# Expanding Role of 23-Chromosome Microarray in Evaluation of Recurrent Pregnancy Loss

**William H. Kutteh, MD, PhD, HCLD**
Clinical Professor of Obstetrics & Gynecology
Division of Reproductive Endocrinology
Vanderbilt University Medical Center
Professor of Gynecology
Director of Fertility Preservation Program
Department of Surgery
St. Jude Children's Research Hospital
Managing Partner/Director,
Recurrent Pregnancy Loss Center
Fertility Associates of Memphis
Memphis, TN

The American College of Obstetrics and Gynecology (ACOG), the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) define Recurrent Pregnancy Loss (RPL) as a disease, distinct from infertility, characterized by two or more failed clinical pregnancies. Recurrent miscarriage is a common obstetrical complications and affects 2% to 4% of reproductive aged women worldwide. Maternal age and prior numbers of miscarriages are important factors in predicting future losses.

The recommended evaluations include consideration of: karyotypes on both partners to look for chromosomal translocations; lupus anticoagulant, anticardiolipin antibodies, and anti-beta-2 glycoprotein-1 antibodies to look for antiphospholipid syndrome; 3-D saline infused ultrasound to look for congenital and acquired uterine anomalies; and blood levels of prolactin, TSH, and hemoglobin A1c to look for hormonal imbalances. Increasingly, clinicians include evaluations for uterine infections and sperm DNA fragmentation. When all these evaluations are completed, only 45% of all pregnancy losses will have a possible explanation. However, in our recent study of over 55,000 products of conception, over 55% of the pregnancy losses could be explained by genetic abnormalities in the miscarriage.

Based on these observations, an updated algorithm for the evaluation of RPL begins with a 24-chromosomal microarray analysis (CMA) on the miscarriage tissue after the second documented pregnancy loss. When the miscarriage is aneuploid and the reason for the loss is explained, only 25% will have an additional abnormal finding on the standard workup. When the result reveals an unbalanced translocation, parental karyotypes should be performed in the standard ASRM workup along with genetic counseling and consideration for PGT-A. In the event that the CMA reveals a euploid miscarriage, then the ASRM evaluation would be recommended and reveals abnormalities in about 80% of couples. Using this strategy, over 90% of all miscarriages in couples with RPL will have a probable or definite cause identified. This emerging strategy is projected to result in a cost savings to the healthcare system.

Further, with this current strategy that includes the standard evaluation plus 23-chromosome microarray testing on the products of conception, less than 10% of recurrent miscarriages remain "truly unexplained". Long term follow-up studies indicate that the prognosis for these patients is very good and can be predicted based on the age of the female partner and the number of prior losses. This classification system, combining "normal versus abnormal" workup with "euploid versus aneuploid" miscarriage, should assist clinicians in determining those who may benefit from preimplantation testing.