

# Classic and Cutting-Edge Strategies for the Management of Early Pregnancy Loss

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## KEYWORDS

- Recurrent pregnancy loss • RPL • Miscarriage • Spontaneous abortion • Aneuploid
- Antiphospholipid • Lupus anticoagulant • Heparin

## KEY POINTS

- There are few conditions in medicine associated with more heartache to patients than recurrent pregnancy loss (RPL).
- The management of early RPL is a formidable clinical challenge for physicians.
- Great strides have been made in characterizing the incidence and diversity of this heterogeneous disorder, and a definite cause of pregnancy loss can be established in more than half of couples after a thorough evaluation.
- In this review, current data are evaluated and a clear roadmap is provided for the evaluation and treatment of RPL.

## INTRODUCTION

Recurrent early pregnancy loss is a profound personal tragedy to couples seeking parenthood and a formidable clinical challenge to their physician. When to evaluate a couple and what constitutes a complete evaluation is, at the time of the writing of this article, in a state of flux. The American College of Obstetricians and Gynecologists (ACOG) has withdrawn its 2001 Practice Bulletin on early RPL and has not issued a replacement for more than 1 year. The American Society for Reproductive Medicine

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(ASRM) has recently released a committee opinion after extensively evaluating available evidence over a 7-year period.<sup>1</sup>

Although spontaneous abortion occurs in approximately 15% of clinically diagnosed pregnancies of reproductive-aged women, recurrent pregnancy loss (RPL) occurs in about 1% to 2% of this same population.<sup>2</sup> Great strides have been made in characterizing the incidence and diversity of this heterogeneous disorder, and a definite cause of pregnancy loss can be established in more than half of couples after a thorough evaluation.<sup>3,4</sup> A complete evaluation includes investigations into genetic, endocrinologic, anatomic, immunologic, and iatrogenic causes. The occurrence of RPL may induce significant emotional distress, and, in some cases, intensive supportive care may be necessary. Successful outcomes occur in more than two-thirds of all couples.<sup>4,5</sup>

## DEFINITION OF PREGNANCY LOSS

The traditional definition of RPL included those couples with 3 or more spontaneous, consecutive pregnancy losses. Ectopic and molar pregnancies are not included. The ASRM has defined RPL as “a distinct disorder defined by 2 or more failed clinical pregnancies.”<sup>1</sup> For purposes of determining if an evaluation for RPL is appropriate, pregnancy “is defined as a clinical pregnancy documented by ultrasonography or histopathological examination.”<sup>1</sup> Several studies have recently indicated that the risk of recurrent miscarriage after 2 successive losses is similar to the risk of miscarriage in women after 3 successive losses; thus, it is reasonable to start an evaluation after 2 or more consecutive spontaneous miscarriages to determine the cause of their pregnancy loss, especially when the woman is older than 35 years of age, or when the couple have had difficulty conceiving.<sup>6</sup>

Those couples with primary RPL have never had a previous viable infant, whereas those with secondary recurrent loss have previously delivered a pregnancy beyond 20 weeks and then suffered subsequent losses. Tertiary recurrent loss refers to those women who have multiple miscarriages interspersed with normal pregnancies.

## RECURRENCE RISK

The main concerns of couples with recurrent miscarriage when they present to our RPL center is to find the cause and to establish the risk of recurrence. In a first pregnancy, the overall risk of loss of a clinically recognized pregnancy loss is 15%.<sup>7,8</sup> However, the true risk of early pregnancy loss is estimated to be around 50% because of the high rate of losses that occur before the first missed menstrual period. Furthermore, as women age, this rate likely increases because of chromosomal errors introduced through meiotic nondisjunction errors during oocyte maturation. Studies that evaluated the frequency of pregnancy loss,<sup>7,8</sup> based on highly sensitive tests for quantitative human chorionic gonadotropin (hCG), indicated that the total clinical and pre-clinical losses in women aged 20 to 30 years is approximately 25%, whereas the loss rate in women aged 40 years or more is at least double that figure. The ability to predict the risk of recurrence is influenced by several factors, including maternal age, parental and fetal karyotypes, the gestational age at which prior losses occurred, and the presence of various maternal laboratory findings.<sup>8–14</sup>

## CAUSES, DIAGNOSIS, AND TREATMENT OF RPL

### *Introduction*

Traditionally, the chief causes of RPL have been believed to be embryonic chromosomal abnormalities, maternal anatomic abnormalities such as a uterine septum, luteal

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