Recurrent Pregnancy Loss (RPL) 2026: Evidence-Based Evaluation and Management for the Generalist

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Recurrent Pregnancy Loss Evaluation and Management

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

- Define RPL using current ASRM and ACOG criteria
- Understand the new ASRM diagnostic algorithm for RPL
- Apply miscarriage tissue genetic testing strategies
- Identify evidence-based treatments
- Avoid ineffective testing and therapies

Why RPL Matters

- Affects approximately 2 to 3 % of reproductive-age couples
- Significant emotional and psychological burden
- Major cause of referral to REI Specialists
- Most couples ultimately achieve live birth

Key Counseling Message:
40 – 70 % of couples will achieve a live birth

De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.
ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

RPL Definition: ACOG and ASRM

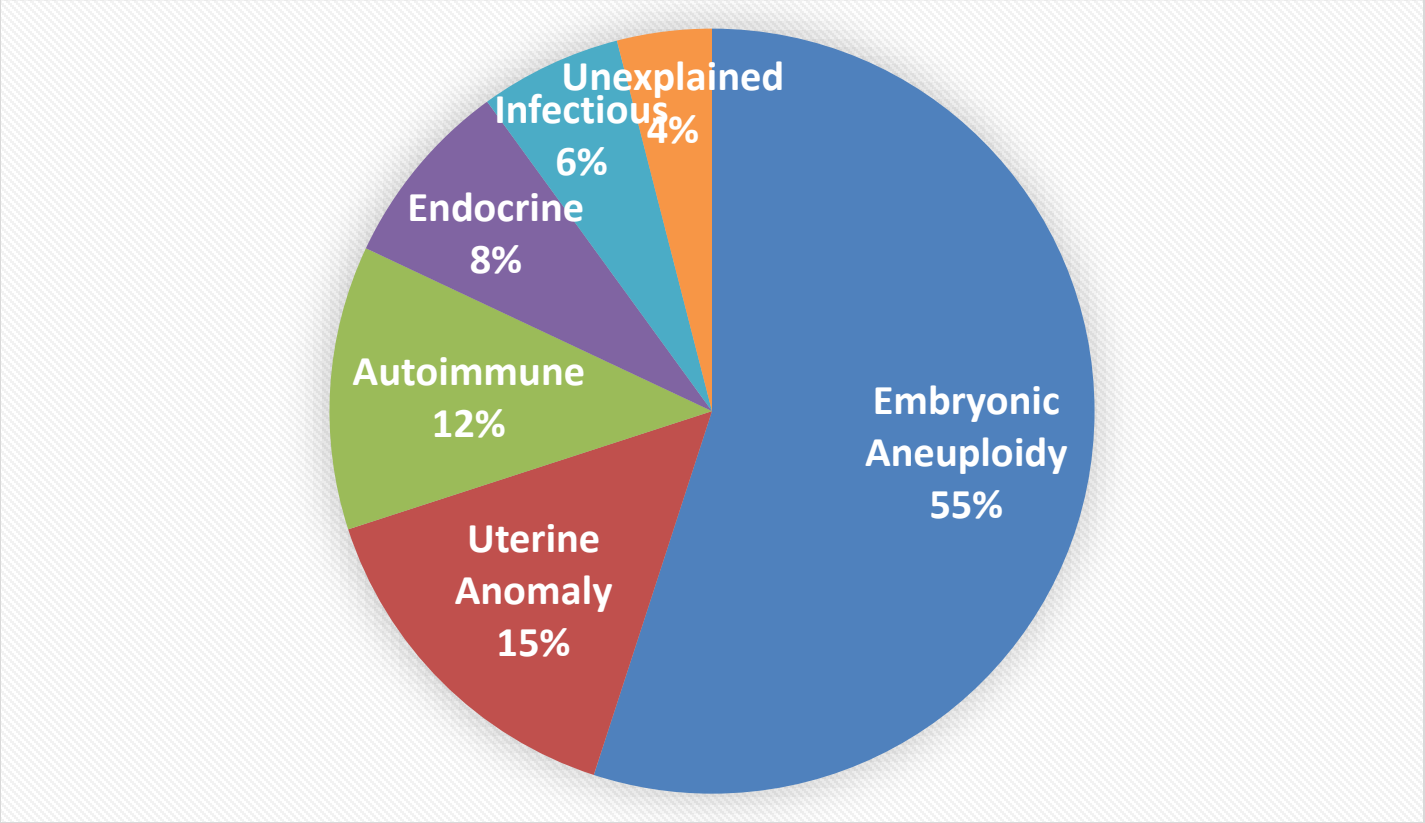
- Two or more losses based on a low or decreasing hCG
- Includes biochemical pregnancy losses
- Losses need not be consecutive
- Excludes ectopic and molar pregnancies

- Two or more failed pregnancies before 22 weeks EGA
- Includes biochemical losses
- Losses need not be consecutive
- Excludes ectopic and molar pregnancies

De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.

ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

Causes of Pregnancy Loss



Key Point: 55 to 60% of first trimester miscarriages are chromosomally abnormal

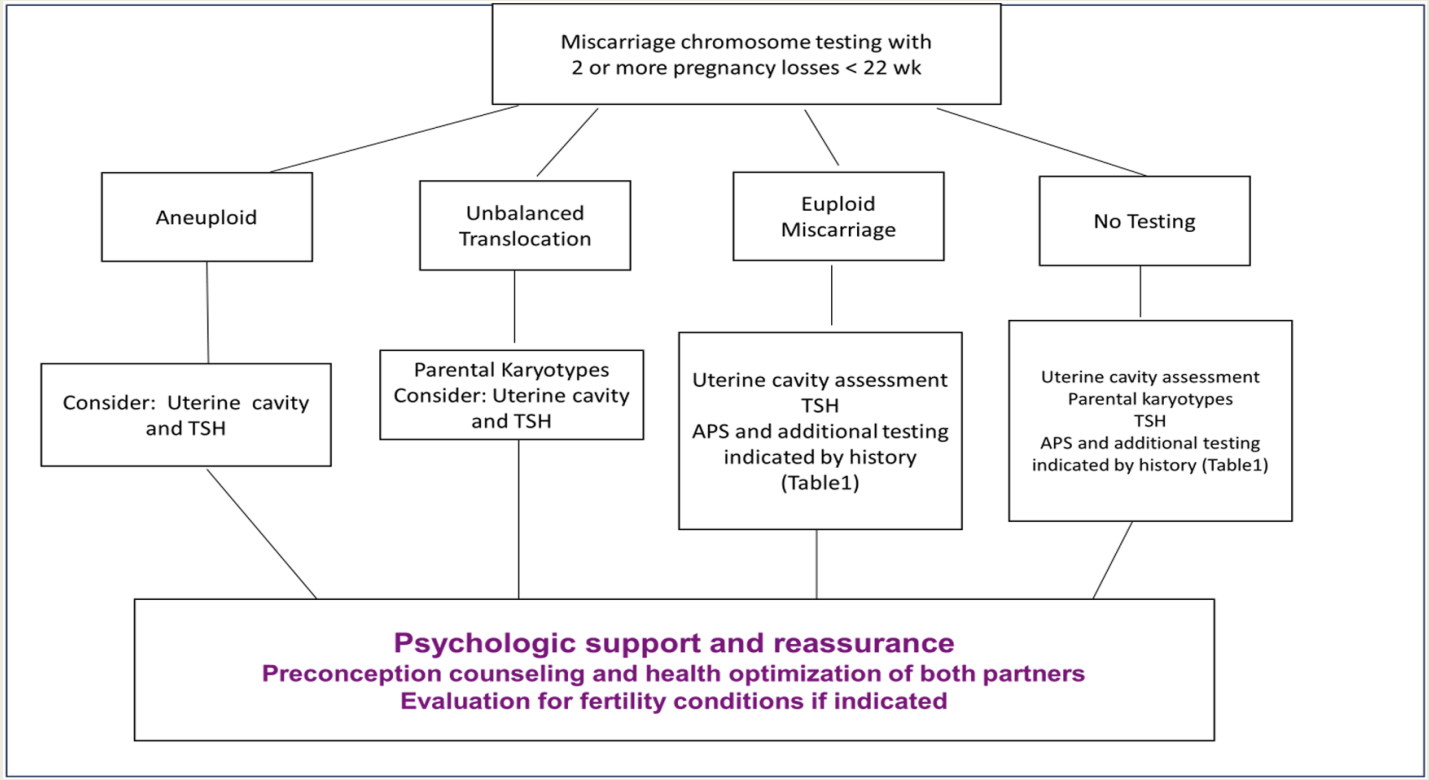
Changes from ASRM 2012 to ASRM 2026

2012	2026
Standard RPL workup first	Miscarriage CMA first
Routine parental karyotypes	Selective parental karyotypes
Limited role for POC testing	Universal offering of POC testing
Little emphasis on male factors	Consider sperm DNA Fragmentation
No stepwise algorithm	Stepwise algorithm

De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.

ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

ASRM 2026 Evaluation of RPL



ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

Why Test the Miscarriage?

- Explains the majority of the losses
- Reduces unnecessary testing
- Psychological benefit
- Improves counseling
- Cost effective

ASRM & ACOG now recommend chromosomal Microarray analysis after the second miscarriage.

De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.

ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

ASRM 2026 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 Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.
De Assis V et al. Clinical Expert Series. Obstet Gynecol. 143:645-59, 2024.

Largest Study of 63,277 Miscarriage Tissue Specimens 24 Chromosome Microarray Test Results

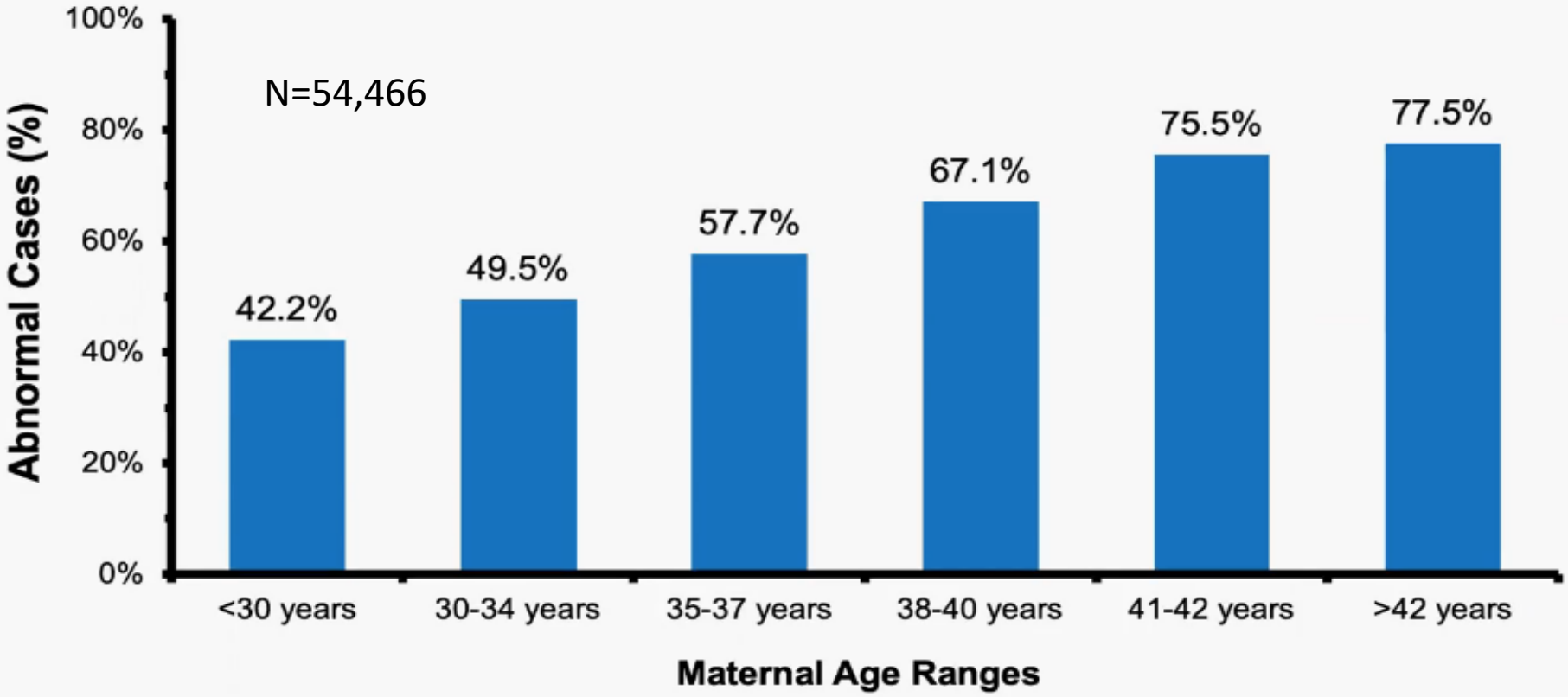
54,466	(86.1%) fetal results
8,559	(13.2%) maternal cell contamination
252	(0.4%) incomplete

37,745/54,466	(59.3%) Abnormal results
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

"Fluffy' outer edges
Tend to float in saline
Whiter than decidua

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

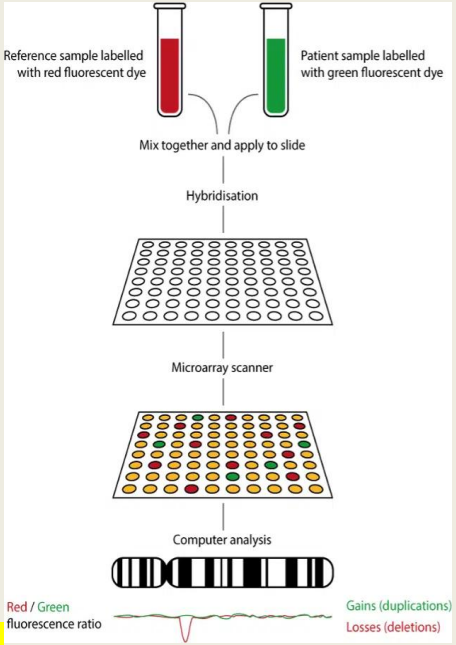
Frequency of Miscarriage Aneuploidy Increases with Maternal Age



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

Microarray Beats Karyotype

- No culture failure, direct test of POC
- Identifies maternal contamination
- Detects microdeletions
- Performed on fresh or paraffin tissue
- Identifies parental source of aneuploidy
- Home collected tissue possible
- Faster turnaround (days vs weeks)
- Lower cost ($250 vs $850)

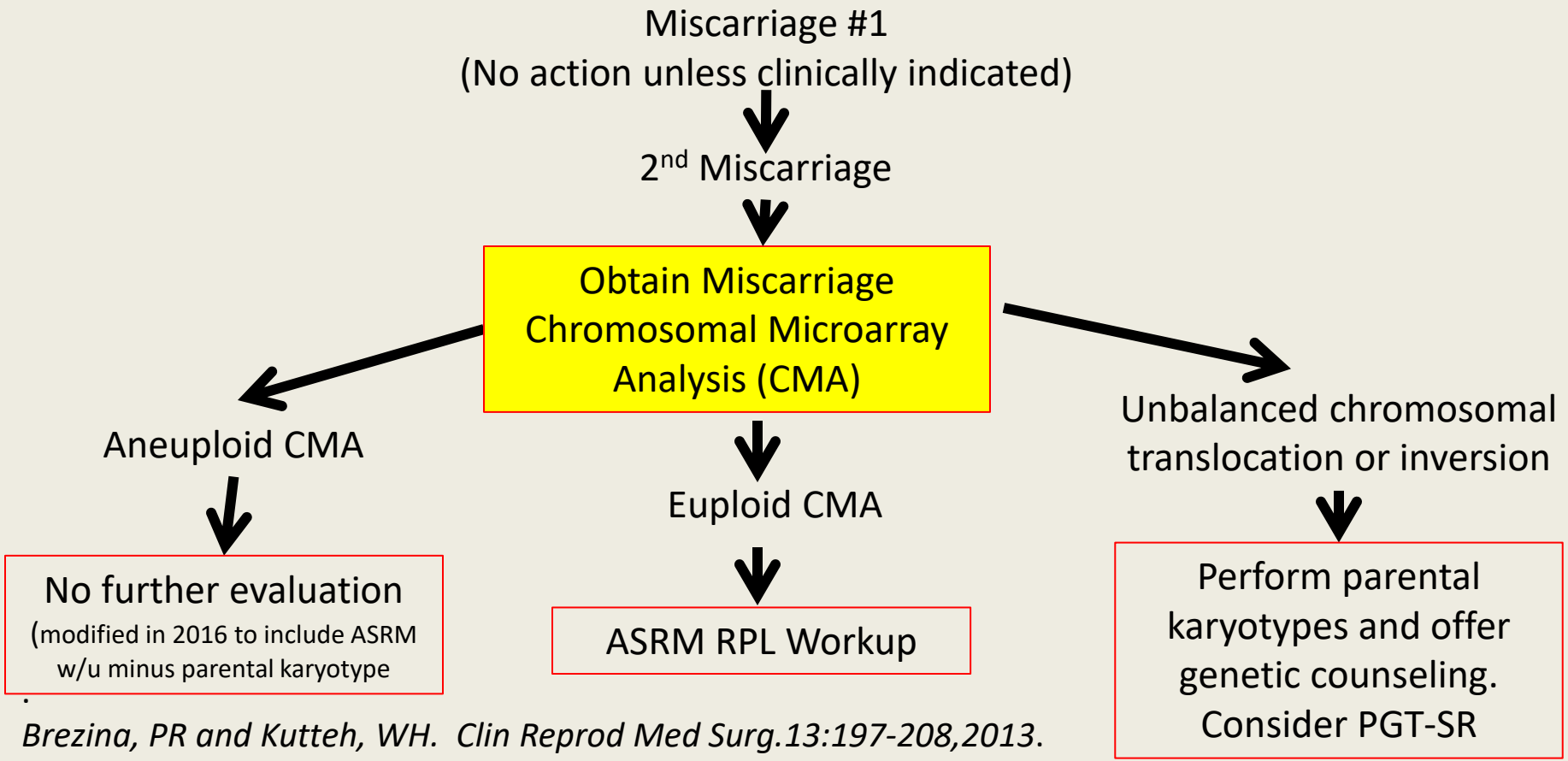


ASRM & ACOG now recommend chromosomal microarray analysis after the second miscarriage.

De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.

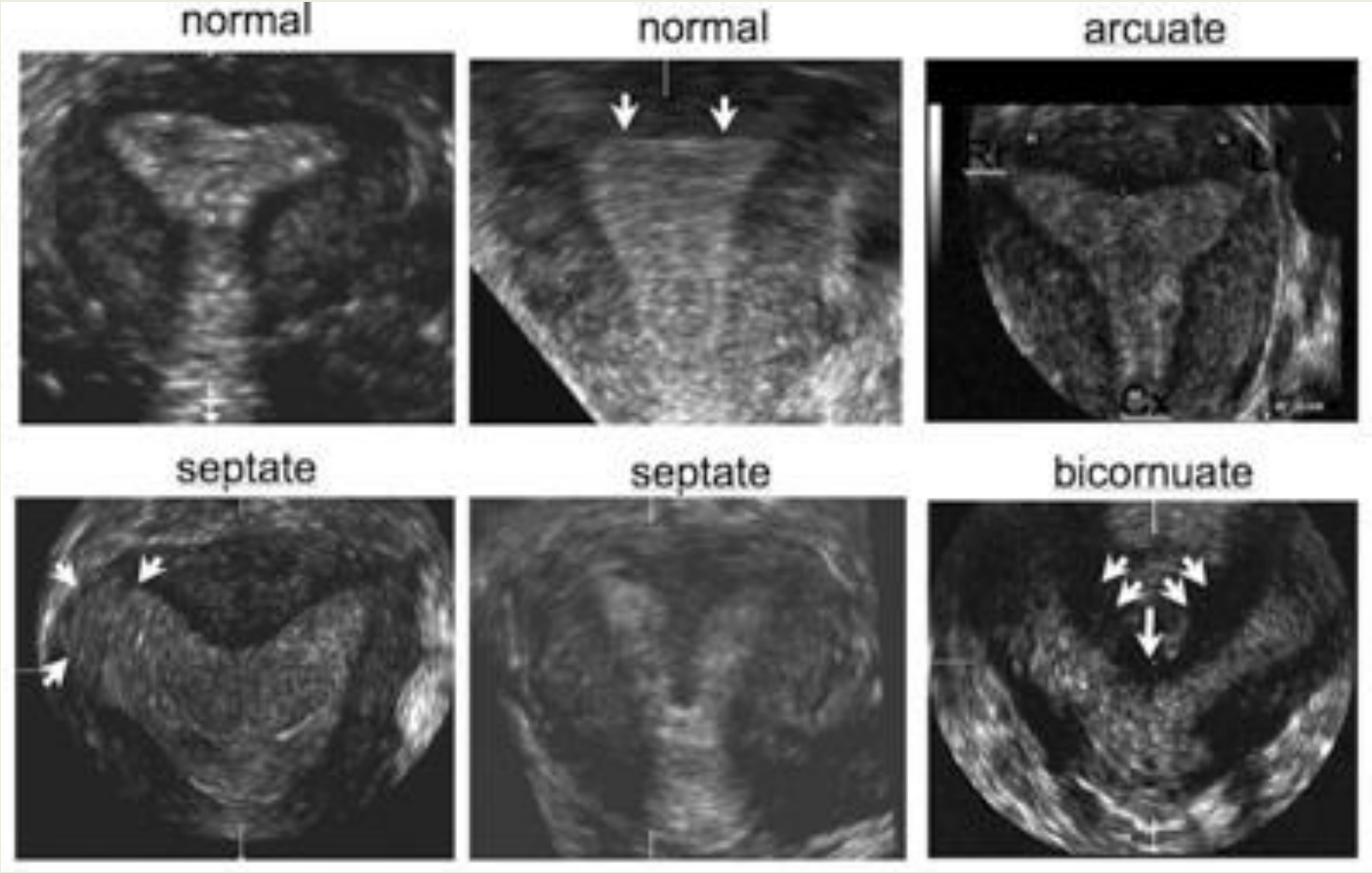
ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

Our 2013 Proposed Evaluation Strategy of RPL is Validated



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

Recommend 3-D Sonohysterography to Evaluate the Uterine Cavity



"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.

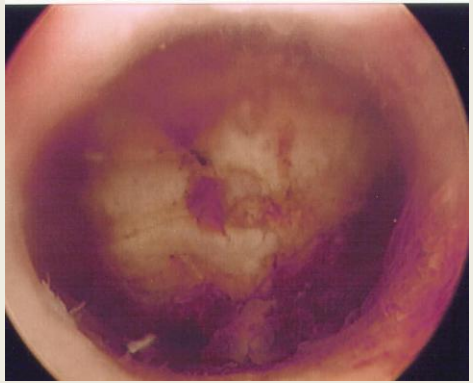
Conclusion(s): The treatment of uterine septa and subsequent outcomes associated with infertility, recurrent pregnancy loss, and adverse obstetrical outcomes are summarized. Resection of a septum has been shown to improve outcomes in patients with recurrent pregnancy loss and to decrease the likelihood 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.)

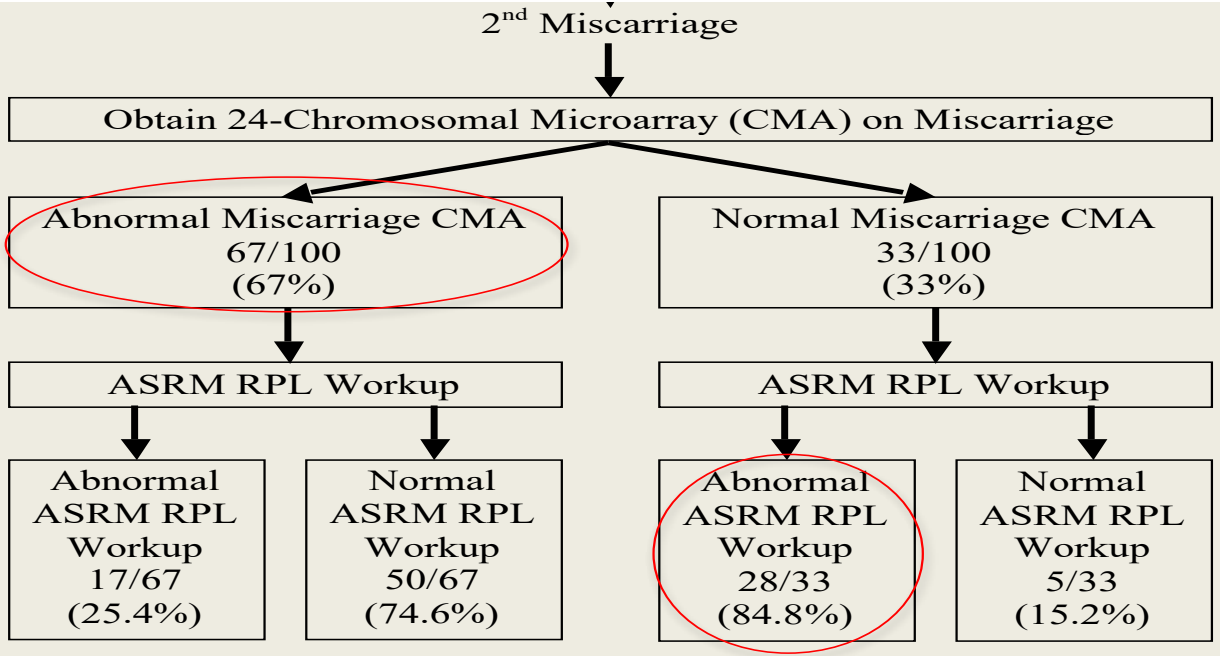
ASRM Practice Committee Myomas. Fertil Steril. 108: 416-425, 2017.

ASRM 2026 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 Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

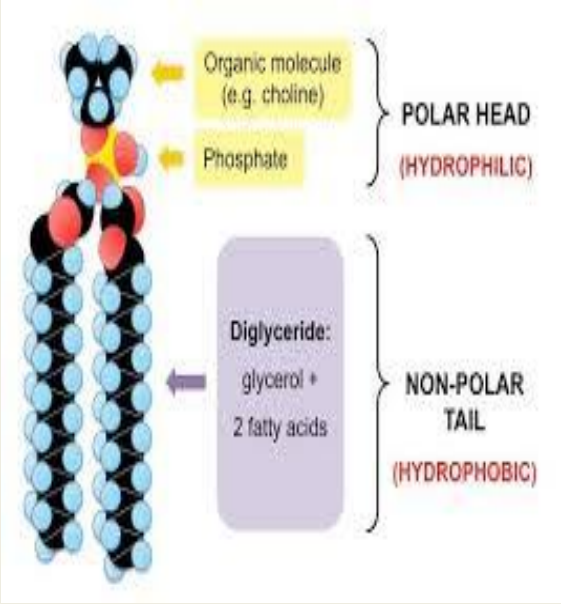
Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients



Popescu F, Kutteh W, Haslow C. Human Reprod. 33:579-587, 2018.

Antiphospholipid Syndrome: The most important treatable cause

Clinical Criteria	Laboratory Criteria
Recurrent loss <10 wk	Lupus anticoagulant
Fetal death > 10 wk	IgG antiCL (> 99%)
Venous Thrombosis	IgM antiCL (> 99%)
Arterial Thrombosis	IgG anti β2- glycoprotein
	IgM anti β2- glycoprotein



Miyakis et al. J Thromb Haemost 4:295 – 306, 2006
De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024
ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

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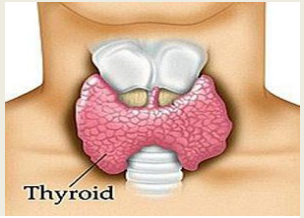
ACOG and ASRM Guidelines- Antiphospholipid Antibodies and Recurrent Loss

"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 Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.
De Assis V et al. Clinical Expert Series RPL. Obstet Gynecol. 143:645-59, 2024.
ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023.

Identify and Correct Thyroid, HgbA1c, Vit D, and Progesterone



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

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

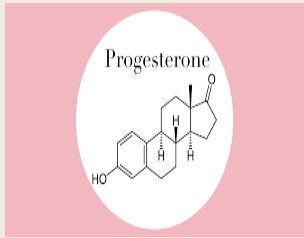
Women with RPL have an increased prevalence of Insulin Resistance and prediabetes.

Check HgbA1c with normal < 5.6.Treat with Metformin ER. Diabetes if HgbA1c over 6.4.

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

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.



Supplement with progestogens when first trimester bleeding or 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.

Endometrial Inflammation is Associated with RPL

Chronic endometritis and recurrent reproductive failure: a systematic review and meta-analysis

Carlo Ticconi[1*†], Annalisa Inversetti[2,3†], Serena Marraffa[1], Luisa Campagnolo[4], Jephtah Arthur[2], Enrica Zambella[2] and Nicoletta Di Simone[2,3]

[1]Department of Surgical Sciences, Section of Gynecology and Obstetrics, University of Rome Tor Vergata, Rome, Italy, [2]Department of Biomedical Sciences, Humanitas University, Milan, Italy, [3]Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS) Humanitas Research Hospital, Milan, Italy, [4]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

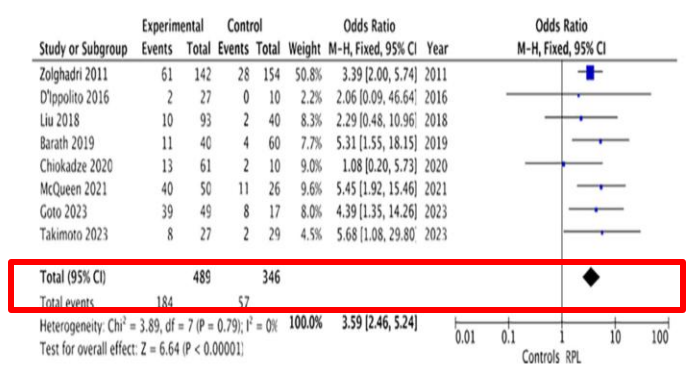


FIGURE 6
Forest plot for chronic endometritis and recurrent pregnancy loss (RPL).

JOURNAL ARTICLE

O-023 Double blind randomised controlled trial of doxycycline in women with recurrent miscarriage and chronic endometritis: The CERM Trial

S Quenby, J Odendaal, N Black, K Fishwick, J Thornton, K Makwana, J Fisher, R Lall, A Coomarasamy, I Granne ... Show more

Human Reproduction, Volume 40, Issue Supplement_1, June 2025, deaf097.023, https://doi.org/10.1093/humrep/deaf097.023

Published: 23 June 2025

Chronic Endometritis Recurrent Miscarriage (CERM) study of 505 RM with CE found no association with outcome or random preconception doxycycline. The screening and treatment of CE should not form part of the routine management of RM.

"A recent high-quality RCT demonstrated no benefit of prescribing doxycycline for CE in RPL. *ASRM RPL: a committee opinion. Fertil Steril 2026.*

Comparison of Non-specific Diagnostic methods for chronic endometritis versus Pathogen-specific culture for endometrial inflammation

Comparison of diagnostic methods for chronic endometritis vs. pathogen-specific culture.

Method	Sensitivity/specificity	Specimen collection	Pathogen-specific	Technician required	Reproducibility	Menstrual phase limitations	Notes
Hysteroscopy	Sensitivity 59%–84% Specificity 69.7%–89%	Office or operating room procedure	No	Surgeon required	Intraclass correlation 0.4–0.78	Yes	Increased cost, poor interphysician reproducibility, high false positive
Histology (H&E)	Sensitivity 75% Specificity 65%	Office endometrial biopsy	No	Skilled pathologist	Interobserver variability 23%–31%	Yes	High false negative, possible cross-reactivity by alternate pathogenesis
CD 138 IHC stain	Sensitivity/specificity greater than histology and hysteroscopy[a]	Office endometrial biopsy	No	Skilled pathologist	Interobserver variability 2.4%–3.2%	Yes	Improves sensitivity and specificity when used with H&E stain, possible cross-reactivity by alternate pathogenesis, risk of vaginal and endocervical contamination
Endometrial culture	Sensitivity 71% Specificity 57%	Office endometrial biopsy	Yes	Laboratory technician	Moderate[b]	No	Risk of vaginal and endocervical contamination, specific and allows pathogen-specific treatment
High endocervical mycoplasma culture	Sensitivity 82% Specificity 98%	Cervical swab	Yes	Laboratory technician	High	No	Specific, cannot rule out other etiology

Note: H& E = hematoxylin and eosin; IHC, immunohistochemistry.

[a] Used as diagnostic standard compared with hysteroscopy and/or histology.

[b] Poor correlation with real time-quantitative polymerase chain reaction. RT-PCR cotesting, suggesting greater threshold of bacteria required for positive culture compared with other diagnostic methods. Reproducibility is thus sample dependent.

Bishop S, Kutteh WH. Targeted treatment with doxycycline for RPL. Fertil Steril. 2026.

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

	RPL Patients (*n*=1583)	RPL Patients Conceived	RPL Patients Delivered	P value (compared to unexplained)
Positive *Mycoplasma*	66 (4.2%)	41/63 (65.1%)	32/41 (78.0%)	0.045
Positive *Ureaplasma*	249 (15.7%)	163/237 (68.8%)	124/163 (76.1%)	0.003
Total Positive	315 (19.9%)	204/300 (68.0%)	156/204 (76.5%)	0.001
Neg Culture (Unexplained)	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. Fertil Steril. 2026;125:852-859.

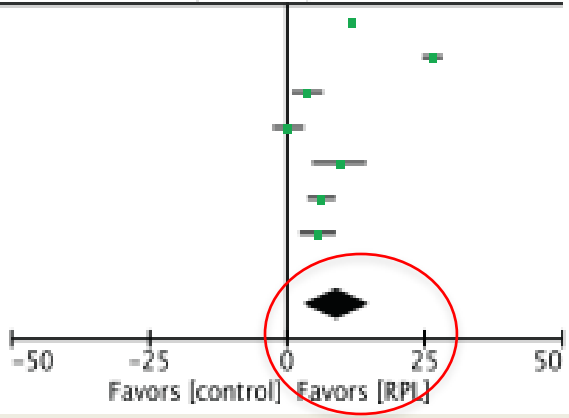
Male Factor- High DFI increases RPL

Recurrent pregnancy loss as 3 or more losses

Study or Subgroup	Recurrent Pregnancy Loss Mean	SD	Total	Fertile Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Absalan 2012	23.3	1.1	30	11.6	0.5	30	14.8%	11.70 [11.27, 12.13]
Carrell 2003	38.3	4.2	21	11.9	1	26	14.6%	26.40 [24.56, 28.24]
Coughlan 2014	10.9	1.9	16	7.2	3.7	7	14.3%	3.70 [0.81, 6.59]
Esquerre-Lamare 2018	6.8	5.6	33	6.6	5.5	27	14.3%	0.20 [-2.62, 3.02]
Imam 2011	23.4	9.9	20	13.9	5.4	20	13.4%	9.50 [4.56, 14.44]
Kumar 2012	28.1	5	45	21.8	4.8	20	14.4%	6.30 [3.74, 8.86]
Ruixue 2013	25.6	11.5	68	20	7.7	63	14.1%	5.60 [2.27, 8.93]
Total (95% CI)			**233**			**193**	**100.0%**	**9.12 [3.16, 15.08]**

Heterogeneity: $Tau^2 = 62.49$; $Chi^2 = 369.78$, df = 6 ($P < 0.00001$); $I^2 = 98\%$

Test for overall effect: Z = 3.00 (P = 0.003)



Assessing sperm DNA fragmentation in couples with RPL should be considered. Alter lifestyle issues (Tobacco, EtOH, Obesity)

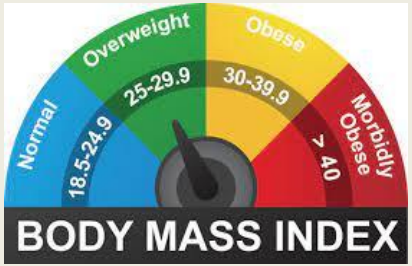
Strong ⊕⊕⊕◯

ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

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)



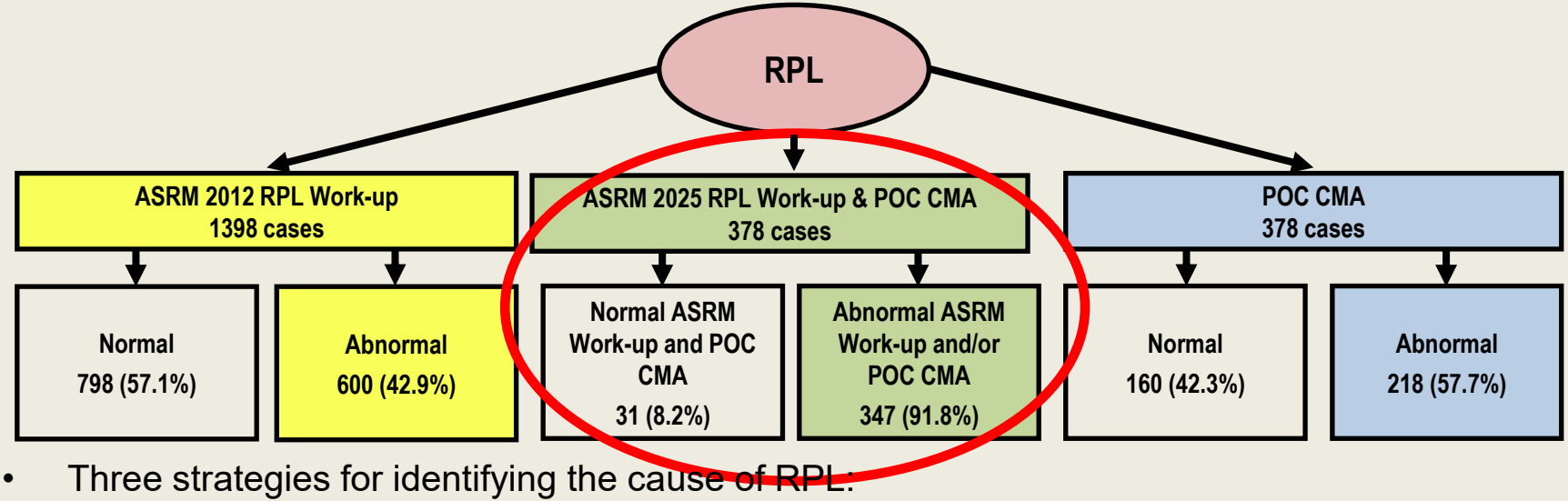
Sepidarkish M. Reprod Health 2018; 15:210

Not Recommended in the Evaluation of RPL

Inherited Thrombophilia	Not Recommended	Factor V Leiden, Prothrombin gene, MTHFR, PAI-1, Protein C & S, Antithrombin
Other Immune Testing	Not Recommended	NK cells, TH1/TH2 ratio, Thyroid antibodies
Endometrial Receptivity Tests	Not Recommended	ERA-Endometrial Receptivity Assay EFT-Endometrial Function Test
Microbiome Testing	Not Recommended	EMMA-Endometrial Microbiome Test

ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

ASRM 2026 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.

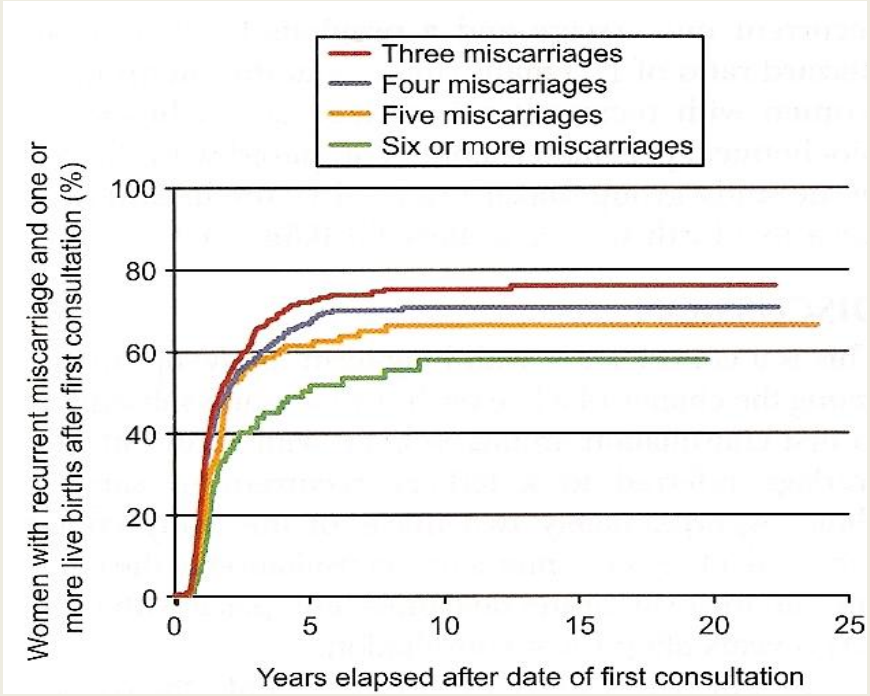
Papas and Kutteh. Curr Opin Obstet Gynecol. 32:371-9,2020.

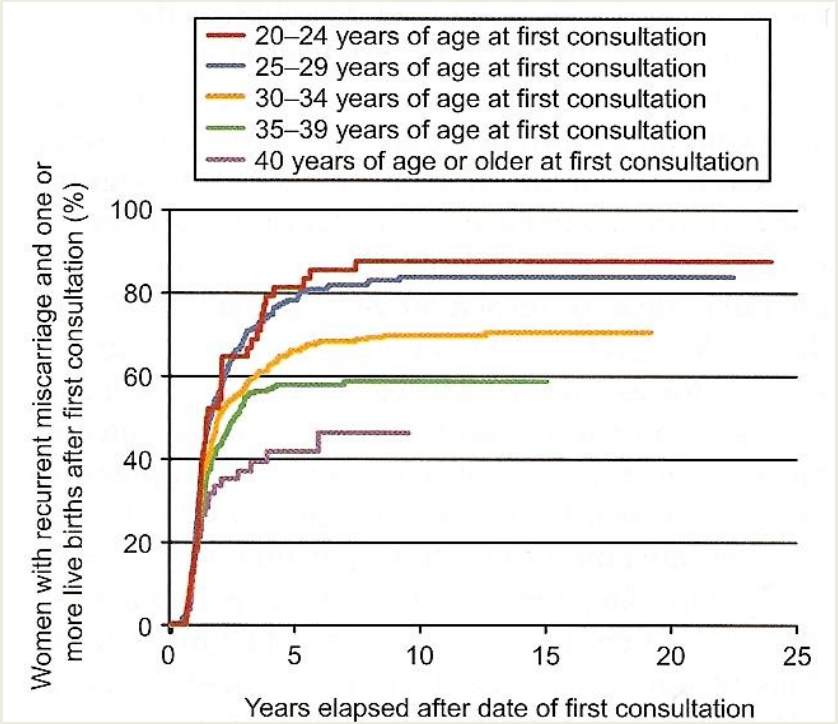
What about “Truly Unexplained RPL”?

- 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 70%
- 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

Practical Take-Home Algorithm for Generalists

- With the second loss, evaluation should start
- Obtain miscarriage chromosomal microarray
- Assess uterine cavity
- Screen for Antiphospholipid syndrome
- Check TSH and HgbA1c
- Consider screen for infections
- Avoid unsupported testing and treatments

Kutteh WH, et al. Role of Genetic Analysis of Products of Conception Rep Biol Med Online. 45:1-12, 2024..
Papas and Kutteh. Curr Opin Obstet Gynecol. 32:371-9,2020
ASRM Recurrent Pregnancy Loss: a committee opinion. Fertil Steril 2026.

Conclusions –RPL

- Over 90% of RPL cases will find an etiology
  (Doubles the number of patients who will get an explanation)
- Miscarriage tissue CMA is now first-line
- APS is the most important treatable cause
- Most couples ultimately achieve a live birth
- Selective testing of parental karyotypes
  (Reduces the cost of RPL evaluation by 50%)
- Ob/Gyns play a critical role in early evaluation
  (Important to collect miscarriage tissue for microarray)

Kutteh WH, et al. Role of Genetic Analysis of Products of Conception Rep Biol Med Online. 45:1-12, 2024..
Papas and Kutteh. Curr Opin Obstet Gynecol. 32:371-9,2020
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