The Status of Genetic Screening in Recurrent Pregnancy Loss

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KEYWORDS

• Aneuploidy • Comprehensive chromosomal screening • Inversion • Miscarriage
• Products of conception • IVF • Preimplantation genetic screening
• Spontaneous abortion

KEY POINTS

- Recurrent pregnancy loss (RPL) is often idiopathic. Approximately 50% of cases have a discernible cause.
- Numerical chromosomal abnormalities in the conceptus are primarily due to maternal meiotic nondisjunction, and the rate and complexity of embryonic aneuploidy are primarily driven by female age.
- Structural chromosomal abnormalities (balanced translocations or inversions) can lead to unbalanced gametes depending on specific recombination and segregation patterns during meiosis. The attendant reproductive risk depends on the type of rearrangement and its parental origin.
- Products of conception may be analyzed by cytogenetics, array comparative genomic hybridization, or single nucleotide polymorphism microarray. Each platform has its respective advantages and disadvantages.
- Preimplantation genetic screening decreases the likelihood of subsequent miscarriage per euploid embryo transfer, but further investigation is required to define the time to viable pregnancy, cumulative live birth rates, and cost of treatment as compared with expectant management.

INTRODUCTION

Spontaneous abortion or miscarriage is defined as the loss of pregnancy before 20 weeks' gestation. Although miscarriage is common, occurring in 15% to 25% of all clinically recognized pregnancies, recurrent pregnancy loss (RPL), defined as the loss of 2 or more clinical pregnancies, is uncommon. It is estimated that approximately

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5% of women will experience 2 consecutive losses, and only 1% will experience 3 or more.[1]

RPL is often idiopathic. Of the 50% of cases that have a discernible cause, most are attributable to the following factors:

- Anatomic (congenital or acquired uterine abnormalities, including a septate, unicornuate, or didelphic uterus; submucosal fibroid; or intrauterine synechiae)
- Endocrine (thyroid disorders, hyperprolactinemia, diabetes mellitus)
- Immunologic (antiphospholipid antibody syndrome)
- Genetic (aneuploidy, structural rearrangements)
- Other (infectious, environmental)

This review focuses on the genetic causes of RPL, along with the appropriate workup of products of conception (POC), and management options, including expectant management (EM) and in vitro fertilization (IVF) with preimplantation genetic screening (PGS).

OVERVIEW OF THE GENETIC CAUSES OF RECURRENT PREGNANCY LOSS

Pregnancy loss can occur because of numerical chromosomal abnormalities, arising from meiotic nondisjunction (eg, trisomy or monosomy), aberrant fertilization (eg, triploidy), or embryogenesis (eg, tetraploidy), or because of structural chromosomal abnormalities, arising from the inheritance of a derivative chromosome (eg, translocations and inversions). Estimates of the incidence and outcome of various karyotypic abnormalities are shown in **Table 1**.[2]

Table 1
Estimated incidence and outcome of various karyotypic abnormalities in 10,000 pregnancies

	Incidence per 10,000 Pregnancies	Spontaneous Abortion (%)	Live Births
Total	10,000	1500 (15)	8500
Normal chromosomes	9200	750 (8)	8450
Abnormal chromosomes	800	750 (94)	50
Specific abnormalities			
Polyploid	170	170 (100)	0
45,X	140	139 (99)	1
Trisomy 16	112	112 (100)	0
Trisomy 18	20	19 (95)	1
Trisomy 21	45	35 (78)	10
Trisomy, other	209	208 (99.5)	1
47,XXY; 47,XXX; 47,XYY	19	4 (21)	15
Unbalanced rearrangement	27	23 (85)	4
Balanced rearrangement	19	3 (16)	16
Other	39	37 (95)	2

These estimates are based on observed frequencies of chromosome abnormalities in miscarriage specimens and live-born infants. It is possible that the frequency of these abnormalities is much higher, though, because many spontaneously abort before clinical recognition.

Adapted from Nussbaum RL, McInnes RR, Willard HF. Principles of clinical cytogenetics and genome analysis. In: Nussbaum RL, McInnes RR, Willard HF, editors. Thompson & Thompson genetics in medicine. 8th edition. Philadelphia: Elsevier; 2016. p. 73; with permission.