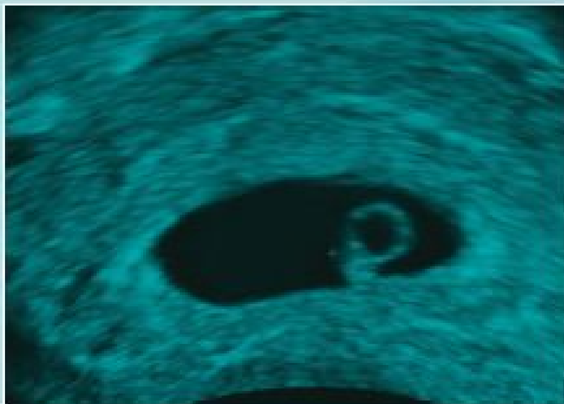
GYNECOLOGY IN PRACTICE
Series editor **Aydin Arici**

Recurrent Pregnancy Loss



Edited by
Ole B. Christiansen

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GYNECOLOGY IN PRACTICE: SERIES EDITOR: AYDIN ARICI

Recurrent Pregnancy Loss

EDITED BY

Ole B. Christiansen

Unit for Recurrent Miscarriage
Fertility Clinic 4071
Rigshospitalet
Copenhagen, Denmark; and
Department of Obstetrics and Gynaecology
Aalborg University Hospital
Aalborg, Denmark

WILEY Blackwell

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John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
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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.

Aydin Arici, MD
Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences
Yale University School of Medicine
New Haven, CT, USA

Contributors

Muhammad A. Akhtar
Clinical Research Fellow, Reproductive Medicine Unit
University Hospitals Coventry and Warwickshire NHS Trust
University of Warwick, Coventry, UK

Adjoa Appiah
Clinical Research Fellow
Early Pregnancy and Gynaecology Assessment Unit
King's College Hospital
London, UK

Juan Balasch
Institute Clínic of Gynecology, Obstetrics and Neonatology
Barcelona, Spain

Ruth Bender Atik
National Director
The Miscarriage Association
Wakefield, UK

Emmy van den Boogaard
Center for Reproductive Medicine
Department of Obstetrics and Gynecology
Academic Medical Center
Amsterdam, The Netherlands

Howard J.A. Carp
Department of Obstetrics and Gynecology
Sheba Medical Center
Tel Hashomer & Tel Aviv University
Tel Hashomer, Israel

Ricard Cervera
Department of Autoimmune Diseases
Institute Clínic of Medicine and Dermatology
Hospital Clínic
Barcelona, Spain

Ole B. Christiansen
Professor, Unit for Recurrent Miscarriage
Fertility Clinic 4071
Rigshospitalet
Copenhagen, Denmark; and
Department of Obstetrics and Gynaecology
Aalborg University Hospital
Aalborg, Denmark

Silvia Daher
Department of Obstetrics
São Paulo Federal University (UNIFESP)
São Paulo, SP, Brazil

AnnMaria Ellard
Nurse Specialist
Miscarriage Clinic
Liverpool Women's Hospital
Liverpool, UK

Roy G. Farquharson
Gynaecologist
Miscarriage Clinic
Liverpool Women's Hospital
Liverpool, UK

Dida Fleisig
Department of Behavioral Sciences
The College of Management Academic Studies
Rishon Le-Zion, Israel

Mariëtte Goddijn
Center for Reproductive Medicine
Department of Obstetrics and Gynecology
Academic Medical Center
Amsterdam, The Netherlands

Ae-Ra Han
Reproductive Medicine
Department of Obstetrics and Gynecology
Department of Microbiology and Immunology
The Chicago Medical School at Rosalind Franklin University of Medicine and Science
Vernon Hills, IL, USA

Barbara E. Hepworth-Jones
Trustee, The Miscarriage Association
Wakefield, UK

Shehnaaz Jivraj
Consultant Obstetrician and Gynaecologist
Jessop Wing, Sheffield Teaching Hospitals Trust
Honorary Senior Lecturer
University of Sheffield
Sheffield, UK

Jemma Johns
Consultant Obstetrician and Gynecologist
Early Pregnancy and Gynaecology Assessment Unit
King's College Hospital
London, UK

Paulien G. de Jong
Department of Vascular Medicine
Academic Medical Center
Amsterdam, The Netherlands

Claudia Kowalik
Department of Obstetrics and Gynecology
Academic Medical Center
Amsterdam, The Netherlands

Joanne Kwak-Kim
Reproductive Medicine
Department of Obstetrics and Gynecology
Department of Microbiology and Immunology
The Chicago Medical School at Rosalind Franklin University of Medicine and Science
Vernon Hills, IL, USA

Elisabeth C. Larsen
Unit for Recurrent Miscarriage
Fertility Clinic 4071
Rigshospitalet
Copenhagen, Denmark

M. Angeles Martínez-Zamora
Institute Clínic of Gynecology, Obstetrics and Neonatology
Barcelona, Spain

Rosiane Mattar
Department of Obstetrics
São Paulo Federal University (UNIFESP)
São Paulo, SP, Brazil

Saskia Middeldorp
Department of Vascular Medicine
Academic Medical Center
Amsterdam, The Netherlands

Henriette Svarre Nielsen
Department of Obstetrics and Gynaecology

University of Copenhagen
Copenhagen, Denmark

Kuniaki Ota
Reproductive Medicine
Department of Obstetrics and Gynecology
Department of Microbiology and Immunology
The Chicago Medical School at Rosalind Franklin University of Medicine and Science
Vernon Hills, IL, USA

Siobhan Quenby
Professor of Obstetrics
Director of the Biomedical Research Unit in Reproductive Health
Warwick Medical School
University of Warwick, Coventry, UK

Gavin Sacks
Associate Professor, University of New South Wales
St George Hospital
Sydney, NSW, Australia; and
Clinical Director, IVF Australia
Hunter Valley, NSW, Australia

Keren Shakhar
Department of Behavioral Sciences
The College of Management Academic Studies
Rishon Le-Zion, Israel

Maria Regina Torloni
Department of Obstetrics
São Paulo Federal University (UNIFESP)
São Paulo, SP, Brazil

Rosa Vissenberg

Center for Reproductive Medicine
Department of Obstetrics and Gynecology
Academic Medical Center
Amsterdam, The Netherlands

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.

Ole B. Christiansen
Professor, DMSc
Unit for Recurrent Miscarriage
Fertility Clinic 4071, Rigshospitalet, Copenhagen, Denmark
and
Department of Obstetrics and Gynaecology
Aalborg University Hospital, Aalborg, Denmark

1

Obtaining the Relevant History

Ole B. Christiansen[1,2]

[1] Unit for Recurrent Miscarriage, Fertility Clinic 4071, Rigshospitalet, Copenhagen, Denmark

[2] Department of Obstetrics and Gynaecology, Aalborg University Hospital, Aalborg, Denmark

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.

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