

RECURRENT PREGNANCY LOSS: UPDATES, BEST PRACTICES AND GUIDELINES FOR EVALUATION AND TREATMENT

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OUR PHYSICIAN TEAM



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Outline for Today's Talk

- 1. Public (mis)perceptions about miscarriage
- 2. Miscarriage facts
- 3. Evaluation and treatment of RPL
- 4. Enhanced evaluation of RPL

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WHAT DOES THE PUBLIC THINK ABOUT MISCARRIAGE?

MOST PEOPLE THINK THAT PREGNANCY LOSS IS RARE



Bardos, et al., Am. J. of Obstet and Gyn. (201

CAUSED BY SOMETHING THEY DID WRONG

Genetic abnormalities of fetus	95 32					
A stressful event	76			13	11	
Long-standing stress	74 13			13	13	
Lifting heavy object	64 17 19			19		
Past sexually transmitted disease	41 28		28		31	
Past abortion	31		25		44	
Intrauterine device	28		35		37	
Not wanting the pregnancy	23	11		66		
Past use of birth control	22	23		55		
Getting into an argument	21	14		65		
Destiny or fate	8 8	84				
Moderate exercise	7 13		80			
Intercourse during pregnancy	4 8	88				
Punishment from God	3 6	91				
Jealousy	3 4 93					
Premarital sex	2 <mark>2</mark> 96					
		Pe	rcentages			
		Agree	Unsure 📕 Disagi	ree		

Bardos, et al., Am. J. of Obstet and Gyn.

(20)



Very

Minally Not

Moderately Extremely

Bardos, et al., Am. J. of Obstet and Gyn.

(20)

THE PUBLIC MISTAKENLY BELIEVES THAT PREGNANCY LOSS IS...

Rare Due to something they did wrong Very upsetting

Guilt, isolation and self-blame

Bardos, et al., Am. J. of Obstet and Gyn. (201

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MISCARRIAGE IS COMMON

1:4-5 pregnancies

1,000,000 in the US annually

Fertilization Outcome



Risk of Miscarriage

<u>GA</u>	Risk of Loss
<6 wks	20-25%
6-10 wks	15%
16-24 wks	2-3%

Risk of Miscarriage

GA	Risk of Loss
<6 wks	20-25%
6-10 wks	15%
16-24 wks	2-3%

But, risk increases with:

- History of prior losses, especially euploid losses
- Advanced maternal age
- Unknown etiology

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Causes of Miscarriage



¹Stephenson et al, Hum Reprod 2002; ²Proctor and Haney, Fert Ster 2003; ³Pabuccu *et al*, Fertil Steril 1997; ⁴Elias *et al.*, J. of Min. Invasive Gynecol, 2015; ⁵Simpson Obstet Gynecol 2007; ⁶ACOG Practice Bulletin, 2011; ⁷Negro et al J Clin Endocrin Metab 2010; ⁸Hirahara *et al*, Fertil Steril 1998;)

Causes and Evaluation of Recurrent Miscarriage



Causes and Evaluation of Recurrent Miscarriage



CAUSES OF PREGNANCY LOSS

Aneuploidy

Everything Else

Aneuploidy is the Most Common Cause of Miscarriage

- Most common class: Trisomies
- Most common aneuploidy: Monosomy X (45 X0)
- Can be highly complex
- Almost always sporadic
- Maternal age is predominant risk factor
- Must also consider molar pregnancies
 - Typically 1 sperm fertilizes empty egg, splits
 - 46XX (90%)

Increased Risk of **Down Syndrome** with Advancing Maternal Age



Increasing Risk of Aneuploidy with Advance Maternal Age



Nagaoka et al, Nat Rev Genetics, 2012

Testing Methods

G-band Karyotyping



+Visualize all chromosomes +Detects translocations +Traditional "gold standard" -Requires **living** cells -Culturing bias -3 week TOT -Cannot exclude MCC, Mole, UPD, -Resolution to 10 Mb

Microarray



+No need for living cells +<10d TOT +Resolution to <100kb +Can be used for rescue karyotyping -Will miss a balanced translocation

Genetic Testing: Bottom line

- 1. Testing of parents: G-band karyotyping
- 2. Testing of POC: SNP microarray
- 3. Preserve all POCs

Treatment for Aneuploidy

- Test parents (G-band karyotyping)
- If abnormalities found-refer for genetic counseling
- IVF with PGS
- Gamete donation (depending on etiology)
- Expectant

When normal is not normal

Scale of Genomic Variation





Causes and Evaluation of Recurrent Miscarriage



Evaluation for Uterine Factor

- 10-50% of RPL
- Concerning anomalies:
 - o Septate uterus (most common)
 - o Polyps
 - o Leiomyomata (intracavitary and intramural)
 - o Adhesions (20% after 3 D&C's)
 - o Tubal disease (recurrent biochemical pregnancies)
- Diagnosis:
 - Hysteroscopy
 - SIS with 3D US
 - MRI (septum vs. bicornuate)
 - HSG (when concerned for tubal disease)

Missed Abortion on Septum



Treatment for Uterine Factor

- Surgical repair when indicate
- Gestational carrier if not correctable
- Repeat evaluation after subsequent loss

Chronic Endometritis

- Presence of CD138+ Plasma Cells
- Doxy 100mg bid x 2-3 weeks



Causes and Evaluation of Recurrent Miscarriage



Evaluation for Endocrine

- ~10% of RPL cases
- Often readily correctible
- Important for overall health

Evaluation for Endocrine

- HgA1c
- TSH/TPO
- Prolactin
- PCOS labs, if indicated

Treatment for Endocrine

- Replenish Vitamin D
- Low sugar diet, weight loss, metformin
- Synthroid. Target TSH<2.5

Causes and Evaluation of Recurrent Miscarriage



Antiphospholipid Syndrome

5% vs 20%, nml vs. RPL

- Induces thrombosis vs.
 endothelial/trophoblast effect.
- Labs: aPL, LAC, β2GP1

Treatment for Antiphospholipid Syndrome

- +APLS?
 - o bASA preconception
 - o Lovenox 60mg sq qd starting with +HCG

Causes and Evaluation of Recurrent Miscarriage



Possible Causes of Recurrent Miscarriages

- Fibrinolysis defects^{2,3} (PAI 4G/5G, ACE I/D)
- Severe Vit D deficiency⁴
- Celiac Disease
- Thrombophilias
- Male factor
- Immunologic dysfunction

¹McQueen et al, Fert Steril, 2014; ²Buchholz et al, Hum Reprod, 2003; ³Su et al., Throm Haemost, 2013; ⁴Ota et al., Hum Reprod 2014

Not Causes of Pregnancy Loss

Moderate stress

- Moderate exercise
- Moderate lifting
- Moderate caffeine

Suggested Basic RPL Evaluation

- History
 - o GA
 - o Menstrual
 - o Thrombosis
 - o Pelvic pain
- Physical exam
 - o Hirsutism
 - o Thyroid enlargement
 - o Acanthosis nigricans
 - o Nipple discharge
 - o Endometriosis

How pTRegs Might Prevent Miscarriage



Adapted from Williams, Z, NEJM 2012

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Hot topics

1.Empiric Progesterone2.Role for Immunotherapy3.How long to wait?

Role for Empiric Progesterone?

- Study Design:RandomizedPlacebo controlledDouble blindMulticenter
- Study subjects: >800 women with >2 losses in 1st Trimester Negative RPL eval
- Intervention:BID PV P4 (micronized progesterone)Starting with +hCG to < 6wk GA</td>Continued to 12 weeks
- **1° outcome:** Live birth (>24wks)

Coomarasamy et al, NEJM 2015

No Benefit from Empiric Progesterone



Coomarasamy et al, NEJM 2015

Empiric Progesterone Conclusions

- No physiological benefic for empiric PV P4
- ? Role with low P4
- ? Role with threatened SAB
- ? Role with subchorionic hematomas
- ? PO vs. IM
- Luteal phase start?

Coomarasamy et al, NEJM 2015

How long to wait until trying to conceive again?

How long to wait until trying to conceive again?

Secondary analysis of EAGer trial

Study Subjects:

1000 women age 18-40 attempting conception

Schliep et al, Obstet & Gynecol, (2016)

How long to wait until trying to conceive again?



Schliep et al, Obstet & Gynecol, (2016)

Conclusion

- There are widespread misconceptions about the incidence and causes of pregnancy loss that contribute to patient suffering
- A wide range of factors may result in pregnancy loss
- Evaluation should start by systematically testing for the known causes of pregnancy loss
- Treatment should be targeted to identified causes of loss

HOW DO WE LOOK FOR CAUSES OF MISCARRIAGE?

Traditional medical evaluation

Traditional miscarriage evaluation

1. Count # chromosomes

2. Test the mother

A New Paradigm for Investigating Embryonic causes of miscarriage



PATIENT M1

32 yo G6P0050

- 6 wk 3d
- Nml RPL evaluation
 - Euploid miscarriages
 - Normal parental karyotypes
 - Normal uterine evaluation
 - Normal TSH/TPO
 - No thrombophilias
 - APLS negative
 - No toxic habits
 - No co-morbidities

TESTING RESULTS

Karyotype: 46 XY

Morphologically abnormal

RNASeq: Increased LINE1 expression





INCREASED LINE1 GENE AND PROTEIN EXPRESSION IN M1



ONGOING APOPTOSIS IN M1





KEY POINTS

Miscarriage is common, though patients may not know this Can begin basic RPL evaluation after second loss Systematic evaluation can find new causes of miscarriage Novel technologies can advance our options for testing

