



Understanding Recurrent Pregnancy Loss

We are sorry you have experienced miscarriage! We understand that miscarriage can be emotionally and physically very stressful and difficult. Your provider will help you create a plan to evaluate potential causes of loss and help you conceive. It is important to know that miscarriages are not your fault, there is not anything an individual can do to prevent a miscarriage from happening. This handout describes the medical causes of miscarriage.

Miscarriages are common and occur in approximately 15-25% of individuals trying to conceive. The majority of miscarriages result from random chromosomal abnormalities (medically called "aneuploidy"), meaning that a single miscarriage is most often an isolated event, and the individual is not at higher risk of subsequent miscarriage.

What is chromosomal aneuploidy?

- Euploidy, or a "normal" number of chromosomes in a human is 46. For example, an individual can be 46 XY (male chromosomal sex) or 46 XX (female chromosomal sex).
- Aneuploidy is when the total number of the chromosomes in the fetus doesn't equal 46. In each embryo, 23 chromosomes come from the egg and 23 come from the sperm.
- Most commonly the egg is the cause of aneuploidy because of the biology of egg development and ovulation. Eggs have been inside the ovaries since that individual was born, as a full set of 46 chromosomes; not until the time of ovulation do the eggs divide, to provide 23 chromosomes to make the baby. If the egg is "sticky" and the division is not equal, a higher or lower number of chromosomes may result in the egg, thus an embryo is created with an abnormal number of chromosomes.
- Examples of aneuploidy include Down's Syndrome, where the egg divides with an extra chromosome 21, and therefore the baby has 47 total chromosomes, or + 21.
- While Down's syndrome results in a live born baby, many of the chromosomal aneuploidies result in an embryo that isn't able to implant (no pregnancy occurs), or that can implant, but then doesn't have the full set of genetic material to divide correctly. This can result in miscarriage, anywhere from 4-12 weeks of pregnancy. If the chromosome aneuploidy is more severe and carries more genetic information, the miscarriage may happen very early (such as a biochemical pregnancy, or an initial positive pregnancy test that then goes away). If the chromosome aneuploidy is less severe and carries less genetic information, the miscarriage may happen later in the first trimester.
- Live born babies can have aneuploidies in Chromosome 13, 18, or 21.

What is recurrent pregnancy loss (RPL)?

When an individual has experienced 2 or more miscarriages, we refer to this as recurrent pregnancy loss. This is distinct from one miscarriage as there can be underlying cause.

The table below shows potential causes of RPL, what test we use to evaluate for each cause, and potential treatment.

<i>Possible cause</i>	<i>Recommended Evaluation- for female partner, genetic for both partners</i>	<i>Treatment</i>	<i>% contribution to RPL, if known</i>
Anatomic: <i>Uterine septum or Uterine adhesions leading to poor implantation</i>	Sonohysterogram and/or 3D ultrasound	Surgical removal of septum or adhesions	12-38%
Autoimmune <i>Antibodies affecting placental implantation and growth</i>	Antiphospholipid antibody panel (ACA, B2-glycoprotein, and LAC)	Lovenox or heparin and aspirin to improve placental implantation and development	5-20%
(cyto)Genetic <i>Balanced reciprocal translocation</i>	Karyotypes of both partners	Pre-implantation testing of embryos (PGT)	2-5%
Hormonal/ ovulatory <i>Ovulatory dysfunction Causing inadequate luteal support</i>	AMH, antral follicle count on ultrasound	Ovulation induction to ensure strong ovulation and therefore strong progesterone levels	Unknown, may be more a factor in biochemical pregnancies/ early losses

Metabolic/ endocrine	TSH(thyroid hormone), TPO (thyroid antibody), PRL (prolactin hormone), HgA1c (blood sugar assessment)	Correct the underlying abnormality (ex: thyroid- levothyroxine medication; elevated HgA1c- metformin)	
<i>Other: infectious?</i>	Not recommended; no clear evidence that infections cause recurrent miscarriages		
<i>Other: inherited thrombophilia?</i>	Not recommended unless patient has a personal history of blood clotting or a first-degree relative with a known thrombophilia	Lovenox	unknown
<i>-Factor V Leiden, prothrombin, Protein C or S, antithrombin</i>			
<i>Other: Male factor?</i>	Not recommended	Avoidance of correctable environmental factors: heat, toxic exposures, smoking	unknown
<i>DNA Fragmentation</i>		Focus on antioxidant rich diet and men's daily multivitamin	
<i>Other: Alloimmune?</i>	Not recommended; this data is not supported nor reproducible	Focus on healthy weight Not recommended: IVIG treatment has been shown to be ineffective in studies	
<i>Natural Killer cells</i>			
Other: Unexplained	This is the diagnosis when no other diagnosis is identified.	Luteal progesterone support; IVF with PGT-A Even without treatment: chance of future successful pregnancy is >50-60%	Up to 50%