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Oxford Textbook of Obstetrics and Gynaecology

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OXFORD
UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 2020

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2019946544

ISBN 978–0–19–876636–0

Printed in Great Britain by
Bell & Bain Ltd., Glasgow

Preface

This comprehensive text book of Obstetrics and Gynaecology consists of 72 chapters that spans over 900 pages. It has 12 subsections for easy navigation by the reader. The book covers all of the important aspects of the subject. Such comprehensive coverage was possible due to the International collaboration of hundreds of world renowned authors. We, as editors of the book, are most grateful to them. The authors are from various countries and have provided the knowledge based on available latest evidence in the literature and guidelines from well recognised National and International Professional organisations.

The editors have been selected to provide their expertise in the areas of feto-maternal medicine, reproductive medicine, uro and general gynaecology and gynaecological oncology. They are from the United Kingdom, Australia and South Africa and hold or have held responsible academic positions and have published extensively. They have contributed significantly to teaching, research and clinical practice. The editors have published books in their own rights and have written for and overseen the production of this book with the benefit of their vast experience. We have given the liberty to individual authors to interpret the evidence in their area of expertise and to provide opinions and advice where evidence is lacking.

The production of the book has been a huge undertaking, and has taken significant time from the submission of the manuscripts to final production. However our authors have been able to update their chapters to circumvent their content becoming out of date. The editors and the publishers are most grateful to them for their effort. This book will be the comprehensive text in Obstetrics and Gynaecology for consultants, postgraduates, midwives, nurses and allied health specialists. We would like to hear your comments and feedback so that we can correct or update the text in the reprint or the next edition.

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September 2019

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Abbreviations

2D	two-dimensional
3D	three-dimensional
5-FU	5-fluorouracil
ABC	airway, breathing, and circulation
ABPM	ambulatory blood pressure monitoring
AC	abdominal circumference
ACA	anticardiolipin antibodies
ACE	angiotensin-converting enzyme
AChR	acetylcholine receptor
ACOG	American College of Obstetrics and Gynecologists
ACTH	adrenocorticotropic hormone
ADPKD	autosomal dominant polycystic kidney disease
AED	antiepileptic drug
AFC	antral follicle count
AFLP	acute fatty liver of pregnancy
aHUS	atypical haemolytic uraemic syndrome
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
AIP	abnormality invasive placenta
AKI	acute kidney injury
ALT	alanine aminotransferase
AMH	anti-Mullerian hormone
AML	active management of labour
aOR	adjusted odds ratio
AP	anteroposterior
APC	antigen-presenting cell
APH	antepartum haemorrhage
APS	antiphospholipid syndrome
ARDS	acute respiratory distress syndrome
ARM	artificial rupture of membranes
ARV	assisted reproductive technology *or* antiretroviral therapy
ASIS	anterior superior iliac spine
ASRM	American Society of Reproductive Medicine
ATP	adenosine triphosphate
AUB	abnormal uterine bleeding
AVP	arginine vasopressin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BV	bacterial vaginosis
CAH	congenital adrenal hyperplasia
CDC	Centers for Disease Control and Prevention
CDH	congenital diaphragmatic hernia
CFU	colony-forming unit
CGH	comparative genomic hybridization
CHB	complete heart block
CHD	congenital heart disease
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIS	carcinoma *in situ*
CKI	chronic kidney injury
CL	cervical length
CNV	copy number variant
COC	combined oral contraceptive
COX	cyclooxygenase
CPD	cephalopelvic disproportion
CPR	cardiopulmonary resuscitation
CRH	corticotropin-releasing hormone
CRL	crown–rump length
CSF	cerebrospinal fluid
CSP	cavum septum pellucidum
CT	computed tomography
CTG	cardiotocography
CTPA	computed tomography pulmonary angiography
CVS	chorionic villus sampling
CVT	cerebral venous thrombosis
D&E	dilatation and evacuation
DFM	decreased fetal movement
DHEA	dehydroepiandrosterone
DIC	disseminated intravascular coagulation
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
dVIN	differentiated vulval intraepithelial neoplasia
EC	emergency contraceptive
ECG	electrocardiogram
ECV	external cephalic version
EFI	Endometriosis Fertility Index
EFM	electronic fetal heart rate monitoring
EFW	estimated fetal weight
EIN	endometrial intraepithelial neoplasia
EOC	epithelial ovarian cancer
EOGBSD	early-onset neonatal group B *Streptococcus* disease
EP	ectopic pregnancy
EPAU	early pregnancy assessment unit
ER	oestrogen receptor
ESHRE	European Society for Human Reproduction and Embryology
ESRD	end-stage renal disease
EVT	extravillous trophoblast
EXIT	ex utero intrapartum treatment
FASP	Fetal Anomaly Screening Programme

FBS	fetal scalp blood sampling
FEV_1	forced expiratory volume in 1 second
FFN	fetal fibronectin
FGM/C	female genital mutilation/cutting
FGR	fetal growth restriction
FHR	fetal heart rate
FIGO	International Federation of Gynecology and Obstetrics
FISH	fluorescence in situ hybridization
FMAIT	fetal alloimmune thrombocytopenia
FRC	functional residual capacity
FSAD	female sexual arousal disorder
FSD	female sexual dysfunction
FSH	follicle-stimulating hormone
FSIAD	female sexual interest and arousal disorder
FSIRS	fetal systemic inflammatory response syndrome
FVL	factor V Leiden
G6PD	glucose-6-phosphate dehydrogenase
GAS	group A *Streptococcus*
GBS	group B *Streptococcus*
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GH	growth hormone
GMC	General Medical Council
GnRH	gonadotropin-releasing hormone
GOG	Gynecologic Oncology Group
GTD	gestational trophoblastic disease
GTN	gestational trophoblastic neoplasia
HAART	highly active antiretroviral therapy
HbA1c	glycated haemoglobin
HBPM	home blood pressure monitoring
HBV	hepatitis B virus
HC	head circumference
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HD	haemodialysis
HDP	hypertensive disorders of pregnancy
HELLP	haemolysis, elevated liver enzymes, and low platelets
HFEA	Human Fertilization and Embryology Authority
HGESS	high-grade endometrial stromal sarcoma
HGSOC	high-grade serous ovarian cancer
HIC	high-income country
HIFU	high-intensity focused ultrasound
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HMB	heavy menstrual bleeding
HNPCC	hereditary non-polyposis colorectal cancer
HPA	human platelet antigen
HPF	high power field(s)
hPL	human placental lactogen
HPO	hypothalamic–pituitary–ovarian
HPV	human papillomavirus
HRAM	high-resolution anorectal manometry
HRT	hormonal replacement therapy
HSDD	hypoactive sexual desire disorder
HSG	hysterosalpingography
HSP	Henoch–Schönlein purpura
HSV	herpes simplex virus
HT	hydroxytryptamine *or* hormone therapy
HUS	haemolytic uraemic syndrome
HyCoSys	hysterosalpingo contrast sonography
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IARC	International Agency for Research on Cancer
IBD	inflammatory bowel disease
ICH	intracranial haemorrhage
ICP	intrahepatic cholestasis of pregnancy
ICS	International Continence Society
ICSI	intracytoplasmic sperm injection
Ig	immunoglobulin
IGRT	image-guided radiation therapy
IL	interleukin
ILT	interstitial laser therapy
IM	intramuscular
IMRT	intensity-modulated radiation therapy
ISSVD	International Society for the Study of Vulvovaginal Disease
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
IUD	intrauterine device
IUFD	intrauterine fetal demise
IUGA	International Urogynecological Association
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IUT	intrauterine blood transfusion
IV	intravenous
IVC	inferior vena cava
IVF	*in vitro* fertilization
IVF-ET	*in vitro* fertilization with embryo transfer
IVH	intraventricular haemorrhage
IVIG	intravenous immunoglobulin
JZ	junctional zone
LABA	long-acting beta-2-agonist
LAC	lupus anticoagulant
LAM	lactational amenorrhoea method *or* levator ani muscle
LARC	long-acting reversible contraception
LAT	labour admission test
LBW	low birth weight
LEEP	loop electrosurgical excision procedure
LFCNT	lateral femoral cutaneous nerve of the thigh
LFT	liver function test
LGA	large for gestational age
LGESS	low-grade endometrial stromal sarcoma
LGSC	low-grade serous carcinoma
LH	luteinizing hormone
linac	linear accelerator
LLETZ	large loop excision of the transformation zone
LMIC	low- and middle-income countries
LMP	last menstrual period
LMWH	low-molecular-weight heparin
LNG-IUS	levonorgestrel-releasing intrauterine system
LUNA	laparoscopic uterosacral nerve ablation
LUTO	lower urinary tract obstruction
LVSI	lymphovascular space invasion
MAS	meconium aspiration syndrome

MBP	mechanical bowel preparation
MCDA	monochorionic diamniotic
MCM	major congenital malformation
MCMA	monochorionic monoamniotic
MDG	Millennium Development Goal
MEC	Medical Eligibility Criteria
MFPR	multiple fetal pregnancy reduction
MG	myasthenia gravis
MHRA	Medicines Healthcare products Regulation Authority
MMC	myelomeningocoele
MMP	matrix metalloproteinase
MOEWS	Modified Obstetric Early Warning Score
MPA	medroxyprogesterone acetate
MR	magnetic resonance
MRgFUS	magnetic resonance-guided focused ultrasound surgery
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSAF	meconium staining of the amniotic fluid
MSU	mid-stream urine
MUI	mixed urinary incontinence
NAAT	nucleic acid amplification test
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for health and Care Excellence
NIH	National Institutes of Health
NIP	national immunization programme
NIPT	non-invasive prenatal testing
NK	natural killer
NSAID	non-steroidal anti-inflammatory drug
NT	nuchal translucency
OA	occipitoanterior
OAB	overactive bladder
OASIS	obstetric anal sphincter injuries
OBGYN	obstetrics and gynaecology
OHSS	ovarian hyperstimulation syndrome
OP	occipitoposterior
OR	odds ratio
OT	occipitotransverse
OVD	operative vaginal delivery
PAI	plasminogen activator inhibitor
PAPP-A	pregnancy-associated plasma protein A
PARP	poly(ADP ribose) polymerase
PBC	primary biliary cholangitis
PCOS	polycystic ovary syndrome
PCR	polymerase chain reaction *or* protein:creatinine ratio
PD	peritoneal dialysis
PDE	phosphodiesterase
PE	pulmonary embolism
PEFR	peak expiratory flow rate
PET	pre-eclampsia/toxaemia
PFMT	pelvic floor muscle training
PFS	progression-free survival
PGD	preimplantation genetic diagnosis
PGM	prothrombin gene mutation
PGS	preimplantation genetic screening
PID	pelvic inflammatory disease
PLD	pegylated liposomal doxorubicin
POI	premature ovarian insufficiency
POP	pelvic organ prolapse
PPH	postpartum haemorrhage
PPROM	preterm prelabour rupture of membranes
PR	progesterone receptor
PRES	posterior reversible encephalopathy syndrome
PSC	primary sclerosing cholangitis
PSN	presacral neurectomy
PSTT	placental site trophoblastic tumour
PTB	preterm birth
PTSD	post-traumatic stress disorder
PUL	pregnancy of unknown location
PVL	periventricular leucomalacia
QI	quality improvement
RAS	renin–angiotensin system
rASRM	revised American Society for Reproductive Medicine
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomized controlled trial
RCVS	reversible cerebral vasoconstriction syndrome
RDS	respiratory distress syndrome
RFA	radiofrequency ablation
RLS	restless legs syndrome
RM	recurrent miscarriage
RPL	recurrent pregnancy loss
RR	relative risk
SCD	sickle cell disease
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCT	sacrococcygeal teratoma
SDG	Sustainable Development Goal
SET	single embryo transfer
SGA	small for gestational age
SHBG	sex hormone-binding globulin
SIS	saline infusion sonography
sIUGR	selective intrauterine growth restriction
SLE	systemic lupus erythematosus
SNRI	serotonin noradrenaline reuptake inhibitor
SPRM	selective progesterone receptor modulator
sPTB	spontaneous preterm birth
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
SUA	single umbilical artery
SUI	stress urinary incontinence
SVT	supraventricular tachycardia
T_3	triiodothyronine
T_4	tetraiodothyronine (thyroxine)
TAUS	transabdominal ultrasound
TBG	thyroxine-binding globulin
TCGA	The Cancer Genome Atlas
TCRE	transcervical resection of the endometrium
TKI	tyrosine kinase inhibitor
TMA	thrombotic microangiopathy
TOLAC	trial of labour after caesarean
tPA	tissue plasminogen activator
TRAP	twin reversed arterial perfusion
TSG	tumour suppressor gene
TTP	thrombotic thrombocytopenic purpura
TTTS	twin-to-twin transfusion syndrome

TVUS	transvaginal ultrasound
TZ	transformation zone
UAE	uterine artery embolization
UBA	urethral bulking agent
UCP	umbilical cord prolapse
UDCA	ursodeoxycholic acid
UES	undifferentiated endometrial sarcoma
UFH	unfractionated heparin
UI	urinary incontinence
uPA	urokinase plasminogen activator
USS	ultrasound screening
UTI	urinary tract infection
UUI	urgency urinary incontinence
uVIN	usual-type vulval intraepithelial neoplasia
V/Q	ventilation–perfusion
VAIN	vaginal intraepithelial neoplasia
VAS	vesicoamniotic shunting
VBAC	vaginal birth after caesarean delivery
VCI	velamentous insertion of the cord
VEGF	vascular endothelial growth factor
VHD	valvular heart disease
VIA	visual inspection with acetic acid
VIN	vulval intraepithelial neoplasia
VLDL	very low-density lipoprotein
VP	ventriculoperitoneal
VSCC	vulval squamous cell carcinoma
VTE	venous thromboembolism
VUR	vesicoureteral reflux
vWD	von Willebrand disease
vWF	von Willebrand factor
VZIG	varicella zoster immunoglobulin
VZV	varicella zoster virus
WHI	Women's Health Initiative
WHO	World Health Organization
WwE	women with epilepsy

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40: The menstrual cycle

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63: Uterine cancer

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2: Ethics in obstetrics and gynaecology

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32: Malpresentation, malposition, and cephalopelvic disproportion

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25: Respiratory diseases in pregnancy

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66: Gestational trophoblastic disease

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66: Gestational trophoblastic disease

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71: Premalignant disease of the genital tract in pregnancy

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58: Faecal incontinence and anorectal dysfunction

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50: Benign disease of the vulva

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22: Antepartum haemorrhage

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65: Premalignant and malignant disease of the vulva and vagina

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67: Chemotherapy and biological, targeted, and immune therapies in gynaecological cancers

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36: Induction of labour

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70: Pathology of tumours of the female genital tract

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62: Premalignant and malignant disease of the cervix

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61: Cancer screening and prevention in gynaecology

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46: Menopause

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27: Fetal monitoring during labour;
38: Miscarriage and recurrent miscarriage

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23: Liver and endocrine diseases in pregnancy

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29: Obstetric emergencies

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55: Violence against women and girls

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42: Polycystic ovary syndrome

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48: Hysteroscopy

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SECTION 1

Basics in Obstetrics and Gynaecology

1

Basic sciences in obstetrics and gynaecology

Stergios Doumouchtsis

Structure and function of the genome

Chromosomes

The normal human genome is diploid and consists of 46 human chromosomes in 23 pairs. Chromosome abnormalities may be related to the number (aneuploidy) or structure of chromosomes. A karyotype describes the number of chromosomes and major structural abnormalities such as deletions, duplications, or translocations.

Meiosis is the cell division process in germline cells, resulting in the production of haploid gametes (ova and sperm). The process of meiosis generates four haploid cells, which can participate in fertilization. *Mitosis* is a process of the cell cycle in somatic cells resulting in the formation of two diploid daughter cells with identical genomes to that of the parental cell.

Genes and gene expression

A *gene* is a sequence of nucleotides in deoxyribonucleic acid (DNA) which codes for a protein. The sequence of nucleotides determines the amino acid sequence of the protein and its function. Each gene is represented twice (alleles) in the complement of genes known as the genome. Genes contain information that determines phenotype.

Genes are made up of exons and introns. Exons code for the protein and introns are spliced out during processing to messenger ribonucleic acid (mRNA). The length of the introns is far greater than that of the exons. The exact function of the introns is unclear. Although the exon sequence is highly conserved between individuals, the intron sequence is not.

Gene expression is the process by which information from a gene is used in the synthesis of a protein or another gene product such as transfer RNA (tRNA) or functional RNA. This process involves transcription of RNA from a DNA template and translation of mRNA into protein.

Although all cells in an organism have the same information in their DNA, only 3–5% of genes are active in a cell. Most of the genome is suppressed, a characteristic of gene expression.

Changes in gene regulation result in the expression of various gene products and the suppression of others. Methods for measuring RNA to evaluate gene expression include northern blot, ribonuclease protection assay, *in situ* hybridization, reverse-transcription quantitative polymerase chain reaction (PCR), and spotted complementary DNA arrays. Genome-wide methods for profiling gene expression include oligonucleotide arrays (microarrays) and transcriptome sequencing.

Epigenetics

Epigenetics is the study of heritable genome modifications in gene expression that are not due to alterations in DNA sequences. DNA methylation and histone modification (acetylation, methylation) are common epigenetic changes and can affect the process of transcription or silencing of gene expression.

Other epigenetic changes include modifications in non-coding RNAs and telomere length. Influences of environmental factors and epigenetic changes in the development of diseases such as cancer have been investigated in recent years. Such factors may include drugs, ultraviolet light, infection, and diet. Geographic differences in the incidence of autoimmune diseases have also been studied (1). Ageing and development of disease is another area of epigenetics involvement.

Molecular biology techniques

Molecular diagnostic tools in clinical genetics are applied for genotyping, detection of mutations, and assessment of chromosomal structural variants.

PCR technology is used to identify mutations. It requires prior knowledge of the DNA sequence of the fragment to be amplified. Real-time PCR allows the simultaneous detection and quantification of a DNA molecule and selection of mutant DNA. Deletion and insertion mutations can be identified using this technique.

PCR can detect organisms such as human immunodeficiency virus (HIV), methicillin-resistant *Staphylococcus aureus*, as well as chromosomal translocations associated with cancers.

Cytogenetic karyotype analysis by chromosomal banding, fluorescence *in situ* hybridization (FISH) on metaphase or interphase nuclei, or array comparative genomic hybridization (CGH) can identify structural variations. The resolution improves from karyotyping to interphase FISH and to array CGH. New sequence variants continue to be discovered with methods that allow analysis of entire genes or genomes.

Ovulation and ovarian function

Control of the hypothalamic–pituitary axis

The hypothalamus is part of the diencephalon. It is separated from the thalamus by the hypothalamic sulcus. Its external boundaries are rostrally the optic chiasm, laterally the optic tract, and posteriorly the mammillary bodies.

Its rostral boundary is a line through the optic chiasm, lamina terminalis, and anterior commissure and the caudal boundary extends from the posterior commissure to the caudal limit of the mammillary body. Dorsolaterally, the hypothalamus extends to the medial edge of the internal capsule (Figure 1.1) (2). The hypothalamus is associated with visceral, endocrine, autonomic, affective, and emotional behaviour.

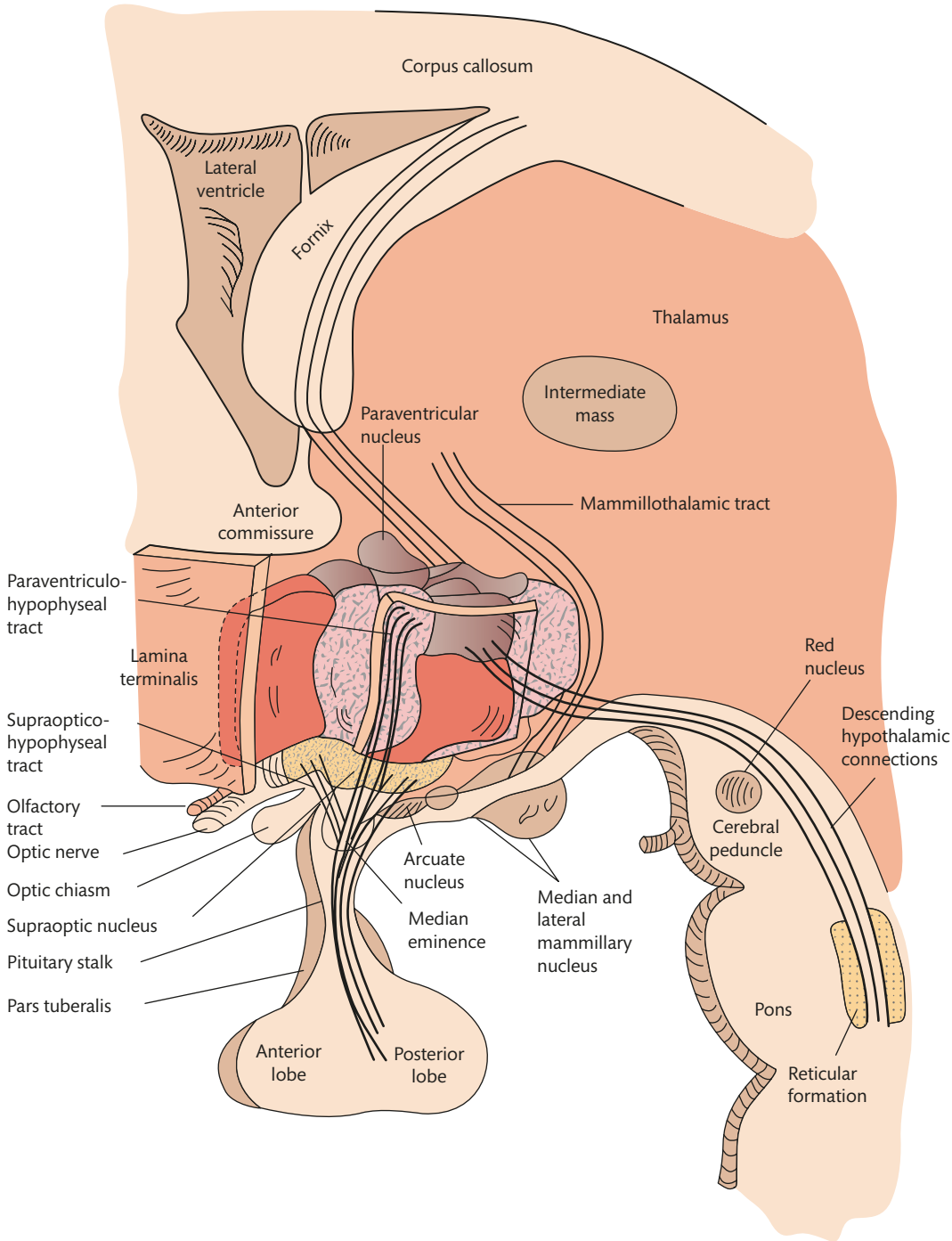

Figure 1.1 The hypothalamic nuclei and hypothalamic–hypophyseal tracts in relation to the thalamus, ventricular system, and brainstem.

Reproduced from Ignacio Bernabeu, Monica Marazuela, and Felipe F. Casanueva, General concepts of hypothalamus-pituitary anatomy, in: *Oxford Textbook of Endocrinology and Diabetes* 2e (eds: John Wass et al.), Oxford University Press, 2011, with permission from Oxford University Press.

The anterior pituitary is connected to the hypothalamus through a portal system. Hormones synthesized in the hypothalamus are transported to the nerve terminals on the hypophyseal portal capillaries. Hormones released into the hypophyseal portal system are transported to the anterior lobe of the pituitary. The posterior lobe of the pituitary consists of nerve terminals which lie in the supraoptic and paraventricular nuclei of the hypothalamus. Oxytocin and vasopressin are synthesized by the posterior pituitary.

Actions of pituitary and ovarian hormones

Gonadotropin-releasing hormone (GnRH) is synthesized in the preoptic area of the hypothalamus and is transported via portal vessels to the anterior pituitary where it stimulates the gonadotrophs to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These glycoproteins share a common alpha-subunit and a specific beta-subunit. They control the steroid synthesis of the testes and ovaries.

Oestrogen and progesterone are the major hormones secreted by the ovarian follicles and the corpus luteum (Figure 1.2).

Ovulation

A rise in FSH secretion stimulates the growth and differentiation of preantral and antral follicles, which in turn stimulates oestrogen secretion with a peak approximately 1 day before ovulation. Then, the mid-cycle surge occurs (3) and is associated with a change from negative feedback control of LH secretion by ovarian hormones to a positive feedback, resulting in a tenfold rise in serum LH and a smaller increase in FSH concentrations. The LH surge leads to substantial changes in the ovary. The oocyte in the dominant follicle completes its first meiotic division. The oocyte is subsequently released from the follicle at the surface of the ovary (4).

Before the release of the oocyte, the surrounding granulosa cells luteinize and produce progesterone. As a result, LH pulses become less frequent by the end of the surge (Figure 1.3).

The increasing serum progesterone concentrations have an effect on the endometrium, leading to cessation of mitoses and 'organization' of the glands.

Endometrial cycle

The average duration of the adult menstrual cycle is 28–35 days. The first day of menses represents the first day of the cycle. The cycle is then divided into two phases: follicular and luteal. The follicular

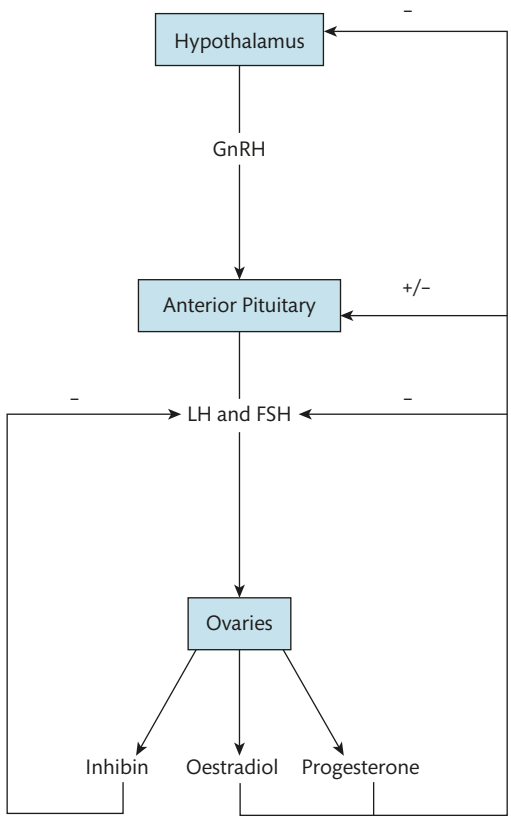

Figure 1.2 Hypothalamic–pituitary–ovarian axis.

Reproduced from S. Arulkumaran, Menstrual disorders, in: *Training in Obstetrics and Gynaecology* (eds. Ippokratis Sarris, Susan Bewley and Sangeeta Agnihotri), Oxford University Press, 2009, with permission from Oxford University Press.

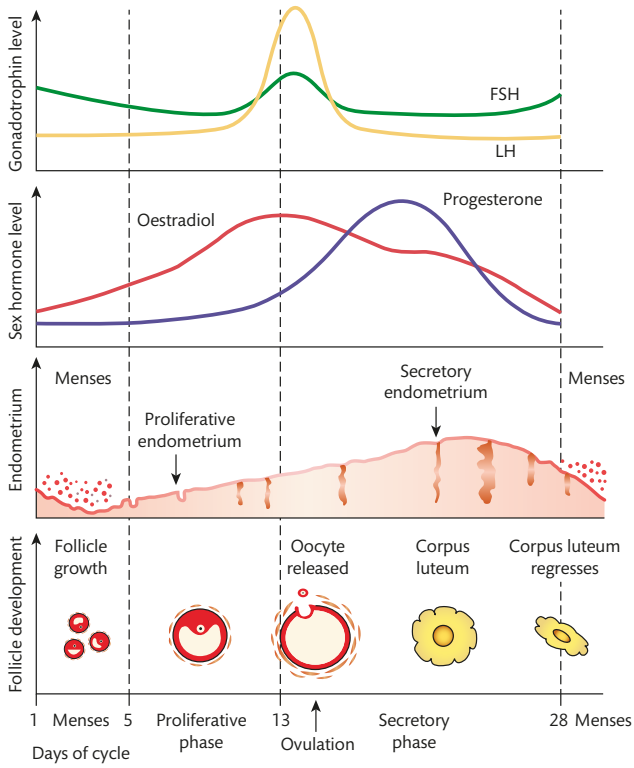

Figure 1.3 The hormonal and endometrial axis of the human menstrual cycle. After menstruation, rising levels of oestrogen exert a negative feedback, reducing follicle-stimulating hormone (FSH) release. Towards mid cycle, still higher levels of oestrogen then exert a positive feedback, causing a sudden peak release of luteinizing hormone (LH), which induces ovulation. An increased level in FSH also occurs. The endometrium during this phase has a thin surface epithelium and the glands are straight, short, and narrow (proliferative/follicular). In the luteal phase, LH levels maintain the corpus luteum, the source of progesterone. The endometrial glands become more tortuous during this phase (secretory/luteal) with secretion in the lumen and increasing fluid separating the stromal cells. If an embryo fails to implant, the corpus luteum deteriorates after about 7 days, with a resulting fall in progesterone and oestrogen concentrations.

Reproduced from S. Arulkumaran, Menstrual disorders, in: *Training in Obstetrics and Gynaecology* (eds. Ippokratis Sarris, Susan Bewley and Sangeeta Agnihotri), Oxford University Press, 2009, with permission from Oxford University Press.

phase begins with the onset of menses and ends on the day before the LH surge. The luteal phase begins on the day of the LH surge and ends at the onset of the next menses. The follicular phase lasts approximately 14–21 days and the luteal phase 14 days. Changes in the intermenstrual interval are primarily due to changes in the follicular phase. The luteal phase remains relatively stable. There is significantly more cycle variability during the first years after menarche and the 10 years before menopause. Menstrual cycle length peaks at the age of 25–30 years and then gradually declines. Between the ages of 20 and 40 years, there is relatively little cycle variability. Women in their 40s may have slightly shorter cycles (5).

During the menstrual cycle, endometrial changes include a proliferative phase and a secretory phase. The proliferative phase is characterized by an increased rate of mitotic division of endometrial glandular cells under the influence of oestradiol, leading to proliferation. The secretory phase is characterized by secretory activity following further proliferation under the influence of oestradiol and progesterone.

Luteinization of corpus luteum occurs 14 days after ovulation in the absence of conception. A rise in FSH is induced by the loss of negative feedback from oestradiol and progesterone, resulting in the start of another cycle. If, however, conception occurs, luteinization does not occur and the corpus luteum is maintained by human chorionic gonadotropin.

Puberty and menopause

Puberty is a process of physical and hormonal changes resulting in sexual maturity and capability of sexual reproduction. The two main physiological events include *gonadarche*, which is the activation of gonadal sex steroid production by the pituitary hormones FSH and LH, and *adrenarche*, which involves the increase in production of androgens by the adrenal cortex.

Thelarche is the appearance of breast tissue. *Menarche* is the onset of menstrual cycles. This is caused by the action of oestradiol on the endometrium and usually is not associated with ovulation. *Spermarche* is the onset of sperm production. *Pubarche* is the appearance of pubic hair, primarily due to the effects of androgens from the adrenal gland. The term also refers to the appearance of axillary hair (**Figure 1.4**).

In puberty, the increased frequency and amplitude of GnRH pulses stimulates secretion of FSH and LH and activates gonadal steroidogenesis.

Leptin is secreted by adipose tissues and along with kisspeptin plays a role in the onset of puberty. *Menopause* is defined as the permanent cessation of menstruation. It is an oestrogen- and progesterone-deficient state with an increase in the secretion of FSH and LH. The cessation of menstrual periods occurs as the ovary no longer contains follicles which are responsive to FSH. It is diagnosed retrospectively after 12 months of amenorrhea without any other cause (**Figure 1.5**).

Lack of oestrogen causes vasomotor symptoms including hot flushes and night sweats as well as mood swings and depression. Long-term effects include lower genital tract atrophy, osteoporosis, changes in lipid metabolism, and an increased risk of cardiovascular disease (6). Menopause usually occurs between 45 and 55 years of

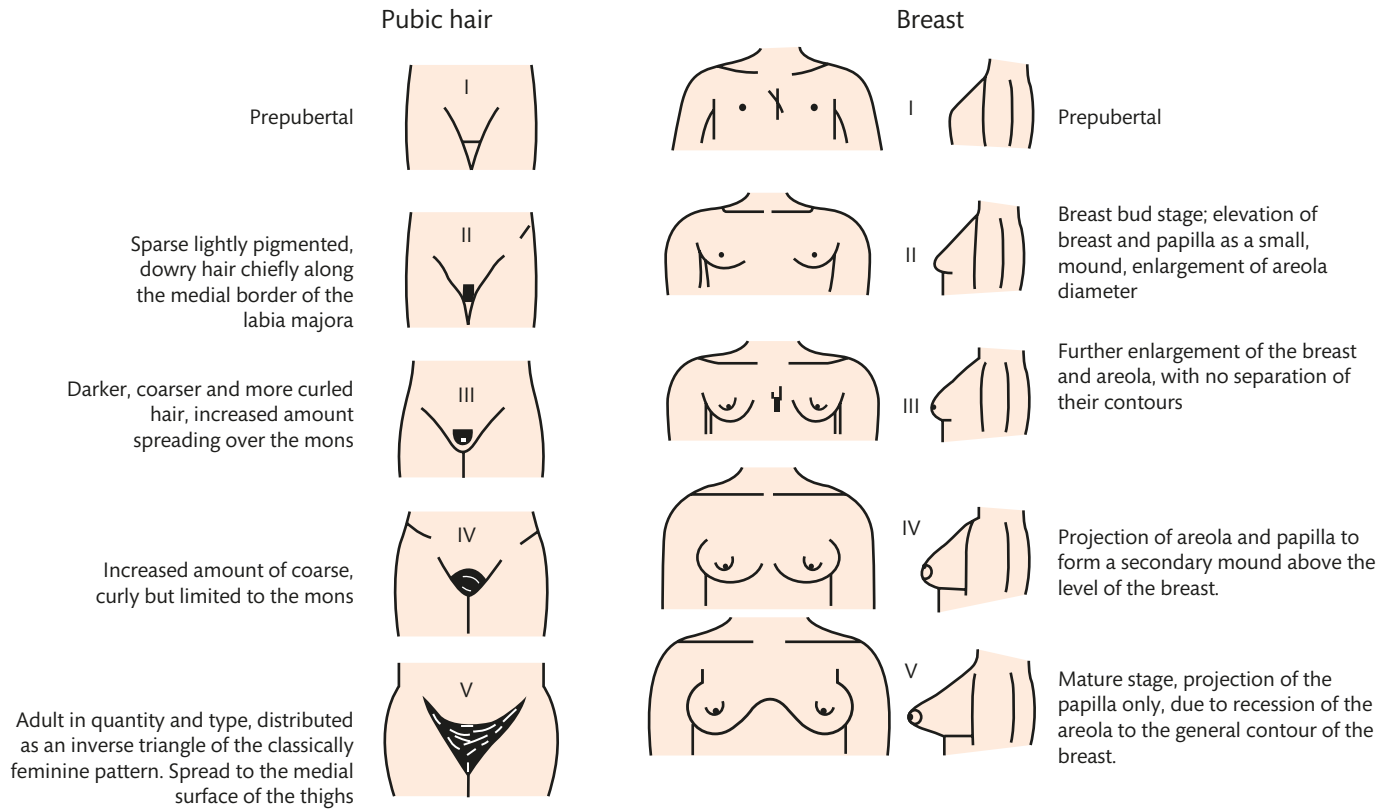

Figure 1.4 Marshall and Tanner stages of breast and pubic hair development.

Reproduced from McVeigh E, Homburg R, and Guillebaud J. *Oxford Handbook of Reproductive Medicine and Family Planning*, Oxford University Press, 2008, with permission from Oxford University Press.

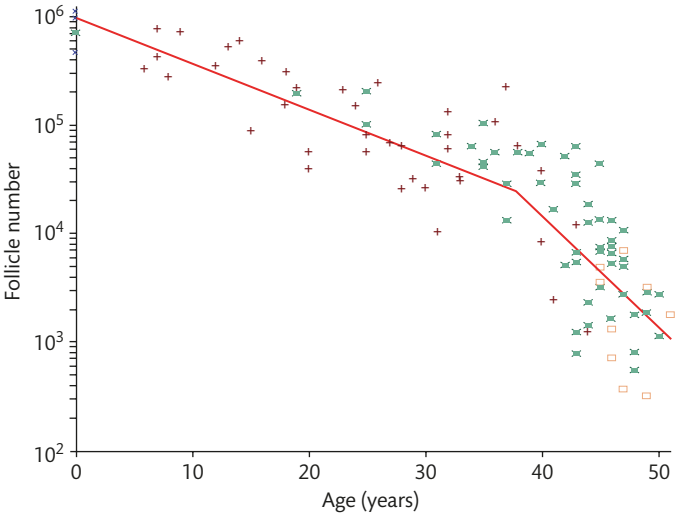

Figure 1.5 Decline in primordial follicle number with age.

Reproduced from Faddy MJ, Gosden RG. A mathematical model of follicle dynamics in the human ovary. *Hum Reprod*. 1995; 10: 770–5 with permission from Oxford University Press.

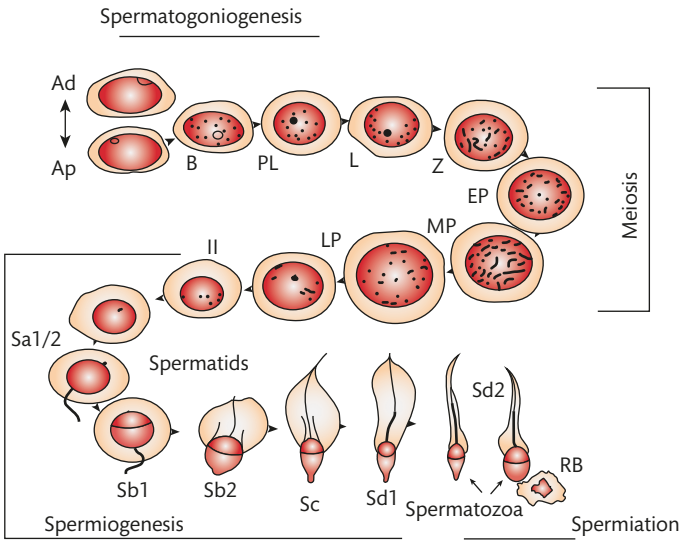

Figure 1.6 Schematic representation of the germ cell types and their development path during human spermatogenic process. Ad, A dark-spermatogonium; Ap, A pale-spermatogonium; B, B-spermatogonium; EP (early), MP (mid), and LP (late), pachytene spermatocyte; II, secondary spermatocyte; L, leptotene spermatocytes; M, mitochondria; PL, preleptotene spermatocytes; RB, residual body; Sa–Sd2, steps of spermatid differentiation (Sd2 spermatids are the mature testicular sperm). The developmental process from spermatogonium to formation of testicular sperm is considered to require at least 64 days (33–35).

Reproduced from C. Marc Luetjens and Gerhard F. Weinbauer, The male gamete: spermatogenesis, maturation, function, in: *Oxford Textbook of Endocrinology and Diabetes* 2e (eds: John Wass et al.), Oxford University Press, 2011, with permission from Oxford University Press.

age. In the United Kingdom, the average age of menopause is 51. Menopause before the age of 40 years is considered abnormal and is referred to as primary ovarian insufficiency (premature ovarian failure).

The transition to menopause, or perimenopause, is characterized by irregular menstrual cycles (7) and hormonal fluctuations, and a variable frequency and severity of symptoms such as hot flashes, sleep disturbances (8), mood changes, and vaginal dryness. It begins on average 4 years before the final menstrual period (9).

Fertilization and implantation

Gametogenesis

The full maturation of spermatozoa takes approximately 64–70 days. FSH causes stimulation of spermatogenesis and LH is responsible for stimulation of Leydig cells and testosterone production.

A large number of spermatogonia are produced by mitosis after puberty and are converted to spermatocytes in the testis. Following the first meiotic division, spermatozoa are released into the seminiferous tubules and then into the vas deferens. The second meiotic division is then completed (Figure 1.6).

Follicular development is characterized by enlargement of the ovum with aggregation of stromal cells to form the thecal cells. When a dominant follicle is selected, the innermost layers of granulosa cells become adherent to the ovum and form the *corona radiata*. A layer of gelatinous material around the ovum forms the *zona pellucida*. The follicle enlarges and bulges through the surface of the ovary and is released at the time of ovulation. The granulosa and the theca internal cells undergo luteinization. Formation of the *corpus luteum* occurs approximately 7 days after ovulation. Unless implantation occurs, it subsequently regresses.

Sperm transport

Once sperms arrive near the cervical os, sperm migration into the cervical mucous occurs with a rate normally of 6 mm/min. Motile spermatozoa reach the uterine cavity and subsequently the fimbrial end of the fallopian tube.

Capacitation and fertilization

Capacitation is the functional maturation of the spermatozoon. It takes place once sperm passes through the epididymis and seminal vesicles. This process continues in the uterus or fallopian tube. Capacitation allows penetration of the zona pellucida by the sperm. Enzymes such as beta-amylase or beta-glucuronidase may act on the membranes of spermatozoa and facilitate sperm penetration. The capacitation process also involves modifications of membrane lipids, loss of cholesterol from plasma membrane, activation of the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway, increases in calcium (Ca^{2+}) uptake and pH, hyperpolarization of membrane potential, and tyrosine phosphorylation (10).

The process of *fertilization* involves the union of the ovum and spermatozoon. When a spermatozoon reaches the cumulus around the ovum, the acrosome reaction is initiated. The outer acrosomal membrane fuses with the plasma membrane surrounding the spermatozoon and lytic enzymes are released. This facilitates the penetration of the oocyte membrane. The sperm head fuses with the oocyte plasma membrane and by phagocytosis the sperm head and mid piece are engulfed into the oocyte. The tail piece is left outside the cell membrane of the oocyte.

The sperm head forms the male pronucleus and with the female pronucleus they form the zygote. After disintegration of the membranes of the pronuclei, fusion of the male and female chromosomes occurs. This is called *syngamy* and is followed by the first cleavage

division. After a series of divisions and at the 16-cell stage, a solid ball of cells called blastomeres forms within the zona pellucida. This is known as a *morula*. A fluid-filled cavity develops within the morula to form the blastocyst.

Implantation

Thirty-six hours after fertilization, the conceptus is transported through the fallopian tube and reaches the uterine cavity approximately 4 days later. The secretory endometrium is receptive to implantation. The second mitotic division of the oocyte is completed after fertilization and is followed by extrusion of the second polar body.

Six days after ovulation, the embryo becomes attached to the mid portion of the uterine cavity. By the seventh day, the blastocyst lies deep in the endometrium.

Physiology of coitus

The sexual response cycle described by Masters and Johnson has four phases in males and females. These phases are excitation, plateau, orgasmic, and resolution (Figure 1.7) (11, 12).

In the male, the excitation phase is associated with increased blood flow to the genitals and compression of venous channels of the penis resulting in erection. In the plateau phase, the penis remains in erection and the testes increase in size. Secretion of clear fluid may appear at the urethral meatus. In the orgasmic phase, reflex contractions of the bulbospongiosus (formerly bulbocavernosus) and ischiocavernosus muscles are followed by ejaculation of semen in spurts. During the resolution phase, penile erection subsides. During this phase, the male becomes refractory to further stimulation.

In the female, the excitation phase involves erection of the clitoris and swelling of the labia minora and vagina, vaginal lubrication, and nipple erection. The orgasmic phase is associated with narrowing of the vaginal introitus and contractions of the pelvic floor muscles. The plateau phase may be sustained in females and result in multiple orgasms. Following orgasm, congestion of the pelvic organs resolves rapidly.

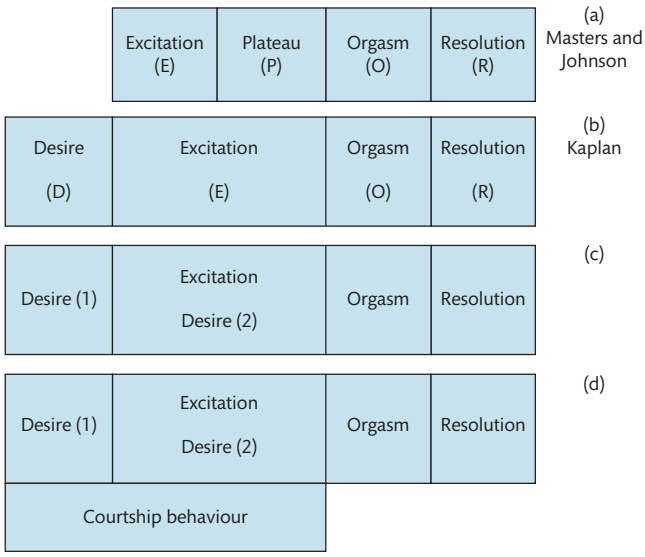

Figure 1.7 The development of the human sexual response model from (a) the original excitation, plateau, orgasmic, and resolution model of Masters and Johnson (11) through (b) the desire, excitation, orgasmic, and resolution model of Kaplan (12) to (c) the proposed modification with desire phase 1 (before initiation of the excitation phase and desire phase 2 during excitation phase) and finally (d) with added courtship behaviour.

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Embryology

Early embryo development

Cells differentiate into an outer layer, the *trophoblast*, and an *inner cell mass*, which will give rise to the *embryo proper*, the *amnion, yolk sac*, and *allantois*. Only two layers of cells intervene between the amniotic sac and yolk sac (Figure 1.8).

The layers of cells adjacent to the amniotic sac form the embryonic *ectoderm*. Ectodermal tissues of the fetus develop from these cells including skin, its appendages, neural tube, and its derivatives (brain, spinal cord, autonomic ganglia, and adrenal medulla). Cells adjacent to the yolk sac form the embryonic *endoderm*. Endodermal tissues include lining of the gut, epithelial cells of thyroid, parathyroid, trachea, lungs, liver, and pancreas. Between ectoderm and endoderm, a third layer of cells develops mainly from ectodermal proliferation. This middle layer forms the *mesoderm*. Mesodermal tissues are bones, muscles, cartilage, and subcutaneous tissues of the skin.

Organogenesis

Ectoderm, mesoderm, and endoderm initially take the form of a circular sandwich. Disproportionate growth of ectoderm results in elongation of the embryonic plate into an oval form. Each end of this plate curves, forming the head and tail folds. The amniotic sac enlarges and completely surrounds the developing embryo and the yolk sac. On the dorsal aspect of the ectoderm, a groove appears from the middle of the head to the tail and changes into the neural tube from which the nervous system develops.

Mesoderm starts to grow laterally and gives rise to the paraxial mesoderm, the intermediate cell mass, and the lateral plate mesoderm (Figure 1.9).

Endoderm grows first laterally and then ventrally to form the gut.

The lateral plate of the mesoderm divides into somatopleure, which remains adjacent to ectoderm, and the splanchnopleure, which grows around the developing gut. The space between the somatopleure and splanchnopleure form the coelomic cavity. This later becomes the pleural and peritoneal cavities.

The paraxial mesoderm develops into vertebrae, dura matter, and muscles of the body wall. The intermediate cell mass grows ventrally into the coelomic cavity and forms the urogenital system. See Figure 1.10.

Development of the genital organs

Genital and urinary systems arise from the intermediate mesoderm. The pronephros appears first and quickly disintegrates. At the caudal end of pronephros, the mesonephric duct (Wolffian duct) develops

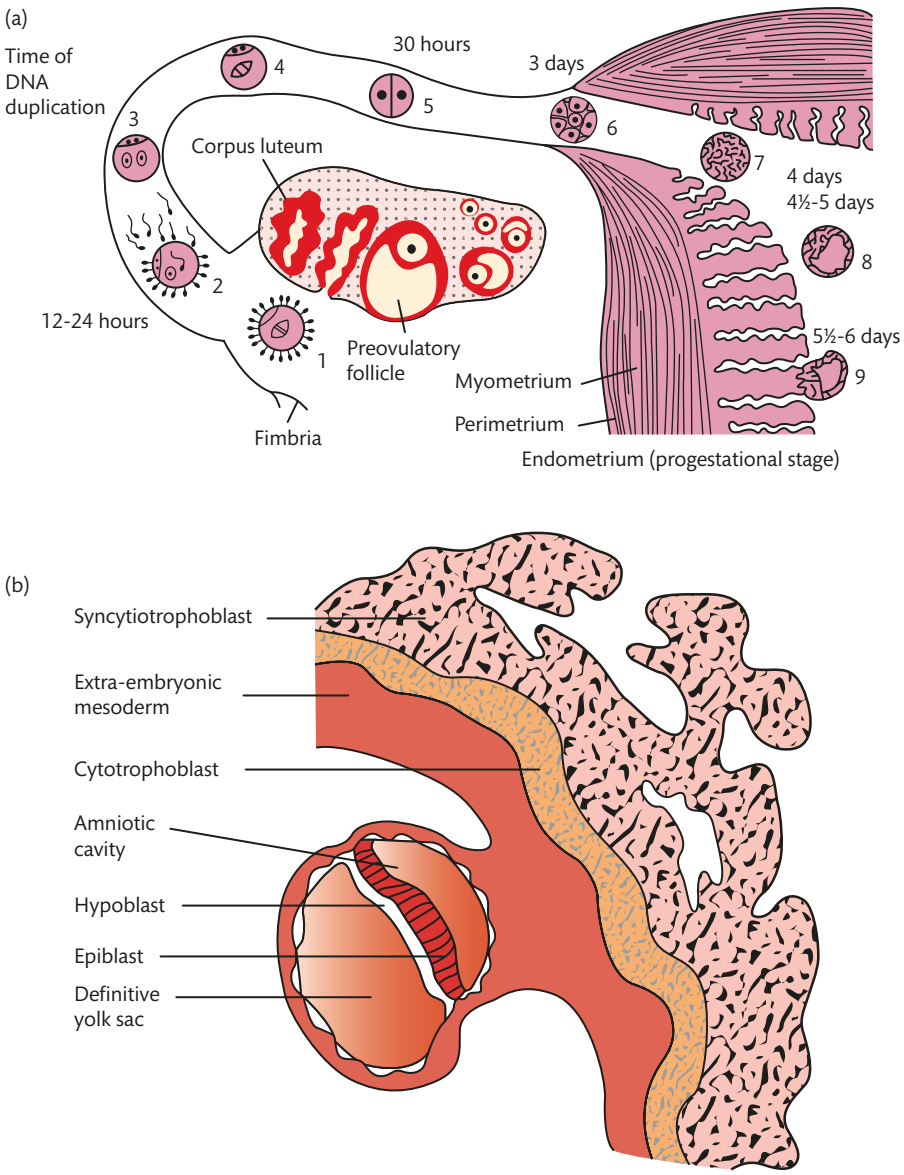

Figure 1.8 (a) Events of the first 6 days of development of a human embryo. 1: oocyte immediately after ovulation; 2: fertilization 12–24 h later results in the zygote; 3: zygote contains male and female pronuclei; 4: first mitotic division; 5: two-cell stage; 6: 3-day morula made up of up to 16 blastomeres; 7: morula stage (16–32 blastomeres) reaches the uterine lining; 8: early blastocyst; 9: implantation occurs at around day 6. (b) The site of implantation at the end of the second week.

and passes down the body to reach the cloaca. The mesonephros develops as a bulge in the dorsal wall of the coelom in the thoracic and lumbar regions. Two important structures appear on the coelomic surface of the mesonephros: (a) the genital ridge from which the gonad will form and (b) the paramesonephric (Mullerian) duct. The paramesonephric duct appears as a groove on the lateral aspect of the coelom and then becomes a tube. See **Figures 1.11–1.14**.

Placental development

Following implantation, the trophoblast completely surrounds the embryo in the form of proliferating cytotrophoblast and a syncytial layer. During the first trimester, a subset of trophoblast cells, the extravillous trophoblast (EVT) cells, become invasive and grow through the outer syncytium into the decidua where they invade maternal spiral arterioles. The trophoblast shell begins to break open, allowing maternal blood to enter the primitive intervillous space where it is utilized by the developing villous placenta and fetus. See **Figure 1.15**.

Development of membranes and amniotic fluid

The embryonic disc lies between the amniotic cavity and the primary yolk sac. The amniotic cavity develops between the embryonic ectoderm and cytotrophoblast. By the 12th postovulatory day, the base of this cavity is formed by embryonic ectoderm and the walls and roof are formed by the cytotrophoblast. Amniotic fluid is initially formed from the primitive cells around the amniotic vesicle.

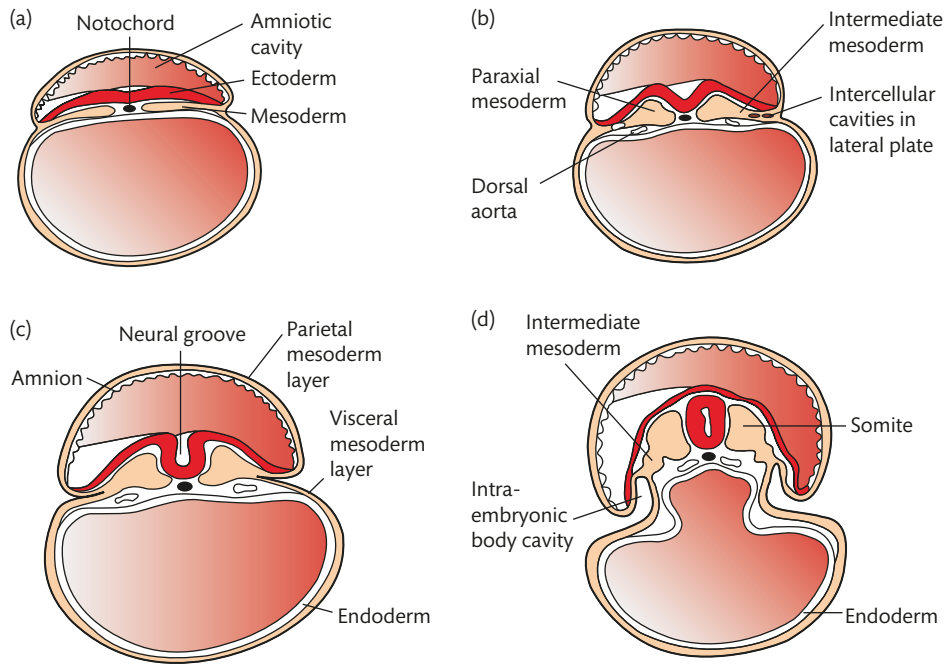

Figure 1.9 Transverse sections showing development of the mesodermal germ layer at days 17 (a), 19 (b), 20 (c), and 21 (d). The thin mesodermal sheet gives rise to paraxial mesoderm (future somites), intermediate mesoderm (future excretory units), and lateral plate, which is split into parietal and visceral mesoderm layers lining the intraembryonic cavity.

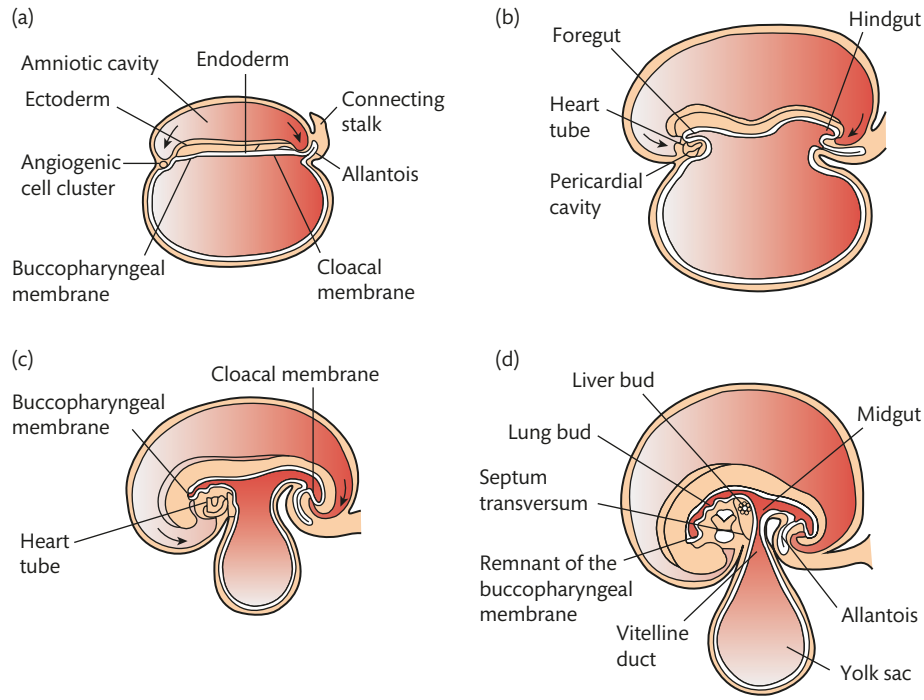

Figure 1.10 Sagittal midline sections of embryos at various stages of development demonstrating cephalocaudal folding and its effect on position of the endoderm-lined cavity. Presomite embryo (a), seven-somite embryo (b), 14-somite embryo (c), and 1-month embryo (d). Note the position of the angiogenic cell clusters in relation to the buccopharyngeal membrane.

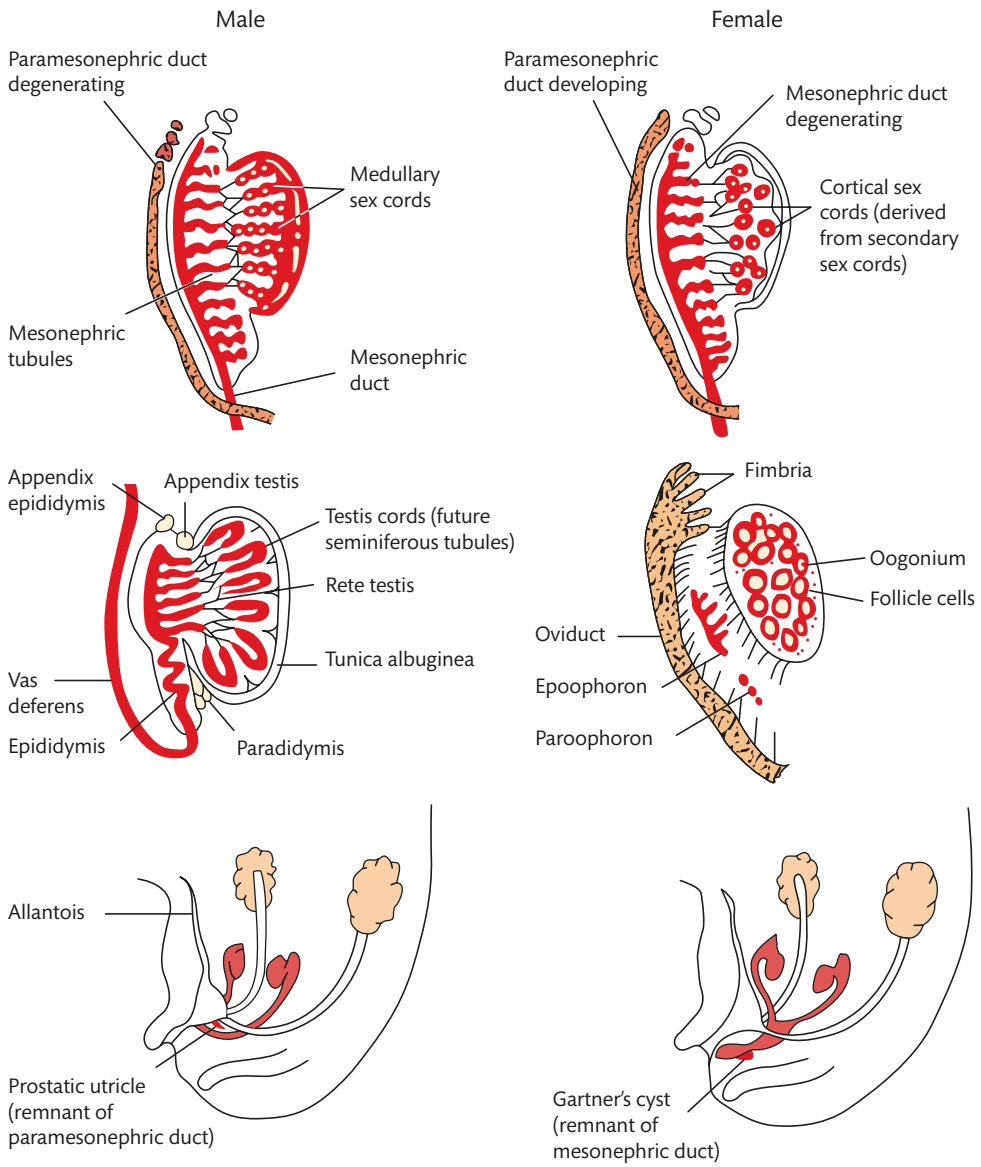

Figure 1.11 Male and female gonadal development. The male and female genital systems are virtually identical through the seventh week. In the male, SRY protein produced by the pre-Sertoli cells causes the medullary sex cords to develop into presumptive seminiferous tubules and rete testis tubules and causes the cortical sex cords to regress. Anti-Müllerian hormone produced by the Sertoli cells then causes the paramesonephric ducts to regress and Leydig cells also develop, which in turn produce testosterone, the hormone that stimulates development of the male genital duct system, including the vas deferens and the presumptive efferent ductules.

Later on, fetal extracellular fluid (ECF) is passed through the fetal skin and umbilical cord.

Pathology

Response to tissue injury

Tissue injury is associated with reversible and irreversible changes of the cell membrane. Potassium is transferred out of the cell and sodium is transferred in accompanied by water. This leads to cellular oedema and a reduction in protein synthesis. There is a switch to anaerobic metabolism. Glycogen is used for energy resulting in lactate production and a drop in pH.

Intracellular enzymes including lactate dehydrogenase, troponins, and creatinine phosphokinase become activated in association with mitochondrial damage. Lysosomal rupture results in release of lysosomal enzymes and autolysis followed by nuclear death.

Tissue growth and differentiation

Growth and differentiation aim to maintain the normal structure of a particular tissue. In tissues with continuous cell loss (blood, skin, mucosa), lost cells are continuously replaced. Stem cells frequently differentiate into a mature form during this process. In the skin, as superficial keratinized cells are shed, basal cells proliferate to replace them. The newly produced basal cells differentiate into squamous cells. When the cell turnover rate is normal,

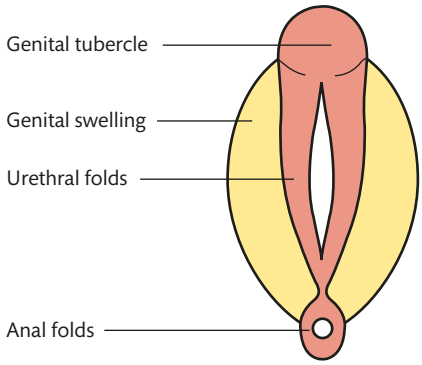

Figure 1.12 Indifferent stages of the external genitalia, approximately 6 weeks.

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the skin appears histologically normal but if the rate is greatly increased, cells do not fully mature, and abnormalities are seen both on physical examination and histologically. The rate of cell proliferation is determined by the cell cycle and controlled by a variety of growth factors and receptors, and regulated by growth control genes. Many of the cellular proto-oncogenes encode for growth factors for receptors.

Placental pathology

The placental involvement in the pathogenesis of pre-eclampsia and particularly the link between pre-eclampsia and reduced placental perfusion has long been recognized (13).

The main defect seems to be related to endovascular trophoblast invasion. In pre-eclampsia, myometrial arteries fail to adapt to physiological change. Trophoblast invasion is impaired. Acute atherosis is common. Blood flow into the intervillous space is therefore decreased in pre-eclampsia.

Fetal growth restriction is associated with reduced uteroplacental blood flow, which in turn can be secondary to defective placentation. Morphological abnormalities of the uterine arteries can be present in cases of fetal growth restriction.

Microbiology

Bacteriology

Bacteria are single-cell prokaryotic microorganisms. They have a single chromosome that is not enclosed in a nuclear membrane. They can have four shapes: cocci (spheres), bacilli (rods), spirilla (spirals), and vibrios (comma-shaped). Genetic information is encoded in the cell DNA. There are two types: chromosomal DNA and extrachromosomal DNA.

Bacterial metabolism is a balance between anabolic and catabolic functions. Their ability to utilize carbohydrates and convert them to glucose as well as oxygen requirement is used to characterize bacteria:

- Obligate anaerobes: oxygen is toxic.
- Aerotolerant anaerobes: anaerobic metabolism, but tolerant to the presence of oxygen.
- Facultative anaerobes: can grow in both anaerobic as well as aerobic conditions.
- Obligate aerobes: require oxygen to grow.
- Microaerophilic organisms: require low oxygen levels only; high levels may be inhibitory.

Bacteria can be Gram positive or Gram negative (**Figure 1.16**). Some bacteria can suspend growth and metabolism in adverse conditions and form resistant spores. Optimum temperature range is between 20°C and 40°C.

Bacteria have four phases of growth:

1. Initial lag phase
2. Exponential growth phase
3. Static phase
4. Death phase.

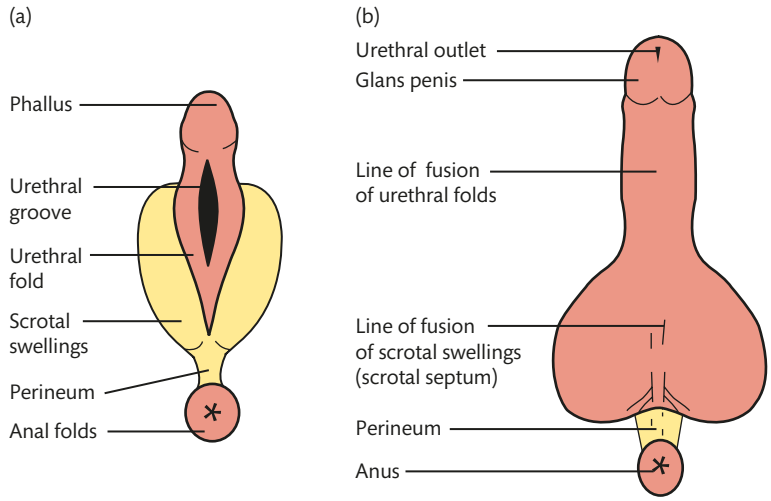

Figure 1.13 Development of the external genitalia in the male at (a) 10 weeks and (b) in the newborn. Genital tubercle extends rapidly to form the phallus, later the penis. Urethral folds close the urogenital sinus and genital swellings become scrotal swellings.

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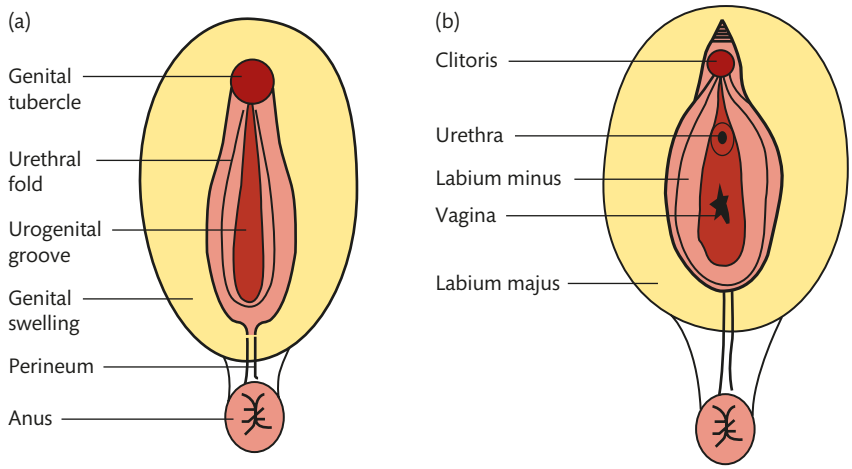

Figure 1.14 Development of the external genitalia in the female at (a) 5 months and (b) in the newborn. Genital tubercle elongates slightly, forming the clitoris. Urethral folds become labia minora and the urogenital sinus remains open. Genital swellings form the major labia.

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Diagnosis of bacterial infection: bacteria are visible under direct microscopy. On a culture they are grown on solid agar or in liquid media and form visible colonies.

Control of infection

Antibiotics, also known as antibacterials, are used in the treatment and prevention of bacterial infections. They act by killing bacteria or inhibiting their growth. Different types of antibiotics have differences in chemical structure, mode of action, or spectrum of effect. Broad-spectrum antibiotics target a wide range of bacteria whereas narrow-spectrum ones target specific types. Antibiotics with bactericidal activities act on the bacterial cell wall (beta-lactam antibiotics: penicillins and cephalosporins as well as vancomycin and teicoplanin) or the cell membrane (polymyxins). Other bactericidal antibiotics target essential bacterial enzymes (rifamycins, lipiarmycin, quinolones, and sulphonamides). Bacteriostatic antibiotics inhibit protein synthesis (macrolides, lincosamides, and tetracyclines).

Sterilization is a process of eradication of microorganisms including the spores.

Disinfection is the removal of all actively dividing organisms. Components of disinfection include cleaning, heat, and chemicals.

Virology

A virus contains a nucleic acid (DNA or RNA) and is surrounded by a protein coat. There is no cytoplasm. Viruses must enter the host cell by endocytosis for their own replication. The virus first adheres to the host cell by binding to a specific receptor molecule.

A viral infection (Table 1.1) (14, p. 152) can cause cell death but can also cause a latent infection remaining in the host cell for many years in a dormant state.

Parasitology

Parasites are unicellular eukaryotic organisms. They can reproduce by simple asexual binary fission or a complex sexual cycle. The protozoa are larger than bacteria.

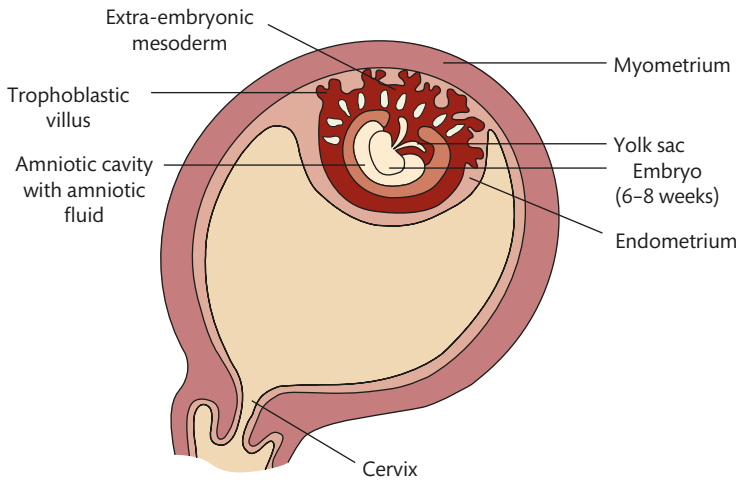

Figure 1.15 The placenta in relation to adjacent structures during early pregnancy.

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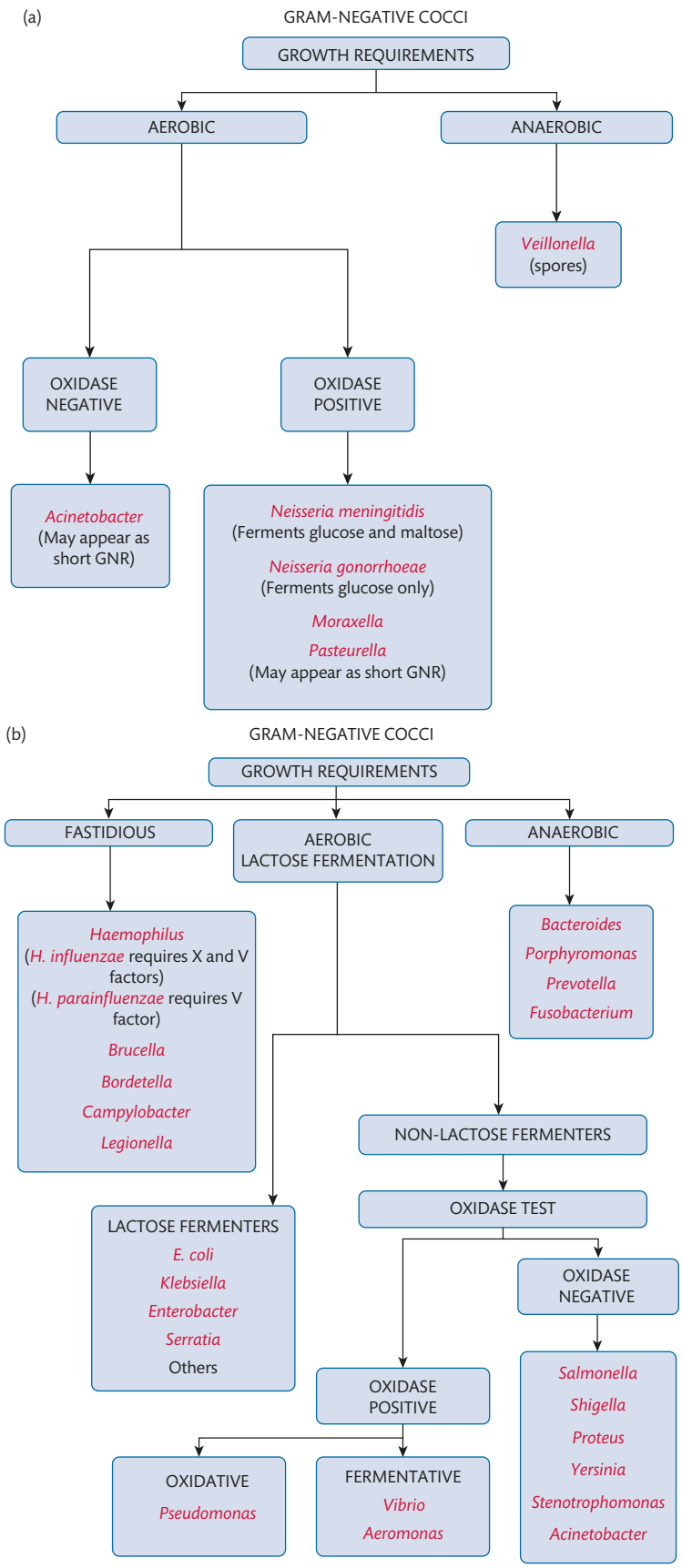

Figure 1.16 (a) Identification of Gram-negative cocci. (b) Identification of Gram-negative rods. (c) Identification of Gram-positive cocci. (d) Identification of Gram-positive rods. GNR, Gram-negative rods.

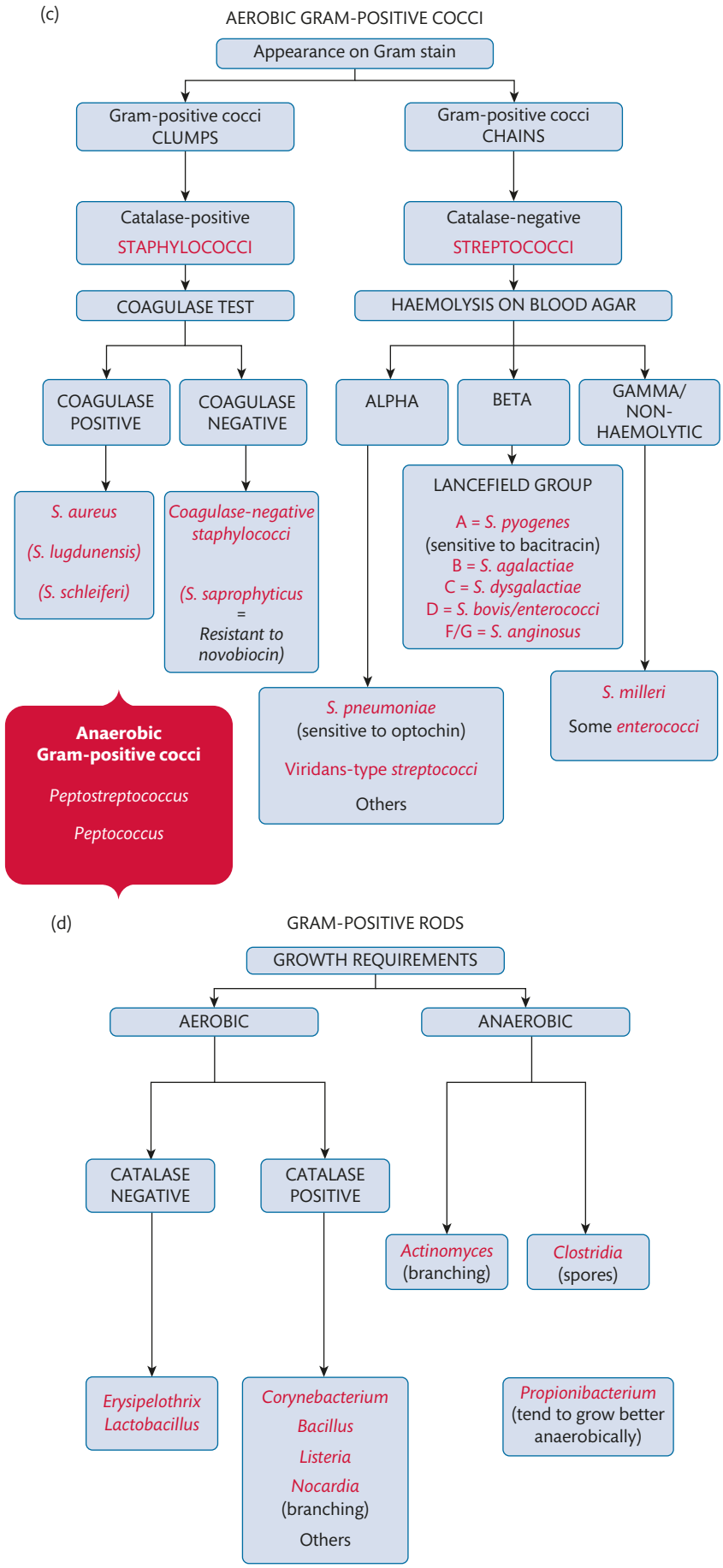
(c)
AEROBIC GRAM-POSITIVE COCCI
Appearance on Gram stain
Gram-positive cocci CLUMPS
Gram-positive cocci CHAINS
Catalase-positive STAPHYLOCOCCI
Catalase-negative STREPTOCOCCI
COAGULASE TEST
HAEMOLYSIS ON BLOOD AGAR
COAGULASE POSITIVE
COAGULASE NEGATIVE
ALPHA
BETA
GAMMA/ NON-HAEMOLYTIC
S. aureus
(S. lugdunensis)
(S. schleiferi)
Coagulase-negative staphylococci
(S. saprophyticus = Resistant to novobiocin)
LANCEFIELD GROUP
A = S. pyogenes
(sensitive to bacitracin)
B = S. agalactiae
C = S. dysgalactiae
D = S. bovis/enterococci
F/G = S. anginosus
S. milleri
Some enterococci
S. pneumoniae
(sensitive to optochin)
Viridans-type streptococci
Others
Anaerobic Gram-positive cocci
Peptostreptococcus
Peptococcus
(d)
GRAM-POSITIVE RODS
GROWTH REQUIREMENTS
AEROBIC
ANAEROBIC
CATALASE NEGATIVE
CATALASE POSITIVE
Actinomyces (branching)
Clostridia (spores)
Erysipelothrix
Lactobacillus
Corynebacterium
Bacillus
Listeria
Nocardia
(branching)
Others
Propionibacterium
(tend to grow better anaerobically)

Table 1.1 Diagnosis of viral infection

Technique	Advantages	Disadvantages
Electron microscopy	Can see if any virus present	Expensive, time-consuming, requirement for complex equipment
Tissue culture	Virus cultures can be made available for further analysis	Slow, expensive
Enzyme immunoassay	Quick, automated, immunoglobulin M assays can diagnose recent infection	Not appropriate for all viruses
Fluorescence microscopy	Mainly for respiratory infections	Expensive
Polymerase chain reaction	Quick, highly sensitive, can be automated	Expensive DNA extraction can be difficult

Intestinal protozoa are common in environments with poor hygiene. *Entamoeba histolytica* is an intestinal amoeba and causes amoebic dysentery. It spreads via the portal veins and may cause amoebic liver abscess. *Giardia lamblia* is a binucleate flagellate protozoan. It causes chronic diarrhoea. *Cryptosporidium parvum* spreads via contaminated drinking water.

Malaria is caused by four types of *Plasmodium: P. falciparum, P. vivax, P. ovale*, and *P. malariae*. The infection is spread by the bite of female *Anopheles* mosquitos and usually occurs in tropical and subtropical areas.

Trypanosoma is spread by the bite of an infected tsetse fly and is prevalent in tropical Africa. It can enter red cells, the nervous system, and the reticuloendothelial system and can also affect the myocardium. Clinical symptoms and signs include fever, drowsiness, coma, and hepatosplenomegaly.

Toxoplasma gondii is the cause of toxoplasmosis. The definitive host of the trophozoites is the cat. Reproduction takes place in its gastrointestinal tract. Humans can become infected either by handling soil contaminated by cat faeces or ingesting infected undercooked meat.

Trichomonas vaginalis is a protozoan that can cause vaginal and urethral infections. It is transmitted sexually and can cause vulvovaginal irritation with a yellow or green, frothy, 'fishy'-smelling discharge.

Mycology

Fungi are eukaryotic organisms, commonly multicellular. The optimal growth temperature for the majority of fungi is between 25°C and 35°C. They are predominantly aerobic but many yeasts can produce alcohol by fermentation as an end product of anaerobic metabolism. They mainly reproduce by the production of asexual spores.

The main groups of pathogenic fungi are the following:

- Moulds: these form powdery colonies on culture due to the presence of abundant spores. Dermatophytes responsible for skin, hair, and nail infections belong to this group.
- True yeasts: unicellular, round or oval fungi. Reproduction is by budding from the parent cell. They appear as characteristically creamy colonies. A major pathogen in this group is *Cryptococcus neoformans*.
- Yeast-like fungi: these appear as round or oval cells and reproduce by budding. The major pathogen in this group is *Candida*, which causes vaginal candidiasis.
- Dimorphic fungi: *Histoplasma capsulatum* is a common member of this group. Infection is usually asymptomatic but may cause lung calcifications.

Immunology

Adaptive immunity

There are four fundamental features of adaptive immunity:

1. Memory
2. Specificity
3. Diversity
4. Tolerance to self.

Memory: the first contact with an infectious agent imparts the memory and then subsequent infection is repelled (i.e. chickenpox). The primary response against a specific antigen occurs on first contact, is slower, and is less vigorous. Future responses are rapid and more efficient.

Specificity: the adaptive immune system is specific to particular pathogens. Contact with one pathogen does not provide protection against other pathogens.

Diversity: this feature adds to the ability to combat different infections. Diversity is partly genetically encoded, but is also the result of recombination between gene segments (15) (**Figure 1.17**).

Tolerance: tolerance to self-antigens is established in early life. Circulating components, which reach the developing lymphoid system in the perinatal period, induce a permanent self-tolerance.

Cellular elements of adaptive immunity

T cells: these are lymphocytes derived from bone marrow stem cells which develop and differentiate in the thymus before travelling down to peripheral lymphoid tissue. There are three main types of T cells: T-helper, suppressor, and cytotoxic cells.

B cells: these are responsible for antibody production. B cells originate from stem cells in the bone marrow and develop and differentiate there.

Null cells: these lymphocytes express neither T- nor B-cell surface markers. However, they do express a mixture of lymphocyte and macrophage surface markers. They bind via the Fc receptor and kill the target cells. Hence, they are also called killer cells.

Antigen-presenting cells (APCs): antigen presentation is the process by which cells express molecules recognizable by T cells. These APCs take up antigen and process and modify it into an immunogenic form before presenting it along with major histocompatibility complex molecules to T cells.

Immunoglobulins, complement, and cytokines are the three principal humoral elements of adaptive immunity.

Innate immunity

Cellular elements of innate immunity are phagocytes and natural killer (NK) cells. The soluble elements are complement, acute phase proteins, and interferon.