Recurrent Pregnancy Loss (RPL) Evaluation and Management

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Recurrent Pregnancy Loss Evaluation and Management

DISCLOSURES: Natera- Unpaid Clinical Research

LEARNING OBJECTIVES: At the conclusion of this presentation the Participant should be able to

- Describe the frequency of abnormal findings for RPL.
- Discuss the current evaluation strategies for RPL from ACOG and ASRM
- Predict the effect of maternal age and prior losses on future live births.
- Explain the role of genetic testing of miscarriage tissue in developing a strategy for the evaluation of RPL.

ACOG: Clinical Expert Series on Recurrent Pregnancy Loss

Clinical Expert Series CME

Evaluation of Recurrent Pregnancy Loss

Viviana de Assis, DO, Claudio Schenone Giugni, MD, and Stephanie T. Ros, MD, MSCI

Recurrent pregnancy loss (RPL) affects approximately 5% of couples. Although RPL definitions vary across professional societies, an evaluation after a second clinically recognized first-trimester pregnancy loss is recommended. Good quality evidence links parental chromosomal rearrangements, uterine anomalies, and antiphospholipid syndrome (APS) to RPL. In contrast, the relationship between RPL and other endocrine, hematologic, and immunologic disorders or environmental exposures is less clear. Anticoagulant therapy and low-dose aspirin are recommended for patients with RPL who have also been diagnosed with APS. Vaginal progesterone supplementation may be considered in patients experiencing vaginal bleeding during the first trimester. Surgical correction may be considered for patients with RPL in whom a uterine anomaly is identified. Evaluation and management of additional comorbidities should be guided by the patient's history rather than solely based on the diagnosis of RPL, with the goal of improving overall health to reduce complications in the event of pregnancy. Most people with RPL, including those without identifiable risk factors, are expected to achieve a live birth within 5 years from the initial evaluation. Nevertheless, clinicians should be sensitive to the psychological needs of individuals with this condition and provide compassionate and supportive care across all stages.

(Obstet Gynecol 2024;143:645–59)
DOI: 10.1097/AOG.0000000000005498

De Assis V. et al Clinical Expert Series RPL. Obstet Gynecol 143:645-659, 2024.

SHORT TITLE: RPL
FULL TITLE: Recurrent Pregnancy Loss: A Committee Opinion Draft
AUTHORS: Practice Committee of the American Society for Reproductive Medicine, American Society for Reproductive Medicine, Washington, DC

Definition and Evaluation of Recurrent Pregnancy Loss

Recurrent pregnancy loss (RPL) is defined as the spontaneous loss of two or more pregnancies, excluding molar or ectopic pregnancies.

A comprehensive evaluation of both maternal and paternal health is essential in managing RPL:

- RPL is defined as two or more spontaneous pregnancy losses.
- Biochemical losses are included in the definition of RPL (corrected from 2012).
- Evaluation includes chromosome testing of miscarriages and uterine cavity assessment (Added from 2012).
- The definition does not require consecutive losses, but clinicians should use judgment on when to initiate workup (corrected from 2012).
- RPL is distinct from infertility and requires specific management strategies.

ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.

RPL Definition: ACOG, ASRM, and ESHRE

- RPL is defined as having 2 or more losses based on a low or decreasing hCG
- Includes consecutive, non-consecutive, and biochemical losses
- Excludes ectopic and molar pregnancies

- RPL is defined by two or more failed losses before 20 weeks EGA
- Includes consecutive, non-consecutive losses, and biochemical losses
- Excludes ectopic and molar pregnancies

- 2+ pregnancy losses before 24 weeks confirmed by urine or serum hCG
- Includes consecutive, non-consecutive, biochemical, and PUL
- Excludes ectopic pregnancy, molar pregnancy, and implantation failure

De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.
ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.
ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023.

Society Guidelines for Workup for RPL(1)

Diagnostic Test	CFAS 2025	ASRM 2025	ACOG 2024	ESHRE 2022
Karyotype on Parents	Option	Option	Option	Option
Miscarriage microarray	Option	Yes	Yes	Option
Uterine Anatomy (3D-SIS)	Yes	Yes	Yes	Yes
Anticardiolipin Antibodies	Yes	Yes	Yes	Yes
Lupus anticoagulant	Yes	Yes	Yes	Yes
Thyroid function (TSH)	Yes	Yes	Yes	Yes
PCOS (HgbA1c)	Yes	Yes	Yes	Option
Tobacco, EtOH, Obesity	Yes	Yes	Yes	Yes

Sierra, S. et al. CFAS Clinical Practice Guideline RPL. RBMO 50 (3) 2025.
De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.
ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.
ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023

Society Guidelines for Workup for RPL (2)

Diagnostic Test	CFAS 2025	ASRM 2025	ACOG 2024	ESHRE 2022
Thrombophilia	No	No	No	No
Hyperprolactinemia	No	Option	No	Option
Microbial Infections	No	Yes	NC	Option
Sperm DNA Fragments	No	Yes	No	Yes
Luteal Phase (low P4)	Option	Option	Option	Option
Vitamin D	NC	NC	Treat	Treat
Ovarian reserve (AMH)	NC	No	NC	Option

Sierra, S. et al. CFAS Clinical Practice Guideline RPL. RBMO 50 (3) 2025. NC= No Comment
De Assis V et al. Clinical Expert Series. Obstet Gynecol. 143:645-59, 2024.
ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.
ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023

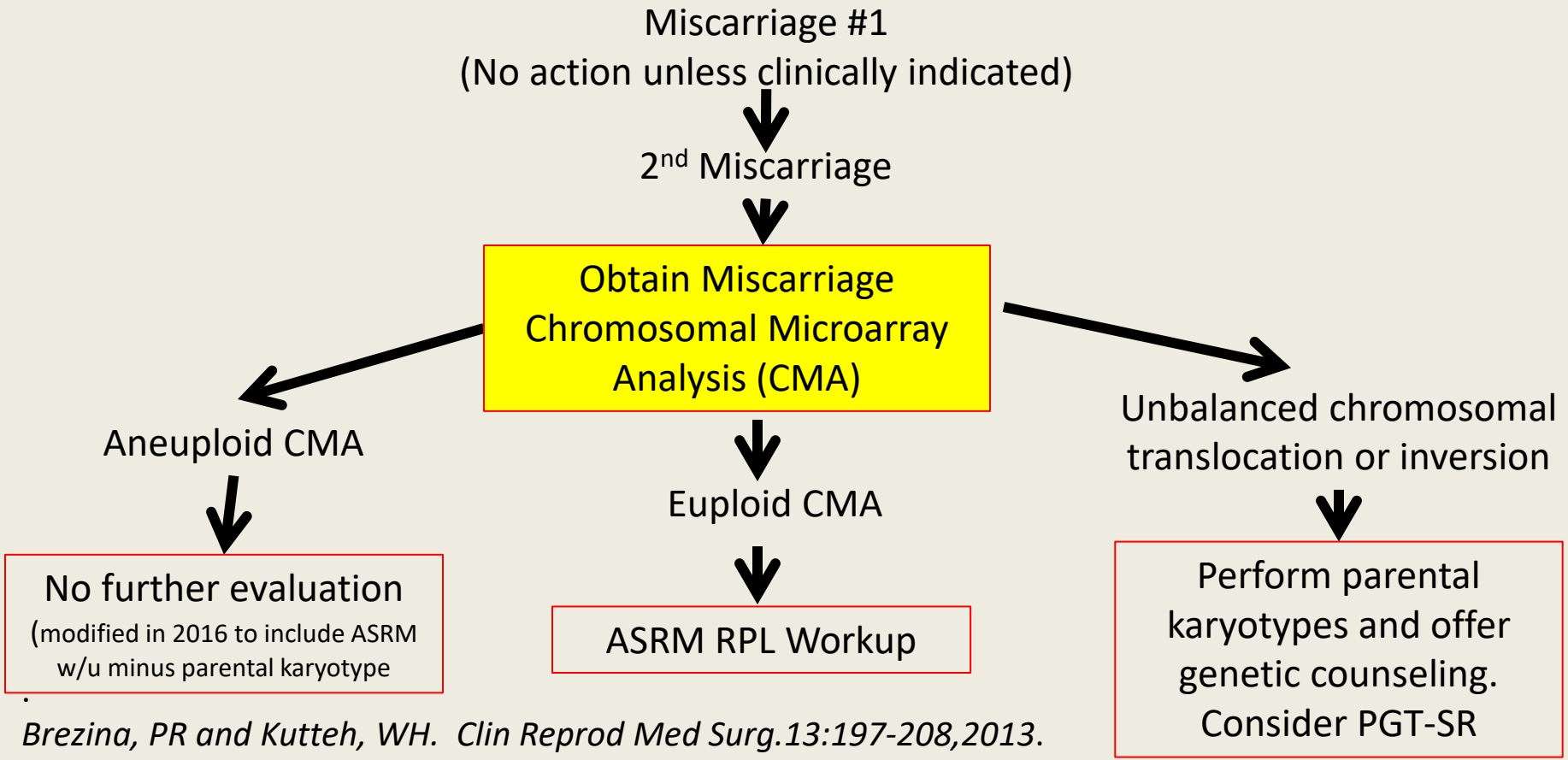
Results of 2012 ASRM Workup for RPL (n=1020)

# of prior losses	2 n=447	3 n=343	≥ 4 n=230	p value 2,3,>4	Control	p value vs Control
Karyotype	2.8%	5.4%	5.2%	NS	0.4%	<0.05
Anatomy	18.7%	18.2%	16.7%	NS	7.5%	<0.05
Lupus AC	5.0%	2.9%	1.9%	NS	0.5%	<0.05
Anticardiolipin	15.6%	13.1%	17.1%	NS	6.7%	<0.05
TSH	8.1%	6.5%	6.2%	NS	3.9%	<0.05
Total Findings	50.2%	46.7%	47.1%	NS	19.0%	<0.05

ASRM 2012 RPL Workup Fails to Provide an Explanation in 50% of RPL Patients!

Jaslow, Carney, & Kutteh. Fertil Steril 93:1234-43, 2010.

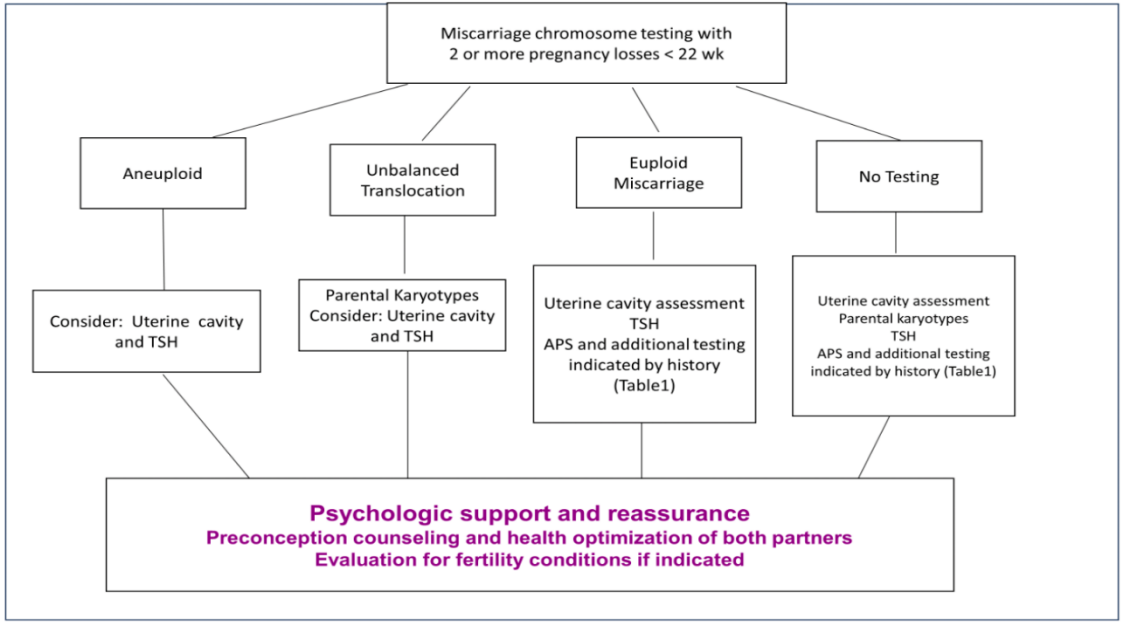
Brezina and Kutteh 2013 Proposed Evaluation of RPL



Brezina, PR and Kutteh, WH. Clin Reprod Med Surg.13:197-208,2013.

ASRM 2025 Proposed Evaluation of RPL

Figure 1. Approach to Recurrent Pregnancy Loss based on chromosome testing of most recent miscarriage



ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.

ASRM 2025 Recommended Testing for RPL

Table 1. Testing in couples/ individuals identified with Recurrent Pregnancy Loss

	Evaluation	Indication	Test
RECOMMENDED:			
	Chromosome Evaluation of clinical miscarriages	All patients	Array-based chromosome testing
	Uterine cavity evaluation	All patients	HSG, saline sonogram, or hysteroscopy

ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.

63,277 Miscarriage Tissue Fresh Specimens
24 Chromosome Microarray Test Results

<u>Acceptable samples from first trimester:</u>
-from OR suction dilation and curettage
-from in-office uterine cavity aspiration
-tissue passed after medical induction
-spontaneously passed pregnancy tissue

54,466	(86.1%) fetal results
8,559	(13.2%) maternal cell contamination
252	(0.4%) incomplete

<u>37,745/54,466</u>	<u>(59.3%) Abnormal results</u>
25,289	(67.0%) Trisomy (16>22>15>21)
2,831	(7.5%) Monosomy
2,529	(6.7%) Triploidy
5,096	(13.5%) Delet, dupl,mosaics

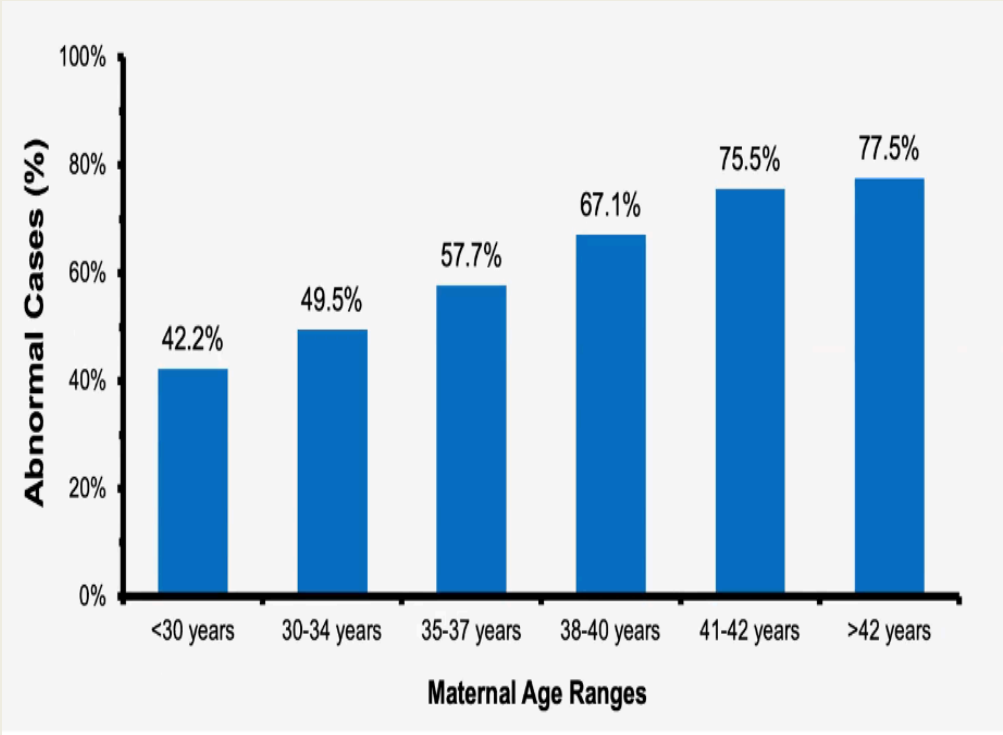
Kutteh, Papas, Meisenbacher, Dahdouh. Reprod Biol Med Online 49:1-12, 2024.

Chromosomal Microarray Results from Miscarriage Tissue (N=54,446)

Success Increases with Gestational Age

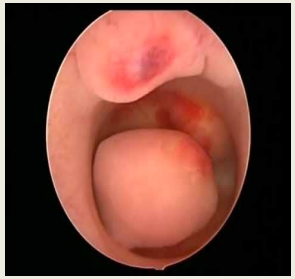
Gestational Age	Percentage of Cases with Fetal Results
<5 weeks	62.9%
5 weeks - 5 weeks 6 days	63.3%
6 weeks - 6 weeks 6 days	77.7%
7 weeks - 7 weeks 6 days	82.6%
8 weeks - 8 weeks 6 days	87.2%
9 weeks - 9 weeks 6 days	87.8%
10 weeks - 10 weeks 6 days	87.4%
11 weeks - 11 weeks 6 days	90.9%
>12 weeks	96.9%

Aneuploidy Increases with Maternal Age

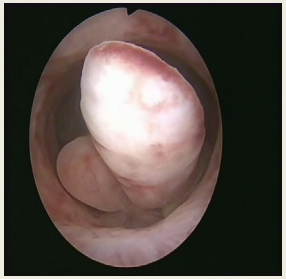


Kutteh, Papas, Maissenbacher, Dahdouh. RBMO 49:1-12, 2024.

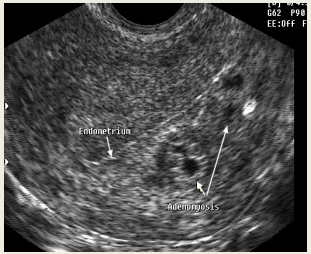
Identify and Correct Uterine Abnormalities



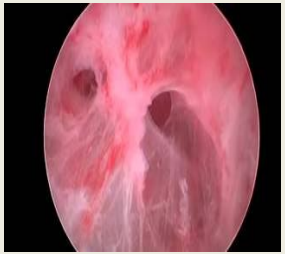
Large Polyps



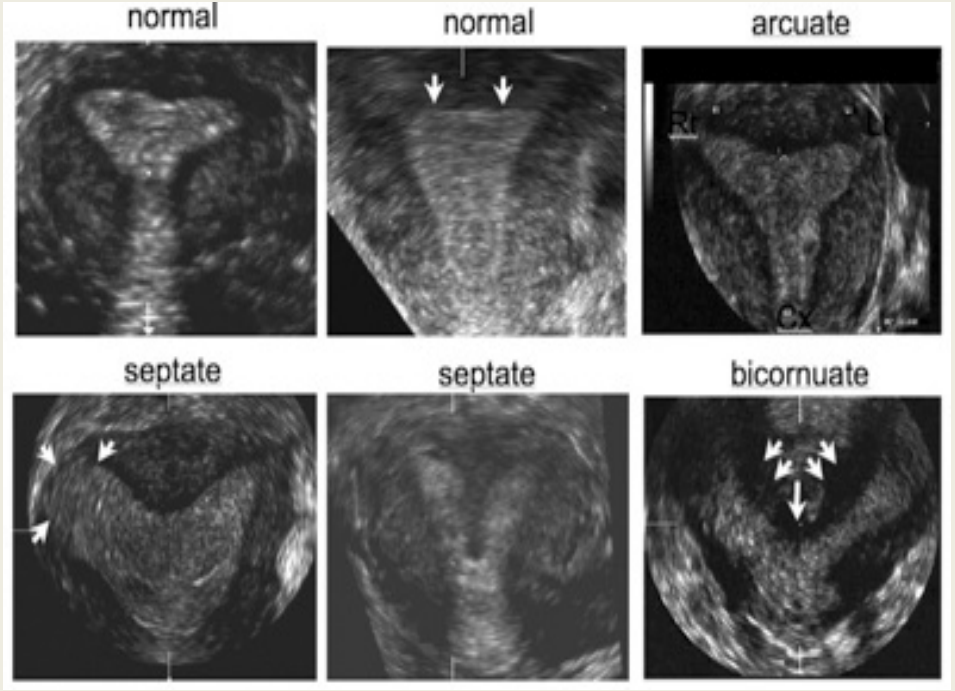
Fibroids



Adenomyosis



Adhesions



3-D Sonohysterography for Uterine Cavity Evaluation

"Resection of a septum has been shown to improve outcomes in patients with RPL"

Evidence-based diagnosis and treatment for uterine septum: a guideline

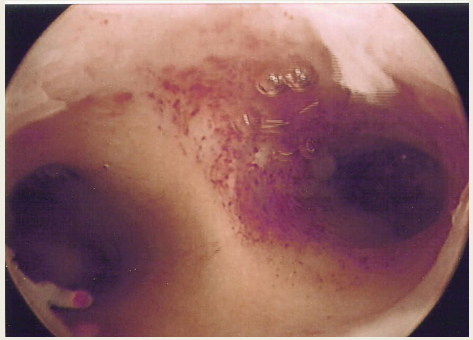
Practice Committee of the American Society for Reproductive Medicine

The American Society for Reproductive Medicine, Washington, D.C.

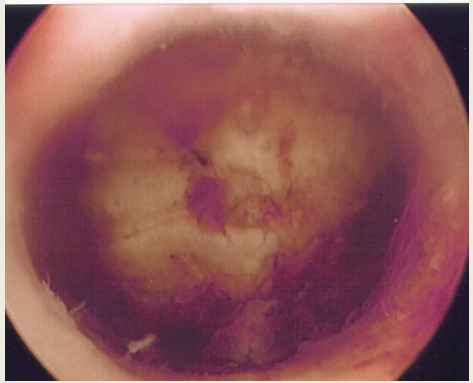
Objective: To provide evidence-based recommendations regarding the diagnosis and effectiveness of surgical treatment of a uterine septum.
Methods: This guideline provides evidence-based recommendations regarding the diagnosis and effectiveness of surgical treatment of a uterine septum. This replaces the last version of the same name (Fertil Steril. 2016 Sep 1;106(3):530-40).
Main Outcome Measure(s): Outcomes of interest included the impact of a septum on underlying fertility, live birth, clinical pregnancy, and obstetrical outcomes.
Result(s): The literature search identified relevant studies to inform the evidence for this guideline.
Conclusion(s): The treatment of uterine septa and subsequent outcomes associated with infertility, recurrent pregnancy loss, and adverse obstetrical outcomes are summarized. Resection of a septum has been shown to improve outcomes in patients with recurrent pregnancy loss and to decrease the likelihood of malpresentation. In the setting of infertility, it is recommended to use a shared decision-making model after appropriate counseling to determine whether or not to proceed with septum resection. (Fertil Steril® 2024;122: 251–65. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Uterine septum, reproductive medicine, diagnosis, treatment

ASRM Practice Committee Uterine Septum. Fertil Steril.122:251-265, 2024.



20 mm uterine septum



After septum resection

"There is fair evidence that myomectomy (open or laparoscopic) for cavity-distorting myomas (including intramural with a submucosal component) improves pregnancy rates and reduces the risk of early pregnancy loss."

Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline

Practice Committee of the American Society for Reproductive Medicine

The American Society for Reproductive Medicine, Birmingham, Alabama

The purpose of this systematic review is to evaluate if uterine myomas impact the likelihood of pregnancy and pregnancy loss, and if myomectomy influences pregnancy outcomes in asymptomatic women. There is insufficient evidence to conclude that the presence of myomas reduces the likelihood of achieving pregnancy. However, there is fair evidence that myomectomy (open or laparoscopic) for cavity-distorting myomas (intramural or intramural with a submucosal component) improves pregnancy rates and reduces the risk of early pregnancy loss. There is fair evidence that hysteroscopic myomectomy for cavity-distorting myomas improves clinical pregnancy rates but insufficient evidence regarding the impact of this procedure on the likelihood of live birth or early pregnancy loss. In women with asymptomatic cavity-distorting myomas, myomectomy may be considered to optimize pregnancy outcomes. (Fertil Steril® 2017;108:416–25. ©2017 by American Society for Reproductive Medicine.)

ASRM Practice Committee Myomas. Fertil Steril. 108: 416-425, 2017.

ASRM 2025 Recommended RPL Evaluation "in Certain Circumstances"

Parental Karyotypes	Miscarriage with unbalanced translocation or no miscarriage testing	Blood karyotype of male and female
Antiphospholipid antibodies	Clinical criteria for antiphospholipid syndrome (APS) -3 or more consecutive losses - personal history of thrombosis	Anti-cardiolipin IgG and IgM Beta-2-glycoprotein IgG and IgM Lupus anticoagulant
Thyroid	Risk factors or symptoms, Euploid miscarriage, or no miscarriage testing	TSH
Chronic Endometritis	Recurrent unexplained losses or concurrent infertility	Endometrial biopsy with CD138 staining
Sperm DNA fragmentation testing	Recurrent unexplained losses or concurrent infertility	Sperm DNA fragmentation Reproductive Urology evaluation
Diabetes	Risk factors or symptoms (PCOS, Obesity, age >40)	HgbA1c
Prolactin	Symptoms of hyperprolactinemia (anovulation, galactorrhea)	Fasting Prolactin

ASRM Practice Committee Opinion RPL Draft May 2025. Replaces 2012 document.

European Health Care – No Parental Karyotypes

A cost-effective approach to medical decision making

Most common parental chromosomal abnormality is a balanced translocation

THE REAL NUMBERS

3,670,000- livebirths in European Union in 2023

73,400- about 2% of couples diagnosed with RPL

3,670- about 0.05% of pregnancies with unbalanced translocations

73- about 2% unbalanced translocation babies survive

THE REAL COST

$146,000,000-insurance bill at $1000/each for karyotypes on both parents

-$73,000,000-give $1,000,000 to each child with unbalanced translocation

THE REAL SAVINGS

$73,000,000 –left over to provide other medical services to Europeans

ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023.

eshre
SCIENCE MOVING PEOPLE
MOVING SCIENCE

ACOG/ASRM/ESHRE: Identify and Treat Autoimmune Abnormalities

"The three antiphospholipid antibodies to test":

1) lupus anticoagulant
2) anticardiolipin
*3) anti-beta-2-glycoprotein 1

ESHRE does not recommend anti-beta-2-glycoprotein testing

"The combination of twice daily unfractionated heparin or low molecular weight heparin and low-dose aspirin appears to confer a significant benefit in pregnancies with aPLs and otherwise unexplained recurrent pregnancy loss;
Comparable efficacy of low molecular weight heparin has not been established"

ASRM Committee Opinion RPL Draft May 2025. *Replaces 2012 document.*
De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.
ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023.
Branch et al., ACOG Bulletin APA 132 Obstet Gynecol. 120:1514-1521,2012.

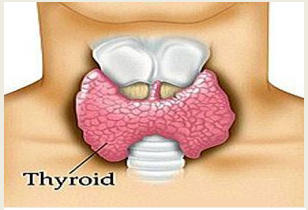
Chronic Endometritis and RPL

Pregnancy Outcome after Treatment for *Mycoplasma/Ureaplasma* in RPL Patients

	RPL Patients (*n*=1583)	Treated or Neg RPL Patients with F/U	Treated or Neg RPL Patients Delivered	P value (compared to no known cause)
Positive *Mycoplasma (TOC neg)*	66 (4.2%)	41/63 (65.1%)	32/41 (78.0%)	0.092 (1 Tail) 0.045 (2 Tail)
Positive *Ureaplasma (TOC neg)*	249 (15.7%)	163/237 (68.8%)	124/163 (76.1%)	0.002 (1 Tail) 0.003 (2 Tail)
Neg Culture (No known cause)	1268 (80.1%)	804/1196 (67.2%)	515/804 (64.1%)	1.00

Bishop S, Troung A, Jaslow C, Kutteh W. Endometritis in Recurrent Pregnancy Loss Patients: Pregnancy Outcome after Treatment and test-of –cure for culture-positive Mycoplasma/Ureaplasma. ACOG Annual Meeting, Minneapolis, MN. May 2025.

Identify and Correct Thyroid, Prediabetes, Progesterone, and Vitamin D



Overt hypothyroidism is associated with RPL and adverse pregnancy outcomes.

The normal range for TSH in non-pregnant reproductive-aged women is 1.0 -4.0 mIU/L

ASRM Committee Opinion Draft May 2025. Replaces 2012 document.

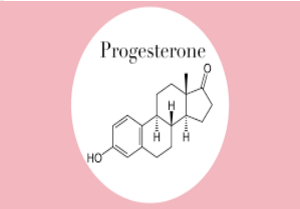
Eliwa J, Ke R, Kutteh W. Thyroid function and Reproduction. Encycl Reprod. 2024.

Women with RPL have an increased prevalence of Insulin Resistance.

Treat with Metformin ER

Craig, Ke, Kutteh. Increase insulin resistance in women with RPL. Fertil Steril 78:487, 2002.

Cortez Y et al. Pregnancy loss is related to prediabetes. PLoS One. 222 Dec 1;17 (12).



Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage:

Meta analysis of Progesterone favors treatment to reduce losses.

Saccone, G et al. Fertil Steril. 107:430-438, 2017.

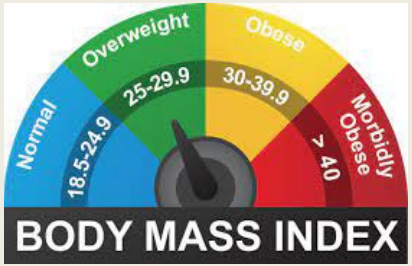
Preconception Vitamin D > 30ng/ml (n=1191) Increased Clinical Pregnancy Rates (RR=1.1,CI 1.01-1.20) and Live Birth (RR=1.15, CI 1.02-1.25)and Decreased Pregnancy Loss

Mumford SG et al. The Lancet 6:725-732,2018.

Correct Lifestyle Factors in Both Partners

Risks of RPL increase 1.5 -2 fold

- Tobacco (>10/day)
- Ethanol (> 3-5/week antenatal)
- Obesity (BMI > 30)
- Caffeine (> 2-3 cups/day)



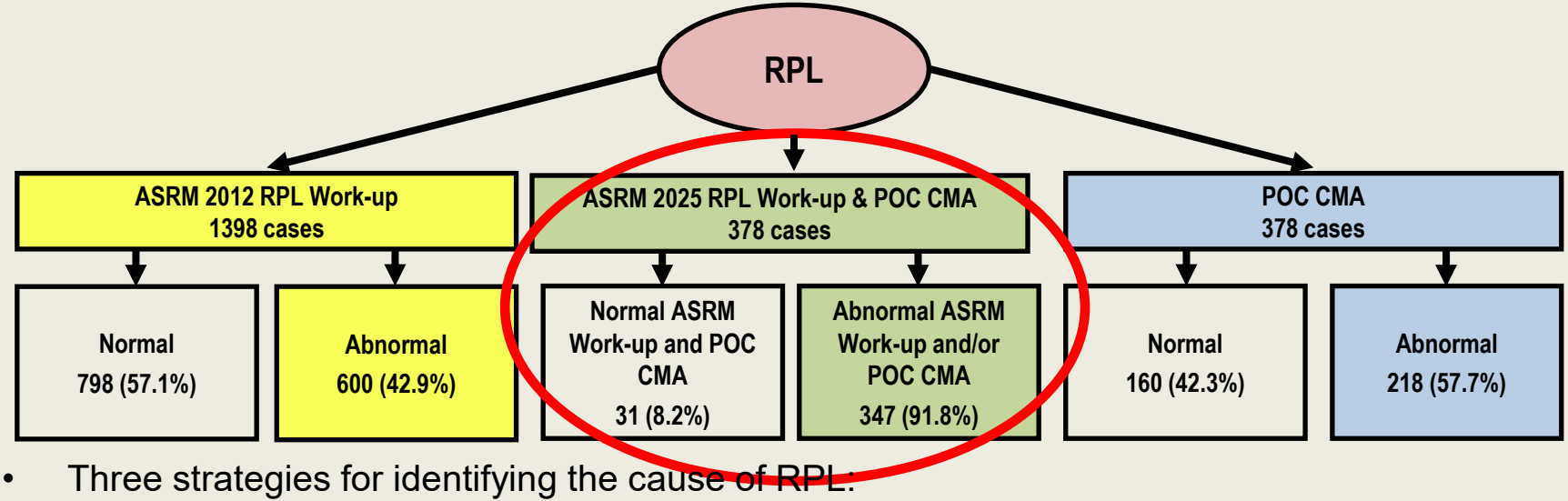
Sepidarkish M. Reprod Health 2018; 15:210

ASRM 2025 Not Recommended in the Evaluation of RPL

Inherited Thrombophilia	Not recommended	Factor V Leiden, Prothrombin gene, MTHFR, protein C, protein S, antithrombin 3, Homocysteine
Autoimmune testing outside of APS	Not recommended	Thyroid antibodies NK cell testing
Endometrial Receptivity Testing	Not recommended	
Microbiome Testing	Not recommended	

ASRM Practice Committee Opinion RPL Draft May 2025. *Replaces 2012 document.*

ASRM 2025 with miscarriage microarray Explains the Loss in Over 90% of RPL Patients



- Three strategies for identifying the cause of RPL:
  - ASRM 2012 work-up: 42.9 % explained (left panel)
  - ASRM 2025 work-up: 91.8% explained (center panel)
  - POC CMA: 57.7% explained (right panel)

Popescu, Jaslow, Kutteh. Hum Reprod. 33:579-587,2018.

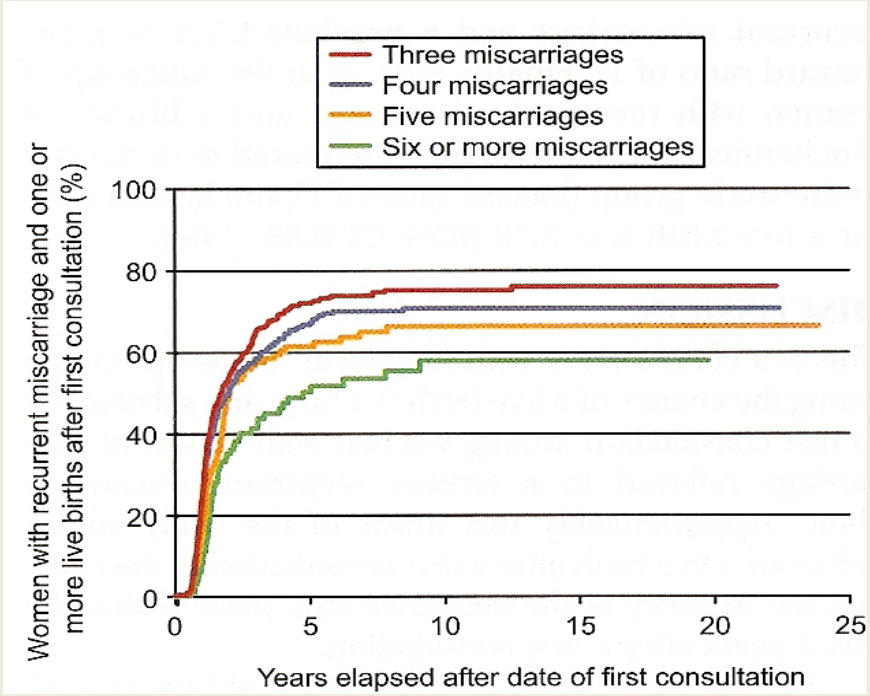
Papas and Kutteh. Curr Opin Obstet Gynecol. 32:371-9,2020.

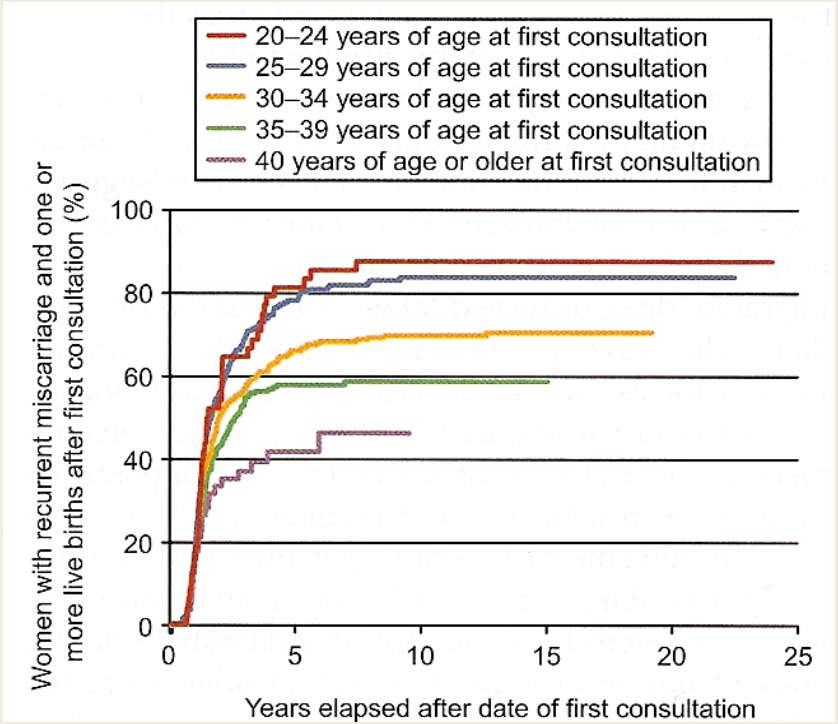
What about “Truly Unexplained RPL”?

- 90% with probable or definite cause
- Only 10 % of RPL couples unexplained
- Full workup completed and normal
- Microarray testing on POC are normal
- Subsequent live birth is 40% to 80%
- Depends on maternal age, # prior losses
- Candidates for RCT and experimental therapy

Kutteh WH, Maisenbacher M, Papas R, Dahdouh E. Role of Genetic Analysis of Products of Conception and PGT-A in the management of early pregnancy loss. Rep Biol Med Online. 45:1-12, 2024..
Papas and Kutteh. Curr Opin Obstet Gynecol. 32:371-9,2020

Future Live Birth based on Number of Losses & Maternal Age
Current Diagnostic and Treatment Strategies





Lund et al. Obstet Gynecol 119: 37-43, 2012

RECURRENT PREGNANCY LOSS
Evaluation and Management

Thank You.

Questions.