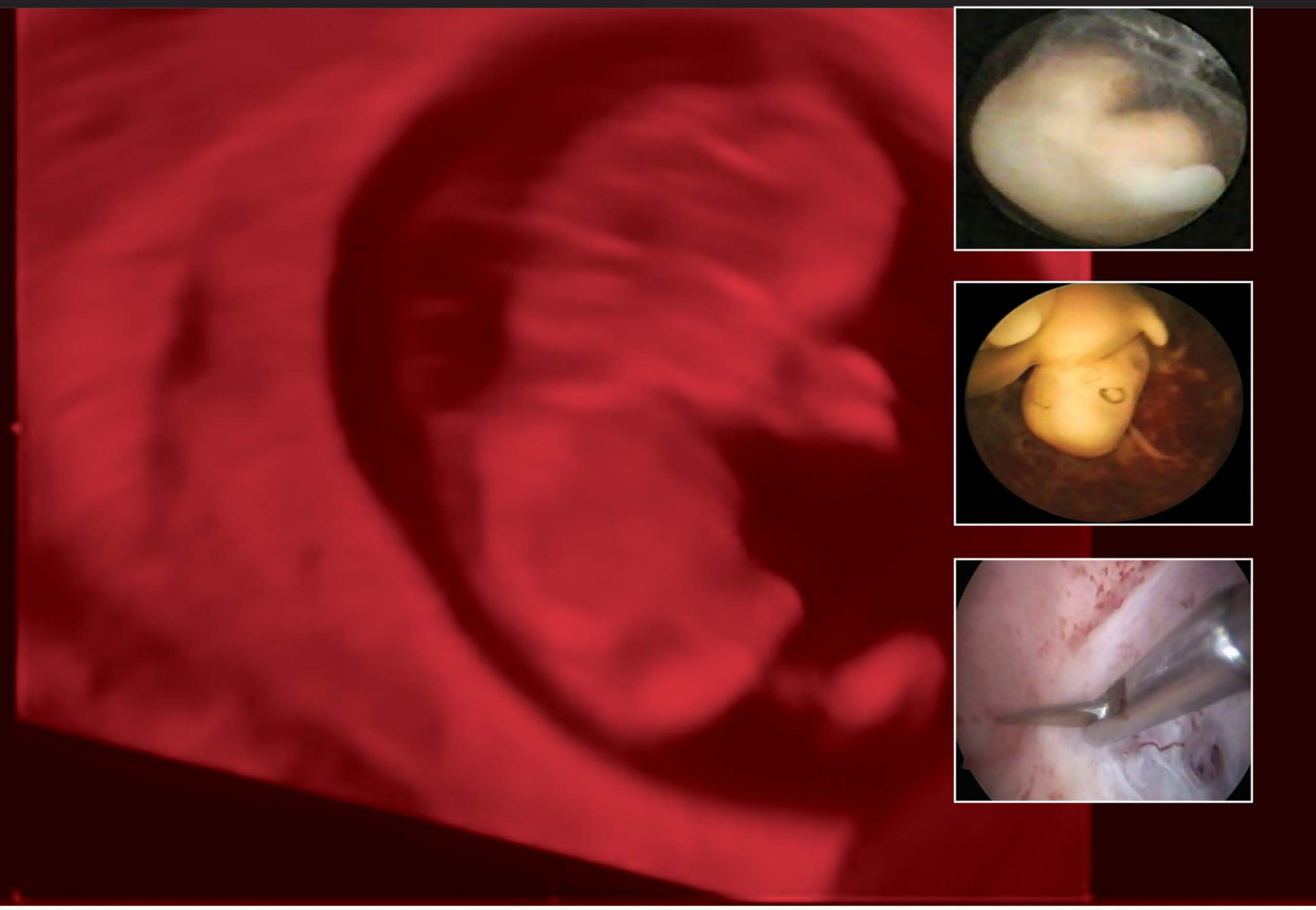
THIRD EDITION

Recurrent Pregnancy Loss



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1 CHAPTER

Overview and Terminology Clarified

Mala Arora

INTRODUCTION

Percy Malpas from Liverpool coined the term "habitual aborter" for women with three or more consecutive abortions.[1] The term is no longer used because of its negative connotations. The word abortion is now replaced by miscarriage,[2] (Table 1) which is defined as the loss of a pregnancy less than 20 weeks gestation or loss of a fetus weighing less than 500 g.[2] The traditional definition of three consecutive miscarriages was proposed by Malpas and seconded by Eastman[3] who in 1946 worked on a community based statistical model and proposed that the group with two losses had a significantly better pregnancy outcome than the group with three or more losses. Further studies by Stirrat confirmed this observation.[4] However, authors personal observations[5] and many other observational studies[9] confirm that pregnancy outcome is no different in the more than two and more than three miscarriage groups.

Royal College of Obstetrics and Gynecology (RCOG) UK continues to define recurrent pregnancy loss (RPL) as three or more consecutive pregnancy losses.[6] The European Society for Human Reproduction and Embryology (ESHRE) special interest group for early pregnancy defined recurrent miscarriage as three early consecutive losses or two late pregnancy losses.[7] However the American College of Obstetrics and Gynecology (ACOG)[8] modified the definition to two or more pregnancy losses confirmed by ultrasound or histopathology of the products of conception. Some others consider RPL to be defined as two or more consecutive miscarriages OR three spontaneous miscarriages which may not be consecutive.

The ACOG definition is clinically more relevant as most clinicians would start investigations for RPL after two consecutive losses. However this would increase the prevalence of RPL to 5% as compared to previous 1% with three or more losses. It would also favorably skew the effect of treatment modalities. Hence it is thought that for research and publication purposes, we retain the definition of three or more losses. Logically, it will be hard to retain the RCOG definition, as changing trends in clinical practice will generate data accordingly. However, this heterogeneity in definition hinders scientific research and gives birth to varying clinical practices globally. Table 2 outlines the heterogeneity of definition in published studies.

The current definition does not include women with ectopic, biochemical pregnancies and pregnancy of uncertain location which has similar emotional consequences for the couple. Each of these conditions is known to be associated

TABLE 1 Old and new nomenclature

Previous term	Recommended term
Spontaneous abortion	Miscarriage
Threatened abortion	Threatened miscarriage
Inevitable abortion	Inevitable miscarriage
Incomplete abortion	Incomplete miscarriage
Complete abortion	Complete miscarriage
Missed abortion	Missed miscarriage
Blighted ovum	Early fetal demise
Septic abortion	Miscarriage with sepsis
Recurrent abortion	Recurrent miscarriage

TABLE 2 Summary of definitions of recurrent miscarriage used in clinical trials

Reference	Definition of recurrent pregnancy loss
Cowchock, 1992	≥2 fetal losses
Silver, 1993	≥1 unexpected fetal death >12 weeks gestation OR ≥2 unexplained first trimester losses
Kutteh, 1996	≥3 consecutive pregnancy losses
Laskin, 1997	≥2 consecutive fetal losses at <32 weeks
Rai, 1997	≥3 consecutive miscarriages
Pattison, 2000	≥3 miscarriages
Farquharson, 2002	>2 fetal losses
Triolo, 2003	≥3 consecutive fetal losses <10 weeks gestation
Clark, 2010	≥2 consecutive fetal losses at <24 weeks gestation

Source: From Bhattacharya S. Recurrent miscarriage: should the definition be revised? In: Arora M, Bhattacharya S, Kumari V (Eds). World Clinics Obsterics and Gynecology Recurrent Miscarriage. 2011;1(1):136.

with a poor obstetric outcome and can be recurrent. Hence the proposal is that we should include ultrasound, histopathological and biochemical evidence of a pregnancy". We may have to set a minimum level of β-human chorionic gonadoltropin (β-hCG) positivity so as to exclude drug-induced positive β-hCG levels in assisted reproductive technique (ART) pregnancies.

Recurrent implantation failure and Pre clinical pregnancy loss/very early pregnancy loss (VEPL) are markers of poor implantation and have a common spectrum with RPL. However the current definition does not take this into consideration. This is because both these entities are in themselves not clearly defined and hence data collection can be skewed. I sincerely feel that this should be part of the definition of RPL. Pre clinical losses with documented beta HCG rise and fall are a clear indication of failed implantation and may result from genetically abnormal embryos. This is the reason why some authors believe that rather than the number of losses, the time to take home a baby from the time of first pregnancy event should also be taken into consideration in the definition.

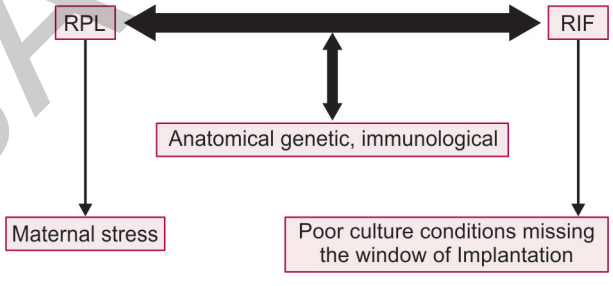
Recurrent implantation failure (RIF) defined as no implantation after replacement of 10 grade-A embryos of day 2/3 maturity or 4 blastocyst of day 5 maturity, fresh and frozen cycles included. A standard definition is still lacking. This is an entity distinct from RPL, although they both have many overlapping causes. They may be described as two ends of the same spectrum (Fig. 1). Recurrent implantation failure is only relevant in the setting of assisted conception cycles, whereas RPL is usually seen in spontaneous conceptions. However women with RIF will need to be evaluated for most causes of RPL as well as laboratory factors as well as the synchronization with the window of implantation which is not relevant to RPL.

Primary recurrent miscarriages are two or more losses with no pregnancy progressing beyond 20 weeks.

Secondary recurrent miscarriages are two or more losses after a pregnancy that has progressed beyond 20 weeks which might have resulted in a live or stillbirth.

This division is not so important as the etiological factors and prognosis is the same in the two groups.[10] Perhaps the incidence of acquired anatomical defects like uterine adhesions and cervical insufficiency may be higher in the secondary RPL group, hence evaluation of the uterine cavity should always be done in this group.

Recurrent pregnancy loss comprises of both early and late pregnancy losses. The spectrum encompasses:



RPL, recurrent pregnancy loss; RIF, recurrent inplantation failure.

Fig. 1: Relationship of recurrent pregnancy loss (RPL) and recurrent implantation failure.

- Preclinical pregnancy loss: This entity is diagnosed by performing serum β-hCG assays in the late luteal phase prior to the onset of the next menstrual cycle
- Clinical pregnancy loss is defined as pregnancy loss following an ultrasound evidence of a gestational sac. Clinical pregnancy loss is divided into:
  - Preembryonic, when no fetal pole is identified (<5 weeks)
  - Embryonic, when a fetal pole is identified (5–10 weeks) and
  - Fetal, more than 10 weeks' gestation
- First trimester loss is loss of a pregnancy less than 12 weeks. More than 80% of miscarriages occur in the first 12 weeks. This may also be addressed as recurrent miscarriages (RM) or recurrent spontaneous miscarriage
- Midtrimester loss occurs between 12 weeks and 28 weeks of pregnancy. The common causes are anatomical defects and antiphospholipid syndrome. These women will benefit with a hysteroscopic evaluation
- Late fetal loss occurs between 28 weeks to term. The most common cause is preterm labor, preterm premature rupture of membranes, preeclampsia (PE), or congenital malformations. Unexplained stillbirth is even more traumatic than unexplained RPL and merits detailed investigations to ascertain a cause (refer to chapter 29). Thrombophilia screening becomes relevant in women with midtrimester and late pregnancy losses.

For the purpose of this book late fetal loss describes pregnancy loss between 12 weeks and delivery.

Recurrent spontaneous miscarriage only deals with 1st trimester losses.

Table 3 defines terminology related to pregnancy loss as proposed by ESHRE - Special interest group for early pregnancy.[11]

TABLE 3 ESHRE nomenclature of early pregnancy events

Term	Definition
Biochemical pregnancy loss	Spontaneous pregnancy loss confirmed by decreasing β-hCG levels but not located on ultrasound scan
Empty sac or anembryonic pregnancy loss	Intrauterine sac with absent fetal pole/yolk sac on ultrasound
Yolk sac miscarriage	Intrauterine gestational sac and yolk sac but no fetal pole on ultrasound
Embryonic miscarriage	Intrauterine gestational sac with yolk sac and fetal pole but no cardiac activity
Fetal miscarriage	Pregnancy loss >10 weeks size with a fetal pole of CRL >33 mm on ultrasound
Ectopic pregnancy	Pregnancy visualized outside the endometrial cavity
Early pregnancy loss	Pregnancy loss <10 weeks gestational age (<8 developmental week)
Late pregnancy loss	Greater than 12 weeks gestation
Pregnancy of unknown location	• No identifiable pregnancy on transvaginal scan with a β-hCG level of 1,500 IU/L • No identifiable sac with on trans-abdominal scan with β-hCG of 6,000 IU/L

β-hCG, β-human chorionic gonadotropin; CRL, crown-rum length.

Personal data from the authors subfertility clinic is presented below to emphasize the number of patients with RPL that seek assisted conception after one, two or three miscarriages (Table 4).

Pregnancy outcomes are presented in table 5.

By far the most common event is a sporadic miscarriage, which occurs in 20–30% of women, and in less than 5% after the documentation of fetal cardiac activity. Sporadic miscarriages do not compromise future obstetric outcomes.[7] Hence, women with a single spontaneous pregnancy loss should not be investigated, as the chances of a live birth subsequently are comparable to no previous loss (Table 5).

There is no statistically significant difference in the numbers that got pregnant, in the group with two miscarriages (25/80 = 31.2%) and the group with three miscarriages (11/39 = 28.2%). The numbers that delivered were 47% in the group with two miscarriages and 42.8% in the group with three miscarriages, which is not statistically significant. As the numbers get smaller it is difficult to make meaningful conclusions.

On the basis of this evidence it was proposed to change the definition of recurrent miscarriages to two consecutive miscarriages 2007, which has now been accepted widely.

Conventionally women with RPL conceived spontaneously. However, we now have a new subgroup of women that present with infertility and RPL. They only conceive with ART. In our personal data from an infertility clinic 10% (118/1,181) of women seeking ART are patients with two or more miscarriages. Experiencing loss of an ART pregnancy is emotionally more traumatic and these couples often have a lower threshhold for investigations and treatment.

However, whether we need to investigate them after one loss or two, will depend on the time to pregnancy and the maternal age.

The link between maternal age and pregnancy loss is now well-documented. Maternal age of 35 and above is associated with a higher incidence of pregnancy loss;the incidence increases progressively with increasing maternal age.

There is a need to constantly revise investigation and treatment guidelines, for patients with RPL in the changing social and medical scenario, due to the following:

- Today women start their reproductive careers late and will not have the time and patience to wait for multiple losses.
- Subgroups of women that miscarry due to anatomical factors or antiphospholipid antibodies have well-defined treatment modalities that can reduce the rate of subsequent miscarriages. Hence to deny them this treatment till they have multiple pregnancy losses seems unjustified.

Hence, women seeking pregnancy through ART may demand to have all investigations including evaluation of the uterine cavity after one miscarriage or biochemical pregnancy.

It may also be proposed that in women greater than 37 years, one miscarriage should prompt genetic screening and replacement of a euploid embryo. Similarly RIF, abnormal gamete morphology, poor quality embryos and advanced maternal/paternal age should have sperm DNA fragmentation index (DFI) and preferably preimplantation genetic screening (PGS) of the trophectodermal cells and replacement of only euploid embryos, prior to complete cessation of gametogenesis.

TABLE 4 **Breakup of total number of patients visiting the clinic according to the number of miscarriages[5]**

0	810
1	224
2	80
3	39
4	16
5	5
7	2
13	1
Total	**1177**

INTERPREGNANCY INTERVAL

Women with a pregnancy loss will often ask "when is it best to try again?" Although the World Health Organisation[13] has recommended 6 months interpregnancy interval between pregnancies, there are studies to suggest that a shorter interpregnancy interval in women with RPL may have better outcomes.[14,15] Having one normal period post a miscarriage is sufficient for a couple desperate to achieve their dreams of parenthood.

TABLE 5 **Outcome in patients with 0, 1, 2, 3, and 4 miscarriages[5]**

No. of abortions	Total no. of patients	No. of pregnant patients (%)	UPT + but lost to follow up	SVD/LSCS/preterm (%)	Miscarriages (%)
0	810	197 (24.32)	81	59/116 (50.86)	57/116 (49.13)
1	224	55 (24.55)	22	17/33 (51.5)	16/33 (48.48)
2	80	25 (31.25)	8	8/17 (47.0)	4/17 (23.52)
3	39	11 (28.2)	4	3/7 (42.85)	4/7 (57.14)
4	16	5 (31.25)	0	2/5 (40.0)	3/5 (60.0)

UPT, urine pregnancy test; SVD, spontaneous vaginal delivery; LSCS, lower segment cesarean section.

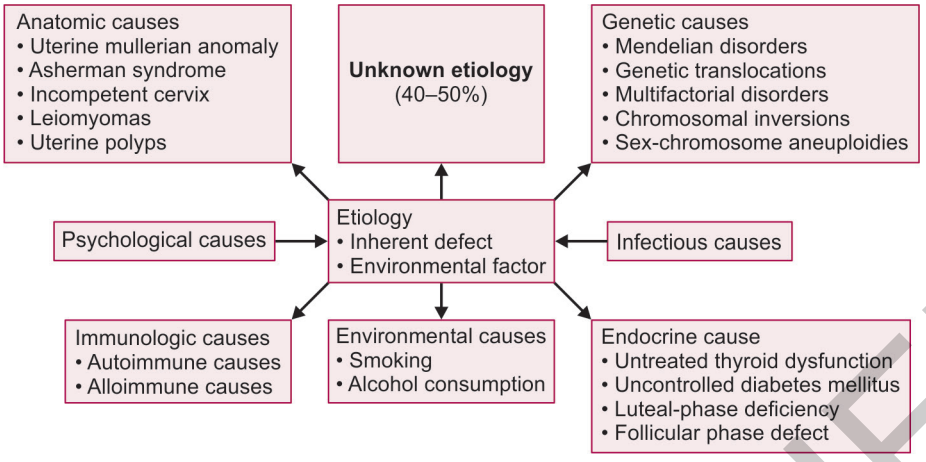


Fig. 2: Causes of recurrent pregnancy loss

CONCLUSION

Definition and terminology of RPL has been revised over the past few years. However, it still needs further modifications which need to be deliberated upon.

The author leaves you to ponder about the known causes of RPL (Fig. 2) and the large group so far unexplained and the discussions in the coming chapters will help us shrink this group in the near future.

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Recurrent Pregnancy Loss

Key Features

- This is the 3rd edition of the well-received previous 2 editions of the title
- The text is extensively revised to incorporate latest research in the field
- Presentation is concise and lucid, which makes this edition more reader friendly
- The topics have been divided into various sections based on etiological factors like genetic, anatomical, infective, and immunological
- The latest diagnostic recommendations from the RCOG (UK) as well as the ACOG (USA) have been incorporated
- An updated section on "Management Options" and a well-illustrated "Role of Ultrasound" are the highlighting features of this edition
- Role of newer treatment options like IVIG, GCSF, IVF/PGS, antioxidants, and lymphocyte immunotherapy have been elaborated
- Chapters are contributed by original researchers in the field from across the world
- This book will form an excellent resource for gynecologists, specialists in reproductive medicine, teaching faculty, and postgraduate students.

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