

FAST FACTS

FF

*Indispensable
Guides to
Clinical
Practice*

Endometriosis

Second edition

by Botros Rizk and Hossam Abdalla

Epidemiology and pathogenesis	9
Endometriosis and infertility	32
Diagnosis of endometriosis	41
Medical treatment of endometriosis	55
Surgical treatment of endometriosis	71
Treatment of infertility associated with endometriosis	81
Assisted reproductive technology and endometriosis	92
Extrapelvic endometriosis	103
Recurrent endometriosis	110
Adenomyosis	117
The doctor–patient partnership	125

HEALTH PRESS

FAST FACTS



***Indispensable
Guides to
Clinical
Practice***

Endometriosis

Second edition

Botros Rizk

Professor and Chief

Division of Reproductive Endocrinology and Infertility

Department of Obstetrics and Gynecology

University of South Alabama, Alabama, USA

Hossam Abdalla

Director of the Lister Fertility Clinic

The Lister Hospital, London, UK



Oxford

Fast Facts – Endometriosis
First published 1998
Second edition September 2003

Text © 2003 Botros Rizk, Hossam Abdalla

© 2003 in this edition Health Press Limited
Health Press Limited, Elizabeth House, Queen Street, Abingdon, Oxford
OX14 3JR, UK
Tel: +44 (0)1235 523233
Fax: +44 (0)1235 523238

Fast Facts is a trademark of Health Press Limited

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the express permission of the publisher.

The rights of Botros Rizk and Hossam Abdalla to be identified as the authors of this work have been asserted in accordance with the Copyright, Designs & Patents Act 1988 Sections 77 and 78.

The publisher and the authors have made every effort to ensure the accuracy of this book, but cannot accept responsibility for any errors or omissions.

Registered names, trademarks, etc. used in this book, even when not marked as such, are not to be considered unprotected by law.

A CIP catalogue record for this title is available from the British Library.

ISBN 1-903734-35-5

Rizk, B (Botros)
Fast Facts – Endometriosis/
Botros Rizk, Hossam Abdalla

Medical illustrations by Dee McLean and Jane Fallows, London, UK.

Typesetting and page layout by Zed, Oxford, UK.

Printed by Fine Print (Services) Ltd, Oxford, UK.

Printed with vegetable inks on fully biodegradable and recyclable paper manufactured from sustainable forests.



Low chlorine



Sustainable forests

Glossary	4
Introduction	7
Epidemiology and pathogenesis	9
Endometriosis and infertility	32
Diagnosis of endometriosis	41
Medical treatment of endometriosis	55
Surgical treatment of endometriosis	71
Treatment of infertility associated with endometriosis	81
Assisted reproductive technology and endometriosis	92
Extrapelvic endometriosis	103
Recurrent endometriosis	110
Adenomyosis	117
The doctor–patient partnership	125
Useful addresses	127
Index	129

Glossary

adhesiolysis: separation/removal of adhesions

adnexal masses: enlarged parts of the Fallopian tubes or ovaries

AFS: American Fertility Society, now known as the ASRM

amenorrhea: absence of menstruation

anovulation: lack of ovulation

ASRM: American Society for Reproductive Medicine

blastocyst stage: stage at which an embryo implants in the uterus

blebs: blister-like lumps filled with fluid

catechol estrogens: hormones derived from amino acids

cervical atresia: closure of the neck of the womb

COH: controlled ovarian hyperstimulation

dyschezia: painful defecation

dysmenorrhea: pain before and during menstruation

dyspareunia: painful sexual intercourse

dysuria: pain on passing urine

endometrial atrophy: pseudopregnancy

endometrioma: tumor of abnormally placed endometrium

estradiol: natural estrogen used to control menopausal symptoms

fecundity rate: fertility ability rating

FSH: follicle-stimulating hormone

GIFT: gamete intrafallopian transfer

glandular epithelia: outer cell layer of glands

GnRH: gonadotropin-releasing hormone

GnRH analogs: drugs which initially superstimulate the pituitary gland to make more GnRH and then shut down GnRH production

GnRH antagonists: drugs which stop the production of GnRH

hematuria: blood in the urine

hirsutism: excessive growth of hair on face and body

humoral immune response: antibody response

hypermenorrhea: heavy menstrual bleeding

hyperplasia: abnormal growth in number of tissue cells, increasing the size of the organ

hyperprolactinemia: abnormally high production of the hormone prolactin

ICSI: intracytoplasmic sperm injection

implantation: penetration of and attachment to lining of womb by fertilized ovum

IUI: intrauterine insemination

IVF: in-vitro fertilization

LH: luteinizing hormone

lysis: destruction of living cells through rupture of membranes

macrophages: scavenging cells of the immune system

mesothelium: lining cells of the peritoneum, pleura and other body parts

metaplasia: abnormal change in tissue as a result of change in cells

occlusion: closing of an opening, or obstruction of a hollow part

oligomenorrhea: abnormally infrequent periods

oophorectomy: surgical removal of ovaries

parenchyma: the functional tissue of an organ

pathognomonic: uniquely characteristic of a disease

periovarian adhesions: adhesions around the ovaries

peritoneal fluid: lubricant secreted by the peritoneum

phagocytosis: destruction of foreign bodies by phagocytes

prostaglandins: hormone-like substances involved in many body processes (e.g. influencing blood clotting, inducing abortion, causing muscle contraction)

retrograde menstruation: retention of menstrual blood in the body

serum immunoassays: method of testing concentration of antibodies

sperm motility: 'swimming' action of sperm in seminal fluid

stroma: the tissue forming the supporting framework of an organ

superovulation: production of more than one or two eggs (ova) at one time

synthetic progestogens: drugs chemically and pharmacologically similar to natural hormone progesterone

uterine fibroids: benign tumors growing in the uterus wall

VEGF: vascular endothelial growth factor

Introduction

Endometriosis, the presence of tissue histologically similar to endometrium outside the uterine cavity and the myometrium, is one of the most common gynecologic conditions in women of reproductive age, but it remains one of the most complicated and baffling. It is estimated that over 5 million women in the USA have endometriosis, and it is thought to affect 10–25% of all women attending gynecologic clinics in the USA and the UK. Sufferers make up a sizeable proportion of those attending gynecologic practices, whether seeking help for infertility or because the condition has become chronic with disabling effects. Although it is not easy to determine how prevalent the disease is among the general population (at present, it can only be confirmed by laparoscopy or laparotomy), there are indications that it is increasing. One factor in this could be the considerable delay between the onset of pain and the surgical diagnosis – in the UK it is 8 years, in the USA it is about 10 years.

In addition to the physical effects of the disease, the psychological impact of endometriosis is also a cause for concern. Every practicing primary care provider and gynecologist should be aware of the feelings of frustration and consequent depression experienced by women with endometriosis.

On numerous occasions women have been referred to psychiatrists as ‘mental cases’, a ‘psychologizing’ of endometriosis that represents the failure of gynecologists to diagnose the condition. In one clinic, out of 850 laparoscopies performed in patients with pain of 6 months’ duration or longer, histologically proven endometriosis or adhesions were found in 92%. After this treatment, their psychological profiles returned to near-normal, because when endometriosis was removed, pelvic pain improved.

We must stop the psychologizing of endometriosis. Gynecologists must not allow frustrated or ill-informed colleagues to dismiss patients as ‘cranks’ rather than diagnose and treat them or refer them to specialists who can do so.

Though the disease has been known for more than a century, it remains a challenge to gynecologists and primary care physicians. *Fast Facts – Endometriosis* presents healthcare professionals with the latest information to enable the patient to be treated with consideration and speed.

Epidemiology

The incidence of endometriosis remains unknown, because the disease is usually recorded as part of another investigation, for example into infertility or chronic pain in the abdomen or pelvis, or during another procedure such as sterilization. Many factors could account for the variations in the estimates of prevalence of endometriosis drawn from different investigations.

Prevalence of endometriosis

On the basis of hospital and surgical records. In the USA in 1980, among women aged 15–44 years, 6.3% of first diagnosis and 6.9% of all diagnoses for genitourinary problems were linked to endometriosis (National Center for Health Statistics). Between 1988 and 1990 the US National Hospital Discharge Survey, covering over 5 million gynecologic diagnoses, put endometriosis as first diagnosis at 11.2%. US Army records (1980–85) show that endometriosis was diagnosed in 6.2% of women undergoing gynecologic surgery. Another review from Houston, Texas, put the prevalence of endometriosis at 10.3%.

Smaller surgical case reports show a range of findings: when laparoscopy was performed for pelvic pain, a prevalence rate of 4–80% was reported for endometriosis compared with 2–80% for infertility. Endometriosis was reported in 4% of over 10 000 women undergoing tubal ligation.

In the UK, endometriosis was noted in 21% of women being investigated for infertility and in 6% being sterilized. For those with chronic abdominal pain, the incidence of endometriosis was 15%; among those having abdominal hysterectomy it was 25%.

On the basis of population studies. In the UK and the USA, three general epidemiological studies of endometriosis have been reported. In the UK, the Oxford Family Planning Association studied a cohort of 17 032 British women between 1968 and 1974. The authors reviewed the women's medical records up until the end of 1990 for a diagnosis of

endometriosis at laparoscopy or laparotomy, identifying 142 in which endometriosis was the first diagnosis. One limitation of this study is that controls did not undergo laparoscopy and therefore some could have undiagnosed endometriosis.

Houston and co-authors reviewed the medical records of white residents of Rochester, Minnesota, USA, from 1970 to 1979, to find newly diagnosed cases of endometriosis. They had four diagnostic groups:

- histologically confirmed disease
- visualization of disease during surgery
- clinically probable diagnosis based on pain and positive examination
- clinically possible diagnosis based on examination alone.

From these data, the authors concluded a prevalence of between 2.5% and 3.3% – assuming that the endometriosis had an average duration of 10 years. However, should the duration be 25 years, the prevalence rate would be 6.2–8.2%. As there is known to be considerable delay in the diagnosis between the onset of pain symptoms and the surgical confirmation, prevalence rates should take this into account.

Kjerulff and colleagues used the self-reporting method (US Health Interview Survey, 1984–92), asking a random sample aged 18–50 years about their gynecologic problems of the previous year. Of 341 617 women surveyed, 211 had been diagnosed with endometriosis and 1666 reported having menstrual disorders. The authors acknowledged that the reported prevalence rates of 6.9/1000 for endometriosis and 53/1000 for menstrual disorders could be underestimates because many respondents were embarrassed to answer personal questions. Others had not reported their symptoms to a physician; some had forgotten about them.

Changes in prevalence. The available data show that gynecologic surgery for endometriosis has been on the rise. In 1965, approximately 130 000 hysterectomies were performed for endometriosis in the USA, compared with 390 000 in 1984 (the proportions are shown in Figure 1.1). Although the general trend was to an increase in the number of hysterectomies performed during this period (Figure 1.2), the proportion carried out for endometriosis rose from 9% to 19%, an

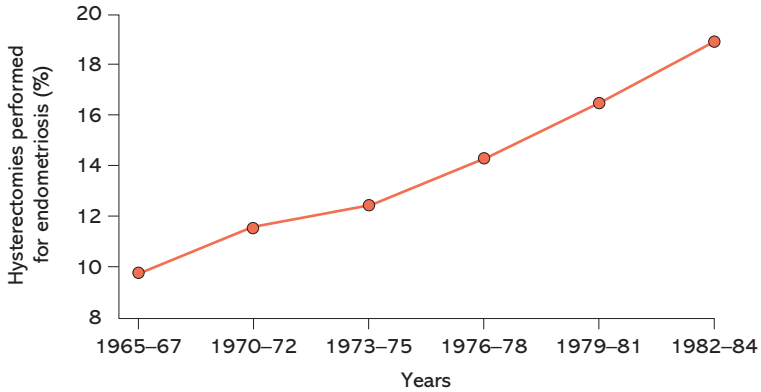


Figure 1.1 Proportion of hysterectomies performed in the USA for endometriosis. Source: US National Center for Health Statistics, Hyattsville, MD 1987.

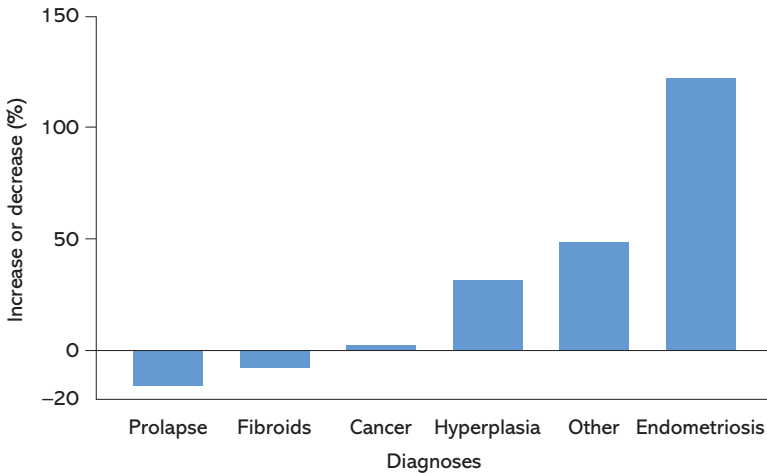


Figure 1.2 Changes in the indications for hysterectomy in the USA between 1965 and 1984. Source: Nezhat et al. 1995.

increase of 120%, which is unmatched by any other condition. It seems likely, given the dramatically increased frequency of surgical intervention for endometriosis, that the prevalence of the disease has increased.

Medical treatment remains the cornerstone of the management of symptoms associated with endometriosis. In adolescents repeated courses of medical therapy will be needed to achieve symptom regression and avoid repeated surgery.

Hormonal therapy

This has been the main medical treatment for endometriosis for half a century. In the 1940s and 1950s, diethylstilbestrol and methyltestosterone were used, but were abandoned because the side effects were too great. In the 1960s, progestogen alone or combined estrogen/progestogen preparations were used in an attempt to produce a state of pseudopregnancy (see below), but again significant side effects rendered the treatment unpopular.

The modern era of hormonal therapy began with the description of danazol by Dmowski et al. in 1971. By 1987, the aggregate pregnancy rate was 40% in 16 studies involving 511 patients with mild endometriosis. However, Evers found the pregnancy rates to be similar to placebo-treated patients in randomized clinical trials, as verified by Collins. The concept of downregulation with GnRH agonist in endometriosis was introduced in 1984 from Quebec City in a pivotal paper by Lemay.

More recently, GnRH antagonists and antiprogesterones have been used, with favorable reports. Aromatase inhibitors are the newest class of medication with the greatest promise for the treatment of endometriosis. In the future, the development of antiangiogenesis therapy and matrix metalloproteinase inhibitors will have a marked impact on the treatment of endometriosis.

Pseudopregnancy. In 1959, Kistner reported the use of Enovid (norethynodrel and mestranol) in 58 women with pelvic endometriosis. It was a landmark in the history of pharmacological treatment of endometriosis, but it lost popularity because of both estrogenic and progestational side effects.

Danazol is a synthetic by-product of testosterone with a half-life of 4.5 hours. Peak levels are reached 2 hours after oral ingestion, and after 8 hours it is no longer detectable. It is metabolized in the liver, and the principal metabolite methylethisterone exhibits mild progestational and androgenic activity.

Danazol has a direct effect on steroidogenesis, including cholesterol cleavage enzymes, and on intracellular steroid receptors. It has an indirect action by decreasing GnRH pulse frequency, which may suppress ovulation.

Side effects. The most common are related to the hyperandrogenic state – weight gain, oily skin and hair, nausea, acne, muscle cramps, hot flashes and hirsutism. Deepening of the voice, though uncommon, is irreversible.

Danazol has multiple metabolic side effects, the most important of which relate to blood cholesterol. It decreases HDL and increases LDL levels, which must be taken into account as the drug is given for long periods (6–9 months). Its use should be avoided in women with a history of liver disease.

Gestrinone is a progesterone agonist/antagonist that has been used in Europe for treatment of endometriosis, but is unavailable in the USA. Gestrinone causes amenorrhea and endometrial atrophy, as do other androgen steroid analogs (e.g. danazol). It acts both centrally and peripherally to reduce estradiol and obliterate the mid-cycle luteinizing hormone (LH) surge.

Gestrinone has a long half-life, allowing oral administration 2–3 times weekly. In randomized clinical trials, gestrinone was effective in reducing the painful symptoms of endometriosis.

Side effects. Gestrinone has similar androgenic symptomatic and metabolic effects to danazol, but fewer hypoestrogenic side effects.

Progestogens. The effect of progestogens on endometrial tissue depends on the dosage, length of treatment and activity of the individual progestogen (Table 4.1).

Side effects include irregular vaginal bleeding, weight gain, fluid retention, breast tenderness and mood changes.