Oocyte Development

Growth phase

Puberty

Graafian follicle

DNA Synthesis,
Genetic recombination,
Meiotic arrest in prophase I
(lampbrush chromosomes)

Maturation signal
Melosis II arrest in metaphase II
Ovulation signal
Fertilization
Release from meiosis II arrest
Re-establishment of diploid state
Mitosis

Ovulation and Oocyte Capture by Oviduct Fimbriae

Fimbriae move to cover the ovary surface and the oviduct initiates rhythmic contractions to move the oocyte toward the uterus.
Fertilization Occurs in the Upper Region of the Oviduct

Total number of sperm/ejaculation range between 280-500 million
Total number of sperm reaching upper oviduct for fertilization range from 1500-3000

Steps in Fertilization

Fertilization Releases the Oocyte From Meiosis II Block

- Activation of a receptor tyrosine kinase pathway
- Activation of PLC → PIP$_3$
- Increased Ca$^{2+}$ concentration
- pH shift (6.8 → 7.2) (H$^+$ → Na$^+$)
- Release from meiosis II block
- Nucleus becomes reprogrammed to initiate mitotic cell cycle
Pronuclei Development, Fusion and Formation of First Mitotic Division Figure

First Cleavage - 24h

Early Cell Division and Formation of the Blastocyst:

Compaction

Hatching

Zona pellucida "hatching" at day 5 post fertilization

Overview of Early Development Leading to Blastocyst Implantation

*Secretes progesterone, estradiol, inhibin A
Abnormal Implantation Sites – Associated with Early Embryo Hatching From the Zona Pellucida

Normal implantation usually occurs along either the posterior or anterior wall of the uterine body.

Abnormal Implantation Sites Expressed as a Percentage
- Abdominal or recto-uterine pouch: 1.2%
- Ampullary: 54%
- Isthmus: 25%
- Fimbrial: 17%
- Interstitial: 2%
- Ovarian: 0.5%
- Cervical: 0.3%

Early Stage of Blastocyst Implantation (Day 6-6.5)
- The villous syncytiotrophoblast cells secrete human placental lactogen (HPL), also called human chorionic somatomammotropin (HCS), estrogen, progesterone and HCG during the course of pregnancy.

Blastocyst Implantation (approximately day 7-7½)
- Blastocyst at Day 13 Completely Embedded in the Endometrial Layer

Representative Stages of Blastocyst Implantation into the Endometrium

Formation of the Trilaminar Germ Disc and Primitive Streak Occurs during Week Two of Development
Cross sectional Representation Showing Cell Movement Through the Primitive Streak to Form the Mesoderm and Endoderm

Schematic representation of cell movement through the primitive streak (ingression). Cells that move through the primitive node give rise to the embryonic axis proper (notochord, axial mesoderm). All others give rise to endoderm, intermediate and lateral plate mesoderm and extraembryonic tissues. (triploblastic organization)

Computer-generated image from a Micro-MRI, actual length 1.5 mm. Image represents a side view of an embryo during its third week of development. The white line is the early embryo.

Embryological Development of the Urogenital System

"Urogenital tract development involves a complex interplay of multiple cell types, and it occurs during a relatively narrow time window. The temporal pattern of gene expression and the spatial relationships of the developing tissues is vitally important for normal development."

- Williams Gynecology, Schorge et al., McGraw-Hill Medical, 2006

"The close association between the müllerian and mesonephric ducts has clinical relevance, because damage to either duct system will most often be associated with damage to both – uterine horn, kidney and ureter."


Embryogenesis of the Female Reproductive Tract

- Origin of reproductive structures is closely tied to early renal development because both are derived from the intermediate mesoderm that occupies the region between the somite and lateral plate mesoderm.
- Forms the longitudinal urogenital ridge that divides into the nephrogenic ridge and the genital ridge.
  - By gestational weeks 3-4 the mesonephric ducts have extended down to merge with the cloaca.
  - By approximately week 5 the uterine buds form from the mesonephric (Woffian) duct near the cloaca and migrate cranially into the metanephric mesenchyme to form the ureter and induce the metanephric kidney.
**PGC Origin and Migration into the Genital Ridge**
- Gonad development is dependent on the presence of primordial germ cells (PGCs).
- PGCs form in the posterior region of the human embryo at the angle between the allantois and the wall of the yolk sac and split into two migratory cell populations.
- These move caudally from the yolk sac wall through the hindgut endoderm (diapedesis) and along and finally up the dorsal mesentery into their respective genital ridges.

**Origin and Development of the Ovaries**
- Genital ridges are paired regions of intermediate mesodermal mesenchyme medial to the developing kidney.
- Induced by actions of the mesonephric tubule cells.
- Appear during week 4 and remain as indifferent gonads until week 7.
- Epithelial cell proliferation cause the region to bulge out into the coelom.
- Mesenchyme cell migration disrupts the 1st sex cords and establishes the ovarian stroma.

**Oocyte Development After PGC Invasion**
- Upon entering the genital ridges, the PGCs associate with the secondary sex cords and cease motility.
- Within sex cords PGCs proliferate giving rise to oogonial nests (germ cell cysts) connected by cytoplasmic bridges. All mitosis ceases by the 3rd trimester of gestation.
- First primary follicles detected at mid-gestation (week 16) and increase to approximately 7 million (week 20).
- Upon cessation of mitosis, oogonia enter meiosis I as primary oocytes and become arrested in prophase at crossover.
- By puberty the number of primary follicles has decreased (via apoptosis) to a little more than 400,000. (?)
The Indifferent gonad

- In the early embryo at the indifferent gonad stage both male and female ducts are observed.
- In females in the absence of the SRY genes, testosterone and AMH (MIS) the mesonephric ducts degenerate and the gonad develops into an ovary.
- The female mesonephric (Wolffian) ducts persist only in vestigial form and are detected either adjacent to the uterus as Gartner's cysts or as the tubular remnants epoöphoron and paroöphoron of the mesovarium.
- In the developing ovary the primitive sex cords degenerate as the genital ridge mesothelium forms the secondary sex cords which will become the granulosa and follicle cells surrounding the oocytes.
- At 4.5 weeks primordial germ cells enter the cortical region of the gonad and remain at that site.

Embryogenesis of the Female Reproductive Tract

- Normal development of the female reproductive tract entails a series of highly orchestrated, complex interactions that direct differentiation of the Müllerian ducts and urogenital sinus (UGS) to form the internal female reproductive tract. Although they originate from different germ layers, the developmental fate of the müllerian ducts (intermediate mesoderm) and UGS (endoderm) are interconnected.
- Abnormalities of the female reproductive tract are usually the result of fusion defects and are often, but not always, associated with various multiple malformation syndromes such as Antley-Bixler, Bardet-Biedl, Johanson-Blizzard or Fraser Syndromes.

Hox genes confer regional specificity along the anterior/posterior axis of animals

- Hox genes are homeotic genes in mouse and human that evolved from their phylogenetic counterparts in Drosophila.
Hox gene expression in the developing female reproductive tract


Origin of the Müllerian (Paramesonephric) Ducts

- Formed by invagination of the coelomic epithelium of the mesonephros, at about week 6, in a cranial → caudal direction, coursing lateral to the mesonephric (Wolffian) ducts toward the midline.
- Cranially the duct opens into the coelom as a funnel-like structure (ostium tubae).

As the two ducts descend caudally and medially they merge at about 10 weeks gestation at the midline in a caudal → cranial direction to form the uterovaginal canal, fusing behind the cloaca, near the mesonephric ducts to terminate at the sinovaginal bulbs adjacent to what will become the urogenital sinus. Mesenchyme surrounding the uterus condenses to form the myometrium. Dissolution of the midline septum is usually completed by 20 weeks.
Congenital Uterine Anomalies (CUAs)

- CUAs may lead to symptoms such as pelvic pain, prolonged or otherwise abnormal bleeding at the time of menarche recurrent pregnancy loss or premature delivery.
- Increased risk of having skeletal or abdominal wall abnormalities or a history of inguinal hernia.
- Renal anomalies occur in 20-30% of Mullerian defects (Oppelt, von Have, Paulsen et al., Fertil. Steril. 87:33%, 2007)
- When a renal anomaly is present it is typically ipsilateral to the CUA.
- Anomalies may be congenital or acquired; karyotypes are usually normal (92%).
- True incidence of anomalies is unknown because in the absence of symptoms most go undiagnosed.
- 97% of women with uterine defects have successful fertility and pregnancy.
- The mean incidence of uterine malformations has been reported as 4.3% for women with normal reproductive outcomes (Grimbizis et al., Hum Reprod Update. 2001 Mar-Apr. 7(2):161-74.)
- Some form of müllerian hypoplasia or agenesis affects one in every 4,000 - 5,000 females.

Abnormalities of Uterine Formation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Anomaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (agenesis/ hypoplasia)</td>
<td>a. Vaginal b. Cervical c. Fundal d. Tubal e. Combined</td>
</tr>
<tr>
<td>Class II (unicornuate)</td>
<td>a. Communicating b. Noncommunicating c. No cavity d. No horn</td>
</tr>
<tr>
<td>Class III (didelphys)</td>
<td>Didelphys</td>
</tr>
<tr>
<td>Class IV (bicornuate)</td>
<td>a. Complete b. Partial</td>
</tr>
<tr>
<td>Class V (separate)</td>
<td>a. Complete b. Partial</td>
</tr>
<tr>
<td>Class VI (Arcuate)</td>
<td>Arooste</td>
</tr>
<tr>
<td>Class VII (DES induced)</td>
<td>DES related</td>
</tr>
</tbody>
</table>

ASRM, American Society of Reproductive Medicine; DES, diethylstilbestrol.

Schematic Representations of Anatomical Abnormalities in Uterine Development

Most commonly formed by defects in müllerian duct fusion and/or septal reabsorption.
Various genetic abnormalities of the uterus that can be detected by a sonographic examination or NMR imaging.
Sonographic observations of abnormal uteri

A. Didelphys uterus with two uterine horns and a single cervical canal. (Ong, C. L., 2016)
B. Septate uterus with the septum (asterisk) separating the endometrial cavity into two. (Indrani K*, Kalyani R and Vidya B, 2016)
C. Bicornuate uterus with two uterine horns containing separate endometrial cavities and a pregnancy (arrow) in the right uterine horn. (Allegrezza, D. M., 2007)
D. Arcuate uterus displaying arcuate configuration of the fundal portion of the uterine cavity. (Olivares K, Tagari M, Stovin P, 2010)

Classification of Congenital Uterine Malformations

<table>
<thead>
<tr>
<th>Classification</th>
<th>Causation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoplasia/agenesis</td>
<td>Arrested bilateral development. Absence of the uterus. Extremely rare (3%).</td>
</tr>
<tr>
<td>Unicornuate</td>
<td>Arrested unilateral development. One uterine horn, one cervix (10%).</td>
</tr>
<tr>
<td>Didelphys</td>
<td>Complete failure of fusion. Two vaginas, two cervices and two uteri (8%).</td>
</tr>
<tr>
<td>Bicornuate</td>
<td>Partial failure of fusion: (26%) Bicollis: one vagina, two cervices and two horns. Unicollis: one vagina, one cervix, two horns.</td>
</tr>
<tr>
<td>Arcuate</td>
<td>Mildest fusion anomaly (18%). Partial indentation of uterine fundus.</td>
</tr>
<tr>
<td>Septate</td>
<td>Failure of septal reabsorption. Complete or partial duplication of the uterine cavities without duplication of horns. Most common (90%).</td>
</tr>
</tbody>
</table>


Clinical Significance of CUAs

- Arcuate uterus – Is typically classified as a normal variant and is not associated with adverse pregnancy outcomes.
- Septate/subseptate uterus – Most common uterine anomaly (30-90%) of all identified uterine malformations. It is more likely to be associated with adverse pregnancy outcomes than other uterine anomalies. Increased risk for spontaneous abortion (21-44%) and preterm delivery (12-33%). Associated with an increased risk of breech presentation and abruption. Pregnancy loss often occurs in 2nd trimester. Live birth rate ranges from 50-72%.
- Bicornuate uterus – Literature reports indicate spontaneous abortion is 38%, preterm birth in 21-23% and fetal survival in 50-60% of patients. Fetal growth restriction and malpresentation in labor also increase.
- Uterus didelphys – 15-20% of women with this anomaly also have unilateral anomalies (obstructed hemivagina; ipsilateral renal agenesis). 65% show this on the right side. Spontaneous abortion rates of 32% and preterm birth (28%) have been reported. Fetal growth restriction is increased. The presence of a septated vagina occurs in 75% of the cases.
- Unicornuate uterus – Associated with a high incidence (45%) of renal abnormalities. Higher risks for endometriosis, premature labor and breech presentations. This condition may be associated with an ectopic ovary. Associated obstetric complications include ectopic pregnancy (3%), first trimester abortion (24%), second trimester abortion (15%), preterm delivery (20%) and fetal demise (4%). Live birth rate is 51%.
Abnormalities of a Didelphys Uterus with the Presence of an Obstruction – OHVIRA syndrome

- In some, though rare cases, the formation of a didelphys uterus is accompanied by either a complete or incomplete unilateral vaginal obstruction, and ipsilateral renal agenesis (Obstructed HemiVagina and Ipsilateral Renal Anomaly). A. Complete vaginal obstruction. B. Incomplete vaginal obstruction. C. Complete vaginal obstruction with a lateral communicating double uterus. D. Magnetic resonance image of OHVIRA syndrome showing uterine didelphys, obstructed hemivagina, and ectopic ureter on MR imaging in a 17-year-old girl. Large arrows - two widely separate uterine horns; asterisk - obstructed left hemivagina distended with fluid; arrowhead - nondilated right hemivagina. Modified from (From: Rock JA, Jones HW Jr: Am J Obstet Gynecol 138:340, 1980).

Mayer-Rokitansky-Küster-Hauser syndrome

Uterine agenesis – a condition whereby the vagina and uterus are underdeveloped or absent due to a failure of Mullerian duct formation. Frequency = 1:4000-10,000 female births (Amer Coll OB-GYN, May, 2013)

Third most common cause of primary amenorrhea after pregnancy and gonadal failure (such as from Turner syndrome).

The first noticeable sign of MRKH syndrome is that menstruation does not begin by age 16 (primary amenorrhea).

Females with MRKH have a normal chromosome pattern (46, XX) and normally functioning ovaries.

They also have normal female external genitalia and normal breast and pubic hair development.

Inheritance pattern is unclear - signs and symptoms of the condition frequently vary among affected individuals in the same family. However, in some families, there is an indication for an autosomal dominant pattern of inheritance.

MRKH syndrome Classifications

Classifications:
- Typical MRKH – Isolated uterovaginal aplasia/hypoplasia. Prevalence – 64%
- Atypical MRKH – Uterovaginal aplasia/hypoplasia with renal malformation or uterovaginal aplasia/hypoplasia with ovarian dysfunction. Prevalence – 24%
- MURCS syndrome – (Mullerian, renal, cervicothoracic, somite) uterovaginal aplasia/hypoplasia with renal malformation, skeletal malformation, and cardiac malformation. Prevalence – 12%
Development of the Urogenital Sinus

- By the 7th week the cloaca is divided by an upper urorectal septum (Tourneux fold) that meets the medial Rathke’s folds forming a separate rectum and urogenital sinus.
- The urogenital sinus can be considered as having three parts:
  - Cephalad (cranial; vesicle) portion which gives rise to the urinary bladder.
  - Pelvis (middle) portion that gives rise to the female urethra.
  - Caudal (phallic) portion giving rise to distal vagina, greater vestibular (Bartholin), urethral and paraurethral (Skene) glands (also known as the lesser vestibular glands).

Development of the Vagina

The upper one third of the vagina developed from the urogenital canal (mesoderm) which is the union of the lower vertical part of the paramesonephric duct (müllerian duct) and the cloacal plate. The lower two thirds of the vagina develop from the paramesonephric or müllerian duct. The müllerian tubercle arises from the endoderm of the urogenital sinus which gives two solid evaginations. The two solid evaginations grow up from the müllerian tubercle, forming what are known as the sinovaginal bulbs. These sinovaginal bulbs fuse together forming a thick cellular plate called the vaginal plate. This plate will form the lower two third of the vagina which is continuous with the vaginal vestibule.

Development of the Vagina

- Epithelial cells of the vaginal plate desquamate (via apoptosis?) during the second trimester causing the canalization of the vaginal lumen.
- The hymen is the partition that remains between the dilated canalized fused sinovaginal bulbs and the urogenital sinus, becoming perforated either shortly before or after birth.
**Vaginal Abnormalities**

- In vaginal atresia, the urogenital sinus fails to contribute the caudal portion of the vagina. The lower fifth to third of the vagina is replaced by 2–3 cm of fibrous tissue, above which lie a well-differentiated upper vagina, cervix, uterine corpus, and fallopian tubes.

- Transverse vaginal septa occur at several locations and may be complete or incomplete. These septa are usually about 1 cm thick (but can be thicker) and located near the junction of the upper third and lower two-thirds of the vagina, however, septa may be present in the middle or lower third of the vagina. Occurrences have been reported as 46%, 35%, and 19% in the upper, middle, and lower portion of the vagina (Rock, et al., Obstet. Gynecol. 59:448, 1982). Perforations are usually central but may be eccentric in location.

- Vaginal septa may also be longitudinal (sagittal or coronal). Longitudinal septa, which rarely produce clinical problems, probably result from abnormal mesodermal proliferation or persisting epithelium.

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**Phenotypic differentiation of the female external genitalia**

During week 3 mesenchyme cells from the primitive streak migrate around the cloacal membrane forming a pair of slightly elevated cloacal folds.

Cloacal folds unite anteriorly forming the genital tubercle.

In week 6 the cloacal membrane subdivides into the urogenital and anal membranes, subdividing the cloacal folds into the urethral and anal folds. Another pair of elevated swellings, the genital swellings appear on each side of the urethral folds. At this point the indifferent stage of external genitalia development has been reached.

From this point the following changes occur:

- The genital tubercle develops into the clitoris.
- The genital swellings become the labia majora.
- Urethral folds develop into labia minora.
- The introitus (vaginal orifice) develops between the urethral folds.

**Ambiguous Female External Genitalia**

21-hydroxylase Congenital Adrenal Hyperplasia (CAH). Is the most common form (90-95% of cases) of this genetic condition causing the adrenal glands to make excess male hormones (androgens). In this case, ovaries, the uterus, fallopian tubes, upper vagina, and other müllerian structures are normally formed.

Prenatal exposure to substances with male hormone activity. Certain drugs, including progesterone (taken in the early stages of pregnancy to stop bleeding) and anabolic steroids, can cause developing female genitals to become more masculinized.

Depending on the severity of hyperandrogenism, a female infant can be mildly affected, obviously ambiguous, or so severely virilized as to appear to be a male. (see Prader scale)


*From: Photo archives, Lucile Packard Children’s Hospital Stanford School of Medicine.*
Molar Pregnancy – The Hydatidiform Mole

- A common complication of pregnancy (1/1000) in the US, with much higher rates seen in Asia.
- An abnormal form of pregnancy in which a non-viable fertilized egg implants in the uterus, but fails to come to term.
- Develops when an egg that is missing its nucleus is fertilized. Etiology of the condition from the oocyte perspective is not well understood.
- Considered a gestational trophoblastic condition that grows into a mass in the uterus with swollen chorionic villi that grow into clusters resembling grapes due to their fluid accumulation/distention.
- A complete mole is caused by a single (90%) or two (10%) sperm combining with an egg which has lost its DNA. The sperm then undergoes reduplication forming a “complete” 46 chromosome set. The genotype is typically 46 XX (diploid), but can also be 46 XY (diploid). These have a higher risk of developing into a choriocarcinoma, a malignant tumor of trophoblast cells, than do partial moles.
- A partial mole occurs when an egg is fertilized by two sperm or by one sperm which reduplicates itself yielding triploid genotypes (69 XXX) or on rare occasions tetraploids (92 XXXY).

Molar Pregnancy – The Hydatidiform Mole (continued)

- In rare cases a hydatidiform mole co-exists within the uterus with a normal viable fetus, due to two conceptuses.
- The diploid set of sperm-only DNA means that all chromosomes have sperm-patterned methylation suppression of genes (imprinting). Leads to overgrowth of the syncytiotrophoblast (androgenic development) with an underdeveloped embryo.
- Experimentally derived dual egg-patterned methylation leads to a channeling of resources to the embryo, with the underdevelopment of the syncytiotrophoblast (gynogenetic development).
- Both conditions reflect the requirement that male and female derived haploid genomes are needed for proper fetal development due to specific parental dependent genomic imprinting.
- Some moles occur in women carrying a mutation in a gene located on chromosome 1, that predisposes them towards molar pregnancy.

Prader-Willi Syndrome – Disorder Due in Part to Imprinting on the Long Arm of Chromosome 15

- Prader-Willi Syndrome (PWS) is a genetic disorder and the most common syndromic cause of obesity (1:10,000 – 30,000 worldwide). Occurs equally in both sexes and all races.
- The genetic defect is lack of expression of the paternally inherited region of chromosome 15 (15q11-q13).
- Normally this region is expressed from the paternal allele, while the maternal allele is hypermethylated, thus “silencing” the transcription of genes on the maternal chromosome.
- Clinical manifestations involve primary neuropsychiatric and endocrine defects with secondary involvement in many different systems including hypogonadism: Incomplete, delayed or abnormal pubertal development.
- Men are thought to be infertile; there are two known case reports of a female PWS patient reproducing.

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or of part of a chromosome, from one parent and no copies from the other parent – a non-disjunctional event that can occur during meiosis.
Human Twinning

“I wish I had a twin, so I could know what I’d look like without plastic surgery”. – Joan Rivers

Incidences of Twinning*

Increases as the population ages (delayed child bearing).
Use of ovulation-enhancing drugs (such as clomiphene).
Increased use of assisted reproductive technologies (ART).

Although the dizygotic (DZ) twinning rate varies widely under different circumstances, the monozygotic (MZ) twinning rate has been remarkably constant, between 3.5 and 4 per 1000 pregnancies.

Murphy and Hey found the rate to have slightly increased in the 1990s. In recent national statistics, 3.3% of 4 million births in the United States were multiples, or 1 in 30 gestations. (Murphy M. and Hey K.: Twinning rates. Lancet 349:349, 1997).

Since 1973, there has been a steady rise in the incidence of twins and triplets.

Origins of Dizygotic Twinning

Non-Identical DZ twins occur when two fertilized eggs implant in the uterine wall that were independently fertilized by two sperm

Dizygotic embryos implanting close to one another may fuse portions of their chorionic membranes and placentas.

* From: Creasy, Robert K., MD; Resnik, Robert, MD; Iams, Jay D., MD; Lockwood, Charles J., MD, MHCM; Moore, Thomas R., MD; Greene, Michael F., MD. Creasy and Resnik’s Maternal-Fetal Medicine: Principles and Practice, Seventh Edition. 2014
The frequency of monozygotic twining is 0.3% of all pregnancies.

**Monozygotic Twins**
- Dichorial/ Diamniotic (33%)
- Monochorial/ Diamniotic (66%)
- Monochorial/ Monoamniotic (rare)

**Monozygotic Twinning Formed as a Result of Cell Splitting Prior to Compaction (8-16 Cell Stage) Leads to the Formation of Two Morulas**
(Dichorial/diamniotic twinning)

**Monozygotic Twinning in Early Development After Compaction (= 16 cell stage) Results in Separate Inner Cell Masses - Placental Vessels May Form Anastomosis With Each Other**
(Monochorionic/diamniotic twins)
Twin-twin transfusion syndrome (TTTS) in MZ pregnancies:

- A serious condition that can occur in identical twins that share a placenta. (3/10,000 births; 15-20% of monochorionic twins)
- Abnormal blood vessel connections form in the placenta and allow blood to flow unevenly between fetuses.
- Causation not due to an arteriovenous shunt but rather when a cotyledon is fed by an artery from one twin and the blood is then drained by a vein into the other twin.
- May exist singly or can be multiple, and blood may shunt in opposing directions.
- The donor fetus continuously shunts blood into the recipient fetus.
- Leads to hypervolemia (hypertension) of the recipient and hypovolemia (hypotension) of the donor. Cardiac compensation (hypertrophy in the recipient) ensues first and can be seen in abortuses afflicted by TTTS. This is followed by a wide spectrum of bodily growth differences. In early pregnancy cardiac failure/death may result in recipient fetus.
- A common symptom is rapid uterine expansion resulting from polyhydramnios of the recipient, presumed to be secondary to excessive fetal urination. It usually manifests between 20 and 30 weeks of pregnancy, can attain enormous proportions, and is considered a frequent cause of preterm labor.

Twin-twin Transfusion Syndrome

A rare, but very serious condition that occurs in 10-15% of monochorionic twins. Abnormal blood vessel connections form in the placenta that allows blood to flow unevenly between fetuses. One twin – called the donor – becomes dehydrated; and the other – called the recipient – develops high blood pressure producing too much urine and over-filling the amniotic sac. If not treated there is a 90% chance of both fetuses dying. Treatment usually occurs between 16 and 26 weeks of pregnancy by laser ablation of affected blood vessels.

Development of Conjoined Twins

Actual cause of this event is unknown. It’s believed that when the embryo splits later than 12 days post-fertilization — usually between 13 and 15 days — separation stops before the process is complete, and the resulting twins are conjoined.
An alternative model of monozygotic twinning. In this model, splitting occurs at the postzygotic 2 cell stage, with each cell forming a distinct individual. If twin blastocysts hatch from the zona pellucida together, dichorionic diamniotic twins will result. If the 2 trophoderm fuses before hatching and the inner cell masses are separated within the shared trophoderm, monochorionic diamniotic twins will result. If the 2 inner cell masses are fused and separated later (after amnion formation) monochorionic monoamniotic twins will result. McNamara et al., A review of the mechanisms and evidence for typical and atypical twinning. Am J Obstet Gynecol 214(2):171-192, 2016.

Alternative Hypothetical Models of Twining Thought to Arise Due to Alternative Reproductive Technologies (ART)

Hypothesis 1 (not shown) accords with the traditional model of monochorionic diamniotic twinning in which placental anastomoses may result in intertwin transfer of blood cells with subsequent blood cell chimerism. Hypothesis 2 follows the traditional model of dizygotic twinning up to the hatching stage. If 2 hatched blastocysts are in close proximity, as with the use of assisted reproductive technologies, trophoderm fusion may occur. Hypothesis 3 involves fertilization of a binucleate follicle in which 2 oocytes exist within a single zona pellucida. In each hypothesis, fusion might also occur after implantation. In rare cases, cells from the inner cell mass may be transferred between twins, resulting in some degree of somatic chimerism (not shown). McNamara, et al., A review of the mechanisms and evidence for typical and atypical twinning. Am J Obstet Gynecol 214 (2):172-192, 2016.

Other alternate hypothetical twinning processes due to ARTs