Endometriosis: Science and Practice

Science merged with clinical practice towards relieving the symptoms of endometriosis

Endometriosis is frequently intensely painful and can lead to infertility causing disruption of women’s lives and relationships. It can be a devastating condition. Major progress has been made in recent years on understanding the causes of endometriosis and developing effective clinical therapies.

Endometriosis: Science and Practice fuses the scientific and clinical approaches. It marries the characteristics of the disease, how it presents and possible causes with medical and surgical approaches to pain therapy, and wider aspects of the disease.

Broad in outlook, focused in application, Endometriosis: Science and Practice covers:

- Pathogenesis
- Disease characterization
- Biological basis of endometriosis
- Diagnosis
- Medical therapies
- Surgical therapies
- Infertility
- Associated disorders

The stellar cast of contributors, led by world-leading editors from the US, Europe and Asia-Pacific, have produced a contemporary tour-de-force that should be on the bookshelf of anyone who provides medical care for women.

Titles of Related Interest

- Stillbirth: Prediction, Prevention and Management
- Chronic Pelvic Pain
- The Placenta: From Development to Disease
- Pregnancy in the Obese Woman: Clinical Management

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Cover: Detail of the Youth of Moses, in the Sistine Chapel, 1481 (fresco)
Endometriosis

Science and Practice

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University of Oxford  
Oxford, UK
Preface

Endometriosis is a multifaceted disease that affects the quality of life of millions of women and their families worldwide. Its diagnosis is complex, and treatments of associated chronic pelvic pain and infertility, which have evolved through multiple disciplines, have unpredictable and often limited effectiveness. Over the past 20 years, studies on the pathogenesis and pathophysiology of endometriosis have increased our understanding of the roles of steroid hormones, genetics, the environment, the immune system, and the peripheral and central nervous systems in disease establishment, progression/regression, and associated signs and symptoms and co-morbidities. Medical and surgical therapies have been informed by some of these biological mechanisms, and clinical trials testing the efficacies of these therapies, along with evaluating risks and alternatives, offer much promise to improve the quality of life of women with endometriosis.

In this book, we have aimed to provide a comprehensive approach to the biology, diagnosis and treatment of endometriosis. We showcase the latest in molecular, genetic and epigenetic research underlying its pathophysiology, the effects of endometriosis on pregnancy outcomes, insights into its pathogenesis from laboratory studies, animal models, and epidemiologic studies, and rigorous evaluation of clinical diagnostics and therapeutics - past, present, and future - to alleviate pain and suffering associated with this disorder. We have engaged leading surgeons, physicians, established researchers, as well as emerging leaders with fresh ideas and approaches, to achieve these goals.

For the cover illustration we have chosen a detail of the fresco “Events from the Life of Moses” (1481) by Sandro Boticelli in the Sistine Chapel in Rome. The young girl is obviously in pain, as reflected by the red glow on her cheeks. She is wearing a girdle consisting of apples (symbolizing fertility) and acorns (symbolizing slow growth and long duration), probably to fend off two of the most important manifestations of endometriosis, infertility and chronic pelvic pain. We hope that learners of all ages and from multiple disciplines, clinicians, researchers, and patients will take an opportunity to see the entire fresco for its beauty and symbolism and will benefit from the knowledge imparted in the pages of this book, which we hope will stimulate new knowledge, so one day we can cure endometriosis or, perhaps, even better, prevent it.

Linda C. Giudice
Johannes L.H. Evers
David L. Healy
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>2D PAGE</td>
<td>two-dimensional polyacrylamide gel electrophoresis</td>
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<td>American Association of Gynecologic Laparoscopists</td>
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<td>antral follicle count</td>
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<td>antigen-presenting cell</td>
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<td>bone marrow-derived mesenchymal stem cells</td>
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<td>continuous combined oral contraceptives</td>
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<td>colony-forming unit</td>
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<td>EFI</td>
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<td>estrogen-progestin</td>
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List of Abbreviations

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<td>gene ontology</td>
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<td>genome-wide association study</td>
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<td>HDACI</td>
<td>histone deacetylase inhibitor</td>
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<td>human leukocyte antigen</td>
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<td>heat shock proteins</td>
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<td>isotope-coded affinity tags</td>
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<td>International Classification of Diseases</td>
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<td>IDC</td>
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<td>International ENDOGENE Consortium</td>
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<td>Ig</td>
<td>immunoglobulin</td>
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<td>insulin-like growth factor</td>
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<td>IGFBP</td>
<td>insulin-like growth factor binding protein</td>
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<td>interleukin</td>
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<td>islet cell tumor</td>
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<td>imaging mass spectrometry</td>
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<td>interferon</td>
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<td>IPA</td>
<td>ingenuity pathway analysis</td>
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<td>insulin receptor substrate, immunoreactive scores</td>
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<td>least function</td>
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<td>LHCGR</td>
<td>luteinizing hormone/chorionic gonadotropin receptor</td>
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<td>levonordestrol-releasing intrauterine system</td>
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<td>loss of heterozygosity</td>
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<td>luteal phase defect</td>
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<td>lipopolysaccharide</td>
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<td>membrane attack complex</td>
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<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
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<td>MAPKK</td>
<td>mitogen-activated protein kinase kinase</td>
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<td>megabase</td>
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<td>Medical Birth Register</td>
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<td>macrophage migration inhibitory factor</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MFR</td>
<td>monthly fecundity rate</td>
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<td>MHC</td>
<td>major histocompatibility complex</td>
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<td>MIS</td>
<td>minimally invasive surgery</td>
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<td>macrophage migration inhibitory factor</td>
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<td>MMP</td>
<td>matrix metalloproteinase</td>
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<td>megabase</td>
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<td>microRNA</td>
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<td>magnetic resonance imaging</td>
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<td>messenger RNA</td>
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### List of Abbreviations

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<td>mass spectrometry, multiple sclerosis</td>
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<td>MSC</td>
<td>mesenchymal stem cells</td>
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<td>midsecretory</td>
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<td>negative predictive value</td>
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<td>notch-regulated ankyrin repeat protein</td>
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<td>plasminogen activator inhibitor</td>
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<td>protease-activated receptor</td>
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<td>peripheral blood</td>
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<td>phosphate buffer saline</td>
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<td>platelet endothelial cell adhesion molecule</td>
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<td>platelet endothelial cell adhesion molecule</td>
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<td>isoelectric point</td>
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<td>prostaglandin</td>
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<td>progesterone receptor</td>
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<td>phytohemagglutinin</td>
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<td>PHE</td>
<td>prollyl hydroxylase domain</td>
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<td>phosphatidylinositol (4,5) bisphosphate</td>
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<td>PIP2</td>
<td>phosphatidylinositol (4,5) bisphosphate</td>
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<td>PIP3</td>
<td>phosphatidylinositol (3,4,5) trisphosphate</td>
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<td>protein kinase A</td>
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<td>protein kinase C</td>
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<td>placental growth factor</td>
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<td>polymorphonuclear neutrophil</td>
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<td>peripheral nervous system</td>
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<td>premature ovarian failure</td>
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<td>premature ovarian insufficiency</td>
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<td>PPAR</td>
<td>peroxisome proliferator-activated receptor</td>
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<tr>
<td>PPROM</td>
<td>premature peritum rupture of membranes</td>
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<td>PPV</td>
<td>positive predictive value</td>
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<td>PR</td>
<td>progesterone receptor</td>
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<td>peroxiredoxin</td>
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<td>prolactin</td>
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<td>PTM</td>
<td>post-translational modification</td>
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<td>QALY</td>
<td>quality-adjusted life-years</td>
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<tr>
<td>Q-RT-PCR</td>
<td>quantitative real-time polymerase chain reaction</td>
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<td>RA</td>
<td>rheumatoid arthritis</td>
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<tr>
<td>rAFS</td>
<td>revised American Fertility Society</td>
</tr>
<tr>
<td>rag2(γc)</td>
<td>recombinant activating gene 2/common cytokine receptor γ chain (γc) double null</td>
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<td>RANTES</td>
<td>regulated on activation normal T-cell expressed and secreted</td>
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<td>rASRM</td>
<td>revised American Society for Reproductive Medicine</td>
</tr>
<tr>
<td>RCOG</td>
<td>Royal College of Obstetricians and Gynaecologists</td>
</tr>
<tr>
<td>RGS1</td>
<td>regulators of G protein signaling 1</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>RTK</td>
<td>receptor tyrosine kinase</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>real-time (reverse transcriptase) polymerase chain reaction</td>
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<tr>
<td>SAA</td>
<td>serum amyloid A</td>
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<tr>
<td>SAGE</td>
<td>serial analysis of gene expression</td>
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<td>SCID</td>
<td>severe combined immunodeficient</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SDF</td>
<td>stromal-derived factor</td>
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<tr>
<td>SE</td>
<td>spin echo</td>
</tr>
<tr>
<td>SEAN</td>
<td>size exclusion/affinity nanoparticles</td>
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<tr>
<td>SELDI-SEM</td>
<td>surface-enhanced laser standard error of the mean</td>
</tr>
<tr>
<td>SERM</td>
<td>selective estrogen modulators</td>
</tr>
<tr>
<td>SF</td>
<td>steroidogenic factor</td>
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<tr>
<td>SFRP</td>
<td>secreted frizzled-related proteins</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age</td>
</tr>
<tr>
<td>SHBG</td>
<td>sex hormone binding globulin</td>
</tr>
<tr>
<td>sICAM</td>
<td>soluble intercellular adhesion molecule</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>SIR</td>
<td>standardized incidence ratios</td>
</tr>
<tr>
<td>siRNA</td>
<td>small interfering RNA</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SLL</td>
<td>second-look laparoscopy</td>
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<tr>
<td>SMA</td>
<td>smooth muscle actin</td>
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<tr>
<td>SMRT</td>
<td>silencing mediator for retinoid and thyroid hormone</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>SP</td>
<td>side population, substance P</td>
</tr>
<tr>
<td>SPARC</td>
<td>secreted protein, acidic, cysteine-rich, osteonectin</td>
</tr>
<tr>
<td>SPRM</td>
<td>selective progesterone modulator</td>
</tr>
<tr>
<td>SRC</td>
<td>steroid receptor co-activator</td>
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<tr>
<td>SRM</td>
<td>selected reaction monitoring</td>
</tr>
<tr>
<td>SRY</td>
<td>sex-determining region on the Y chromosome</td>
</tr>
<tr>
<td>SS</td>
<td>Sjögren syndrome</td>
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<tr>
<td>STAR</td>
<td>steroidogenic acute regulatory protein</td>
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<tr>
<td>StAR</td>
<td>steroidal acute regulatory protein</td>
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<tr>
<td>T</td>
<td>Thomsen–Friedenreich-like</td>
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<td>TCDD</td>
<td>tetrachlorodibenzo-p-dioxin</td>
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<tr>
<td>TDF</td>
<td>testis-determining factor</td>
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<td>testicular dysgenesis syndrome</td>
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<td>TES</td>
<td>thoracic-endometriosis syndrome</td>
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<td>TF</td>
<td>tissue factor</td>
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<td>TFI</td>
<td>tubal factor infertility</td>
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<td>TGF</td>
<td>transforming growth factor</td>
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<td>TGF-βR2</td>
<td>transforming growth factor-β receptor 2</td>
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<tr>
<td>TFIF</td>
<td>transforming growth factor-β induced factor</td>
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<tr>
<td>TIAR</td>
<td>tissue injury and repair</td>
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<td>TIMP</td>
<td>tissue inhibitor of metalloproteinases</td>
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<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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<tr>
<td>TOP-MS</td>
<td>desorption/ionization time of flight mass spectrometry</td>
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<td>Treg</td>
<td>regulatory T-cells</td>
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<td>TSA</td>
<td>trichostatin A</td>
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<tr>
<td>TSSS</td>
<td>total symptom severity score</td>
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<tr>
<td>Tgase-2</td>
<td>tissue transglutaminase 2</td>
</tr>
<tr>
<td>TTP</td>
<td>time to pregnancy</td>
</tr>
<tr>
<td>TURE</td>
<td>transurethral resection of endometriosis</td>
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<td>transvaginal sonography</td>
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<td>transvaginal ultrasound</td>
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<td>UNC</td>
<td>ureteroneocystostomy</td>
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<td>urokinase-type plasminogen activator</td>
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<td>visual analog scores</td>
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<td>vascular endothelial growth factor</td>
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<tr>
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<td>von Hippel–Lindau</td>
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<td>vimentin</td>
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<td>VIP</td>
<td>vasointestinal peptide</td>
</tr>
<tr>
<td>VPA</td>
<td>valproic acid</td>
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<tr>
<td>WBC</td>
<td>white blood cell</td>
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<tr>
<td>WMD</td>
<td>weighted mean difference</td>
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1 History, Epidemiology, and Economics
Introduction

A reconstruction of the history of progress made in identifying, describing, and treating the condition we call endometriosis is neither simple nor easy because for almost 90 years endometriosis and adenomyosis, with the possible exception of ovarian endometrioma, were considered as one disease called “adenomyoma.” As such, historians must deal first of all with a controversy over who was the first to identify the benign, non-neoplastic presence of ectopic endometrium within the uterine wall or in the peritoneal cavity and structures. In addition, they must be aware that the early history of endometriosis is interwoven with the early history of adenomyosis, since it was not until the mid 1920s that the two conditions were finally separated.

Who identified endometriosis?

The history of medicine is full of controversies over who “discovered” a specific disease. In certain cases this is due to a desire to attribute the discovery to a researcher from a given country; in others, it is due to conflicting evidence, as sometimes disagreement focuses on the criteria utilized to attribute the discovery.

The latter situation is typical of endometriosis, a condition that does not lend itself to a purely clinical diagnosis. This is why, before embarking on a search for who “discovered” (a better word is definitely “identified”) it, it is necessary to fix a set of criteria, first and foremost what constitutes the “essence” of endometriosis. Some favor clinical descriptions, rather than histology or pathogenesis. Knapp, for instance, believed that the first descriptions of endometriosis can be found in Theses and Dissertations published in Belgium and The Netherlands during the second half of the 17th century [1], whereas Batt believes that endometriosis was discovered when the presence of heterotopic endometrial tissue was first described, even though the conditions were all labeled “sarcomas” [2].

We are of the opinion that the identification of the conditions we today distinguish in peritoneal and ovarian endometriosis and in adenomyosis (globally here called END-AD) must be based on the observation of the presence of endometrial glands and stroma outside the uterine cavity and on the specification that this invasion was “benign” in nature. Using these criteria, we will critically examine published information on the history of endometriosis.

The first information that needs to be evaluated is contained in a publication by Vincent Knapp [1]. In it, he explained that the disease we name endometriosis was already identified 300 years ago. His conclusion was based on a series of 11 inaugural dissertations presented at European universities between 1690 and 1795. The Disputatio Inauguralis Medica de Ulceribus Uteri by Daniel Christianus Schron presented at the University of Jena in 1690 is now sometimes cited as the first description of endometriosis [3]. However, close scrutiny of some of the original manuscripts from this period has shown that the descriptions evidenced signs of inflammation such as pus, uterine wounds or erosions that were linked to manipulation, an abortion or a syphilitic lesion. The symptoms described were those of an infection and included pain, insomnia, fever, vaginal lesions, dysuria, purulent urine (if the lesion involved the bladder) or purulent stool (if the lesion involved the intestines). There were no descriptions in the Disputatio Inauguralis or in the other later dissertations that could be interpreted as being indicative of endometriosis. Sadly, Vincent Knapp passed away a few months after publication of his manuscript and a letter to the Editor of Fertility and Sterility remained without response [4].

A point that has been overlooked is that, without a microscope, these early authors had no way to even predict the presence of endometrial tissue outside the uterus. Therefore, applying the
above-mentioned criteria, it becomes a physical impossibility for endometriosis to have been described during the 17th and 18th centuries. In addition, in those days abdominal surgery could not be performed and so, either the lesions were superficial and therefore could not be “endometriotic” in nature, or they could have been observed only at macroscopic autopsy examination and there is no trace of this having been the case.

More complex is the situation with regard to Carl Rokitansky, who in 1860 described what Batt called “three phenotypes of endometriosis containing endometrial stroma and glands” [2]. The first consisted of two varieties labeled Sarcoma adenoids uterinum (invading the uterine muscular wall) and Cystosarcoma adenoids uterini (a cystic variety associated to myometrial hypertrophy). The second, named Cystosarcoma adenoids uterini polyposum, invaded the endometrial cavity forming a polyp and the third Ovarian-Cystosarcoma invaded the ovary [5]. In an early paper on the history of endometriosis [6] we omitted any reference to Rokitansky on the basis of the “malignant nature” of his descriptions. Indeed, Rokitansky specifically mentioned:

… a sarcoma tissue in the form of papillary excrescences grow into the space of the cyst-like degenerated tubules. The slit-like, lacunar clefts scattered within the sarcoma produce on cross-section a granular appearance. The circumscribed nodes, which can be shelled-out, and appear incorporated in the sarcoma mass, doubtless originate from the filling of the great cyst spaces by intruding tumor tissue – a common appearance, which is especially pronounced in cystosarcoma adenoids mammarium.

To us, this is the description of a malignant tissue. Batt, however, insists that, in spite of the nomenclature, Rokitansky was aware of the benign nature of these invasions and that therefore he was the first to identify “the benign invasion of endometrial glands and stroma into the peritoneal cavity and organs” [2].

Setting aside the question of the nature of the lesions observed by Rokitansky, it is their origin that created a fierce controversy, with pathologists of the fame of von Recklinghausen [7] contending that lesions that were then called “adenomyoma” were the result of displacement of Wolffian or mesonephric vestiges.

When we examine the many and detailed descriptions of “mucosal invasions” of the peritoneal cavity and organs published at the end of the 19th and during the early part of the 20th century, we must conclude that the majority of pathologists rejected the hypothesis that the glands they observed were “endometrial.” As late as 1918, Lockyer, in detailing the various theories on the origin of epithelial glands and stroma found in the pelvis outside the uterine cavity, was unable to resolve the question of their origin. He wrote: “Nothing but the topography of the tumor, nothing but laborious research entailing the cutting of serial sections in great numbers, can settle the question as to the starting point of the glandular inclusions for many of the cases of adenomyoma” [8]. Therefore, earlier researchers who described mucosal invasions in the abdominal cavity, but failed to consider these invasions as being made of endometrial cells, cannot be considered as having “discovered” END-AD.

It was the surgeon Thomas Cullen (Fig. 1.1A) who described for the first time both the morphological and clinical picture of END-AD. In the preface to his book Adenomyoma of the Uterus, Cullen [9] wrote in 1908:

One afternoon in October 1882, while making the routine examination of the material from the operating room I found a uniformly enlarged uterus about four times the natural size. On opening it I found that the increase in size was due to a diffuse thickening of the anterior wall … Examination of the sections showed that the increase in thickness was due to the presence of a diffuse myomatous tumor occupying the inner portion of the uterine wall, and that the uterine mucosa was at many points flowing into the diffuse myomatous tissue.

Over the following years Cullen collected 90 uteri with adenomyomata and described the various presentations of “adenomyomata” in the myometrial wall, uterine horn, subserosa and uterine ligaments and showed in the uterus the continuity between the endometrial glands and the glandular structures
in the myometrium (Fig. 1.2). In addition, he was the first to describe decidualization of the stromal cells during pregnancy, providing the functional proof that the cells were of endometrial origin (Fig. 1.3). He was also the first to describe the symptoms of the uterine adenomyoma, and concluded rather optimistically:

I cannot help feeling that anyone who reads the chapter on symptoms will agree with us that diffuse adenomyoma has a fairly defined clinical history of its own and that in the majority of cases it can be diagnosed with a relative degree of certainty.

In 1920 Thomas Cullen [10] drew a scheme with the classic sites of adenomyotic lesions in the pelvis (Fig. 1.4). Adenomyoma involved ectopic endometrial-like tissue in the myometrial wall, rectovaginal septum, hilus of the ovary, uterine ligaments, rectal
wall, and umbilicus. There is no doubt that Cullen considered uterine adenomyoma, ovarian endometriosis, and deep endometriosis as one disease characterized by the presence of adenomyomatous tissue outside the uterine mucosa.

It is customary to consider John A. Sampson (see Fig. 1.1B) as the discoverer of endometriosis and indeed, his work on peritoneal and ovarian endometrioma provided the first theory on the pathogenesis of the disease. His original observation came when he operated on women at the time of menstruation and found that the peritoneal lesions were bleeding similarly to what happens in eutopic endometrium (Fig. 1.5) [11]. This proved to him that the tissue outside the uterus was of endometrial origin. In 1927 Sampson postulated that the presence of endometrial cells outside the uterus was due to tubal regurgitation and dissemination of menstrual shedding [12].

Clearly, peritoneal endometriosis became the signature of the disease and with the introduction of laparoscopy in the 1960s, a golden tool became available for visual diagnosis and surgical therapy. As a result, endometriosis was divorced from the uterus and research became focused on how fragments of menstrual endometrium implant on peritoneal surfaces and invade the underlying tissues. Since menstrual regurgitation and implantation could not explain a variety of ectopic localizations, other mechanisms were proposed, such as peritoneal metaplasia, transportation through veins or lymphatics, embryonic vestiges, transformation of bone marrow and stem cells.

Clinical issues

Awareness in the clinic

During the mid-20th century, endometriosis became a major clinical issue. In 1932 Hill Jr [13] reported on a series of 1200 patients who, between 1927 and 1931, were operated upon for pelvic pathology. In 135 women (11%), aberrant endometrium was detected at microscopy. Amongst these cases, 20 had adenomyomata of the uterus and 115 peritoneal endometriosis. The majority of the patients were between 20 and 45 years of age, with the youngest being 16 years old and the oldest 61. Thirty percent of the patients were sterile. As menstrual problems were absent in 51%, the aberrant endometrium was assumed to have caused little if any of the menstrual disorders and the symptoms were believed to have been caused principally by the associated pathology. The most important individual symptom was pain and tenderness over the site of the growths during the menstrual period; this, however, was the exception and not the rule. On the other hand, acute complications of endometriosis were also described during this period, such as the spontaneous rupture of an endometrial ovarian cyst [14] and obstructing rectovaginal endometriosis [15].

Pelvic pain related to menstruation was, according to Counseller [16], the principal reason for seeking relief through surgery. There was usually a 10-year history from the onset of disease and the symptoms were progressive. Surgical treatment was either radical or conservative, depending on the extent. In cases of uterine adenomyosis, conservative treatment was performed by complete excision of the lesions from the myometrium plus a presacral neurectomy when the lesion was limited to the uterus. Other heterotopic lesions were treated by complete excision whenever possible or by surgical loop diathermy or partial resection when the lesions were located in the sigmoid or the rectovaginal septum.

In the 1940s endometriosis was described as a not uncommon disease, with various clinical appearances. At times a widespread distribution of lesions within the peritoneal cavity was noted. The majority of the lesions occurred on the peritoneum, cul-de-sac, rectovaginal septum, and ovaries. Less frequent locations included the umbilicus, the round ligaments, rectosigmoid, and laparotomy scars. Larger lesions may consist of a more or less solid tumor, an adenomyoma, or may be in the nature of a hemorrhagic cyst. Surgery was the treatment of choice. In this connection,
Benson and Sneeden argued in 1958 that confusion had developed because of the unfortunate and illogical inclusion of uterine adenomyosis with pelvic endometriosis, which, according to them, only occasionally co-exist [17].

In terms of pathogenesis, Javert [18] developed a composite theory of benign metastasis on the basis of his surgical experience with 1371 patients over a period of 17 years. He observed that the spread of benign endometrium is essentially the same as for endometrial carcinoma, with direct extension into lymphatics or blood vessels of the myometrium, or between the muscle bundles, thereby producing adenomyosis uteri, while exfoliation and implantation of endometrial cells at menstruation, during curettage or from a nidus in the tube produced lesions on peritoneal surfaces; finally, lymphatic and venous spread produced lesions in adjacent or distal organs. He explained the increase in the number of cases during the last 4 years of his observation by the tendency towards smaller families, widespread use of contraception, fewer cervical dilations, fewer uterine suspension operations and the use of more intravaginal tampons during menstruation. He believed that pregnancy was the best prophylactic and curative treatment for endometriosis, since it interrupts the cyclical homeo-plasia during which time the endometrium lies dormant. Javert favored hysterectomy and bilateral salpingo-oophorectomy as the procedure of choice in older women.

In 1955, Henriksen [19] presented a review of 1000 cases of proven endometriosis. The disease was diagnosed on an awareness of the possibility of its existence, a careful history and a thorough retropelvic examination. Although the disease tended to regress following castration, some patients exhibited clinical and histological evidence of continued activity following ovariectomy. Henriksen also noted a frequent involvement of the bowel and concluded that endometriosis is an important possible factor in problems affecting both the small and large bowel. Proper management is based on the surgeon’s appreciation of the natural history of the disease, the evaluation of factors such as age, severity of symptoms, extent of disease, desire for children, and the patient as a whole. He concluded that fortunately, the value of conservatism in the surgical management of the disease was becoming more widely appreciated.

**Introduction of endoscopic techniques**

New pelvic endoscopic techniques were introduced in gynecology in the late 1940s, whereas peritoneoscopy has been utilized in gastroenterology and general surgery since the late 1930s. Initial clinical applications of the new technique were made in the 1940s, soon widened to include differentiating between causes of intraabdominal bleeding (including bleeding from rupture of a follicular cyst), between appendicitis and salpingitis and in order to decide whether or not gunshot or stab wounds were penetrating into the abdominal cavity.

In 1944 Decker and Cherry [20] proposed culdoscopy as a new procedure for pelvic visualization in gynecology and claimed that the procedure was invaluable in the investigation of pelvic tumors, small ovarian disease, endometriosis, ectopic pregnancy and especially helpful in the detailed study of primary and secondary sterility in women. Starting in 1967, Semm (see Fig. 1.1C) transformed peritoneoscopy into modern laparoscopy by improving the optical system, removing the source of light from the abdominal cavity and creating an automatic control of gas insufflation into the abdomen [21]. Technical improvements in laparoscopy quickly produced new information on endometriosis and expanded gynecological application of endoscopic surgery, to the extent that in the early 1970s leading gynecologists in Europe and the US concluded that laparoscopy was the preferred tool for diagnosis and surgery of endometriosis.

**Attempts to create a classification of endometriosis**

In an editorial published in Obstetrics and Gynecology in 1966, Beecham [22] claimed that a tedious effort to detail endometriotic location and lesion “would serve no purpose.” He therefore presented a simple classification scheme of four stages that used physical and operative findings and stated that such a scheme would be appropriate to follow patients being managed by medical or surgical therapies. Others tried staging systems similar to those used for malignancy staging, but these classification methods were unable to correlate staging with clinical outcome. As a result, none of the attempts to classify endometriosis made before 1978 received widespread acceptance.

In a collaborative effort Acosta and co-workers [23] proposed a classification that divided the disease into mild, moderate, and severe based on surgical findings. Using this staging system with retrospective data, a direct relationship was established between initial stage of the disease and pregnancy rates. Disease also was automatically classified as severe in the presence of an endometrioma larger than 2 cm in size. Peritubal and periovarian adhesions separated mild from moderate disease, because ovarian adhesions were recognized as having a damaging effect on fertility. Many physicians objected that this classification system had several disadvantages, because of the arbitrariness of the staging and the inability to distinguish unilateral from bilateral disease. Buttram, then, in 1979 [24], proposed an expanded classification based on the Acosta scheme that allowed for more flexibility and less ambiguity. Despite modifications, none of the classifications received widespread acceptance or use; this prompted the American Fertility Society (AFS) to create a panel to design a classification system for endometriosis; its recommendations were published in 1979 [25].

The AFS classification scheme stratified endometriosis into mild, moderate, severe, and extensive disease and for the first time used a weighted point score that included assessment of the extent of endometriosis (two-dimensional) and presence of adhesions in the peritoneum, ovaries, and tubes. It also allowed for assessment of unilateral versus bilateral disease. The size of endometriomas was weighted differently, as was the presence of filmy versus dense adhesions. An anatomical drawing was included to aid in surgical finding documentation and a cumulative score was attained. From the outset, critics began to point out the shortcomings of the new classification: the point scores were recognized as
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arbitrarily assigned and it was anticipated that changes in the assignment would be based on clinical studies and disease progression or response to treatment. The evaluation of pregnancy success suggested that the AFS classification revealed significant differences only if categories were combined (mild plus moderate versus severe plus excessive). Pregnancy success was also significantly reduced if an ovarian endometrioma was greater than 3 cm or had ruptured [26]. While the features of infertility were emphasized, they were not necessarily related to pelvic pain.

In 1985, in response to all the problems identified, a revised scheme of the AFS classification was presented (the so-called rAFS) [27]. As the new system still had flaws similar to its predecessor, the AFS stated that the system would be subject to revision as clinical data became available. In 1996, Vercellini et al [28] concluded that the endometriosis stage was not consistently related to pain symptoms, while in 1997, Guzick et al [29] stated that the use of an arbitrary weighted system for assigning scores to individual categories of disease, or for computing a total score, has limited the overall effectiveness of the classification system to predict pregnancy. Limitations of the rAFS classification include arbitrariness of the scoring system, limited reproducibility, failure to consider the morphological type of the lesion and a limited value of the system to aid in the evaluation and management in the setting of pelvic pain. These and other critical opinions led in 1997 to the publication of a Revised American Society for Reproductive Medicine classification of endometriosis: 1996 [30].

Diversity of lesions
Peritoneal endometriosis
In the 1980s it became evident that peritoneal endometriosis has multiple appearances including microscopic foci, early-active (red, glandular or vesicular), advanced (black, puckered), and healed (white, fibrotic) forms. These lesions may represent replacement of mesothelium by an endometrial epithelium or endometrial polyp formation [31,32]. However, the anatomical distribution of ectopic endometrium, as assessed by laparoscopy in a series of 182 consecutive patients, supported Sampson’s hypothesis of retrograde menstruation as the primary model of development of endometriosis [33]. Laparoscopic observations [34] suggested that early lesions appear and disappear “like mushrooms on the peritoneal surface.” The importance of even very small lesions became evident when, in a prospective study of artificial insemination in women with minimal endometriosis, Jansen [35] found reduced fecundability. Awareness of the existence of subtle endometriosis produced an increase in the diagnosis of endometriosis, although clinical significance of early lesions remained controversial [36–38]. From all published evidence, Evers [39] concluded that peritoneal endometriosis appears to be a dynamic disease, especially in the early phase, with subtle, atypical lesions emerging and vanishing again. The dynamic phase of the disease may involve a varying interval of each patient’s life (e.g. a period of amenorrhea or pregnancy). Laparoscopy at the end of medical suppression of the activity of the implants may lead to the erroneous conclusion that treatment has been effective. The final answer to the question of whether endometriosis is a progressive disease will have to come from long-term prospective investigations studying spontaneous evolution of peritoneal lesions without therapeutic interference.

Vercellini et al [28] analyzed the prevalence and severity of dysmenorrhea, intermenstrual pain and deep dyspareunia in relation to morphological features of peritoneal endometriosis. A statistically significant association was observed only with deep dyspareunia. Fresh, papular, atypical lesions might cause functional pain, whereas “old,” black nodules immersed in infiltrating scars might provoke mainly organic pain. Belasch et al [40] found a high prevalence of superficial endometriosis in biopsies from the uterosacral ligaments in both patients with chronic pelvic pain and asymptomatic (fertile and infertile) women.

Rectovaginal endometriosis
As the case of infertility, investigators found poor correlation between lesion characteristics or stage of disease and pelvic pain. Cornillie et al [41] noted a strong correlation between pelvic pain and the depth of invasion, with severe pelvic pain in the presence of implants more than 10 mm deep. Lesions more than 5 mm deep were also found to be histologically more active than superficial lesions. Koninckx et al [42] found no correlation between types of endometriotic lesions, total surface area of endometriosis-invaded areas, and amount of pain.

Three subgroups of deep endometriosis were suggested by Koninckx and Martin [43]: type I is conically shaped and seems to be formed by infiltration; type II is deeply located, covered by adhesions and probably formed by retraction; type III is a spherical nodule located in the rectovaginal septum and causes the most severe and largest lesion. They considered type III as a form of adenomyosis.

In the late 1990s, rectal endoscopic ultrasonography was proposed to diagnose the presence of deep bowel infiltration and select patients for surgery [44,45].

In recognition of some of the shortcomings of the rAFS classification in the evaluation of pelvic pain, the American Society for Reproductive Medicine (formerly the AFS) formed a subcommittee which developed a form for the preoperative assessment of pain quality and location on examination and their correlation with operative findings, including adhesion type, description of peritoneal lesion type by morphological appearance and the mean diameter and depth of invasion [46].

Ovarian endometrioma
Ovarian endometriosis can present itself as chocolate cysts of various size, deep non-cystic lesions, surface pits and plaques, and very early lesions. In an detailed study of 29 ovary specimens with chocolate cysts, Hughesdon [47] found that in all except three cases, the ovarian endometrioma was a pseudocyst with an essentially similar structure: the ovary is adherent to the posterior side of the parametrium, the inside is constituted by invaginated ovarian cortex, endometriotic tissue is found at the site of adhesion
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and a thin layer of superficial endometrium-like tissue extends to cover partially or fully the invaginated cortex (Fig. 1.6).

Hughesdon described four further characteristic features of ovarian endometriomas (Fig. 1.7). First, primordial and ripening follicles are found in the wall of the cyst. Second, the ovary does not invaginate uniformly, but remains on one side more or less normal. Third, on the extended side the wall is relatively thin and the attenuation of layers on this side is usually too great to reveal the original structure. Fourth, the identity of the cortex on the inner side is frequently obscured by smooth muscle metaplasia.

Hughesdon concluded that ectopic endometrium does not simply erode its way into the ovary: the ovary is actively invaginated, thus providing a pseudouterus. The structure demonstrated that the relation to the surface is primary and not secondary, such as would have been implied by Sampson’s original title of “perforating hemorrhagic cysts of the ovary” and by Halban’s lymphatic theory. Hughesdon also discussed the few cases with so-called “deep” ovarian endometriosis and demonstrated on serial sections that although deep, non-cystic lesions are, in a gross sense, in the ovary, the associated layering shows that they have originated at the surface. He concluded that

Figure 1.6 Cross-section of the uterus and ovaries. Both ovaries were adherent to the posterior surface of the uterus. Sampson interpreted the adhesions as sequelae of perforation of the endometriotic cysts and the adenomyoma on the posterior side of the uterus as spreading of the endometrioma over the surface of the uterus and early invasion. Reproduced from Sampson [11] with permission from American Medical Association.

(A) Lining
(Junctional layer
(B) Adhesion
(D) Inner cortex
(C) Outer cortex
(E) Cavity
(F) Tumica albuginea
(G) Serous papilloma
(H) Medulla
(I) Broad ligament

Figure 1.7 (A) Schematic diagram showing the various layers of the endometrial cyst of the ovary and other landmarks. (B) Section of left ovary showing adhesions above, cavity below, surrounded successively by thickened invaginated cortex, U-shaped medulla, and remainder of cortex, with broad ligament below. Reproduced from Hughesdon [47] with permission from Elsevier.
the findings weigh heavily against the benign lymphatic metastasis theory and favor a surface origin by implantation or metaplasia.

Using an endoscopic technique, Brosens et al [49] investigated a series of endometriotic cysts in situ in young women with infertility and confirmed that the wall of the cyst is cortex. In a few cases ovulation has occurred in the cyst and both cavities were linked. In such cases the endometrial tissue colonized the luteal cyst, showing that, under such circumstances, endometriosis can invade the ovary. They distinguished two types of endometriotic cysts: the red type which is lined by a surface epithelium and a thin layer of highly vascularized stroma without glands covering partially or completely the whitish or slightly pigmented wall, and the black type where the wall is lined by dark, pigmented and fibrotic tissue with scanty vascularization. They also found that at the site of invagination and adhesions, the cortical wall was retracted and the implants were of the mucosa type with glandular structures. They suggested that surgery should be adapted to the type of endometrioma by ablation of the superficial endometriotic lining for the whitish wall and excision of the fibrotic wall for the black wall and the implants at sites of inversion and adherence.

In the 1980s imaging techniques such as magnetic resonance imaging [50–52] and transvaginal ultrasonography [53–55] were used to differentiate ovarian endometriomas from other non-endometriotic masses. While ovarian endometriomas are easily detected at laparoscopy and ultrasonography, small ovarian endometriomas may go unnoticed unless they are detected by puncture [56]. Nezhat et al [57] have proposed to distinguish between three types of ovarian endometriomas according to size, cyst contents, ease of capsule removal, adhesion of the cyst to other structures, and location of the superficial endometrial implants relative to the cyst wall. Nisolle et al [58] suggested that peritoneal, ovarian, and rectovaginal endometriosis are three different entities with a different structure and pathogenesis, respectively implantation, metaplasia, and mesodermal müllerian differentiation.

**Stage V endometriosis**

Canis et al [59] proposed to add a most severe stage of endometriosis to include patients with extensive disease, especially with bilateral dense adhesions; the addition of this stage is justified in their view by the fact that poor results in terms of restoring fertility are consistently obtained with conservative therapy in their view by the fact that poor results in terms of restoring fertility are consistently obtained with conservative therapy. Using their revised classification scheme, a plan to proceed quickly toward in vitro fertilization (IVF) would be uniformly recommended for all stage V patients. It must be stressed that in patients with severe endometriosis, Pal et al [60] found with IVF a reduced fertilization potential of preovulatory oocytes.

**Malignancy**

In 1990, Heaps et al [61] reviewed a series of 205 cases reported in the English literature of malignant neoplasms arising from endometriotic foci. The ovary was the primary site (79%), whereas extragonadal sites represented 21%. Endometroid carcinomas accounted for 69% of the lesions and the remaining cases included clear cell carcinomas, sarcomas, and rare cell types. Heaps suggested that the actual frequency of malignancy arising in endometriosis may be higher than reported.

### Modern therapeutic approaches

#### Hormonal therapy

The hormonal management of the symptoms associated with endometriosis was first possible almost 70 years ago, by the availability of the first synthetic steroid hormones and, interestingly enough, androgens preceded estrogens as therapeutic agents.

**Androgen therapy**

The first suggestion to utilize the newly identified steroid hormones as therapeutic agents came from Geist and Salmon [62] who, in 1941 in an article in JAMA, advocated the use of androgens in gynecological disorders. Following this lead, in 1943 Hirst [63] reported the results obtained with the use of testosterone propionate in two cases of women with severe endometriosis: treatment resulted in a reduction in swelling and relief of pain and he recommended the use of this form of treatment when radical surgical excision was contraindicated or refused by the patient.

The following year, Miller [64] published a case of endometriosis of the rectal wall and ovaries, treated preoperatively with testosterone propionate. He stated: “Testosterone propionate can be used in diminishing the activity and decreasing the size of the lesions in endometriosis so that radical surgery can be performed with less danger.”

In spite of the positive results obtained, the undesirable side-effects of hirsutism, acne, and deepening of the voice occurred sufficiently often to cause the clinician and patient considerable concern. For this reason, androgen therapy never really took off and other avenues began to be explored. In 1958, commenting on the use of androgens, Kistner [65] noted that “androgenic substances, while adequately documented as having produced desirable results in endometriosis, probably exert their effect through inhibition of gonadotrophic substances although direct effect of the substance upon the endometriotic area has been suggested.” This awareness prompted endocrinologists and gynecologists to test other gonadotropin-inhibiting substances.

**Estrogens**

In the late 1940s, the availability of a non-steroidal, synthetic estrogen, diethylstilbestrol (DES), prompted another line of experimental treatment for severe endometriosis.

We know today that estrogens are intimately involved with the growth of ectopic endometrial foci and therefore, with today’s wisdom, estrogens would be, if anything, contraindicated. Indeed, although in all likelihood not an endocrine disease, endometriosis