

Recurrent Pregnancy Loss (RPL) Evaluation and Management

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Recurrent Pregnancy Loss Evaluation and Management

DISCLOSURES: Ferring and Natera- 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 recommended by ASRM
- Predict the effect of maternal age and prior losses on predicting future live births.
- Explain the role of genetic testing of miscarriage tissue in developing a strategy for the evaluation of RPL.



ACOG, ESHRE and ASRM Definition: RPL



- RPL is defined as having 2 or more miscarriages
- A miscarriage is a loss of a pregnancy in the uterus documented by a **low or decreasing level of hCG or ultrasound exam** (patient FAQ)
- After two miscarriages a thorough physical exam and testing are recommended



- 2+ pregnancy losses before 24 weeks, **consecutive not required**
- Excludes ectopic pregnancy, molar pregnancy, implantation failure
- Losses have been **confirmed by urine or serum hCG** and includes biochemical losses and pregnancies of unknown location



- RPL is defined by two or more failed consecutive pregnancies before 20 weeks of gestation
- Pregnancy must be **visualized by ultrasound or documented by histopathology**

ACOG Patient FAQ's online 2023. ESHRE Guideline Recurrent Pregnancy Loss. Dec 2022.

ASRM Committee Opinion Fertil Steril. 99:63, 2013. Assis et al. Clinical Expert Series. Obstet Gynecol. 143:645-59, 2024

Updated Society Guidelines for Workup for RPL(1)

Diagnostic Test	ACOG 2024	RCOG 2022	ASRM 2013	ESHRE 2022	Kutteh 2024
Karyotype on Parents	Yes	Option	Yes	No	Option
Miscarriage microarray	Yes	Yes	Option	Option	YES
Uterine Anatomy (SIS)	Yes	Yes	Yes	Yes	YES
Anticardiolipin Antibodies	Yes	Yes	Yes	Yes	YES
Lupus anticoagulant	Yes	Yes	Yes	Yes	YES
Thyroid function (TSH)	Yes	Yes	Yes	Yes	YES
PCOS (HgbA1c)	Yes	Yes	Yes	No	YES

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

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

Updated Society Guidelines for Workup for RPL (2)

Diagnostic Test	ACOG 2024	RCOG 2022	ASRM 2013	ESHRE 2022	Kutteh 2024
Thrombophilia	No	No	No	No	NO
Hyperprolactinemia	No	NC	Yes	Option	Option
Microbial Infections	NC	Option	No	Option	YES
Sperm DNA Fragments	No	NC	Yes	Yes	Option
Luteal Phase (low P4)	Option	Yes	No	Yes	YES
Vitamin D	Treat	NC	NC	Option	YES
Ovarian reserve (AMH)	NC	NC	No	Option	Option
Tobacco, Etoh, Obesity	Yes	Yes	Yes	Yes	YES

Papas & Kutteh. Curr Opin Obstet Gynecol. 32:371-9, 2020. NC=no comment.

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

Results of ASRM Workup for RPL

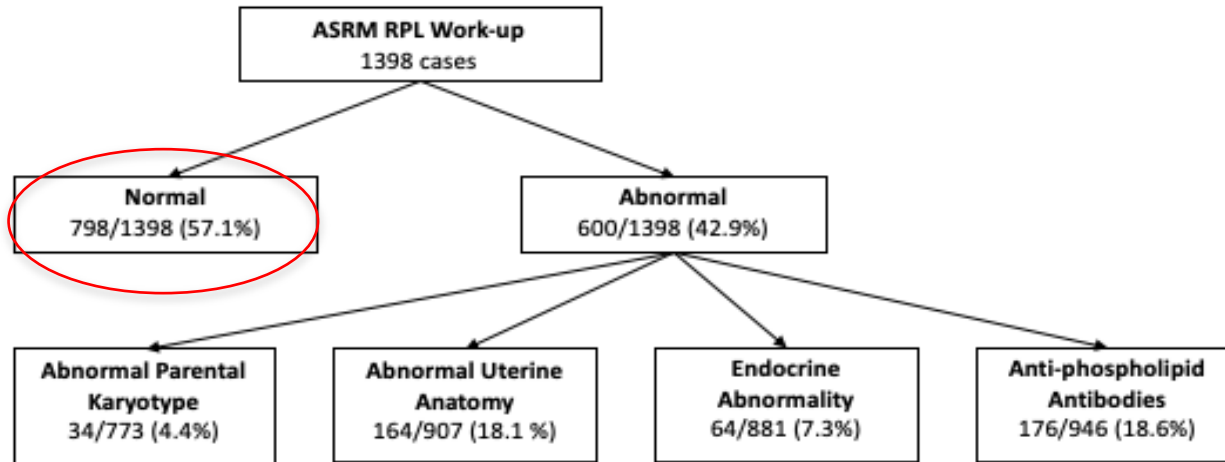
Frequency of abnormal tests in 1020 women with RPL

Control	# of prior losses	2 n=447	3 n=343	≥ 4 n=230	P value 2,3,>4
0.4%	Parental genetics	2.8%	5.4%	5.2%	NS
7.5%	Anatomy	18.7%	18.2%	16.7%	NS
0.5%	Lupus anticoagulant	5.0%	2.9%	1.9%	NS
6.7%	Anticardiolipin	15.6%	13.1%	17.1%	NS
3.9%	TSH	8.1%	6.5%	6.2%	NS

Control values significantly lower than 2,3, or 4 losses individually or combined.

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

ACOG/ASRM/ESHRE RPL Workup Fails to Provide an Explanation in more than 55% of Patients!



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

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

Papas R & Kutteh. Curr Opin Ob Gyn. 32:371-379, 2020.

ASRM/ACOG/ESHRE Evaluations for RPL Differ

- GENETIC (parents and miscarriage)
- ANATOMIC (congenital and acquired)
- HORMONAL (thyroid, Vit D, P4, HgbA1c)
- IMMUNOLOGIC (APA, Thyroid, NK cells)
- MALE (sperm DNA fragmentation)
- LIFESTYLE (tobacco, alcohol, obesity)
- OTHER FACTORS (thrombophilia, infectious)

ESHRE Recurrent Pregnancy Loss Guidelines. Human Reprod. Jan 2023

ASRM Committee Opinion Fertil Steril. 99:63, 2013

Kutteh WH. Novel strategies for the management. Semin Reprod Med 33:161, 2015.

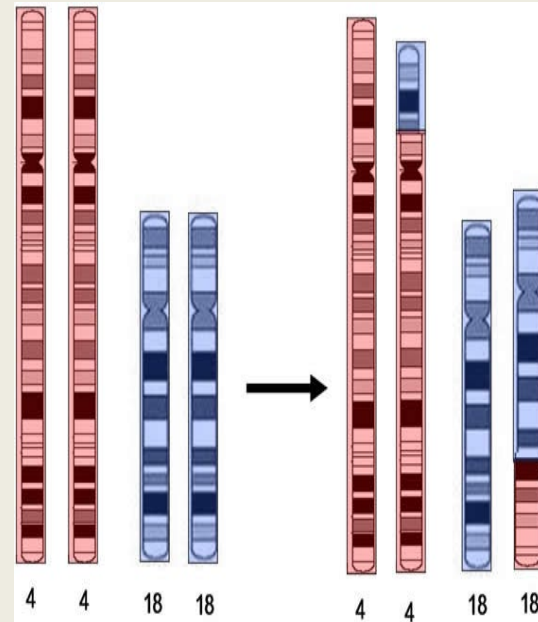
Clinical Expert Series Obstet Gynecol 143:645-59.2024.

Parental Genetic Abnormalities

(found in 3-5% of couples with RPL)

- Reciprocal translocation 59%
- Robertsonian translocation 27%
- Inversions 9%
- Sex chromosome aneuploidy 4%
- Supernumerary chromosome 1%

Most common parental abnormality
is a balanced translocation



Balanced translocation

Fetal chromosome Abnormalities-Miscarriage Tissue

Chorionic Villi



“Fluffy” outer edges
Tend to float in saline
Whiter than decidua

Good

Maternal Decidua



Uniform edges
Pink, dense and sheet like

Bad

Gestational age of samples ranges from first trimester

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

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

2013 Proposed Algorithm for the Initial Evaluation of Recurrent Pregnancy Loss

Miscarriage #1
(No action unless clinically indicated)

↓
2nd Miscarriage

↓
**Obtain Miscarriage
Chromosomal Microarray
Analysis (CMA)**

↙
Aneuploid CMA

↓
Euploid CMA

↘
Unbalanced chromosomal
translocation or inversion

↓
No further evaluation

↓
ASRM RPL Workup

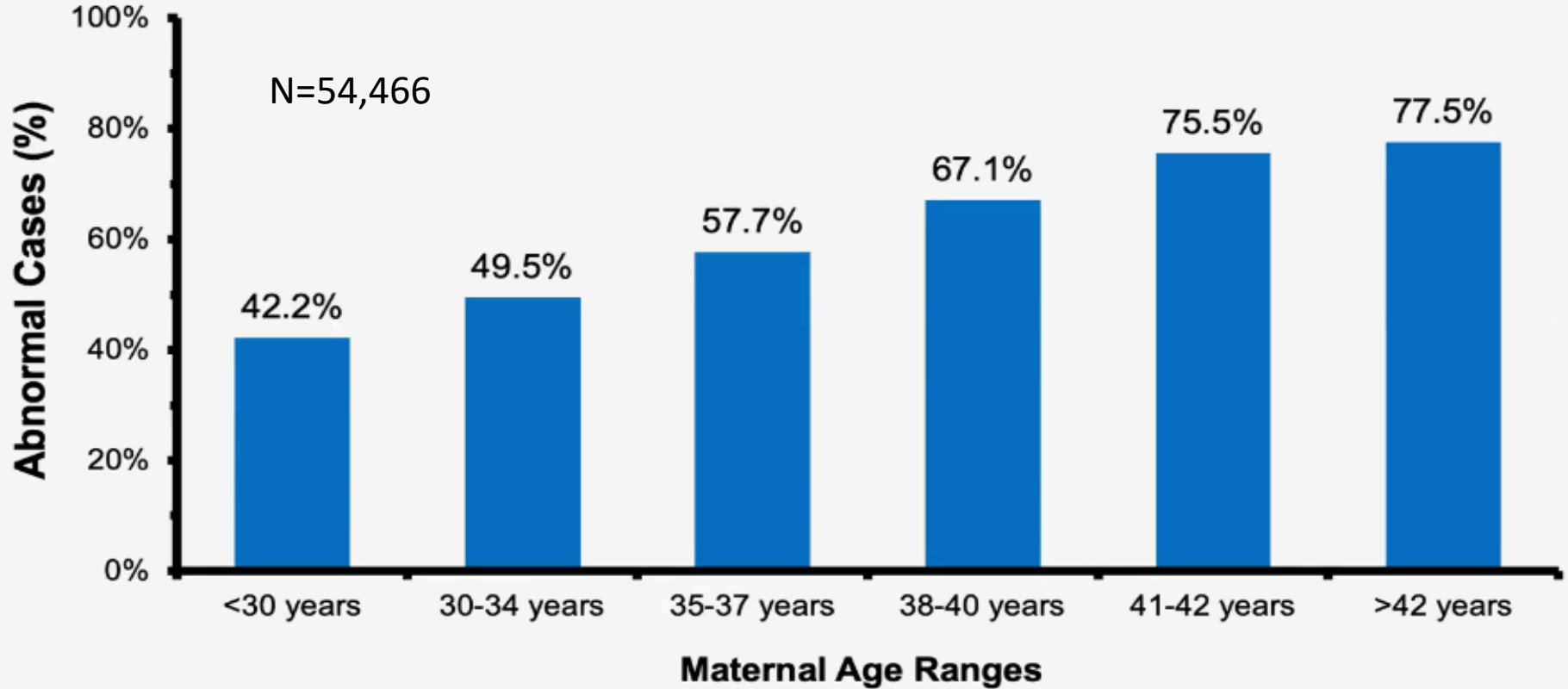
↓
Perform parental
karyotypes and offer
genetic counseling.
Consider PGT-SR

Successful Chromosomal Microarray Results from POC Increase with Gestational Age

Gestational Age	N=54,466	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%

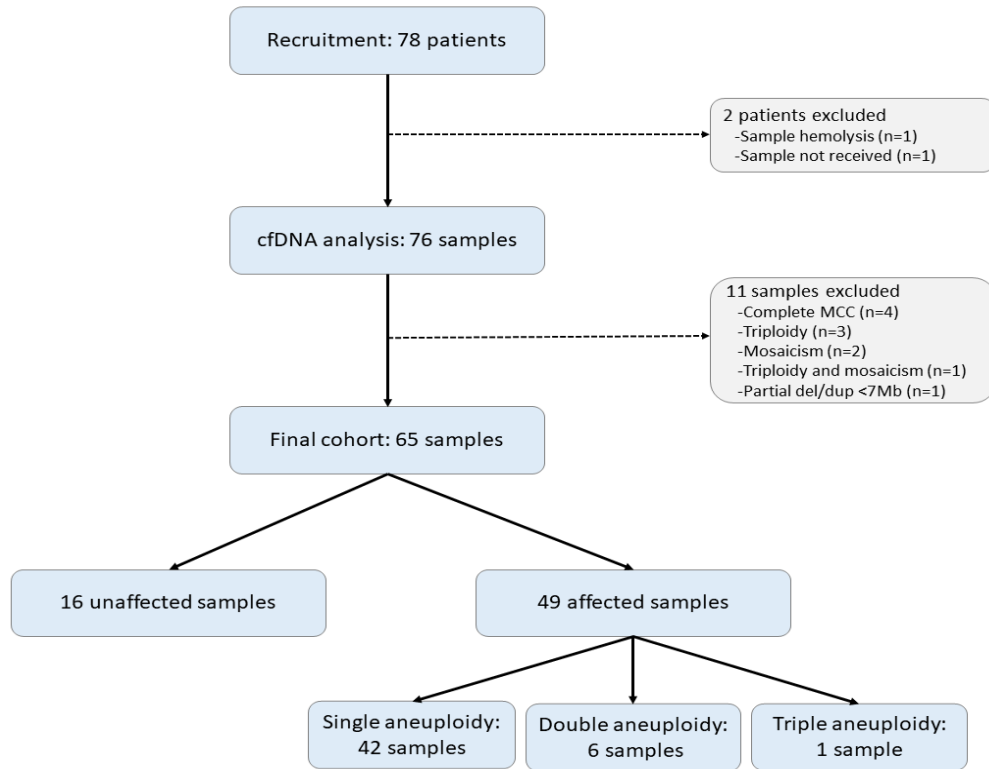
Kutteh, Papas, Maissenbacher, Dahdouh. RBMO 49:1-12, 2024.

Abnormal Chromosomal Microarray Results from POC Increase with Maternal Age



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

The use of maternal cell-free DNA analysis to identify fetal aneuploidies in early pregnancy loss



- 65 patients with miscarriage
- POC CMA + maternal cf DNA

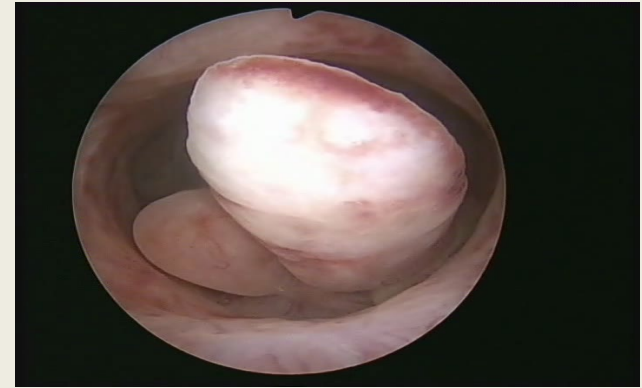
Sample Level Calculations	Sensitivity (%)	Specificity (%)
Full concordance^a	69.4 (34/49)	100 (16/16)
Partial concordance^b	73.5 (36/49)	100 (16/16)

Kutteh et al. J Clin Med. 13.2024. In press. Yaron et al. Human Reprod. 35:1222-29, 2020.

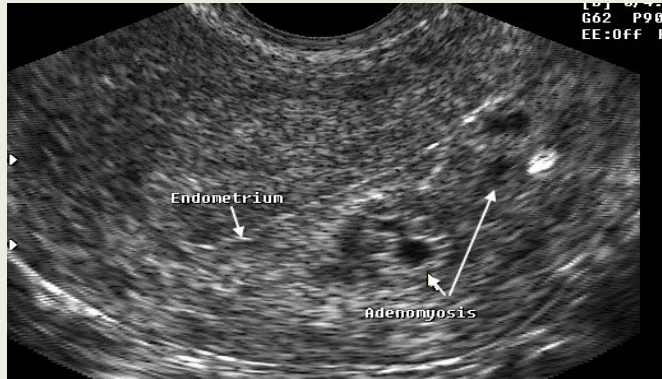
Identify and Correct Acquired Uterine Pathology



Large Polyps



Uterine
Fibroids

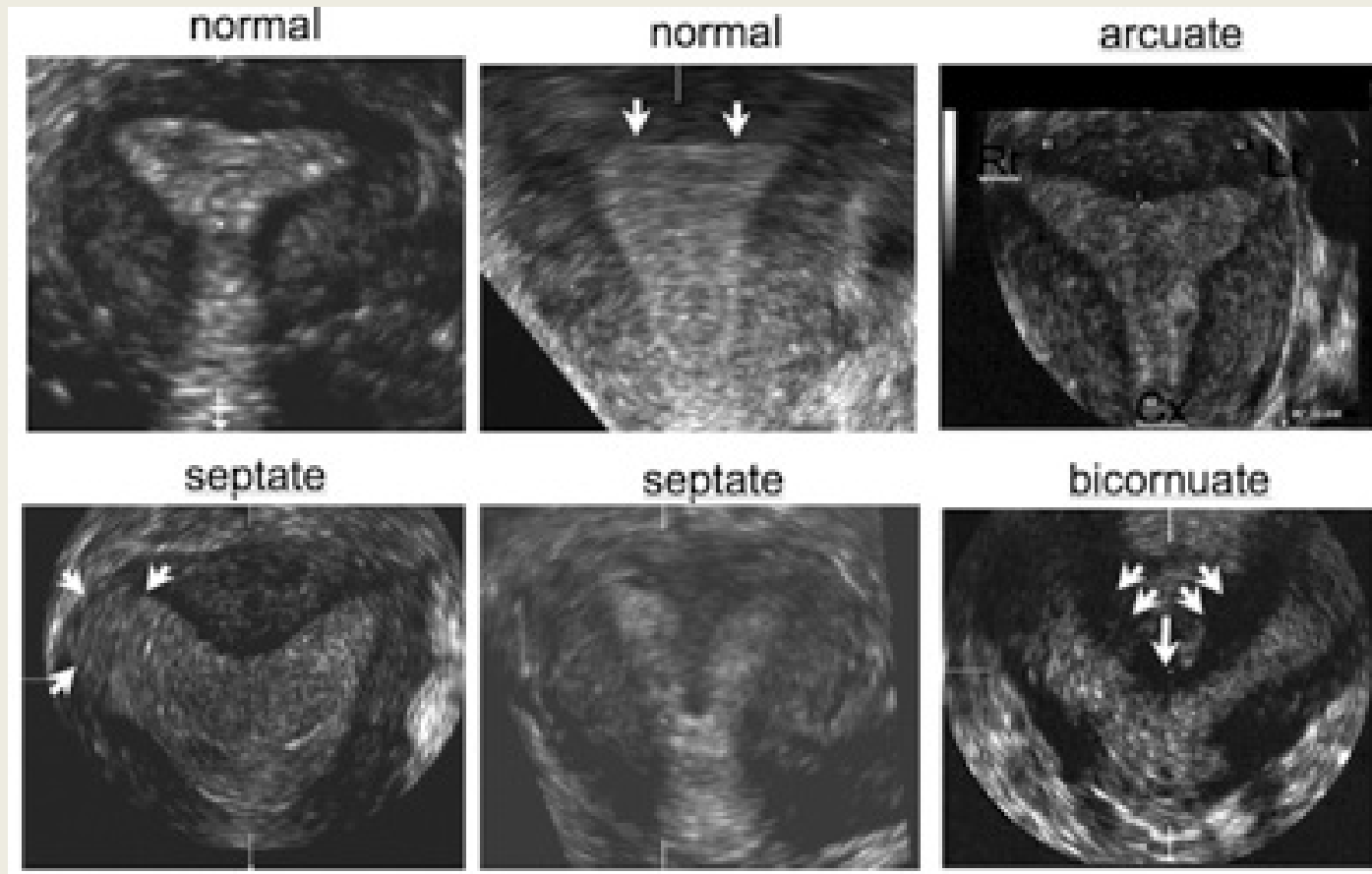


Adenomyosis



Intrauterine
Adhesions

3-D Sonohysterography for the Evaluation of the Uterine Cavity



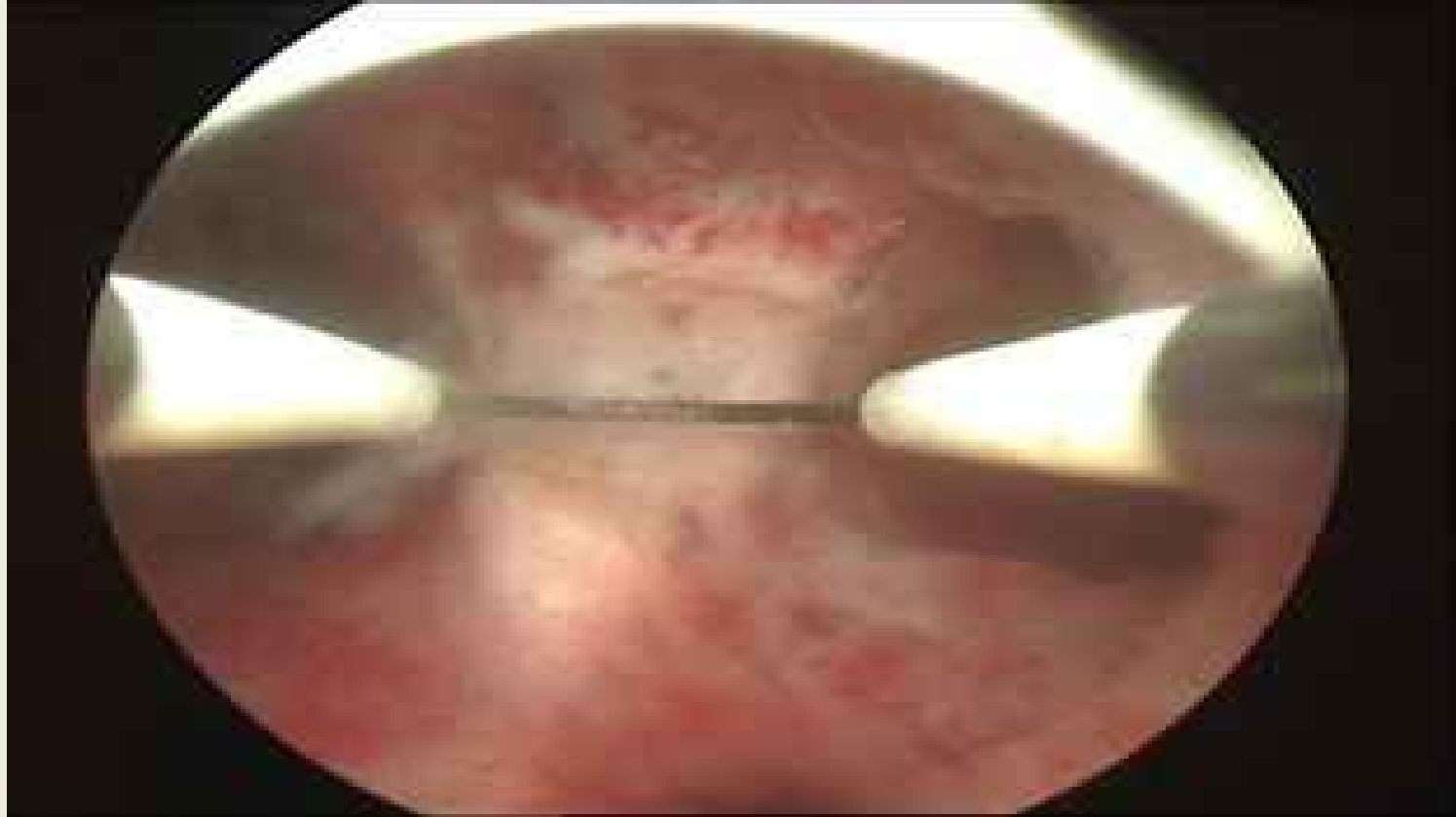
Septate Uterus

- Mullerian ducts develop at week 6, fuse by week 10, and are normally resorbed by week 20
- Caused by failure of septal resorption
- Most common congenital uterine anomaly
- May project from fundus to upper 1/3 of vagina
- Spontaneous pregnancy loss rate between 30% and 65%
- Loss due to avascular tissue, poor endometrial development
- Consensus is to correct by hysteroscopy if >10 to 15mm

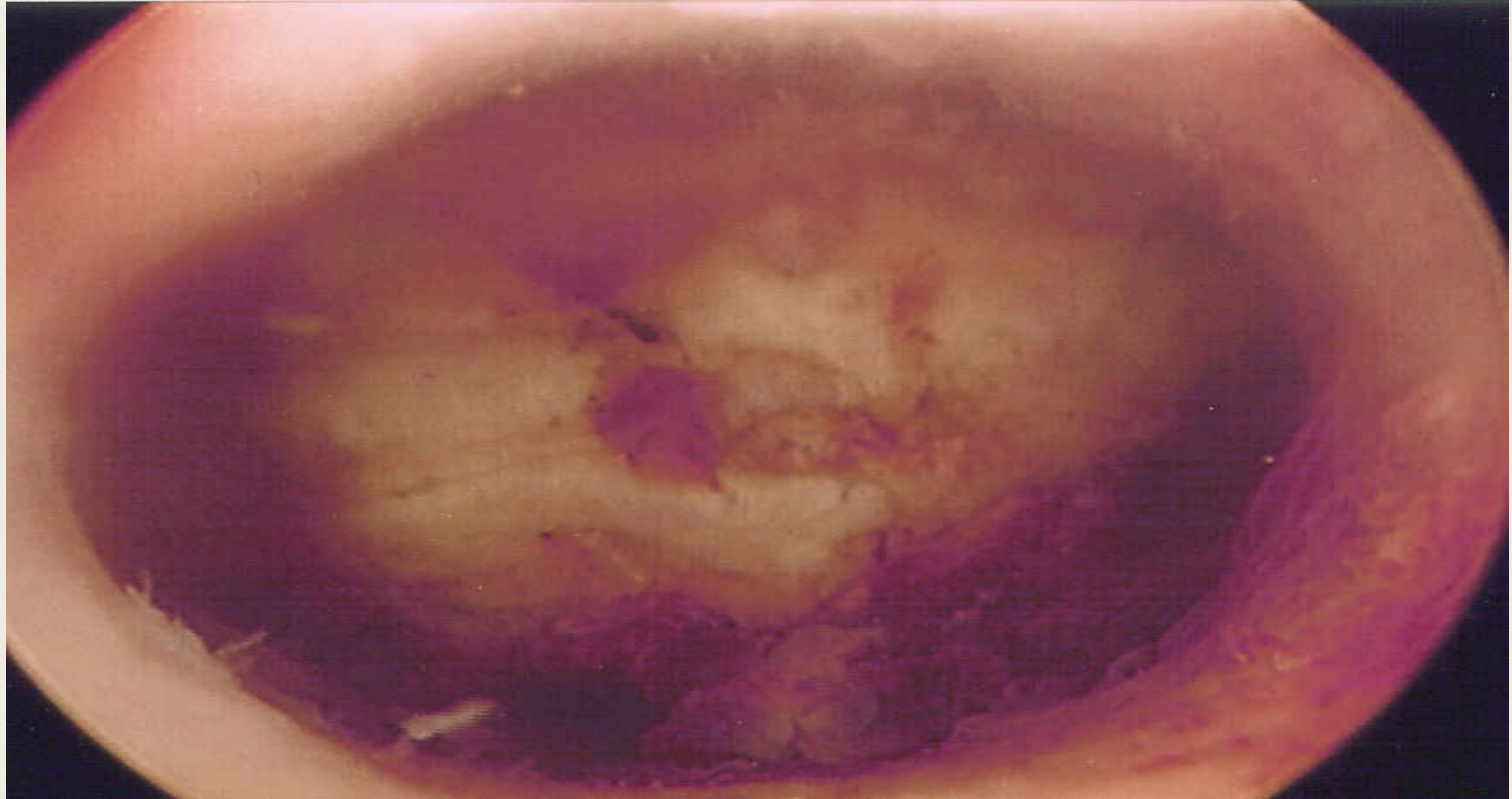
Hysteroscopic view of 20mm Uterine Septum



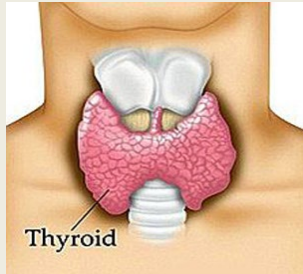
Cutting through avascular septum



Uterine Cavity Normalized after Resection



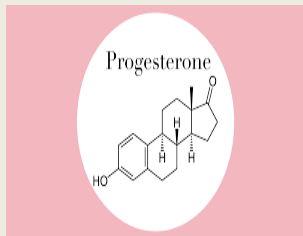
Identify and Correct Thyroid, Vitamin D, and Progesterone



Overt hypothyroidism is associated with RPL and adverse pregnancy outcomes.
The normal range for TSH in non-pregnant reproductive-aged women is 1.0 -2.5 mIU/L
Eliwa J, Ke R, Kutteh W. Thyroid function and Reproduction. Encycl Reprod. 2024.



Preconception Vitamin D > 30ng/ml Increased Clinical Pregnancy Rates
and Live Birth and Decreased Pregnancy Loss
Mumford SG et al. The Lancet 30 May 2018.



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.

PCOS, Insulin Resistance, Prediabetes and RPL

PATIENTS: Non-pregnant: RPL=74, controls=74
matched for age, race, and BMI

MEASURED: Fasting insulin >20 mU/ml or fasting glucose to insulin ratio <4.5

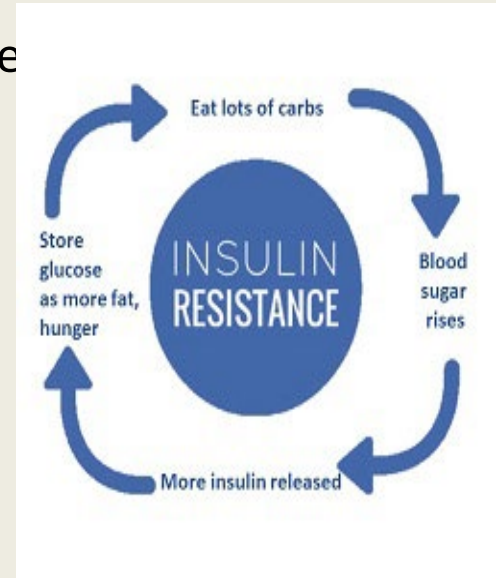
RESULTS: 27% (20/74) RPL patients had IR

9.5% (7/74) controls had IR . Odds Ratio 3.55.

95% Confidence Interval (1.4-9.1)

CONCLUSION: Women with RPL have an increased prevalence of Insulin Resistance.

Treat with Metformin ER

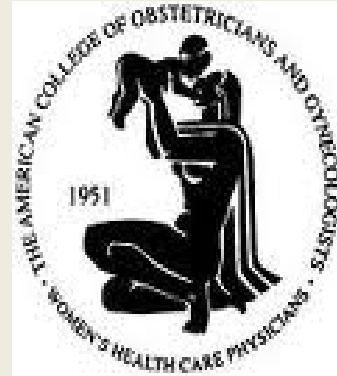


Identify Autoimmune Abnormalities

“The three antiphospholipid antibodies that should be tested”

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

*ASRM Practice Committee Fertil Steril 98:1103-1111, 2012
Branch et al., ACOG Bulletin 132 Obstet Gynecol. 120:1514-1521,2012.*



Research Diagnostic Criteria for APS

Clinical Criteria

Laboratory Criteria

Recurrent loss <10 wk

Lupus anticoagulant

Fetal death > 10 wk

IgG antiCL (> 99%)

Venous Thrombosis

IgM antiCL (> 99%)

Arterial Thrombosis

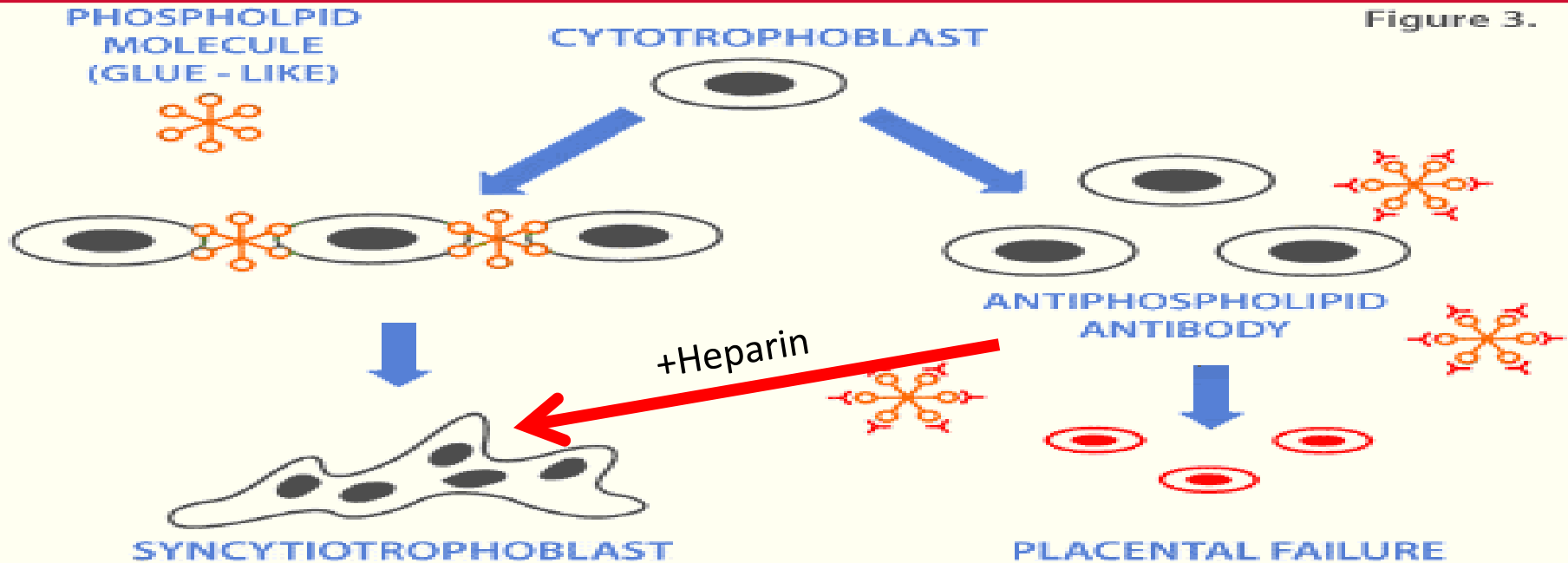
IgG anti β 2- glycoprotein

IgM anti β 2- glycoprotein

Miyakis et al. J Thromb Haemost 4:295 – 306, 2006

Antiphospholipid Antibodies Inhibit Growth and Development of In Vitro Explants of Human Cytotrophoblast Cells

(Syncytiotrophoblast formation restored with Heparin In Vitro)



Anti-inflammatory and anticoagulation effects of Heparin on Placenta!

Kutteh WH. Curr Opin Obstet Gynecol 26:260-265, 2014.

Pathophysiology of aPL

IT' S NOT JUST ANTICOAGULATION !

- Inhibit hCG release from placental explants
- Block of in vitro trophoblast migration & invasion
- Inhibit formation of giant, multinucleated cell
- Inhibit of trophoblast cell adhesion molecules (alpha 1 and 5 integrins, E and VE cadherins)
- Activate complement on the trophoblast surface inducing an inflammatory response

ACOG, ASRM and ESHRE 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 Practice Committee Fertil Steril 98:1103-1111, 2012

ACOG Bulletin 132 Obstet Gynecol. 120:1514-1521,2012

ESHRE Recurrent Pregnancy Loss Guidelines Human Reprod. Jan 2023.

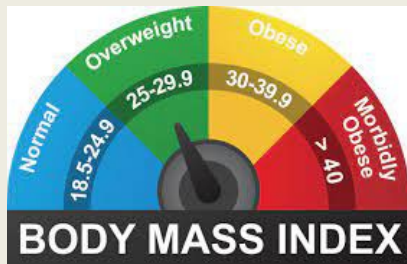


Correct Lifestyle Factors in Both Partners



Risks of RPL increase 1.5 -2 fold

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



Potential Evaluations for RPL

- GENETIC (parents and miscarriage)
- ANATOMIC (congenital and acquired)
- HORMONAL (thyroid, Vit D, P4, HgbA1c))
- IMMUNOLOGIC (APA, Thyroid, NK cells)
- LIFESTYLE (tobacco, alcohol, obesity)
- **OTHER FACTORS (thrombophilia, infectious)**

ESHRE Recurrent Pregnancy Loss Guidelines. Human Reprod. Jan 2023

ASRM Committee Opinion Fertil Steril. 99:63, 2013

Kutteh WH. Novel strategies for the management. Semin Reprod Med 33:161, 2015.

Clinical Expert Series Obstet Gynecol 143:645-59.2024.

Inherited Thrombophilias and Pregnancy

**NO ROUTINE TESTING IS INDICATED for failed Recurrent Pregnancy Loss.
TEST ONLY IF PERSONAL HISTORY OR A STRONG FAMILY HISTORY OF THROMBOSIS.**

Also, no evidence to test for or treat with anticoagulation:

MTHFR polymorphisms

Promoter mutations of PAI-1

Protein Z deficiency

Enhancing mutations of clotting factors

Alternate mutations in Factor V genes

ESHRE Recurrent Pregnancy Loss Guidelines. Human Reprod. Jan 2023

ASRM Committee Opinion Fertil Steril. 99:63, 2013

ACOG Practice Bulletin #197. July 2018



Screening for Infectious Causes of RPL

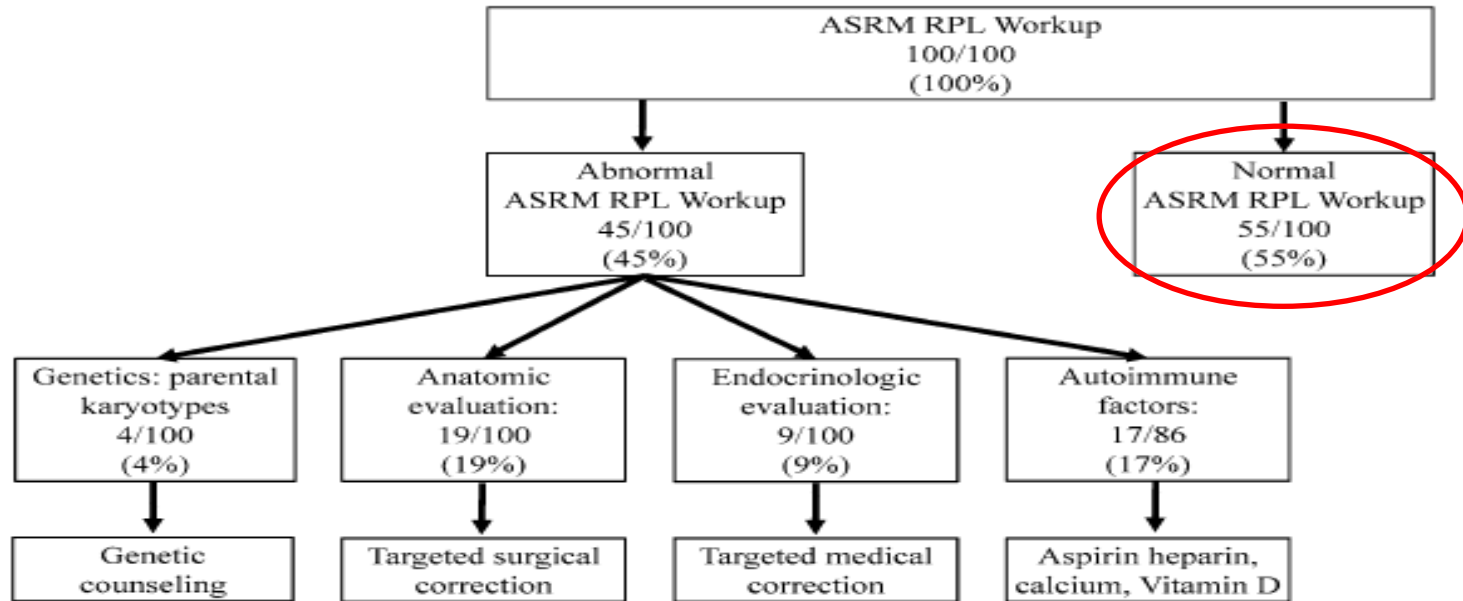
(Cultures, CD138+, EMMA, ALICE),

Both Partners Treated. Condoms Used During Treatment.
Successful Outcome in over 75% after TOC negative.

	RPL Patients (<i>n</i> =1583)	TOC NEG (Doxycycline 100 mg bid x 14 days)	Failed Doxycycline TOC NEG (Levofloxacin 500 mg daily x 14 days)
Positive <i>Mycoplasma</i>	66 (4.2% of 1583)	61 (92.4%)	61 + 2 = 63 (95.5%)
Positive <i>Ureaplasma</i>	249 (15.7% of 1583)	205 (82.3%)	205 + 22 = 237 (95.2%)

50% of RPL Are Unexplained after Workup

THERE IS A BETTER WAY!

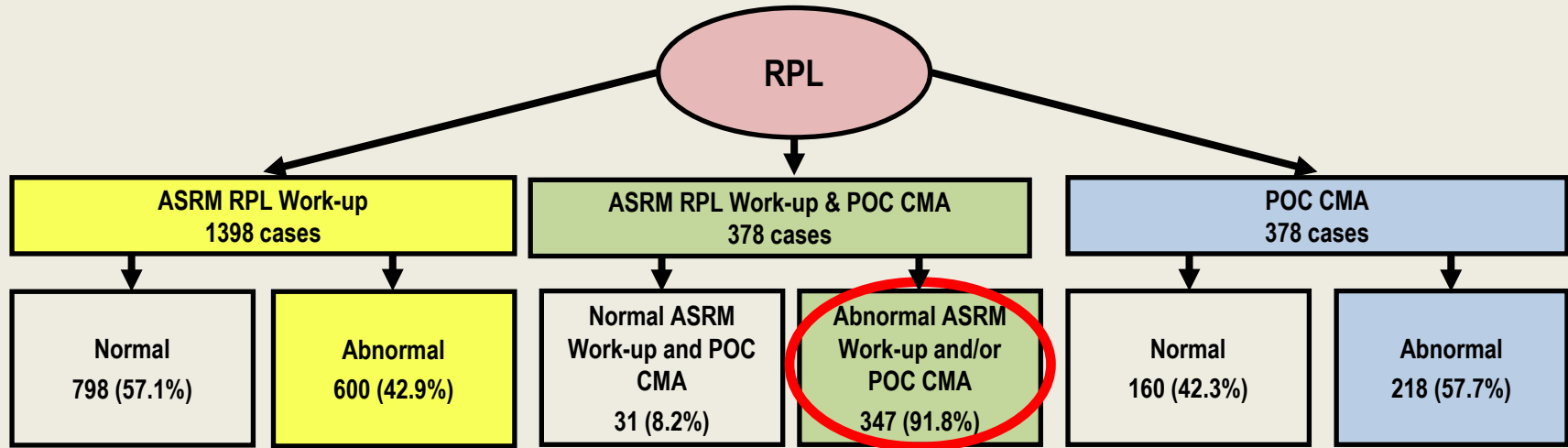


2 Frequency of American Society of Reproductive Medicine—recurrent pregnancy loss (ASRM RPL) workup abnormalities among patients evaluated and the recommended treatment for each abnormality result. See 'Materials and Methods' for details of evaluation.

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

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

Modified ASRM Work-up + POC CMA Explains the Loss in Over 90% of RPL Patients





- Three strategies for identifying the cause of RPL:
 - ASRM work-up: 42.9 % explained (left panel)
 - Modified ASRM + POC CMA: 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.

Which RPL patients might benefit from PGT?

	EUPLOID LOSS by POC CMA or NGS/maternal cfDNA	ANEUPLOID LOSS by POC CMA or NGS/maternal cfDNA	Unbalanced Robertsonian Translocation or Inversion by POC CMA or NGS /maternal cfDNA  ~3% (11 cases) Expectant Management (6 months) Parental Karyotyping Genetic Counseling & PGT-SR
ASRM/ESHRE/RCOG EXPLAINED	~34% (129 cases) <div style="border: 1px solid black; padding: 5px; margin: 5px;"> Treat Aetiology Expectant Management (6 months) </div> Limited role for PGT-A	~14% (53 cases) <div style="border: 1px solid black; padding: 5px; margin: 5px;"> Treat Aetiology Expectant Management (6 months) </div>	
ASRM/ESHRE/RCOG UNEXPLAINED	~8% (30 cases) 'Truly Unexplained' Expectant Management (6 months) Experimental Therapies & Research Limited role for PGT-A IVF & Embryo Cryopreservation +/- Surrogacy for Recurrent documented Euploid Losses	~41% (155 cases) Expectant Management (6 months) PGT-A for Recurrent documented Aneuploid Losses	<div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <1% No result by POC-CMA </div>
For RPL cases with Infertility, AMA, DOR or Male Factor 			IVF +/- ICSI +/- PGT-A if >= 2 Blastocysts

What about “Truly Unexplained RPL”?

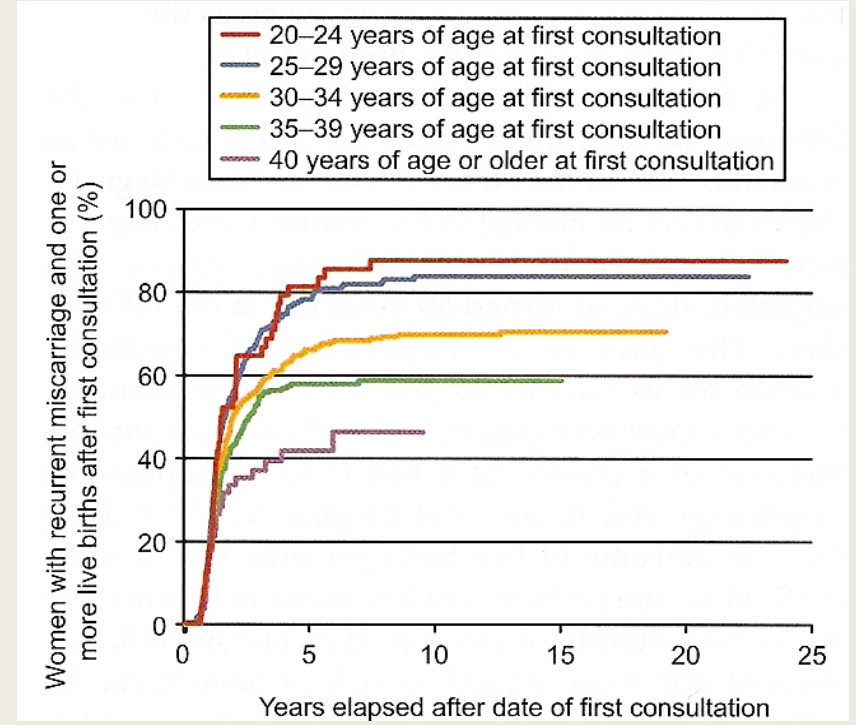
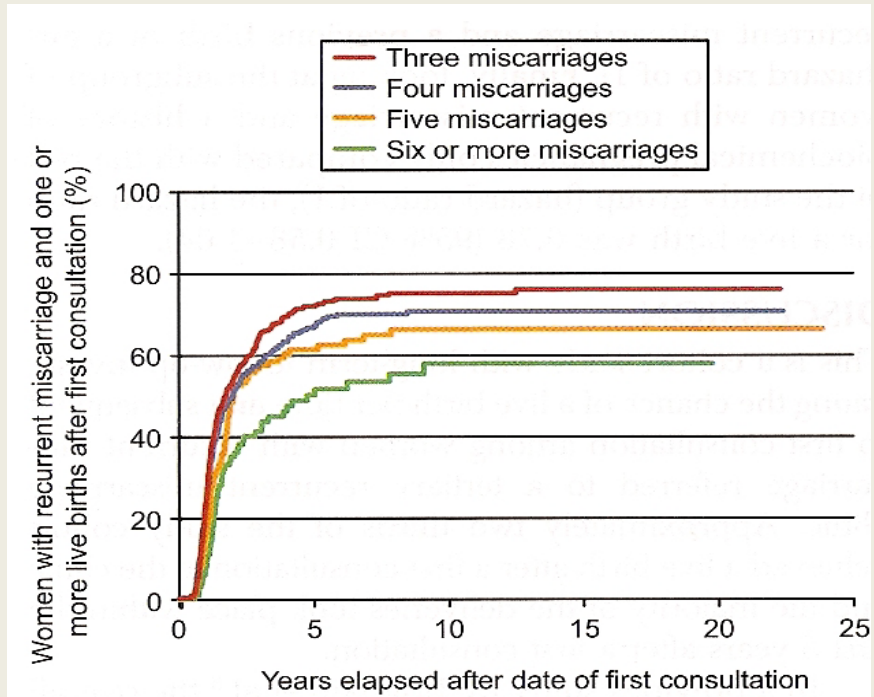
- 90% with probable or definite cause
- Only 10 % of RPL couples unexplained
- Full workup completed and normal
- Chromosomes on POC are normal
- Subsequent live birth is 40% to 80%
- Depends on maternal age, # prior losses
- Candidates for RCT and experimental therapy

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*. In Press, 2023.

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.

