Delaware Valley Institute of Fertility & Genetics
Conceptions

Recurrent Pregnancy Loss by Dr. Akas Jain

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One of the most difficult situations for a patient and her care providers is when the joy of finding out she is pregnant is turned into the sadness that accompanies early pregnancy loss. Few areas in medicine present the level of uncertainty, frustration, and emotional stress as what we see with recurrent pregnancy loss (RPL). The American Society of Reproductive Medicine (ASRM) defines RPL as 2 or more failed pregnancies prior to 20 weeks gestation and recommends a “thorough investigation” after 3 or more losses. Though 15% of all clinical diagnosed pregnancies result in miscarriage, only 1-2% of women will have as many to be diagnosed with recurrent pregnancy loss.

Over time, this definition has remained the same but many physicians may begin the evaluation after the second loss. The greatest statistical evidence to perform the evaluation earlier is that the probability of having a loss after 2 miscarriages is about 30% compared to about 33% after 3 losses.

What makes the work-up and treatment even more confusing for patients is that they may hear different opinions and theories as to why the miscarriages are occurring. Due to a lack of scientific evidence in this area, many helpless patients find themselves undergoing needless and expensive treatment, often not even covered by their insurance. At DVIF&G, we understand the fear and hesitation many couples have about not only getting pregnant again, and also of having to deal with yet another miscarriage. Our evaluation is tailored to help diagnose the cause of the pregnancy losses and also to plan treatment in a way to overcome that problem. Below is a summary of the various types of causes of RPL.

Genetics: The most common cause for pregnancy loss is a chromosomal abnormality with the fetus. This usually occurs due to a chromosomal mismatch that happens when sperm and egg meet (normally 23 chromosomes from the sperm join 23 chromosomes from the egg to form a normal 46 chromosome cell). This type of miscarriage is seen in 60-85% of losses, and is very rarely (less than 2-4%) due genetic issues with either sperm or egg that result in translocation (transfer of a part of a chromosome to another which may result in extra or missing genetic material (resulting in a miscarriage) or a normal amount of material.

It is not uncommon for older women to experience frequent miscarriages – mainly due to chromosomal abnormalities noted in the fetus. It presents a particularly difficult road for these patients, as it may not only be difficult to conceive, but also to maintain the pregnancy.

The table below shows the association of maternal age to risk of having a miscarriage (spontaneous abortion):

Maternal Age (years)	Spontaneous Abortion (%)
15-19	9.9
20-24	9.5
25-29	10.0
30-34	11.7
35-39	17.7
40-44	33.8
≥ 45	53.2

Anatomical: The uterus may have structural abnormalities such as fibroids, polyps, and scar tissue from prior losses or pregnancies. This may effect implantation or the continued progress of an otherwise normal pregnancy. In some case, patients have congenital anomalies such as a uterine septum, unicornuate or bicornuate uterus that also associated with recurrent loss or preterm labor. By performing a careful evaluation using 3D ultrasound and office hysteroscopy, we have been able to find many abnormalities that have either not been investigated or have been missed. Many of these anomalies can be surgically corrected, allowing RPL patients to achieve the similar live birth rates to patients without any uterine abnormalities.

Endocrine and hormones: Close to 20% of RPL patients may have an abnormality involving insulin resistance and diabetes mellitus, elevated prolactin levels, and thyroid dysfunction. The basic laboratory evaluation of a woman suffering from recurrent losses should include tests that will help find these disorders. Polycystic ovarian syndrome (PCOS) presents a very interesting association with RPL. Studies have found evidence of PCOS in up to 40% of women with RPL.

It is understood that the placenta takes over the burden of carrying the pregnancy after 7-9 weeks gestation. Prior to that, the responsibility of sustaining the pregnancy falls on the corpus luteum, or post-ovulatory cyst that continues to produce progesterone. There is also a strong belief that a shortened or deficient post-ovulation (luteal) phase is associated with early pregnancy loss. Historically, this defect was investigated by performing an endometrial biopsy in the luteal phase to find a histologic discrepancy in the development of the endometrium. Due to a wide variation of normal vs. abnormal results, this methodology has fallen out of favor and is not commonly used. While many physicians treat a defective luteal phase by adding progesterone supplementation, the most effective way to manage this situation is with ovulation stimulation to enhance follicular growth with the expectation of having more progesterone production after ovulation to support the early pregnancy.

Thromobophilic disorders: Certain factors may cause increased blood clotting in small network of vessels in the placenta. This has been associated with miscarriages, pregnancy complications, second trimester loss, and also thromobosis and stroke. While the cause of this phenomenon is not completely understood, it is believed that autoimmunity (body attacking itself) along with genetic factors are involved. Antiphospholipid syndrome (autoimmunity) is diagnosed when high levels of antiphosophlipid antibodies (APA), anticardiolipin antibodies (ACA) and lupus anticoagulant (LAC) are found.

Other causes of thrombophilia stem from chromosomal abnormalities related to certain clotting factors. These include Prothrombin gene mutation, Factor V Leiden, Antithrombin III, Protein C & S, plasminogen activator inhibitor-1 (PAI-1), and more controversially, hyperhomocysteinemia (MTHFR mutuation). Thrombophilia disorders are commonly treated by low dose aspirin therapy, heparin, or low-molecular weight heparin.

Other controversial causes: While many care providers screen for active infection, it is not truly known how much of an effect the presence of an infection has on pregnancy loss. Despite the strong relationship between infection and preterm labor, the association with miscarriage is not well defined. Specifically, mycoplasma hominis and ureaplasma urealyticum have been implicated with little scientific data to support this claim. These bacteria have a high prevalence in the general population and the screening and treatment of these organisms is not recommended.

Perhaps the most controversial of RPL treatments is that of a supposed alloimmune response to a perceived “foreign” pregnancy (maternal immune response to the pregnancy). While the body undergoes changes to accommodate a pregnancy, some theorize that disorders in this process may result in rejection. Research into natural killer (NK) cells and placental HLA factor has yielded some positive information, but the evaluation and treatment of these syndromes is often expensive and may not yield beneficial results. Some fertility centers offer intravenous immunoglobulin (IVIG) therapy to help “treat” pregnancy loss patients. ASRM’s official statement on IVIG therapy is that the treatment is “unproven” and should be considered “experimental” and only be approved in a research setting.

Regardless of the cause of the recurrent losses, many couples feel a deep sense of sorrow or hopelessness with each loss. While medical expertise can help to diagnose and treat your condition, we also understand the emotional toll this process can take on the patient and the couple’s relationship. Our physician and support staff provide the care you will need to understand and treat this condition and move forward as we help grow your family.

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