Ovulation-Fertilization
Implantation-Early Development

Diagram showing the stages of embryogenesis, from ovulation to implantation, with key stages labeled.
Maturation of the Ovum

- Development of the Graafian Follicle
- Ovulation
- Formation of Corpus Luteum
Menstrual Cycle

Hormonal cycle

Endometrial cycle

Ovarian cycle
Signs and Symptoms of Ovulation

1. Body Temperature increase

2. Cervical Mucus Changes
   - Increase in amount
   - Becomes thin, watery, and clear
   - Ferning
   - Stretchable: Spinnbarkheit
   - Alkaline
Four Main Hormones

• **FSH -- Follicle Stimulating Hormone**
  – Begins Growth and Maturation of graafian follicle

• **LH -- Luteinizing Hormone**
  – assists in continued growth of graafian follicle

• **ESTROGEN**
  – responsible for proliferation of endometrium

• **PROGESTERONE**
  – Pro-gestation. Corpus luteum produces progesterone and endometrium get ready for implantation
Conception

Maturation of Ovum and Sperm Cells

– Pregnancy comes about from the union of a female germ cell, ovum with a male germ cell, the spermatozoon.
– One ovum per month is discharged from the ovary.
– It is transported into the fallopian tube where it begins its journey through the tube in search for the sperm. Viable for 12-24 hours
Fertilization

(a) Sperm cell

(b) Three phases of fertilization

Phase 1: Sperm undergoes acrosome reaction and penetrates corona radiata

Phase 2: Sperm penetrates zona pellucida

Phase 3: Sperm and oocyte plasma membranes fuse

(c) Phase 1 of fertilization
Fertilization

• Life begins at the time fertilization of the ovum
• The zygote formed is a single cell which develops into fully formed adult
• Prenatal development is the process in which an embryo or fetus gestates during pregnancy, from fertilization until birth.
Gestation Period

- The gestation period of

  a) *Germinal Period* - This begins at fertilization and extend till the third week.

  b) *Embryonic period* – This extend from $4^{th}$ ~ $8^{th}$ week, involving changes in shape and external appearance.

  c) *Fetal period* – This extends from $3^{rd}$ month upto termination of pregnancy.
**Fertilization**

- When intercourse occurs, millions of sperm travel in search of an ova. During travel through the female reproductive system, capicitation occurs.
- Capicitation is the removal of plasma membrane and loss of seminal fluid.
- This leaves the sperm ready for fertilization.
As the sperm swarm around the ova, the Acrosome caps of Sperm release zona digesting enzymes.

These enzymes break down the barrier and one sperm is able to penetrate – fertilization occurs.
- Usually occurs in the distal portion of the fallopian tube
- Once sperm penetrates ova, physiological barrier renders the ova impenetrable by other sperm, thus only one sperm enters a single ova

- Each contributes 23 Chromosomes making a Total of 46 chromosomes

- Sex of baby determined at this time. X = female, Y = male
Results of Fertilization

• Stimulates the secondary oocyte to complete its second meiotic division
• Restores normal diploid number (46) of chromosomes in zygote
• Results in variation in human beings
• Determines the chromosomal sex of the embryo
• Causes metabolic activation of zygote & initiates cleavage (cell division of zygote)
Fertilized Ovum begins its travel to the uterus
Cellular Multiplication

- The fertilized zygote begins its travel through the fallopian tube toward the uterus.

- Meiosis II complete and mitotic division trigger

- Cell / mitotic division (cleavage) occurs

- Morula eventually forms a fluid filled cavity within the cell mass.
  - Inner solid cell mass is called Blastocyst
  - Outer cell mass that surrounds the cavity is the Trophoblast
Cleavage

- Zygote
- 2-cell stage
- 4-cell stage

Polar bodies
Zona pellucida
Cleavage

• Repeated *mitotic* division of zygote
• Begins about 30 hours after fertilization
• There is rapid increase in number of cells. The cells, *blastomeres*, become smaller with each division
• Normally occurs as the zygote passes along the uterine tube to the uterus
• During cleavage, zygote lies within the *zona pellucida*
Cleavage

• After **nine-cell** stage, the cells become compactly arranged: **compaction**

• **12-16 cell** stage is called **morula**. It is formed about 3 days after fertilization and enters the uterus
Cleavage

1. Begins ~ 12 hours post-fertilization
2. Zygote divides into 2 cells (mitosis)
3. 46 chromosomes in zygote = 46 chromosomes in both daughter cells
4. 2 cell into 4 cell stage (24 – 36 hours)
5. 4 cell into 8 cell stage (36 – 72 hours)
6. 16 cell stage -- Morula
Morula

• ~ 16 cell stage
• Develops ~ 72 hours (3 days) from fertilization
• Morula enters the uterus ~ after 3 days in oviduct
Morula

72 hours post-fertilization entering uterus
Blastocyst

- Morula, once entering the uterine cavity, floats freely
- Morula begins to accumulate fluid and forms a cavity between its cells
- Once cavity appears, it is now called a blastocyst.
Cleavage

- Internal cells of the morula, **inner cell mass**, are surrounded by a layer of cells that form the **outer cell mass**

- Fluid filled space called the **blastocyst cavity (blastocele)** appears inside morula

- Blastomeres are separated into:
  - Outer cell layer, the **trophoblast**, which gives rise to embryonic part of placenta
  - Centrally located, **inner cell mass (embryoblasts)** which gives rise to embryo
Morula and blastocyst

Morula
12-16 cells
Day 3

Compaction

Inner cell mass

Blastocoele

Trophoblast cell layer

Blastocyst
32-64 cells
Days 4/5

Days 6/7
Cleavage

- At this stage, the conceptus is called **Blastocyst**. It has two poles: **embryonic** & **abembryonic**
- **Zona pellucida** gradually degenerates and disappears
- Blastocyst takes its nourishment from **uterine secretions** and enlarges in size. It is ready to get attached and implanted to the uterine wall
Blastocyst
Two Distinct Cell Types

Inner cell mass – will form the embryo

Trophoblasts – will form the invading placenta

Inner cell mass cells – will form the embryo
Implantation

Small finger-like projections extend from the trophoblast and blastocyes embedded within the uterine wall
The Zona Pellucida
Sperm Interaction with the Zona

Zona Pellelucida

Attachment

Binding

Acrosome Reaction Induction

Acrosome Reaction

ZP3
Implantation

• Blastocyst floats for 2–3 days
• Implantation begins 6–7 days after ovulation
  – Trophoblast adheres to a site with the proper receptors and chemical signals
  – Inflammatory-like response occurs in the endometrium
Endometrium
Uterine endometrial epithelium
Inner cell mass
Trophoblast
Blastocyst cyst cavity
Lumen of uterus
Implantation

- Trophoblasts proliferate and form two distinct layers
  1. Cytotrophoblast (cellular trophoblast): inner layer of cells
  2. Syncytiotrophoblast: cells in the outer layer lose their plasma membranes, invade and digest the endometrium
Endometrial stroma with blood vessels and glands

Syncytiotrophoblast

Cytotrophoblast

Inner cell mass (future embryo)

Lumen of uterus
Implantation

• Begins 6 days after fertilization:

➢ The blastocyst attaches to the endometrial epithelium, usually adjacent to the embryonic pole
Implantation

- Trophoblast proliferates rapidly and differentiates into two layers:
  - inner cellular cytотrophoblast,
  - outer mass of syncytiotrophoblast (multinucleated protoplasm with no cell boundaries)
- Finger like processes of syncytiotrophoblast extend through the endometrium and invade the endometrial connective tissue
Implantation

• By the end of 7th day, the blastocyst gets implanted in the superficial compact layer of endometrium and derives its nourishment from the eroded endometrium.
Implantation

• The blastocyst gradually embeds deeper in the endometrium

• By 10th day it is completely buried within the ‘Functional layer’ (stratum compactum + stratum spongiosum) of the endometrium
Implantation

• The defect in the endometrial epithelium is filled by closing plug (day 10)

• The defect gradually disappear as the endometrial epithelium is repaired (day 12 & 13) by the proliferation of the surrounding cells
Implantation

• Small cavities, the lacunae appear in syncytiotrophoblast, and get filled with maternal blood, establishing primitive uteroplacental circulation
Normal Implantation Sites

- The implantation site determines the site of formation of the placenta.
- Normally it occurs in the upper part of the body of uterus, more often on the posterior wall.
Abnormal Implantation Sites

- **Uterine:**
  - Implantation in the lower segment leads to *placenta praevia*

- **Extrauterine:** leading to ectopic pregnancies
  - Fallopian tube
  - Ovary
  - Abdominal cavity
Abnormal Implantation Sites
Molecular Control of Implantation
Molecular Control of Implantation
Molecular Control of Implantation

For LIF and other gp130 cytokines, heparin can activate STAT3.

Heparin can block L-selectin on blastocyst.

EGF signaling can activate STAT3.

Heparin increases shH-EGF.

Microvilli on syncytiotrophoblast.

Heparin decreases trophoblast apoptosis.

Regulation of changes in surface epithelium.

Heparin can increase IL-1 and GM-CSF.

Endometrial stroma.

Heparin improves invasion by increasing MMPs and decreases TIMPs.

Luminal epithelium.

Growth factors and cytokines.

Heparin increases IGF-1 and decreases TGFbeta-1.

Growth factors and cytokines.

Endometrial glands.
Decidua

After implantation, the endometrium becomes more thickened, the cells enlarge, and is now called the Decidua.

- **Decidua Basalis**
  part directly under the blastocyst

- **Decidua capsularis**
  portion that is pushed out by the growing blastocyst and covers the blastocyst

- **Decidua Parietalis** --portion which is not in immediate contact with the ovum
Trophoblast
Outer layer of cells

Blastocyst
INNER CELL MASS

Placenta
Chorion

Fetus
Amnion
hCG is produced

- hCG is **human chorionic gonadotropin**
- It is produced by the trophoblasts starting on day 6
- hCG is a hormone
- hCG causes endometrium of uterus to grow and proliferate
- hCG prevents the menstrual cycle from occurring
- This is why a female misses her periods when she is pregnant
Week 2

- Implantation continues
- Erosion of maternal blood vessels
- Complete emersion into endometrium of uterus
Cellular Differentiation

• At 10 – 14 days of age, the blastocyst or beginning zygote begins cellular differentiation into the primary germ layers.

• All tissues, organs, and systems develop from these layers.
The trophoblast differentiates into cytотrophoblast & syncytiotrophoblast.

Cells of the cytотrophoblast divide and migrate externally.

They lose their cell membranes to form the syncytiotrophoblast.

The syncytiotrophoblast erodes the maternal tissues, so lacunae filled with maternal blood surround columns of syncytiotrophoblast.

These columns of syncytiotrophoblast will form primary villi.
Week 2 – The Two-Layered Embryo (Blastodisc)

- Bilaminar embryonic disc formed when the inner cell mass divide and forms into two sheets
  - Epiblast (5) and the hypoblast (2)
    - Together make up the bilaminar embryonic disc or blastodisc
Bilaminar germ disc

The inner cell mass is differentiated into:

a- **Epiblast** = endoderm (small cuboidal cells facing the blastocyst cavity and

b- **Hypoblast** = ectoderm (tall columnar cells facing the amniotic cavity).

Both layers will form the **bilaminar germ disc**.

Cavities develop within the epiblast and coalesce to form the amniotic cavity.

- The epiblast (future ectoderm) will surround the amniotic cavity (amnioblast) so forming the **amniotic membrane**.

Fig. 34: Drawing of a 9 day human blastocyst.
-The hypoblast cells (future endoderm) migrate and line the inner surface of cytотrophoblast so forming the exocoelomic membrane (flat cell from the endoderm) which limits a space called the exocoelomic cavity (primary or primitive yolk sac).

-It is formed in the ventral aspect of the embryonic disc.
Week 3 – Three-Layered Embryo

- Primitive streak – raised groove on the dorsal surface of the epiblast
- Gastrulation – a process of invagination of epiblast cells. A very incredibly important step in development as this process forms the
  - Endoderm – formed from migrating cells that replace the hypoblast
  - Mesoderm – formed between epiblast and endoderm, these cells divide and spread and form parts of the amnion and yolk sac.
  - Ectoderm – formed from epiblast cells that stay on dorsal surface
Ectoderm
• nervous
• skin, hair, nails
• sensory organs

Mesoderm
• muscle
• connective tissue
• blood vessels
• bone marrow

Endoderm
• Genitourinary
• Respiratory--larynx, trachea, lungs
• Digestive
• Developmental “time line” of the three primary germ layers
Weeks 3-4

- Development of cardiovascular and nervous systems
Following the Germ Layers and changes in the Embryo
Following the Germ Layers and changes in the Embryo
Week 4 – The Body Takes Shape

- Folding of embryo laterally and at the head and tail
  - Primitive gut – formed by lateral folding
  - "Tadpole shape" by day 24
Embryonic Period
Weeks 4-8

• Week 4
  – anterior end of neural tube closes to form the brain and the posterior end closes to form the spinal cord
  – Heart begins to beat
  – Eyes appear
  – Limb Buds for arms and legs
  – CR = 4 mm
• **Week 5**
  - Head grows larger
  - Hand and feet plates develop
  - Facial features begin to develop
  - CR = 8 mm.
• Week 6
  – Fetal circulation is established
  – Chambers form in the heart
  – Upper lip and palate start fusing
  – Eyes move to front of face
  – Fingers are webbed
  – External ear develops
• Week 7
  – Eyelids start to form
  – Fingers develop; elbows visible
  – Diaphragm separates abdomen from chest
  – Bronchi develop
  – Arms and legs move
• Week 8
  – Fingers and toes distinct
  – Skeletal ossification begins
  – Testes and ovaries are distinguishable
  – Heart has four chambers
  – Circulation through umbilical cord occurs

– *** ALL essential external and internal structures are present and now will continue to grow
Germ Layer Destinations

- Ectoderm – forms brain, spinal cord, and epidermis
- Endoderm
  - Forms inner epithelial lining of the gut tube
  - Forms respiratory tubes, digestive organs, and urinary bladder
Germ Layer Destinations

- Mesoderm – forms muscle, bone, dermis, and connective tissues
  - Somites divide into sclerotome, dermatome, and myotome
  - Intermediate mesoderm – forms kidneys and gonads
  - Splanchnic mesoderm
    - Forms musculature, connective tissues, and serosa of the digestive and respiratory structures
    - Forms heart and most blood vessels
  - Somatic mesoderm – forms dermis of skin, bones, and ligaments
The Germ Layers in Week Four

- Ectoderm
- Somite
- Intermediate mesoderm
- Notochord
- Endoderm
- Neural tube
- Somatic portion of lateral mesoderm
- Developing coelom
- Splanchnic portion of lateral mesoderm
- Yolk sac
- Dermatome
- Myotome
- Sclerotome
- Kidney and gonads (intermediate mesoderm)
- Visceral serosa (splanchnic mesoderm)
- Smooth muscle and connective tissues of gut (splanchnic mesoderm)
- Peritoneal cavity (coelom)
- Neural tube (ectoderm)
- Epidermis (ectoderm)
- Gut lining (endoderm)
- Limb bud
- Parietal serosa (somatic mesoderm)
- Dermis (somatic mesoderm)
- Spinal cord
- Vertebral column
- Kidney
- Rib
- Outer body wall:
  - Trunk muscles
  - Parietal serosa
Week 5-8 – The Second Month of Embryonic Development

- Limb buds form
- Embryo first looks recognizably human
- Head is disproportionately large
- All major organs are in place
Weeks 5-8

- Embryo will develop all structures that an adult has by the end of week 8
Embryo/Fetus

• Embryonic period is weeks 1-8
• Fetal period begins on week 9 and goes until birth at 38 weeks.
• Embryonic period is characterized by development of structures (organs).
• Fetal period is characterized by growth of those structures.
# Fetal Period

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Fetal Period
Weeks 9-40

12 weeks

18 weeks

32 weeks gestation

16 weeks

24 weeks
Fetal Period Facts & Stats

• A time of maturation and rapid growth
• Cells are differentiating during the first half of the fetal period
• Normal births occur 38 weeks after conception
• Premature birth is one that occurs before 38 weeks
Developmental Events of the Fetal Period

- Eyes & ears take on human form
- Neck becomes evident & head is almost as large as rest of body
- Liver is large in relation to size of body
- Bone formation begins as do weak muscle contractions
- Limbs are formed and digits are separated
- Cardiovascular system is functioning and heart is pumping (since week 4)
- Size: 3 cm (crown to rump)
Developmental Events of the Fetal Period

- Head is still large (body is elongating) & brain development continues and retina is formed
- Differentiation of epidermis & dermis occurs
- Liver is large, hard palate fusion starts, smooth muscle appears in hollow visceral organs
- Blood cells formation gets underway in bone marrow & spleen
- Notochord is being replaced by bone
- Gender determination is possible in ultrasound viewing
- Size: 9 cm (crown to rump)
Developmental Events of the Fetal Period

- Sucking actions occur & eye movement is seen (eyes still closed)
- Body starts to catch up to head size & limbs appear more proportionate
- Hard palate is fused
- Kidneys take on normal appearance
- Joint cavities present & most bones are distinct
- Size: 14 cm (crown to rump)
Developmental Events of the Fetal Period

- Eyelashes & eyebrows present, fatty skin secretion covers the body, lanugo covers the skin
- Quickening occurs
- Fetal position is attained (due to space restrictions)
- Limbs reach normal proportions
- Size: 19 cm
Weeks 9-12

- Head size increases
- Face is well formed
- Nails appear
- Eyelids appear and close and fuse shut
- Kidneys excrete urine
- Intestines are forming; peristalsis begins
- Heartbeat can be heard via ultrasound
- Tooth buds appear for the baby teeth
Weeks 13-16

• Lips form, facial contour develops
• Ossification of bone begins
• Meconium begins to form in the intestines
• Hair present on scalp
• Sex can be determined visually
Weeks 17-20

- Hair abundant on head
- Lanugo covers the body
- Vernix begins to form
- Myelination of spinal cord begins
- Suck and swallow begin
- Quickening occurs ~ 18 weeks
Weeks 21-24 weeks

- Respiratory movement with air sacs formed
- Surfactant production begins ~ 24 weeks
- Brain appears mature
- Eyebrows and eyelashes can be seen
- Reacts to sudden noise with active movement
Weeks 25 - 28

• Eyelids open and close
• Capillaries proliferate around the lungs’ alveoli making gas exchange possible
• Skin has wrinkled red appearance
• Rapid brain development
Developmental Events of the Fetal Period

- Body size & weight increase
- Eyes open
- Fingernail & toenails are developed
- Skin is wrinkled & red, subcutaneous fat is just starting to accumulate
- Bone marrow becomes sole site for blood cell development
- Testes descend into scrotum
- Size: 28 cm
Weeks 29-32

- Subcutaneous fat forms
- Testes start descending
- Fingernails and toenails are complete
- Bones are fully developed, but still soft and pliable
Weeks 33 - 40

- Limbs start to flex
- Muscle tone is developed
- Lanugo disappears
- Body begins to store fat
- Maternal antibodies transfer to the fetus
- Exhibits sleep and awake patterns
Developmental Events of the Fetal Period

- Fat accumulation occurs in subcutaneous layer
- Size: 36 cm
- Weight: 2.7 – 4.1 kg.
Teratogens

- Risk factors such as environmental substances
  - Smoking
  - Alcohol
  - Drugs
  - Viruses
  - Occupational hazards