Northwest Perinatal Center

Perinatal Progress

Recurrent Pregnancy Loss

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Recurrent pregnancy loss (RPL) is a controversial and emotionally charged topic. Families who experience RPL endure much stress and grief without many clinical answers. Providers are often unable to give families a cause for their losses due to inconsistent definitions and lack of practical guidelines to approach the problem. This combination may make coping difficult and decisions on how to proceed with expanding their family challenging. This issue of *Perinatal Progress* aims to summarize the current literature and provide a uniform strategy for evaluating, informing and managing patients experiencing RPL.

In general, 15-20% of all 1st trimester pregnancies end in miscarriage; however, the risk of 1st trimester miscarriage does increase with age.[1,2,3,4] The risk of one 1st trimester miscarriage at the age of 20-24 is 11%, compared to 50-55% at the age of 40-44.[3]

As expected, repeated miscarriages occur less frequently, with a 2-5% incidence of two consecutive miscarriages. However, the third consecutive miscarriage occurs with a higher frequency than chance alone (1% compared to the risk by chance of 0.3%).[2,3] Similarly, the risk for miscarriage in a subsequent pregnancy increases with additional prior pregnancy losses (Table 1). These data suggest that there may be other factors contributing to repeated miscarriages.

Table 1: Risk of miscarriage by number of prior losses[5]

PRIOR LOSSES	RISK
None	11 - 13%
1	14 - 21%
2	24 - 29%
3	31 - 33%

Definition

The definition of RPL varies according to the author, which makes studying it and determining which couples to counsel and treat challenging. Differences exist in the clinical criteria for diagnosing a loss, the number of losses required to be considered RPL, and whether or not they are consecutive. ACOG does not currently have a statement defining RPL. Other organizations range in the definition from two non-consecutive clinical miscarriages to three consecutive pregnancy losses.[4,6]

Our goal is to assist in identifying women at increased risk for future losses who may benefit from an intervention to reduce the risk of recurrence. With this in mind, narrowing the target population provides the best opportunity to accurately identify women at greatest risk. While the risk of a future loss does increase after two consecutive miscarriages, the ability to detect a pathologic condition contributing to the losses beyond spontaneous aneuploidy does not improve until three losses. **For that reason, we recommend deferring a formal evaluation until three consecutive, clinically-recognized spontaneous abortions.**

With the expanding use of ultrasound monitoring for ovulation induction and highly sensitive pregnancy tests, more women are now aware of preclinical miscarriages prior to six weeks of gestation. Pregnancy complicated by early loss can be detected by a urine or serum hCG test, an ultrasound demonstrating an intrauterine anembryonic or non-viable embryonic sac, or histopathology from a tissue sample from dilation and curettage. However, early losses prior to sonographic recognition are most commonly sporadic and due to aneuploidy. For the purposes of determining whether evaluation for RPL is appropriate, **pregnancy is defined as a one documented by ultrasonography or histopathological examination.** Ideally, a threshold of three or more losses should be used, but there is room for exceptions in evaluation of two first trimester losses, especially when these losses are documented as embryonic.

Causes

Genetic

Aneuploidy. Approximately 60% of early pregnancy losses are due to numeric chromosome errors, such as trisomy, monosomy, or polyploidy.[4] After 10 weeks, this frequency drops to only 5%.[2] It is important to consider

Table 2: Causes of recurrent pregnancy loss

CAUSE	RATE
GENETIC	
Sporadic: aneuploidy	age dependent
Inherited: parental translocation	2 - 5%
MATERNAL MEDICAL CONDITIONS	
APS	15%
Endocrine disorders	
Uncontrolled diabetes	
Overt thyroid disease	
UTERINE ANATOMIC VARIATIONS	13%
Congenital	
Acquired	
UNEXPLAINED	40%

that with advancing maternal age the chance of repeated miscarriages due to spontaneous aneuploidy increases. For example, a 40-year-old woman has a 12.5% chance of having three sporadic miscarriages based solely on the mathematical expected rate of spontaneous age-related aneuploidy. As such, an extensive and expensive work-up for other causes may not be advantageous.

Parental translocation. Heritable genetic conditions, such as balanced translocations, are a less common cause and occur in 2-5% of couples with RPL.[4] Parental karyotyping can identify such balanced rearrangements, and, if found, genetic counseling regarding future risks should follow. However, a more effective strategy may be to examine the karyotype of products of conception with follow-up parental testing when an unbalanced structural genetic abnormality is found. Parental karyotyping after a euploid or aneuploid abortus is typically of lower yield. Of note, one must also consider the possibility of maternal contamination when the karyotype result is 46,XX. Reflex maternal cell contamination studies can be helpful in this setting.

For couples with balanced translocations, preimplantation genetic diagnosis (PGD), chorionic villus sampling (CVS), or amniocentesis are options for future diagnosis. With PGD, an unaffected embryo may be implanted by in vitro fertilization (IVF). However, there is insufficient evidence to support an increase in live birth rate and it is not currently a recommended treatment.[4]

Maternal Factors

Antiphospholipid syndrome. Antiphospholipid syndrome (APS) is associated with RPL. Antibodies are more commonly present in women with RPL than controls.[7] When three or more unexplained consecutive spontaneous losses occur before the 10th week of pregnancy and both maternal anatomic and hormonal abnormalities plus parental chromosomal causes have been excluded, testing for APS is appropriate. Antiphospholipid antibodies are commonly either falsely positive or transiently present. As a result, confirmatory testing at least 12 weeks after an initial positive test with persistent antibodies is required for the diagnosis (Table 3). Among women with APS and RPL without a history of venous thromboembolism (VTE), treatment with low-dose aspirin and heparin has been shown to reduce the risk of pregnancy loss by approximately 50%.[8]

Table 3: Laboratory criteria for antiphospholipid syndrome

1	Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart. It is interpreted as either present or absent. Testing for lupus anticoagulant is ideally performed before the patient is treated with anticoagulants; **OR**
2	Anticardiolipin antibody of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma, present in medium or high titer (i.e., greater than 40 GPL or MPL, or greater than the 99th percentile) on two or more occasions at least 12 weeks apart; **OR**
3	Anti-ß2-glycoprotein I of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma (in titer greater than 99th percentile for a normal population as defined by the laboratory performing the test), present on two or more occasions, at least 12 weeks apart.

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Endocrine disorders. Poorly-controlled diabetes and thyroid dysfunction are associated with 1st trimester miscarriage. While well-controlled diabetes is not associated with RPL, the risk of miscarriage increases exponentially with increasing hemoglobin A1c levels in the 1st trimester. Improved control reduces the risk of miscarriage, as well as other complications of diabetes. Treatment of overt thyroid disorder yields medical and obstetric benefits. Treatment of subclinical hypothyroidism remains controversial and is not currently recommended. Testing for diabetes and thyroid disorder is only recommended when there are additional clinical signs or symptoms of the condition.

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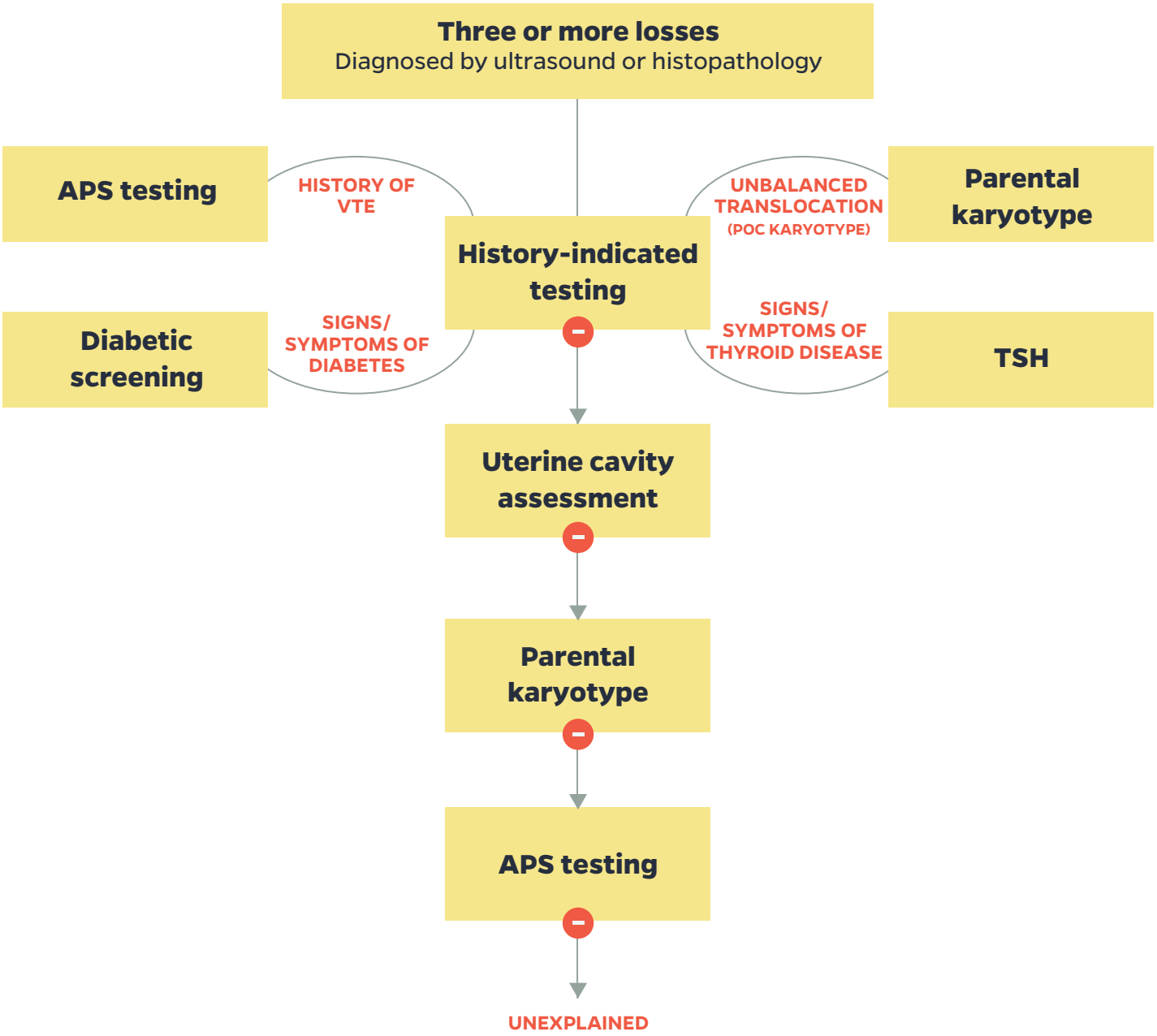
Protocol for targeted and sequential evaluation of recurrent pregnancy loss



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While some reports have suggested an increased prevalence of inherited thrombophilias among women with RPL, prospective studies have not confirmed these findings.[1,3,4] Studies using heparin or low-molecular weight heparin therapy to reduce the risk of RPL fail to demonstrate a benefit.[1] Therefore, **a thrombophilia evaluation should only be considered among women with a prior VTE and is not recommended among women with RPL.** The use of heparin and low-dose aspirin is not recommended in the absence of APS.

Reproductive Organ Conditions

Both congenital and acquired uterine malformations are detected in 10-25% of women with RPL. The most common congenital anomaly is a septate uterus, found in approximately 5% of women with RPL and is suspected to be related to vascular insufficiency.[3] Acquired uterine cavity deformations (fibroids, polyps, adhesions) are also more common among women with RPL compared to the general population. The most common of these is fibroids, found in approximately 6% of women with RPL.

Because of its high prevalence among women with RPL with possibility for correction, uterine cavity assessment is an initial step in the evaluation of RPL. Evaluation of uterine anomalies can be performed with a variety of imaging techniques. Saline infusion sonography detects most uterine anomalies with the exception of non-communicating unicornuate uterus and is typically the most accessible imaging technique. Hysterosalpingogram is a comparable alternative diagnostic tool. While more costly and invasive, MRI and intraoperative hysteroscopy with chromopertubation can also be used.

While most experts recommend hysteroscopic resection of a uterine septum in women with RPL, no randomized controlled trials studying septum resection are available to support this recommendation. Furthermore, pregnancy outcomes among nulliparous women with a septum are good, even without surgical treatment. Since surgical repair of a bicornuate or unicornuate uterus is complicated and invasive and most women with these anomalies have good obstetrical outcomes, repair is not generally advised.[2] Myomectomy for the indication of RPL is also not advised, as the benefits are uncertain and the surgery poses subsequent pregnancy risks.

Unexplained

In approximately 40-50% of couples, no etiology will be identified following an evidence-based work-up. For these women, karyotyping of the conceptus is important to establish that this risk is not a random event. Optimizing lifestyle factors, including smoking cessation, reduced alcohol consumption, and weight loss may improve outcomes. Long-term follow-up of women with RPL is encouraging, with several studies demonstrating live birth rates of approximately 50-60%.[1,9,10] One study further delineated that women with unexplained RPL under age 30 have a 75% chance of live birth within two years and women age 40 have a 40% chance of live birth in two years.[11] It is likely, in part because of these good outcomes without treatment, that historic treatment trials for unexplained RPL have been largely unsuccessful.

Recent studies have not shown that treatment with low molecular weight heparin and/or low-dose aspirin in women with RPL improved live birth rates.[2,10,12,13] While progesterone deficiency during the luteal phase has been proposed as a cause of miscarriage, screening for a deficiency is problematic as there is no clear threshold for normal progesterone values, which vary considerably from one person to another. While a Cochrane Review of four small trials showed a significantly lower risk of miscarriages among women who received progesterone compared to placebo, the quality of these trials was considered poor.[14] Furthermore, a recent randomized controlled trial studying progesterone therapy of women

Table 4: Available treatment for RPL by cause

CAUSE	TREATMENT	EVIDENCE
Sporadic aneuploidy	None	
Inherited parental translocation	IVF with PGD	Expert opinion
Antiphospholipid syndrome	ASA 81 mg + heparin	RCTs
Diabetes/Thyroid disorder	Medical management	
Septate uterus	Septum resection	Expert opinion
Other uterine anomalies or deformations	No intervention	Expert opinion
Unexplained	None	RCTs no benefit of ASA, LMWH or progesterone

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Dr. Lannon grew up in Winston-Salem, North Carolina. She attended the University of North Carolina, Chapel Hill for her undergraduate degree in nutritional science, as well as her medical degree and Master of Public Health in epidemiology. She completed her OB/GYN specialty training at OHSU and her maternal-fetal medicine fellowship at the University of Washington, where she remained on faculty until 2015. She was honored in 2015 with a teaching award by the Council on Resident Education in Obstetrics and Gynecology division of the American Congress of Obstetricians and Gynecologists. Her particular interest includes managing anticipated and unanticipated preterm birth. She has published on the timing of very preterm cesarean deliveries, timing of antenatal steroids, infectious causes of preterm labor, the risk of adverse obstetric outcomes among Native American women and the use of antihypertensive medication in pregnancy.

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with unexplained RPL did not result in improved live birth rates.[9] **Therefore, empiric low-dose aspirin, heparin, low-molecular weight heparin, and progesterone are not currently recommended for the treatment of RPL.**

Conclusions

Recurrent pregnancy loss is relatively common and poses substantial psychological effects on the family. However, the formal evaluation should be directed by the patient's clinical history and exam in order to optimize yield and properly direct treatment. While treatment regimens are largely understudied and ineffective, the long-term prognosis for pregnancy is fortunately good.

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