CHAPTER 4
Developmental Abnormalities
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Outline
- Glossary of terms, 28
- Introduction, 29
- Failure of development (aplasia), 30
- Failure of canalization (atresia), 30
- Malposition (ectopia), 31
- Disordered structure (dysplasia), 32
- Midline and sequestration abnormalities, 32
- Cystic fibrosis (mucoviscidosis), 34
- Disordered sex development (DSD), 35

GLOSSARY OF TERMS

**Agenesis** Complete failure of development of an organ or tissue.

**Ambiguous genitalia** A birth defect where the external genitals are undifferentiated, and lack the typical appearance of either male or female.

**Anencephaly** A lethal abnormality due to failure of the cranial neural folds to close leading to failure of brain development (preventable by maternal use of folic acid).

**Aplasia** Incomplete or retarded development of an organ or tissue, leaving a rudimentary structure.

**Association** A nonrandom appearance of a group of anomalies that are the result of different etiologic factors.

**Atresia** Failure of a duct to canalize.

**Complex gonadal dysgenesis** Describes germ cell aplasia accompanied by chromosomal abnormalities.

**Congenital** A developmental abnormality which is present at birth.

**Deformation** Is the result of prolonged mechanical trauma to the embryo (e.g. club feet deformity due to oligoamnion).

**Disruption** Is the result of sudden vascular or mechanical trauma by bands to the embryo (e.g. loss of limbs or fingers).

**Dysgenesis** Describes abnormal organ development in the embryo.

**Dysplasia** A congenital disorder of structure manifested as abnormal gross shape of an organ, disorganized tissue pattern or atypical cytomorphology.

**Ectopia** The presence of an organ or a tissue away from its normal location.

**Extrophy** A congenital defect of lower anterior bladder wall exposing the urinary bladder.

**Gastrochisis** A ventral anterior abdominal wall defect exposing abdominal organs.

**Gonadal dysgenesis** Is a congenital disorder characterized by loss of germ cells accompanied by fibrosis (hence the name streak gonad), the associated hormonal failure leads to infertility and absence of secondary sexual characteristics.

**Hermaphrodite** The presence of both testicular and ovarian tissues in the same or opposite gonad (recent term ovotestis DSD).

**Hypoplasia** Failure of an organ to achieve its full size for the age of individual (underdevelopment).

**Karyotype** Is the chromosomal makeup of the individual (23 pairs including 22 pairs autosomal controlling somatic function and one pair sex chromosomes, xx in females and xy in males).

**Malformations (or birth defects)** Are structural or functional disorders present at birth and arising at the time of organogenesis (3-8 weeks of gestation).

**Mixed gonadal dysgenesis** Describes an individual with normal gonad on one side and a streak fibrotic ovary on the other side.

**Mosaicism** Denotes the presence of two or more populations of cells with different genotype in one individual.

**Pseudohermaphrodite** A sex genotype is associated with the opposite sex phenotype (Recently named 46xx DSD or 46xy DSD).

**Sequence** A syndrome with anomalies occurring in a specific sequential order.

**Sequestration** The detachment and separation of a part of surface epithelium and its inclusion in the underlying stroma.
Sex reversal The change of a gender from one sex to another, may be natural (in fish) or induced (in birds), but in human, the term is restricted to reconstructive surgery of genitalia in intersex patients.

Streak ovary Is an ovarian dysgenesis characterized by germ cell aplasia (corresponding to Sertoli cell only syndrome in males), examples are Turner syndrome, Swyer syndrome and PERRAULT syndrome.

Spina bifida Defect of closure of vertebral arches and neural tube folds.

Syndrome A group of anomalies that occur together and are the result of a single etiologic genetic cause.

Teratogen A factor that causes a birth defect by disturbing organogenesis.

Teratology The study of birth defects.

INTRODUCTION

Congenital disorders are defined as structural or functional abnormalities (e.g. metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life. These abnormalities caused 2.761 million deaths during the neonatal period in 2013 world wide. Congenital heart disease and neural tube disorders were the most common causes of mortality. Congenital disorders include five main types, namely: malformations, disruptions, deformations, syndromes, and associations. Congenital malformations, also known as birth defects, are not uncommon. Thus, in USA, 15% of new births have minor defects and 3% have major defects that need surgical treatment. The etiology may be genetic (25%), environmental (5%), multifactorial (25%) or idiopathic (45%). A list of proven teratogenic agents to human are presented in (Table 4-1) which are etiologically related to birth defects.

Gestation is divided into two periods, namely: embryonic period (the first 8 weeks) and the fetal period (from 8 to 38 weeks). The development of systems occur in the embryonic period, whereas, the fetal period is the time of functional maturation. System developments occur at different times in a sequential archer (Table 4-2). Teratogenic agents are lethal to the embryo during the first three weeks, but teratogenic risk is possible during the period (3-8 weeks) reaching a maximal risk at the fifth week: Affection of a particular system by a malformation is largely dependent on exposure to a teratogenic agent at the time of its development. The following are three common birth defects and their related teratogenic agents: (1) cardiac defects (Rubella virus, thalidomide, lithium and aminopterin), (2) cranio-facial defects (Aminopterin, amphetamines and mofetil) and (3) Neuro-developmental disorders (folic acid antagonists, aminopterin and methotrexate, cocaine, cyto- megalovirus, Herpes simplex virus, toxoplasmosis and irradiation). Many of these defects are preventable by avoiding maternal exposure to teratogens. The present chapter covers important developmental malformation which may be submitted to the surgical pathologist. Other congenital abnormalities which present as systemic disease (hematologic or metabolic) are outside the scope of this review.

### Table 4-1 Proven Teratogenic Agents

<table>
<thead>
<tr>
<th>Infectious agents</th>
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<tbody>
<tr>
<td>Rubella virus</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Herpes simplex virus</td>
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<tr>
<td>Varicella virus</td>
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<td>Toxoplasmosis</td>
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<th>Physical agents</th>
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<tr>
<td>Irradiation</td>
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<tr>
<th>Chemical agents</th>
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<tr>
<td>Alcohol</td>
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<td>Cocaine</td>
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<tr>
<td>Angiotensin</td>
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<tr>
<td>Coumarin</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>Androgens</td>
</tr>
<tr>
<td>Aminopterin</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Hydantooin</td>
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<tr>
<td>Cis-retinoic acid (Vit. A)</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Misoprostal</td>
</tr>
<tr>
<td>Tetracycline</td>
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<tr>
<td>Thalidomide</td>
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<tr>
<td>Valproate</td>
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<table>
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<th>Maternal conditions</th>
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<td>Diabetes, Obesity</td>
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### Table 4-2 Time of Organogenesis in Human Embryo (3-10 weeks)

<table>
<thead>
<tr>
<th>System</th>
<th>Time /days</th>
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<tbody>
<tr>
<td>Nervous</td>
<td>23</td>
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<tr>
<td>Placenta</td>
<td>25</td>
</tr>
<tr>
<td>Limbs</td>
<td>29</td>
</tr>
<tr>
<td>Gut</td>
<td>31</td>
</tr>
<tr>
<td>Face</td>
<td>37</td>
</tr>
<tr>
<td>Heart septa</td>
<td>45</td>
</tr>
<tr>
<td>External genitalia</td>
<td>47</td>
</tr>
<tr>
<td>Gonads</td>
<td>72</td>
</tr>
</tbody>
</table>

(Sadler, 2012)
FAILURE OF DEVELOPMENT
(APLASIA)

Aplasia is incomplete or retarded development of an organ or tissue, leaving a rudimentary structure. It should be differentiated from two other terms, namely: agenesis is complete failure of development of an organ or tissue, leading to its absence, and hypoplasia is inadequate regeneration of cells, resulting in suboptimal numbers. The following are four illustrative examples of aplasia:

1. Bone Marrow Aplastic Anemia
   This refers to defective cell renewal of hematopoietic cells by stem cells. This defect may involve one cell lineage (erythropenia or leukopenia) or affect all three cell types (pancytopenia) shown in (P 4-1).

2. Sertoli Cell Only Syndrome
   This is the result of microdeletion of Yq11 region of Y chromosome in males. Complete germ cell aplasia (P 4-2) results in azoospermia, but, hypofunction of germ cells (hypoplasia) leads to oligospermia. In this syndrome, interstitial cells and secondary sex characters are present and follicular stimulating hormone (FSH) is high in serum.

3. Thymic Aplasia (Di George syndrome)
   This results from deletion of 22q11.2. The main manifestation is immunodeficiency due to the reduced numbers of T-lymphocytes. Other features include cardiac anomaly (tetralogy of Fallot), cleft palate, hypoparathyroidism with hypocalcemia and intellectual, as well as, behavior difficulties.

4. Aganglionic Megacolon
   This is also known as Hirschsprung disease. The estimated incidence is about one in every 5000 births, with male predominance (4:1). The pathogenesis is related to mutation of RET proto-oncogene and other genes (RELN and EAL) responsible for the migration of vagal ganglionic cells of neural crest to the colon. The absence of ganglion cells results in colonic dismotility and constipation. Enterocolitis is a potentially fatal complication of this disease which may be also associated with other serious congenital anomalies.

   Four gross patterns of Hirschsprung disease are recognized: the classic short distal segment (80%), the long segment extending to the splenic flexure (10%) and total colonic aganglionosis (5%). Ganglionic cells are located in submucosa and muscle layers with normal number of 1-5 per mm (average 3), and are confirmed by markers (calretenin, NSE and Bel-2). Aganglionic Hirschsprung (P 4-3) is present at birth, but, hypoganglionic colon (one ganglion/mm) may first present in childhood.

FAILURE OF CANALIZATION
(ATRESIA)

Atresia is defined as failure of a duct to canalize. The following are three illustrative examples:

1. Esophageal atresia
   The esophagus and trachea develop closely together as diverticula from pharyngeal pouch and foregut respectively. These structures are initially solid, then canalize. Five variants of esophageal atresia are recognized (Fig 4-1), the most common (85%) is a proximal esophageal pouch and a distal tracheobronchial fistula. Aspiration pneumonia is a serious complication.

2. Biliary atresia
   Congenital extrahepatic biliary atresia (EHBA) is present in about 1 per 12,000 live births. The onset of obstructive jaundice may be at birth or develop 1-2 months later. Biliary atresias are classified into

   ![Fig 4-1 Various types of esophageal atresia. A. Esophageal atresia with distal tracheoesophageal fistula (85% of cases), B. Isolated esophageal atresia (10%) and C. H shaped type esophageal atresia (5%).](image)

   ![Fig 4.2 Types of biliary atresia (black coloured). A. Type I is distal atresia of common bile duct. B. Type II is atresia of proximal bile ducts (95% of cases). Only type I is associated with dilated gall bladder.](image)
a proximal type affecting the hepatic ducts and a distal type affecting the bile duct (Fig 4-2).

Biliary atresia may be associated with cystic dilatation of proximal biliary system (choledochal cyst) of intrahepatic or extrahepatic locations. Liver biopsy is diagnostic and is characterized by bile duct proliferation, cholestasis, periportal fibrosis and inflammation (P 4-4). The serious complications of biliary cirrhosis, namely liver failure, will develop rapidly without surgical intervention.

3. Imperforate anus

Early in embryonic life, there is a common endodermal chamber (the cloaca) into which both bladder and rectum open. The cloaca is separated from surface ectoderm by the cloacal membrane (Fig 4-3 A). The cloaca is later divided into an anterior (urinary) and posterior (rectal) chambers by the down growth of a urorectal septum.

The posterior part of cloacal membrane is named the anal membrane. Resorption of the anal membrane by the 8th week of embryonic life creates the anal canal (Fig 4-3 B).

Imperforate anus represents an atresia of anal membrane. It is classified into two main types, namely: low and high depending on the relation of rectal pouch to pelvic floor (Fig 4-3 C and D). The atresia is commonly associated with fistulas that vary according to sex. High imperforate anus associated with urinary fistula is most difficult to repair, hence the poor functional results after surgery.

MALPOSITION (ECTOPIA)

The ectopia may affect the entire organ, or an additional tissue of the organ, hence the name accessory structure.

Ectopic Organs

1. Ectopic thyroid. An ectopic thyroid may be located anywhere along the path of its descent during embryologic development. The most common site is the base of tongue (lingual thyroid), but may also lie high up in the neck at the level of hyoid bone.

2. Ectopic kidney. There are two main types of ectopia (a) intrapelvic kidney, where it presents as unexplained mass and subjected to unnecessary nephrectomy, and (b) Contralateral ectopic kidney in which one kidney crosses to the other side, whereas, its ureter remains in its original location. Obstructive uropathy (hydro nephrosis) is the main complication.

3. Ectopic testis. Two types are recognized, namely: (a) Undescended testis, the testis is located in any place along its descent (lumbar, iliac or inguinal). An intrabdominal testis will not function properly, and remains fetal in type (P 4-5) and is at high risk to develop germ cell tumors (seminoma) and (b) A true ectopic testis is the one which has completed its descent, but is located outside the scrotum (e.g. at external ring, root of penis, femoral triangle or perineum).

4. Ectopic thymus. The thymus develops in the neck from the 3rd pharyngeal pouch, then descend to the anterior mediastinum.

Fig 4-3 Development of anal canal and types of imperforate anus. A. The endodermal cloaca is a common chamber for bladder and rectum. B. Down growth of the urogenital septum divides the cloaca into an anterior urogenital and a posterior rectal cavities which open to the exterior after disappearance of the cloacal membrane, C. Low imperforate anus resulting from failure of cloacal membrane to breakdown, D. High imperforate anus in a male associated with rectovesical fistula is rather difficult to repair.
Ectopic Accessory Tissues

1. Accessory breast tissue. This may occur in axilla, or anywhere along the mammary line which extends from the axilla to the pubic region.

2. Accessory spleens. These are rounded encapsulated structures of splenic tissue (1-3 cm in diameter) which may be encountered during laparotomy and misdiagnosed as lymphoma by frozen section. Accessory spleens are present in 20% of population and common sites are: splenic hilum (50%), behind pancreas (30%), mesocolon and splenic ligaments (20%).

3. Ectopic pancreatic tissue. This is observed in the stomach or small intestine including Meckel diverticulum (P 4-6).

4. Ectopic pregnancy. The most common site is the uterine tube (95% of cases). Other sites include: the ovary or peritoneum (Douglas pouch or omentum). Pregnancy associated ectopic decidua (deciduosis) is also encountered in peritoneum, lymph nodes, ovary and cervix.

5. Endometriosis. The most common sites are pelvic structures (ovaries, tubes and colon). It may develop at anterior abdominal wall after caesarian section. Endometriosis may also affect the uterine cervix, vagina and even the female external genitalia. The presence of both endometrial glands and stroma distinguish the lesion from adenocarcinoma (P 4-7).

DISORDERED STRUCTURE (DYSPLASIA)

Dysplasia is defined as a congenital disorder of structure of an organ or tissue. Two examples are discussed.

Fibrous Dysplasia of Bone

This congenital (but nonhereditary) bone disease is an example of mesenchymal mutation of the gene GNAS (located on chromosome 20q13) during embryogenesis. This gene codes for a guanine nucleotide-binding protein (G protein) with subsequent activation of the enzyme adenyl cyclase with overproduction of AMP (adenosine monophosphate). The latter activates mesenchymal progenitor cells to proliferate, with failure to differentiate to osteoblasts, hence the lack of mature lamellar bone formation. Recent studies have confirmed the monoclonal nature of these cells. Two main clinical types are recognized, namely: monostotic (70%) and polyostotic type (30%). The monostotic type is solitary and commonly involves craniofacial and long bones, whereas, the polyostotic type is multifocal and may rarely (3%) be associated with endocrine syndromes.

The classic histologic features of fibrous dysplasia include: thin curvilinear irregular trabeculae lacking osteoblastic rimming, surrounded by bland fibroblastic cells (P 4-8). Rare variants are osteofibrous dysplasia and chondrofibrous dysplasia in which mature bone and cartilage many be evident, (P 4-9 and 4-10).

The three main complication of fibrous dysplasia are: skeletal deformities, fractures and rarely malignant change in patients with polyostotic disease. The resulting sarcomas include: osteosarcoma, fibrosarcoma, chondrosarcoma and malignant fibrous histiocytoma.

Renal Cystic Dysplasia

Renal dysplasia, better named multicystic renal dysgenesis is the most common renal mass in infants (<1 year), with an incidence of 1 per 4000 live births. The molecular mechanism involves mutations of genes which control epithelia-mesenchyme interaction (WT1, EYA1, SIX1 and PAX2). Embryonic renogenesis is an example of this interaction, since normally, the epithelium of the ureteric bud (mesonephros) produce growth factors which induce epithelium in the mesenchyme of (mesonephros), thus establishing the continuity of renal duct system.

Grossly, the affected kidney is irregular in shape with multiple cysts (P 4-11 A). The histology is characterized by disorganized pattern, immature collecting tubules with cystic change and undifferentiated mesenchyme which may contain cartilage (P 4-11 B). The three main complications of renal dysplasia are hypertension, renal infections and Wilms tumor.

MIDLINE AND SEQUESTRATION ABNORMALITIES

These developmental abnormalities result from either failure of neural folds to close and form the neural tube, or failure of maxillo-facial folds or body folds to close. The resulting developmental abnormalities are either defects or sequestration cysts. The latter is derived from separation of surface ectoderm which may occur at fusion lines.

Midline Defects

1. Intracranial. Including anencephaly or absence of brain, a fatal condition due to failure of fusion of neural folds. Another example is agenesis of corpus callosum.

2. Craniofacial. Includes encephaloceles (nasal or occipital) and harleip and cleft palate.

3. Chest. Includes defect of anterior chest wall due to agenesis of sternum and cardiac septal defects.

4. Abdomen. A defect in upper anterior abdominal
wall (gastroschisis) will expose stomach and intestine, whereas, a defect of lower ventral abdominal wall (ectopia vesica). A defect of urethral folds will result in epispadius and hypospadias.

5. Spina bifida. This involves incomplete development of the vertebral arches, with or without defects of neural tube (Fig 4-4). The lumbosacral region is the most common site. This disorder is preventable by folic acid during pregnancy.

Midline Cysts
1. Intracranial. Including craniopharyngeal suprasellar cyst, colloid cyst and dermoid cyst.
2. Head and neck. Including palatal cyst, thyroglossal cysts (Fig 4-5 and P 4-12) and bronchogenic cysts (P 4-13) which are typically located at suprasternal region or over the manubrium. They arise from foregut and lined by respiratory epithelium. Two other laterally located developmental cysts are the external angular dermoid cyst and branchial cyst (Fig 4-6). Dermoid cysts (P 4-14) form as a result of sequestration of skin below surface at lines of fusion during development. Branchial cysts arise due to failure of obliteration of the second branchial cleft (or failure of fusion of second and third branchial arches) are typically located at anterior border of sternomastoid muscle. (P 4-15)

3. Mediastinal cysts. Thymic cysts are located in the anterior mediastinum, whereas, cysts derived from foregut (bronchial, esophageal and enteric) are located in posterior mediastinum. Pericardial mesothelial cysts are located at the costophrenic angle.

4. Abdominal cysts. These includes vitelline cyst and unachal cyst. Vitelline cyst arises from remnants of vitelline duct which connects the yolk sac to small

Fig 4-4 Spina bifida and neural tube defect (NTDs). A. Spina bifida occulta due to failure of vertebra to fuse distal to the spinal cord and the defect is covered by skin. B. Meningocele is a fluid filled sac of meninges protruding from the defect, but the spinal cord is in its normal location. C. In meningocele the sac contains neural tissue and, D. Rachischisis is due to failure of normal tube to close resulting in spina bifida and exposure of the neural tissue. Most spinal cord defects occurs in the lumbosacral area and are preventable by maternal use of folic acid during pregnancy.

Fig 4-5 Development of thyroid and common sites of thyroglossal cysts. The thyroid gland derives from an invagination of foregut endoderm at the base of the tongue (Foramen cecum) and descends in midline to below thyroid cartilage. The thyroglossal duct provides a route for this descent. Cysts of thyroglossal duct are most common in the hyoid bone.
intestine in the embryo (Fig 4-8). Urachal cyst arises from remnants of allantois which connects the urogenital sinus to umbilicus (P 4-16).

**CYSTIC FIBROSIS (MUCOVISCIDOSIS)**

Cystic fibrosis is a hereditary disorder of exocrine glands, resulting from disturbance of transmembrane electrolyte transport, leading to the development of multiple cysts filled with viscid mucin. The incidence is about one case per 2500 live births.

**Molecular Mechanism**

The disease is inherited as autosomal recessive and results from mutation of CFTR gene 7q 31.2 (cystic fibrosis transmembrane conductance regulator). The function of cell membrane electrolyte channel is tissue specific. In sweat glands, under normal conditions, both Na and Cl ions are not transported in sweat, but, in cystic fibrosis both ions are expelled in sweat. Conversely, the reverse occurs in the lungs, whereas, in cystic fibrosis there is excessive transport of Na, Cl and water from bronchial channels across epithelium, leading to dehydration of mucin in the lumen, plugging and obstruction of air ways with cystic change.

**Pathologic Features**

Multiple organ systems are affected, namely; the pancreas, liver, lungs, salivary glands, sweat glands and testis (agenesis of vas with obstructive azoospermia). The cystic lesions (P 4-17 and 4-18) are complicated by inflammation, parenchymal atrophy and organ failure. Pulmonary affection is the most serious. Pulmonary fibrosis, emphysema and respiratory failure are the usual cause of death.
DISORDERED SEX DEVELOPMENT (DSD)

These are defined as congenital conditions associated with atypical development of chromosomal, gonadal or anatomical sex. The nomenclature and treatment were revised in 2005 and the term disordered sex development (DSD) replaced previous terms of intersex and hermaphroditism (Houk LP, 2006). The overall incidence of DSD is about 1:5500 births. Congenital adrenal hyperplasia and mixed gonadal dysgenesis are the most common types, contributing over 50% of all cases.

Development of Gonads (Gonadogenesis)

Originally and throughout the 7th week of gestation, the gonads of males and females are identical, composed of indifferent gonad and two tubular structures, namely: the mullerian duct (MD) and wolffian duct (WD) which terminate into the cloaca. However, the genotype of sex chromosomes is different (XX in females and XY in males). The SRY gene, located in Y chromosome, codes for a protein (testis determining factor) that regulates male sexual differentiation (Fig. 4-9).

By the 8th week of gestation, SRY gene is expressed leading to the development of a functioning testis, with leydig cells secreting testosterone and sertoli cells secreting antimullerian hormone (AMH). Testosterone is converted in testis by the enzyme 5-α-reductase to a more biologically active hormone dihydrotestosterone (DHT). In males, MIH causes regression of mullerian ducts, whereas, androgens cause the development of the wolffian system into the male duct system, as well as, the development of male external genitalia. Targets for androgens include: germ cells, prostate, external genitalia, bone, brain and adipose tissue. Testosterone exerts its effect by binding to androgen receptors in target cells.

The gonads of female embryo differentiate into ovaries at the 12 week of gestation and secrete estrogen. In absence of SRY gene, wolffian duct undergoes regression, whereas, in presence of estrogen the mullerian duct differentiate to the female duct system (uterine tube, uterus and inner vagina), as well as, the development of female external genitalia (Fig 4-9).

Classification

Fig. 4-9 Normal gonadogenesis in males and females. Key factor for the different sex differentiation is the presence of SRY gene on the Y chromosome in males and its absence in females, leading to the development of testes in males and ovary in females. The genital conducting system is formed from mullerian duct in females and Wolffian duct in males. In females Wolffian duct undergo passive regression due to absence of testosterone, but, in males mullerian ducts undergo active regression due to the effect of antimullerian hormone. The phenotype of the external genitalia is determined by the type of sex hormone expressed.
The new classification of DSD is based mainly on karyotyping and histology of the gonads (Table 4-3). Two main groups are recognized, namely: group I with normal karyotype and group II with abnormal karyotype.

**Group I. Normal Karyotype**

In this group, the chromosomal constitution and gonadal structure are normal, but the external genitalia are of the opposite sex. The defect in this group is in the differentiation of external genitalia as a result of hormonal disturbance during embryonic life. This group includes the following disorders.

1. **XX DSD** (*female pseudo-hermaphroditism*). This is the result of three main causes: (a) *Virilizing adrenogenital syndrome*. The adrenal cortex is capable of producing cortisone, aldosterone and testosterone from cholesterol through different enzymes. In case of congenital adrenal hyperplasia (CAH), because of 21-hydroxylase deficiency, the synthesis of cortisone and aldosterone are blocked with a shift of synthesis pathway to androgens resulting in verilization. (b) *Defect of aromatase enzyme* also leads to increase of intrauterine androgens due to failure of conversion of testosterone to estradiol, (c) *administration of androgens or progesterone during pregnancy*.

2. **XY DSD** (*Male pseudohermaphroditism*). This also results from three main causes: (a) *feminizing adrenogenital syndrome* due to a defect of testosterone synthesis by the adrenal or testis (Leydig cell defect). (b) *Androgen insensitivity syndrome (AIS)* due to mutation of androgen receptor genes. The testis shows bilateral and multinodular hyperplasia of Leydig cells which is reversible on cortisone therapy. (C) *5-alpha-reductase deficiency* resulting in decreased production of dihydro-testosterone (DHT) from testosterone leading to failure of differentiation of external genitalia.

**Group II. Abnormal Karyotype DSD**

In this group, there is abnormality of karyotype (sex chromosomes) leading to gonadal dysgenesis with progressive loss of germ cells resulting in a streak gonad (P 3-18). The abnormal karyotype may be a loss or gain of a sex chromosome, gene mutation, or a true mosaicism (two cell population with different genotype). The external genitalia may be a well-defined sex or ambiguous (Fig 4-10). So, the defect in this group is in gonadogenesis resulting in difficulty in sex determination. This group includes the following 6 disorders:

1. **45XO dysgenesis** (*Turner Syndrome*). There is deletion of one X chromosome, bilateral streak gonads (P 3-18), but a female phenotype.

2. **46XY female complete gonadal dysgenesis** (*Swyer Syndrome, female sex reversal*) is due to mutation of SRY gene in Y chromosome leading to failure of male development, streak gonads and female phenotype.

3. **47XXY Dysgenesis** (*Klinefelter syndrome*) results from gain of one or more X chromosome in males (usually XXX).

   Histologically, the gonads show germ cell aplasia, fibrosed atrophic tubules, but, hyperplasia of Leydig cells (P 4-20). The phenotype is a sterile hypovirilized male.

4. **46XX male DSD** (*XX male sex reversal*). The genetic disorder in this syndrome is translocation of SRY gene from the Y to the X chromosome, hence although the genotype is female (XX) the phenotype is male due to expression of the translocated SRY gene.

5. **45XO/46XY mosaicism** (*Mixed gonadal dysgenesis*). In this case, the chromosomal abnormality is genetic mosaicism leading to the formation of two different gonads, namely; an undescended fetal testis in one side (Sertoli cell only), a streak gonad on the other side and external genitalia is ambiguous.

6. **Ovotesticular DSD** (*true hermaphroditism*). This is a rare form of gonadal dysgenesis caused by 46XX/46XY chimerism or mosaicism (due to mutation of DMRT1 gene. It is characterized by the coexistence of both testicular and ovarian tissue in the same individual (P 4-21) with ambiguous external genitalia.

**Complications of DSD**

The 4 main complication of DSD are sterility, psychologic and behavior disorders, systemic complications including obesity, endocrinopathies, and increased risk of malignancy. The risk of neoplasia is almost restricted to male patients with DSD. Thus, patients with klinefelter syndrome are at a high risk of breast cancer.
Also, male children with adrenogenital syndrome will develop bilateral testicular tumor masses simulating interstitial cell tumors and may be subjected to unnecessary orchidectomy. The highest risk of testicular germ cell malignant tumors (about 30% of cases) is reported in male patients with gonadal dysgenesis who may develop seminoma or gonadoblastoma (P 4-22), but, lower risk in male patients with XY DSD (9%) and ovotesticular DSD (5%). Conversely, in females no gonadal cancer risk was reported in Turner syndrome and rare reports of dysgerminoma in Swyer syndrome.

### REFERENCES