SECTION 1

Basic Principles

1 Intrauterine growth and development

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Introduction

The birth of a healthy, full-term infant is the result of the successful orchestration of a multitude of individual developmental events. These processes are affected by genetic and environmental influences starting before conception and extending throughout gestation. Congenital abnormalities, which are present in up to 5% of human births, usually result from abnormalities in very early development. For example, many organ systems form between four and eight weeks after fertilization (Table 1.1), making them particularly vulnerable to teratogenic exposure during this period. The majority of congenital abnormalities can be detected *in utero* by routine ultrasound imaging [1]. For those that may be fatal to the fetus or neonate or result in severe life-long disability, the option of fetal surgical intervention is becoming increasingly possible [2]. However, the widespread adoption of fetal interventions for prenatal correction of congenital abnormalities has not yet been established and most techniques are currently experimental [2, 3]. By far the greatest obstacle to successful outcomes after fetal interventions is preterm birth and its associated complications [3].

In this chapter, we summarize the current understanding of processes involved in implantation and organogenesis, the major developmental abnormalities that are amenable to surgical intervention during gestation and/or delivery, development of the fetus, and factors that affect its growth and development.

Early development and placentation

Human development begins with the formation of the zygote soon after fertilization. Initial zygotic cleavage results in two cells (blastomeres), which undergo further divisions (cleavage) within the zona pellucida surrounding the zygote. Cleavage occurs without an increase in cytoplasmic mass, so each division results in successively smaller blastomeres. The blastomeres are compacted to form the morula within four days of fertilization. Fluid spaces within the morula then coalesce to form the blastocyst cavity, marking the formation of the blastocyst. This coincides with differentiation of the inner cell mass (which will ultimately form the embryo), located at the embryonic pole, from the trophoblast (which makes up the wall of the blastocyst) and degradation of the zona pellucida (Figure 1.1).

About one week after fertilization, the embryonic pole of the blastocyst attaches to the uterine endometrial epithelium. The trophoblast cells differentiate into an inner cytotrophoblast layer and an outer syncytiotrophoblast, which begins to invade the endometrium and erode maternal capillaries and venules. Lacunae then form, containing maternal blood and endometrial

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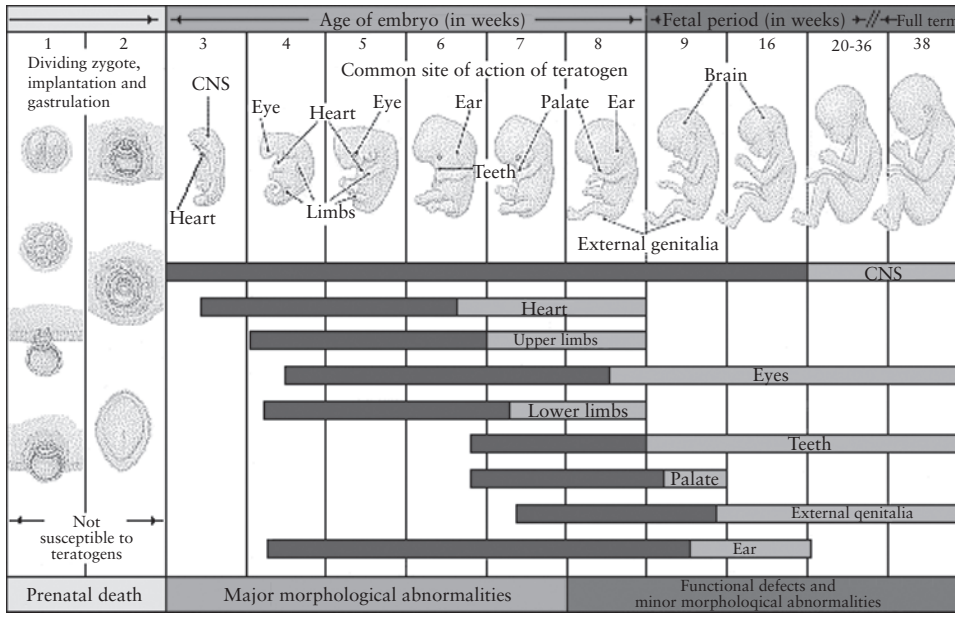

Fig. 1.1 Schematic illustration of critical periods of development before birth, showing the timing of vulnerability to teratogens. Highly sensitive periods for organs and systems are shown in dark shading; less sensitive periods are shown in light shading. Reproduced from Moore K, Persaud TVN, editors. The Developing Human: Clinically Oriented Embryology. 8th edn. Philadelphia: Saunders; 2008. P. 473 with permission from Elsevier. (See also Plate 1.1.)

gland secretions. Secretions of the endometrial glands support the growth of the embryo during the first trimester, resulting in uniform autonomous growth despite potentially very different maternal environments between individual pregnancies [4]. During this period, organogenesis progresses in a low oxygen environment, protected from the potentially mutagenic effects of oxygen free radicals [4].

Normal placentation is dependent on the low oxygen levels present at this time and the privileged immune environment that acts to protect the conceptus from maternal rejection [4, 5]. As the lacunar network increases in volume, maternal arteries in the endometrium begin to contribute to the developing placental circulation and tissue oxygen levels begin to rise. The anatomical relationships between the maternal circulation and invading embryonic tissues, necessary for exchange, are established by the end of the third week after fertilization.

At the end of the second week after fertilization, chorionic villi form from the cytotrophoblast over the entire chorionic surface of the embryo. Eventually, villi adjacent to the uterine lumen regress; those adjacent to the embryo proper branch extensively into the decidua of the endometrium to begin to form the placenta. Failure of normal placentation is considered the root cause for several pregnancy diseases including preeclampsia, a vascular disease of pregnancy that is characterized by maternal hypertension, vascular endothelial cell activation, inflammation and proteinuria [6]. The prevalence of hypertensive diseases in pregnancy (preeclampsia is the most common form) is 6–8% in the USA [7]. It is potentially fatal for mother and fetus, and thus contributes significantly to rates of labor induction and early delivery; it accounts for 10–12% of inductions and 2.5–3% of elective cesarean deliveries in Australia [8].

Table 1.1 Timing of structural and functional development of major organs.

Organ	Anatomical origin	Onset of function
Adrenals	The adrenal cortex arises from mesenchymal cells (mesoderm), superior to the developing gonads, at 6 weeks. The adrenal medulla is formed from an adjacent sympathetic ganglion (ectoderm) during the eighth week.	Dihydroepiandosterone sulfate is synthesized at 6–8 weeks. Cortisol is produced from progesterone at 8–12 weeks.
Heart	The angioblastic cords, which arise from splanchnic mesenchyme (mesoderm) fuse to form the primitive endothelial heart tube at ~22 days. Folding of the heart tube and septation to form left and right atria and ventricles are complete by 8 weeks.	Myogenic contractions first begin on day 21–22. Coordinated contractions resulting in forward flow occur by 4 weeks. The conducting system of the heart originates with the formation of the sinoatrial node during the fifth week.
Lungs	The lower respiratory tract begins as the laryngotracheal tube by budding of endoderm, into the surrounding splanchnic mesenchyme, from the ventral primitive foregut during weeks 4–5. Bronchial buds form and progressively branch to form the conducting and respiratory regions of the lungs. Lung structural development (airway branching and alveolarization) continues until after birth.	The fetal lungs actively secrete fluid that expands the lungs, which is critical for normal lung growth. Clearance of lung liquid at birth allows the initiation of gas exchange. Production of pulmonary surfactant, which is critical for lung function after birth, is initiated at ~24 weeks.
Kidneys	After the pronephroi and mesonephroi, the metanephroi develop during the 5th week as the ureteric bud penetrates metanephric mesoderm. Ureteric bud branching forms the renal tubules, which are invaginated by glomeruli to form nephrons (the functional unit of the kidney). Nephrogenesis is complete before full term.	Glomerular filtration begins at approximately the 9th week. The fetal kidneys produce copious dilute urine, which provides the majority of amniotic fluid volume.
Gonads	Sexual differentiation of the gonads does not occur until the seventh week after fertilization. The undifferentiated gonads arise from mesodermal epithelium and underlying mesenchyme, medial to the mesonephros, during the 5th week to form the gonadal ridges. Primary sex chords (of epithelial origin) then penetrate the underlying mesenchyme. The undifferentiated gonads consist of an epithelial cortex and mesenchymal medulla by 6 weeks. Primordial germ cells, present in the yolk sac endoderm early in the 4th week, migrate to the primary sex chords during the 6th week.	
Testis	Under the influence of the SRY gene, the primary sex chords develop into extended and anastomosed seminiferous tubules at approximately 7 weeks. The epithelial cells of the tubules give rise to the sertoli cells; spermatogonia arise from the primordial germ cells.	Testosterone production by the developing testis begins at ~8 weeks. Spermatogenesis does not occur until puberty.
Ovaries	The ovaries are first apparent at ~10 weeks. The primary sex cords degenerate and secondary sex chords develop from the cortical epithelium to form primordial follicles at ~12 weeks, which contain oogonia, differentiated from primordial germ cells, surrounded by follicular cells derived from the secondary sex chords.	Ovarian steroidogenesis begins after the 28th week of gestation. Ovulation does not occur until puberty.

(*Continued*)

Table 1.1 (*Continued*)

Organ	Anatomical origin	Onset of function
Brain	The nervous system arises from the neural folds (ectoderm) on the dorsal surface of the embryonic disc at ~3 weeks. During week 4 the prosencephalon, mesencephalon (which gives rise to the midbrain and superior and inferior colliculi), and rhombencephalon (demarcated from the spinal cord by the cervical flexure) form. During the 5th week the prosencephalon gives rise to the telencephalon (which gives rise to the cerebral cortex and basal nuclei) and diencephalon (which forms the retina, thalamus, and hypothalamus); the metencephalon (which forms the pons and cerebellum) and myelencephalon (which becomes the medulla) form from the rhombencephalon.	Disorganized neural activity is likely to be present from 5–6 weeks. Synapses do not form substantially until 17 weeks and peak later in gestation, continuing postnatally (in combination with synaptic pruning). Fetal responsiveness indicative of higher brain function does not occur until the second half of gestation. Fetal behavioural (sleep) states are indirectly identifiable (based on the presence of rapid eye movements) at 28–31 weeks.
Liver	The liver forms from a ventral outgrowth of the foregut in the fourth week.	Hematopoiesis begins in the liver during the 6th week. Bile formation begins during the 12th week.
Spleen	The spleen begins to develop during the 5th week, from mesenchymal cells in the dorsal mesentery. The splenic circulation is established during weeks 6–7.	Lymphoid colonization of the spleen begins during week 18.
Pancreas	The pancreas originates as two buds from the developing duodenum (endoderm) within the ventral mesentery during the 5th week. These buds fuse and their separate ducts anastomose during gut rotation.	Insulin secretion begins in the 10th week.
Pituitary	Ectoderm of oral origin begins to form the adenohypophysis of the pituitary (pars tuberalis, pars distalis, pars intermedia) at the beginning of the 4th week. At this stage the neurohypophysis (median eminence, infundibular stem, pars nervosa) begins to form as an infundibulum of the diencephalon.	Adrenocorticotrophic hormone (ACTH) is released by the pituitary by 8 weeks.
Thyroid	The thyroid develops at ~24 days from endoderm at the base of the primitive pharynx and attains its adult appearance and anatomical location by 7 weeks.	Thyroid hormone production begins at 10–12 weeks.
Thymus	The thymus develops from epithelial cells (endoderm) of the third pharyngeal pouch, which penetrate the surrounding mesenchyme (which later forms thin septae between thymic lobules). T cell progenitors (hematopoietic stem cells) begin to populate the thymus from 7 weeks.	Mature T cells are evident in the fetal thymus from 8 weeks.
Gastrointestinal tract	During the 4th week, the primitive foregut arises when embryonic folding incorporates the dorsal part of the yolk sac into the embryo. The digestive tract epithelium and glands arise from endoderm and the layers of the wall of the digestive tract are derived from the surrounding splanchnic mesenchyme; ectoderm gives rise to oral and anal epithelia.	Meconium appears in the small bowel during the 14th week and accumulates in the colon from 18 weeks. Some gastrointestinal hormones are secreted from as early as 8 weeks.

Organogenesis

One week after fertilization, the inner cell mass of the blastocyst gives rise to the bilaminar embryonic disc, consisting of the embryonic epiblast and hypoblast. Gastrulation, which begins at the start of the third week, is the process whereby the bilaminar embryonic disc becomes trilaminar (consisting of ectoderm, endoderm, and mesoderm) at the initiation of morphogenesis.

The ectoderm eventually differentiates into the tissues of the central and peripheral nervous systems (meninges; brain; spinal cord; sensory epithelia of the visual, auditory, and olfactory systems), the epidermis, hair and nails, mammary glands, adrenal medulla, and pituitary. The mesoderm becomes the connective tissues, dermis, bone, muscles (cardiac, striated and smooth), circulatory system and spleen, kidneys, gonads, and reproductive tracts, adrenal cortex and pericardium, pleural membranes, and peritoneum. The endoderm gives rise to the epithelial linings of the respiratory and gastrointestinal tracts, liver, pancreas, urinary bladder and urethra, thyroid and parathyroid, thymus, tonsils, and parts of the auditory canal and Eustachian tube.

The timing of formation and onset of function of the major organs is shown in Table 1.1.

Congenital abnormalities amendable to fetal intervention

Congenital diaphragmatic hernia (CDH)

The lower respiratory tract, including the trachea, bronchi, and lungs, appears initially as a branch of the foregut on days 26 and 27 after fertilization. The diaphragm forms between weeks 6–14 of gestation. Closure of the diaphragm, usually between weeks 8–10, results from fusion of the septum transversum, pleuroperitoneal membranes, dorsal mesentery of the esophagus, and body wall. Human and mouse studies have identified a number of genes associated with failure of diaphragmatic closure [9, 10]. Failure of normal closure allows herniation of the abdominal contents into the thorax, compromising the space available for the developing lungs. The incidence of CDH is approximately 4.5/10 000 births but may occur in as many as 1 in 1000 pregnancies [11]. CDH occurs in the absence of other congenital anomalies in 60–70% of cases [12]. The greatest morbidity and mortality occur postnatally and result from potentially life-threatening lung hypoplasia (and coincident pulmonary hypertension). Though frequently fatal before the advent of antenatal detection and modern postnatal management [10], survival rates may now be as high as 80% depending on the severity of the thoracic volume compromise [13].

Surgical closure of the fetal diaphragm, with repositioning of the herniated abdominal contents to permit improved lung growth, has been tested clinically using open and fetoscopic techniques in a small number of centers, but was abandoned after a small trial showed no improvement in survival [14]. Critically, in fetuses with hepatic herniation (the most severely affected and with the poorest prognosis), repositioning of the liver compromised umbilical venous blood flow and resulted in fetal death [13]. Further, simple closure of the diaphragmatic defect does not provide sufficient stimulus for adequate lung growth postoperatively. A current surgical approach for CDH involves "fetoscopic" occlusion of the trachea to cause accumulation of fetal lung fluid, which stimulates lung growth [14], with postnatal correction of the diaphragmatic defect [13]. The result of a randomized trial is expected shortly. While tracheal occlusion reliably stimulates lung growth, alveolar epithelial cell differentiation is altered [15] and surfactant secretion is inhibited [16], resulting in poor postnatal respiratory function. Careful timing of tracheal occlusion and its relief before birth stimulate growth and maturation of the preterm lungs sufficiently to permit adequate postnatal respiratory function [14].

Fetal hydronephrosis

The kidneys, ureters, bladder and urethra start to develop in the form of the primitive pronephros early in the 4th week after fertilization. Although the pronephroi and intermediate mesonephroi regress as development progresses, the metanephroi, which develop into the permanent kidneys, form in part from some of these primary structures. The permanent kidneys start development at the beginning of the 5th week post conception and become functional in the 9th week.

Fetal hydronephrosis arises in 2–9 per 1000 fetuses [17], is diagnosed based on dilatation of the urinary tract as measured by obstetric ultrasound, and can

be caused by obstruction of the urinary tract at any level. Abnormal development of the urinary collecting system, rather than the kidneys themselves, is the likely cause in the majority of cases. In most of those diagnosed prenatally, especially those showing only minor renal distension, there is spontaneous resolution. However, as fetal urine is the major contributor to amniotic fluid volume, urinary tract obstruction can lead to oligohydramnios, with diverse sequelae. Postnatally, disease results from renal function abnormality or failure, poor bladder function, respiratory insufficiency secondary to pulmonary hypoplasia due to oligohydramnios, and oligohydramnios-induced musculoskeletal abnormalities.

Posterior urethral valves are the most common cause of lower urinary tract obstruction in males [18], which appears as bilateral hydronephrosis, dilated ureters and bladder, and a thickened bladder wall. If these signs are detectable in fetuses aged less than 24 weeks of gestation, death or chronic postnatal renal failure occur in up to 50% of cases (18). Uteropelvic junction obstruction is the most common cause of prenatally diagnosed hydronephrosis, with a male-to-female ratio of 3:1; 20–25% of cases are bilateral. Obstruction of the uterovesicular junction is characterized by ureteric and renal pelvis dilatation on ultrasound; it has a male-to-female ratio of 4:1 and is bilateral in 25% of cases. With severe bilateral obstruction, fetal intervention may be indicated [17, 19] and may involve ultrasound-guided percutaneous placement of shunts to establish communication between the dilated urinary tract and the amniotic cavity or open fetal surgery to correct the underlying defect. Such interventions do not improve renal function but restoration of amniotic fluid volume may reduce respiratory morbidity [20].

Placement of vesico-amniotic shunts is reported as successful in 50% of cases; only half of successfully placed shunts remain in position until the end of gestation and complications may be fatal [17, 19]. Experimental animal models of urinary obstruction reveal that the associated renal dysplasia is not reversed by removal of the obstruction, and poor postnatal renal function is not avoided [18].

Sacrococcygeal teratoma

These teratomas result from a persistence of the primitive node, at the cranial end of the embryonic primitive streak, which forms intra-embryonic mesoderm until the end of the 4th week and thereafter usually regresses. They are the most common tumor observed in newborns, with an incidence of 1 in 20 000–40 000 (female:male incidence 3:1) [21]. Most sacrococcygeal teratomas diagnosed neonatally have good outcomes after resection but, when coupled with polyhydramnios, hydrops, placentomegally, and/or rapid growth of the teratoma, are frequently fatal for the fetus [3, 22]. A large teratoma can have substantial metabolic demands, and vascular shunts within the teratoma can result in high-output fetal cardiac failure. Sacrococcygeal teratomas can be graded according to their location, from type I (completely external) to type IV (completely internal): type I is the only type considered amenable to fetal intervention [21], which may be by tumor excision or vascular ablation. Reports of either approach are limited, with varying degrees of success [3].

Neural tube defects

Failure of closure of the embryonic neural tube during the 3rd and 4th week after conception brings about the most common forms of CNS abnormality [23]. The majority of neural tube defects involve the lumbosacral spine and overlying skin [23]. In spina bifida there is cystic herniation of meninges (meningocele), spinal cord (myelocele), or both (myelomeningocele) through a defect in the vertebral column. Spina bifida is the most common form of neural tube defect and carries significant risk of devastating outcome [24]. Its incidence in the USA was 20/100 000 live births in 2001, after a reduction in incidence of around 24% following the introduction of folic acid supplementation [25]. Anencephaly, in which the neural tube defect occurs cranially and much of the brain tissue is absent, is uniformly fatal. The rate of detection of neural tube defect by routine ultrasound scanning is higher than for thoracic and abdominal abnormalities [1].

Without prenatal intervention, outcome is usually poor because although the gross anatomical defect can be easily repaired surgically, the nerves are dysplastic causing life-long disability [26]. A secondary complication of spina bifida is herniation of the hindbrain, which can lead to brainstem dysfunction, the leading cause of postnatal death in infants [24].

Preliminary animal experimentation and data from a human randomized trial indicate that, by closing the neural tube defect during gestation, the adverse consequences of exposure of the spinal cord are lessened and hindbrain herniation is resolved [26].

Amniotic bands

Amniotic bands may constrict fetal body parts in 1 in 3000 to 1 in 15 000 live births [27]. The developmental origin of amniotic bands is believed to be either early rupture of the amnion and subsequent entanglement of fetal parts with remnants of the amniotic membrane or an intrinsic developmental anomaly that leads to banding, as suggested by the association of amniotic bands with apparently independent developmental abnormalities such as polydactyly and cleft palate [28]. Amniotic banding can result in a spectrum of abnormalities including digit or limb amputation, craniofacial, visceral, and other bodily defects. Umbilical cord entanglement by amniotic bands can result in fetal death. Fetal structural abnormalities caused by amniotic banding are readily identifiable by routine ultrasound and Doppler assessment of distal blood flow can be used to identify severity of the constriction [27].

There are few reports of prenatal intervention for resection of amniotic bands, with varying degrees of success probably related to the severity of arterial blood flow compromise [27]. As for all other forms of fetal intervention, *in utero* correction of amniotic banding shows some promise in selected cases but further research is required to identify those patients for whom the risks of surgery are outweighed by improved outcome.

Twin–twin transfusion

Division of a single morula or blastocyst before differentiation of embryonic cells yields monozygotic ("identical") twins, of whom approximately two-thirds will share their placenta. These monochorionic twins are at risk of twin–twin transfusion syndrome due to a deficit and imbalance of the obligatory vascular anastamoses (arterial–arterial, venous–venous or arterial–venous) between their placental circulations. The donor twin becomes hypovolemic, oliguric, and hence oligohydramniotic, hypertensive and growth restricted. The increased blood volume of the recipient twin results in polyuria and hence polyhydramnios, hypertension, and myocardial hypertrophy [29]. Mortality from twin–twin transfusion can be as high as 70% [30].

There are several criteria for diagnosis and assessment of twin–twin transfusion by ultrasound, based on anatomical and cardiovascular characteristics [29]. Adverse outcome of twin–twin transfusion can be predicted during the first and second semesters using ultrasound to assess fetal size, the location of the placental equator and discordant amniotic fluid volumes [31].

A large multicenter randomized controlled trial showed that laser ablation of placental vascular anastomoses improved perinatal survival and short-term neurological outcome compared to amnioreduction (previously the main treatment) [32]. One prospective series of *in utero* laser ablation reported normal neurological outcome at 3 years of age in 86.8% of survivors [33].

Fetal growth and development

Organogenesis is completed approximately 8 weeks after conception, by which time all major organs are identifiable. Individual organs continue to grow and increase in complexity to full-term, and indeed most organs continue to grow and mature until body growth ceases. Organs grow as a result of mitosis and/or cellular hypertrophy with cellular differentiation and deposition of extracellular matrix. During embryogenesis, growth is regulated largely by the genome and less so by levels of nutrient and oxygen supply. However, with increasing demands imposed by the greater size and metabolic activity of the fetus, supply of nutrients by the placenta becomes more important, although genetic and epigenetic factors can influence growth. In most cases of restricted fetal growth, reductions in growth below the genetic potential result from limited nutrient or oxygen availability via the placenta, or a reduced ability to utilize these nutrients. Increased fetal growth above normal growth (large for gestational age) is often due to an oversupply of nutrients and growth factors, as in maternal diabetes.

Growth of the fetal body and individual organs can be assessed throughout at least the latter half of gestation by real-time ultrasound. Common measurements used to monitor fetal growth include biparietal

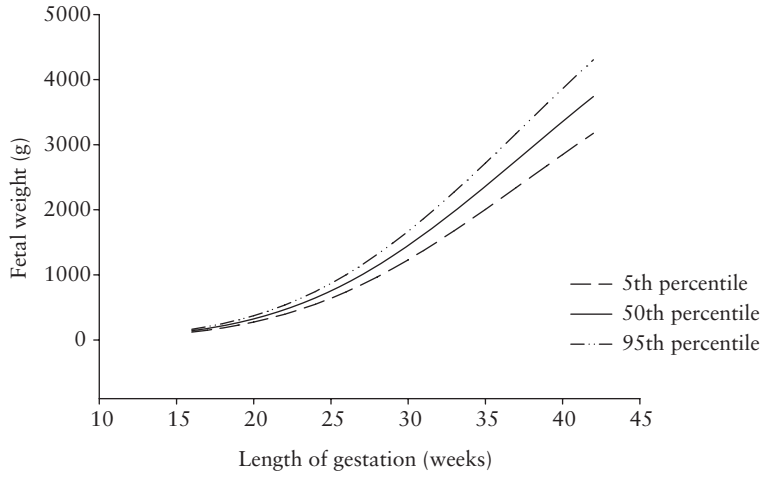

Fig. 1.2 Fetal body weight during the latter half of human gestation, calculated from ultrasound measurements of abdominal circumference and femur length. Reproduced from Chitty L, Altmann D. Appendix: Charts of Fetal Measurements. In: Rodeck C, Whittle M, editors. Fetal Medicine: Basic Science and Clinical Practice. 2nd edn. London: Churchill Livingstone; 2009. p. 721–66 with permission from Elsevier.

diameter, head circumference, femur length, and abdominal circumference. Fetal body weight can be estimated from abdominal circumference and femur length (Figure 1.2). During late gestation, the rate of bone growth declines and may almost cease near term (Figure 1.3). Thus in the final weeks of pregnancy, weight gain is largely due to increases in fat deposition and soft tissue growth; the deposited fat, which is largely brown adipose tissue, is beneficial in supporting survival after birth. Preterm infants are usually deficient in fat deposits, especially brown adipose tissue, which increases the risk of hypothermia and hypoglycemia. After 40 weeks of gestation, there is a marked decline in fetal growth and weight gain with an increasing risk of fetal distress; most fetuses are delivered by 42 weeks.

Fetal growth restriction

There is an inverse relationship between birthweight percentile and adverse perinatal outcome, with the greatest neonatal morbidity and mortality seen in infants with birthweights below the third percentile [34]. Furthermore, the adverse effects of restricted fetal growth can be life-long [35]. Intrauterine growth restriction (IUGR) can be defined as the failure of the fetus to achieve its genetic growth potential and by definition affects 3–10% of all pregnancies. IUGR should be distinguished from small for gestational age (SGA), which is defined as a fetal or neonatal body weight less than the 3rd or 10th percentiles. Fetuses that are SGA may be small for genetic reasons and may not be suffering from IUGR. Although IUGR has numerous causes, a common factor is placental dysfunction, which causes a chronic reduction in the delivery of nutrients and/or oxygen to the fetus. The major influence of placental dysfunction on fetal growth is seen during the latter half of gestation, and most commonly during the third trimester when fetal demands are greatest. IUGR is usually diagnosed by comparing ultrasound measurements of head size, abdominal circumference, and long-bone length against growth charts appropriate for the population; values falling below the 10th percentile are suggestive of IUGR.

Symmetric vs. asymmetric IUGR

Depending on the stage of gestation in which nutrient restriction occurs, IUGR may differentially affect head and body size. Symmetric IUGR accounts for 20–30% of IUGR fetuses; all organs are decreased proportionally suggesting that nutrient has been restricted throughout much of gestation. Asymmetrical IUGR

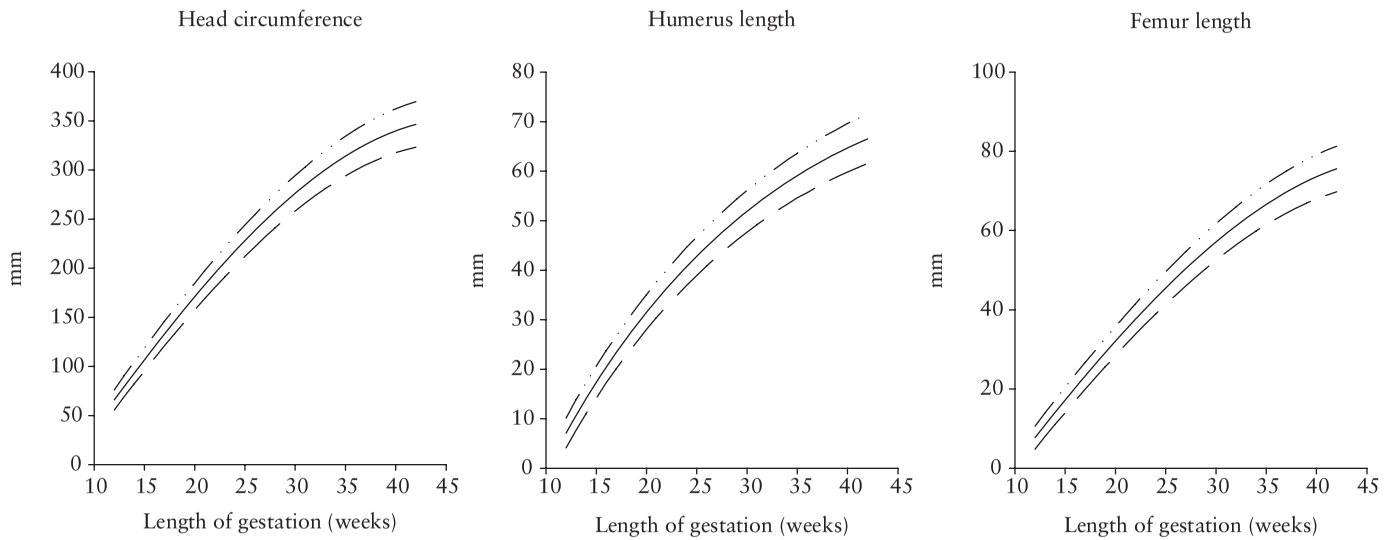

Fig. 1.3 Fetal skeletal dimensions measured by ultrasound during the latter half of human gestation. Data are represented for three percentiles; 5th (— —) 50th (——) and 95th (—··). Reproduced from Chitty L, Altmann D. Appendix: Charts of Fetal Measurements. In: Rodeck C, Whittle M, editors, Fetal Medicine: Basic Science and Clinical Practice. 2nd edn. London: Churchill Livingstone; 2009. p. 721–66 with permission from Elsevier.

is thought to result from placental dysfunction later in gestation, and is typified by a greater reduction in abdominal size (i.e. liver volume and abdominal fat) than head size. This "head sparing" is considered to be due to preserved blood flow and nutrient/oxygen delivery to the brain; the fetal heart and adrenal glands may also be relatively spared [36].

Determinants of fetal growth

It has been estimated that 30–50% of the variation in fetal body weight is due to genetic factors and around 60% to the intrauterine environment [37]. There is evidence that IUGR is heritable, and that maternal genes affect fetal growth more than paternal genes. In up to 25% of fetuses with early onset IUGR (mostly symmetric IUGR) chromosomal abnormalities can be identified; these may act via effects on placental vascularization. The recent application of DNA arrays to prenatal diagnosis will likely reveal a greater percentage of IUGR reflects chromosome abnormalities.

A wide range of environmental factors are known to affect fetal growth, many of which are associated with nutrient supply or nutrient utilization. The number of fetuses affects fetal growth, especially in the third trimester. Fetuses of a multiple gestation are smaller than singletons of the same sex and age because nutrient supply via the utero-placental circulation has to be shared; this is supported by the difference in size increasing with advancing gestation, as the nutrient demands of the fetus increase (Figure 1.4). Pregnancy complications that can inhibit fetal growth are more common in multiple gestations. Blood samples taken from the umbilical cord show that umbilical vein PO_2 and pH progressively decline and PCO_2 increases during the latter half of gestation (Figure 1.5); values in SGA fetuses typically lie towards the 95th percentile [38]. In general, female fetuses are smaller than males, which probably results from differences in placental function as well as genetic and/or endocrine factors [39]. Although they tend to be smaller, female preterm infants are known to have better outcomes than males [40].

Maternal factors affecting fetal growth

Maternal and uterine size, maternal nutrition, uterine blood flow, and oxygen carrying capacity can all influence fetal growth. Major causes of IUGR include disease states that affect maternal vascular function, such as hypertension, diabetes, and preeclampsia; each of these can impair uteroplacental perfusion, which in turn reduces the availability of oxygen and nutrients to the fetus. These maternal disease states account for 25–30% of IUGR in fetuses that are free of anomalies. With maternal hypertension, the incidence of IUGR is directly correlated with disease severity [41].

Maternal weight at the time of conception and weight gain during pregnancy account for about 10% of variation in birthweight. Maternal nutrition is a significant determinant of fetal growth, even in developed countries. Nutrition is an even more important factor in the etiology of IUGR in developing countries, and the incidence of IUGR is greatly increased during times of famine. Reduced maternal protein intake, as well as global caloric intake, can restrict fetal growth. IUGR is more common in teenage pregnancies, and in general the risk of IUGR is increased in a mother who is still growing [42].

Maternal hypoxemia has multiple causes including heart disease, lung disease (e.g. moderate to severe asthma), severe anemia, sickle cell anemia, and high altitude. These conditions can cause IUGR by chronically restricting oxygen delivery to the placenta and hence the fetus. Maternal hyperthermia can also lead to IUGR, as a result of maternal infections or high environmental temperature. Maternal infections such as rubella and cytomegalovirus (CMV) and parasites such as malaria are thought to account for 5–10% of IUGR. Some 20% of neonates have experienced a viral infection in utero. CMV is the most frequent viral cause of IUGR in developed countries.

The single most avoidable cause of IUGR is maternal tobacco smoking. Causality is well established as the degree of IUGR is directly related to the number of cigarettes smoked [43]. The effects of smoking on fetal growth are likely to be mediated by hypoxemia and impaired growth and vascular function of the placenta. Placental mass is known to be reduced in smokers and placental pathology is more common. Elevated maternal carboxyhemoglobin in smoking women reduces the oxygen carrying capacity of maternal blood, limiting oxygen availability to the fetus. Furthermore, inhaled carbon monoxide may pass to the fetus and reduce the oxygen carrying capacity of fetal hemoglobin. The nicotine in cigarettes is known to release maternal catecholamines, which may constrict the uteroplacental arteries,

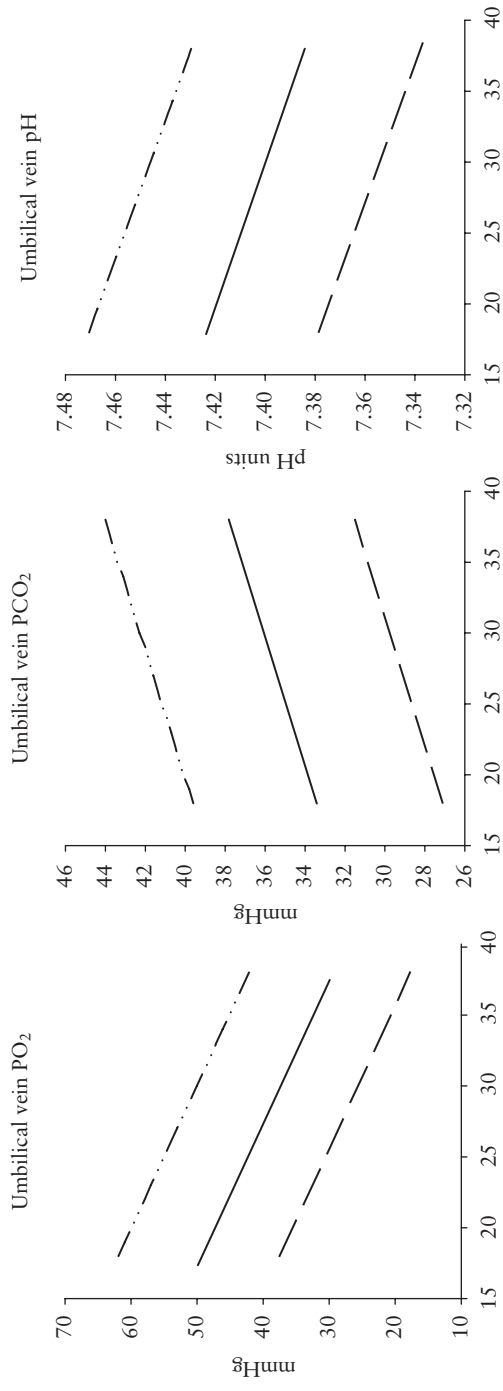

Fig. 1.4 Umbilical vein PO_2, PCO_2 and pH measured by cordocentesis during the latter half of human gestation. Data are presented for three percentiles; 5th (— —) 50th (——) and 95th (—··—). Reproduced from Chitty L, Altmann D. Appendix: Charts of Fetal Measurements. In: Rodeck C, Whittle M, editors, Fetal Medicine: Basic Science and Clinical Practice. 2nd edn. London: Churchill Livingstone; 2009. p. 721–66 with permission from Elsevier.

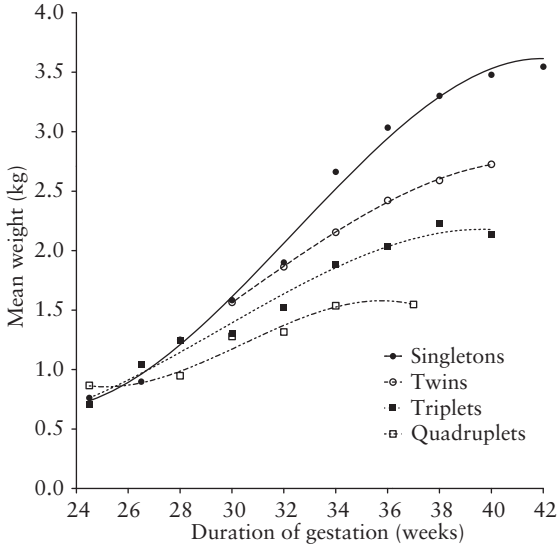

Fig. 1.5 Fetal body weights during the latter half of human gestation in singletons, twins, triplets and quadruplets. Data taken from McKeown and Record, 1952 [62] with permission.

thereby reducing placental perfusion and oxygen delivery to the fetus. Nicotine readily crosses the placenta, and activation of α-2 nicotinic receptors in the fetus can inhibit cell division which may contribute to IUGR [44]. Maternal smoking increases the risk of preterm birth as well as IUGR, both of which increase the risk of perinatal morbidity. IUGR in women who smoke and who use recreational drugs may be caused in part by inadequate maternal nutrition.

High levels of alcohol intake during gestation can also lead to IUGR [45] in a dose-related manner. Mechanisms underlying the IUGR are unclear, but alcohol may impair development of the placenta and its vasculature [46]. Zinc availability to the fetus [47] and insulin like growth factors (IGFs) may also be affected [48].

Placental factors affecting fetal growth

The placenta is intimately involved with the supply of nutrients and oxygen to the fetus and hence plays a major role in fetal growth. Such factors include placental size, micro-architecture (villus and vascular density), and umbilical blood flow. Placental disease associated with IUGR includes conditions such as preeclampsia and abruption. In addition to placental pathology, placental transporters and binding proteins, placental nutrient utilization and production, and hormone synthesis can all affect fetal growth [37]. The weight of the fetus correlates with placental weight, suggesting a functional relationship. However, placental mass provides only a rough guide to functional capacity of the placenta. During the later stages of pregnancy the weight of the placenta increases slowly, but placental function is increased by structural changes within the placenta that facilitate nutrient delivery to the fetus. These changes include an increase in total villous surface area (by division and elongation of villi), proliferation and dilatation of fetal capillaries and a progressive thinning of tissue interposed between fetal and maternal blood. In addition, fetal blood flow through the placenta increases dilatation of the umbilical-placental vessels. Nutrient transport across the placenta increases with advancing gestation, not only due to an increased surface area for exchange, but also due to an increased density of specific transporter proteins.

Restriction of fetal growth by placental dysfunction is usually most marked during the latter half of gestation, when fetal nutrient requirements are greatest. Measurements of growth in IUGR fetuses show that the greatest divergence from normal growth profiles occurs during the second half of gestation, when many organs are undergoing differentiation and are hence vulnerable to nutrient restriction. IUGR is usually accompanied by, and probably causally related to, abnormal blood flow in the uteroplacental or umbilical-placental circulations. The severity of IUGR and the associated changes in uterine blood flow are related to the depth of interstitial extravascular trophoblast invasion. Histologically, uteroplacental vascular insufficiency is associated with persistent muscularization of the spiral arteries, lack of endovascular trophoblast, and narrowing or thrombosis of the spiral arteries [49].

Fetal factors affecting growth

In addition to the fetal genome, fetal factors that can affect its growth include the ability to utilize nutrients and to produce or respond to hormones and growth factors. Fetal growth is dependent in particular upon hormones produced by the fetal thyroid, pancreas, and kidneys, as experimental ablation or the congeni-

tal absence of these organs impairs fetal growth as well as the maturation of specific tissues [37]. It is apparent that fetal hormones such as thyroxine and insulin are important for normal tissue growth and differentiation and that their effects are largely mediated by anabolic effects on fetal metabolism. Insulin-like growth factors (IGFs) of fetal origin are also involved and may mediate the effects of thyroxine and insulin on fetal growth. Disruption of the IGF-I or IGF-II genes or receptors for IGFs in the fetus leads to IUGR, and these effects may be mediated by inhibitory effects on placental growth. Interestingly, growth hormone appears to play little role in fetal growth although it is present in high concentrations in fetal blood, and is important for postnatal growth.

Glucocorticoids of fetal origin are increasingly produced during late gestation and have major effects on tissue growth and differentiation. The characteristic reduction in fetal growth rate near the end of gestation is considered to be due to the rapid increase in glucocorticoid release at this time; this effect may be exaggerated in IUGR fetuses in which circulating concentrations of glucocorticoids are elevated. Glucocorticoids inhibit tissue growth and stimulate cellular differentiation during late fetal life, in preparation for birth; organs known to mature functionally and structurally under the influence of fetal glucocorticoids include the lungs, liver, and gastrointestinal tract.

Macrosomia

The term macrosomia refers to fetal growth beyond a specific weight, usually above 4500 g in progeny of non-diabetic women; morbidity increases sharply beyond 4500 g. Methods used to predict birthweight and outcome include assessment of risk factors, clinical examination, and ultrasound measurement of the fetus. However, the accuracy of ultrasound in predicting fetal macrosomia has been unreliable and an accurate diagnosis of macrosomia can be made only by weighing the newborn after delivery [50].

A number of risk factors predispose to macrosomia. Women who previously delivered an infant weighing more than 4000 g are 5–10 times more likely to deliver a second than women without such a history [51]. Women who are obese before pregnancy are more likely than women of normal weight to have macrosomic infants; indeed morbidly obese women (>135 kg or a BMI >35 kg/m^2) are eight times more likely to deliver an infant exceeding 4500 g than women of normal bodyweight [52]. High levels of weight gain during pregnancy also increase the risk of neonatal macrosomia, more so for obese than non-obese women [53]. Multiparity is also associated with macrosomia for reasons that are unknown [54]. Gestational age greater than 40 weeks increases the risk of macrosomia, and the incidence increases to 2.5% beyond 42 weeks [55]. Maternal birthweight is another risk factor, which suggests that genetic factors are involved. Women whose own birthweight exceeded 3600 g are twice as likely to deliver infants greater than 4000 g than women whose birthweight was less than 3600 g [56]. Both pregestational and gestational diabetes are associated with fetal macrosomia. Much of the variation in birthweights remains unexplained and most infants greater than 4500 g do not have identifiable risk factors [57].

Fetal macrosomia increases the risk of both maternal and fetal morbidity. Macrosomia causes arrest of fetal descent and prolongs the second stage of labor; as a result, rates of operative delivery and hence postpartum hemorrhage increase. Although the diagnosis of fetal macrosomia is imprecise, prophylactic cesarean delivery is usual if the fetus exceeds 4500–5000 g. For the infant, the most serious complication of macrosomia is shoulder dystocia, which complicates 1.4% of vaginal deliveries; when birthweight exceeds 4500 g the risk of shoulder dystocia increases from 1.4% to 9–24% of vaginal deliveries. Interestingly, prophylactic cesarean delivery for an estimated fetal weight of more than 4000 g does not appear to reduce the overall risk of shoulder dystocia. Fetal injuries most commonly associated with macrosomia and shoulder dystocia are fracture of the clavicle and damage to the nerves of the brachial plexus, C5 and C6, producing Erb Duchenne paralysis. Macrosomic infants have a greater prevalence of depressed 5-minute Apgar scores and an increased rate of admission to the NICU, usually due to complications of birth.

Long-term programming effects of altered fetal growth

An increasing number of epidemiological studies from both developing and developed countries show that alterations in fetal growth influence the risk of

later illness. Overweight infants are more likely to be overweight in later life than normal weight newborns, and to suffer adult-onset diseases. There is now strong evidence that insults experienced by the fetus leading to low birthweight, such as placental insufficiency and fetal nutrient restriction, affect health during postnatal life; this is often referred to as developmental programming [35]. Low birthweight due to preterm birth can also have long-term effects on health, so it is necessary to distinguish between these two quite separate causes of low birthweight. Major illnesses of later life that are considered to have prenatal origins or prenatal risk factors include hypertension, hyperlipidemia, and glucose intolerance (collectively known as Metabolic Syndrome X), as well as obesity, type 2 diabetes, renal disease, neurocognitive impairments, and pulmonary disease. It appears that a restricted supply of nutrients or oxygen permanently impairs the development of the affected organs. Fetal responses to the initial insult may increase the chances of immediate survival but may result in persistent alterations in organ development.

Organs known to be structurally and functionally affected by IUGR include the brain, heart, arteries, liver, pancreas, kidneys, lungs, skeletal muscle, and small intestine. Each of these tissues and organs may be particularly vulnerable at different stages of gestation or postnatal development. For example, in the human kidney, nephrogenesis occurs only during late gestation and ceases by term. IUGR occurring before the end of nephrogenesis has been shown to reduce the final number of nephrons, whereas IUGR occurring after the cessation of nephrogenesis does not affect nephron number [58]. In the lungs, alveolarization occurs between late gestation and 1–3 years after birth; late gestational IUGR, as well as early postnatal growth restriction, can reduce the final number of alveoli [59]. Similarly, the myocardium develops largely before birth, and the final number of cardiomyocytes is established soon after birth. Fetal growth restriction due to restricted placental function can permanently reduce the number of cardiomyocytes [60], which could increase the risk of cardiac disease later in life, especially when cardiac function is under challenge. It is increasingly evident that developmental programming can involve epigenetic mechanisms, as well as permanent alterations in organ structure [61]. This is an important topic related to human health and disease, and one that requires much more research.

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