited to 285 women total [29]. In this trial, the live birth rates reflected delivery at 34 weeks gestation or greater.

- While a 2017 meta-analysis reported a decreased risk of miscarriage (relative risk [RR] 0.72, 95% CI 0.53-0.97) and increased live birth rate (RR 1.07, 95% CI 1.02-1.15) with first-trimester progestogen supplementation compared with placebo or no treatment, the effects were modest, and multiple types of progestogens were used, which limits the interpretation and clinical applicability of the information [30].

- A 2011 meta-analysis reported a reduction in miscarriage with progesterone treatment for women with three or more consecutive pregnancy losses, but this older meta-analysis included fewer women (132 women in the treatment group) and the identified studies were viewed as being of low quality based on methodology [31].

It is not known if treatment with intramuscular progesterone or other progestins would improve the live birth rate in women with RPL. Additionally, as the therapeutic effect of progesterone may be related to immune modulation, it is possible that earlier initiation of progesterone, such as during the luteal phase, may improve outcome [32]. As an example, in a small study of women with RPL (defined as two or more unexplained pregnancy losses <10 weeks of gestation), luteal phase treatment with micronized progesterone improved the 10-week pregnancy rate for the subgroup with elevated nCyclinE expression (>20 percent), compared with their prior pregnancy success (69 versus 6 percent). Live birth rates were not reported. However, as benefit was seen in only one subgroup of women in a small study, we do not prescribe luteal phase micronized progesterone in women with RPL.

Human menopausal gonadotropin — An observational study reported that controlled ovarian stimulation via human menopausal gonadotropin (hMG) administration appeared effective for treatment of endometrial defects in women with RPL [33]. The mechanism may be correction of a luteal phase defect or stimulation of a thicker endometrium, thus leading to a better implantation site. Our clinical experience supports the efficacy of this treatment, although not all societies support its use [25].

In vitro fertilization and preimplantation genetic diagnosis — Studies evaluating the value of in vitro fertilization (IVF) in women with RPL have yielded mixed results [34]. Embryos of women with unexplained RPL have a higher incidence of aneuploidy for chromosomes 13,16,18, 21, 22, X, and Y than embryos obtained from healthy women [35]. In a retrospective cohort study of 300 women with RPL, the pregnancy, live birth, and miscarriage rates were similar for women who underwent IVF with preimplantation screening (PGS) and women who elected expectant management [34]. Of the 168 retrievals performed 38 cycles (23 percent) were cancelled because of poor embryo yield or quality. Of the 130 completed PGS cycles, 103 (74 percent) yielded at least one euploid embryo. (See "Preimplantation genetic testing".)

Oocyte donation — Poor quality oocytes may be responsible for 25 percent of pregnancy losses [36]. Ovum donation can overcome this problem and has been associated with a live birth rate of 88 percent in women with RPL [36]. The success of ovum donation, even when the male partner's sperm is utilized for fertilization, suggests the absence of a significant paternal contribution to the etiology of RPL. (See "Oocyte donation for assisted reproduction".)

Gestational carrier — A gestational carrier may be considered by women with RPL or recurrent IVF implantation failures not associated with recurrent embryonic aneuploidy or obvious intrinsic gamete factors (eg, single gene

defects, diminished oocyte and embryo quality). Women who decide to pursue this route should undergo a thorough evaluation as to the etiology of the RPL or failed IVF. (See "Gestational carrier pregnancy".)

INEFFECTIVE OR UNPROVEN THERAPIES

The following therapies are not supported by data, and we do not recommend them.

Aspirin with or without heparin — Trials have reported that neither aspirin [37,38] nor aspirin plus anticoagulants improve the live birth rate of women with unexplained RPL [39,40]. Data specific to individuals with RPL include:

- In a trial comparing aspirin and nadroparin, 364 women with unexplained RPL were randomly assigned to receive daily aspirin (80 mg), aspirin plus nadroparin (2850 international units), or placebo. Aspirin or placebo was begun preconceptionally and nadroparin was started as soon as a viable pregnancy was documented by ultrasound. Among the 299 women who became pregnant, the live-birth rates for combination therapy, aspirin alone, and placebo were not significantly different: 69, 62, and 67 percent, respectively.

- Another trial randomly assigned 294 women with ≥2 consecutive unexplained pregnancy losses at ≤24 weeks to treatment with enoxaparin and low dose aspirin or no treatment; both groups received intensive pregnancy surveillance [40]. Medical therapy did not reduce the rate of pregnancy loss, which was 22 percent with drug treatment and 20 percent without it.

While a post hoc per-protocol analysis of a multicenter trial reported that, compared with placebo, low-dose aspirin initiated prior to conception and continued throughout pregnancy was associated with fewer pregnancy losses, the study population had experienced one to two prior losses and not RPL [41].

Low-molecular weight heparin — Low-molecular weight heparin (LMWH) is frequently offered to women with unexplained recurrent miscarriage. However, trials show no benefit to LMWH treatment in women without an inherited thrombophilia [42-44]. One double-blind trial randomly assigned 258 pregnant women who had a history of unexplained RPL (two or more consecutive miscarriages before 15 weeks gestation) and a negative thrombophilia work-up to either subcutaneous daily LMWH (enoxaparin 40 mg) or placebo [42]. Enoxaparin treatment did not improve the chance of a live birth. In another trial of 449 women with RPL and no thrombophilia, there were no differences in live birth rates between women randomly assigned to dalteparin 5000 international units daily versus placebo (86 and 87 percent) [43].

Human chorionic gonadotropin — Human chorionic gonadotropin (hCG) therapy during early gestation may be useful in preventing miscarriage since endogenous hCG is known to play a critical role in the establishment of pregnancy [15]. A systematic review of four trials involving 180 women with RPL found hCG therapy was associated with a significantly reduced risk of miscarriage (odds ratio [OR] 0.26, 95% CI 0.14-0.52), particularly in women with oligomenorrhea [45]. However, there were important methodological weaknesses in two of these studies. To date, there is insufficient evidence to recommend the use of hCG to prevent pregnancy loss in women with a history of unexplained RPL. Large randomized controlled trials are needed.

Clomiphene citrate — By increasing serum FSH, clomiphene citrate increases follicular number and serum estradiol levels, which should lead to an increase in the number of corpora lutea and a higher midluteal progesterone concentration [46]. Two randomized trials comparing clomiphene with progesterone for treatment of inadequate luteal phase demonstrated similar pregnancy rates (20 to 30 percent) with each treatment [47]. Clomiphene, unlike progesterone, does not prolong the luteal phase, thereby lessening the anxiety and period of uncertainty of infertile couples concerning possible conception. Due to the anti-estrogen effect of clomiphene on the endometrium, we do not use clomiphene in women with RPL.

Immune therapy with intravenous immunoglobulin — Systematic reviews have consistently found no beneficial effect of immunotherapy for treatment of RPL [13,14,48,49]. The general findings are illustrated by the following two examples:

- A systematic review of 20 trials of high quality showed that immunotherapy did not result in a statistically significant improvement in live births compared with untreated controls [13]. Four types of immunotherapy were evaluated: paternal cell immunization (OR 1.23, 95% CI 0.89-1.70; 12 studies including 641 participants); third party donor cell immunization (OR 1.39, 95% CI 0.68-2.82; three studies including 156 participants); trophoblast membrane infusion (OR 0.40, 95% CI 0.11-1.45; one study including 37 participants); and intravenous immune globulin (OR 0.98, 95% CI 0.61-1.58; eight studies including 303 participants).

- Another systematic review evaluated three randomized and two cohort trials of immunotherapy treatment specifically in patients who failed IVF; a total of 373 patients were involved in these trials [48]. Patients treated with IVIG showed a consistently higher live birth rate than untreated controls; this benefit was statistically significant when the trial results were pooled in meta-analysis. However, there were many differences among these trials, such as the preparations used, the timing of the intervention (preconception, postconception, both), and dose, as well as the immunological abnormalities of the patients. In addition, some controls received heparin and aspirin while others did not receive any therapy. Thus, appropriate use of this therapy remains unclear.

Immune therapy of RPL should be considered experimental, and used only in the setting of a clinical trial regulated by an Institutional Review Board.

Glucocorticoids — Glucocorticoids have several anti-inflammatory effects, including suppression of natural killer cell activity, but do not appear to be effective for preventing RPL. This was illustrated by a trial in which 202 women with RPL and a variety of autoantibodies (antinuclear, anti-DNA, antilymphocyte, anticardiolipin, lupus anticoagulant) were randomly assigned to receive either prednisone (0.5 to 0.8 mg per kilogram of body weight per day) and aspirin (100 mg per day) or placebo for the duration of the pregnancy [15]. The two groups did not have a statistically significant difference in rate of live birth (66 and 56 percent, respectively).

Oral administration of glucocorticoids for treatment of RPL has been abandoned because of uncertain efficacy and a clearly demonstrable increase in complications, such as preterm premature rupture of membranes, gestational diabetes, and maternal hypertension [15]. Alternative methods of glucocorticoid treatment, which are under investigation, may be safer [16].

Other medications and/or combinations — While medications that impact endometrial development and immune function have showed initial promise, there are inadequate data to support their use. Combined treatment with prednisone, progesterone, aspirin, and folate does not appear to be beneficial.

- Sitagliptin – A study that evaluated the impact of sitagliptin, an inhibitor of dipeptidyl-peptidase IV, reported improved endometrial mesenchymal stem-like progenitor cell (eMSC) colony counts in the endometrium for patients treated with sitagliptin compared with placebo [50]. Reduced eMSC colony counts have been associated with impaired decidualization [51,52]. However, the study was small and did not assess the clinically important outcomes of pregnancy or live birth rates. While sitagliptin may be a promising future treatment, adequately powered clinical trial data are needed before this drug is prescribed for routine clinical use in patients with RPL.

- **Granulocyte colony stimulating factor (G-CSF)** – Preliminary studies have supported a possible role for use of recombinant human G-CSF in patients with RPL [53]. Similar to sitagliptin above, the pilot study for G-CSF was small and did not assess the clinically important outcomes of pregnancy or live birth rates. Adequately powered clinical trial data are needed before this drug is prescribed for routine clinical use in patients with RPL.

- **Combined medical therapy** – An observational study compared 50 pregnant women who were treated before and during pregnancy with a combination of prednisone (20 mg/day), progesterone (20 mg/day), aspirin (100 mg/day), and folate (5 mg every second day) with 52 women who were not treated during the same observation period [54]. The first-trimester miscarriage rate was 19 percent in the treated group and 63 percent in the control group; this difference was not statistically significant. The live birth rates in the treated group and control groups were 77 and 35 percent, respectively (p = 0.04). With combined treatment of four agents, it is unclear

which of the treatments was beneficial. The nonrandomized design and small number of cases also limit the usefulness of this study.

FUTURE PREGNANCY PROGNOSIS

Continued pregnancy loss — The greatest risk of recurrent loss occurs during the period up to the time of previous miscarriage.

The likelihood of successful pregnancy in women with a history of RPL was evaluated in a single center cohort study of 987 women [55]. At five years after the initial visit to a tertiary care center for RPL, 67 percent of women had a live birth. Increasing maternal age and a higher number of miscarriages at time of initial visit were associated with a significant decrease in the likelihood of having a live birth. Another study of women with unexplained RPL showed that 167 of 222 women who conceived subsequently had a successful pregnancy beyond 24 weeks of gestation (75 percent) [56].

In women with recurrent early first trimester pregnancy loss, the presence of fetal cardiac activity is reassuring of subsequent viable delivery, although the pregnancy loss rate remains above that of the general population. A literature review of studies examining fetal loss rates after sonographic demonstration of fetal cardiac activity reported the rate of such losses in women with RPL was 5 to 22 percent compared with 7 to 15 percent in infertile populations and 3 to 6 percent in controls [57].

Second trimester pregnancy loss is significantly associated with recurrent second trimester loss and future spontaneous preterm birth. After a second trimester pregnancy loss, one study reported 39 percent of women had a preterm delivery in their next pregnancy, 5 percent had a stillbirth, and 6 percent had a neonatal death [58]. In another study of 30 women with second trimester loss, the frequency of recurrent second trimester loss was 27 percent and the frequency of subsequent preterm birth was 33 percent [59].

Other obstetric issues — Women with a history of RPL who become pregnant may be at higher risk for developing fetal growth restriction and premature delivery, but not for gestational hypertension or diabetes. As an example, a retrospective cohort study compared 2030 women with RPL to over 28,000 control women and reported an increased incidence of preterm birth (8 versus 5.5 percent), very preterm birth <32 weeks gestation (2.2 versus 1.2 percent), and perinatal death (1.2 versus 0.5 percent) for the women with RPL [60]. A different study that compared 162 women with RPL to control women additionally reported increased rates of fetal growth restriction (13 versus 2 percent) and cesarean delivery (36 versus 17 percent) [61].

Obstetric management depends upon the underlying cause of RPL, if known.

SOCIETY GUIDELINE LINKS

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

INFORMATION FOR PATIENTS

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

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

Basics topics (see "Patient education: Repeated miscarriage (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Couples in whom chromosomal abnormalities are discovered in one or both partners or the abortus are generally referred for genetic counseling, which should include information about the probability of having a chromosomally normal or abnormal conception, and options for managing this risk. (See 'Parental karyotype abnormality' above.)
- Uterine abnormalities are managed surgically if the defect is a surgically correctable cause of pregnancy loss, such as a uterine septum, intrauterine adhesions, or submucosal myoma. These conditions can be treated hysteroscopically. (See 'Uterine abnormalities' above.)
- For women with unexplained RPL, we recommend **not** using supplemental vaginal progesterone (**Grade 1B**). Use of vaginal progesterone once a pregnancy has been established does not improve live birth rates. It is not known if intramuscular progesterone or other progestin therapies provide a benefit. (See 'Progesterone' above.)
- We recommend **not** using immunotherapy (**Grade 1A**) or glucocorticoids (**Grade 1B**) for treatment of RPL. These drugs are not effective and may be harmful. (See 'Immune therapy with intravenous immunoglobulin' above and 'Glucocorticoids' above.)
- We suggest treatment of women with hyperprolactinemia and RPL (**Grade 2B**). (See 'Hyperprolactinemia' above.)
- A variety of treatments have been offered to couples with unexplained RPL. We start with low risk, simple, and less expensive interventions and, if unsuccessful, move on to higher risk, more complex and expensive options. (See 'Treatment options for unexplained recurrent pregnancy loss' above.)
- Women with a history of RPL who become pregnant may be at higher risk for developing fetal growth restriction and premature delivery. Detection of fetal cardiac activity in early pregnancy is reassuring of subsequent viable delivery, although the pregnancy loss rate remains above that of the general population. (See 'Future pregnancy prognosis' above.)

REFERENCES

1. Harger JH, Archer DF, Marchese SG, et al. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstet Gynecol 1983; 62:574.
2. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 1997; 12:387.
3. Laurino MY, Bennett RL, Saraiya DS, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Couns 2005; 14:165.
4. Munné S, Cohen J, Sable D. Preimplantation genetic diagnosis for advanced maternal age and other indications. Fertil Steril 2002; 78:234.
5. Werlin L, Rodi I, DeCherney A, et al. Preimplantation genetic diagnosis as both a therapeutic and diagnostic tool in assisted reproductive technology. Fertil Steril 2003; 80:467.

6. Otani T, Roche M, Mizuike M, et al. Preimplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. Reprod Biomed Online 2006; 13:869.
7. Mastenbroek S, Twisk M, van Echten-Arends J, et al. In vitro fertilization with preimplantation genetic screening. N Engl J Med 2007; 357:9.
8. Heinonen PK, Saarikoski S, Pystynen P. Reproductive performance of women with uterine anomalies. An evaluation of 182 cases. Acta Obstet Gynecol Scand 1982; 61:157.
9. Patton PE, Novy MJ, Lee DM, Hickok LR. The diagnosis and reproductive outcome after surgical treatment of the complete septate uterus, duplicated cervix and vaginal septum. Am J Obstet Gynecol 2004; 190:1669.
10. Mollo A, De Franciscis P, Colacurci N, et al. Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertil Steril 2009; 91:2628.
11. Tomaževič T, Ban-Frangež H, Virant-Klun I, et al. Septate, subseptate and arcuate uterus decrease pregnancy and live birth rates in IVF/ICSI. Reprod Biomed Online 2010; 21:700.
12. Ansari AH, Kirkpatrick B. Recurrent pregnancy loss. An update. J Reprod Med 1998; 43:806.
13. Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev 2014; :CD000112.
14. Hutton B, Sharma R, Fergusson D, et al. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG 2007; 114:134.
15. Regan L, Rai R. Epidemiology and the medical causes of miscarriage. Baillieres Best Pract Res Clin Obstet Gynaecol 2000; 14:839.
16. Ogasawara M, Aoki K. Successful uterine steroid therapy in a case with a history of ten miscarriages. Am J Reprod Immunol 2000; 44:253.
17. Christiansen OB, Larsen EC, Egerup P, et al. Intravenous immunoglobulin treatment for secondary recurrent miscarriage: a randomised, double-blind, placebo-controlled trial. BJOG 2015; 122:500.
18. Marqusee E, Hill JA, Mandel SJ. Thyroiditis after pregnancy loss. J Clin Endocrinol Metab 1997; 82:2455.
19. Bliddal S, Feldt-Rasmussen U, Rasmussen ÅK, et al. Thyroid Peroxidase Antibodies and Prospective Live Birth Rate: A Cohort Study of Women with Recurrent Pregnancy Loss. Thyroid 2019; 29:1465.
20. Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006; 91:2587.
21. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Hum Reprod 2002; 17:2858.
22. Hirahara F, Andoh N, Sawai K, et al. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertil Steril 1998; 70:246.
23. Practice Committee of the American Society for Reproductive Medicine. Current clinical irrelevance of luteal phase deficiency: a committee opinion. Fertil Steril 2015; 103:e27.
24. Green-top Guidelne No. 17. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage. Royal College of Obstetricians & Gynaecologists. Published April 2011, Updated February 2017. www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf (Accessed on May 10, 2019).
25. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open 2018; 2018:hoy004.
26. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database Syst Rev 2019; 2019.
27. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol 2018; 132:e197.

28. Coomarasamy A, Williams H, Truchanowicz E, et al. A Randomized Trial of Progesterone in Women with Recurrent Miscarriages. N Engl J Med 2015; 373:2141.
29. Coomarasamy A, Devall AJ, Cheed V, et al. A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy. N Engl J Med 2019; 380:1815.
30. Saccone G, Schoen C, Franasiak JM, et al. Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. Fertil Steril 2017; 107:430.
31. Coomarasamy A, Truchanowicz EG, Rai R. Does first trimester progesterone prophylaxis increase the live birth rate in women with unexplained recurrent miscarriages? BMJ 2011; 342:d1914.
32. Choi BC, Polgar K, Xiao L, Hill JA. Progesterone inhibits in-vitro embryotoxic Th1 cytokine production to trophoblast in women with recurrent pregnancy loss. Hum Reprod 2000; 15 Suppl 1:46.
33. Li TC, Ding SH, Anstie B, et al. Use of human menopausal gonadotropins in the treatment of endometrial defects associated with recurrent miscarriage: preliminary report. Fertil Steril 2001; 75:434.
34. Murugappan G, Shahine LK, Perfetto CO, et al. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod 2016; 31:1668.
35. Hassold TJ. A cytogenetic study of repeated spontaneous abortions. Am J Hum Genet 1980; 32:723.
36. Remohí J, Gallardo E, Levy M, et al. Oocyte donation in women with recurrent pregnancy loss. Hum Reprod 1996; 11:2048.
37. Mumford SL, Silver RM, Sjaarda LA, et al. Expanded findings from a randomized controlled trial of preconception low-dose aspirin and pregnancy loss. Hum Reprod 2016; 31:657.
38. Blomqvist L, Hellgren M, Strandell A. Acetylsalicylic acid does not prevent first-trimester unexplained recurrent pregnancy loss: A randomized controlled trial. Acta Obstet Gynecol Scand 2018; 97:1365.
39. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 2010; 362:1586.
40. Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 2010; 115:4162.
41. Naimi AI, Perkins NJ, Sjaarda LA, et al. The Effect of Preconception-Initiated Low-Dose Aspirin on Human Chorionic Gonadotropin-Detected Pregnancy, Pregnancy Loss, and Live Birth : Per Protocol Analysis of a Randomized Trial. Ann Intern Med 2021.
42. Pasquier E, de Saint Martin L, Bohec C, et al. Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial. Blood 2015; 125:2200.
43. Schleussner E, Kamin G, Seliger G, et al. Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss: a multicenter trial with a minimization randomization scheme. Ann Intern Med 2015; 162:601.
44. Rodger MA, Hague WM, Kingdom J, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet 2014; 384:1673.
45. Scott JR, Pattison N. Human chorionic gonadotrophin for recurrent miscarriage. Cochrane Database Syst Rev 2000; :CD000101.
46. Bohnet HG, Kato K, Trapp M, et al. Different hormonal patterns in human menopausal gonadotropin-treated, clomiphene citrate-treated, and untreated conception cycles. Fertil Steril 1986; 45:469.
47. Murray DL, Reich L, Adashi EY. Oral clomiphene citrate and vaginal progesterone suppositories in the treatment of luteal phase dysfunction: a comparative study. Fertil Steril 1989; 51:35.

48. Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF). J Assist Reprod Genet 2006; 23:1.
49. Egerup P, Lindschou J, Gluud C, et al. The Effects of Intravenous Immunoglobulins in Women with Recurrent Miscarriages: A Systematic Review of Randomised Trials with Meta-Analyses and Trial Sequential Analyses Including Individual Patient Data. PLoS One 2015; 10:e0141588.
50. Tewary S, Lucas ES, Fujihara R, et al. Impact of sitagliptin on endometrial mesenchymal stem-like progenitor cells: A randomised, double-blind placebo-controlled feasibility trial. EBioMedicine 2020; 51:102597.
51. Lucas ES, Dyer NP, Murakami K, et al. Loss of Endometrial Plasticity in Recurrent Pregnancy Loss. Stem Cells 2016; 34:346.
52. Brighton PJ, Maruyama Y, Fishwick K, et al. Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium. Elife 2017; 6.
53. Scarpellini F, Klinger FG, Rossi G, Sbracia M. Immunohistochemical Study on the Expression of G-CSF, G-CSFR, VEGF, VEGFR-1, Foxp3 in First Trimester Trophoblast of Recurrent Pregnancy Loss in Pregnancies Treated with G-CSF and Controls. Int J Mol Sci 2019; 21.
54. Tempfer CB, Kurz C, Bentz EK, et al. A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: a matched-pair study. Fertil Steril 2006; 86:145.
55. Lund M, Kamper-Jørgensen M, Nielsen HS, et al. Prognosis for live birth in women with recurrent miscarriage: what is the best measure of success? Obstet Gynecol 2012; 119:37.
56. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 1999; 14:2868.
57. Bricker L, Farquharson RG. Types of pregnancy loss in recurrent miscarriage: implications for research and clinical practice. Hum Reprod 2002; 17:1345.
58. Goldenberg RL, Mayberry SK, Copper RL, et al. Pregnancy outcome following a second-trimester loss. Obstet Gynecol 1993; 81:444.
59. Edlow AG, Srinivas SK, Elovitz MA. Second-trimester loss and subsequent pregnancy outcomes: What is the real risk? Am J Obstet Gynecol 2007; 197:581.e1.
60. Field K, Murphy DJ. Perinatal outcomes in a subsequent pregnancy among women who have experienced recurrent miscarriage: a retrospective cohort study. Hum Reprod 2015; 30:1239.
61. Jivraj S, Anstie B, Cheong YC, et al. Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. Hum Reprod 2001; 16:102.

Topic 5444 Version 50.0

Contributor Disclosures

Togas Tulandi, MD, MHCM Consultant/Advisory Boards: AbbVie [Gonadotropin-releasing hormone antagonist]. **Haya M Al-Fozan, MD** Nothing to disclose **Charles J Lockwood, MD, MHCM** Nothing to disclose **Kristen Eckler, MD, FACOG** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→