CLINICAL ASPECTS OF EARLY EMBRYONIC DEVELOPMENT

Meconium Aspiration Syndrome (MAS)

Although the pathway for fetal defecation exists, this does not usually occur. In most cases the first defecation occurs postnatally; the bile-stained fecal matter is called **meconium.** In 10 - 15% of all deliveries, the neonate's amniotic fluid is meconium-stained, indicating some amount of *in utero* defecation. Even though about one-third of such neonates will have some meconium in their lungs, only about 5% of children born with meconium-stained amniotic fluid will actually have a condition known as Meconium Aspiration Syndrome. This potentially serious disease is characterized by respiratory distress and pneumonia. It used be thought that the toxic affect of meconium on pulmonary tissue caused MAS. However, the most recent article I read suggests that the neonatal respiratory distress is primarily caused by pulmonary arteriolar vasoconstriction that is a byproduct of a pre-existing fetal asphyxia unrelated to meconium in the amniotic fluid. It does seem that a lung with pulmonary arteriolar vasoconstriction is more susceptible to damage by the irritating effects of meconium, so the pneumonia may be due the presence of meconium. However, if meconium gets into lungs that are otherwise healthy, the lung is unlikely to be adversely affected.

Amniotic Fluid Volume and Its Abnormalities

Amniotic fluid volume reaches a maximum of about 1000 ml at eight months, then falls again to about 500 ml at term. In late gestation, the fetus contributes 800-1200 ml daily to amniotic fluid volume via urination, 170 ml daily from its lungs, and 25 ml daily from its oronasal membrane (Brace RA 1997 Physiology of amniotic fluid volume regulation. Clin Obstet Gynecol 40:280-289). The fetus removes about 1000 ml daily by swallowing, and another 200-500 ml of amniotic fluid reaches the fetal vasculature by crossing the amniochorionic membrane that lies over the placenta . A very small amount (~10 ml daily) reaches the maternal vasculature by crossing the amniochorionic membrane peripheral to the placenta.

Oligohydramnios - This is defined as less than half the normal volume of amniotic fluid for any particular time in gestation. The most important fetal cause is failure of the kidneys to develop (renal agenesis). The consequences of prolonged oligohydramnios are bad: (a) defective development of fetal joints because the squished fetus can't move normally, (b) underdevelopment of the lungs (pulmonary hypoplasia) thought to arise because the fetus may need to breathe in amniotic fluid for the lungs to develop normally, and (c) compression of the umbilical cord, which is fatal.

(Poly)hydramnios - This is defined as more than twice the normal volume of amniotic fluid for any particular time in gestation. Most cases are idiopathic, and more than half of these resolve on their own. The drug indomethacin can be used to treat hydramnios, but in cases of twin-twin transfusion syndrome (see below) the excess fluid is serially withdrawn by syringe. Unresolved hydramnios makes the mother uncomfortable and may lead to premature rupture of the amniochorionic membrane and delivery. It is also associated with a higher than normal incidence of intrauterine and neonatal death, for reasons that are unclear. Fetal causes of polyhydramnios are chiefly (1) anencephaly, which disrupts the neural basis of swallowing, and (2) esophageal or duodenal atresia *(atresia* is defined as absence or closure of a normal opening or tube), which prevent swallowed fluid from being absorbed. These are bad things to have. All cases of polyhydramnios should be investigated to rule out such causes.

Twinning

Excluding incidences arising from *in vitro* fertilization, twins occur in slightly more than 1% of births. There are fundamentally two different ways to get twins:

(1) The mother may release two oocytes, which are then fertilized by two separate sperms, producing two separate zygotes. Not surprisingly, these are called **dizygotic (DZ) twins.** They are no more closely related that any other siblings and are commonly referred to as fraternal twins. Obviously, each pre-embryo will develop into its own blastocyst that implants separately into the uterus. Each twin will have its own separate placenta (which, however, may fuse with its sib's placenta at the edges if the sites of implantation are close to one another), separate chorion (derived from the cytotrophoblast sphere), and separate amnion (derived from the inner cell mass). They are said to be **dichorionic twins.** Dizygotic twins occur naturally twice as frequently as monozygotic twins (see below). The propensity to have DZ twins runs in families (i.e., there is a genetic component to multiple ovulation) and also increases with the age of the mother.

(2) One oocyte is fertilized by one sperm, thereby producing one zygote, which at a later stage of development divides into two separate embryos. These are **monozygotic (MZ) twins.** They have identical DNA and are commonly referred to as identical twins. There are three ways for MZ twins to arise, depending on when the doubling event occurs.

(a) About 30% of the time, MZ twins arise because an early cleavage stage (2- 8 cells), or the morula (16-32 cells), splits into two parts. Such twins will be just like DZ twins in having separate placentae, chorions, and amnions. Inspection of the afterbirth (delivered placenta and fetal membranes) will not distinguish dichorionic MZ twins from those that are DZ.

(b) About 69% of the time, MZ twins arise because two separate inner cell masses form within a single blastocyst. Since it is the sphere of cytotrophoblast that implants and forms the placenta and chorion, such twins will share a placenta and chorion. On the other hand, each ICM forms its own embryonic disc/amnion/yolk sac. Hence, such twins are **monochorionic diamnionic.** Fifteen to 20% of monochorionic diamnionic twins experience a significant arteriovenous anastomosis in the placenta. This anastomosis shunts one twin's umbilical artery blood into channels that drain into the other twin's umbilical vein. The donor twin is smaller, hypovolemic (i.e., has low blood volume), oliguric (i.e., produces too little urine), and (as you might have deduced from the previous condition) oligohydramniotic. The recipient is larger, hypervolemic (i.e., has high blood volume), polyuric (produces too much urine), and polyhydramniotic. The hypervolemia requires the heart to pump harder, and thus the recipient is prone to cardiac problems. This condition, called twin-twin transfusion syndrome (TTS), is associated with a high morbidity and mortality for both twins.

(c) The remainder of MZ twins arise when two primitive streaks form within a single embryonic disc (some books say they arise when there is an incomplete division of the ICM, but this is a distinction without a difference). They obviously share a single

placenta and chorion and, furthermore, they exist within the same amniotic cavity. Hence they are said to be **monoamnionic twins.** About half of monoamnionic twins are conjoined. Whether conjoined or not, monoamnionic twins have a high intrauterine mortality due to the likelihood of their umbilical cords becoming twisted, occluding blood supply.

There is no correlation between the likelihood of having MZ twins and either maternal age or family history.

Sacrococcygeal Teratoma

This is the most frequent tumor of a neonate. It occurs when the tail-end of primitive streak doesn't completely revert to ectoderm. The result is a tumor near the tip of the coccyx that may contain any kind of differentiated tissue (e.g., hair, muscle, teeth), but also may contain undifferentiated cells that can become malignant.

Neural Tube Defects in the Region of the Spinal Cord

Most of the named spinal cord malformations **(spinal dysraphisms)** are due either to failure of proper fusion of the neural folds, or imperfect development of the cord at the site of seemingly normal fusion. These are accompanied by defective development of the dorsally overlying bone and/or skin. Those spinal dysraphisms associated with absent dorsal parts of vertebral arches (laminae and spinous processes) are called **spina bifidas.**

(Open) Myelomeningocele - The most common type of spinal cord defect is called **myelomeningocele** (or meningomyelocele) by clinicians, but is called "myeloschisis" by embryologists. I will use the clinical term. Sometimes clinicians use the name "open myelomeningocele", but there is no other type. Regardless, this condition refers to a neural tube defect resulting from a localized failure of the spinal neural folds to meet and fuse. It usually occurs in the low thoracic, lumbar, or sacral regions. In myelomeningocele, the abortive neural tissue is exposed to amniotic fluid or covered by only a thin epithelium. As a result, **alpha-fetoprotein** is able to leak into the amniotic fluid and usually can be detected in the maternal blood serum. Definitive diagnosis is made by ultrasound.

In myelomeningocele there is very little in the way of normal neural structure at the site of the defect. As a result, the affected person will be paralyzed in body regions served by the involved spinal cord segments and all segments caudal to them. There will also be inability to perceive sensation from those same parts of the body. Hydrocephalus (i.e., an abnormal increase in the amount of CSF within the brain) is a very frequent accompaniment of myelomeningocele, as is the **Arnold-Chiari malformation** of the hindbrain. Among this malformation's components is displacement of part of the cerebellum and medulla into the cervical vertebral canal. Compression of the brain stem and stretching of the lower cranial nerves may lead to severe symptoms. Some people think the Arnold-Chiari malformation is mechanical in origin (the brain being pulled down by tethered spinal cord), others think it is an associated defect in brain development. After birth, myelomeningocele is “repaired” by surgery. The neural placode is dissected from neighboring tissue and allowed to drop into the vertebral canal. It is then covered with the patient’s dura and skin, or with commercially available substitutes if

necessary.

It now possible to operate on fetuses while they are still in the womb. A recent study compared the outcomes of prenatal myelomenigocele repair (at 19 - 26 weeks of gestational age) to those of postnatal repair (Adzick NS *et al.* 2011 A randomized trial of prenatal versus postnatal repair of myelomenigocele. N Eng J Med 364:993-1004). At twelve months of age, the children who had undergone prenatal surgery had a significantly lower incidence of hindbrain herniation, and significantly fewer of them required shunts to address hydrocephalus. At 30 months, the children operated on prenatally had less severe cognitive and motor deficits. On the negative side, the mothers of the prenatally repaired fetuses had more complications of pregnancy, and more often needed to be delivered prematurely,

Meningocele - The second most common type of spinal cord defect is **meningocele.** In this case, the dura and arachnoid protrude though a localized vertebral arch defect and make a bulge beneath the skin of the back, which is often thinner than normal. The dorsal surface of the spinal cord is usually connected to the inner surface of the meningeal bulge by a fibrous cord. Meningoceles do not usually cause neurologic deficits at birth, and will do so later in life only if left untreated, or if there is some underlying spinal cord defect (usually not the case).. The surgical treatment of meningocele has a more important goal that cosmesis. It allows normal growth of the spinal cord by removing factors that tether it to the surface.

Myelocystocele - The least common kind of spinal dysraphism is called **myelocystocele.** It is similar to meningocele, except that the dorsal part of the spinal cord doesn't form properly and is represented by a thin epithelium (ependyma) that joins with the meninges in herniating through the region of a vertebral arch defect. Depending on the degree of the spinal cord malformation, there may or may not be neurologic deficits at birth. Even if there are no such deficits at birth and the child is surgically treated to eliminate spinal cord tethering, later in life some minor deficits can often be revealed by careful neurologic examination.

Spinal Dermal Sinus - This is an anomaly of neural tube closure that need not be associated with spina bifida. It is characterized by a midline pit or dimple in the skin of the back marking the site where the epidermis was connected to the neural tube during the final stage of neural tube closure. Spinal dermal sinuses in the intergluteal fold almost always end blindly and are harmless. Those superior to the intergluteal fold usually lead to a narrow channel (tract) that reaches the subarachnoid space or spinal cord. These sinus tracts provide a path for infection to travel to the spinal meninges and/or cord. Even if an infection does not develop, if the tract attaches to the cord, the latter may be tethered by its connection to the skin, resulting in neurologic symptoms as the child grows. Consequently spinal dermal sinuses superior to intergluteal fold should be investigated by ultrasound or MRI to determine the depth of their tracts.

Spina Bifida Occulta - More common than all the conditions previously discussed is something called spina bifida occulta. In this condition there occurs failure of one or two vertebral arches to form dorsal to the spinal cord. There may be no indication of this except by palpation or Xray, or there may a tuft of hair overlying the site. The fact that it can sometimes (but rarely) be associated with minor neurologic deficits suggests that its cause may be related to neural tube formation and development, in which case it would be considered a spinal dysraphism. To

distinguish spina bifida occulta from the other instances of spina bifida mentioned above, the latter are often grouped under the term spina bifida cystica.

Neural Tube Defects in the Region of the Brain

The various defects of spinal cord formation described above have their counterparts in the cranial region. Even more common than open myelomeningo-cele is the brain's equivalent condition, called **anencephaly.** As you might deduce, it arises from failure of fusion of the most rostral parts of the neural folds that surround the anterior opening (i.e, anterior neuropore) of the neural tube. The accompanying failure of the roof of the cranium to form is called cranium bifidum, or cranioschisis, but these terms are not commonly used. Anencephaly is a fatal condition (with the sole exception of Bill Jungers).

Pleuropericardial Membrane Defect

If a pleuropericardial membrane fails to join the midline mesoderm on one side, the pericardial cavity will be in open continuity with the pleural cavity on that side. This is rare, and generally of no consequence unless one gets a pleuritis, which then turns into a pericarditis, or vice versa.

Congenital Diaphragmatic Hernia

Failure of a pleuroperitoneal membrane to develop or fuse with the septum transversum (most commonly on the left side) leads to an open passageway from the peritoneal to the pleural cavity. This passageway is called a **foramen of Bochdalek.** Depending on its size, abdominal organs may herniate into the fetal chest, compromising the space for the lungs to develop. The resulting pulmonary hypoplasia is often fatal. More rarely, when the foramen is small, the Bochdalek hernia may be delayed until infancy.

Lumbocostal Trigone

Rarely, muscle cells may fail to invade the posterolateral portion of the diaphragm arising from the 12th rib and lateral arcuate ligament. Such a region, represented only by apposed pleura and peritoneum, is called a lumbocostal trigone. It represents a weak spot through which abdominal contents may herniate into the chest, usually not until adulthood. Such hernias have a covering sac of serous membrane. No one knows if a lumbocostal trigone is somehow related to development of the pleuroperitoneal membrane, but surgeons still refer to hernias through the trigone as Bochdalek hernias.