

Index

- AAA (arterioarterial anastomoses), 345
 AAV (adeno-associated virus), 540
 abdominal tumors, 486–487
 hepatic tumors, 486–487
 antenatal natural history, 486
 clinical presentation, 486
 hemangiomas, 486
 hepatoblastomas, 486
 mesenchymal hamartoma, 486
 postnatal management, 487
 prenatal management, 486–487
 abortion
 prenatal termination, 172–173
 spontaneous, 228
 acardiac twinning, 402
 acidosis. *See* prolonged fetal acidosis
 ACOG (American College of Obstetricians and Gynecologists), 91
 ACS. *See* antenatal corticosteroids
 acyclovir, 229
 ADCC (antibody-dependent cell-mediated cytotoxicity) assays, 92
 adeno-associated virus (AAV), 540
 adenosine, 184
 adult diseases, fetal origins of
 in animal studies, 9–12
 CVD and, 9
 DOHaD concept through, 9
 cancers, 8
 CHD, 8–9
 prevalence of, 8
 chronic lung disease, 8
 CVD, 8–9
 in animal studies, 9
 prevalence of, 8
 DOHaD concept for, 8–9
 in animal and human studies, 9
 environmental factors, fetal responses to, 10–15
 adaptive responses, 10–11, 14–15
 disruptive responses, 10
 epigenetic modifications, 15
 maternal adaptations to pregnancy, 14
 measurement techniques for, 10–12
 placental development, 14–15
 fetal development
 functions of, 8–9
 growth markers in, 8–9, 14
 timing of birth, 14
 under-nutrition and, 13
 in human studies, 9
 cardiovascular control in, 12–13
 DOHaD concept through, 9
 interventions for, 15–16
 pathophysiological conditions of, 8
 type 2 diabetes, 8
 AF. *See* amniotic fluid
 Alagilles syndrome, 33
 alcohol use
 fetal growth optimisation and, 288–289
 fetal growth restriction and, 266–267
 alloantibodies. *See* red cell alloantibodies
 $\alpha\beta$ T lymphocytes, 217
 American College of Obstetricians and Gynecologists (ACOG), 91
 amiodarone, 171, 184
 amniocentesis, 583
 amnioinfusion, 210
 for oligohydramnios, 210–211
 meconium aspiration syndrome, 211
 amniopatch procedure, 209, 522
 amnioreduction, 203–204
 for monochorionic twins, 373–375
 preparation for, 203–204
 techniques for, 203–204
 for TTTS, 353
 amniotic fluid (AF). *See also* oligohydramnios; polyhydramnios
 circulation of, 194, 196
 composition of, 191–192
 definition, 191
 fetal water components, 191
 fluid inflows, 194
 clinical scenarios, 193
 lung fluid production, 194
 from oral-nasal secretions, 194
 urine production, 194
 fluid outflows, 195–196
 clinical scenarios, 193
 from fetal swallowing, 195
 intramembraneous flow, 195–196
 formation of, 192–194
 membrane water flux, 192
 placental water flux, 192–194
 inhibition of prostaglandin synthesis, 204–214
 volume of, 191–192
 regulation mechanisms, 196
 amniotic fluid stem cells, 533
 amniotic membrane, 520–522
 in animal models, 521
 healing mechanisms in, 520–521
 in tissue explants, 521–522
 in women, 521–522
 anastomoses, 345
 aneuploidy. *See* chromosomal aneuploidy; non-aneuploidy copy number variants
 angiogenic placental growth factors, 346–347
 animal models
 amniotic membrane in, 521
 for artificial wombs, 83–87
 failures with, 84
 for congenital heart disease, 133–134, 158–161
 cystic fibrosis in, 543–544
 Deciphering the Mechanisms of Developmental Disorders programme, 136–144. *See also* cardiac defects
 bicuspid aortic valve defects, 141–144
 outflow defects, 139–143
 septal defects, 136–140
 for embryology development process, 20–21
 for in-utero spina bifida repair with fetoscopy, 476
 muscular dystrophy in, 545
 NTDs, 450
 for open fetal repair surgery, 456–457
 for preterm birth, 302–303
 animal studies, for adult diseases, fetal origins of, 9–12
 CVD and, 9
 DOHaD concept through, 9
 antenatal corticosteroids (ACS), 329–330
 for fetal and neonatal alloimmune thrombocytopenia, 104–105
 for preterm birth
 multiple pregnancies, 329–330
 neonatal outcomes and, 320–321
 perinatal brain injury, 337–338
 antibiotic therapies, for preterm birth, 318–319
 antibodies
 in fetal immune systems, 216
 in red cell alloimmunization, 91
 clinically relevant, 91
 fetomaternal hemorrhage, 91
 red cell alloantibodies, 91
 antibody-dependent cell-mediated cytotoxicity (ADCC) assays, 92

Index

- anticipated emotions, 63
 antigen presenting cells (APCs), 215, 217
 anti-platelet agents, 289
 aortic stenosis, critical, 149–150
 aortic valvuloplasty, 147, 150
 hemodynamic improvements, 148–152
 Linz criteria for, 150
 APCs. *See* antigen presenting cells
 APCs (antigen presenting cells), 215, 217
 Arnold-Chiari II malformation, 456
 array comparative genomic hybridization (CGH), 129–130
 ART. *See* artificial reproductive technology
 arterioarterial anastomoses (AAA), 345
 arteriovenous anastomoses (AVA), 345
 artificial reproductive technology (ART). *See also* in vitro fertilization; multiple pregnancies
 fetal growth restriction and, 267
 artificial womb
 animal models, 83–87
 failures with, 84
 development of, 83
 ECMO technology, 83–87
 EVE model, 87
 future applications of, 87
 prematurity and, 83
 co-morbidity risks, 83
 pumpless technology in, 84–87
 advantages of, 87
 cerebral autoregulation with, 87
 EXTEND, 85–86
 pump-supported technology in, 84–85
 ASD (atrial septal defect), 117
 aspirin therapy
 fetal growth and, 289–290
 for stillbirths, 52
 atrial ectopic, 178–180
 atrial ectopic tachycardia, 167–168
 atrial flutter, 167–168, 171–173, 181–183
 management of, 182–184
 close monitoring in, 182
 with pharmacological therapy, 182–184
 atrial isomerism, 114
 atrial septal defect (ASD), 117
 atrial situs inversus, 113–114
 atrioventricular septal defect (AVSD), 117
 atrioventricular valve abnormalities, 119
 Australia, IMPACT network in, 564
 auto-immune AV block, 186–187
 management of, 187. *See also specific treatment therapies*
 AV block related to congenital heart disease, 186
 AVA (arteriovenous anastomoses), 345
 AVSD (atrioventricular septal defect), 117
 azithromycin, 238
 B lymphocytes, 216–218
 Ballantyne syndrome, 225
 Bare Lymphocyte syndrome, 513
 Barker, David, 280
 BCC (bipolar cord coagulation), 395–396
 Beckwith-Wiedemann syndrome, 486
 bedrest
 for multiple pregnancies, 325–327
 for preterm birth prevention, 319
 beta-agonists, 187
 bicuspid aortic valve defects, 141–144
 binary decision regulation, 33
 bioreactor systems, 528–529
 bipolar cord coagulation (BCC), 395–396, 420, 422–423
 birth. *See* timing of birth
 birth defects, notch
 signaling and, 33. *See also specific birth defects*
 bladder exstrophy, 536
 blindness, from preterm birth, 334
 blocked atrial bigeminy
 tachycardias, 185–186
 management of, 185–186
 Bohring-Opitz syndrome, 44
 bone grafting, 536
 Boost Brittle Bones Before Birth (BOOSTB4) project, 73
 BPS. *See* bronchopulmonary sequestrations
 bradycardias, 185
 definition of, 185
 fetal, 475–476
 management of, 185
 with 1:1 AV conduction, 185
 brain injury. *See* perinatal brain injury
 Brazil, in-utero spina bifida repair in, 469–470
 Breus' mole, 254–257
 British Isles Network of Congenital Anomaly Registers, 572–573
 bronchopulmonary
 sequestrations (BPS), 442–443, 483–484
 antenatal natural history, 483
 clinical presentation, 483–484
 fetal hydrops and, 483
 postnatal management, 483–484
 prenatal management, 483
 tension hydrothorax and, 483
 Brown, Louise, 404
 Bruner, Joseph, 467
 Canada, Global Obstetrics Network in, 563
 cancers. *See also specific cancers*
 fetal origins of, 8
 canonical Wnt signaling pathway, 27–28
 carbon dioxide (CO₂) safety, in in-utero spina bifida repair, 474–476
 carbonic anhydrase and, lack of, 475
 fetal bradycardia, 475–476
 fetal membrane exposure, 476–477
 hypercapnia-metabolic acidosis, 475
 prolonged fetal acidosis, 475–476
 carbonic anhydrase, 475
 cardiac conduction system (CCS), 119–120
 cardiac defects, Deciphering the Mechanisms of Developmental Disorders programme, 134–139
 classification of, by type, 135–139
 penetrance of, 134–135, 137
 by phenotype, 134, 136
 prevalence of, 134–135, 137
 cardiac development and formation, 110–112. *See also* cardiac morphogenesis; *specific diseases*
 cardiac neural crest cells, 111–112
 cardiac progenitor cells, 112
 cell lineage in, 113
 congenital heart disease and, 110, 116
 epicardium derived cells, 112
 first heart field, 110–111
 hypoplastic left heart syndrome, 118
 posterior second heart field, 117
 atrial septal defect, 117
 atrioventricular septal defect, 117
 second heart field, 110–111
 with TTTS, 347–349
 assessment methods, 347
 endothelins, 348–349
 natriuretic peptides, 348–349
 valve anomalies, 118–119
 atrioventricular abnormalities, 119
 semilunar abnormalities, 118–119
 ventricular septal defect, 117–118
 cardiac morphogenesis, 112–117. *See also* cardiac defects; *specific diseases*
 heart malformations with looping disturbances, 113–114
 atrial isomerism, 114
 atrial situs inversus, 113–114
 laterality defects, 113–114
 situs defects, 113–114
 looping defects, 114
 congenitally corrected transposition of the great arteries, 114
 with parvovirus B19 during pregnancy, 225
 septation anomalies, 114–117
 common arterial trunk, 114–115
 double inlet left ventricle, 116
 double outlet right ventricle, 115–116
 tetralogy of Fallot, 115
 transposition of the great arteries, 116–117
 structural heart disease, 112
 ventricular inversion, 114
 cardiac neural crest cells (NCC), 111–112
 cardiac pacing, 151
 cardiac rhythm assessment, 176–178
 with echocardiographic techniques, 176–188
 cardiac tumors, 482–483
 rhabdomyomas, 482–483
 cardiovascular control, 12–13
 cardiovascular disease (CVD), fetal origins of, 8–9
 in animal studies, 9
 prevalence of, 8
 care settings, 4
 CAT (common arterial trunk), 114–115
 CCAMs (congenital cystic adenomatoid malformations), 442
 cCMV (congenital cytomegalovirus), 231
 CCS (cardiac conduction system), 119–120

Index

- CCTGA (congenitally corrected transposition of the great arteries), 114
- CDH (congenital diaphragmatic hernia), 3, 77, 535–536
- cell interactions, 22–25
dominant, 23
morphogen gradients, 23–25
signaling, 23
Sonic hedgehog morphogen, 24–27
- central nervous system diseases, gene therapy for, 544
- cerebral palsy, from preterm births, 334
- cerebrospinal fluid (CSF) leakage, 456–457
- cervical cerclage, for preterm birth, 327–329
abdominal approach, 316–317
for asymptomatic women with a short cervix, 316
cervical approach, 316–317
prophylactic cerclage, 328
rationale for, 316
for symptomatic women, 316
ultrasound-indicated cerclage, 328
- cervical competence, 307
- cervical pessary, for preterm birth, 328–329
random clinical trials for, 317
rationale for, 317
with short cervix, 329
for unselected twins, 328–329
- cervical ripening, 304–305
- cervical shortening, 317
- cervical teratomas, 78–79, 480–482
antenatal natural history, 480
clinical presentation, 480–489
EXIT procedure, 482
imaging of, 480–489
long-term outcomes, 482
postnatal management, 482
prenatal management of, 481–482
- cervix length
cervical cerclage and, 316
cervical shortening, 317
multiple pregnancies and, 327, 329
progesterone therapy, 315–316
- CGH (array comparative genomic hybridization), 129–130
- CHAOS (congenital high airway obstruction syndrome), 79, 445–446, 536
- CHARGE syndrome, 157
- CHD. *See* coronary heart disease
- Chervenak, Frank, 71
- chest tumors, 483–484
- BPS, 442–443, 483–484
antenatal natural history, 483
clinical presentation, 483–484
fetal hydrops and, 483
postnatal management, 483–484
prenatal management, 483
tension hydrothorax and, 483
- CPAM, 485–486
antenatal natural history, 485
clinical presentation, 485
fetal hydrops and, 485
postnatal management, 485–486
prenatal management, 485
types of, 485
- chickenpox, during pregnancy, 226–231
clinical presentation, 226
epidemiology of, 226
fetal consequences, 228
congenital varicella syndrome, 228–230
intrauterine fetal death, 228
premature birth, 228
spontaneous abortion, 228
management of, 228–231
contagion during pregnancy, 228–229
maternal diagnosis of, 226–228
with clinical maternal presentation, 226–228
through laboratory confirmation, 228
neonatal consequences, 228
shingles, 228
varicella, 228
prenatal diagnosis, 229
rash from, development of, 229–231
fetal management, 229–230
maternal treatment, 229
during perinatal period, 230–231
- Children's Hospital of Philadelphia (CHOP), 459–460
open fetal surgery at, 459–460
- CHIV (chronic histiocytic inter-villositis), 257
choline deficiency, 452
- CHOP. *See* Children's Hospital of Philadelphia
- chorion regression syndrome, 256
- chorionic membrane, 520
- chorionicity, 325
- chromosomal aneuploidy, 126
- chromosomal microarray analysis (CMA), 38–42
advantages of, 42–43
CNVs and, 39–40
conventional karyotyping, 38–39
G-banding, 38
disadvantages of, 42–43
expanded use of, 39–43
FISH, 38–39
history of, 38
methodology of, 40
profile depicting deletion, 40
QF-PCR, 38–40
SNP microarray, 40
VOUS rate in, 43
VUS detection, 40–42
Diagnostic yield in, 43
- chromosome karyotyping, 129
- chronic histiocytic inter-villositis (CHIV), 257
- chronic hypoxia, 159–160
- chronic lung disease. *See* lung disease
- CID (cytomegalic inclusion disease), 232
- clarithromycin, 238
- clindamycin, 238
- CMA. *See* chromosomal microarray analysis
- CMV. *See* cytomegalovirus
- CNVs (copy number variants), 39–40
non-aneuploidy, 126
- CO² safety. *See* carbon dioxide safety
- collagen
in fetal membrane repair, 524–525
in tissue engineering, 534
- common arterial trunk (CAT), 114–115
- congenital anomaly registers, 570–577
aetiological research through, 577
conflicts of interest in, 578
data usage with, 573–577
prenatal screening test evaluation, 575–577
for rare diseases, 575
surveillance through, 574–578
in England and Wales, 572–573
British Isles Network of Congenital Anomaly Registers, 572–573
National Congenital Anomaly and Rare Diseases Registration Service, 573–574
National Congenital Anomaly System, 572
- EUROCAT, 570–572
geographical coverage of, 571
long-term outcomes through, 577
- congenital bladder neck obstruction, 426–430
aetiology, 426–427
clinical approach to, 433–435
epidemiology, 426–427
pathophysiology, 427
prenatal management, 427–430
clinical scoring system, 428
clinical staging systems in, 429–431
diagnosis in, 427–429
fetal urinalysis in, 429–430
parental counseling in, 430
staging systems in, 429–431
ultrasonographic prognosis, 427, 429
- congenital cystic adenomatoid malformations (CCAMs), 442
- congenital cytomegalovirus (cCMV), 231
- congenital diaphragmatic hernia (CDH), 3, 77
antenatal assessment, 495–499
associated structural anomalies, 495
genetic testing, 495–496
imaging in, 496–499
stomach position, 499
fetal membranes and, 520
gene therapy for, 543–544
GERD, 494
muscular-skeletal complications, 495
natural course of, 494–495
neurobehavioral outcomes, 494–495
persistent pulmonary hypertension, 494
prevalence rates for, 494
survival rates for, 494
tissue engineering for, 535–536
ultrasound for, 496–498
liver position on, 496–498
for lung size, 496–497
- congenital heart defects, 148–149
interatrial septum restrictions, 148–149
semilunar valve stenosis, 148–151
- congenital heart disease (CHD). *See also* Deciphering the Mechanisms of Developmental Disorders programme
animal models, 133–134, 158–161
AV block related to congenital heart disease, 186

Index

- birth incidence of, 123
causes of, 123–124
cerebral consequences of
 brain development studies,
 160–161
 etiology of, 157
 imaging of, 159–160
 incidence rates of, 157
 neuroprotective
 interventions, 161–162
 risk factors, 157–158
 white matter involvement,
 158
CHARGE syndrome, 157
clinical presentation of, 133
Down's syndrome, 157
elastin localization in, 126
embryology and, 110, 116
etiology of, 123
 environmental factors in,
 123
gene identification methods,
 127–128
 positional cloning, 127–128
 species comparisons
 through, 128
genetic factors for, 123–127,
 133
 chromosomal aneuploidy,
 126
 from family studies,
 123–126
 gene mutations, 125–127
 non-aneuploidy copy
 number variants, 126
genetic testing, 129–130
 array comparative genomic
 hybridization, 129–130
 chromosome karyotyping,
 129
 consent issues, 131
 FISH, 129
 investigation strategies,
 128–129
 phenotypes from mutations,
 128–129
genome sequencing, 130–131
 data interpretation issues,
 130–131
incidence rates for, 133
isolated, 127
maternal hyperoxygenation,
 161–164
Noonan syndrome and, 157
syndromic, 126–127
22Q11 deletion syndrome, 157
Williams syndrome and, 157
congenital high airway obstruction
 syndrome (CHAOS), 79,
 445–446, 536
congenital pulmonary airway
 malformation (CPAM),
 485–486
 antenatal natural history, 485
 clinical presentation, 485
 fetal hydrops and, 485
 postnatal management,
 485–486
 prenatal management, 485
 types of, 485
congenital toxoplasmosis,
 236–237
congenital varicella syndrome,
 228–230
congenital Zika virus syndromes
 (CZS)
 amniocentesis for, 583
 diagnosis of, 583–585
 maternal-fetal transmission,
 585
 in newborns, 582
 during pregnancy, 582
 in US, 583
 prognosis with, 583–585
 research difficulties with,
 585–586
 risks of, 585
 signs and symptoms of,
 583–584
 symptomatic infection at birth,
 585
congenitally corrected
 transposition of the great
 arteries (CCTGA), 114
consent. *See also* informed
 consent
 for genetic testing, for
 congenital heart disease,
 131
 in prenatal diagnostic testing,
 45
conventional karyotyping, 38–39
 G-banding, 38
copy number variants (CNVs),
 39–40
 non-aneuploidy, 126
Core Outcomes in Women's and
 Newborn Health
 (CROWN), 565
coronary heart disease (CHD)
 fetal origins of, 8–9
 prevalence of, 8
 tissue engineering for, 536
corticosteroids
 antenatal, 329–330
 for fetal and neonatal
 alloimmune
 thrombocytopenia,
 104–105
 for fetal growth restriction, 273
 for toxoplasmosis, 238
cotrimoxazole, 238
counseling. *See* parental
 counseling
CPAM. *See* congenital
 pulmonary airway
 malformation
creatine, 295–296, 340
CRISPR gene editing complex,
 22, 548–549
critical aortic stenosis. *See* aortic
 stenosis
critical pulmonary stenosis.
 See pulmonary stenosis
CROWN (Core Outcomes in
 Women's and Newborn
 Health), 565
CSF (cerebrospinal fluid)
 leakage, 456–457
CVD. *See* cardiovascular disease
cystic fibrosis, 543–544
 in animal models, 543–544
cystoscopic technique, for
 LUTO, 432–433
cytomegalic inclusion disease
 (CID), 232
cytomegalovirus (CMV), during
 pregnancy, 218–219,
 231–235
 causes of, 231
 cytomegalic inclusion disease,
 232
 epidemiology of, 231
 through congenital
 infection, 231
fetal growth restriction and, 268
fetal infection
 classification of, 235
 management strategies for,
 232–236
 prenatal diagnosis of, 232
 severity criteria for, 233–234
 spectrum of infection,
 232–233
imaging for, 233–234
 with MRI, 234
 with ultrasound, 233–238
incidence rates of, 231
 through maternal infection,
 231–232
 gestational age during, 233
 intrauterine treatment,
 234–235
 prognosis markers, 234
 selective fetal growth
 restriction, 387
CZS. *See* congenital Zika virus
 syndromes
Deciphering the Mechanisms of
 Developmental Disorders
 (DMDD) programme,
 134–144
animal models, cardiac defects
 in, 136–144
bicuspid aortic valve defects,
 141–144
outflow defects, 139–143
septal defects, 136–140
cardiac defects, 134–139
 classification of, by type,
 135–139
 penetrance of, 134–135, 137
 by phenotype, 134, 136
 prevalence of, 134–135, 137
scale of, 134
scope of, 134
decision-making
 case studies in, 61–62
 emotions and, 63
 anticipated, 63
 immediate, 63
 information for, 62–64
 comprehension limits for,
 62
 processing limits for, 62
 intuition and, 62–63
 rationality and, 63
 with physician assistance, 64–67
 with graphics, 66–67
 through numbers of risks,
 65–66
 risk communication with,
 64–66
 through verbal terms, 65
 preferences as influence on,
 66–67
 as process, 61
 risk comprehension and
 perception, 63–64
 shared, 64–67
 components and steps in,
 64–65
 informed consent, 70
 paternalistic approaches in
 contrast with, 64
 support strategies of, 67
 values as influence on, 66–67
delivery
 with fetal growth restriction,
 259–260, 283
 management of, 272–273
 gestational age at, with IVF,
 406
 induced preterm, 370
dendritic cells (DCs), 215
development defects. *See also*
 specific defects
 FGF signaling pathway and,
 31–32
developmental disability, FR and,
 406
Developmental Origins of Health
 and Disease (DOHaD)
 concept, 8–9
 in animal and human
 studies, 9
 for fetal growth restriction, 280
diabetes. *See* type 2 diabetes
dichorionic triplet pregnancy,
 419–420
dichorionic twins, 398
diet and nutrition
 fetal growth optimisation and,
 287–288
 fetal growth restriction and,
 266
 for NTDs, 451–452
 in preterm birth prevention
 strategies, 319

Index

- differential prenatal diagnostic testing, 1–2
digoxin, 170, 173, 184
DILV (double inlet left ventricle), 116
disease registers, 570
 definition of, 570
 purpose of, 570
DMD. *See* Duchenne muscular dystrophy
DMDD programme.
 See Deciphering the Mechanisms of Developmental Disorders programme
DOHaD concept. *See* Developmental Origins of Health and Disease concept
dominant cell interactions, 23
donor cell engraftment, 517
Doppler ultrasound.
 See ultrasound
DORV (double outlet right ventricle), 115–116
double inlet left ventricle (DILV), 116
double outlet right ventricle (DORV), 115–116
Down's syndrome, 157
 fetal growth restriction and, 259
Duchenne muscular dystrophy (DMD), 514–515
 clinical experience, 515
 dystrophin expression, 514
 metalloproteinases, 514–515
 mortality rates, 515
 pathophysiology of, 514
 preclinical studies, 514–515
 steroid treatment therapy, 514
Dutch Obstetric Consortium, 564
dystrophin expression, 514
early onset fetal growth restriction, 264
early twin-to-twin transfusion syndrome, 363–364
 diagnostic considerations, 363
 outcomes for, 364–365
 polyhydramnios and, 363
 surgical considerations for, with fetoscopic laser ablation, 363–364
 alternatives to, 364
echocardiographic techniques, 176–188
echocardiography, for fetal dysrhythmia, 176–177
 magnetocardiograms, 177–178
 M-mode, 176
 pulsed wave Doppler, 177–188
 tissue velocity imaging, 177
echogenic cystic lesions (ECL), 251
 echogenic lung lesions, 442–446
 antenatal prognosticators, 443
 BPS, 442–443
 CCAMs, 442
 delivery with, 440–445
 evaluation of, 445
 fetal hydrops and, 444–445
 hybrid, 443
 macrocytic lesions, 444
 management of, 443–445
 microcytic lesions, 444–445
 fetal lobectomy, 444
 laser surgery for, 444
 RFA for, 444–445
 sclerotherapy for, 445
 steroid therapy for, 444
 natural history of, 443
 postnatal surgical resection and, 445
ECL (echogenic cystic lesions), 251
ECMO (extracorporeal membrane oxygenation), 80, 83–87
EFE (endocardial fibroelastosis), 151
EGF (epidermal growth factor), 527
elastin localization, 126
electro-mechanical activation of fetal heart, 166–167
embryology. *See also* cardiac development and formation
 cell interactions, 22–25
 dominant, 23
 morphogen gradients, 23–25
 signaling, 23
 Sonic hedgehog morphogen, 24–27
 congenital heart disease and, 110, 116
 development process in, 20–22
 animal models for, 20–21
 CRISPR gene editing complex, 22
 growth factor in, 23
 organoids in, 22
 signaling pathways in, 20, 22–23
 structural development in, 20–21
 gene therapy and, 549–550
 in limb buds, 26–27
 in neural tubes, 26–27
 signaling pathways in
 in development process, 20, 22–23
 FGF, 31–32
 in hedgehogs, 25–27
 notch, 32–33
 TGF β , 29–31
 Wnt, 27–29
 embryonic stem cells, 532
EMMPRIN (extracellular matrix metalloproteinase inducer), 306
emotions, decision-making and, 63
 anticipated emotions, 63
 immediate emotions, 63
endocardial fibroelastosis, 151
endocardial fibroelastosis (EFE), 151
endogenous repair, with stem cells, 527
endothelial cells, in fetal and neonatal alloimmune thrombocytopenia, 99–100
endothelins, 348–349
endovascular EVT, 249
England and Wales.
 See United Kingdom
epicardium derived cells (EPDC), 112
epidermal growth factor (EGF), 527
epignathus tumors, 482
erythropoietin, 340
eSET, fetal reduction and, 412–413
 medical advantages of, 405–407
ethics. *See also* informed consent
 with fetal reduction, 413
 in prenatal diagnostic testing, 45
 for consent, 45
 for feedback of results, 45
 for health professionals' responsibilities, 45
 for population diversity, 45
EUROCAT, 570–572
 geographical coverage of, 571
European Medicines Agency, 555
EVE (Ex-Vivo uterine Environment) model, 87
ex utero intrapartum treatment (EXIT) procedure, 2, 4, 77, 446
 with cervical teratomas, 482
EXIT-to-resection, 79–80
 ECMO, 80
EXTEND (EXtra-uterine Environment for Neonatal Development), 85–86
extracellular matrix metalloproteinase inducer (EMMPRIN), 306
extracorporeal membrane oxygenation (ECMO), 80, 83–87
EXtra-uterine Environment for Neonatal Development (EXTEND), 85–86
Ex-Vivo uterine Environment (EVE) model, 87
FBS (fetal blood sampling), 103
fetal and neonatal alloimmune thrombocytopenia (FNAIT)
 antenatal treatment strategies, 103–106
 with corticosteroids, 104–105
 fetal blood sampling, 103
 immunoprophylaxis, 105
 intrauterine platelet transfusion, 103
 with intravenous immunoglobulin, 103–104
 mode and timing of birth, 105–106
 causes of, 101
 clinical characteristics for, 101
 diagnosis for, 101
 laboratory analysis, 101–102
 with MRI, 103
 with ultrasound, 103
 incidence rates for, 100–101
 intracranial hemorrhage as complication of, 99–103
 intravenous immunoglobulin in antenatal treatment strategies, 103–104
 in neonatal management, 106
 neonatal management of with intravenous immunoglobulin, 106
 monitoring of platelet counts, 106
 platelet transfusions, 103, 106
 treatment strategies, 106
 obstetric management with, 101–106
 preconception counseling, 101–102
 risk assessment and monitoring, 102–103
 pathophysiology, 99–100
 endothelial cells, 99–100
 glycoproteins, 99–100
 human leukocyte antigen, 100
 placental function, 100
 platelet counts and, 99
 monitoring of, 106
 platelet transfusions and, 103, 106
fetal anemia. *See* red cell alloimmunization
fetal blood sampling (FBS), 103
fetal bradycardia, 475–476
fetal cardiac interventions
 aortic valvuloplasty for, 147, 150
 hemodynamic improvements, 148–152
 Linz criteria for, 150

Index

- benefits of, 147–149, 152
functional improvements, 152
hemodynamic improvements, 148–152
valvular growth, 152
ventricular growth, 152
cardiac pacing, 151
complications of, 152
for congenital heart defects, natural history of, 148–149
interatrial septum restrictions, 148–149
semilunar valve stenosis, 148–151
critical aortic stenosis, 149–150
critical pulmonary stenosis, 150–151
exceptions to, 151–152
endocardial fibroelastosis, 151
fetal pacing, 146
future applications of, 152–154
case selection for, 153–154
outcome assessment for, 153–154
procedural modifications, 153
study populations for, 153
technical developments, 153
historical approach to, 146–149
for hypoplastic left heart syndrome, 146, 150
imaging, 147–148
with ultrasound, 147
information sources, 149
interatrial septostomy, 150
maternal hyperoxygenation and, 146–151
pulmonary atresia with intact ventricular septum, 150–151
randomized controlled trials, 146
rationale for, 146–147
risks of, 152
stenting and, 150
fetal cardiovascular disease, 2
fetal development. *See also* fetal growth restriction
functions of, 8–9
growth markers in, 8–9, 14
timing of birth, 14
undernutrition and, 13
fetal dysrhythmias. *See also* tachycardias; *specific dysrhythmias*
cardiac rhythm assessment, 176–178
with echocardiographic techniques, 176–188
differential diagnosis of, 179–180
irregular fetal heart rhythm, 178–180
atrial ectopics, 178–180
isolated ectopics, 178–179
management of, 178–180
suggested protocols, 178
ventricular ectopics, 178–180
fetal growth
clinical trials for, 296
creatine for, 295–296
gene therapy and, 552
melatonin for, 295
N-acetylcysteine, 295
optimisation of, 287–289
alcohol use and, cessation strategies for, 288–289
diet and nutrition, 287–288
with pre-existing maternal conditions, 289
substance abuse and, cessation strategies for, 288–289
with supplements, 287–288
tobacco use and, cessation strategies for, 288–289
pre-conception health and, 287–288
prevention strategies, 289–292, 295–296
with anti-platelet agents, 289
aspirin therapy, 289–290
heparin therapy, 289–292
low molecular weight heparin therapy, 289–292
small for gestational age and, 264, 283–284
treatment strategies, 290–295
hydrogen sulphide, 294
nitric oxide donors, 291
non-pharmaceutical approaches, 295
phosphodiesterase type-5 inhibitors, 290–296
plasma exchange, 294
plasmapheresis, 294
proton pump inhibitors, 294
statins, 294
uteroplacental circulation and, 294–295
alternative targeting techniques, 295
placental gene therapy, 295
vascular endothelial growth factor and, 294–300
fetal growth restriction (FGR)
alcohol use and, 266–267
artificial reproductive technology and, 267
biophysical profile with, 272
birth delivery with, 259–260, 283
management through, 272–273
causes of, 265, 279
congenital, 267–268
fetal, 267–268
investigation of, 271
maternal, 265–267
medical conditions, 265–266
placental, 265–268
chorion regression syndrome, 256
clinical practice implications, 258–260
placental pathology and, 258
clinical presentation of, 264
clinical trials for, 296
cytomegalovirus and, 268
definition of, 264–265, 279
Developmental Origins of Health and Disease concept for, 280
diagnosis of, 248. *See also* ultrasound
diet and nutrition as factor for, 266
Down's syndrome and, 259
early onset, 264
echogenic cystic lesions, 251
etiology of, 279
gene therapy for, 274
genetic factors, 267
gross pathology of, 251–255
categories of, 254
hemorrhagic pathology, 253–254
intervillous thrombosis, 254
histopathology of placenta, 252, 256
immune injury to placenta, 257–258
chronic histiocytic inter-villositis, 257
massive perivillous fibrinoid deposition, 257
sonographic assessment for, 257–258
long-term consequences of, 280
management of, 270–274
through fetal heart rate monitoring, 272
through fetal surveillance, 271–272
for future pregnancies, 274
through timing and mode of delivery, 272–273
maternal immune system, 251–253
monochorionic twins and. *See also* selective fetal growth restriction
detection and diagnosis of, 384–386
growth discordance and, by trimester, 385–386
ultrasound imaging of, 384
multiple gestation and, 268
obstetric disorders and, 546–558
perinatal morbidity from, 279
perinatal mortality from, 279
placental causes of, 254–257
Breus' mole, 254–257
fetal thrombotic vasculopathy, 254–257
placental formation and, 248–253
clinical implications of, 249–250
endovascular EVT, 249
histiotrophic nutrition, 249
interstitial EVT, 249
trophoblast compartment, 250–251, 253
of villi, 250, 252
placental insufficiency and, 287
placental villi
developmental pathology of, 253, 257
formation of, 250, 252
prevention strategies for, 273
previous medical history, 268–269
risk factors for, 288
screening for, 254, 268–270, 284. *See also specific types*
with biochemical markers, 270, 281–282, 284
during first trimester, 281–282
integrated tests in, 259
morphological assessments from, 259
during second trimester, 282
during third trimester, 282
severe, 259
small for gestational age as distinct from, 264, 283–284
smooth muscle cells, 251, 288
substance abuse and, 266–267
thrombotic pathology, 253–254
chronic abruption in, 254
villous infarction, 254
tobacco use and, 266–267
treatment therapies for, 273–274, 282–284
corticosteroids, 273
disease-modifying, 282–283
gene therapy, 274
heparin, 273
low-dose aspirin, 273
magnesium sulphate, 273
with novel drugs, 284
sildenafil, 273–274
villitis of unknown etiology, 257
fetal heart rate monitoring, 272
fetal hydrops. *See* hydrops
fetal lobectomy, 444
fetal lung lesions. *See* echogenic lung lesions

Index

- fetal medicine. *See also* Global Obstetrics Network
in Canada, 562
clinical studies, 561
low participation rates in, 561
multicentre design for, 561–562
historical development of, 561–562
in US, 562
- fetal membrane repair, 522–529
alternative strategies for, 525–526
amniopatch procedure, 522
bioreactor systems, 528–529
with collagen, 524–525
endogenous repair with stem cells, 527
fetoscopic instrumentation in, 529
with fibrin, 522–524
limitations of, 524
future perspectives on, 525–529
bioinspired adhesive strategies, 525–527
with gelatin, 524–525
imaging for, 528
in vitro sealing, 525
mechanotransduction mechanisms, 528–529
plug approaches, 525
regenerative factors of, 527
sudden fetal death, 524–525
- fetal membranes
amniotic membrane, 520–522
in animal models, 521
healing mechanisms in, 520–521
in tissue explants, 521–522
in women, 521–522
CDH and, 520
chorionic membrane, 520
exposure of, 476–477
imaging for, 520, 522–523
MMC and, 520
sealing techniques, 520
separation of, 520
TTTS and, 520
types of, 520
- fetal organs and tissues, vector targeting for, 549–550
- fetal pacing, 146
- fetal phenotypes, 92
- fetal pleural effusions. *See* pleural effusions
- fetal reduction (FR)
development of, 404
developmental disability and, 406
diagnosis of
with FISH, 410–411
with NIPS, 411
with PGS, 411
- eSET and, 412–413
medical advantages of, 405–407
ethical issues with, 413
gender determination and, 411–412
historical development of, 406–408
IVF and, 404
management strategies for, 410–411
transcervical CVS, 410
multiple pregnancies and, 404–409, 413
from IVF, 404
monozygotic twins, 406–411
risks of, 407
neurological disability and, 406
pregnancy loss and, 405–407
pregnancy outcomes with, 408–410
increasing maternal age and, 409
twin-to-twin transfusion syndrome and, 410
selective termination in, 409–410, 412
societal issues with, 413–414
technological issues with, 413–414
- fetal stem cells, 533
gene therapy with, 550–551
for thalassaemias, 543
- fetal surgery. *See also* in-utero spina bifida repair; open fetal surgery
evolution of, 467
- fetal swallowing, 195
- fetal therapy
candidate identification for, 2
grading systems in, 2
care settings for, 4
for CDH, 3
development of, as subspecialty, 1
criteria for, 1
EXIT for, 2, 4
fetal cardiovascular disease and, 2
for FETO, 3–4
goals of, 2–3
through treatment, 3
hydrops and, 2
for LUTO, 430–433
complications with, 433
cystoscopic technique, 432–433
PLUTO trial for, 431–432
vesicoamniotic shunting, 430–433
overview of, 3–5
for PPROM, 4
prenatal diagnosis in, 1–2
differential, 1–2
through genetic testing, 1–2
- primary, 1–2
tools in, 1–2
prognostic assessment in, 1–2
risk-benefit assessment for, 3–4
scope of, 2–3
for spina bifida, 454
techniques for, 2
laser ablation, 2
tissue engineering in, 534–535
immunology, 534
physiology and, 534–535
scale and access, 535
- TTTS and, 2
- Fetal Therapy Centers, requirements for, 4–5
- fetal thrombotic vasculopathy (FTV), 254–257
- fetal tumors. *See also specific tumors*
diagnosis of, 480
fetal urinalysis, 429–430
fetal water components, 191
feticide. *See* selective feticide
- FETO (fetoscopic tracheal occlusion), 3–4, 535–536
- fetomaternal hemorrhage (FMH), 91. *See also* red cell alloimmunization
- fetoscopic laser ablation
for early twin-to-twin transfusion syndrome, 363–364
alternatives to, 364
for late twin-to-twin transfusion syndrome, 364–365
alternatives to, 365
- fetoscopic laser coagulation of placental vessels (FLCPV), 353–359
clinical outcomes from, 358–359
complications from
early, 357–358
late, 357–358
maternal, 357
development of, 354
instruments for, 354–355
learning curve for, 356–357
operative time for, 356
peri-operative care for, 357
for selective fetal growth restriction, 395
as surgical procedure, 354–355
technique for, 355–356
for TRAP, 401–402
- fetoscopic laser surgery. *See also* fetoscopic laser ablation
for monochorionic twins, 375–377
for twin anemia polycythemia sequence, 370
- fetoscopic tracheal occlusion (FETO), 3–4, 535–536
- fetuses with structural abnormalities.
See prenatal diagnostic testing
- FGF (fibroblast growth factor), 527
- FGF signaling pathway, 31–32
developmental defects and, 31–32
limb development, 31
- FGR. *See* fetal growth restriction
- FHF (first heart field), 110–111.
See also cardiac morphogenesis
- fibrin repair, 522–524
limitations of, 524
- fibroblast growth factor (FGF), 527
- fibronectin, 312
- first degree heart block, 186
- first heart field (FHF), 110–111. *See also* cardiac morphogenesis
- FISH (fluorescence in-situ hybridisation), 38–39
- FLCPV. *See* fetoscopic laser coagulation of placental vessels
- flecainide, 170, 173, 184
- fluid inflows, for amniotic fluid, 194
clinical scenarios, 193
lung fluid production, 194
from oral-nasal secretions, 194
urine production, 194
- fluid outflows, with amniotic fluid, 195–196
clinical scenarios, 193
from fetal swallowing, 195
intramembraneous flow, 195–196
- fluorescence in-situ hybridisation (FISH), 38–39
for congenital heart disease, 129
for fetal reduction, 410–411
- fluorinated steroids, 187
- FMH (fetomaternal hemorrhage), 91
- FNAIT. *See* fetal and neonatal alloimmune thrombocytopenia
- folate deficiency, 451
- folic acid deficiency, 451–452
- Fowler syndrome, 44
- FR. *See* fetal reduction
- France, Global Obstetrics Network in, 564
- Fraser syndrome, 446
- FTV (fetal thrombotic vasculopathy), 254–257
- $\gamma\delta$ T lymphocytes, 218

Index

- gastroesophageal reflux (GERD), 494
gastroschisis, 535
Gaucher disease, 513–514
 background for, 513–514
 clinical experience with, 514
 pathophysiology of, 513
 preclinical studies, 514
 types of, 513–514
G-banding, 38
GDM. *See* gestational diabetes mellitus
gelatin repair, 524–525
gender determination, fetal
 reduction and, 411–412
gene editing
 in gene therapy, 548–549
 CRISPR program, 548–549
gene identification methods,
 congenital heart disease,
 127–128
 positional cloning, 127–128
 species comparisons through,
 128
gene therapy
 for AAV, 540
 advantages of, 540
 adverse consequences of,
 552–554
 on fetal growth and
 development, 552
 transgenic protein
 expression, 553–554
 vector delivery procedure,
 554
 vector spread, 553
 vector toxicity, 553
 vector-mediated
 genotoxicity, 553
candidate diseases for, 541. *See also specific diseases*
for CDH, 543–544
for central nervous system
 diseases, 544
for cystic fibrosis, 543–544
for fetal growth restriction, 274
with fetal stem cells, 550–551
 for thalassaemias, 543
gene editing in, 548–549
 CRISPR program, 548–549
for genodermatoses, 545–546
for hemophilias, 541–542
hFIX genes, 542
human applications, 554–555
 clinical translation issues,
 555
 ethical considerations, 554
 Phase I trials, 554–555
 pre-clinical testing, 554
 toxicology studies, 554
 in treatment practice, 555
for lysosomal storage diseases,
 544
 for muscular dystrophy,
 544–545
 in animal models, 545
 ultrasound and, 545
for obstetric disorders,
 546–547
 FGR and, 546–558
 for preterm births, 546
 VEGF and, 542–546
postnatal, 540
prenatal gene transfer vectors,
 547–548
 immune responses to vector
 and transgenic protein,
 552
 length of expression, 551–552
 practical considerations,
 551–552
 types of, 547–548
 vector silencing, 552
scope of, 540
for sickle cell disorders,
 542–543
for thalassemias, 542–543
 fetal stem cells, 543
 for HSCT, 542
vector targeting
 for embryos, 549–550
 for fetal organs and tissues,
 549–550
genetic testing
 for CDH, 495–496
 for congenital heart disease,
 129–130
 array comparative genomic
 hybridization, 129–130
 chromosome karyotyping, 129
 consent issues, 131
 FISH, 129
 investigation strategies,
 128–129
 phenotypes from mutations,
 128–129
for fetal therapy, 1–2
for preterm birth history, 308
genome-wide association
 studies, 308
genodermatoses, gene therapy
 for, 545–546
genome sequencing, for
 congenital heart disease,
 130–131
 data interpretation issues,
 130–131
genome-wide association studies
 (GWAS), 308
genomics. *See* prenatal genomics
GERD. *See* gastroesophageal
 reflux
German measles. *See* rubella
Germany, in-utero spina bifida
 repair in, 468–469
gestational diabetes mellitus
 (GDM), 50–51
 co-morbidity risks, 50
 diagnosis of, 50
 screening for, 50
 treatment therapies, 51
 Type 1, 50
 Type 2, 50
Global Obstetrics Network
 (GONet), 562–565
 in Canada, 563
 collaborative output of,
 564–566
 education through, 564
 individual participant data
 meta analyses, 564–565
 CROWN and, 565
 Dutch Obstetric Consortium,
 564
 in France, 564
 goals of, 562
 mission of, 562
 NICHD, 562–563
 in UK, 563–564
glycoproteins, 99–100
GONet. *See* Global Obstetrics
 Network
Gratacos classification, for
 selective fetal growth
 restriction, 388–389
GWAS (genome-wide
 association studies), 308
haemophilias, 541–542
 hFIX genes, 542
 for HSCT, 542
Hajdu-Cheney syndrome, 33
HDFN (hemolytic disease of the
 fetus and newborn), 91
head and neck tumors, 480–482.
 See also cervical
 teratomas
 epignathus, 482
 intracranial tumors, 483
heart block, 186–188
 auto-immune AV block,
 186–187
 management of, 187. *See also specific treatment therapies*
 AV block related to congenital
 heart disease, 186
 fetal surveillance for, 187–188
 first degree, 186
 isolated non-immune AV
 block, 186
 second degree, 186
 third degree, 186
heart malformations with
 looping disturbances,
 113–114
 atrial isomerism, 114
 atrial situs inversus, 113–114
 laterality defects, 113–114
 situs defects, 113–114
hemangiomas, 486
hematopoietic disorders,
 512–513. *See also specific disorders*
 background of, 512
 clinical experience, 513
 clinical trials, 513
 preclinical studies, 512–513
hematopoietic stem cell
 transplantation (HSCT),
 512
 gene therapy and, 542
 in utero transplantation,
 512–513, 517. *See also specific disorders*
 cell sources, 512
 thalassemias and, 542
hematopoietic stem cells,
 216–217, 512
hemolysis, red cell
 alloimmunization and, 92
 ADCC assays for, 92
 fetal phenotypes and, 92
 serological testing, 92
hemolytic disease of the fetus and
 newborn (HDFN), 91
heparin therapy, 273
 in fetal growth prevention
 strategies, 289–292
hepatic tumors, 486–487
 antenatal natural history, 486
 clinical presentation, 486
 hemangiomas, 486
 hepatoblastomas, 486
 mesenchymal hamartoma, 486
 postnatal management, 487
 prenatal management,
 486–487
hepatoblastomas, 486
hFIX genes, 542
HICs. *See* high-income countries
HIF (hypoxic inducible factor),
 159
HIFU. *See* high-intensity focused
 ultrasound
high-income countries (HICs),
 48
high-intensity focused
 ultrasound (HIFU), 422
histiotrophic nutrition, 249
HIV (human immunodeficiency
 virus), 219–220
HLA (human leukocyte antigen),
 100
HLHS (hypoplastic left heart
 syndrome), 118, 146, 150
Hong Kong Maternal Fetal
 Medicine Network, 564
HSCT. *See* hematopoietic stem
 cell transplantation
human blood gas data, 476
human gestational clocks,
 303–304
 immunological clock
 hypothesis, 304

Index

- human gestational clocks (cont.)
 mechanical clock theory,
 303–304
 placental clock theory, 303
- human immunodeficiency virus (HIV), 219–220
- human leukocyte antigen (HLA), 100
- human parturition, 302–303
- human studies, for adult diseases,
 fetal origins of, 9
 cardiovascular control in,
 12–13
 DOHaD concept through, 9
- hybrid echogenic lung lesions,
 443
- hydrogen sulphide, 294
- hydrops, fetal, 2
 BPS and, 483
 CPAM and, 485
 echogenic lung lesions and,
 444–445
 intrauterine transfusions and, 95
 from parvovirus B19, 225–227
 polyhydramnios and, 201–202
 supraventricular tachycardia
 and, 167, 171–173, 181
- hypercapnia-metabolic acidosis,
 475
- hyperoxygenation. *See* maternal
 hyperoxygenation
- hyperplasia, of uterus, 304
- hypertrophy, of uterus, 304
- hypoplastic left heart syndrome
 (HLHS), 118, 146, 150
- hypoxia. *See* chronic hypoxia
- hypoxic inducible factor (HIF), 159
- hysterotomies, 77
- iatrogenic multiple pregnancies,
 326
- iatrogenic preterm birth, 326,
 333–334
- iatrogenic preterm premature
 rupture of membranes
 (iPPROM), 207–209
- ICH (intracranial hemorrhage),
 99–103
- identical twins. *See* monozygotic
 twins
- idiopathic polyhydramnios,
 202–203
- imaging. *See specific imaging
 modalities*
- immediate emotions, 63
- immune system, fetal
 antibodies, 216
 antigen presenting cells
 dendritic cells, 215, 217
 macrophages, 215
 B lymphocytes, 216–218
 congenital infections, 218–221
 cytomegalovirus, 218–219
 human immunodeficiency
 virus, 219–220
 pathogen causes of, 218
 Toxoplasma gondii, 220
 functional programming of,
 216–217
 hematopoietic stem cells,
 216–217
 historical development of, 215
 macrophages, 215
 major histocompatibility
 complex molecules, 215
 maternal infections and,
 exposure to, 220–221
 natural killer cells, 216
 neutrophils, 215
 ontogeny of, 216
 pathogen-associated molecular
 patterns, 215
 regulatory T cells, 218
 T lymphocytes, 215–216
 $\alpha\beta$ T lymphocytes, 217
 $\gamma\delta$ T lymphocytes, 218
 T-cell receptors, 215–216
 Toll-like receptors, 215
 Zika virus, 220
- immunoglobulins.
 See intravenous
 immunoglobulin
- immunological clock hypothesis,
 304
- immunology, 534
- immunoprophylaxis, 105
- IMPACT network, 564
- in vitro* fertilization (IVF)
 embryos transferred, maternal
 age and, 405
 fetal reduction and, 404
 gestational age at delivery,
 406
 monozygotic twinning
 through, 406–411
 multiple pregnancies from,
 404–409
- in vitro* sealing, in fetal
 membrane repair, 525
- indomethacin, 204
- induced pluripotent stem cells,
 532–533
- induced preterm delivery, 370
- infections, fetal. *See also* immune
 system; *specific infections*
 congenital, 218–221
 cytomegalovirus, 218–219
 human immunodeficiency
 virus, 219–220
 pathogen causes of, 218
 Toxoplasma gondii, 220
 cytomegalovirus, during
 pregnancy
 classification of, 235
 management strategies for,
 232–236
 prenatal diagnosis of, 232
 severity criteria for, 233–234
 spectrum of infection,
 232–233
- inflammation, preterm birth and,
 304–307
 oxytocins/oxytocin receptor
 system, 305
 preterm premature rupture of
 membranes, 306–307
 prostaglandin regulation, 305
 vaginal host-microbe
 interactions, 306–307
- information, for decision-
 making, 62–64
 comprehension limits for, 62
 processing limits for, 62
- informed consent, 69–74
- information standards, 69–70
- respect for autonomy, 69
- respect for persons, 69
- settings for fetal therapy,
 71–74
 for accepted fetal treatment,
 73–74
 for innovative treatment, 72
 for therapy trials, 72–73
- shared decision-making and,
 70
 interpretive model of, 70
- inositol, 452
- interatrial septostomy, 150
- interatrial septum restrictions,
 148–149
- interstitial EVT, 249
- intervillous thrombosis, 254
- intestinal adenomatous
 polypsis, 486
- intracranial hemorrhage (ICH),
 99–103
- intracranial tumors, 483
- intrafetal coagulation
 interventions, 400–401
 with laser ablation, 401
- intrafetal laser, 421
- intramembraneous flow, for
 amniotic fluid, 195–196
- intrauterine exchange
 transfusions (IUEs), 94
- intrauterine growth restriction
 (IUGR), 201
 sIUGR, 378–379
- intrauterine platelet transfusion
 (IUPT), 103
- intrauterine transfusions (IUT),
 369–370
 intrahepatic root punctures,
 95
 placental cord root punctures,
 95
- for red cell alloimmunization,
 93–95
 complications from, 94–95
 hydrops and, 95
 imaging for, 94
 long-term outcomes, 95
 preparations for, 93
 timing of, 94
 transfusion process, 94
- intravenous immunoglobulin
 (IVIG), 96, 187
 with fetal and neonatal
 alloimmune
 thrombocytopenia
 in antenatal treatment
 strategies, 103–104
 in neonatal management, 106
- intuition, decision-making and,
 62–63
 rationality and, 63
- in-utero spina bifida repair, with
 fetoscopy, 468–477
 animal models for, 476
 in Brazil, 469–470
 CO² safety in, 474–476
 carbonic anhydrase and,
 lack of, 475
 fetal bradycardia, 475–476
 fetal membrane exposure,
 476–477
 hypercapnia-metabolic
 acidosis, 475
 prolonged fetal acidosis,
 475–476
 in Germany, 468–469
 human blood gas data and,
 476
 at Texas Children's Fetal
 Center, 470–474
 fetoscopic outcomes, 473–474
 technique at, 470–473
 in USA, 468–469
- iPPROM (iatrogenic preterm
 premature rupture of
 membranes), 207–209
- irregular fetal heart rhythm,
 178–180
 atrial ectopics, 178–180
 isolated ectopics, 178–179
 management of, 178–180
 suggested protocols, 178
 ventricular ectopics, 178–180
- isolated congenital heart disease,
 127
- isolated ectopics, 178–179
- isolated non-immune AV block,
 186
- IUEs (intrauterine exchange
 transfusions), 94
- IUGR. *See* intrauterine growth
 restriction
- IUPT (intrauterine platelet
 transfusion), 103
- IUT. *See* intrauterine
 transfusions
- IVIG. *See* intravenous
 immunoglobulin
- Kabuki syndrome, 44
- laser ablation. *See also* fetoscopic
 laser ablation; fetoscopic
 laser coagulation of
 placental vessels

Index

- for early twin-to-twin transfusion syndrome, 363–364
 - for fetal therapy, 2
 - intrafetal coagulation intervention with, 401
 - late onset fetal growth restriction, 264
 - late twin-to-twin transfusion syndrome, 364–365
 - outcomes for, 365
 - surgical considerations for, with fetoscopic laser ablation, 364–365
 - alternatives to, 365
 - laterality defects, 113–114
 - lesions. *See specific types of lesions*
 - lidocaine, 185
 - limb buds, 26–27
 - limb development, FGF signaling pathway and, 31
 - LMWH (low molecular weight heparin) therapy, 289–292
 - looping defects, 114
 - congenitally corrected transposition of the great arteries, 114
 - low molecular weight heparin (LMWH) therapy, 289–292
 - low-dose aspirin therapies, 273
 - lower urinary tract outflow obstruction (LUTO), 205–206. *See also* congenital bladder neck obstruction
 - fetal therapy for, 430–433
 - complications with, 433
 - cystoscopic technique, 432–433
 - PLUTO trial for, 431–432
 - vesicoamniotic shunting, 430–433
 - incidence rates for, 426
 - lung disease, chronic, fetal
 - origins of, 8
 - lung fluid production, 194
 - lung masses, open fetal surgery for, 78–79
 - LUTO. *See* lower urinary tract outflow obstruction
 - Lye, Steven, 303
 - lymphocytes. *See specific lymphocytes*
 - lysosomal storage diseases, 544
 - macrocytic lung lesions, 444
 - macrophages, 215
 - magnesium sulphate therapy, 185, 273, 338–339, 463
 - magnetic resonance imaging (MRI)
 - for cytomegalovirus, 234
 - for fetal and neonatal alloimmune thrombocytopenia, 103
 - for neuroblastoma, 489
 - for open fetal surgery, 79
 - for SCT, 490
 - for Wilms' tumor, 488
 - major histocompatibility complex (MHC) molecules, 215
 - Management of Myelomeningocele Study (MOMS trial), 72, 457–464
 - challenge guidelines after, 463–464
 - at CHOP, 459–460
 - exclusion criteria for, 458
 - inclusion criteria for, 458
 - outcomes for, 458
 - obstetric, 459
 - timing of fetal repair surgery in, 459
 - MAS (meconium aspiration syndrome), 211
 - massive perivillous fibrinoid deposition (MPVFD), 257
 - maternal hyperoxygenation, 146–151, 161–164
 - maternal infections, fetal exposure to, 220–221
 - McCullough, Laurence, 71
 - mechanical clock theory, 303–304
 - mechanotransduction
 - mechanisms, for fetal membrane repair, 528–529
 - meconium aspiration syndrome (MAS), 211
 - melatonin, 295, 340
 - membrane water flux, 192
 - Mendelson, Carol, 304
 - mesenchymal hamartoma, 486
 - mesenchymal stem cells (MSC), 512
 - mesoblastic nephroma, 487–488
 - antenatal natural history, 488
 - metalloproteinases, 514–515
 - methylenetetrahydrofolate reductase (MTHFR) enzyme, 450
 - MHC (major histocompatibility complex) molecules, 215
 - microarrays. *See* chromosomal microarray analysis; single nucleotide polymorphism microarray
 - microcystic lung lesions, 444–445
 - fetal lobectomy, 444
 - laser surgery for, 444
 - RFA for, 444–445
 - sclerotherapy for, 445
 - steroid therapy for, 444
 - microwave ablation (MWA), 401, 420–422
 - mild thrombocytopenia, 99
 - Miller syndrome, 44
 - mirror syndrome, 225
 - MMC. *See* myelomeningocele
 - M-mode echocardiography, 176
 - moderate thrombocytopenia, 99
 - MOMS trial. *See* Management of Myelomeningocele Study
 - monoamniotic twin pregnancy, 419
 - monochorionic twins, 346. *See also* multiple pregnancies
 - acardiac twinning and, 402
 - complications with, 418
 - FGR and. *See also* selective fetal growth restriction
 - detection and diagnosis of, 384–386
 - growth discordance and, by trimester, 385–386
 - ultrasound imaging of, 384
 - follow-up assessments for, 381
 - long-term
 - neurodevelopmental outcome, with TTS, 373–377
 - amnioreduction treatment, 373–375
 - with laser surgery, 375–377
 - randomized controlled trials, 375–377
 - selective intrauterine growth restriction and, 378–379
 - selective termination of. *See* selective termination
 - single fetal demise with, 379–380
 - TAPS and, 377–378
 - TRAP and, 379, 400
 - selective termination with, 418
 - TTS with, 373–377
 - cerebral injury and, through neuroimaging, 373
- monozygotic twins, 406–411. *See also* multiple pregnancies
 - placenta of, 344
 - TTS with, 344
- morphogen gradients, 23–25
- Sonic hedgehog morphogen, 24–27
- morphogenesis. *See* cardiac morphogenesis
- motor dysfunction, from preterm birth, 334
- MPVFD (massive perivillous fibrinoid deposition), 257
- MRI. *See* magnetic resonance imaging
- MSC (mesenchymal stem cells), 512
- MTHFR (methylenetetrahydrofolate reductase) enzyme, 450
- multiple pregnancies. *See also* monozygotic twins
 - adverse outcomes for, 325
 - chorionicity and, 325
 - epidemiology of, 325
 - for twins, 325
 - fetal growth restriction and, 268
 - fetal reduction and, 404–409, 413
 - from IVF, 404–409
 - monozygotic twins, 406–411
 - preterm birth and, 326–330
 - antenatal corticosteroids for, 329–330
 - bedrest for, 325–327
 - cervical cerclage for, 327–329
 - cervical length measurement and, 327, 329
 - cervical pessary for, 328–329
 - iatrogenic, 326
 - prevention strategies, 327–329
 - progesterone and, 329
 - risk factors for, 326–327
 - screening for, 327
 - in specialized antenatal clinics, 327
 - spontaneous, 326
 - tocolytic drugs for, 329
 - uterine activity monitoring, 327
- prevalence of, 325
- risk factors
 - maternal socio-demographic status, 326–327
 - obstetric history, 327
 - for preterm birth, 326–327
 - risks of, 407
- muscular dystrophy, 544–545. *See also* Duchenne muscular dystrophy
 - in animal models, 545
 - ultrasound and, 545
- MWA (microwave ablation), 401, 420–422
- myelomeningocele (MMC), 456–457. *See also* Management of Myelomeningocele Study
 - cerebrospinal fluid leakage and, 456–457
 - fetal membranes and, 520
 - open fetal repair surgery for, 3, 456–457, 459–461, 463
 - animal models for, 456–457
 - challenge guidelines for, 463–464

Index

- myelomeningocele (MMC)
(cont.)
 complications from, 464
 improvements in, 460–463
 modifications to, 460–463
 timing of, 459
 perioperative management of, 463
 tissue engineering for, 535
 tocolytics for, 463
myeloschisis, 456
- N-acetylcysteine (NAC), 295, 340
- National Congenital Anomaly and Rare Diseases Registration Service, 573–574
- National Congenital Anomaly System, 572
- National Institute of Child Health and Human Development (NICHD), 562–563
- natriuretic peptides, 348–349
- natural killer (NK) cells, 216
- natural scaffolds, 534
- NCC (cardiac neural crest cells), 111–112
- neonates
 chickenpox in, 228
 shingles and, 228
 varicella, 228
 CZS in, 582
 intervention strategies for preterm births, 319–320
 toxoplasmosis in, 237–238
 twin anemia polycythemia sequence for, 369
 placental presentation, 369
- neural tube defects (NTDs). *See also* spina bifida
 animal models, 450
 definition of, 449
 MTHFR enzyme, 450
 open, 449
 open fetal surgery for, 77–78
 pathophysiology, 449–452
 diet and nutrition factors, 451–452
 environmental risk factors, 450–452
 genetic risk factors, 449–450, 453
 maternal risk factors, 450–451, 453
 maternal vitamin deficiencies, 451–452
 substance abuse factors, 452
 prevalence rates, 449, 453
 prevention strategies, 452–454
 with folic acid, 452–453
 with inositol, 453–454
 neural tubes, 26–27
- neuroblastoma, 489–490
 antenatal natural history, 489
 clinical presentation, 489
 MRI imaging, 489
 postnatal management, 490
 prenatal management, 489–490
 neurological disability, fetal reduction and, 406
 neutrophils, 215
 New Zealand, IMPACT network in, 564
 next generation sequencing (NGS), 36, 42–45
 diagnostic yield of, 43
 whole exome sequencing, 44
 categorization of, 44
 nucleotide alterations identification, 44
- NICHD (National Institute of Child Health and Human Development), 562–563
- NIHF (non-immune hydrops fetalis), 438
- NIPS (non-invasive prenatal screening), 411
- NIPT (non-invasive prenatal testing), 37
- nitric oxide donors, 291
- NK (natural killer) cells, 216
- non-aneuploidy copy number variants, 126
- non-immune hydrops fetalis (NIHF), 438
- non-invasive prenatal screening (NIPS), 411
- non-invasive prenatal testing (NIPT), 37
- Noonan syndrome, 157
- notch intracellular domain, 33
- notch signaling pathway, 32–33
 binary decision regulation, 33
 birth defects and, 33
 inductive interactions, 33
 notch intracellular domain, 33
 organ development and, 33
 nucleotide alterations, identification of, 44
- obstetric cholestasis, 48–50
 UCDA treatment with, 50
- obstetric disorders, 546–547
 FGR and, 546–558
 for preterm births, 546
 VEGF and, 542–546
- oesophageal atresia, 536–539
- oligohydramnios, 204–206
 amnioinfusion for, 210–211
 meconium aspiration syndrome, 211
 assessment of, systematic approach to, 205
 definition of, 204–205
 etiology of, 205
 lower urinary tract outflow obstruction, 205–206
- preterm premature rupture of membranes and, 208
- pulmonary hypoplasia and, 205–206, 208
 in second trimester, 205–206
 secondary consequences of, 205
 in third trimester, 210
 1:1 AV conduction, 185
 open fetal repair surgery, for MMC, 3, 456–457, 459–461, 463. *See also* in-utero spina bifida repair; spina bifida
 animal models for, 456–457
 challenge guidelines for, 463–464
 complications from, 464
 improvements in, 460–463
 modifications to, 460–463
 timing of, 459
 open fetal surgery
 CDH and, 77
 defined, 77
 EXIT procedure in, 77
 EXIT-to-resection, 79–80
 ECMO, 80
 fetoscopic techniques compared to, 77
 historical development of, 77
 hysterotomies, 77
 imaging of, 79–80
 with MRI, 79
 for lung masses, 78–79
 for neural tube defects, 77–78
 for teratomas, 78–79
 for cervical teratomas, 78–79
 for CHAOS, 79
 open neural tube defects, 449. *See also* spina bifida
 oral-nasal secretions, 194
 organ development, notch signaling pathway and, 33
 organoids, 22
 osteogenesis imperfecta, 515–517
 case studies for, 516–517
 clinical experience, 516–517
 clinical presentation of, 515
 donor cell engraftment, 517
 postnatal stem cell transplantation for, 516
 preclinical studies, 515–516
 outflow defects, 139–143
 oxytocin receptor system, 305
 oxytocins, 305
- pacing. *See* cardiac pacing; fetal pacing
- Page study (Prenatal Assessment of Genomes and Exomes study), 36
- PAR (population attributable risk), 54
- parental counseling, 430
- partner smoking, stillbirth and, 55
- parvovirus B19, during pregnancy, 224–226
 Ballantyne syndrome, 225
 clinical presentation of, 224
 management issues with, 226
 epidemiology for, 224
 fetal consequences, 225–226
 cardiac issues, 225
 hydrops, 225–227
 management issues, 226
 with clinical features, 226
 with patient contact history, 226
 maternal infection, 224–225
 clinical manifestations of, 224
 fetal damage, 225
 serological diagnosis, 224–225
 vertical transmission risks, 225
 mirror syndrome, 225
 prenatal diagnosis, 225–226
 pathogen-associated molecular patterns (PAMPs), 215
 PCP Wnt signaling pathway, 28–29
 PDGF (platelet-derived growth factor), 527
- Percutaneous vesicoamniotic shunting versus conservative management for Lower Urinary Tract Obstruction (PLUTO) trial, 431–432
- perinatal brain injury, from preterm birth, 335–340
 delivery factors for, 337
 imaging of, 335–336
 mechanisms of, 335
 neuroprotective therapies, 336–340
 antenatal corticosteroids, 337–338
 with creatine, 340
 with erythropoietin, 340
 magnesium sulphate, 338–339
 melatonin, 340
 with N-acetylcysteine, 340
 with stem cells, 340
 subgroup analysis, 339
 pathophysiology of, 335–336
 prevention strategies for, 336–337
- peripartum pleural effusions, 440
- periventricular leukomalacia, 335
- permanent junctional reciprocating tachycardia, 167–168
- persistent pulmonary hypertension, 494

Index

- persistent sinus tachycardia, 182
 persistent tachycardia, 171–173
 PGF (placental growth factor), 287
 PGS (pre-implantation genetic screening), 411
 phosphodiesterase type-5 inhibitors, 273–274, 290–296
 placenta, development of, 14–15.
 See also fetal growth restriction
 placental aging, 307–308
 placental clock theory, 303
 placental gene therapy, 295
 placental growth factor (PGF), 287
 placental insufficiency, 287
 placental villi
 developmental pathology of, 253, 257
 formation of, 250, 252
 placental water flux, 192–194
 placental-steal effect, 546
 Planar Polarity Wnt signaling pathway, 27
 plasma exchange, 294
 plasmapheresis, 187, 294
 platelet counts, with fetal and neonatal alloimmune thrombocytopenia, 99
 monitoring of, 106
 platelet transfusions and, 103, 106
 platelet transfusions, 103, 106
 platelet-derived growth factor (PDGF), 527
 pleural effusions, fetal. *See also* echogenic lung lesions
 CHAOS, 445–446
 diagnosis of, 438
 investigation of, 438
 management of, 439–441
 peripartum, 440
 with thoracoamniotic shunting, 439–441
 with thoracocentesis, 439–440
 NIHF, 438
 pleurodesis, 441
 prevalence of, 438
 primary, 438
 prognosticators for, 439
 ultrasound imaging of, 438–439
 pleurodesis, 441
 PLUTO (Percutaneous vesicoamniotic shunting versus conservative management for Lower Urinary Tract Obstruction) trial, 431–432
 polyhydramnios, 200–203
 assessment of, 201–202
 definition of, 200
 development of, 200
 early twin-to-twin transfusion syndrome, 363
 etiology of, 200–201
 fetal causes of, 201
 fetal hydrops and, 201–202
 idiopathic, 202–203
 intrauterine growth restriction and, 201
 treatment options, 202–203
 twin-to-twin transfusion syndrome, 201–202
 population attributable risk (PAR), 54
 positional cloning, 127–128
 posterior second heart field, 117
 atrial septal defect, 117
 atrioventricular septal defect, 117
 postnatal gene therapy, 540
 postnatal stem cell transplantation, 516
 PPROM. *See* preterm premature rupture of membranes
 preferences, in decision-making, 66–67
 pregnancy. *See also* fetal development; multiple pregnancies; *specific topics*
 CZS during, 582
 in US, 583
 fetal reduction outcomes, 408–410
 increasing maternal age and, 409
 selective termination, 409–410
 twin-to-twin transfusion syndrome and, 410
 maternal adaptations to, 14
 prolonged, 52–53
 induction of labor for, 52
 maternal age as factor in, 52
 with red cell alloimmunization, 92–93
 abandoned monitoring techniques for, 93
 with Doppler monitoring, 92–93
 with ultrasound monitoring, 93
 timing of birth, 14
 pregnancy loss, fetal reduction and, 405–407
 pre-implantation genetic screening (PGS), 411
 premature birth, 228. *See also* preterm birth
 Prenatal Assessment of Genomes and Exomes (PAGE) study, 36
 prenatal diagnostic testing, 1–2.
 See also chromosomal microarray analysis
 differential, 1–2
 ethics in, 45
 for consent, 45
 for feedback of results, 45
 for health professionals' responsibilities, 45
 for population diversity, 45
 through genetic testing, 1–2
 incidence rates, 38
 issues with, 45
 long-term issues with, 45
 NGS for, 36, 42–45
 diagnostic yield of, 43
 whole exome sequencing, 44
 primary, 1–2
 tools in, 1–2
 prenatal gene transfer vectors, 547–548
 immune responses to vector and transgenic protein, 552
 length of expression, 551–552
 practical considerations, 551–552
 types of, 547–548
 vector silencing, 552
 prenatal genomics. *See also* prenatal diagnostic testing
 development of, 36–38
 NGS, 36
 NIPT, 37
 PAGE study, 36
 screening pathways for, 37
 in UK, 36–37
 prenatal termination, with supraventricular tachycardia, 172–173
 preterm birth. *See also* multiple pregnancies; perinatal brain injury
 aetiology of, 304, 308, 311
 in animal models, 302–303
 categories of, 333
 cervical cerclage and, 316–317
 abdominal approach, 316–317
 for asymptomatic women with a short cervix, 316
 cervical approach, 316–317
 rationale for, 316
 for symptomatic women, 316
 cervical competence and, 307
 cervical pessary for, 317–318
 random clinical trials for, 317
 rationale for, 317
 cervical ripening and, 304–305
 cervix length and
 cervical cerclage and, 316
 cervical shortening, 317
 progesterone therapy, 315–316
 definition of, 302, 333–334
 diagnosis of, 312–320
 composite tools for, 313
 with intact membranes, 313
 epidemiology of, 311
 extracellular matrix metalloproteinase inducer and, 306
 functional progesterone withdrawal and, 304
 gene therapy for, 546
 genetics and, 308
 genome-wide association studies, 308
 human gestational clocks and, 303–304
 immunological clock hypothesis, 304
 mechanical clock theory, 303–304
 placental clock theory, 303
 human parturition and, control of, 302–303
 hyperplasia of uterus and, 304
 hypertrophy of uterus and, 304
 iatrogenic, 326, 333–334
 inflammation and, 304–307
 oxytocins/oxytocin receptor system, 305
 progesterone and, 307
 prostaglandin regulation, 305
 vaginal host-microbe interactions, 306–307
 mortality rates of, 308
 neonatal outcomes and, intervention strategies for, 319–321
 with antenatal corticosteroids, 320–321
 with magnesium sulphate, 319–320
 neurodevelopmental consequences of, 334, 336
 behavioral outcomes, 334
 blindness, 334
 cerebral palsy, 334
 cognitive outcomes, 334
 motor dysfunction, 334
 sensorineural hearing loss, 334
 placental aging and, 307–308
 prediction of, 311–312
 biomarkers for, 312
 cervical length scanning, 312
 preterm premature rupture of membranes, 306–307, 314
 antibiotic therapy with, 318
 prevalence rates, 333–334
 prevention strategies with antibiotics, 318–319
 bed rest, 319

Index

- preterm birth. (cont.)
 through diet and nutrition, 319
 with intact membranes, 318–319
 with probiotics, 319
progesterone and, 314–316
 delivery methods, 314
 functional progesterone withdrawal, 304
 in high risk asymptomatic patients, 314–315
 inflammation and, 307
 for patients with a short cervix, 315–316
 rationale for use of, 314
risk factors for, 311–323, 333–342
spontaneous, 326
tocolytic drugs and, 302, 318
 long-term outcomes for, 318
 rationale for use of, 318
preterm premature rupture of membranes (PPROM), 4, 206–209, 306–307
 iatrogenic, 207–209
 incidence rates for, 207
 interventions for, 209
 latency period for, 208–209
 oligohydramnios and, 208
 preterm birth and, 306–307, 314, 318
 pulmonary hypoplasia, 207–208
 randomized controlled trials for, 210
 in second trimester, 205–206
 spontaneous, 206, 208–209
 amniocentesis and, 206
 therapeutic intervention strategies for, 209–210
 amnioinfusion, 210
 amniopatch, 209
 in third trimester, 210
primary pleural effusions, 438
primary prenatal diagnostic testing, 1–2
probiotics, 319
profile depicting deletion, 40
progesterone, 304, 307
 cervix length and, 315–316
 multiple pregnancies and, 329
preterm birth and, 314–316
 delivery methods, 314
 functional progesterone withdrawal, 304
 in high risk asymptomatic patients, 314–315
 inflammation and, 307
 for patients with a short cervix, 315–316
 rationale for use of, 314
prolonged fetal acidosis, 475–476
prolonged pregnancy, stillbirth and, 52–53
 induction of labor for, 52
 maternal age as factor in, 52
propranolol, 185
prostaglandin regulation, 305
prostaglandin synthesis inhibitors, 305
proton pump inhibitors, 294
pulmonary atresia with intact ventricular septum, 150–151
pulmonary hypoplasia
 oligohydramnios and, 205–206, 208
 preterm premature rupture of membranes and, 207–208
pulmonary stenosis, critical, 150–151
pumpless technology, in artificial wombs, 84–87
 advantages of, 87
 cerebral autoregulation with, 87
 EXTEND, 85–86
pump-supported technology, in artificial wombs, 84–85
pyrimethamine, 238
quantitative fluorescent polymerase chain reaction (QF-PCR), 38–40
radiofrequency ablation (RFA), 395–396, 401, 419–421, 446
randomized controlled trials (RCTs)
 for fetal cardiac interventions, 146
 for monochorionic twins, 375–377
 for preterm premature rupture of membranes, 210
RAS (renin-angiotensin system), 348
rashes, from chickenpox, during pregnancy, 229–231
 fetal management, 229–230
 maternal treatment, 229
 during perinatal period, 230–231
rationality, in decision-making, 63
RCOG (Royal College of Obstetricians and Gynaecologists), 91
RCTs. *See* randomized controlled trials
red cell alloantibodies, 91
red cell alloimmunization
 alternative treatments, 95–96
 intravenous immunoglobulins, 96
 therapeutic plasma exchange, 96
American College of Obstetricians and Gynecologists on, 91
antibodies, 91
 clinically relevant, 91
 fetomaternal hemorrhage, 91
 red cell alloantibodies, 91
future perspectives on, 96
HDFN and, 91
hemolysis risks, 92
 ADCC assays, 92
 fetal phenotype, 92
 serological testing, 92
incidence rates, 91
intrauterine transfusions for, 93–95
 complications from, 94–95
 hydrops and, 95
 imaging for, 94
 long-term outcomes, 95
 preparations for, 93
 timing of, 94
 transfusion process, 94
pregnancy monitoring with, 92–93
 abandoned techniques in, 93
 with Doppler, 92–93
 with ultrasound, 93
prevention strategies, 91
Royal College of Obstetricians and Gynaecologists on, 91
screening strategies, 91
timing of birth with, 96
reduced fetal movements (RFM), 53
 clinical management of, 53
 maternal perception of, 53
 treatment strategies for, 53
regulatory T cells, 218
renal tumors, 487–491
 clinical presentation, 487–488
 mesoblastic nephroma, 487–488
 antenatal natural history, 488
neuroblastoma, 489–490
 antenatal natural history, 489
 clinical presentation, 489
 MRI imaging, 489
 postnatal management, 490
 prenatal management, 489–490
postnatal management, 488
prenatal management, 488
SCT, 490–491
 antenatal natural history, 490–491
 clinical features, 490
 fetal intervention, 491
 MRI imaging, 490
 postnatal management, 491
 prenatal management, 491
Wilms' tumor, 487–488
 MRI imaging, 488
 sonographic features, 487–488
renin-angiotensin system (RAS), 348
RFA (radiofrequency ablation), 395–396, 419–421, 444–445
RFM. *See* reduced fetal movements
rhabdomyomas, 482–483
Royal College of Obstetricians and Gynaecologists (RCOG), 91
rubella, during pregnancy, 240–242
 clinical presentation of, 240
 epidemiology of, 240
 fetal infection, 241
 maternal-fetal transmission, 241
 prenatal diagnosis, 241
 management of, 241–242
 through detection of ultrasound abnormalities, 242
 maternal infection, 240
 clinical manifestations of, 240
 laboratory findings, 240
 pathophysiology of, 240
 prevention methods for, 242
sacroccygeal teratomas (SCT), 490–491
 antenatal natural history, 490–491
 clinical features, 490
 fetal intervention, 491
 MRI imaging, 490
 postnatal management, 491
 prenatal management, 491
salbutamol, 187
scaffolds, in tissue engineering, 532–534
 collagen, 534
 natural, 534
 synthetic, 533–534
Schinzel-Giedion syndrome, 44
sclerotherapy, 445
SCT. *See* sacroccygeal teratomas
second degree heart block, 186
second heart field (SHF), 110–111. *See also* cardiac morphogenesis
second trimester
 oligohydramnios during, 205–206
 preterm premature rupture of membranes during, 205–206

Index

- selective fetal growth restriction (sFGR), in monochorionic twins, 385–386
classification of, 389, 392–393
evaluation of, 393
clinical risks for, 392–393
congenital infections, 387
cytomegalovirus and, 387
diagnosis of, 388
discordant anomalies, 387
expectant management of, 393–395
fetal therapy, 395–396
bipolar forceps cord coagulation, 395–396
fetoscopic laser coagulation, 395
radiofrequency ablation, 395–396
Gratacos classification of, 388–389
incidence rates for, 392
placental anatomy, 389
placental pathophysiology of, 387–388
territories discordance, 392
pregnancy outcomes, 389
prognosis of, 388–389
selective termination of, 418–419
severity algorithm for, 395
Type I, 389, 392–394
Type II, 389, 392–394
Type III, 392–395
selective feticide, 370
selective intrauterine growth restriction (sIUGR), 378–379
selective termination, of
pregnancy, 409–410
with BCC, 420, 422–423
with dichorionic triplet pregnancy, 419–420
with HIFU, 422
with intrafetal laser, 421
of monoamniotic twin pregnancy, 419
for monochorionic twins
comparison of techniques, 422–423
complications from, 422
discordant structural anomalies, 419
indications for, 418–420
sIUGR, 418–419
TAPS, 419
techniques and methods for, 420–422. *See also specific techniques and methods*
TRAP, 418
TTTS, 419
with MWA, 420–422
with radiofrequency ablation, 419–421
semilunar valve abnormalities, 118–119
semilunar valve stenosis, 148–151
sensorineural hearing loss, from preterm birth, 334
septal defects, 136–140
septation anomalies, 114–117
common arterial trunk, 114–115
double inlet left ventricle, 116
double outlet right ventricle, 115–116
tetralogy of Fallot, 115
transposition of the great arteries, 116–117
septostomy, 353–354
serological testing, for red cell alloimmunization, 92
severe fetal growth restriction, 259
severe thrombocytopenia, 99
SGA (small for gestational age), 264, 283–284
shared decision-making, 64–67
components and steps in, 64–65
informed consent and, 70
interpretive model of, 70
paternalistic approaches in contrast with, 64
SHF (second heart field), 110–111. *See also* cardiac morphogenesis
shingles, in neonates, 228
sickle cell disorders, 542–543
signaling pathways
in embryology development, 20, 22–23
FGF, 31–32
developmental defects and, 31–32
limb development, 31
notch, 32–33
binary decision regulation, 33
birth defects and, 33
inductive interactions, 33
notch intracellular domain, 33
organ development and, 33
TGF β , 29–31
mutations in, 30–31
Wnt, 27–29
canonical, 27–28
modulation of, 29
PCP, 28–29
Planar Polarity, 27
sildenafil citrate, 273–274, 290–296
single fetal demise, with monochorionic twins, 379–380
single nucleotide polymorphism (SNP) microarray, 40
situs defects, 113–114
sIUGR (selective intrauterine growth restriction), 378–379
sleep practices, stillbirth and, 53–54
population attributable risk, 54
small for gestational age (SGA), 264, 283–284
SMCs (smooth muscle cells), 251, 288
smoking. *See* partner smoking; tobacco use
smooth muscle cells (SMCs), 251, 288
SNP (single nucleotide polymorphism) microarray, 40
somatic cell nuclear transfer, 532
Sonic hedgehog morphogen, 24–27
sotalol, 170–171, 173, 184
spina bifida, 449. *See also* in-utero spina bifida repair
animal models for, 467–474
fetal therapy for, 454
genetic risk factors, 449–450
MOMS trial and, 467
prevalence rates for, 452–453, 456
prognosis rates for, 456
tissue engineering for, 535
two-hit hypothesis, 467
spiramycin, 238
spontaneous abortion, 228
spontaneous preterm birth, 326
spontaneous preterm premature rupture of membranes (sPPROM), 206, 208–209
amniocentesis and, 206
sPPROM (spontaneous preterm premature rupture of membranes), 206, 208–209
statins, 294
stem cells, 340
endogenous repair with, 527
hematopoietic, 216–217, 512
MSC, 512, 522
in tissue engineering, 532–533
amniotic fluid, 533
embryonic, 532
fetal, 533
induced pluripotent, 532–533
stenosis. *See* aortic stenosis; pulmonary stenosis
stenting, 150
steroid therapy
for Duchenne muscular dystrophy, 514
for microcystic lung lesions, 444
stillbirth
gestational diabetes mellitus and, 50–51
co-morbidity risks, 50
diagnosis of, 50
screening for, 50
treatment therapies, 51
Type 1, 50
Type 2, 50
in HICs, 48
incidence rates, 48
obstetric cholestasis and, 48–50
UCDA treatment with, 50
previous medical history of, 51–52
prolonged pregnancy and, 52–53
induction of labor for, 52
maternal age as factor in, 52
reduced fetal movements and, 53
clinical management of, 53
maternal perception of, 53
treatment strategies for, 53
risk factors, 48–53
with gestational diabetes mellitus, 50
previous stillbirths, 51–52
sleep practices and, 53–54
population attributable risk, 54
tobacco use and, 55–56
adverse outcomes as result of, 55
cessation of smoking approaches, 55
partner smoking and, 55
treatment therapies
aspirin therapy, 52
for gestational diabetes mellitus, 51
for obstetric cholestasis, 50
for reduced fetal movement, 53
villitis of unknown aetiology, 51–52
structural heart disease, 112. *See also* congenital heart disease
substance abuse
fetal growth optimisation and, 288–289
for fetal growth restriction, 266–267
NTDs and, 452
sudden fetal death, 524–525
sulindac, 204
sulphonamide, 238
supplements, fetal growth optimisation and, 287–288
supraventricular tachycardia (SVT), 166, 181–182
atrial ectopic tachycardia, 167–168
atrial flutter, 167–168, 171–173

Index

- supraventricular tachycardia (SVT) (cont.)
 AV reentrant tachycardia, 167–168
 electro-mechanical activation of fetal heart, 166–167
 fetal hydrops and, 167, 171–173, 181
 functional characteristics with, 167
 management and treatment of, 168
 with direct fetal treatment, 171
 efficacy of, 171–174
 management of, 182–184
 close monitoring in, 182
 with pharmacological therapy, 182–184
 mechanisms of, 167–168
 medications for, 168–171, 173.
 See also specific drugs
 clinical usage information, 170
 electrophysiological characteristics, 169
 permanent junctional reciprocating tachycardia, 167–168
 persistent tachycardia and, 171–173
 prenatal termination with, 172–173
SVT. *See* supraventricular tachycardia
syndromic congenital heart disease, 126–127
synthetic scaffolds, 533–534
- T cells, regulatory, 218
T. cruzi (*Trypanosoma cruzi*), 220
T. gondii (*Toxoplasma gondii*), 220
T lymphocytes, 215–216
 $\alpha\beta$ T lymphocytes, 217
 $\gamma\delta$ T lymphocytes, 218
tachycardias, 180–185. *See also* heart block
 atrial ectopic, 167–168
 atrial flutter, 167–168, 171–173, 181–183
 blocked atrial bigeminy, 185–186
 management of, 185–186
bradycardias, 185
 definition of, 185
 management of, 185
 with 1:1 AV conduction, 185
 definition of, 180
 permanent junctional reciprocating, 167–168
 persistent, 171–173
 sinus, 182
- trigeminy, 185–186
 management of, 185–186
 ventricular, 182
tadalafil citrate, 290–296
TAPS. *See* twin anemia-polycythemia sequence
TAS (thoracoamniotic shunting), 439–441
T-cell receptors, 215–216
tension hydrothorax, 483
teratomas. *See also* cervical teratomas; sacrococcygeal teratomas
 open fetal surgery for, 78–79
 for cervical teratomas, 78–79
 for CHAOS, 79
terbutaline, 187
tetralogy of Fallot (TOF), 115
Texas Children's Fetal Center, in-utero spina bifida repair at, 470–474
 fetoscopic outcomes, 473–474
 surgical technique, 470–473
TGA (transposition of the great arteries), 116–117
TGF β signaling pathway, 29–31
 mutations in, 30–31
thalassaemias, 542–543
 fetal stem cells, 543
 for HSCT, 542
therapeutic plasma exchange (TPE), 96
third degree heart block, 186
third trimester
 oligohydramnios during, 210
 preterm premature rupture of membranes during, 210
 thoracoamniotic shunting (TAS), 439–441
 procedural aspects of, 441
 thoracocentesis, 439–440
thrombocytopenia. *See also* fetal and neonatal alloimmune thrombocytopenia
 classification of, 99
timing of birth, with red cell alloimmunization, 96
tissue engineering
 conditions of interest, 535
 fetal interventions, 535
 for gastroschisis, 535
 for MMC, 535
 for spina bifida, 535
 in fetal therapy, 534–535
 immunology, 534
 physiology and, 534–535
 scale and access, 535
 post-natal interventions, 535–536
 for bladder exstrophy, 536
 for bone grafting, 536
 for CDH, 535–536
 for CHAOS, 536
 for CHD, 536
- for fetal trachea occlusion, 535–536
 oesophageal atresia, 536–539
scaffolds, 532–534
 collagen, 534
 natural, 534
 synthetic, 533–534
somatic cell nuclear transfer, 532
stem cells, 532–533
 amniotic fluid, 533
 embryonic, 532
 fetal, 533
 induced pluripotent, 532–533
TLRs (Toll-like receptors), 215
tobacco use
 fetal growth optimisation and, 288–289
 fetal growth restriction and, 266–267
 stillbirth and, 55–56
 adverse outcomes as result of, 55
 cessation of smoking approaches, 55
 partner smoking and, 55
tocolytic drugs, 329
 for MMC, 463
 for preterm birth, 302, 318
 long-term outcomes for, 318
 rationale for use of, 318
TOF (tetralogy of Fallot), 115
Toll-like receptors (TLRs), 215
TOPS (twin oligohydramnios-polyhydramnios sequence), 353, 368. *See also* twin-to-twin transfusion syndrome
TOTAL (Tracheal Occlusion to Accelerate Lung Growth) trial, 72
Toxoplasma gondii (*T. gondii*), 220, 235
toxoplasmosis, during pregnancy, 235–240
 causes of, 220, 235
 congenital, 236–237
 epidemiology, 235–236
 seroprevalence in, 235–236
 management of, 238–239
 intrapartum, 239
 in-utero treatment, 238–239
 with medications, 238
 postnatal, 239
maternal infection, 236
 clinical manifestations, 236
 laboratory findings, 224–236
 prenatal diagnosis after, 237
 in neonates, 237–238
 prevention strategies for, 239–240
- TPE (therapeutic plasma exchange), 96
Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial, 72
transcervical CVS, 410
transfusions. *See* intra-uterine transfusions
transgenic protein expression, 553–554
transposition of the great arteries (TGA), 116–117. *See also* congenitally corrected transposition of the great arteries
TRAP. *See* twin reversed arterial perfusion sequence
trigeminy tachycardias, 185–186
 management of, 185–186
trimethoprim, 238
triplet births. *See* dichorionic triplet pregnancy; multiple pregnancies
trophoblast compartment, 250–251, 253
Trypanosoma cruzi (*T. cruzi*), 220
TTTS. *See* twin-to-twin transfusion syndrome
twin anemia-polycythemia sequence (TAPS)
 antenatal diagnosis, 368–369
 classification system in, 368
 with ultrasound, 368–369
 incidence rates for, 367
 neonatal diagnosis, 369
 placental presentation, 369
 pathogenesis of, 367–368
 perinatal outcomes, 370
 selective termination for, 419
 spontaneous, 367
 treatment for, 369–370
 expectant management in, 369
 fetoscopic laser surgery, 370
 induced preterm delivery, 370
 intra-uterine transfusions, 369–370
 selective feticide, 370
twin births. *See* multiple pregnancies
twin oligohydramnios-polyhydramnios sequence (TOPS), 353, 368. *See also* twin-to-twin transfusion syndrome
twin reversed arterial perfusion sequence (TRAP), 379–380
 diagnosis of, 398–400
 with ultrasound, 399, 401
 fetal interventions, 400–402

Index

- fetoscopic laser coagulation, 401–402
 timing of, 402
 ultrasound guided bipolar coagulation, 402
 intrafetal coagulation, 400–401
 with laser ablation, 401
 with microwave ablation, 401
 with radiofrequency ablation, 401
 ultrasound imaging, 401
 in monochorionic twins, 379, 400
 selective termination with, 418
 natural history of, 400
 pathophysiology of, 398–399
 prevalence rates for, 398
 selective termination for, 418
 twins. *See specific topics*
 twin-to-twin transfusion syndrome (TTTS), 2, 201–202, 410
 angiogenic placental growth factors, 346–347
 detection rates for, 363
 development of, 344–345
 diagnosis of, 363
 early, 363–364
 diagnostic considerations, 363
 outcomes for, 364–365
 polyhydramnios and, 363
 surgical considerations for, with fetoscopic laser ablation, 363–364
 fetal cardiovascular effects, 347–349
 assessment methods, 347
 endothelins, 348–349
 natriuretic peptides, 348–349
 fetal membranes and, 520
 fluid homeostasis factors with, 348–349
 late, 364–365
 outcomes for, 365
 surgical considerations for, with fetoscopic laser ablation, 364–365
 with monochorionic twins, 346
 monochorionic twins and, 373–377
 cerebral injury and, through neuroimaging, 373
 with monozygotic twins, 344
 placental angioarchitecture and, 345–346
 anastomoses and, 345
 renal system factors with, 348
 renin-angiotensin system and, 348
 selective termination with, 419
 treatment options for, 353–359. *See also* fetoscopic laser coagulation of placental vessels
 amnioreduction, 353
 septostomy, 353–354
 22Q11 deletion syndrome, 157
 Type 1 gestational diabetes mellitus, 50
 Type 2 diabetes, fetal origins of, 8
 Type 2 gestational diabetes mellitus, 50
 Type I sFGR, 389, 392–394
 Type II sFGR, 389, 392–394
 Type III sFGR, 392–395
 UCDA (ursodeoxycholic acid), 50
 UK. *See* United Kingdom
 ultrasonographic prognosis, for congenital bladder neck obstruction, 427, 429
 ultrasound
 for CDH, 496–498
 liver position on, 496–498
 for lung size, 496–497
 for cervical cerclage, 328
 for cytomegalovirus, 233–238
 Doppler
 ductus venous, 271–272
 MCA, 271–272
 for red cell alloimmunization, 92–93
 for fetal and neonatal alloimmune thrombocytopenia, 103
 in fetal cardiac interventions, 147
 for fetal growth restriction, 269–270, 280
 with ductus venous Doppler, 271–272
 for fetal biometry, 269, 280
 for fetal vessels, 280
 for fetal well-being, 269–270
 with MCA Doppler, 271–272
 for monochorionic twins, 384
 selective screening with, 282
 universal screening with, 269, 282
 with uterine artery Doppler, 258–259, 270–271, 280
 HIFU, 422
 for muscular dystrophy, 545
 for pleural effusions, 438–439
 for red cell alloimmunization, 93
 for TRAP, 399
 for twin anemia polycythemia sequence, 368–369
 ultrasound guided bipolar coagulation, 402
 United Kingdom (UK)
 congenital anomaly registers in, 572–573
 British Isles Network of Congenital Anomaly Registers, 572–573
 National Congenital Anomaly and Rare Diseases Registration Service, 573–574
 National Congenital Anomaly System, 572
 Global Obstetrics Network in, 563–564
 United States (US)
 in-utero spina bifida repair in, 468–469
 NICHD in, 562–563
 urinalysis. *See* fetal urinalysis
 urinary tract obstruction.
See congenital bladder neck obstruction; lower urinary tract outflow obstruction
 urine production, 194
 ursodeoxycholic acid (UCDA), 50
 US. *See* United States
 uterine activity, monitoring of, for multiple pregnancies, 327
 uterus
 hyperplasia of, 304
 hypertrophy of, 304
 vaginal host-microbe interactions, 306–307
 values, decision-making influenced by, 66–67
 valve anomalies, 118–119
 atrioventricular abnormalities, 119
 semilunar abnormalities, 118–119
 valvuloplasty. *See* aortic valvuloplasty
 variant of unknown significance (VOUS) rate, 43
 variants of uncertain significance (VUS) detection, 40–42
 varicella, in neonates, 228
 vascular endothelial growth factor (VEGF), 287, 294–300, 346–347
 gene therapy for, 542–546
 venovenous anastomoses (VVA), 345
 ventricular ectopics, 178–180
 ventricular inversion, 114
 ventricular septal defect (VSD), 117–118
 ventricular tachycardias, 182
 very severe thrombocytopenia, 99
 vesicoamniotic shunting, 430–433
 villitis of unknown etiology (VUE), 51–52, 257
 villous infarction, 254
 vitamin B12 deficiency, 451–452
 VOUS rate (variant of unknown significance rate), 43
 VSD (ventricular septal defect), 117–118
 VUE (villitis of unknown etiology), 51–52, 257
 VUS detection (variants of uncertain significance detection), 40–42
 VVA (venovenous anastomoses), 345
 WHO. *See* World Health Organization
 whole exome sequencing, 44
 categorization of, 44
 nucleotide alterations identification, 44
 Williams syndrome, 157
 Wilms' tumor, 487–488. *See also* mesoblastic nephroma
 MRI imaging, 488
 sonographic features, 487–488
 Wnt signaling pathway, 27–29
 canonical, 27–28
 modulation of, 29
 PCP, 28–29
 Planar Polarity, 27
 World Health Organization (WHO), 580
 xDiagnostic yield, 43
 Zika virus, 220
 prenatal diagnosis in developing countries, 580–581
 recommendation and guidelines for, 581
 for maternal infection diagnosis, 581
 in preconception period, 581
 in South America, as epidemic, 581
 WHO response to, 580
 zinc concentrations, 452