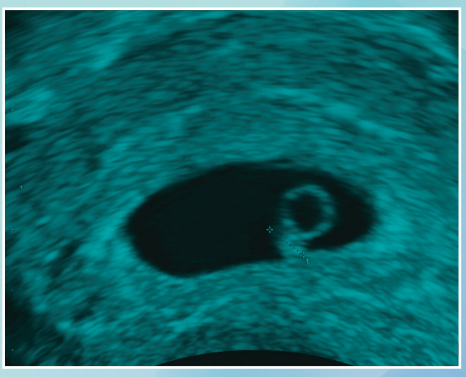
GYNECOLOGY IN PRACTICE

Series editor **Aydin Arici**

Recurrent Pregnancy Loss



Edited by

Ole B. Christiansen

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Series Foreword

In recent decades, massive advances in medical science and technology have caused an explosion of information available to the practitioner. In the modern information age, it is not unusual for physicians to have a computer in their offices with the capability of accessing medical databases and literature searches. On the other hand, however, there is always a need for concise, readable, and highly practicable written resources. The purpose of this series is to fulfill this need in the field of gynecology.

The *Gynecology in Practice* series aims to present practical clinical guidance on effective patient care for the busy gynecologist. The goal of each volume is to provide an evidence-based approach for specific gynecologic problems. "Evidence at a glance" features in the text provide summaries of key trials or landmark papers that guide practice, and a selected bibliography at the end of each chapter provides a springboard for deeper reading. Even with a practical approach, it is important to review the crucial basic science necessary for effective diagnosis and management. This is reinforced by "Science revisited" boxes that remind readers of crucial anatomic, physiologic, or pharmacologic principles for practice.

Each volume is edited by outstanding international experts who have brought together truly gifted clinicians to address many relevant clinical questions in their chapters. The first volumes in the series are on *Chronic Pelvic Pain*, one of the most challenging problems in gynecology, *Disorders of Menstruation, Infertility*, and *Contraception*. These will be followed by volumes on *Sexually Transmitted Diseases, Menopause, Urinary Incontinence, Endoscopic Surgeries*, and *Fibroids*, to name a few. I would like to express my gratitude to all the editors and authors, who, despite their other responsibilities, have contributed their time, effort, and expertise to this series.

Finally, I greatly appreciate the support of the staff at Wiley-Blackwell for their outstanding editorial competence. My special thanks go to Martin Sugden, PhD; without his vision and perseverance, this series would not have come to life. My sincere hope is that this novel and exciting series will serve women and their physicians well, and will be part of the diagnostic and therapeutic armamentarium of practicing gynecologists.

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Preface to the First Edition

Recurrent pregnancy loss (RPL), which is almost synonymous with recurrent miscarriage (RM), is defined as a minimum of three (or two) spontaneous losses of intrauterine pregnancies before gestational week 22. It is a cause of involuntary childlessness that among physicians and in the general population is much less recognized than childlessness due to failure to conceive (infertility) or stillbirth. This is mainly due to the fact that whereas there are many established public and private IVF clinics taking care of couples with infertility, as well as many clinics specialized in obstetrics and fetomaternal medicine that take care of women with stillbirths, most women with RPL are being managed in clinics of general gynecology by physicians who often have their main interest in gynecological surgery. A second reason for the invisibility of RPL is that many patients with very early miscarriages or biochemical pregnancies are not coming into contact with hospitals or gynecologic specialists because they have no need for surgical or medical treatment and therefore remain unknown to the secondary and tertiary health-care system. A third reason for the invisibility of RPL may be that since very few treatment options with documented efficacy exist, few physicians feel motivated to take care of these patients. In my experience, only well-educated psychologically strong patients will be able to mobilize the mental energy required to consult one of the few (often distantly located) clinics that have specialized in RPL management. The majority of RPL patients become stuck in the system because few recognize their problems and even fewer can offer them treatments.

Since only a minority of RPL cases are fully recognized by the secondary and tertiary health-care system, no valid registration of the size of the problem exists. Estimates showing that 1% of all women suffer RPL are based on studies conducted 30 years earlier at a time when detecting early pregnancy loss had limited possibilities (no high-resolution vaginal ultrasound, insensitive hCG tests). The real and current prevalence of RPL may be considerably higher than 1% and is also dependent on how the condition is defined: two or more losses versus three or more.

The main goal of this book is to highlight the condition and to help practitioners and gynecologists cope with patients in clinical practice. All chapters are written by specialists who have taken care of patients with RPL in clinical practice and have done recognized research. The reader may be confused by the different opinions put forward by the contributing specialists: some find specific investigations and treatments sufficiently validated to use them or recommend their use in RPL whereas others discourage their use due to limited documentation. In my opinion, this disagreement primarily reflects the fact that there is an urgent need for further specialization and high-quality research in this area. However, the disagreement also reflects the different conditions under which the specialists meet RPL patients: those from private clinics dependent on charging the patients will often have a more liberal approach to tests and treatments while specialists from public clinics who do not charge patients will typically adhere to a more conservative approach to tests and treatments.

As part of the publisher's *Gynecology in Practice* series, the aim of the book is to provide gynecologists in practice or in training with a clinical guide for use in the office or at the bedside.

Therefore, the contributors of the chapters have been asked to write in a practical and concise tone with few references to facilitate easy readability.

I thank all the authors for contributing excellent chapters covering their areas of expertise and for their efforts to write in the expected practical style. I hope that the book will be helpful for improving the management of RPL in clinical practice and for creating public awareness on this hidden cause of childlessness.

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Obtaining the Relevant History

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Introduction

In most clinics, patients referred with a diagnosis of recurrent miscarriage (RM) will normally come to a first consultation with a physician where information about the reproductive history and other medical information are collected, blood samples are taken, and other relevant investigations are carried out or planned.

Whereas authors in the area of RM often spend plenty of space in their articles to list the abundance of investigations undertaken in their clinic: hysteroscopy, endometrial biopsy, parental or fetal karyotyping, screening for thrombophilia, autoantibodies and microbiobes in addition to endocrine investigations, they spend very little space (if any) to describe the stringency and accuracy through which information has been obtained from the patients themselves or their hospital records. This reflects the modest emphasis most authors lay on reproductive and disease history compared with information obtained from other kind of investigations.

In this chapter, I will review information that we aim to collect at the first consultation at my clinic because we (i) find it important for assessing the spontaneous prognosis for live birth and (ii) it can often point toward etiological factors before any results from ultrasonic and laboratory investigations are obtained.

The relevant information achievable from the patients themselves or their case records can be divided into demographic data, reproductive history, disease history, and family history. The information should be obtained from both partners but the information concerning the women must be considered the most important.

Demographic data

The most important demographic data are information about parental age, body mass index (BMI), lifestyle, social class, and occupational factors in addition to information about the partner.

Recurrent Pregnancy Loss, First Edition. Edited by Ole B. Christiansen.

Parental Age

High maternal age is one of the strongest negative prognostic factors known. Maternal age over 41–42 years will be decisive for a conservative treatment approach since the dominant risk factor for miscarriage in this age group is embryonal aneuploidy (especially trisomies), which can only be actively treated by IVF with egg donation. The impact of high paternal age on risk of miscarriage and RM is difficult to study since parental ages are strongly correlated and the only couples that are really informative are those few comprising a young woman and an elderly male. The evidence provided so far suggests that high paternal age per se indeed increases the risk of miscarriage, although much less than high maternal age.

BMI

The patients should be weighted and the height measured at the first consultation to obtain a reliable BMI since both BMI below 20 and over 30 have in some studies been reported to decrease the prognosis for live birth in women in the background population and among RM patients. However, a recent study from my clinic showed that high BMI did not exhibit any impact on subsequent miscarriage rate in RM patients with regular menstrual cycles who can conceive spontaneously. BMI may therefore only have an impact on subsequent miscarriage rate in patients with polycystic ovary syndrome who normally only can conceive after ovulation induction. Whether normalization of an abnormal BMI will improve the pregnancy prognosis in terms of miscarriage rate in these patients is still to be documented, but clearly, weight loss will decrease the risk of gestational diabetes and other late pregnancy complications.

Lifestyle Factors

The most important lifestyle factors of importance for RM are consumption of coffee, alcohol, and tobacco in addition to the extent of leisure-time exercise during pregnancy. Drug abuse is rare in RM women but should be monitored. Whereas information about coffee consumption is trustworthy, information about alcohol and tobacco use will probably be underestimated. In my clinic we tell patients that daily consumption of four or more cups of coffee (and tea and cola with an equivalent caffeine content) during pregnancy should be avoided since several studies have reported that this increases the risk of miscarriage in the general population.

Any use of alcohol at least in the first half of pregnancy should be strongly discouraged since just one to two drinks a week in the first trimester have been shown to double the miscarriage risk and there is also an increased risk of fetal alcohol syndrome.

Whereas there is no good proof that tobacco use increases the risk of early miscarriage, the patients should try to reduce smoking, primarily to diminish the risk of late pregnancy complications such as intrauterine growth retardation, preterm birth, and placental abruption – conditions strongly associated with both RM and smoking.

Information should be obtained about leisure-time exercise since recent research suggests that some kinds of high-impact exercise, defined as exercise more than 75 min a week, may increase miscarriage risk <14th week significantly with relative risks of 3.6–4.2 in pregnant women from the general population. Therefore, patients should be interviewed specifically about what kind of exercise they perform and for how many hours a week. If it is estimated that the patient practises too much "dangerous" exercise, she should be encouraged to reduce its intensity and duration.

Social Class

Low social class and low educational level are risk factors for perinatal complications such as preterm birth, which can only partly be explained by a more unhealthy lifestyle (high BMI, smoking, drinking) among low social class women. In my clinic, we ask the couples about their occupation and this information will in most instances provide a rough estimate of their social status. Whereas the social factors cannot be changed by interventions at the RM clinic, extra surveillance in the third trimester should be provided for some of these patients due to the higher risk of late pregnancy complications.

Occupational Factors

Patients should be interviewed in details about their working situation. Is their working situation very stressful? Are they standing many hours a day or are they lifting heavy burdens? Do they have changing working times including night work? Are they working with hazardous chemicals or radiation? Although the documentation that improvement of working conditions indeed improves perinatal outcome is poor, RM patients with risky work conditions should be encouraged to change the conditions and support be provided to implement the changes (letters to the employers, etc.). Patients with night work may be encouraged to only work by day time in the next pregnancy, diminish working load, or get pregnancy leave.

Partner

Patients with RM are almost always married or live in an established partnership. In my clinic, the husband is asked whether he has fathered pregnancies in previous relationships and about the outcome of these pregnancies. In addition, he is asked about health status with particular focus on congenital or testicular disorders and intake of medicine.

An increasing number of our RM couples are immigrants from the Middle East, with tradition for inter-cousin marriages. Therefore, it is important to obtain information about whether the couples are related. There may be an increased risk of miscarriage in first-cousin marriages and definitely an increased risk of malformations and autosomal recessive diseases in the offspring. This may be an indication for closer-than-normal ultrasonic fetal monitoring during pregnancy. If a first-cousin couple with RM continues to miscarry in spite of other treatments, the possibility of offering insemination with donor sperm should be mentioned to the couple, but due to culture and religion, this offer will rarely be accepted.

CAUTION

Most published studies put little emphasis on lifestyle and occupational factors, although these may affect pregnancy outcome more than factors found by blood tests.

Too much emphasis should not be put on the importance of a moderately increased BMI since its impact on miscarriage risk in RM is unclear and the effect of weight loss on miscarriage risk is undocumented.

Many patients with RM seek an explanation for their miscarriages in some self-inflicted factor, for example, intake of a specific food ingredient, a stressful event, a jump, or a heavy lift. Such self-guilt can be enhanced if the importance of lifestyle factors for RM is over-exaggerated when talking with the patients.

Reproductive history

Clinical Appearance of Pregnancy Losses

In my clinic, considerable time is spent to get valid information about the patients' reproductive history, especially about the gestational ages at the time of previous fetal demise and the ultrasonographic and hormonal measurements undertaken in each pregnancy. This information is obtained from questionnaires sent to the patients before the first consultation in order to give them time to collect relevant data from hospital records and other documents and to recall events.

At the first consultation, every effort is done to integrate information from written records and the patients' own information in order to answer four main questions relating to each pregnancy: (i) was it confirmed by a urinary pregnancy test or serum-hCG measurement? (ii) were there signs of intrauterine pregnancy by ultrasound (intrauterine gestational sac, yolk sac, or embryonal echo with or without fetal heart action)? (iii) were chorionic villi detected by histology after uterine curettage? and (iv) at which gestational age had the fetal demise probably happened?

Other information relating to previous pregnancies is also thoroughly collected: mode of conception, results from karyotyping of miscarriages, identity of the partner for each pregnancy, and perinatal data relating to pregnancies progressing to the second/third trimester. Any treatment attempts in each pregnancy are also registered.

Our efforts to register detailed data from previous pregnancies are primary due to the fact that the number of previous pregnancy losses is the strongest prognostic factor for further miscarriage/live birth after RM. It is thus important to confirm that the patients had really had pregnancy losses by documenting a positive urine or serum-hCG measurement and not merely irregular cycles. It is also important to know whether a pregnancy has been documented by ultrasound or histology and not only by hCG detection since biochemical pregnancies (also called pregnancies of unknown location = PULs) may influence the prognosis after RM differently from clinical miscarriages. Some gynecologists and specialist societies such as the American Society of Reproductive Medicine do not recognize the importance of PULs in the RM diagnosis. However, my group has documented that PULs in the reproductive history indeed matter – in a multivariate analysis of variables of importance

for subsequent pregnancy outcome in 499 RM patients, each PUL reduced the prognosis for subsequent live birth significantly and almost to the same degree as each clinical miscarriage.

We also found that primary RM patients with a history of exclusively PULs exhibit a very high (16%) frequency of clinical tubal pregnancy at some time point in their reproductive history. This may indicate that the pregnancy losses in many of these patients may be spontaneously resorbed ectopic pregnancies due to tubal damage rather than intrauterine losses. We suspect that these patients have a subtotal tubal damage and as a consequence, we offer them IVF treatment in the next pregnancy – providing them with a good chance for live birth (see Chapters 8 and 17).

CAUTION

Some patients exaggerate the number of pregnancy losses in order to qualify for being referred to a dedicated RM clinic and qualify for active treatment at the clinic. These patients can be identified by doing an extensive collection of information from files from hospitals and general practitioners.

Gestational Age of Pregnancy Losses

Information about time of fetal demise, not to confound with the time of discovery of fetal death, is important, especially when we are dealing with pregnancy losses in the early second trimester (13th–18th week gestation). It has been reported in several studies that when fetal death is documented to have happened after 13th week, it is associated with a much higher risk of new second trimester miscarriage or extreme early birth compared with an early miscarriage (see Chapter 5). Some miscarriages detected by ultrasound in the second trimester have, evaluated from the size of the dead fetus, probably happened in the first trimester. Since the impact of a "real" second trimester loss on the risk of new late loss or preterm birth seems to be much greater than the impact of a first trimester loss, in my clinic much efforts are done to collect relevant information in order to distinguish between "real" and "false" second trimester losses in the history.

TIPS AND TRICKS

Questionnaires requesting information about time and place for previous pregnancy losses and about investigations undertaken in each pregnancy should be mailed to new patients 3 weeks prior to initial consultation.

Perinatal Data

Information about outcome of previous births or stillbirths is important to obtain. Our studies have shown that in patients with secondary RM, the birth of a boy compared with a girl prior to RM decreases the prognosis for live birth in the first pregnancy after referral by 22% corresponding to an OR for birth of 0.37 (95% CI 0.2–0.7). If the firstborn boy was born preterm or had birth weight <2500 g, the prognosis seems to be reduced even more.