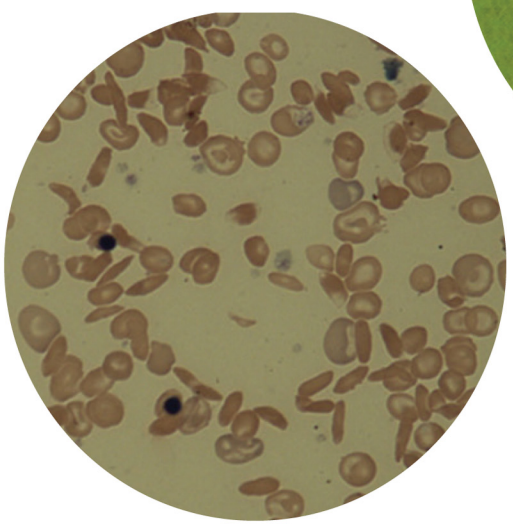
Obstetrics & Gynaecology

An Evidence-based Text for the MRCOG

THIRD EDITION

David M. Luesley and Mark D. Kilby



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David M. Luesley
University of Birmingham, UK

Mark D. Kilby
University of Birmingham, UK

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Contributors

Adam H Balen DSc FRCOG
Professor of Reproductive Medicine and Surgery, Chair of The British Fertility Society, The Leeds Centre for Reproductive Medicine, Seacroft Hospital, Leeds

Smriti Bhatta MBBS MD MRCOG
Senior Clinical Fellow, Aberdeen Fertility Centre, University of Aberdeen, Aberdeen, Scotland

Siladitya Bhattacharya MBBS MRCOG MD
Professor of Reproductive Medicine & Head, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland

Jenny Blackman
Post CCT Fellow, Royal Devon and Exeter Hospital, Exeter

Kate Bramham
Women's Health Academic Centre, St Thomas' Hospital, King's College London, London

Linda Cardozo OBE MD FRCOG
Professor of Urogynaecology, King's College Hospital, London

Susan V Carr FFSRH DRCOG MPhil
Associate Professor, Department of Obstetrics and Gynaecology, University of Melbourne, and Head of Psychosexual Service, Royal Womens Hospital, Melbourne and Chair Australian Society of Psychosocial Obstetrics and Gynaecology, Melbourne, Australia

Ying Cheong MD FRCOG
Associate Professor & Honorary Consultant in Obstetrics and Gynaecology, Subspecialist in Reproductive Medicine and Surgery, Faculty of Medicine University of Southampton, Southampton

Ben Chisnall
Foundation Year 1 Doctor at Oxford University Hospitals NHS Trust, Oxford

Duncan S Cochran MBBS(Lond) FCARCSI
Consultant Anaesthetist, Sandwell and West Birmingham NHS Trust, Birmingham

Arri Coomarasamy MBChB MD FRCOG
Professor of Gynaecology and Reproductive Medicine, College of Medical and Dental Sciences, University of Birmingham and Consultant in Gynaecology, Reproductive Medicine and Surgery, Birmingham Women's NHS Foundation Trust, Birmingham

Sarah M Creighton MD FRCOG
Consultant Gynaecologist, University College London Hospital, UCL Institute of Women's Health, London

Hilary OD Critchley BSc MBChB MD FRCOG FRANZCOG FFRSH FMedSci
Professor of Reproductive Medicine, Honorary Consultant Obstetrician and Gynaecologist, University of Edinburgh, Centre for Reproductive Biology, Edinburgh, Scotland

Margaret Cruickshank MB ChB MD FRCOG
Professor of Gynaecology, Department of Obstetrics and Gynaecology, Aberdeen Maternity Hospital, Aberdeen, Scotland

Andrew Currie BM DCH FRCPCH FRCP Ed
Consultant Neonatologist, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester

Rebecca Deans MBBS MMED RANZCOG CREI
Lecturer and Gynaecologist, University of New South Wales, Royal Hospital for Women, and Sydney Children's Hospital, Sydney, Australia

Rima Dhillon
Specialist Trainee in Obstetrics and Gynaecology, University Hospital Coventry and Warwickshire, Coventry

Shuchi Dixit
Consultant Obstetrician and Gynaecologist, Derby Teaching Hospitals NHS Foundation Trust, Derby

Gabrielle Downey MD FRCOG
Consultant Obstetrician and Lead Colposcopist at City Hospital, Dudley Road, Birmingham

Timothy Draycott
Consultant Obstetrician, University of Bristol, Bristol

James Drife MD FRCOG FRCPEd FRCSEd FCOGSA FFSRH
Emeritus professor of Obstetrics and Gynaecology, University of Leeds, Leeds

Abey Eapen
Clinical Research Fellow, University of Birmingham/Birmingham Women's Hospital, Birmingham

Diana Fothergill BSc Med Sci Hons MB ChB FRCOG
Emeritus Consultant Obstetrician and Gynaecologist, The Jessop Wing, Sheffield Teaching Hospitals NHS Trust, Sheffield

Caroline Fox MBChB MD MRCOG
Subspecialty Trainee in Maternal and Fetal Medicine, Birmingham Women's Foundation NHS Trust, Birmingham

Fieke E M Froeling MD PhD MRCP
NIHR Academic Clinical Lecturer, Specialist Registrar in Medical Oncology, Division of Cancer, Department of Surgery and Cancer, Imperial College London, London

Islam Gamaleldin
Speciality Registrar Obstetrics and Gynaecology, Southmead Hospital, Bristol

Ilias Giarenis MRCOG
Subspecialty Trainee in Urogynaecology, King's College Hospital, London

Joanna Girling
Consultant Obstetrician and Gynaecologist, Lead Division 3 and Speciality Lead Reproductive Health & Childbirth NW London CRN, West Middlesex University Hospital, Isleworth

Mahalakshmi Gurumurthy MRCOG
Consultant Gyanecological Oncologist, Aberdeen Royal Infirmary, Aberdeen, Scotland

Lubna Haque MBBS MRCOG
Consultant Gynaecologist & Colposcopist, Luton & Dunstable University Hospital NHS Foundation Trust, Luton

Hoda Maaly Harb
Specialist Registrar in Obstetrics and Gynaecology, University of Birmingham, Birmingham

Alexander Heazell MBChB (Hons) PhD MRCOG
Senior Clinical Lecturer in Obstetrics, Maternal and Fetal Health Research Centre, University of Manchester and St Mary's Hosptial, Manchester

Mary Higgins
Consultant in Obstetrics, Gynaecology, Sub-specialist in Maternal Fetal Medicine, National Maternity Hospital / University College Dublin, Dublin

James Hounslow
Senior Registrar in Obstetrics and Gynaecology, Princess Anne Hospital, Southampton

Kulsum Jaffer BSc MBBS FRCOG FFSRH
Consultant in Sexual and Reproductive Health, Heart of Birmingham Teaching Primary Care Trust, St Patrick's Centre, Birmingham

Nina Johns BSc MBChB MRCOG
Consultant Obstetrician, Birmingham Women's Hospital, Birmingham

Tracey A Johnston MD FRCOG
Consultant in Maternal Fetal Medicine, Birmingham Women's NHS Foundation Trust, Birmingham

Davor Jurkovic
Department of Obstetrics and Gynaecology, University College Hospital, London

Lucy Kean DM FRCOG
Consultant Obstetrician Subspecialist in Maternal and Fetal Medicine, Nottingham University Hospitals, Nottingham

Louise Kenny MB ChB hons PhD MRCOG
Professor of Obstetrics and Gynaecology, University College Cork, Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital, Director, The Irish Centre for Fetal and Neonatal Translational Research (INFANT), Cork, Ireland

Mohammed Khairy MD MRCOG
Subspecialty Trainee in Reproductive Medicine and Surgery, Birmingham Women's Fertility Centre, Birmingham Women's Hospital, Birmingham

Yakoub Khalaf MB BCh MSc MD FRCOG
Consultant Gynaecologist & Sub-Specialist in Reproductive Medicine and Surgery, Director of the Assisted Conception Unit & HFEA Person Responsible, Guy's and St Thomas' Hospital Foundation Trust, Guy's Hospital, London

Mark D Kilby DSc MB BS MD FRCOG FRCPI
Professor in Fetal Medicine, Centre for Women's and Children's Health, University of Birmingham, and Fetal Medicine Centre, Birmingham Women's Foundation Trust, Birmingham

Sailesh Kumar MB BS MMed O&G FRCS MRCOG FRANZCOG DPhil Oxon
Honorary Senior Lecturer and Consultant in Maternal and Fetal Medicine, Centre for Fetal Care, Imperial College London, Queen Charlotte's and Chelsea Hospital, London

William L Ledger MA DPhil Oxon MB ChB FRCOG
Head of School, Women's & Children's Health, UNSW Australia and Head of Reproductive Medicine Department, Royal Hospital for Women, Randwick, Australia

Simon Leeson FRCOG
Consultant Gynaecologist and Oncologist, Betsi Cadwaladr University Health Board, Wales

Will Lester
Consultant Haematologist, University Hospital Birmingham and Birmingham Women's Hospital, Birmingham

David M Levy FRCA
Consultant Obstetric Anaesthetist, Anaesthetics Directorate, Nottingham University Hospitals, Queens Medical Centre Campus, Nottingham

David M Luesley MA MD FRCOG
Emeritus Professor of Gynaecological Oncology, University of Birmingham, Birmingham

Sheila McLean LLB MLitt PhD LLD FRSE FRCGP FRCP(Edin) FRSA
Emeritus Professor of Law and Ethics in Medicine, University of Glasgow, Glasgow, Scotland

Fiona L Mackie MRes, MBChB
Clinical Research Fellow, University of Birmingham, and Birmingham Women's NHS Foundation Trust, Birmingham

Melanie C Mann FRCOG FFFP Dip GUM
Consultant in Sexual and Reproductive Health, Worcestershire Health and Care Trust, Alexandra Hospital, Redditch

Bill Martin
Consultant in Maternal and Fetal Medicine, Birmingham Women's Hospital, Birmingham

Pierre L Martin-Hirsch MRCOG
Consultant Gynaecological Oncologist, Central Lancashire Teaching Hospitals, Preston

Abi Merriel MRCOG
Clinical Research Fellow, University of Birmingham, Birmingham

Mostafa Metwally MD FRCOG
Consultant Gynaecologist and Subspecialist in Reproductive Medicine, The Jessop Wing and Royal Hallamshire Hospital, Sheffield

Michele P Mohajer BM BS FRCOG MD
Consultant in Maternal and Fetal Medicine, Royal Shrewsbury Hospital, Shrewsbury

R Katie Morris PhD MRCOG
Senior Clinical Lecturer in Fetal Medicine, Centre for Women's and Children's Health, University of Birmingham, and Fetal Medicine Centre, Birmingham Women's Foundation Trust, Birmingham

Rajeshwari Myagerimath
Consultant Obstetrician and Gynaecologist, Arrowe Park Hospital, Wirral University Teaching Hospital NHS Foundation Trust, Wirral

Catherine Nelson-Piercy MA FRCP
Consultant Obstetric Physician, Guy's and St Thomas' Foundation Trust and Imperial College Healthcare Trust, and Professor of Obstetric Medicine, King's College London, London

David Nunns MD MRCOG
Consultant Gynaecological Oncologist, Nottingham City Hospital, Nottingham

Sue Pavord MBChB FRCP FRCPath
Consultant Haematologist, Oxford University Hospitals NHS Foundation Trust, Oxford

Alexander M Pirie MB ChB(Edin) BSc(Hons) FRCP(Edin) FRCOG
Consultant in Obstetrics & Maternal Medicine, Honorary Senior Clinical Lecturer, Birmingham Women's Hospital, Birmingham

Richard Porter MA MSc FRCOG
Consultant Obstetrician and Gynaecologist, Royal United Hospital, Bath

Sam Pretlove MBChB PhD MRCOG
Consultant in Maternal & Fetal Medicine,
Birmingham Women's Foundation Trust, Birmingham

Nirmala Rai
Cancer Sciences, University of Birmingham, Birmingham

Angie Rantell BSC HONS RN
Lead Nurse Urogynaecology / Nurse Cystoscopist, King's College Hospital, London

Nicholas Reed MRCP(UK), FRCR, FRCP&S (Glas)
Consultant Clinical Oncologist, Beatson Oncology Centre
Gartnavel General Hospital, Glasgow, Scotland

Fiona M Reid MD MRCOG
Consultant Urogynaecologist, The Warrell Unit, St Mary's Hospital, Manchester

Alexandra Rice
Registrar in Obstetrics and Gynaecology, South East Scotland Deanery, Edinburgh, Scotland

Devender Roberts
Consultant in Maternal and Fetal Medicine, Liverpool Women's Hospital, Crown Street, Liverpool

Dudley Robinson MBBS MD MRCOG
Consultant Urogynaecologist and Honorary Senior Lecturer, Department of Obstetrics and Gynaecology, King's College Hospital, London

Lynne Robinson
Consultant Obstetrician and Gynaecologist, Birmingham Women's Foundation Trust, Birmingham

Stuart Rundle MRCOG
Speciality Trainee in Obstetrics and Gynaecology, Royal Devon and Exeter NHS Foundation Trust, Child and Women's Health, Exeter

Janice Rymer MD FRCOG FRANZCOG FHEA
Professor of Gynaecology, School of Medical Education, King's College London, London

Ghada Salman
Department of Obstetrics and Gynaecology, University College Hospital, London

Michael J Seckl BSc MBBS PhD FRCP
Professor of Molecular Oncology, Charing Cross Hospital Campus of Imperial College London, London

Tara Jayne Selman MRCOG PhD
Consultant in Fetal Medicine, Birmingham Women's NHS Foundation Trust, Birmingham

Andrew Shennan MB BS MD FRCOG
Professor of Obstetrics, Women's Health Academic Centre, St Thomas Hospital, Kings College London, London

Sushma Srikrishna FRCOG
Consultant Urogynaecologist, Department of Urogynaecology, King's College Hospital, London

Sudha Sundar
Senior Clinical Lecturer/Consultant in Gynaecological Oncology, Pan Birmingham Gynaecological Cancer Centre, City Hospital and School of Cancer Sciences, University of Birmingham, Birmingham

Jennifer A Tamblyn
Clinical Research Fellow Obstetrics & Gynaecology, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham

Myles Taylor BA MRCOG PhD
Consultant Obstetrician & Gynaecologist, Subspecialist in Fetal & Maternal Medicine, Royal Devon and Exeter NHS Foundation Trust, Child and Women's Health, Exeter

Ganesh Thiagamoorthy MBBS MRCOG
Subspeciality Trainee in Urogynaecology, Department of Urogynaecology, King's College Hospital, London

Jane Thomas MBChB MSC MRCOG MFSRH
Editor Cochrane Gynaecology and Fertility Group, Gynaecologist, University College London Hospital, London

Peter J Thompson MB BS FRCOG
Consultant Obstetrician, Birmingham Women's Hospital, Birmingham

John Tidy BSc MD FRCOG
Professor of Gynaecological Oncology, Royal Hallamshire Hospital, Sheffield

Clare Tower MBCHB PHD MRCOG
Consultant in Obstetrics and Fetal Maternal Medicine, St Mary's Hospital, Manchester

Graham Tydeman BSc FRCOG
Consultant Obstetrician and Gynaecologist, NHS Fife, Scotland

Tina Sara Verghese
Clinical Research Fellow, University of Birmingham and Birmingham Women's NHS Foundation Trust, Birmingham

Christine P West MD FRCOG
Consultant Gynaecologist, Royal Infirmary of Edinburgh, Edinburgh, Scotland

Sarah Wharin
Leicester Royal Infirmary, University Hospitals Leicester NHS Trust, Leicester

Catherine White
Clinical Director, St Mary's Sexual Assault Referral Centre, St Mary's Hospital, Manchester

Denise Williams MSc FRCP
Consultant Clinical Geneticist, Birmingham Women's NHS Foundation Trust, Birmingham

Jenny Williamson FFSRH
Menopause Trainer and Chair of the West Midlands Menopause Society, University of Birmingham and Birmingham Women's NHS Foundation Trust, Birmingham

Nowmi Zaman
Specialty Trainee Year 3 in Obstetrics and Gynaecology, Birmingham Women's NHS Foundation Trust, Birmingham

Preface

It is often difficult to know when a new edition of an established textbook is required. It certainly feels as if the intervals get shorter and the demands of updating are greater with each new edition. However, there are constant revisions of our professional guidelines and new developments in the specialities of obstetrics and gynaecology are emerging.

Comparing the content of this, the third edition, with the first edition published in 2004 is both rewarding and somewhat frightening. The rapid pace at which new knowledge and new evidence becomes available seems likely to overwhelm our ability to organise and present it in a format that will fulfil the requirements of aspiring obstetricians and gynaecologists and continue to provide an easily accessible source of information for those practising as specialists.

The popularity of the previous two editions signifies that we are achieving these objectives and the tested template of aligning the text to the RCOG curriculum appears to meet the needs of most readers. The basic core knowledge upon which our discipline is built does not evolve as rapidly as other aspects of our specialism and an in-depth understanding of this core knowledge is an essential prerequisite to success in the MRCOG examination and a solid basis on which to build a career as a practising specialist. It is natural with the passage of time that contributors to our previous editions will have retired or moved on elsewhere and it is right to bring in new contributors who have enthusiasm and often bring a fresh perspective to their subject matter.

We remain of course immensely grateful for the grounding provided by our previous contributors. It is their previous efforts, and the skilful updating and rewriting of our new contributors, that have maintained the high quality of the presented material. Updating, adding and omitting provides a massive editorial challenge if the 'feel' of the text is to be preserved. We believe that we have done the best that we can and that this textbook will continue to be an invaluable companion to the higher training of obstetricians and gynaecologists and a useful repository of knowledge and evidence for those in established practice.

To reiterate the final paragraph of our last preface: *Textbooks do not make good doctors but good doctors must practise from a sound basis of knowledge.* We believe that this, the third edition, continues to satisfy the goals that were laid out in the first edition.

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List of abbreviations used

5-FU	5-fluorouracil
7-DHCO	7-dehydrocholesterol
AAA	arterio-arterial anastomatosis
ABC	airway, breathing, circulation
AC	abdominal circumference
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
AChE	acetylcholinesterase
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
aCL	anticardiolipin
ACOG	American Congress of Obstetricians and Gynecologists
ACTH	adrenocorticotrophic hormone
ADPKD	autosomal dominant polycystic kidney disease
AEDF	absent end-diastolic flow
AED	anti-epileptic drug
AF	amniotic fluid
AFC	antral follicular count
AFE	amniotic fluid embolism
AFI	amniotic fluid index
AFLP	acute fatty liver of pregnancy
AFP	alpha-fetoprotein
AFS	American Fertility Society
AFV	amniotic fluid volume
AGA	appropriate for gestational age
AHA	American Heart Association
AIDS	acquired immunodeficiency syndrome
AIS	adenocarcinoma *in situ*
ALF	acute liver failure
ALO	*Actinomyces*-like organism
ALSO	advanced life support in obstetrics
ALT	alanine transaminase
AMH	anti-Müllerian hormone
ANA	antinuclear antibody
AP	antecedent pregnancy; anterior to posterior
APACHE	Acute Physiology and Chronic Health Evaluation
APH	antepartum haemorrhage
APL	antiphospholipid
APLS/APS	antiphospholipid syndrome
APSN	atypical placental site nodule
APTT	activated partial thromboplastin time
AR	androgen receptor
ARB	angiotensin II type 1 receptor blocker (angiotensin receptor antagonist)
ARC	antenatal result and choice
AREDV	absent or reversed end-diastolic flow
ARM	artificial rupture of membranes
ART	antiretroviral therapy; assisted reproduction technique
ASA	American Society of Anesthesiologists
ASCUS	atypical squamous cells of undetermined significance
ASD	atrial septal defect
ASRM	American Society of Reproductive Medicine
AST	aspartate aminotransferase (aspartate transaminase)
ATP	adenosine triphosphate
AUB	abnormal uterine bleeding
AUM	ambulatory urodynamic monitoring
AVA	arteriovenous vessel
AVM	arteriovenous malformation
AZT	zidovudine
β-hCG	beta-human chorionic gonadotrophin
β-IFN	beta-interferon
BASHH	British Association for Sexual Health and HIV
BCG	bacille Calmette Guérin
BCPT	Breast Cancer Prevention Trial
BCSH	British Committee for Standards in Haemotology
BEP	bleomycin, etoposide, cisplatin
BFLUTS	Bristol Female Lower Urinary Tract Symptoms
BG	blood glucose
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
BMJ	British Medical Journal
BNF	British National Formulary
BP	blood pressure
BPD	biparietal diameter
bpm	beats per minute
BPP	biophysical profile
BPS	bladder pain syndrome
BSAC	British Society for Antimicrobial Chemotherapy
BSCC	British Society for Cervical Cytology
BSO	bilateral salpingo-oopherectomy
BV	bacterial vaginosis
bvm	bag–valve–mask
BW	birthweight
CAH	chronic active hepatitis; congenital adrenal hyperplasia
CAIS	complete androgen insensitivity syndrome
cAMP	cyclic adenyl monophosphate
CASA	computer-assisted sperm analysis
CBT	cognitive behavioural therapy
CC	clomifene citrate
CCC	clear-cell carcinoma

CCAML	congenital cystic adenomatous malformation of the lung
CCG	Clinical Commissioning Group
CCP	cyclic citrullinated peptide
CCSS	Childhood Cancer Survivor Study
CDSR	Cochrane Database of Systematic Reviews
CEA	carcinoembryonic antigen
CEE	conjugated equine oestrogen
CEFM	continuous electronic fetal monitoring
CEMACH	Confidential Enquiry into Maternal and Child Health
CEMD	Confidential Enquiry into Maternal Death
CEPOD	Confidential Enquiry into Perioperative Death
CESDI	Confidential Enquiry into Stillbirth and Death in Infancy
CEU	Clinical Effectiveness Unit
CF	cystic fibrosis
cffDNA	cell free fetal DNA
CFU	colony-forming units
CGH	comparative genomic hybridisation
CGIN	cervical glandular intraepithelial neoplasia
CHC	combined hormonal contraception
CHIVA	Children's HIV Association
CHM	complete hydatidiform mole
CI	confidence interval
CIGN	cervical intraepithelial glandular neoplasia
CIN	cervical intraepithelial neoplasia
CIS	carcinoma *in situ*
CKD	chronic kidney disease
CL	corpus luteum
CMA	Canadian Medical Association
CMACE	Centre for Maternal and Child Enquiries
CMV	cytomegalovirus
CNS	central nervous system
CNV	copy number variant
COC(P)	combined oral contraceptive (pill)
CODAC	cause of death and associated conditions
COH	controlled ovarian hyperstimulation
COMET	Comparative Obstetric Mobile Epidural Trial
COS	controlled ovarian stimulation
COX-2	cyclooxygenase-2
CP	cerebral palsy
CPD	cephalo-pelvic disproportion
CPM	confined placental mosaicism
CPR	cardiopulmonary resuscitation
CQC	Care Quality Commission
CRH	corticotrophin-releasing hormone
CRL	crown–rump length
CRP	C-reactive protein
CS	caesarean section
CSA	child sexual abuse
CSE	child sexual exploitation; combined spinal–epidural
CSF	cerebrospinal fluid
CSII	continuous subcutaneous insulin infusion
CSM	Committee on Safety of Medicines
CT	computed tomography
CTG	cardiotocography
CTOCS	collaborative trial of ovarian cancer screening
CTPA	computed tomography pulmonary angiogram
CVA	cerebrovascular accident
CVP	central venous pressure
CVS	chorionic villus sampling
CXR	chest X-ray
CYP	cytochrome p450
D&C	dilatation and curettage
D&E	dilatation and evacuation
DARE	Database of Reviews of Effectiveness
DAT	direct antiglobulin test
DC	dichorionic
DC/DA	dichorionic diamniotic
DES	diethylstilbestrol
DEXA	bone mineral density scan
DF	degrees of freedom
DFID	Department for International Development
DH	Department of Health
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DI	donor insemination
DIC	disseminated intravascular coagulopathy
DKA	diabetic ketoacidosis
DLE	diathermy loop excision
DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetate
DMSO	dimethyl sulphoxide
DOB	date of birth
DS	donated sperm
DSD	disorders of sex development
dsDNA	double-stranded DNA
DV	ductus venosus
DVP	deepest vertical pool/pocket
DVT	deep venous thrombosis
DySIS	dynamic spectral imaging system
DXA	dual-energy X-ray absorptiometry
E2(V)	oestradiol (valerate)
E3	oestriol
E3G	oestrone-3-glucuronide
EAS	external anal sphincter
EBM	evidence-based medicine
EC	emergency contraception; endometrial carcinoma
ECG	electrocardiogram
ECL	echogenic cystic lesion

ECOG	Eastern Cooperative Oncology Group
ECV	external cephalic version
EDF	end-diastolic flow
EDTA	ethylenediaminetetraacetic acid
EE	ethinylestradiol
EEG	electroencephalogram
EFM	electronic fetal monitoring
EFW	estimated fetal weight
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
EIA	enzyme immunoassay
EMA	etoposide, methotrexate, actinomycin D
EMG	electromyography
ENA	extractable nuclear antigen
ENG	etonogestrel
EPA	early pregnancy assessment
ER	extended-release; oestrogen receptor
ERCP	endoscopic retrograde cholangiopancreatography
ERCS	elective repeat caesarean section
ERP	enhanced recovery programme
ERPC	evacuation of products of conception
ERT	oestrogen replacement therapy
ESA	erythropoiesis-stimulating agent
eSET	elective single embryo transfer
ESG	European Society of Gynaecology
ESHRE	European Society of Human Reproduction and Embryology
ESMO	European Society of Medical Oncology
ESR	erythrocyte sedimentation rate
ESSIC	European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis
ET	embryo transfer
ETT	endotracheal tube; epithelial trophoblastic tumour
FA	fertility awareness
FAI	free androgen index
FAS	fetal alcohol syndrome
FBC	full blood count
FBS	fetal blood sampling
FDA	Food and Drug Administration (USA)
FDP	fibrin degradation product
FDV	first desire to void
FET	frozen embryo transfer
FEV	forced expiratory volume
FFLM	Faculty of Forensic and Legal Medicine
fFN	fetal fibronectin
FFP	fresh frozen plasma
FFPRHC	Faculty of Family Planning and Reproductive Healthcare
FGM	female genital mutilation
FGR	fetal growth restriction
FHR	fetal heart rate
FIGO	International Federation of Gynaecology and Obstetrics
FISH	fluorescence in-situ hybridisation
FL	femur length
FM	fetal movement
FMAIT	fetal maternal alloimmune thrombocytopenia
FME	forensic medical examiner, previously known as a police surgeon
FOCSS	familial ovarian cancer screening study
FRHM	familial recurrent hydatidiform mole
FSH	follicle stimulating hormone
FSRH	Faculty of Sexual and Reproductive Healthcare
FTA-Abs	fluorescent treponemal antibody absorption (test)
FTP	failure to progress
FVL	factor V Leiden
GA	general anaesthetic; gestational age
GABA-A	gamma-aminobutyric acid type A
GAG	glycosaminoglycan
GBS	group B *Streptococcus*
GCIG	Gynaecologic Cancer Intergroup
G-CSF	granulocyte colony-stimulating factor
GDF	growth differentiation factor
GDG	Guideline Development Group
GDM	gestational diabetes mellitus
GH	growth hormone
GHRH	growth hormone-releasing hormone
GI	glycaemic index
GIFT	gamete intrafallopian tube transfer
GMC	General Medical Council
GnRH	gonadotrophin-releasing hormone
GOG	Gynecologic Oncology Group
GP	general practitioner
GR	glucocorticoid receptor
GRADE	grading of recommendations, assessment, development and evaluation
GRIT	Growth Restriction Intervention Trial
GS	gestational sac
GT	gestational thrombocytopenia
GTD	gestational trophoblastic disease
GTN	gestational trophoblastic neoplasia; glyceryl trinitrate
GTT	gestational trophoblastic tumour
GUM	genito-urinary medicine
HAART	highly active antiretroviral therapy
HAPO	hyperglycaemia and adverse pregnancy outcomes
Hb	haemoglobin
HbSS	sickle cell anaemia
HBV	hepatitis B virus; honour-based violence
HC	head circumference; hybrid capture
hCG	human chorionic gonadotrophin
HCM	hypertrophic cardiomyopathy
HCV	hepatitis C virus

HDFN	haemolytic disease of the fetus and newborn
HDL	high-density lipoprotein
HDN	haemolytic disease of the newborn
HDU	high dependency unit
HELLP	syndrome of haemolysis, increased liver enzymes and low platelets
HERS	Heart and Oestrogen Progestogen Study
HES	Hospital Episode Statistics
HFEA	Human Fertilisation and Embryology Authority
HGSC	high-grade serous carcinoma
HGUS	high-grade undifferentiated sarcoma
HIE	hypoxic–ischaemic encephalopathy
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMB	heavy menstrual bleeding
hMG	human menopausal gonadotrophins
HNPCC	hereditary non-polyposis colorectal cancer
HP	hidradenoma papilliferum
hPL	human placental lactogen
HPLC	high-performance liquid chromatography
HPO	hypothalamic–pituitary–ovarian
HPV	human papilloma virus
HQIP	Healthcare Quality Improvement Partnership
HR	hazard ratio; high risk
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HS	harmonic scalpel; hidradenitis suppurativa
HSDD	hypoactive sexual desire disorder
HSG	hysterosalpingography
HSIL	high-grade squamous intraepithelial lesions
HSV	herpes simplex virus
HSV-1	herpes simplex type 1 virus
HSV-2	herpes simplex type 2 virus
HTA	Health Technology Assessment Database; Human Tissue Authority
HUS	haemolytic uraemic syndrome
IADPSG	International Association of Diabetes and Pregnancy Study Group
IBD	inflammatory bowel disease
IBIS	International Breast Cancer Intervention Study
IBS	irritable bowel syndrome
IC	interstitial cystitis
ICH	intracranial haemorrhage
ICIQ	International Consultation on Incontinence Questionnaire
ICP	intracranial pressure
ICS	International Continence Society; intra-operative cell salvage
ICSI	intracytoplasmic sperm injection
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IDU	injecting drug user
IE	infective endocarditis
Ig	immunoglobulin
IGF-1/2	insulin-like growth factor 1/2
IGFBP	insulin-like growth factor binding protein
IgG	immunoglobulin G
IgM	immunoglobulin M
IGT	impaired glucose tolerance
IH	immune hydrops
IHD	ischaemic heart disease
IIQ	Incontinence Impact Questionnaire
ILCOR	International Liaison Committee on Resuscitation
IM	intramuscular
IMB	intermenstrual bleeding
IMSI	intracytoplasmic morphological sperm injection
INI	integrase inhibitor
IOL	induction of labour
IQ	intelligence quotient
IQR	interquartile range
ISD	intrinsic sphincter deficiency
ISSHP	International Society for the Study of Hypertension in Pregnancy
ISSVD	International Society for the Study of Vulvovaginal Diseases
ISVA	independent sexual violence advisor
ITP	idiopathic/immune thrombocytopenic purpura
ITT	intention to treat
IUCD	intrauterine contraceptive device
IUD	intrauterine death; intrauterine device
IUFD	intrauterine fetal death
IUGA	International Urogynaecology Association
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IUS	intrauterine system
IUT	intrauterine transfusion
IV	intravenous
IVD	instrumental vaginal delivery
IVF	in-vitro fertilisation
IVF-ET	IVF and embryo transfer
IVM	in-vitro maturation
IVS	intravaginal slingplasty
IVU or IVP	intravenous urogram
KHQ	King's Health Questionnaire
LAC	lupus anticoagulant
LAM	lactational amenorrhoea method
LARC	long-acting reversible contraception
LBC	liquid-based cytology
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LEEP	loop electrosurgical excision procedure
LFT	liver function test

LGESS	low-grade endometrial stromal sarcoma
LGSC	low-grade serous carcinoma
LH	luteinising hormone
LHCGR	shared leutinizing hormone/hCG receptor
LLETZ	large loop excision of the transformation zone
LMP	last menstrual period
LMS	leiomyosarcoma
LMWH	low-molecular-weight heparin
LN	lymph node
LNG	levonorgestrel
LNG-IUS	levonorgestrel-releasing intrauterine system
LoC-IUT/SDI	letter of competence in intrauterine techniques/subdermal implants
LOD	laparoscopic ovarian drilling
LP	lichen planus
LS	lichen sclerosus
LSIL	low-grade squamous intraepithelial lesion
LUNA	laparoscopic uterine nerve ablation
LUTS	lower urinary tract symptom
LV	liquor volume
MA	monoamniotic
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure; morbidly adherent placenta
MAR	mixed antibody reaction
MAS	McCune–Albright syndrome; meconium aspiration syndrome
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
MC	monochorionic; mucinous carcinoma
MCA	Mental Capacity Act; middle cerebral artery
MCAD	medium-chain acyl-coenzyme A dehydrogenase deficiency
MC/DA	monochorionic diamniotic
MCH	mean corpuscular haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
MCP-1	monocyte chemotactic peptide-1
MDG	Millennium Development Goal
MDKD	multicystic dysplastic kidney disease
MDMA	3,4-methylenedioxymethamphetamine
MDR	multidrug-resistant
MDRD	modified diet in renal disease
MDT	multidisciplinary team
MEA	microwave endometrial ablation
MeSH	medical subject heading
MEWS	modified early warning system
MFPR	multi-fetal pregnancy reduction
MG	myasthenia gravis
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIG	metformin with insulin in gestational diabetes
MIN	multicentric intraepithelial neoplasia
MIS	Müllerian inhibiting substance
MLPA	multiplex ligation-dependent probe amplification
MLS	Maternal Lifestyles Study
MMF	mycophenolate mofetil
MMP	matrix metalloproteinase
MMR	maternal mortality rate
MMT	methadone maintenance treatment
MNC	modified natural cycle
MOET	managing obstetric emergencies and trauma
MoM	multiple of the normal median
MPA	medroxyprogesterone acetate
MPD	maximum pool/pocket depth
MRC	Medical Research Council
MRCS	maternal request caesarean section
MRg-FUS	magnetic resonance-guided focused ultrasound
MRI	magnetic resonance imaging
MRKH	Mayer–Rokitanksy–Kuster–Hauser syndrome
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	multiple sclerosis
MSAFP	maternal serum alpha-fetoprotein
MSH	melanocyte-stimulating hormone
MSM	men who have sex with men
MSU	midstream urine
MSV	Mauriceau–Smellie–Veit
MTCT	mother-to-child transmission
MTX/FA	methotrexate with folinic acid
MUP	motor nerve unit potential
MVA	manual vacuum aspiration
MVP	maximum vertical pool/pocket
NAAT	nucleic acid amplification tests
NANC	non-adrenergic non-cholinergic
NAS	neonatal abstinence syndrome
NCCN	National Comprehensive Cancer Network
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCSP	National Chlamydia Screening Programme
NET-EN	norethisterone enanthate
NFP	natural family planning
NGF	nerve growth factor
NHS	National Health Service
NHSCSP	National Health Service Cervical Screening Programme
NHSLA	NHS Litigation Authority
NICE	National Institute for Health and Care Excellence

NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
NIDDM	non-insulin-dependent diabetes mellitus
NIH	National Institute of Health; non-immune hydrops
NIPT	non-invasive prenatal testing
NMG	neonatal myasthenia gravis
NNT	number needed to treat
NNTB	number needed to treat to benefit
NOMAC	nomegoestrol acetate
NPEU	National Perinatal Epidemiology Unit
NPSA	National Patient Safety Agency
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NSC	National Screening Committee
NST	non-stress test
NT	nuchal translucency
NTD	neural tube defect
NYHA	New York Heart Association
OA	occiput anterior
OAA	Obstetric Anaesthetists' Association
OAB	overactive bladder
OC	obstetric cholestasis
OCP	oral contraceptive pill
OCR	optical character recognition
OGTT	oral glucose tolerance test
OHSS	ovarian hyperstimulation syndrome
OI	ovulation induction
OMR	optical mark reader
ONS	Office for National Statistics
OR	odds ratio
OROS	oxybutynin preparation using an osmotic system
OSAT	objective structured assessment of technical skill
OWAM	organisation with a memory
PAIS	partial androgen insensitivity syndrome
PAMG-1	placental alpha macroglobulin-1
PAPP-A	pregnancy-associated plasma protein-A
PARP	poly ADP ribose polymerase
PBC	primary biliary cirrhosis
PCA	patient-controlled analgesia
PCB	postcoital bleeding
PCEA	patient-controlled epidural analgesia
PCOS	polycystic ovary syndrome
PCR	polymerase chain reaction
PDA	patent ductus arteriosus
PDS	polydioxanone suture
PE	pulmonary embolism
PECOT	population, exposure, comparison, outcome and time
PEEP	positive end-expiratory pressure
PEFR	peak expiratory flow rate
PEP	post-exposure prophylaxis
PEPSE	post-exposure prophylaxis for HIV following sexual exposure
PET	positron emission tomography; pre-eclampsia
PFMT	pelvic floor muscle training
PFR	peak flow rate
PG	prostaglandin
PHM	partial hydatidiform mole
PI	pulsatility index
PICO	population, intervention, comparison, outcome
PID	pelvic inflammatory disease
PIH	pregnancy-induced hypertension
PI/r	ritonavir-boosted protease inhibitor
PIVKA	prothrombin induced by vitamin K absence
PLCO	prostate, lung, colon and ovarian cancer
PlGF	placental growth factor
PM	postmortem
PMB	post-menopausal bleeding
PMCS	perimortem caesarean section
PMDD	premenstrual dysphoric disorder
PMR	perinatal mortality rate
PMS	premenstrual syndrome
PND	perinatal death notification
POEC	progesterone-only emergency contraception
POI	premature ovarian insufficiency; progestogen-only implant
POIC	progestogen-only injectable contraception
POP	progestogen-only pill
POP-Q	Pelvic Organ Prolapse Quantification
PORTEC	postoperative radiation therapy in endometrial carcinoma
PORTO	prospective observational trial to optimise paediatric health in IUGR
PPH	postpartum haemorrhage
PPI	proton pump inhibitor
PPIUS	Patient Perception of Intensity of Urgency Scale
PPROM(T)	preterm premature rupture of membranes (close to term)
PPS	pentosan polysulphate
PPT	postpartum thyroiditis
PR	progesterone receptors
PROM	pre-labour rupture of membranes
PROMPT	Practical Obstetric Multiprofessional Training
PSN	placental site nodule
PSN	presacral neurectomy
PSTT	placental site trophoblastic tumour
PT	prothrombin time
PTNS	posterior tibial nerve stimulation
PTSD	post-traumatic stress disorder
PTU	propylthiouracil
PUFA	polyunsaturated fatty acids

PUL	pregnancy of unknown location
PUVA	psoralens and ultraviolet A
QALY	quality-adjusted life years
QF-PCR	quantitative fluorescence polymerase chain reaction
QoL	quality of life
RA	rheumatoid arthritis
RAADP	routine antenatal anti-D prophylaxis
RCA	root cause analysis
RCM	Royal College of Midwives
RCOG	Royal College of Obstetricians and Gynaecologists
RCPCH	Royal College of Paediatrics and Child Health
RCR	Royal College of Radiologists
RCT	randomised controlled trial
ReCoDe	Relevant Condition at Death
REDF	reversed end-diastolic flow
REM	rapid eye movement
RFM	reduced fetal movement
rFSH	recombinant FSH
Rh	Rhesus
RI	resistance index
RiCoF	ristocetin-induced cofactor activity
RITA	radiofrequency interstitial thermal oblation
RLU/PC	relative light unit/positive controls
RMI	risk of malignancy index
ROBUST	RCOG operative birth simulation training
RPOC	retained products of conception
RPR	rapid plasma reagin
RR	relative risk
RRSO	risk-reducing salpingo-oopherectomy
RTA	road traffic accident
RT-PCR	reverse transcriptase–polymerase chain reaction
SADS	sudden adult death syndrome
SANDS	Stillbirth and Neonatal Death Society
SARC	sexual assault referral centre
SCBU	special care baby unit
SCC	squamous cell carcinoma
SCCOHT	small-cell cancer of hypercalcaemic type
SCCOPT	small-cell cancer of pulmonary type
SCD	sickle cell disease
SCD	sudden cardiac death
SCI	spinal cord injury
SCJ	squamo-columnar junction
SD	standard deviation
SDP	single deepest pool/pocket
SDV	strong desire to void
sEMG	static and dynamic surface electromyography
sENG	endoglin
SERM	selective oestrogen receptor modulator
SFH	symphisio-fundal height
sFLT	soluble fms-like tyrosine kinase-1
SGA	small for gestational age
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHBG	sex hormone-binding globulin
SIADH	syndrome of inappropriate anti-diuretic hormone
SIDS	sudden infant death syndrome
SIGN	Scottish Intercollegiate Guidelines Network
SIMS	single-incision mini sling
SLE	systemic lupus erythematosus
SMBE	simulation-based medical education
SMD	standardised mean difference
SMR	severe mental retardation
SNRI	serotonin noradrenaline reuptake inhibitors
SOA	Sexual Offences Act
SOAP	subjective, objective, assessment, plan
SPR	screen positive rate
SPRM	selective progesterone modulator
SROM	spontaneous rupture of membranes
SRY	sex-determining region of the Y chromosome
SSR	surgical sperm retrieval
SSRI	selective serotonin reuptake inhibitor
STAN	ST analysis
STD	sexually transmitted disease
STI	sexually transmitted infection
STIC	serous tubal intraepithelial carcinoma
STUMP	smooth muscle tumour of unknown malignant potential
STV	short-term variability
SUDEP	sudden unexpected death in epilepsy
SVD	spontaneous vaginal delivery
SVT	supraventricular tachycardia
T3	triiodothyronine
T4	thyroxine
TA	transabdominal
TAH	total abdominal hysterectomy
TAMBA	Twins and Multiple Births Association
TAP	transversus abdominis plane
TAPS	twin anaemia polycythaemia sequence
TB	tuberculosis
TBA	thermal balloon ablation
TBG	thyroid-binding globulin
TCA	tricyclic antidepressant
TDF	testis-determining factor
TED	thromboembolic deterrent/disease
TENS	transcutaneous electrical nerve stimulation
TIA	transient ischaemic attack
TIBC	total iron-binding capacity
TLH	total laparoscopic hysterectomy
TM-ET	transmyometrial embryo transfer
TPHA	*Treponema pallidum* haemagglutination assay

TRAP	twin reversed arterial perfusion
TRH	thyrotrophin-releasing hormone
TRUFFLE	Trial of Randomised Umbilical and Fetal Flow in Europe
TSH	thyroid-stimulating hormone
TTN	transient tachypnoea of the newborn
TTP	thrombotic thrombocytopenic purpura
TTTS	twin–twin transfusion syndrome
TV	*Trichomonas vaginalis*
TVS	transvaginal ultrasound scanning
TVT	tension-free vaginal tape
UA	umbilical artery
UAE	uterine artery embolisation
UDCA	ursodeoxycholic acid
UDI	urogenital distress inventory
U&E	urea and electrolyte
uE3	unconjugated oestriol
UFH	unfractionated heparin
UGT	uridine 5'-diphosphate glucuronosyltransferase
UKGTN	UK Genetic Testing Network
UKMEC	UK Medical Eligibility Criteria
UKOSS	UK Obstetric Surveillance System
UPA	ulipristal acetate
UPP	urethral pressure profilometry
UPSI	unprotected sexual intercourse
US(S)	ultrasound (scan)
USI	urodynamic stress incontinence
UT	uterus
UTI	urinary tract infection
UV	umbilical vein
VACTERL	vertebral, anal, cardiac, trachea-oesophageal, renal, limb association
VaIN	vaginal intraepithelial neoplasia
VAS	vibro-acoustic stimulation
VBAC	vaginal birth after caesarean section
VCU	videocystourethrogram
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
VIN	vulval intraepithelial neoplasia
VLP	virus-like particles
VP	vasa praevia
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VVA	veno-venous anastomatoses
vWD	von Willebrand's disease
vWF	von Willebrand factor
VZIG	varicella zoster IgG
VZV	varicella-zoster virus
WBC	white blood cell
WHI	Women's Health Initiative
WHO	World Health Organization
WHOMEC	WHO Medical Eligibility Criteria
WY	woman years
ZIFT	zygote intrafallopian transfer

How to use this book

The following features are used throughout the book to highlight the key information and to clearly identify the evidence base.

MRCOG standards

An MRCOG standards box at the start of a chapter lists the relevant standards and/or theoretical and practical skills relating to the topic. Where there are no standards specified in the MRCOG curriculum, we have given a summary of best practice.

EBM

Evidence-based medicine boxes are included to provide a rapid summary of the evidence relating to the interventions and treatments discussed in each chapter. Where evidence is limited, this is also stated.

KEY POINTS

Key points boxes summarise the main points in a section or chapter.

Evidence scoring

It is one of the key principles of this book that doctors assess the quality and applicability of available evidence.
The evidence considered by the authors has been graded according to the structure below, in accordance with the system used in Guidelines published by the RCOG.

Classification of evidence levels

A systematic review or meta-analysis

B one or more well-designed randomised controlled trials

C non-randomised controlled trials, cohort study, etc.

D retrospective, uncontrolled

E 'expert opinion'

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SECTION ONE

Introductory/General

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Chapter 1 Evidence-based medicine and medical informatics

Jane Thomas

MRCOG standards: Epidemiology and statistics

- Demonstrate the skills needed to critically appraise scientific trials and literature
- Understand the production and application of clinical standards, guidelines and care pathways and protocols
- Understand the difference between audit and research
- Understand how to perform, interpret and use clinical audit cycles
- Understand how to plan a research project
- Demonstrate a full understanding of common usage of computing systems, including the principles of data collection, storage, retrieval, analysis and presentation

INTRODUCTION

This chapter outlines some key concepts of clinical epidemiology and statistics that will help you to understand the terms used within this book, in clinical research and in the MRCOG examination.

Traditionally, medical practice was based on pathophysiological mechanisms of disease and the experience of authoritative experts. The term 'evidence-based medicine' (EBM) was first coined by Gordon Guyatt around 1990 to describe the process of bringing critical appraisal of research evidence to the bedside and basing clinical decisions on clinical research evidence, clinical expertise and patients' values.[1] This title was intentionally provocative.[2] Developing in parallel with EBM there was recognition that randomised controlled trials are the best way of establishing the effectiveness of treatments, and recognition, that whilst a single study is useful, pooling the findings from all studies provides the best evidence.[3] *Effective Care in Pregnancy and Childbirth*[4] was the first attempt in medicine to look thoroughly for research evidence and systematically summarise the effect of treatments in a clinical area. This led on to the setting up in 1993 of the Cochrane Collaboration, an international network to prepare, maintain and disseminate systematic reviews.

EBM has evolved, and there is now greater emphasis on evidence in the context of patients' values and preferences. Critical appraisal of a body of evidence takes time, and it is inefficient use of resources to search the literature for every treatment of every patient. Increasingly, therefore, processed research, such as systematic reviews, summary digests of reviews or evidence-based clinical guidelines, can offer the highest level evidence on which to base decisions.[2] Nevertheless, it remains important that clinicians can appreciate the principles of EBM so that they can distinguish what is trustworthy reliable evidence from what is not.[2] *Testing Treatments*[3] and the website 'Bad Science' provide an accessible introduction to the use and abuse of evidence.[5]

The practice of EBM comprises five steps:[6] these steps are also used by guideline developers to develop evidence-based clinical guidelines:

1. defining a clinical question,
2. finding the best evidence,
3. appraising the evidence for its validity (closeness to the truth), impact (size of effect) and applicability (usefulness in clinical practice),
4. integrating the findings of the critical appraisal with clinical expertise and patient values,
5. reviewing (auditing) clinical practice and the efficiency of the above steps.

STEP 1. SETTING THE CLINICAL QUESTION

Generating an answerable clinical question that is precise and specific is the basis of EBM. The development of a search strategy will flow from this. Focused clinical questions include four components, abbreviated as 'PICO':[6,7]

- **P** – the population: a description of the patients, such as their age, parity, clinical problem and the healthcare setting;

- **I** – the intervention(s) (or exposure): these are the main actions, such as treatment, diagnostic test or risk factor;
- **C** – the comparison group: for example, placebo or an alternative treatment;
- **O** – the outcome: for example, the change in health expected as a result of the intervention.

The type of study that will be sought is determined by the type of clinical question. For example, for a question about treatment, the highest level of evidence is based on randomised controlled trials (RCTs); for diagnostic test accuracy, studies that compare the 'new' test to a 'gold standard' test are needed; for questions about prognosis, studies that follow up groups of patients for a specified period of time (cohort studies) are needed. For a question about risk factors, cohort or 'case–control studies may be more appropriate. For cohort studies, the intervention may be an exposure (rather than a treatment intervention) and additional factors (length of follow-up or time) may be included. This is sometimes a population, exposure, comparison, outcome and time (PECOT) question.[7]

An example of a vague clinical question is: 'Should we use antibiotic prophylaxis at caesarean section?' This question could be focused in a number of ways.

- *Population:* are you interested in all caesarean sections, or a specific subgroup such as emergency or repeat caesarean section? The country in which you are practising, and the resources available, may also be important to specify.
- *Intervention*: antibiotic prophylaxis. Do you want to specify the antibiotic? Are you interested in the dose/duration of use?
- *Comparison:* is this compared with no antibiotics or with another intervention or another antibiotic – or to a different dose or treatment schedule?
- *Outcome:* what will be different as a result of giving the antibiotics? Will they reduce postoperative wound infection, or other outcomes such as endometritis or urinary tract infection (UTI), or other measures of febrile or infective morbidity such as length of hospital stay? What are the possible adverse effects or risks, for example allergy? What are the longer-term problems for mother or baby?

An example of a focused question is: 'For women having emergency caesarean section, does co-amoxiclav reduce the risk of postoperative endometritis compared with amoxicillin?' This is a question about treatment, so we would look for systematic reviews of randomised control trials.

STEP 2. FINDING THE BEST EVIDENCE

Where to search

There are numerous different library databases; different databases index different journals and they may be general or topic specific. MEDLINE is produced by the US National Library of Medicine and is widely available free of charge through PubMed. EMBASE has a greater European emphasis in terms of the journals it indexes and has a higher level of pharmacologic, content. Nursing and midwifery research may not be indexed by MEDLINE or EMBASE: to find such research, databases such as MIDIRS, BNI and CINAHL should be searched. Psychological literature is indexed on Psychinfo or Psychlit. The best resource for high-quality systematic reviews is the Cochrane Library:

- Cochrane Database of Systematic Reviews (CDSR)
- Database of Reviews of Effectiveness (DARE)
- Health Technology Assessment Database (HTA) (this includes UK and international HTA assessments).

DARE and HTA are also available on www.tripdatabase.com and www.crd.york.ac.uk. The latter also includes a new database, PROSPERO, an international prospective database of systematic reviews in health and social care. Systematic reviews are often also published in peer-reviewed journals and are indexed on library databases. The Cochrane Library has the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, it can be useful to include a citation search of ISI Web of Science or SCOPUS, which will locate research papers that have referenced the papers you intend to include in your research.

There are two online databases specifically for guidelines:

1. AHRQ National Guidelines Clearing House, www.guideline.gov (2500 guidelines, free to search and with links to most guidelines)
2. The Guidelines International Network library, http://www.g-i-n.net/library/international-guidelines-library, with 6500 guidelines, is free to search but you need membership to access guidelines.

Summaries of guidelines are now often also published in journals. If included in the guidelines clearing house they can be found through PubMed, a search of Turning Research Into Practice (TRIP) www.tripdatabase.com or alternatively an internet search for the websites of guideline producers such as NICE SIGN or specialist societies.

- Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/index.html)
- National Institute for Health and Care Excellence (NICE) (http://guidance.nice.org.uk/CG/Published)
- Royal College of Obstetricians and Gynaecologists (RCOG): http://www.rcog.org.uk
- Canadian Medical Association (CMA) (http://www.cma.ca/clinicalresources/practiceguidelines)

Developing a search strategy

Within general library databases, methodological indexing of study design has greatly improved. Specific strings of search terms that identify study designs, for example systematic

reviews or RCTs, are available: these are designed to have high sensitivity. A good example of these is available in the Cochrane Handbook[8] – search filters. There are methodological filters, which aim to include all relevant papers, but this may result in relatively low precision. Making your search more precise may be at the expense of sensitivity, i.e. a higher proportion of citations retrieved by your search may be relevant, but it might not include all relevant citations on the topic if these have not been indexed in a way that the filters would pick up.

Developing a search strategy usually involves combining free text and controlled text terms. Using the components of your clinical question (population, intervention, comparison, outcome and study design), make a list of the synonyms, abbreviations and spelling variations (e.g. labor or labour) that might have been used by the authors to describe the concept. If you already know of relevant papers, scan them for more possible search terms. This list can be your 'free text' terms.

The next stage is to list useful controlled text terms or subject headings. In MEDLINE, these are known as MeSH (Medical Subject Headings). In most databases they will be found in the thesaurus or index. If you know of a relevant paper, check the subject headings under which it is indexed.

Having developed a focused four-part question (PICO), create a separate search strategy for each component. The next stage is to combine these searches. Combination is achieved by 'Boolean Logic' and works in a manner similar to combining numbers in algebra. Boolean Logic uses the terms 'and', 'or' and 'not' to create a set of results that should contain papers relevant to the clinical question. For example, combining cervical *and* cancer will retrieve all the papers that contain both terms. Combining cervical *or* cancer will retrieve all papers in which either one or both terms are found. To find papers relating to postoperative infection, it would be necessary to combine both the lists of controlled and free text terms for both words with *or*. Combining induction *not* labour will retrieve all papers that contain the word induction but do not also include the term labour. Care should be used when combining terms with *not*, as it will exclude any papers that discuss both the term of interest and the one to be excluded. All databases also have useful search commands and symbols, but these vary among databases.

If you are conducting a systematic review, either for publication or as the evidence base for a guideline, it is good practice to keep your search strategies and record:

- how many articles were found by the search,
- the number and source of any other records identified,
- any duplicate reports, which should be removed
- the number of records screened
- the number of full text records assessed,
- those included in a qualitative and quantitative assessment (a meta-analysis),
- exclusions – with the reason.

This information should be combined into a flow chart and published along with your review.[9]

STEP 3. APPRAISING THE EVIDENCE

The best evidence for guiding practice is an accurate, complete summation of current research knowledge such as systematic reviews.[3] In order to minimise bias, the methods of a systematic review should be explicit and well structured[9] and should include clearly defined PICO questions, an extensive search of the literature, appraising the quality of studies located by the search with explicit criteria, and analysing the research findings using appropriate methods. Data from each of the individual studies may be pooled and analysed using a technique known as meta-analysis. Clinical guidelines should be based on systematic reviews, so it is important that you are able to understand the principles of appraising clinical guidelines, systematic reviews and the primary studies on which they are based, so that you are able to judge the validity and applicability of the conclusions to your specific circumstances.

Improved reporting standards of primary and secondary research through statements such as PRISMA,[9] CONSORT 2010,[10] STARD[11] and STROBE[12] ensure the information necessary for critical appraisal is more likely to be available. In addition there are numerous guides to critical appraisal.[6,13]

Critical appraisal is the process of deciding if the research you have found can help you in answering your clinical question. The first filter is: 'Does this paper address my clinical question?' (i.e. is PICO the same or similar to that in your question?) If there are some slight differences, what are these?[6]

The second stage is to look at the study design (the methods section of a paper). The acceptable study design is determined by your clinical question. For questions about treatment interventions, RCTs or systematic reviews of RCTs provide the least biased estimate of effectiveness.[3,6,8] For diagnostic test accuracy, studies that compare the 'new' test to a 'gold standard' test are needed. For questions about prognosis, studies that follow up groups of patients for a specified period of time (cohort studies) are needed.

Bias

A systematic review summarises the results from a body of research, usually RCTs but also observational studies. Quality assessment is an essential part of the process of systematic review. If the 'constituent studies' are flawed, the conclusions of systematic reviews may also not be valid.[6,13] Bias is a systematic difference between groups that distorts the comparison so that the 'true' effect is either exaggerated or reduced. The quality of a study is the degree to which the study design, conduct and analysis have minimised bias. External validity examines the extent to which the results of a study are applicable to other clinical circumstances, i.e. its generalisability. Internal validity examines the extent to which systematic error (or bias) is minimised within the study. Such biases include:

- **selection bias** – the difference in the patient characteristics (such as prognosis) between comparison groups. In an RCT this is minimised by the method of randomisation

(only non-predictable is acceptable) and by keeping allocation concealed to prevent subversion;
- **performance bias** – differences in the provision of care apart from the treatment under evaluation (achieved through blinding patients, assessors and analysts);
- **detection bias** – differences in the measurement or assessment of outcomes;
- **attrition bias** – the occurrence and handling of patient withdrawals or attrition;
- **reporting bias** – many outcomes may be measured but may not all be reported, reporting is varied dependent on findings, positive findings are more likely to be published and published sooner.

Different study types are prone to different biases; therefore, there are different validity checklists for different studies based on the conduct, design and analysis.[6,8] Appraising the quality of a study is dependent not only on what was done but on how the study was reported, and it is essential that the research is published so that the findings contribute to what is known.[5]

Understanding RCTs and systematic reviews of RCTs

For the MRCOG, it is important to understand the design of an RCT and of reviews of RCTs; therefore, the rest of this section focuses only on appraising RCTs. The RCT is the 'gold standard' method for evaluating the effectiveness of therapeutic interventions as it gives the least biased estimate of effect of treatment interventions.[3,5]

A confounder is a factor (such as disease severity) that may influence the choice of treatment and the outcome of care. Confounding is one reason for the tendency of non-randomised trials to overestimate treatment effects when compared with RCTs. With a well-conducted RCT, randomisation will create groups that are comparable with respect to any known or unknown potential confounding factors (providing the sample size is sufficiently large). The key questions to ask when appraising (assessing possible bias and quality) an RCT are outlined below, with an explanation of why these are important.[8] The first four questions relate to study validity, and the fifth to interpreting the results.

1. Was the assignment of treatment randomised?

The process of randomisation requires that those recruiting to a trial or participating in the trial cannot predict which group the subjects will be allocated to. The process of randomisation involves two stages:

(i) generation of an unpredictable allocation sequence (random number),
(ii) concealment of this sequence from those enrolling participants in the trials.

Failure to secure the concealment of the sequence may allow selective enrolment depending on prognostic factors. A trial in which it is possible to predict the treatment allocation is more likely to be biased. The 'gold standard' for randomisation used in large multicentre trials is 'central computer' randomisation. The use of sealed envelopes (especially if they are not sequentially numbered) may be subverted (for example by holding the envelope up to the light); methods that could be predictable are date of birth, alternate days and hospital number.

2. Were the groups similar at the start of the trial?

The aim of randomisation is the creation of groups that are comparable with respect to any known or unknown potential confounding factors (providing the sample size is sufficiently large). Randomisation reduces bias in those selected for treatment and guarantees that treatment assignment is not based on patients' prognosis. RCTs will have eligibility criteria, but within these trials report the characteristics of the patients according to the treatment received in Table 1 of the results section. The characteristics (such as age, parity) of the two groups should not be different.

3. Were the groups treated equally?

Apart from the intervention being studied, the groups should be treated identically – differences in treatment between groups may occur if treatment allocation is known. This is called performance bias and can be minimised by standardisation of the care protocol and by 'blinding'. RCTs may blind patients, and those administering treatment, assessing outcomes and analysing the data. If they are aware of allocation, the treatment of both patient groups may differ or patients themselves may deviate from protocols because of awareness of allocation.

Detection (or measurement) bias applies to the measurement or assessment of the outcome. This should be standardised across all patients. Again, knowledge of treatment allocation may influence assessors. For an objective outcome (such as death), this may be less important, but, for outcomes that are subjective, interpretation may differ if the assessor has prior knowledge of allocation. This bias can be minimised by using objective outcomes and by ensuring that those assessing outcomes are unaware of treatment allocation. This approach is used in surgical RCTs: although the surgeon undertaking the treatment has to be aware of the treatment allocation, identical surgical dressings are used for all patients, and the assessment of recovery is done by another person who is not aware of treatment allocation.

4. Are all the patients accounted for at the conclusion?

The process of randomisation gives us comparable groups at the start of a trial, but results are valid only if we can account for all these patients at the end of the trial. Therefore, once randomised, a patient should be included in the analysis of that group even if he or she discontinues therapy, crosses over