Recurrent Pregnancy Loss 2019
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Definition
• Recurrent pregnancy loss or “habitual abortion” is the loss of 2 or more pregnancies before 20 weeks gestation.
• ~5% of women will have 2 consecutive Ab’s
• < 1% will have 3 or more losses

RPL Overview
• Uterine cavity problems eq adhesions, fibroids, and septum. Order saline infusion sonogram (SIS)
• Genetic issues eq balanced translocation. Order karyotype on parents
• Luteal phase defect. ? Endometrial biopsy. Best-Luteal length < 13 days from LH surge.
• Autoimmune evaluation- ACOG- LA,ACA, Anti-B2-glycoprotein 1 antibody. ?MTHFR deficiency
• Alloimmune disorders - unproven
RPL Overview
• Inherited Thrombophilia’s eg Leiden factor 5 def.- screen if >8week loss or +cardiac, or hx of placental insufficiency or thrombosis eg PIH,IUGR,or Placental abruption.
• Endocrine – Hypothyroidism. Subclinical hypo. TSH> 2.50 and or +TPO. Treat with LT4 25-50mcg. PCO not associated with increase loss
• Infectious – BV, possible mycoplasma. No great data

Question
• Past obstetric history is important in predicting miscarriage risk. True or false

Normal Reproductive Performance
• 30 to 60% Pregnancy loss rate (clinical plus preclinical) by week 12 as determined by highly sensitive HCG assay testing of young cycling women.
• Obstetric history is an important factor eg women whose only or last pregnancy ended in loss have a higher miscarriage risk compared to women with no prior pregnancy and women in which the last pregnancy was a success
• Clinical miscarriage rate increases with age being as high as 50% in >40 yr. olds.
Reproductive Performance of the RPL Patient

- Risk of loss after 3 consecutive miscarriages is 30-45%
- If one prior live born the chance is ~30%; With no prior live born infant ~ 40-45%
- Once FHR seen on US RPL patients had 23% loss rate vs 5% in controls.

Reproductive Performance of RPL Patients

- Higher genetic abnormality rate in PGD studies on embryos from RPL patients than seen in control non-RPL IVF pts.
- Significantly higher rates of Preterm delivery(13%), Small for gestational age(13%), perinatal loss(2.5%), and CS birth (36%) over controls in UK study of 162 pregnancies of RPL pts.

Genetics and Miscarriage

- 50-70% of early losses are random numeric chromosomal errors Trisomy, monosomy and polyploidy
- How many more are due to undetectable genetic problems?
- Autosomal trisomy’s as a group are the most common(50%). Highest single chromosomal abnormality is 45X(25%) Turner’s syndrome.
- RPL patients have a higher chance of a normal chromosomal (euploid) miscarriage compared to the miscarriage of normal reproductive women. Why?
Genetics and RPL

- Pregnancy after aneuploidy loss yields 68% term rate vs 41% in euploid loss pts.
- Most recommend getting a karyotype of the abortus or the parents after two or more consecutive miscarriages
- 2-5% of RPL couples will have a balanced translocation or Robertsonian translocation

Question

- Is it better to have: 1. a 45X miscarriage or 2. a 46XY miscarriage in terms of future miscarriage risk

Evaluation of RPL

- History: OB performance, uterine surgery, clotting abnormalities, DES, thyroid disease, smoking and ETOH use, and Ovarian reserve deficiency issues.
- Physical exam: thyroid, galactorrhea, Lupus evidence, uterine abnormalities.
Evaluation: Uterine Factor

- HSG
- Saline infusion sonography (SIS)
- 3D US – as sensitive as MRI at less cost
- HS – HSG and SIS may miss 5-10% intrauterine pathology
- MRI – rarely needed except in complex mullerian abnormality cases

Uterine Factors and RPL

- Submucous and large cavity distorting intramural myomas are significant. Intramural fibroids less than 5cm with no cavity distortion of no proven significance re RPL or infertility.
- Intrauterine adhesions
- Septate uterus

Uterine Factor Treatment

- HS resection of myomas, polyps, and adhesions provides least invasive approach. Cytotec helpful with softening the cervix
- HS septum repair improves reproductive outcome in RPL patients
Question
• The most common uterine anomaly associated with RPL is A. bicornuate uterus B. didelphic uterus C. septate uterus

Septate uterus
• Significant decrease in miscarriage with septoplasty - 80% term delivery vs 65% AB rate if untreated
• Not associated with renal or ureteral abnormalities seen with the other mullerian defects

Uterine Factor Treatment
• Gestational Carrier via ART. Most applicable in severe IUA cases and severely deformed multiple myoma uterine factor situations
Luteal Phase Defect (LPD) Evaluation

- Serum P of little value
- Best diagnosis may be LH surge to menses <13 days.

LPD Treatment

- Find source eg TSH, PRL, PCOS
- Clomiphene citrate
- Progesterone IM or vaginal suppositories may be of value
- FSH stimulation
- ACOG: relationship of LPD and RPL is controversial. It has not been shown conclusively that P or FSH works. ACOG practice bulletin 24:FEB 2001.

Genetic Factor Evaluation

- 2-5% chromosomal abnormality rate in RPL couples.
- Balanced and Robertsonian translocations most common.
- Generally ordered after 3 losses but reasonable after 2 consecutive losses
- Genetic abnormalities more common if there is previous malformed or mentally retarded child.
Genetic Factor Treatment

- Genetic counseling
- PGT in IVF treatment
- Noninvasive PNT, CVS, amniocentesis
- Donor egg, Donor sperm
- Donor embryo
- Adoption

Question

- The most common genetic cause found in parents of RPL is?

Infection Evaluation

- There is NO good evidence that bacterial or viral infections are a cause of RPL. There is some evidence that bacterial vaginosis (BV) may increase miscarriage both in the second trimester.
- ACOG recommends against empiric antibiotic treatment. Fritz & Speroff recommend a 2 week course of azithromycin, erythromycin or doxycycline when there is cervicitis, mycoplasma or chronic BV.
Thrombophilia Evaluation

• Prospective cohort studies have NOT shown an increase in inherited clotting disorders i.e., ATIII def., Protein C and S defect, Leiden factor 5 mutation, PT gene mutation(G20210A) and RPL

• Inherited Thrombophilia should be screened when miscarriage is >8 weeks or after detection of fetal heart activity and/or if there is a history of placental thrombosis/insufficiency i.e. PIH, IUGR in the present pregnancy or a prior pregnancy.

Thrombophilia Evaluation

• Intervillous blood flow is not present until 8 weeks gestation, therefore it is unlikely that clotting problems cause loss before this time.

• No good studies to document treatment of clotting problems solves RPL problem.

• Paucity of data about untreated outcome in women with thrombophilia, however recent studies show heparin alone or in combination with aspirin is beneficial. Aspirin alone has no value.

• ACOG does not recommend testing RPL pts for thrombophilia. ACOG practice bulletin 24 2001

Thrombophilia Treatment

• Heparin or Lovenox alone or in combination with aspirin 81mg

• Aspirin alone is of no value

• More data is needed to clarify treatment in thrombophilia RPL cases
Antiphospholipid Antibody

- ACL, LAC and Anti B2glycoprotein are directed at platelets and vascular endothelium leading to thrombosis.
- Generally assoc. with 2nd and 3rd trimester loss.
- Antiphospholipid syndrome defined by LAC or ACL detection in a patient with one of the following: a prior thrombotic problem; 3 or more miscarriages at < 10 weeks; a fetal death; or a premature delivery < 34 weeks associated with severe preeclampsia.

Antiphospholipid Antibody Treatment

- Low dose heparin 5000u bid or lovenox 40mg qd.
- Prednisone and ASA no benefit in randomized controlled studies.
- ASA plus Heparin in randomized trials showed 70-80% successful del vs 20-40% in control group.

Alloimmune Disorders and RPL

- Theories starting 30 yrs. ago re antipaternal lymphocytotoxic antibodies and increased major histocompatibility complex HLA area similarity between father and mother were proposed. Neither of these ideas has proven to relate to RPL.
- Recent animal data suggest an increase in Natural Killer (NK) cell activity at the decidua may be associated with miscarriage. Linkage in humans has not been shown. NK cell testing is not recommended.
Alloimmune and RPL

- Empiric ASA in RPL pts vs controls showed no value.
- IVIG (intravenous immunoglobulin) treatment is of no value period. It does carry risk of viral and prion transmission and anaphylaxis reactions
- Paternal lymphocyte transfusion has no proven benefit
- The above is ACOG’s position and Fritz & Speroff 2011 textbook opinion.

True or false

- The best treatment for RPL patients with a positive Lupus anticoagulant antibody or ACA is Heparin or Lovenox - True
- RPL patients with significant major histocompatibility HLA sharing have improved pregnancy outcomes with IV immunoglobulin therapy - False

ACOG Conclusions

- RPL pts should be tested for LAC, ACA, and Anti-B2 glycoprotein with pts that are positive treated with heparin or lovenox. Low dose ASA may be added.
- Endocrine – Hypothyroidism is associated with miscarriage; diabetes and PCO is not clearly associated with RPL. Metformin does not decrease miscarriage in PCO
ACOG Conclusions (limited or inconclusive evidence).

- LPD and RPL assoc. is controversial. If dx is sought than do endometrial biopsy or better, count luteal phase length from LH surge- normal >13 days
- LPD treatment with Progesterone is of questionable value. Best treated with Clomiphene citrate.

ACOG conclusions (consensus or expert opinion)

- RPL couples should be tested for balanced translocation. IVF PGT can be used to treat. Donor oocyte/sperm and Donor embryo also options
- HS resection of uterine septum IUA and submucous fibroids or significant polyps is advisable

Conclusions

- RPL is relatively common.
- > 50% RPL is unexplained
- Our challenge is to find the few pts we can help and avoid empirical treatments.
- Face to face explanation of RPL issues is the best approach.