# Is it time for new guidelines for recurrent pregnancy loss integrating genetic testing of products of conception and preimplantation genetic testing?

Miscarriage is the most common complication of pregnancy and occurs in approximately 20% of all identified conceptions. When an individual couple experiences multiple events of pregnancy loss before 20 weeks' gestation, this is termed recurrent miscarriage or recurrent pregnancy loss (RPL). On the basis of current evaluation by international societal guidelines, more than 50% of RPL will remain unexplained with no identifiable cause (1). In this issue of *Fertility and Sterility*, Mumusoglu et al. (2) have presented an excellent systematic review and meta-analysis with the objective of addressing the role of preimplantation genetic testing for aneuploidy (PGT-A) in patients with unexplained RPL. They evaluated several key aspects and provided preliminary answers: the likelihood of a live birth in a subsequent spontaneous pregnancy (depends on maternal age and number of prior losses); whether women with unexplained RPL have a higher rate of aneuploidy (probably not); whether euploid blastocysts offer comparable live birth rates in patients with unexplained RPL and those with no RPL (yes); whether the endometrium is less selective in unexplained RPL (no); and whether PGT-A increases the live birth rate or reduces pregnancy losses until delivery (probably yes to both). Their meta-analysis provided some insight to their queries; however, the investigators acknowledged that some studies provided low-quality evidence.

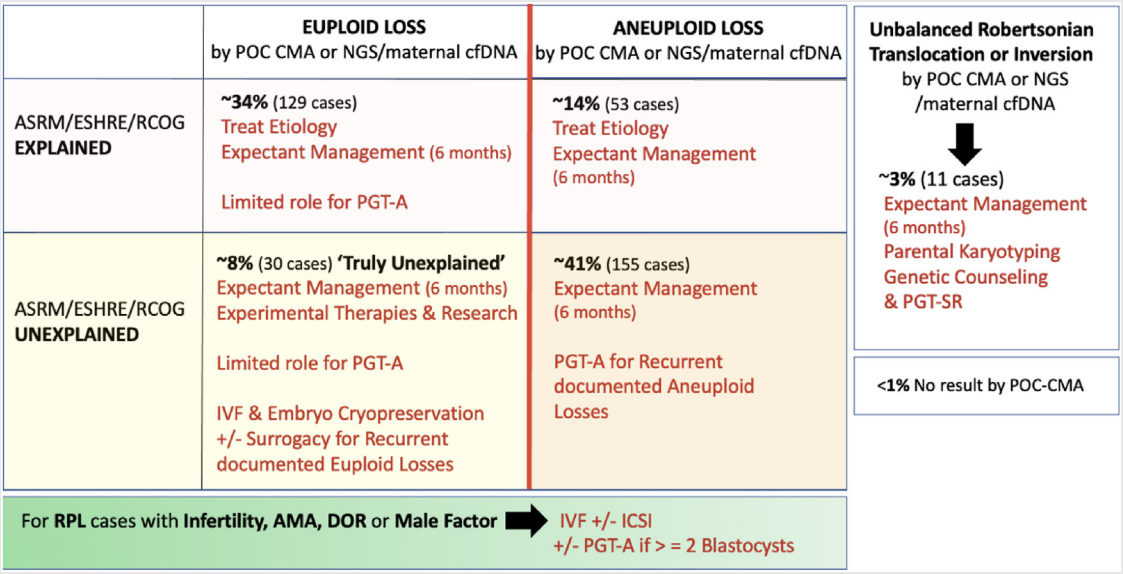
In 2013, we proposed the genetic testing of products of conception (POC) of miscarriages using 23-chromosome microarray (CMA). Thousands of POC samples have been evaluated using CMA, which clearly demonstrates the efficacy of this technology. Overall, we reported that the aneuploidy rate for spontaneous miscarriages in all women at 57.5% (31,551/54,912) was identical to the aneuploidy rate for miscarriages in patients with RPL of 57.7% (218/378) (3). There are important benefits when using CMA vs. traditional karyotyping for POC genetic analysis including the facts that CMA does not need tissue culture, can be used on nonviable miscarriage tissue, and allows for maternal cell contamination to be ruled out, hence reducing the number of false-negative 46,XX results. Arguments in favor of new guidelines for RPL integrating POC CMA or next-generation sequencing (NGS) along with the possible role of PGT in some patients with RPL are discussed in this commentary article.

An improved classification of RPL on the basis of the euploid or aneuploid status of the POC combined with the standard RPL workup can provide a possible explanation for a pregnancy loss to 90% of patients and may help to direct clinicians to subsets of patients with RPL, which may benefit from PGT (Fig. 1) (1, 3). For women with RPL who have an otherwise normal RPL evaluation with POC aneuploidy identified as the explanation for the loss (41% of all patients with RPL), expectant management for 6 months can be suggested on the basis of maternal age, patient's wish, and number of prior losses. For those with recurrent POC aneuploidy or after 6 months of expectant management, a discussion about the use of PGT-A could be advised. For the 3% of couples with RPL where the POC CMA aneuploidy is an unbalanced translocation or an inversion, thus making it known that one of the parents has a translocation or inversion, genetic counseling with expectant management vs. PGT-structural rearrangement should be discussed. In patients with a euploid result on POC with an abnormal finding on the standard RPL workup (approximately 34% of RPL cases), the abnormal finding (autoimmune, hormonal, and anatomic) should be corrected, and the patient should be observed expectantly. In this subset of patients with a euploid pregnancy loss, there would be a limited role of PGT-A except in patients with RPL combined with infertility, advanced maternal age, decreased ovarian reserve, or male factor. Approximately 14% of couples with RPL will have aneuploidy on POC plus an abnormal finding on the standard RPL evaluation. It seems reasonable that the abnormality should be corrected followed by expectant management for 6 months. After that interval, no further testing is advised, and the couple should be counseled about PGT-A. The recently introduced concept of "truly unexplained RPL" represents only 8% of all evaluated RPL cases. Indeed, we believe that those patients with truly unexplained RPL with a completely negative standard RPL workup including euploid POC on CMA should be the focus of investigational new therapies (e.g., immunological therapy and heparin) and enrolled in experimental studies.

Beyond POC testing, we believe that evaluation and management using the currently recommended guidelines including immune, anatomic, and/or endocrine etiologies should continue. Expectant management still has a role today for many RPL cases, such as those that remain unexplained. Not all patients with RPL will necessarily benefit from in vitro fertilization and PGT-A. For instance, PGT-A should be considered when recurrent fetal aneuploidy is believed to play an important role, such as in the presence of a negative RPL workup with the presence of fetal aneuploidy on POC. Perhaps the need for in vitro fertilization with PGT-A should be individualized generally on the basis of the results of the RPL evaluation, the results of CMA or NGS testing on POC, the woman's age, and her ovarian reserve. Despite their many advantages, POC genetic testing with CMA or NGS and PGT are not without drawbacks. We acknowledge the fact that they may increase cost and potentially overwhelm certain public systems. Additionally, these technologies may not be available everywhere.

The standard RPL evaluation combined with CMA or NGS on POC can provide a proven or possible explanation for the pregnancy loss in over 90% of cases (1, 3). The additional categorization of the pregnancy loss as euploid vs. aneuploid coupled with the classification of the standard RPL evaluation as explained or unexplained should help to identify patients who are candidates for expectant management vs. PGT-A. New society guidelines for the management of RPL are needed with the inclusion of the following updates:

## FIGURE 1




Proposed recommendations for the management of recurrent pregnancy loss (RPL) using "explained vs. unexplained" combined with "euploid vs. aneuploid" to determine candidates for expectant management, treatment, or preimplantation genetic testing for aneuploidies (PGT-As) or structural rearrangements (PGT-SRs), vs. experimental therapy. The numbers are based on the American Society for Reproductive Medicine (ASRM) guidelines for the evaluation of RPL and the results of 23-chromosome microarray testing (CMA) analysis of products of conception (POC) from 378 prospectively recruited couples. AMA = advanced maternal age; cfDNA = cell-free deoxyribonucleic acid; DOR = decreased ovarian reserve; ESHRE = European Society of Human Reproduction and Embryology; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; NGS = next-generation sequencing; RCOG = Royal College of Obstetricians and Gynaecologists. (From Kutteh et al. [3]. Reprinted by permission of the publisher.)

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- Clarify the definition of pregnancy as a positive pregnancy test without ultrasound documentation or histopathology (4).
- Recommend inclusion of CMA or NGS testing on POC with the second and subsequent loss (2, 3, 5).
- In couples who have unexplained losses after the standard RPL workup and aneuploid results on POC, encourage the use of PGT-A after 6 months of expectant management after proper counseling (sooner if infertility, advanced maternal age, decreased ovarian reserve, or male factor) (2, 5).

## CRediT Authorship Contribution Statement

**William H. Kutteh:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Ralph S. Papas:** Conceptualization, Formal analysis, Methodology. **Elias M. Dahdouh:** Conceptualization, Formal analysis, Writing – review & editing.

## Declaration of Interests

W.H.K. has nothing to disclose. R.S.P. has nothing to disclose. E.M.D. has nothing to disclose.

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