



Recurrent Pregnancy Loss (RPL)

- Aaron Lim, M.D., M.B.A.
- Dept of Obstetrics-Gynecology
- Kaiser Downey Medical Center
- Assistant Clinical Professor
- UCLA David Geffen School of Medicine



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I have nothing to disclose



OBAMACARE

The American Medical Association has weighed in on Obama's health care package. The **Allergists** were in favor of scratching it, but the **Dermatologists** advised not to make any rash moves. The **Gastroenterologists** had sort of a gut feeling about it, but the **Neurologists** thought the Administration had a lot of nerve. Meanwhile, **Obstetricians** felt certain everyone was laboring under a misconception, while the **Ophthalmologists** considered the idea shortsighted. **Pathologists** yelled, "Over my dead body!" while the **Pediatricians** said, "Oh, grow up!"

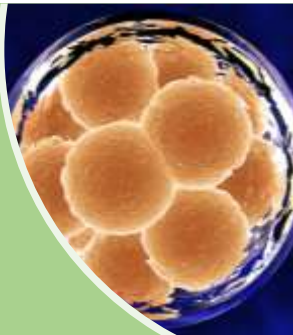
OBAMACARE

The **Psychiatrists** thought the whole idea was madness, while the **Radiologists** could see right through it. **Surgeons** decided to wash their hands off the whole thing, and the **Internists** claimed it would indeed be a bitter pill to swallow. Meanwhile, the **Plastic Surgeons** thought that this proposal would “put a whole new face on the matter”. The **Podiatrists** thought it was a step forward, but the **Urologists** were pissed off at the whole idea. **Anesthesiologists** thought the whole idea was a gas, and those lofty **Cardiologists** didn't have the heart to say no. In the end, the **Proctologists** won out, leaving the entire decision up to the _____ in Washington.



CONTENTS:

- Objectives
- Pre-Test
- Definition of RPL
- Causes
- Treatment
- Post-Test



OBJECTIVES

By the end of this presentation, the audience will be able to:

- Know the definition of RPL
- Understand the risk factors of RPL
- Become aware of the potential causes of RPL
- Familiarize the diagnostic tests to order
- Offer appropriate treatment for known causes of RPL
- Counsel patients about treatment options for unexplained RPL



Pre-Test QUIZ

- Per ASRM criteria, the definition of recurrent pregnancy loss is:
 - Two or more consecutive failed clinical pregnancies as documented by US or histopathologic examination
 - Three or more consecutive pregnancy losses including biochemical pregnancies
 - At least 2 pregnancy losses and they don't have to be consecutive
 - All of the above fulfill the ASRM criteria for RPL
- Factors that may influence miscarriage include:
 - Maternal age
 - Gestational age
 - History of previous miscarriage
 - All of the above are influencing factors
- The recommended first line treatment for pregnant women with APS is:
 - Aspirin alone
 - Heparin alone
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Pre-Test QUIZ

- Which form of uterine anomaly pose the highest risk of miscarriage:
 - Arcuate uterus
 - Bicornuate uterus
 - Septate uterus
 - Unicornuate uterus
- According to the most recent trial, which therapy is proven to decrease miscarriage in women with unexplained RPL:
 - Aspirin
 - Progesterone (either vaginal or injectable)
 - Heparin
 - Prednisolone
- Which inherited thrombophilia is associated with RPL:
 - Factor II mutation (prothrombin gene mutation)
 - Factor V Leiden mutation
 - Anti-thrombin III deficiency
 - None of the above has been shown to cause RPL

DEFINITION of RPL

- Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination*
 - Do NOT include these following pregnancies:
 - Biochemical pregnancy loss
 - Spontaneously resolved pregnancy of unknown location
 - Molar and ectopic pregnancies
- Three consecutive pregnancy losses, which are not required to be intrauterine*

*Practice Opinion – ASRM, 2012
 *Oste AM, et al. Human Reproduction. May 2014; 29(5):931-7

Early vs Late Pregnancy Loss

- **Early:** occurs before 12 wks gestation (80%)
- **Late:** occurs between 13 to 22 wks (20%)

Primary vs Secondary RPL

- **Primary:**
 - Pregnancy loss in women who have never carried to viability
- **Secondary:**
 - Pregnancy loss in a women who has had a previous live birth
 - Prognosis for successful pregnancy better than primary RPL

INCIDENCE*

- 15% of pregnant women experience sporadic loss of a clinically recognized pregnancy
- 5% experience two consecutive clinical pregnancy losses
- 1% have three consecutive pregnancy losses
 - 0.3% - probability or chance of 3 consecutive miscarriages
 - $(15\%) \times (15\%) \times (15\%) = 0.3\%$
 - 1% is higher than that expected by chance alone (0.3%)

Salat-Baroux J, et al. Recurrent spontaneous abortion. Reprod Nutr Dev. 1988; 28:1555.

INFLUENCING FACTORS

- Maternal Age
- Gestational Age
- Previous miscarriage
- Multiple gestation
- Subfertility

% Pregnancy Loss by Maternal Age*

Maternal Age	SAB (%)
20-24	11.1
25-29	11.9
30-34	15
35-39	24.6
40-44	51
≥ 45	93.4

*Nyobi AM, et al. Maternal age and fetal loss: Population based register linkage study. *BMJ* 2000; 320:1708-12.

% Pregnancy Loss by Gestational Age

Gestational Age (wks)*	SAB (%)
< 6	22 - 57
6-10	15
> 10	2-3

*Recurrence risk increases as gestational age at the time of loss increases

% Subsequent Pregnancy Loss by Pregnancy History

# of SAB	SAB (%)
0	11-13
1	14-21
2	24-29
3	31-33

Interpregnancy Interval Prognosis*

GA of SAB	Interpregnancy Interval	SAB Rate
First Trimester	< 3 mos	12%
First Trimester	> 9 mos	12%
Second Trimester	< 3 mos	22%
Second Trimester	> 9 mos	11%

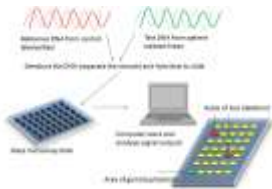
*Roberts CL, et al. Association between interpregnancy interval and the risk of recurrent loss. Human Reprod. Dec 2016; 31(12):2834-40.

Prognosis

- Previous aneuploid miscarriage has a better prognosis than previous recurrent euploid miscarriage
- Chromosomal Microarray (CMA) may be the only test which can give a definite cause behind a miscarriage

*Carp H, et al. Embryonic karyotype in recurrent miscarriage with parental karyotypic aberrations. Fertil Steril 2006; 85:446-50.

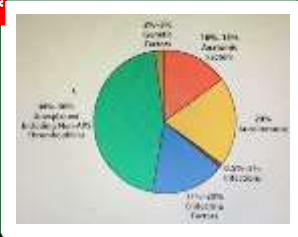
Chromosome MicroArray



CMA is a technology used to determine if there are small scale (microduplication or missing) (microdeletion) pieces of genetic information. These gains and losses are called copy number variants (CNVs). A CNV can be of no medical consequence; pathogenic resulting in physical and/or intellectual consequences; or protective against disease (e.g. HIV infection).

Etiologies of Early RPL

- Idiopathic (40-50%)
- Autoimmune (20%)
- Endocrine (17-20%)
- Anatomic (10-15%)
- Genetic (2-5%)
- Infectious (0.5-5%)
- Environmental (?)



Ford HB, et al. Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy. Rev Obstet Gynecol 2009 Spring; 2(2): 76-83.

IDIOPATHIC

- Chromosomal Analysis of POC – recommended after 2nd consecutive SABs:
 - ~60% have chromosomal abnormalities, with the most common being autosomal trisomies
 - Aneuploid miscarriage has a better prognosis than euploid miscarriage
 - ~40% remained unexplained (i.e, euploid chromosome)

UTERINE FACTORS

- 3.2% - 6.9% - have a major uterine anomaly*
- 2D sonogram – can identify only half of congenital uterine anomalies
- Gold standard: combined HSC + LSC
- Recommended imaging studies:
 - 3-D sonogram
 - MRI
 - Saline infusion sonogram (SIS) – 92% accuracy
 - Hysterosalpingogram (HSG) – high false positive rate

*Suguro-Ogasawara M, et al. Uterine anomaly and recurrent pregnancy loss. *Semin Reprod Med* 2011; 29:514-21.

UTERINE FACTORS

- Mullerian Anomalies – most cannot be corrected
 - Septate Uterus
 - First trimester miscarriage risk – 25% to 47%
 - Can be surgically resected
 - Miscarriage risk returns to baseline after surgical correction
 - Bicornuate Uterus
 - Unicornuate Uterus
 - Didelphic Uterus

} No effect on fertility nor 1st trimester miscarriage
May cause late 2nd trimester miscarriage or PTD
- Uterine Intracavitary Lesions – corrected with surgery
 - Submucous myoma (removal resulted in increase in live birth rate from 23.3% to 52%)*
 - Endometrial polyp
 - Intrauterine synechiae

*Sottilis H, et al. The prevalence and impact of fibroids and their treatment on the outcome of pregnancy in women with recurrent miscarriage. *European Society of Human Reproduction & Embryology*. Sept 2011.

HEMATOLOGIC FACTORS

- Acquired thrombophilia
 - Antiphospholipid syndrome (APS)
- Inherited thrombophilia
 - Factor V Leiden mutation
 - Protein C activity
 - Protein S level
 - Anti-thrombin III deficiency
 - Prothombin gene (Factor II) mutation
 - MTHFR gene mutation

ACQUIRED THROMBOPHILIA ANTIPHOSPHOLIPID SYNDROME

- A systemic autoimmune disease with the presence of antiphospholipid antibodies (aPL) formed against the person's own tissues
 - aPL damages cell membranes and cells lining blood vessels
 - damages to blood vessels lead to interference with coagulation
 - the only proven thrombophilia that is associated with adverse pregnancy outcomes
 - 5%-15% of women with recurrent miscarriage have clinically significant aPL titers

ANTIPHOSPHOLIPID SYNDROME

- Diagnosis: clinical history + laboratory tests (two positive tests performed \geq 12 wks apart)
 - Clinical hx of at least one of the following:
 - Hx of DVT or PE (pulmonary embolism)
 - Recurrent early miscarriages
 - One unexplained late miscarriage
 - Early onset severe preeclampsia
 - Plus one of the following abnormal blood tests:
 - Presence of medium to high positive Anti-cardiolipin IgG
 - Positive lupus anticoagulant
 - Positive beta-2 glycoprotein
- Treatment: combination Baby ASA + Heparin
 - Decreased miscarriage rate by 54%

Empson M, et al. Prevention of recurrent miscarriage for women with APS. Cochrane Database Syst Rev. 2005;2:CD002859.

INHERITED THROMBOPHILIAS

- No association between inherited thrombophilias & RPL:

Thrombophilia	Prevalence in miscarriages (%)	Prevalence in controls (%)	OR (95% CI)	P-value
Factor V Leiden	10.0	10.0	1.0	0.99
Prothrombin G20210A	10.0	10.0	1.0	0.99
Methylenetetrahydrofolate reductase C677T	10.0	10.0	1.0	0.99
Factor II G445C	10.0	10.0	1.0	0.99
Factor III G307A	10.0	10.0	1.0	0.99
Factor VII G1019A	10.0	10.0	1.0	0.99

- **NO** evidence that the use of anticoagulants improves the chance of live birth in these women
- Conclusion: Testing for inherited thrombophilia is **NOT** recommended for women with recurrent miscarriages

Se Jang PG, et al. Testing for inherited thrombophilia in recurrent miscarriage. Semin Reprod Med 2011; 29: 540-7.

INFECTION

- Bacterial vaginosis*: risk factor for:
 - Preterm delivery
 - Late miscarriage
 - No association with early miscarriage
- NOT recommended tests:
 - TORCH titer
 - Mycoplasma or Ureaplasma culture*

*Leitch H, et al. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. Best Practice Res Clin Obstet Gynecol 2007; 21:379-90.
 *Summers PK, et al. Microbiology relevant to recurrent miscarriage. Clin Obstet Gynecol 1994 Sept; 37(3): 722-9.

ENDOCRINE FACTORS

- PCOS: Elevation of LH &/or testosterone – NOT associated with increased miscarriage rate*
- Insulin Resistance (IR)*: meta-analysis concluded that IR is associated with the susceptibility to recurrent miscarriages
- Luteal Phase Defect: NOT a valid cause of infertility or RPL
- Thyroid Disorder*: pregnant women with subclinical hypothyroidism have an increased risk of recurrent miscarriages. TPO antibody screen in NOT recommended.

*Sail R, et al. Polycystic ovaries and recurrent miscarriage: A reappraisal. Human Reprod 2000; 15:612-5.
 *Zi, et al. Association between recurrent miscarriages and insulin resistance: A meta-analysis. J Biol Regul Homeost Agents 2013; 27:225-31.
 *Picconi C, et al. Thyroid autoimmunity and recurrent miscarriage. Am J Reprod Immunol 2011; 66: 452-6.

IMMUNOLOGIC FACTORS

- Natural Killer (NK) cells*
 - Peripheral immunological dysfunction is observed with recurrent miscarriages
 - Women with recurrent miscarriages have signs of generally exaggerated inflammatory immune responses both before and during pregnancy
 - No standardized counting and parameters of NK cells
 - Treatment trials underway (oral prednisolone & IV Ig)
 - Immunological test is NOT currently recommended





*Miszane D, et al. Profile of Maternal CD4 T-cell effector function during normal pregnancy and in women with a history of recurrent miscarriage. Clin Sci (Lond) 2014; 126:347-54.

MALE FACTORS

- Higher recurrent miscarriages seen in couples who underwent IVF with ICSI
- Researches have found these men to have an increase in their sperm DNA fragmentation
- 15.2% of men with azoospermia have sperm DNA fragmentation
- Prospective studies are needed before testing for sperm DNA fragmentation in clinical practice
- Conclusion: testing for sperm ploidy or DNA fragmentation is currently **NOT** recommended

Robinson L, et al. The effect of sperm DNA fragmentation on miscarriage rates. Hum Reprod 2012; 27:2908-17.

ROUTINE INVESTIGATION + TREATMENT Recurrent Early Miscarriage

- **Chromosome Analysis:**
 - Couples
 - Product of Conception Genetic Counseling
IVF + PGS
- **Uterine Structure Study:**
 - 3-D sonogram; or
 - Saline infusion sonogram; or
 - Pelvic MRI; or
 - Combined HSC + LSC Surgical correction
- **Thrombophilia Investigation:**
 - Anti-cardiolipin ab, plus
 - Lupus anticoagulant, plus
 - Beta-2 Glycoprotein Baby ASA + prophylactic heparin
- **Endocrinology Tests:**
 - HgbA1c, fasting glucose & insulin
 - TSH Healthy Lifestyle
Levothyroxine supplement

EVIDENCE-BASED TREATMENT Unexplained Recurrent Miscarriages

- **Baby ASA:**
 - Recent trial failed to support any role of aspirin in unexplained RPL
 - Routine use of ASA is **NOT** recommended (Evidence Level II)
- **Progesterone:**
 - Meta-analysis of 4 randomized trials showed a statistically **significant reduction** in miscarriages
- **Low Molecular Weight Heparin (Lovenox):**
 - Its usage is **NOT** recommended in the absence of APS (Evidence Level II)
- **Steroid (Prednisolone):**
 - There is **NO** robust evidence to recommend steroid use (EL III)

EVIDENCE-BASED TREATMENT

Unexplained Recurrent Miscarriages

- Combined ASA + Heparin vs Placebo:
 - No difference in live birth
 - Significant side effects in treatment group
- HCG (Ovidrel):
 - Recent Cochrane review failed to find quality evidence to support its usage in preventing miscarriage
- Immunoglobulins (IVIG):
 - Administration for treatment is NOT justified outside the context of research (EL III)
- IV Intralipid Solution:
 - No evidence of benefit; well controlled large scale studies required before it can be recommended for routine use (EL III)

UNEXPLAINED RPL EMPIRIC SUPPORTIVE CARE

- Most important therapy in idiopathic RPL
 - Antenatal counseling
 - Psychological support
 - Frequent follow up
- **86% vs 33%** - subsequent pregnancy success rate for women who received supportive care ($p < 0.001$)¹⁰

¹⁰Stray-Pederson B, et al. Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol. 1998 Jan 5; 148(1): 140-6.

SUMMARY

Basic Workup:

- Anticardiolipin antibody
- Lupus anticoagulant
- Beta-2 Glycoprotein
- Paternal & maternal Karyotypes
- TSH, HgbA1c, Fasting Glucose, Fasting insulin
- One of the following procedures:
 - Saline Infusion Sonogram
 - Office Hysteroscopy
 - 3-D sonogram
 - Pelvic MRI

Therapy:

- APS: Combination ASA + Heparin
- Chromosome translocation or inversion:
 - Genetic counseling
 - Consider IVF + PGS
- Uterine Factor: Surgical correction
- Hypothyroidism: Levothyroxine
- Insulin Resistance: Healthy Lifestyle
- Diabetes: Goal – HgbA1c < 7%
 - Healthy lifestyle
 - Medication Adherence
- Unexplained RPL:
 - Supportive Care
 - Progesterone therapy

Post-Test QUIZ

- Per ASRM criteria, the definition of recurrent pregnancy loss is:
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Child interrupts dad's interview with the BBC!



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QUESTIONS?



SUGGESTIONS?

Being Health Care Providers.....

*"We make a living
by what we get,
we make a life by
what we give."*

— Winston Churchill