Delaware Valley Institute of Fertility & Genetics
Conceptions
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Understanding Recurrent Pregnancy Loss

By David R. Corley, M.D., FACOG

Assisted reproductive technologies (ART) and other scientific advances have made it possible for thousands of couples to fulfill their dream of creating a family of their own. Study after study is conducted to help couples conceive. For some couples, however, their joy soon turns to despair when they experience early pregnancy loss. When this occurs again, they often turn to a fertility expert for help.

Although some studies have been conducted to uncover the mystery of recurrent pregnancy loss (RPL), many more need to be conducted. At this time theories abound but not much clinical evidence is available to support them. Here's the latest information on the factors that may cause RPL.

What is recurrent pregnancy loss (RPL)?

As many as 15 percent of clinically recognized pregnancies end in miscarriage between the 4th and 20th week of gestation. RPL is usually defined as three consecutive losses, but most couples will seek medical help after the first or second loss. Tests are available to evaluate the more common causes of RPL; but, unfortunately, in more than half of the cases no definitive cause for the losses can be found.

Chromosomal abnormalities are found in 50 to 85 percent of spontaneous miscarriages. Most of theses involve either the addition or loss of an entire chromosome. Balanced translocations are the most common inherited chromosomal abnormality, occurring in about 2 to 4 percent of couples experiencing RPL. A balanced translocation occurs when parts of one chromosome are incorporated into a different chromosome.

Uterine abnormalities, such as a uterine septum or uterine adhesions have been linked to RPL. Unicornuate, Bicornuate, and Didelphys are not associated with early pregnancy loss. They are only associated with pregnancy loss after the first trimester.

Hormone/metabolic disorders that have been associated with RPL include luteal phase defect and polycystic ovarian syndrome (PCOS). The luteal phase defect may result in a disrupted endometrial lining. This can lead to problems with the embryo properly implanting itself in the uterus. In PCOS, the elevated LH and/or elevated testosterone levels may be responsible for RPL. Well-controlled diabetes and thyroid disease are not associated with RPL.

Autoimmune disorders such as Systemic Lupus Erythematosus are associated with loss in the second and third trimester but not with early pregnancy loss. However, Antiphospholipid Syndrome may be associated with about one in five patients with RPL. Alloimmune abnormalities disrupt the mechanism that allows a mother to tolerate her semi-allogeneic baby. In other words, the mother is unable to establish a defense mechanism to protect her newly developing baby from her body's immune response. The mother's immune system begins to treat the baby as a foreign body.

Although no definitive studies have been conducted to determine the actual autoimmune response from the mother that causes RPL to occur in these cases, the following mechanisms have been suggested. They include cytotoxic antibodies, decreased blocking antibodies, and

An expert in early pregnancy loss and gestational wellness, David R. Corley, M.D., FACOG, is a reproductive endocrinologist with extensive experience in vitro fertilization (IVF) and in working with infertile couples. Dr. Corley completed a fellowship in reproductive endocrinology at the University of Louisville School of Medicine with advanced training in laparoscopic and microsurgical techniques, ovulation induction, and IVF. He is Director of DVIF&G's Early Pregnancy Loss and Gestational Wellness program. He recently shared his research on Recurrent Pregnancy Loss with his peers at Virtua Hospital-Voorhees.

failure to suppress the maternal immune response at the maternal/fetal interface. Since little is known about the mechanisms that prevent the immunologic rejection of a developing baby in a successful pregnancy, it has been difficult to establish any of the above as a leading factor in RPL. Evidence for this theory, however, has not been scientifically validated. Women with normal pregnancies have been found to possess some of these immune defects that are thought to cause RPL. While several small studies seem to support these mechanisms as a cause of RPL, large randomized trials and analysis of multiple trials have failed to show a specific treatment benefit for RPL patients.

Thrombophilias presents an intriguing theoretical risk for RPL. Because of an increased production of several clotting factors, pregnancy is known to be a hypercoagulable state. This means that the body forms clots easily, most of them in the veins where the blood circulation is slow. Pregnancy, therefore, increases the risk of venous thromboembolism five to six fold, a serious condition where a blood vessel is blocked by a blood clot, or

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thrombus, where a blood clot may become detached from its site of formation. An inherited Thrombophilic disorder would only add to this hypercoagulable state, increasing the risk of uteroplacental clot formation and disrupting uteroplacental blood flow therefore resulting in fetal distress. Thrombophilias has been associated with 2nd and 3rd trimester loss but not found conclusively to be involved with early pregnancy loss. The most common Thrombophilic defects seen are factor V Leiden and Prothrombin G20210A mutations which are present in 8 % and 3%, respectively, of the general Caucasian population and less in African American and Asians.

Unfortunately, **no explanation** for recurrent pregnancy loss is found in more than 50 percent of couples. This could be because a subtle loss of genetic material responsible for the coding of a critical protein may not be found in a standard chromosomal analysis, and possibly, the Thrombophilias play an even greater role in early pregnancy loss than previously thought.

Stress may also play a more vital role in RPL. Very little is known of the effect stress has on the early developing pregnancy. Even when a clinical cause for RPL can be identified, the accompanying anxiety and stress that the couple experiences from thinking that the loss could happen again must be taken into account. Stress has already been shown to increase blood pressure, decrease libido, and even cause changes in female hormones that can lead to deviations in the menstrual cycle (luteal phase defects) and PCOS. Both have been associated with early pregnancy loss.

Helen Statham, Ph.D. a researcher from the University of Cambridge in England, evaluated 1,356 women who had experienced early pregnancy loss and found that they were more anxious about problems with subsequent pregnancies than mothers who had never miscarried. In another study conducted by Deborah James, Ph.D., of Carleton University in Canada, 72 women who had miscarried had elevated levels of depression, anxiety, and stress. According to Dr. James, these women either blamed themselves or their doctors for their early pregnancy losses. Still another study conducted at the Louisville School of Nursing found a link between previous early pregnancy loss on depressive symptoms, pregnancy-specific anxiety, and prenatal attachment for parents during later pregnancies. According to this study the previous stress experienced from early pregnancy loss is carried over to the current pregnancy.

A recent study conducted at Humboldt University in Berlin, Germany suggests that stress and/or pregnancy-related hormones, such as corticotropin releasing hormone, adrenocorticotropin, prolactin, and progesterone, might interact with certain cells to cause changes in cytokine production. Since a well-balanced interaction of the nervous system and endocrine network is crucial to maintain a pregnancy, this alternation in the number of cytokines may indeed contribute to RPL.

These findings should heighten awareness of the mixture of hope and fear expectant parents experience after suffering previous pregnancy losses. More studies need to be conducted to determine the full extent of stress on RPL.

No matter what the cause of early pregnancy loss, the good news is that the majority of couples with RPL go on to achieve successful pregnancies. ■

DVIF&G Endorses These Websites

In the modern age of the information superhighway, often fertility patients turn to the Internet for research and guidance. Most websites offer solid information on how to locate an appropriate physician and treatment center, what criterion defines a fertility patient, and what the general steps are in pursuing treatment.

Not all websites, however, are created equally. Some websites may offer bias or misinformation, leaving patients misguided and disillusioned. It is important to rely on those websites that are endorsed by credible fertility practices, such as the Delaware Valley Institute of Fertility & Genetics (DVIF&G), and reproductive associations, such as the American Society of Reproductive Medicine (ASRM). Below is a list of websites reviewed by DVIF&G and found to be reliable and informative.

- DVIF&G website http://www.dvifg.com
- American Society of Reproductive Medicine http://www.asrm.org
- Society of Reproductive Technologies http://www.sart.org
- American Fertility Association http://www.theafa.org
- Resolve http://www.resolve.org
- Infertility Health Resources http://www.ihr.com
- International Council of Infertility Information http://www.inciid.org/dissemination
- National Institute of Health: MedlinePlus http://www.medlineplus.com

DVIF&G recently welcomed Angela Santoro, RD to its growing staff. A Registered Dietitian, Santoro (pictured above) will provide nutritional counseling and educational literature to patients in DVIF&G's Lawrenceville, NJ office as a medical nutrition therapist. She received her B.S. in Foods and Nutrition from the College of St. Elizabeth and has over eights years of experience as a clinical dietitian and educator. She previously worked at Princeton Medical Center and is currently on the staff at Robert Wood Johnson University Hospital at Hamilton.

Ms. Santoro is also an active member of the American Dietetic Association and the NJ Dietetic Association. She lives in Bordentown, NJ and recently gave birth to a beautiful daughter after receiving treatment at DVIF&G.

To set up an appointment for a medical nutrition therapy consultation with Ms. Santoro or any of DVIF&G's medical nutrition therapists, please call (856) 988-0072.

Share Your Baby Pictures

If you would like to share your baby's photos with other DVIF&G patients, you can upload them at **www.startfertility.com** or **www.dvifg.com**, the DVIF&G website. Just fill out the necessary information, upload your photo, and your child's picture will be included. What a great way to share your joy and to give others hope.

"The shortest answer is doing."

— English proverb

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Happy Birthday to . . .

John Paul Landau, born on May 27, 2005, to Suzanne and Wilfridio Landau.
Perry Joseph Stanger, born on May 28, 2005, to Julie and Joseph Stanger.
Isabella Elizabeth Bennett, born on June 5, 2005, to Michele and Jim Bennett.
Daniel Edward Allen, born on June 14, 2005, to Gina and Randy Allen.
Rudolph Brian Rotter, born on June 20, 2005, to Amanda and Rudolph Rotter.
Brandon Wyatt Trad, born on June 24, 2005, to Christine and Jerry Trad.
All the babies and parents are doing well. Thank you, DVIF&G!

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Delaware Valley Institute of Fertility & Genetics
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6000 Sagemore Drive—Suite 6102
Marlton, NJ 08053

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EDITOR: Christine Norris

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Delaware Valley Institute of Fertility & Genetics
6000 Sagemore Drive—Suite 6102
Marlton, NJ 08053
(856) 988-0072

10 LaSalle Drive
Vineland, NJ 08360
(856) 794-8080

3100 Princeton Pike
Bldg 4, Suite D
Lawrenceville, NJ 08648
(609) 895-0088

Visit our web site at:
www.startfertility.com

Happy Birthday to . . .

Haley Ann Swanson, born on May 8, 2004, to Kristina and Eric Swanson.
Camille Aubrey Morgan, born on July 20, 2004, to Verita and Mark Morgan.
Samantha Faranelli, born on March 22, 2005, to Sue Heckman and Steve Farinelli.
Justin Lawrence Emerle, born on April 20, 2005, to Jennifer and Michael Emerle.
Morgan Gall, born on April 20, 2005, to Brook and Darin Gall.
Katelyn Nicole Deal, born on April 21, 2005, to Linda and Charles Deal.
Denise Isabel Talley, born on April 23, 2005, to Wanise and Wayne Talley.
Samuel Albrecht, born on May 6, 2005, to Sophia and Doug Albrecht.
Evan Talbot Stuart, born on May 12, 2005, to Laura and Roy Stuart.
Molly Emma Angelo, born on May 24, 2005, to Lisa and Bill Angelo.

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George S. Taliadouros, M.D., FACOG, the founder of DVIF&G, recently attended the 32nd Meeting of ISOBM at Biomedicum in Helsinki, Finland where some of his work on glycoprotein hormone isoforms was presented. Clinical investigation is an intregal part of patient care, providing information to effectively identify and treat infertility problems.