



**University of
Lancashire**

Introduction to Y2 Development Biology & Placenta development

AY 25-26, UM2010

Maryam Rajid

Lecturer in Medical Sciences (Anatomy & Development)

mrajid@lancashire.ac.uk

Where opportunity creates success

How will we approach Development in Year 2?

Will encompass a lot more embryology and associated clinical birth defects.

In core block:

- **Implantation and placenta development & maturation (This lecture).**
- **Birth defects: An introduction to birth defects.**

Development of each organ system will be introduced in the order of Y2 module blocks:

- **GU:** Urogenital system (Urinary system, Reproductive system and Subfertility)
- **MSK:** Musculoskeletal, Limb & Skin development
- **NE:** Neurodevelopment, Endocrine development and Head & Neck development.
- **GI:** Gastrointestinal development
- **CVR:** Cardiovascular development (Heart dev.) and Development of the lungs (Respiratory dev.)

How will we approach Development in Year 2?

There will be **four live review sessions**, during these sessions we will be doing:

- Summaries
- Q&As
- Quizzes

No new material!



Learning Outcomes for this lecture:

- Summaries the morphological events that lead to the formation of the placenta and relate their development to anomalies in pre-natal development.

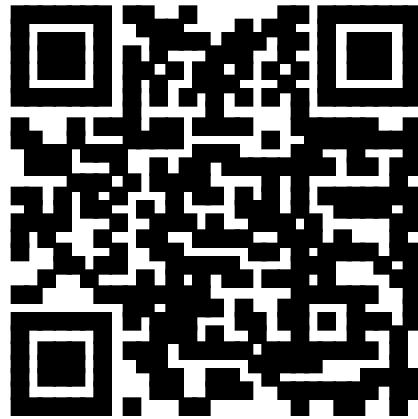


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Introduction to the Placenta

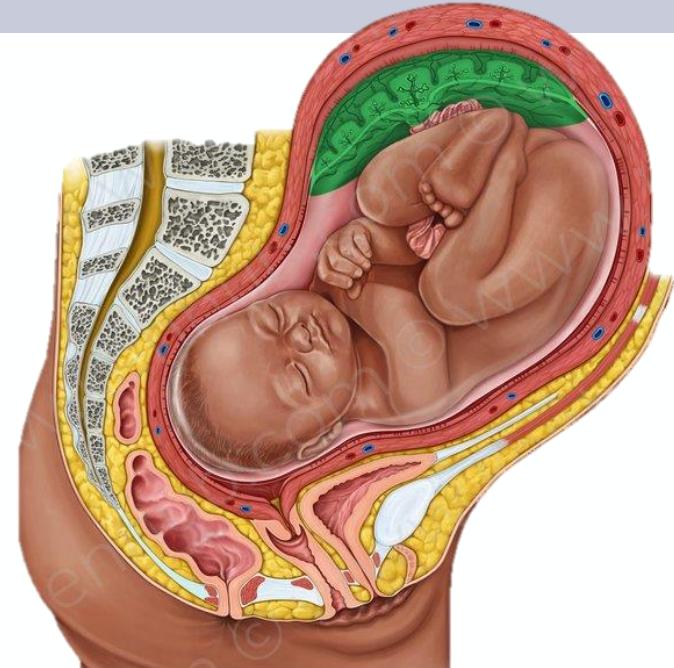


What is a placenta?

A temporary organ of pregnancy found in the uterus. It is a fetomaternal organ. The placenta is the meeting point of two circulatory systems: fetal circulation and maternal circulation (Fetomaternal junction).

Three major function(s) of the placenta:

1. Fetal respiration, nutrition and excretion
2. Fetal protection and immunity
3. Endocrine (hormone production) for maintenance of pregnancy



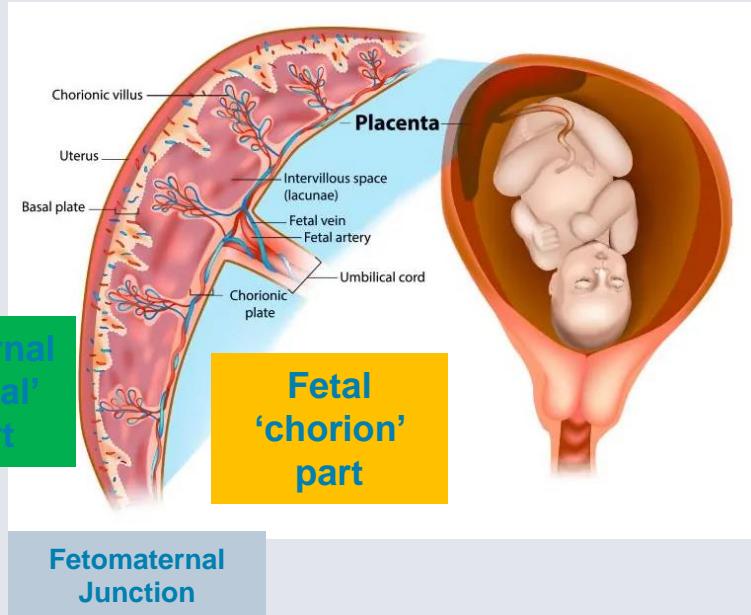
Structure of the placenta

Proudly changing to



Maternal
'Basal'
part

Fetomaternal
Junction



Fetomaternal organ, three main components:

- **Fetal part:** Chorionic plate (sac and villi) derived from **Trophoblast cells**
- **Maternal part:** Basal or Decidual plate derived from **uterine endometrium**
- **Fetomaternal junction:** Contact zone between maternal blood and fetal chorionic tissue.
 - Primary site of nutrient and gas exchange between mother and fetus.
 - Maternal antibodies also crosses the placenta to fetus.

Placenta also secretes hormones (e.g. sex steroids) to maintain the pregnancy and functions as an immunological barrier between the mother and the fetus, creating an immunologically privileged site.

Within the pre-natal development timeline, the placenta starts formation as soon as its implants within the uterus body.

1st Trimester *Embryonic period

(2nd & 3rd Trimester)

Week 0-2: Cell division
(AFTER fertilization
includes blastogenesis
and implantation)

Week 3-8: Embryonic period
(Organogenesis)

Week 9-38: Fetal period (Growth
and cell function)

Placenta growth is much faster than embryonic growth during 1st trimester because the embryo needs to establish access to nutrition and waste disposal in preparation for significant fetal growth in 2nd and 3rd trimester.



Placenta Development

Part 1: Implantation

Part 2: Placenta development

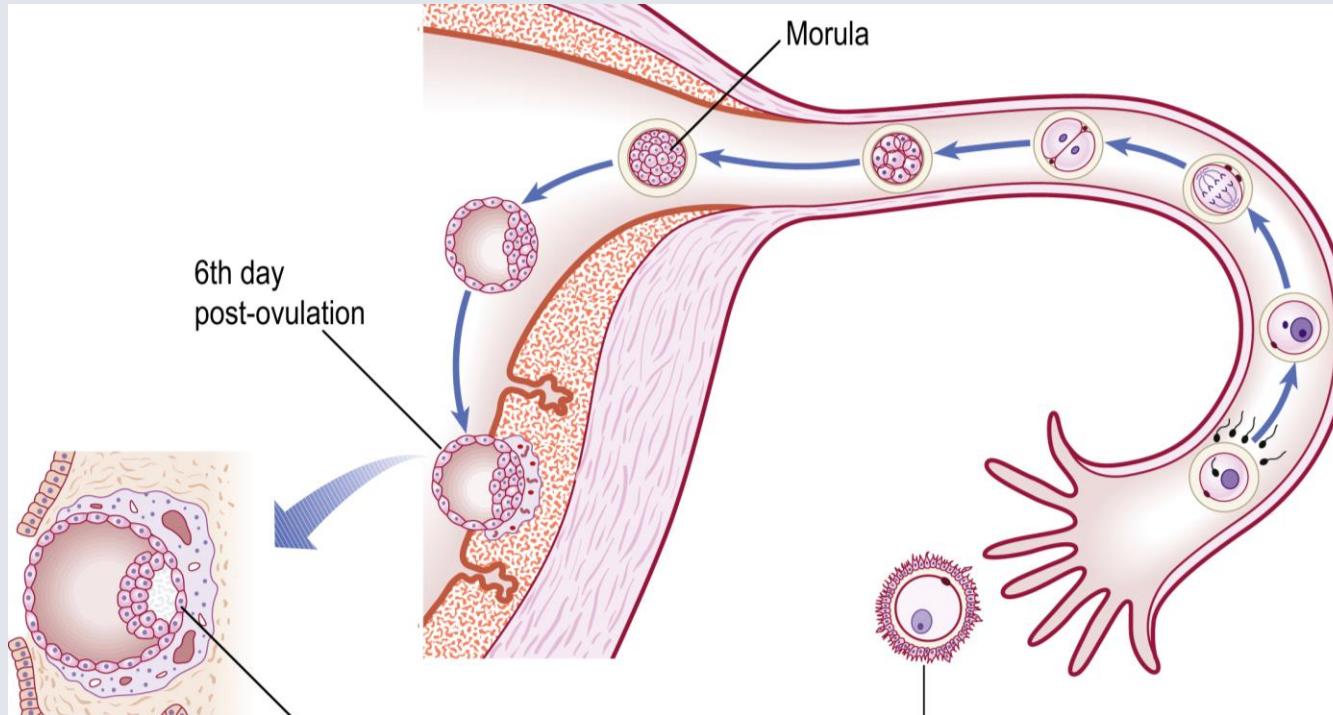




Part 1: Implantation

- Getting ready for Implantation
- Implantation
- Implantation sites & abnormalities

Period of cell division and implantation (YR1 Revision)





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Question slide

What structure is shed during blastocyst 'hatching'?

Outer cell mass

0%

Inner cell mass

0%

Zona pellucida

0%



##/##

Join at: vevox.app

ID: 195-021-189

Results slide

What structure is shed during blastocyst 'hatching'?

Outer cell mass

##.##%

Inner cell mass

##.##%

Zona pellucida

##.##%

RESULTS SLIDE

Getting ready for implantation

For a viable pregnancy, the pre-embryo (conceptus) needs to implant into the uterine wall.

We need 4 key events to have already occurred for implantation to happen:

1. Fertilisation
2. Travel towards the uterus body
3. Blastogenesis (formation of blastocyst)
4. Zona pellucida shedding

Other immunological and physiological-hormonal factors to make the maternal body receptive to the conceptus

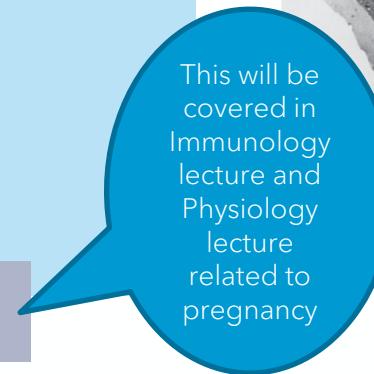


Inner Cell Mass (ICM) – will become the embryo

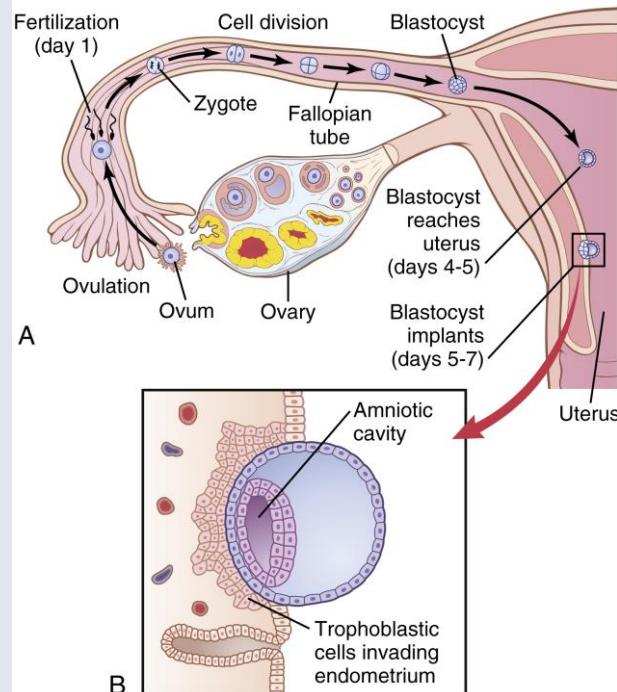


BIOLOGY 11e, Figure 12.13 (Part 2)
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This will be covered in Immunology lecture and Physiology lecture related to pregnancy



Getting ready for implantation



Zygote travels towards the fallopian tube and cleavage i.e cell division occurs concurrently.

Fertilized egg or ovum becomes the zygote and as it travels down the fallopian tube it eventually transforms into **the blastocyst**.

The **blastocyst** needs to travel towards the body of the uterus for implantation.

- This is done by muscular contraction of the fallopian tube and passive movement by fluids in the uterine tube.
- Zona Pellucida (ZP) is a smooth membrane that protects the fertilized ovum and aids movement through the fallopian tubes into the uterus.

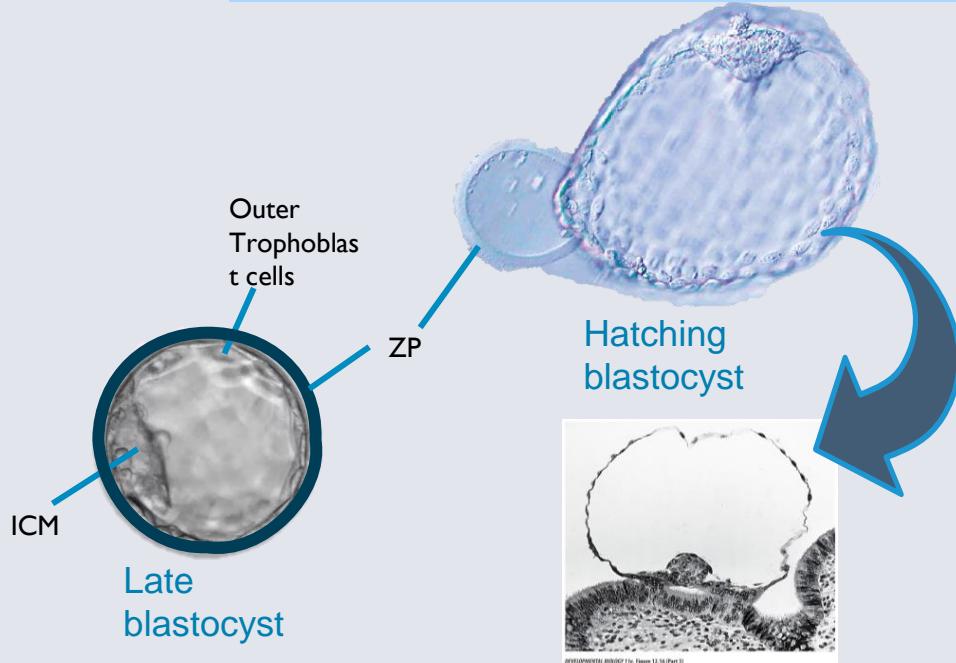
Getting ready for implantation

Zona pellucida acts as a protective barrier:

- **Sperm-oocyte interaction:** During fertilisation ZP acts to prevent polyspermy.
- **Embryo-uterine interaction:** During cell cleavage, ZP prevents premature implantation of the cleaving zygote.

Removal of the ZP or 'hatching' enables the blastocyst to implant onto the uterine wall.

Pre-mature implantation can lead to miscarriage because the uterine lining and maternal hormone levels are not at optimal levels to receive the growing conceptus.

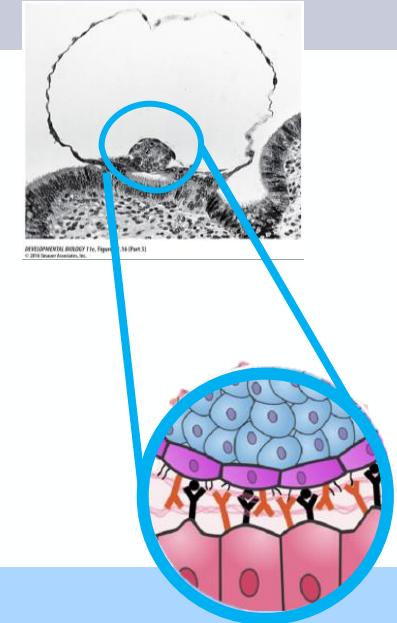


Blastocyst preparing to implant into uterine wall

Implantation: Embedding of the pre-embryo into the uterine wall



- By end of week 1: Implantation process begins with the attachment of the blastocyst onto the uterine endometrium wall. Fully embedded (implanted) within endometrium by d14 dev age or end of week 2 dev.
- Initial implantation of blastocyst is a result of **receptors on the endometrial epithelial cells of the uterus** (e.g. MUC1 receptor) that **recognises specific proteins** on the **surface of the outer trophoblast cells** (of the blastocyst) (e.g. L-selectin).



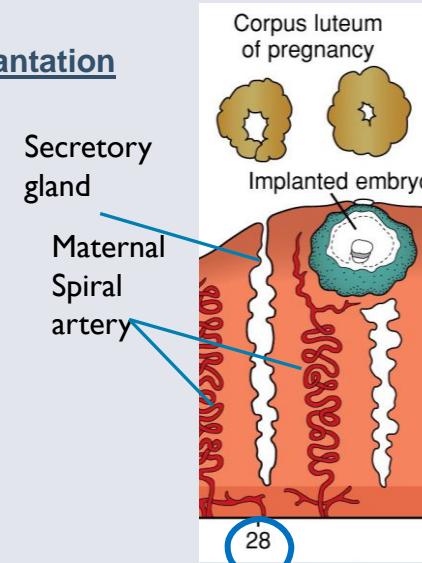
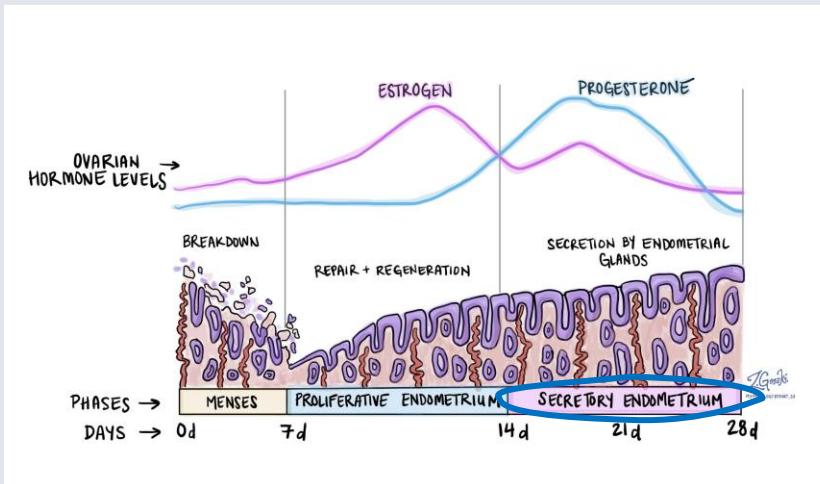
Implantation Failure:

Failure of blastocyst-endometrial interaction is a major cause of infertility and recurrent pregnancy loss.

Implantation: Embedding of the pre-embryo into the uterine wall

Implants generally between secretory glands.

- Uterus in mid-secretory phase of menstrual cycle also known as implantation window.



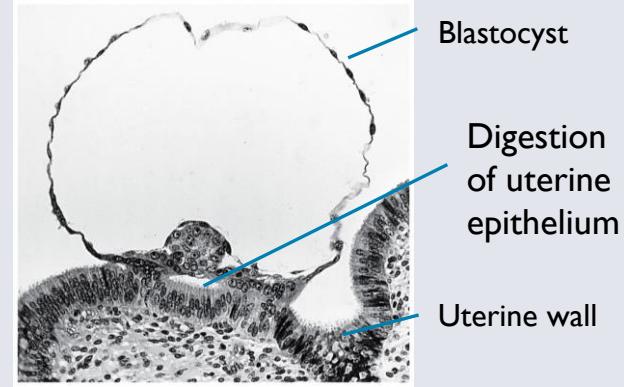
D28 after LNMP: menstruation or implantation and maintenance of pregnancy

Implantation: Embedding of the pre-embryo into the uterine wall

Trophoblast cells facilitates implantation:

Producing digestive enzymes – breakdown components of the endometrial cells and extracellular matrix to facilitate invasion.

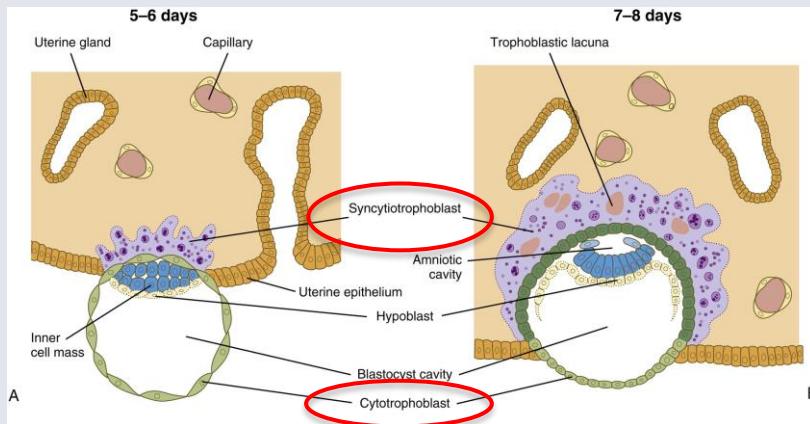
Modulate maternal immune response – protects embryo from maternal immune system that destroys foreign tissue.



DEVELOPMENTAL BIOLOGY 11e, Figure 12.16 (Part 3)
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Implantation

During week 2-The ‘Week of Twos’



- **Aids in implantation:** Together the **Cytotrophoblast** and **Synctiotrophoblast** “burrow” into the endometrium of the uterus and pulls the embryo deeper within.
- These **cells derived from trophoblast layer** represents the future tissue interface between embryo and mother i.e **THE PLACENTA**.

During implantation, the blastocyst grows in complexity.

Outer **trophoblast cells** differentiates into two layers:

1. Cellular layer of **Cytotrophoblast**
2. Syncytial layer of **Synctiotrophoblast**

The outer **Synctiotrophoblast** is highly invasive with active finger-like processes which expands rapidly into the maternal tissue.

- Produces further digestive enzymes to break down the extracellular matrix between the endometrial cells.

The inner **Cytotrophoblast** is more densely packed with obvious cell structure, comprises of a single cell layer.

- Contributes to formation of the placental (Chorionic) villi.

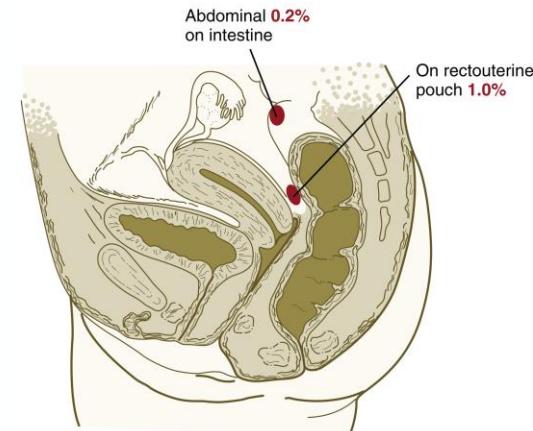
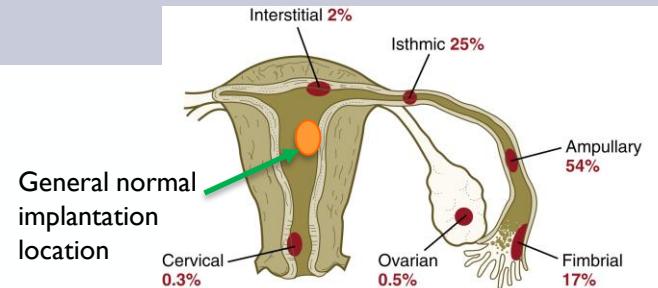
Clinical correlates: Abnormal Implantation

Abnormal implantation can cause ectopic pregnancy.

Majority are tubal pregnancies-Implants in ampullary region or anywhere along the of fallopian tube.

- **Causes?** Any factor that delays or prevents transport of the cleaving zygote to the uterus (e.g. blockage of the fallopian tube caused by scarring due to disease or surgery).

Other abnormal sites: Ovarian, outside of the uterus (in peritoneal cavity, on the abdominal intestines/organs), cervical (placenta previa).

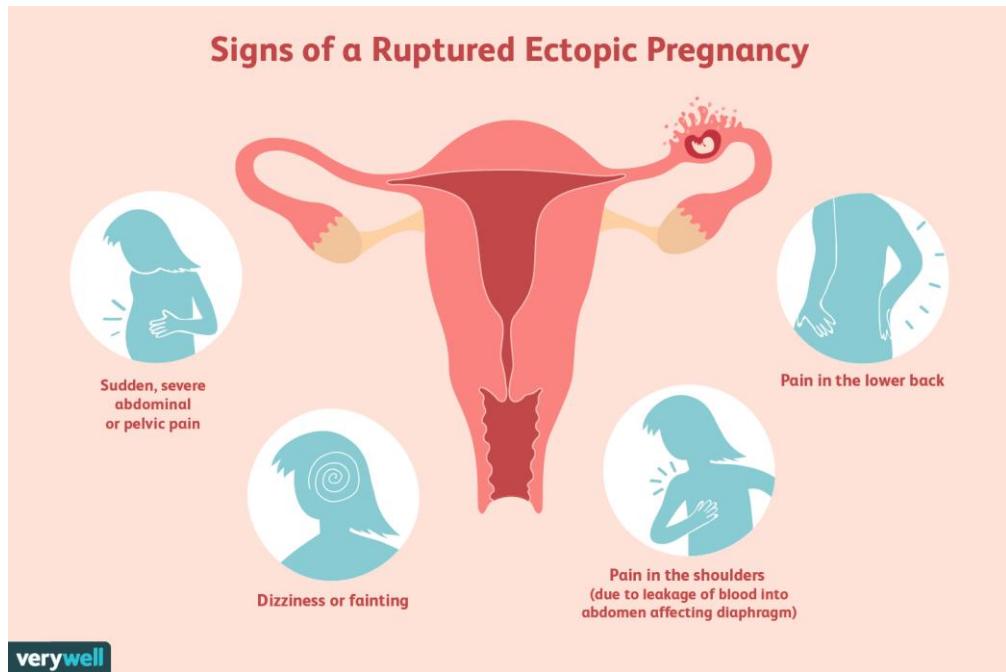


Clinical correlates: Abnormal Implantation



Ectopic pregnancies can go unnoticed or cause mild symptoms—confused with normal pregnancy symptoms until complication arises. This is when the embryo cells invade the blood vessels of surrounding tissue or rupturing the tissue itself.

- Ectopic pregnancy is typically not viable because the fertilised egg cannot get enough blood supply to support its growth.



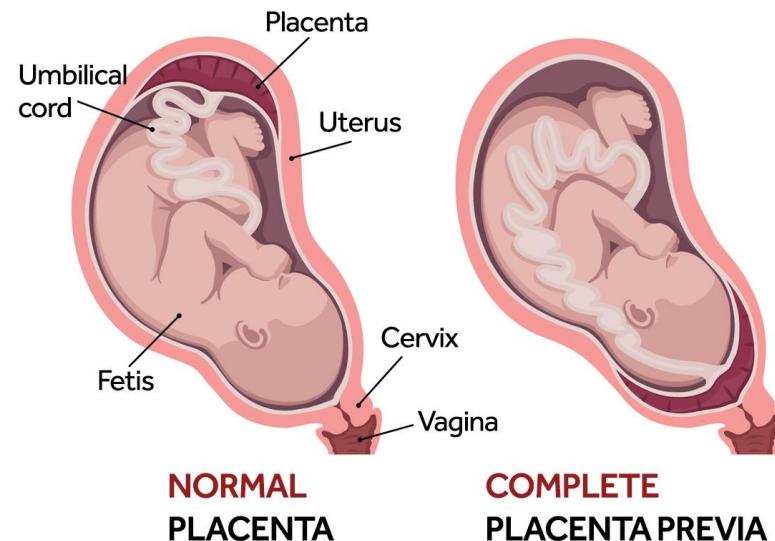
Clinical correlates: Abnormal implantation



In normal cases, the placenta moves away from the cervix as the uterus grows, preventing it from obstructing the baby's passage during delivery.

Abnormal implantation can also cause issues with the positioning of the placenta.

- **Placenta previa or low laying placenta**

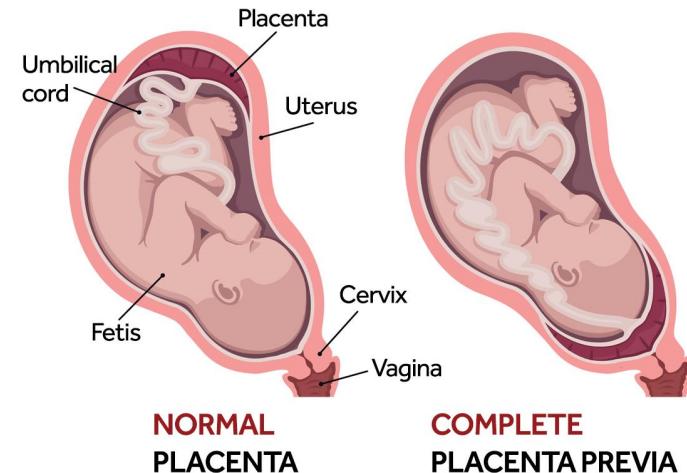


Clinical correlates: Abnormal implantation



Placenta previa or low laying placenta

- It is caused by the blastocyst implanting too low at the bottom of the uterus, over the cervix or near it causing placenta to grow and cover the internal os of cervix.
- Less area of surface contact for placenta to attach and can also end up covering the external os, therefore blocking the cervical canal.
- Mechanical straining of the cervical canal and thinning of lower part of uterus during 3rd trimester can cause late-pregnancy bleeding.
- Baby may not be born vaginally due to higher risk of hemorrhage.
- Fetus is born via cesarean section.



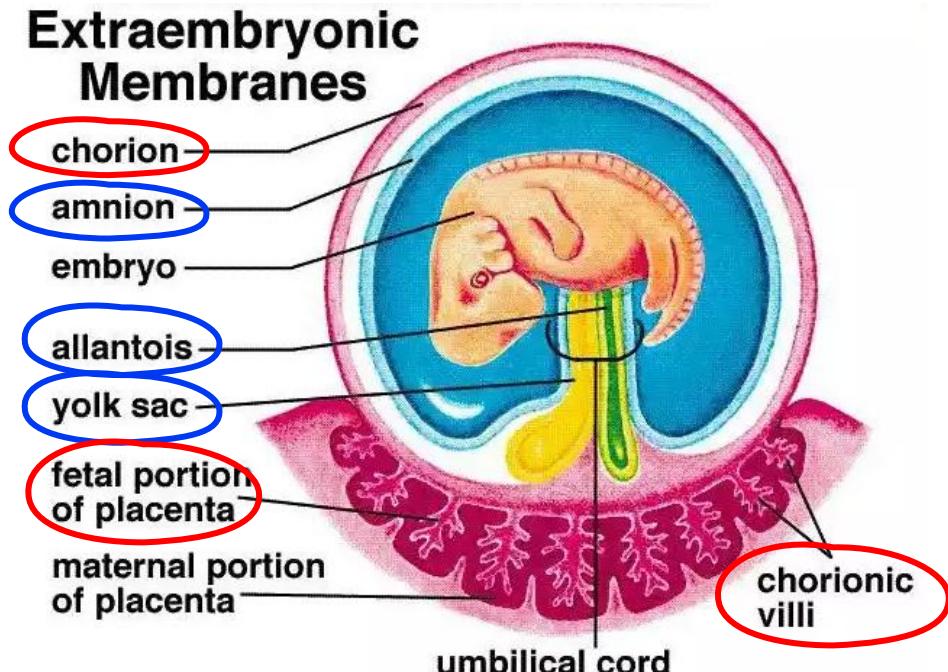


Part 2: Placenta Development

- Extraembryonic membranes
- Early Placenta development
- Maturation of the Placenta
- Placenta anatomy
- Amniochorionic membrane
- Placenta abnormalities

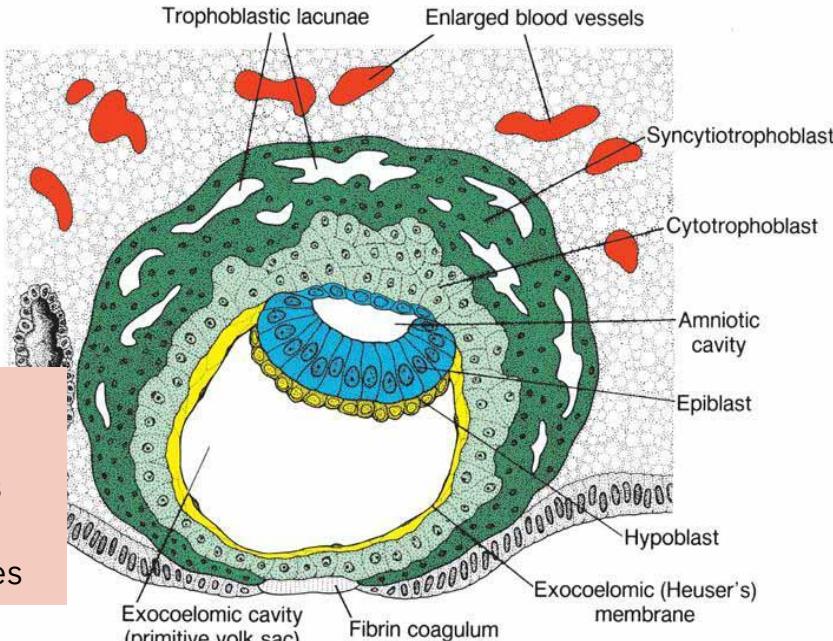
Extraembryonic membranes

- Structures derived from the blastocyst which do not contribute to the embryo.
- Extraembryonic tissues/membranes:
 1. Amnion
 2. Allantois
 3. Yolk sac
 4. Chorion
- Derived from either embryoblast (ICM) or Trophoblast (OCM)
- The **chorion** is the fetal part of the placenta and is derived specifically from trophoblast cells.



Early placental development

1) Lacunar stage (d9-12):

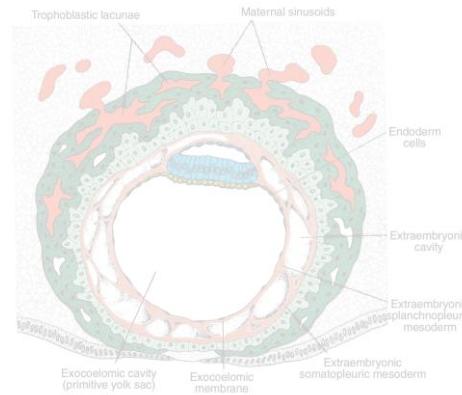


At this early lacunar stage the lacunae is empty.
Lacunae=lakes

9 Days

○ Syncytiotrophoblast:

- Outer invasive cells. Cells are not dense but "loose".
- Forms gaps or holes called lacunae.**

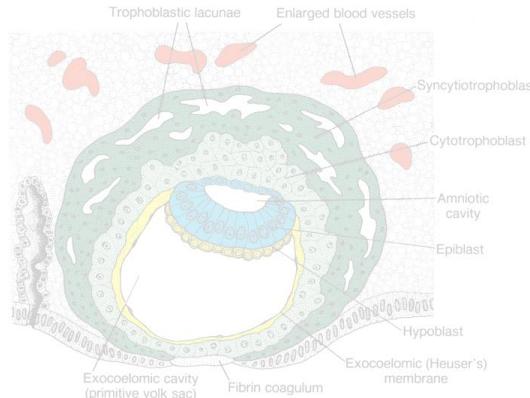


12 Days

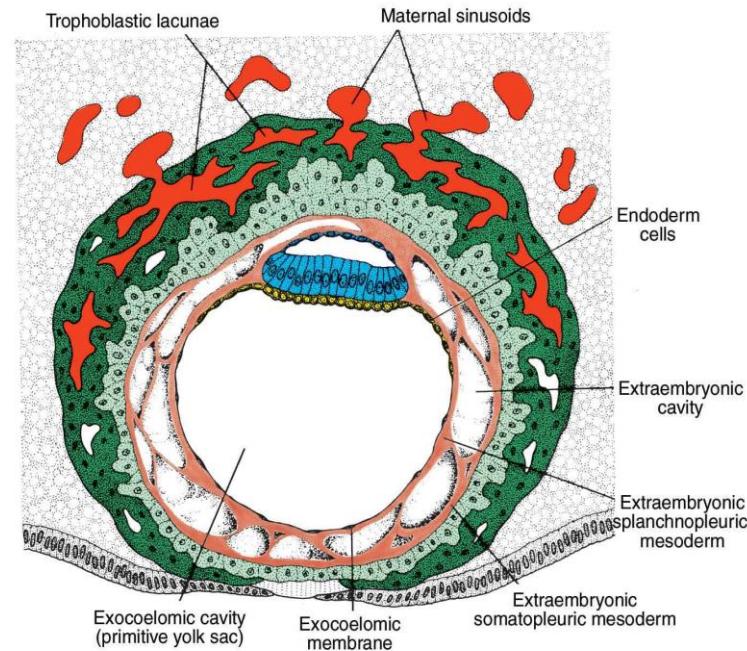
Early placental development

1) Lacunar stage (d9-12):

- Lacunae form into networks.
- **Syngtiotrophoblastic lacunae** secrets lytic enzymes as it reaches the maternal blood vessels causing the b.v endothelial lining to become more fragile.
- **Blood flows out** of the broken-down arteries **into the lacunae** creating 'blood lakes'.



9 Days



12 Days

This explains maternal bleeding or "spotting" that can occur between d10-12 after conception. Known as **implantation bleeding** and may be mistaken for light menstrual flow.

Clinical correlates: Pregnancy testing

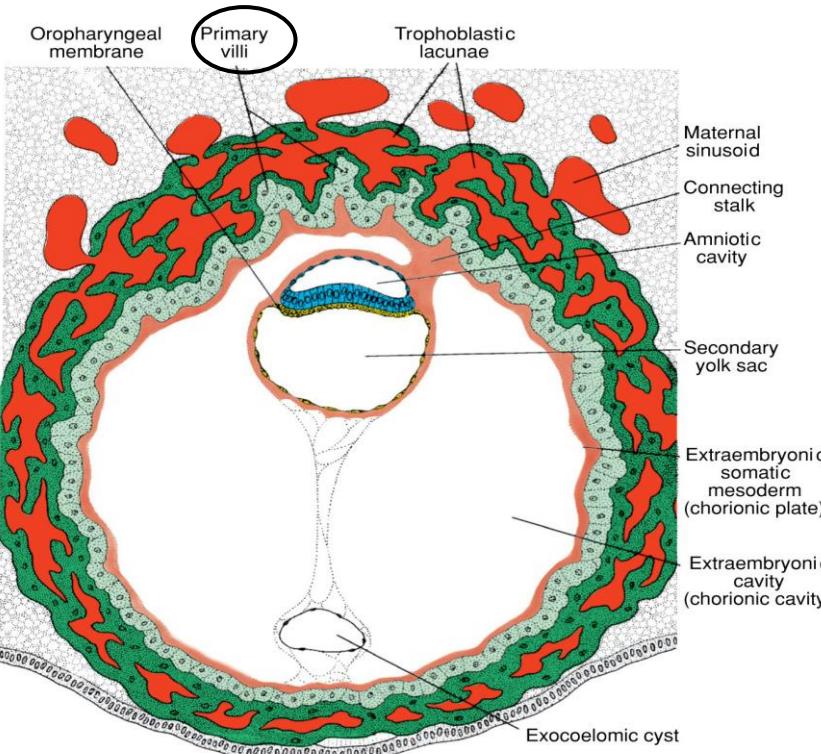


Synctiotrophoblast produces **human chorionic gonadotrophin (hCG) hormones**.

- hCG enters the **maternal blood via the lacunae**.
- hCG acts to take over **hormonal activity of the corpus luteum in the ovary** during pregnancy.
- Highly sensitive to radioimmunoassays: hCG used as basis in pregnancy test kits.
- Quantitative measurement of hCG can determine the age of fetus.
- Too much hCG can be an indicator of twins or pathology (e.g. molar pregnancy).



Early placental development

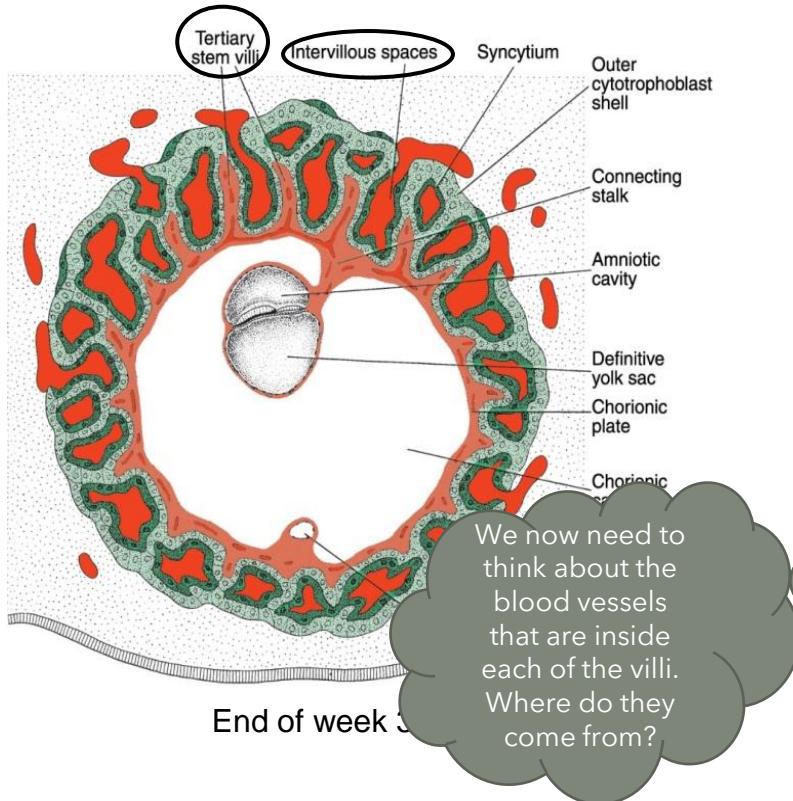


13 days

2) Early villous stage (d13-28):

- **Cytotrophoblasts** starts to create villi by migrating into the syncytiotrophoblast.
 - **Primary villi** consists inner cytotrophoblast and outer syncytiotrophoblast.
 - These villi becomes the functional units for gas/nutrient exchange from maternal blood *via diffusion* into the embryonic cavities.

Early placental development

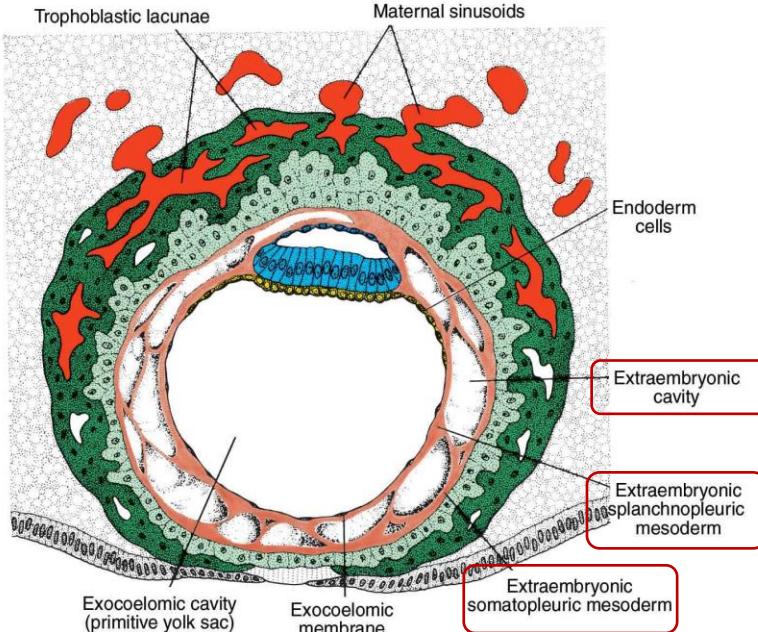


2) Early villous stage (d13-28):

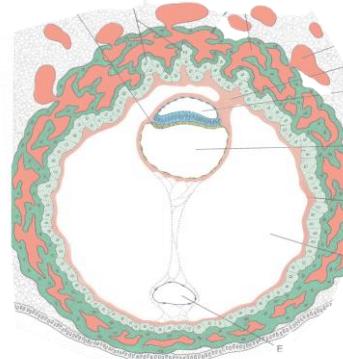
- **Lacunae** merges in between the cytotrophoblast villi projection forming **intervillous space**.
- **Maternal 'spiral artery' blood fills the intervillous space:** Fetomaternal 'contact' zone between maternal blood and fetal chorionic villi.
- Key aspect of transformation from primary villi to tertiary villi is its vascularisation.

A **primitive uteroplacental circulation** needs to be established to meet the needs of the growing embryo.

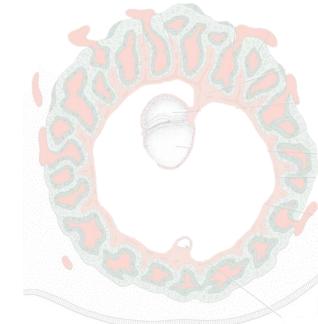
3) Formation of Chorionic plate & cavity



12 Days



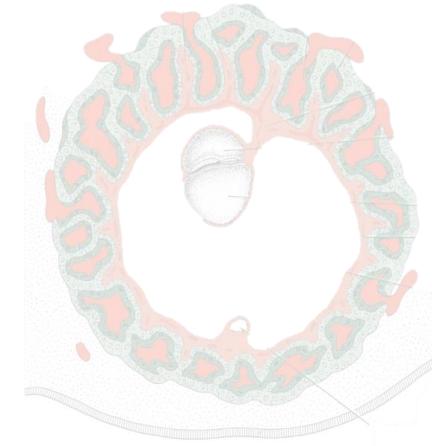
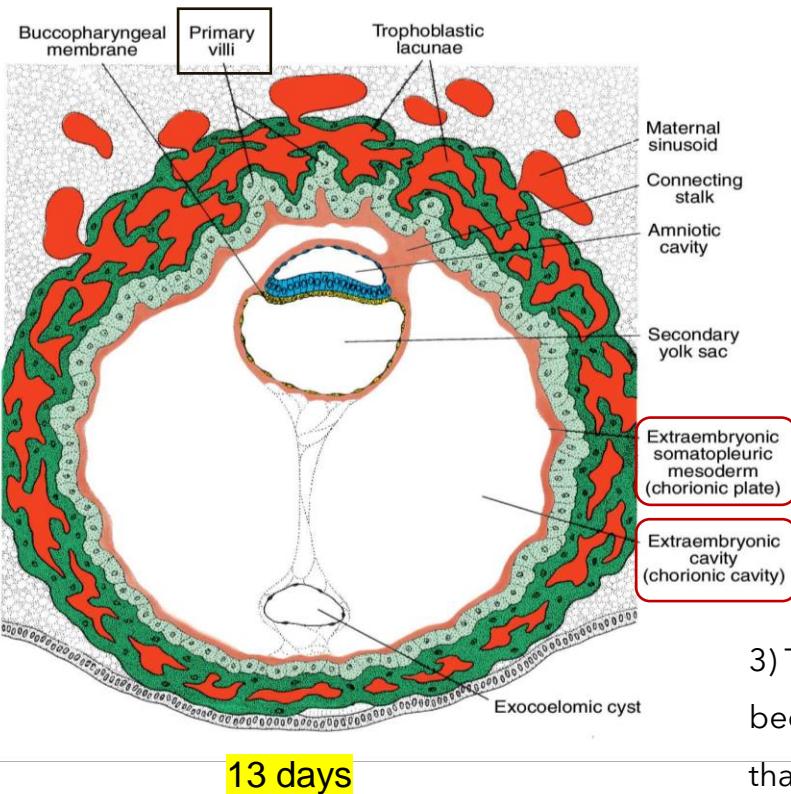
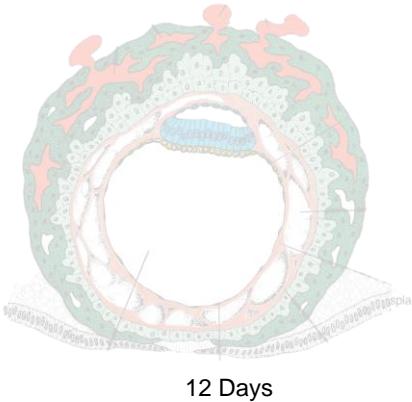
13 days



End of week
3

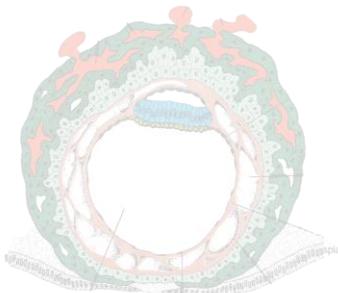
- 1) New population of cells appear called **extraembryonic mesoderm**. It lines the inner surface of the cytotrophoblast and outer layer of the primitive yolk sac. **Isolated extraembryonic cavities appear.**

2) The extraembryonic cavities fuses to form one large **chorionic cavity**.



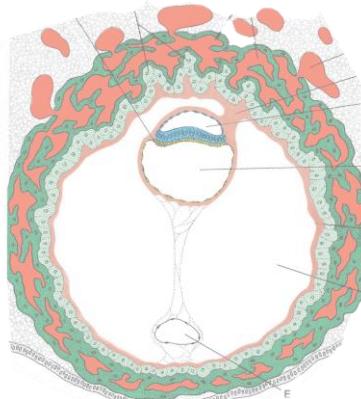
End of week 3

3) The **extraembryonic mesoderm** becomes the **chorionic 'bed' plate** that *infiltrates* the **Cytotrophoblastic**, **Primary villi** → **Secondary villi**.

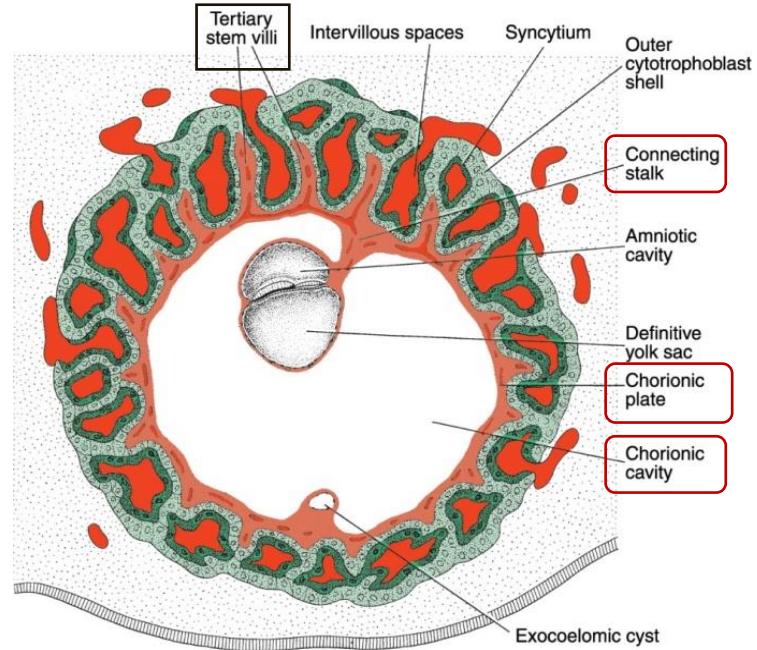


12 Days

- 4) **Chorionic plate** gives rise to the **mesodermal cores** and differentiates **to form the villi blood vessels, Secondary villi**
→ **Tertiary villi.**



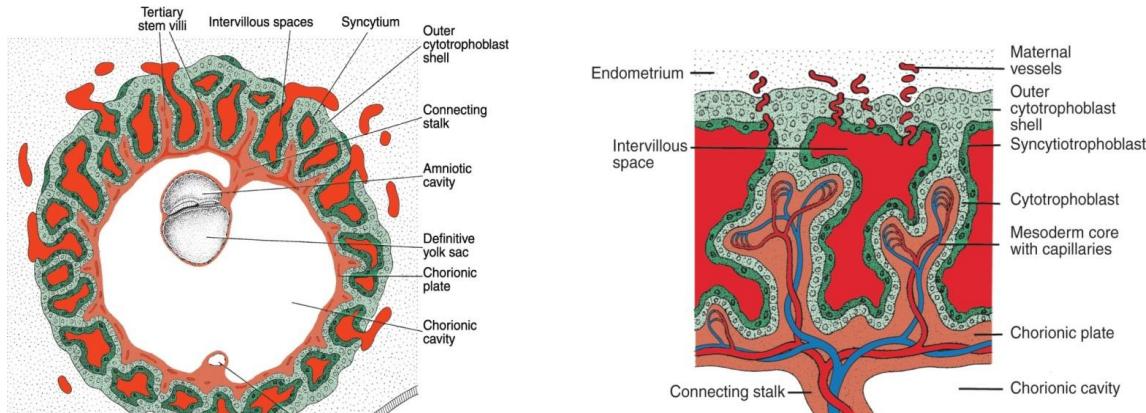
13 days



End of week 3

- 5) Extraembryonic mesoderm meets **as the connecting stalk (primitive umbilical cord)** as it lines the extraembryonic cavity.

Early placenta development

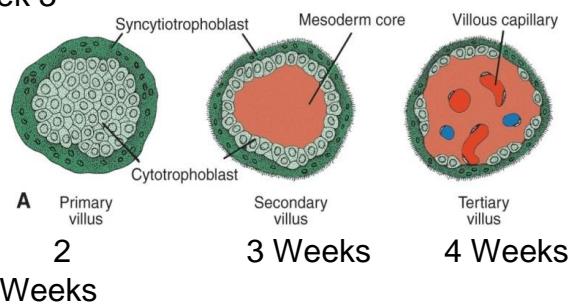


End of week 3

4 Weeks

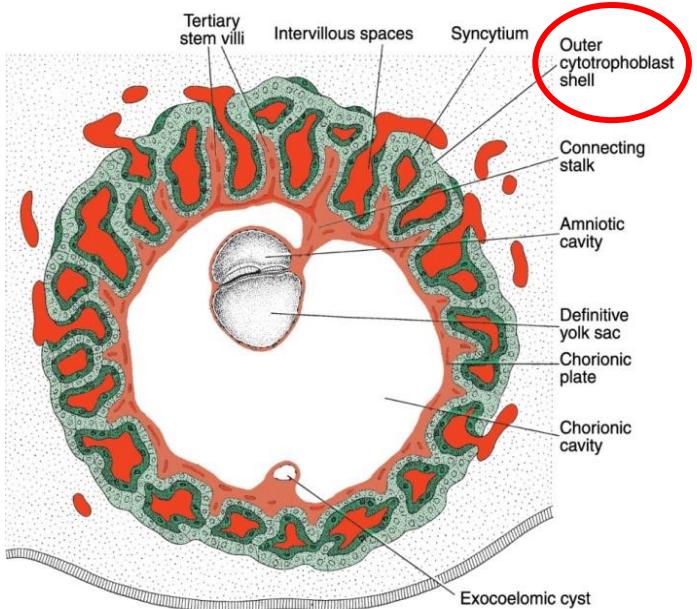
Primary → Secondary → Tertiary villi.

- Tertiary villi (terminal villi) develop through vascularisation.



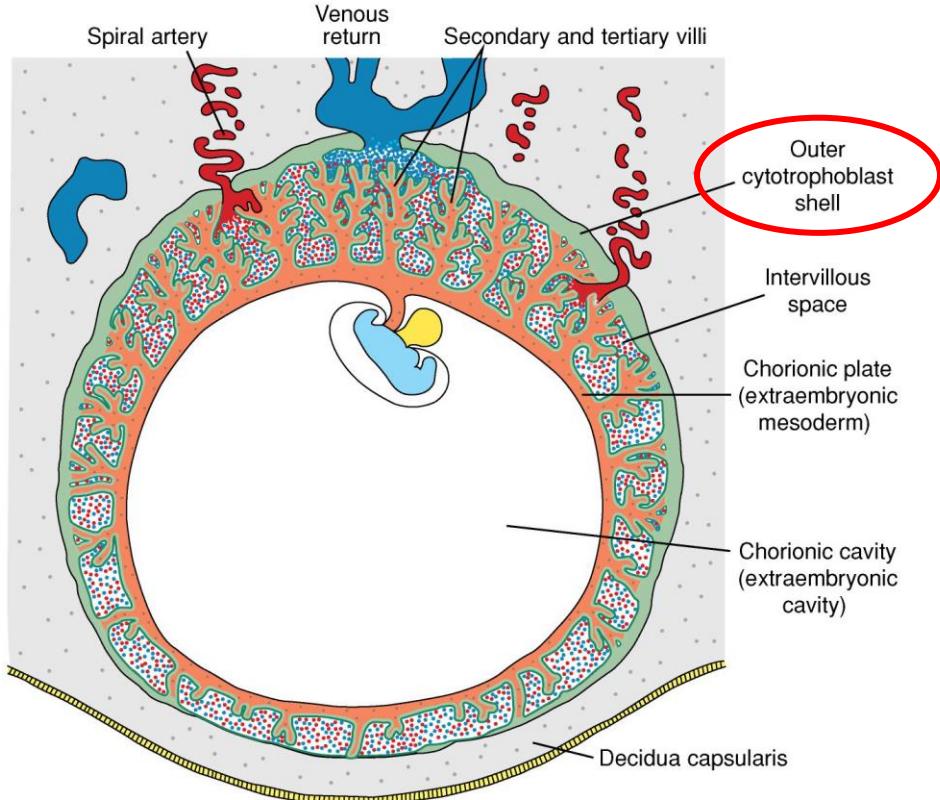
Chorionic veins carry oxygenated blood to fetus from placenta.

Chorionic arteries carry deoxygenated blood from fetus to placenta.



End of week 3

- The cytrophoblast continues to grow and crosses the syncytiotrophoblast to create an **outer cytotrophoblastic shell**.



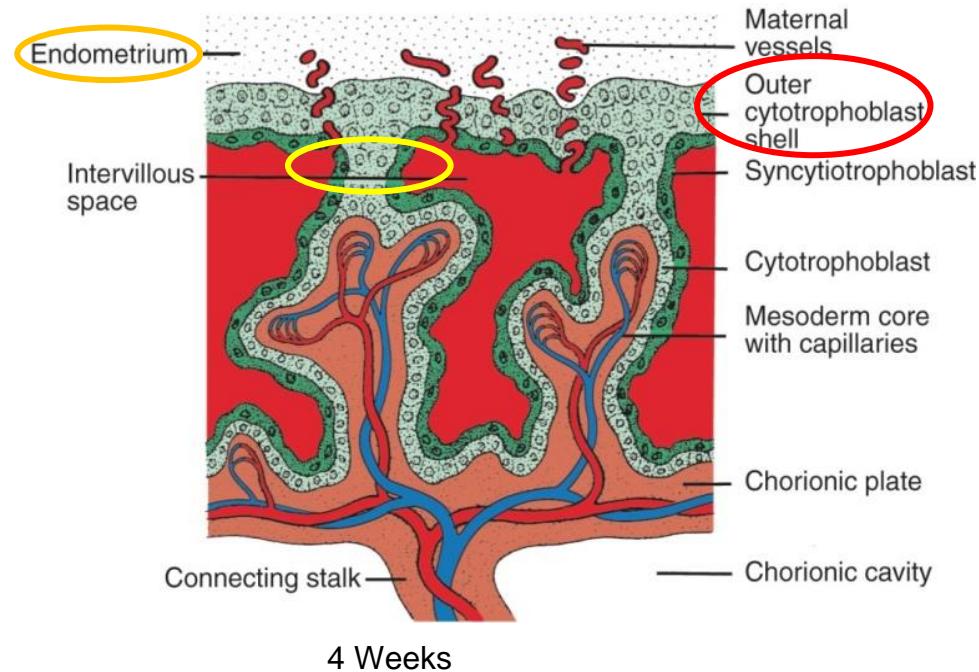
4-5 weeks

Early Placenta development

This **outer cytotrophoblastic shell**

acts to:

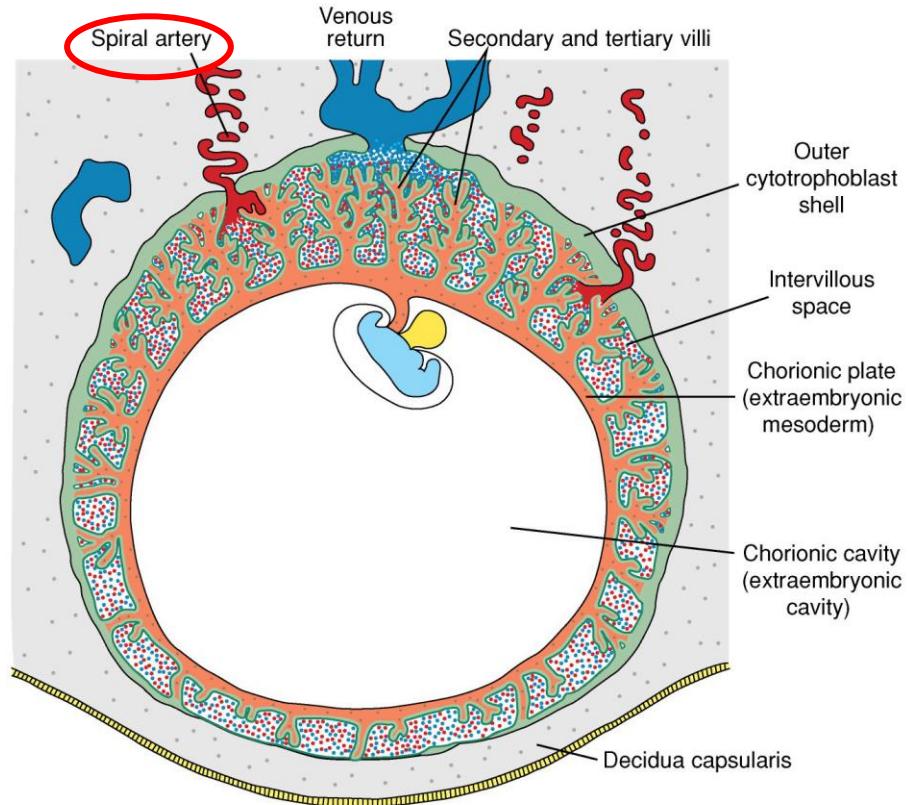
- **Stabilises** the villous 'trees' by connecting to the trees top ends- anchoring the tertiary villi.
- **Interconnects** with the endometrium (maternal part of placenta).



Early Placenta development

By week 4, embryonic heart begins
beating and blood circulation is
established in embryo.

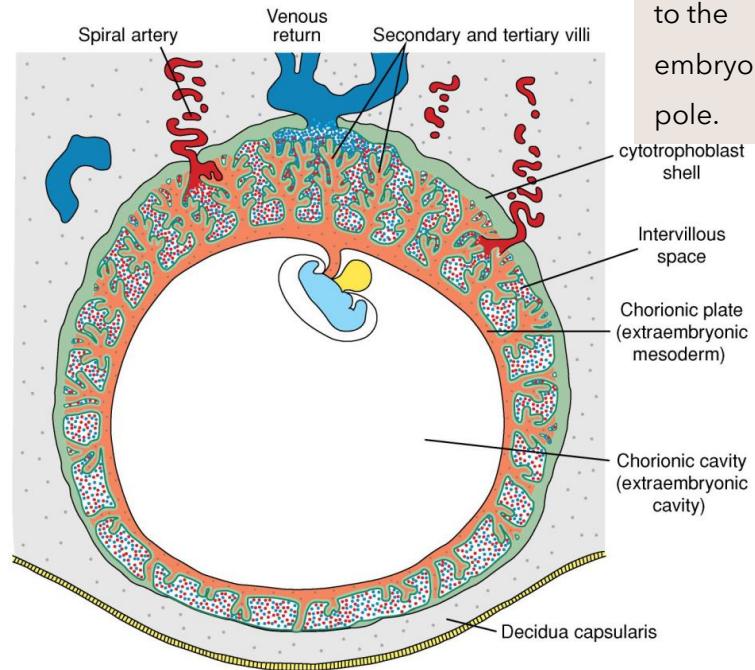
- **Maternal blood** reaches the placenta by **spiral arteries** that drain into the **intervillous spaces**.
Maternal veins drain these spaces.



Note that the well-developed villi are restricted to the embryonic pole.

Maturation of the placenta

- During weeks 4-8, as the placenta develops and matures the chorionic villi changes in composition with more 'villus branches' containing blood vessels and umbilical vessels have started to form in the connecting stalk.
- The aim is to create as much surface area as possible for the exchange of nutrients and waste.
- Chorionic tertiary villi= functional units of the placenta.



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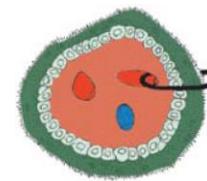
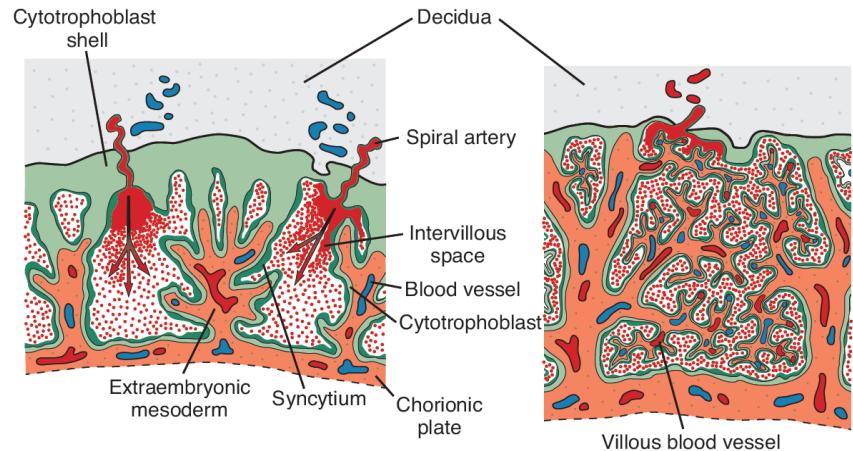
Maturation of the placenta

Placental barrier or maternal-fetal blood

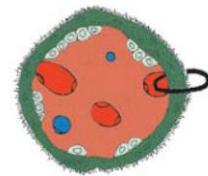
barrier:

- Maternal and fetal blood is always separated by a layer of Syncytiotrophoblast.
- Placenta barrier thins in later pregnancy by **degradation of cytotrophoblast** and **further thinning of the syncytiotrophoblast** to allow for **more efficient metabolic exchange**.

The **1st trimester** is relatively **hypoxic**: Diffusion alone is not an efficient process during early placenta **embryo** dev., however it serves to:
1) Provide nutrients under low O₂ this **reduces risk of free radical damage** during **sensitive embryonic period**. 2) low O₂ **promotes angiogenesis in placenta**



4 Weeks



4 Months

- Barrier formed by
1. Syncytium
 2. Cytotrophoblast
 3. Connective tissue
 4. Endothelium

- Barrier formed by
1. Syncytium
 2. Endothelium

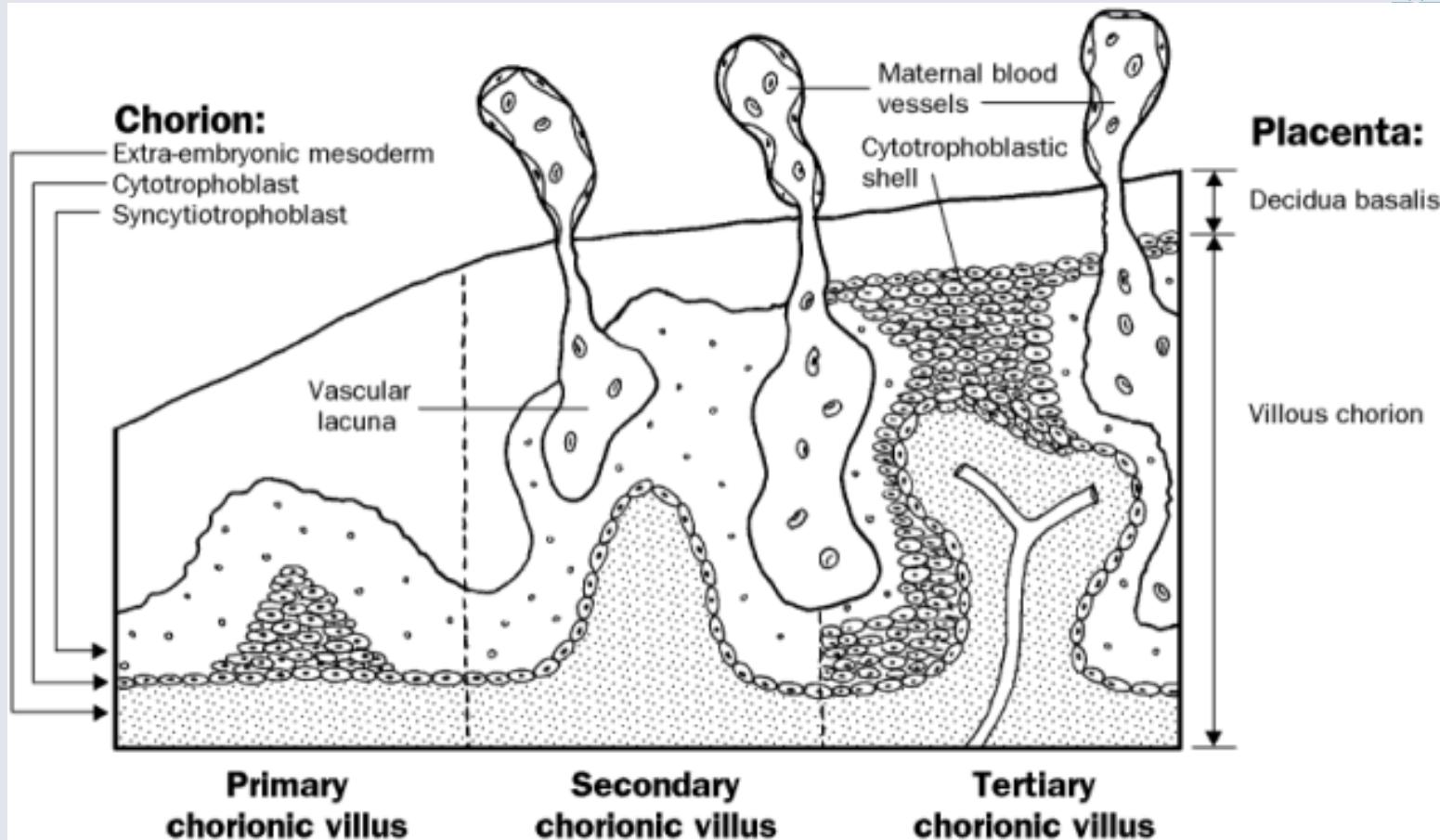
Placental barrier

Harmful substances that CAN cross the placental barrier:

- Carbon monoxide
- Most virus (including HIV, polio, measles)
- Most drugs (alcohol, cocaine, nicotine, caffeine, anesthetics, anticancer)
- Syphilis (*Treponema pallidum*) and Parasites (*Toxoplasma gondii*)
- Anti-Rh antibodies (IgG).

Substances that CANNOT cross the placental barrier:

- Most bacteria
- Most proteins (it may cross but slowly), protein hormones, insulin
- IgM immunoglobulins
- Maternal triglycerides, cholesterol and phospholipids
- Some drugs (e.g. Anticoagulant-heparin).



**Primary
chorionic villus**

**Secondary
chorionic villus**

**Tertiary
chorionic villus**

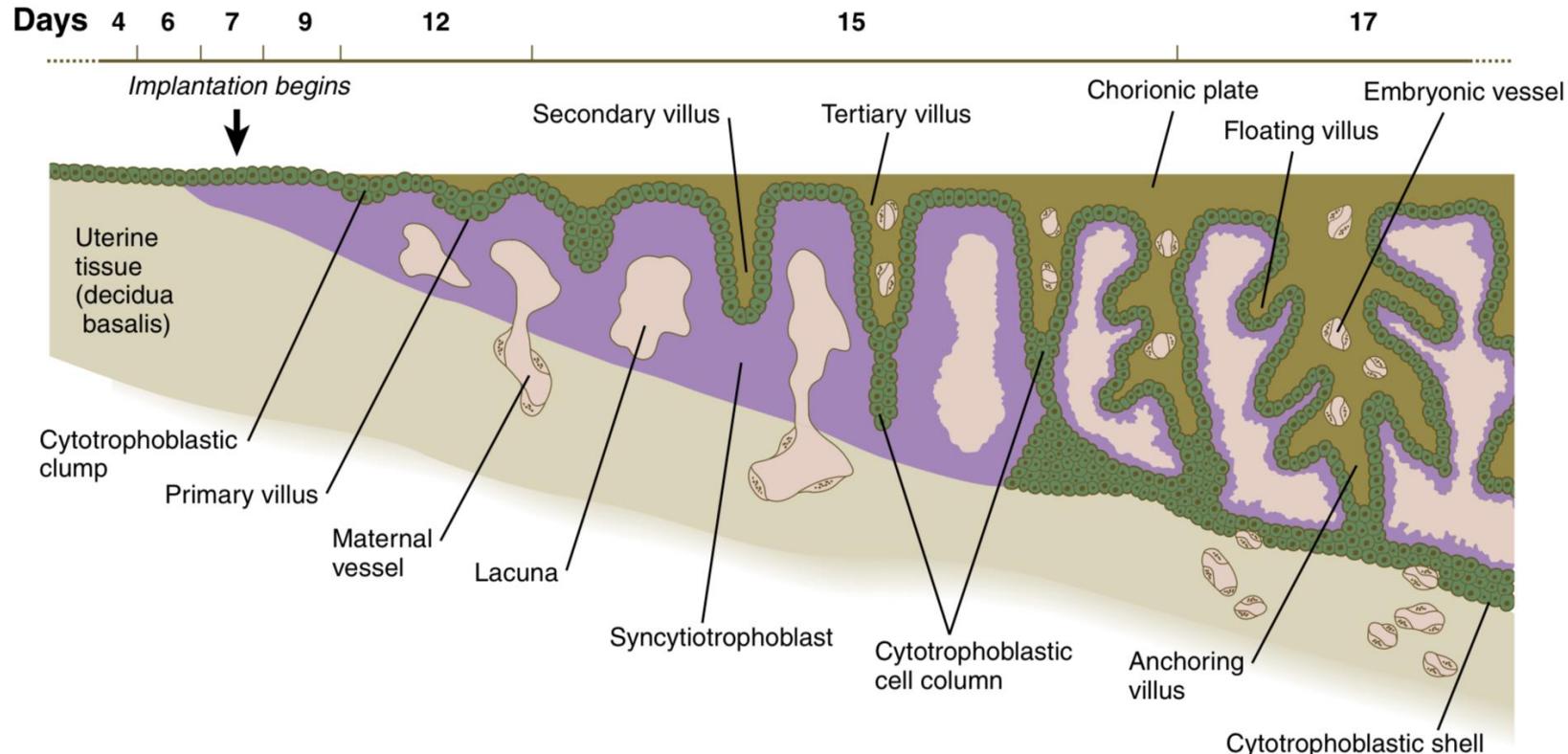


Fig. 7.5 Stages in the formation of a chorionic villus, starting with a cytotrophoblastic clump at the far left and progressing over time to an anchoring villus at right.

Placenta anatomy

Decidua basalis: Maternal part of placenta

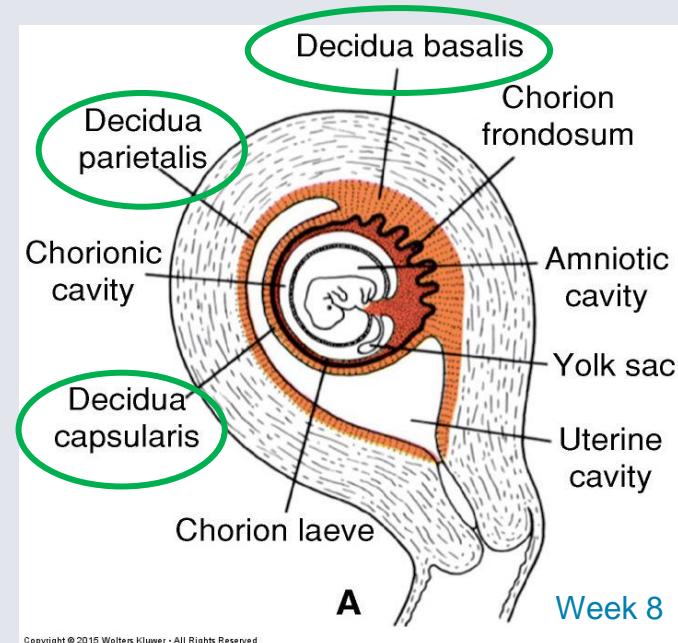
Decidua is specialised *endometrium lining of the uterus*

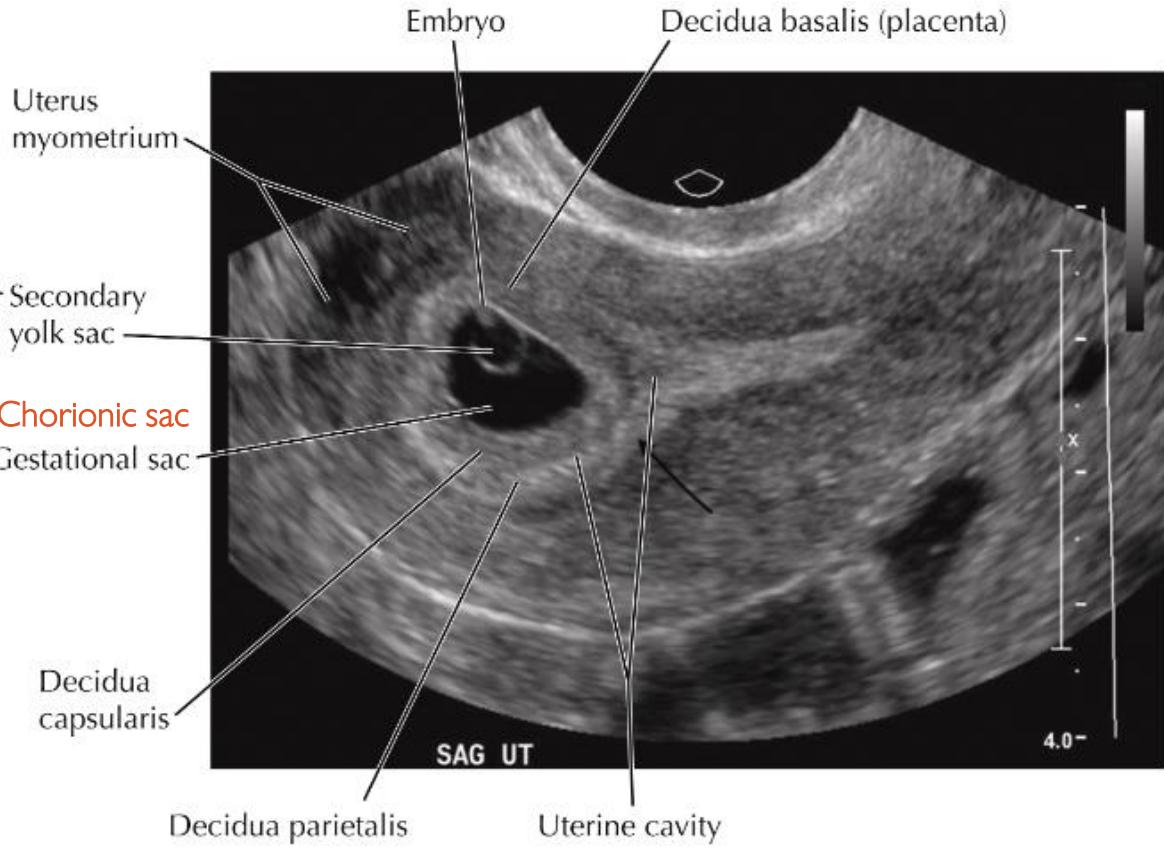
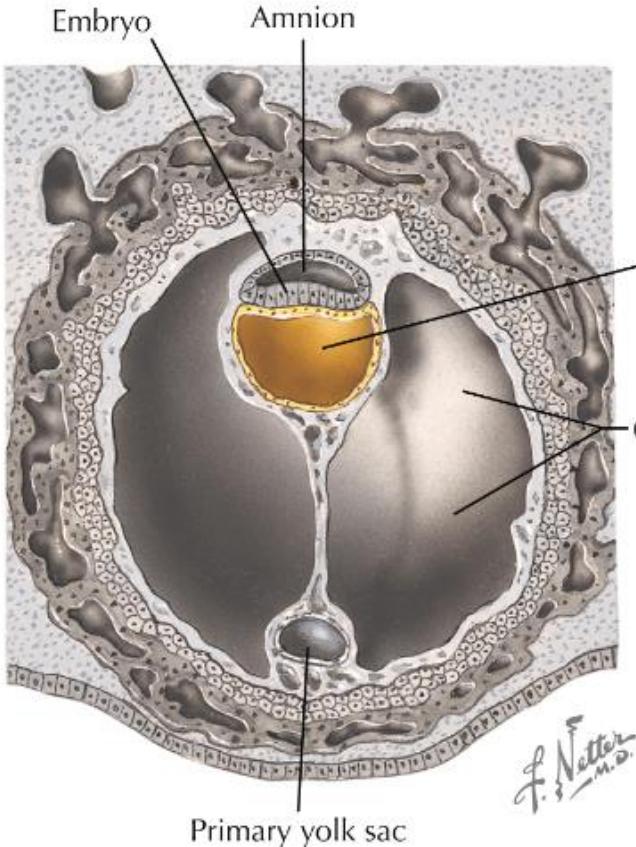
that forms during pregnancy and contributes to the maternal part of the placenta.

Topographically, it has different parts in relation to embryo:

- **Decidua basalis** forms the **maternal 'basal' plate** that interdigitates with the fetal 'chorion' plate.
- **Decidua capsularis** encloses the embryo.
- **Decidua parietalis** lines the uterus wall.

Important function of decidual cells: protection against uncontrolled invasion by syncytiotrophoblast while also protecting the embryo from maternal immune cells (maternal immune tolerance).





Clinical application: Decidua regions are recognisable during ultrasound and are important in diagnosing early pregnancy.

Placenta anatomy

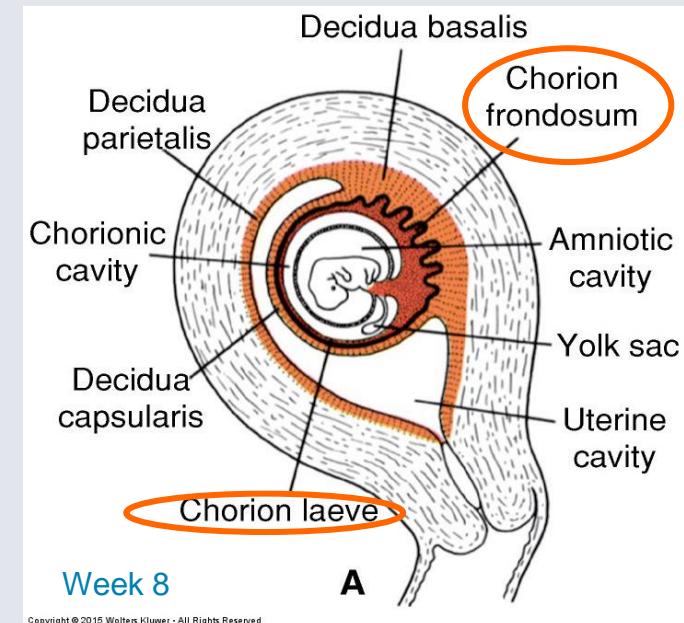
Chorion frondosum: Fetal part of placenta

Chorion membrane surrounding the embryo, *initially has villi all over.*

However, **bushy villi consolidates at the embryonic pole side** of the chorion membrane called **Chorion frondosum:**
➤ which *interlocks with the **decidua basalis**.*

Eventually, the villi in other parts of the chorion regresses:

- The **chorion laeve** is the **smooth chorion side and is avascular**, where the villi dies off due to being compressed against the **decidua capsularis**.

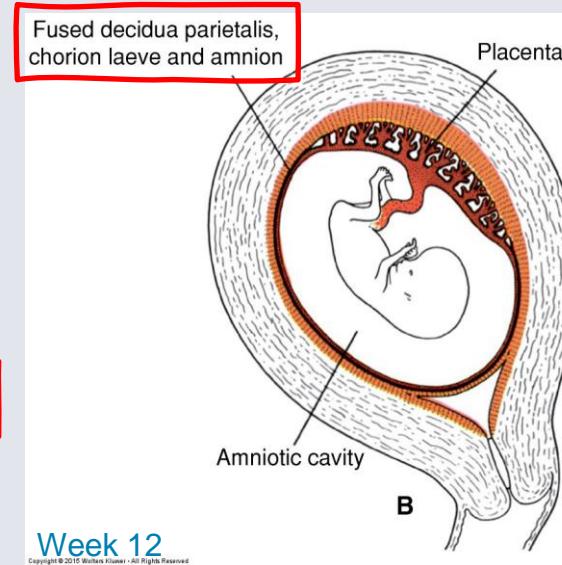
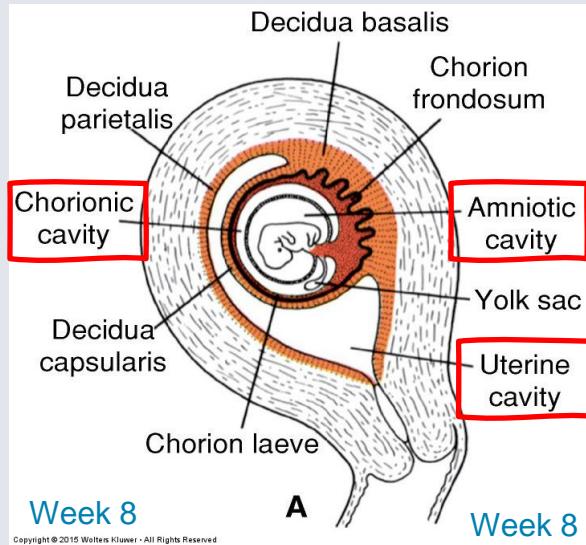


Week 8

A

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Fusion of fetal membranes and cavities



- There are three extraembryonic cavities: **amniotic cavity, chorionic cavity and uterine cavity.**
- By week 12, the amniotic cavity expands with amniotic fluid ***obliterating the chorionic cavity.*** The amnion membrane and chorion membrane fuses= **amniochorionic membrane.**
- **This membrane ruptures during labour.**

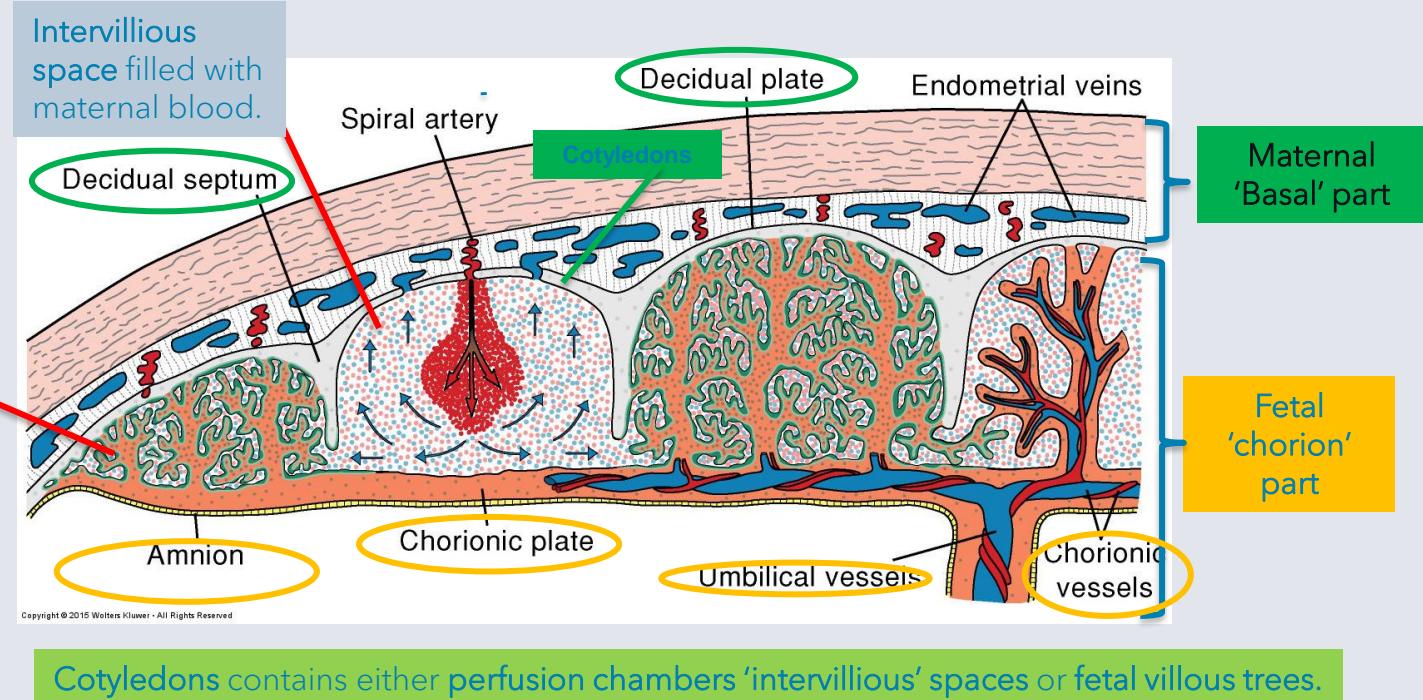
By week 12, all extraembryonic cavities are obliterated with exception of the amniotic cavity.

- By end of week 12, the growth of fetus and continual expansion of the amniotic cavity eventually ***obliterates the uterine cavity.***
- This causes further fusion between the decidua and the amniochorionic membrane **improving stability of the fetal membranes.**

Placenta anatomy

By beginning of 4th month:

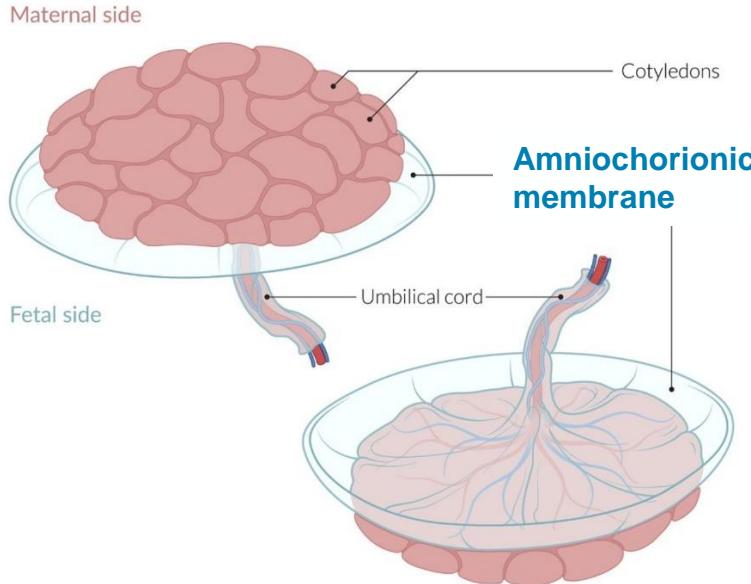
Placenta has two components: 1) Fetal part-Chorion frondosum, 2) Maternal part-decidua basalis and the in between is the Fetomaternal zone



Note the disappearance of the cytotrophoblast.

Placenta anatomy

Full Term Placenta



Mature placenta weighs approx. 500g, is about 2cm thick and has a diameter of 15-20 cm.

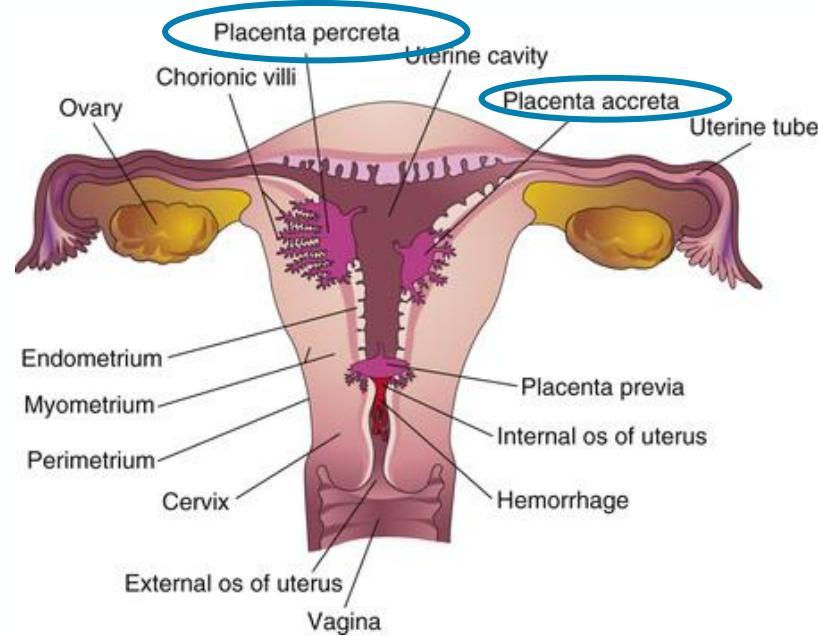


Clinical correlates:

After birth, the placenta must be inspected to ensure it has detached completely from the uterine wall. If this does not occur, there is a risk of postpartum hemorrhage. The check is performed by inspecting for the completeness of all placental cotyledons.

Clinical correlates: Trophoblast invasion

- **BALANCING ACT** – Trophoblast are highly invasive and needs to be actively controlled by maternal decidua via immunosuppression.
- **Over-invasion of trophoblastic cells** into the uterus wall can cause **abnormal adherence of the placenta**. This is called placenta accreta/percreta.
- **Chorionic villi penetrates beyond endometrium** into myometrium (accreta) but this can go beyond to towards the uterine serosa (percreta) and even potentially to nearby organs.
- **Placenta cannot separate normally during delivery** – Severe haemorrhage results.

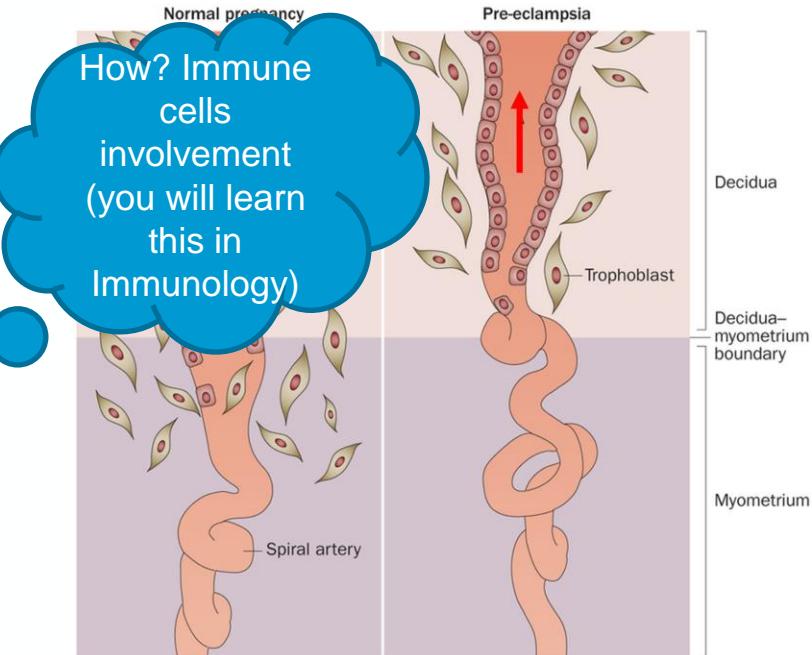


Clinical correlates: Trophoblast invasion



Fetomaternal junction

- Maternal spiral arteries provides **blood supply** to both the endometrium and the placenta.
- These spiral arteries *need to be structurally transform during early pregnancy* to allow greater transport of maternal blood to the placenta.
- **EVT- Extravillous trophoblast cell** (derived from cytотrophoblast cells) invade the **spiral arteries** and **remodels it**.
- **Spiral arteries remodelling:** Arteries is transformed to be capable of accepting higher vol. of blood, blood flow is at **HIGH conductance** at a **LOWER pressure with REDUCED velocity**.



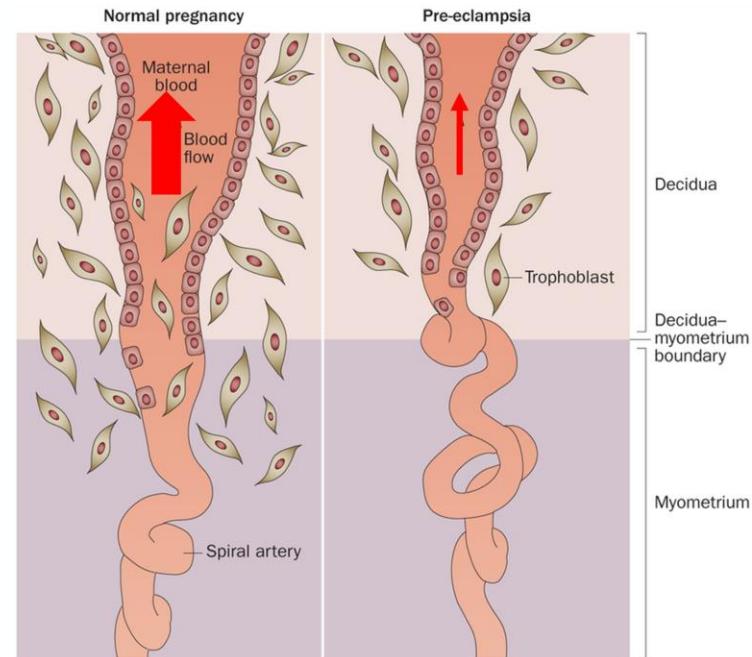
Clinical correlates: Trophoblast invasion

What happens if there is insufficient trophoblastic cells?
Placental vascular abnormality → Pre-clampsia.

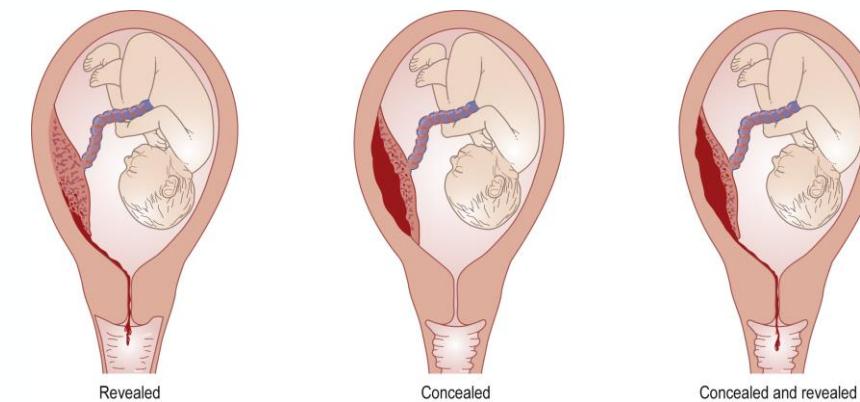
Placenta vascular abnormality due to failure of spiral artery remodelling.

- Caused by: Insufficient invasion of EV trophoblastic cells → narrow spiral artery (no remodelling) → reduced placenta perfusion → ischemic placenta.
- Ischemic placenta releases antiangiogenic substances → maternal *hypertension & proteinuria (Pre-eclampsia)*.
- Untreated will become **eclampsia (Fatal convulsions)**.
- Leads to **fetal growth restriction (FGR) or miscarriage**.

Fetomaternal junction



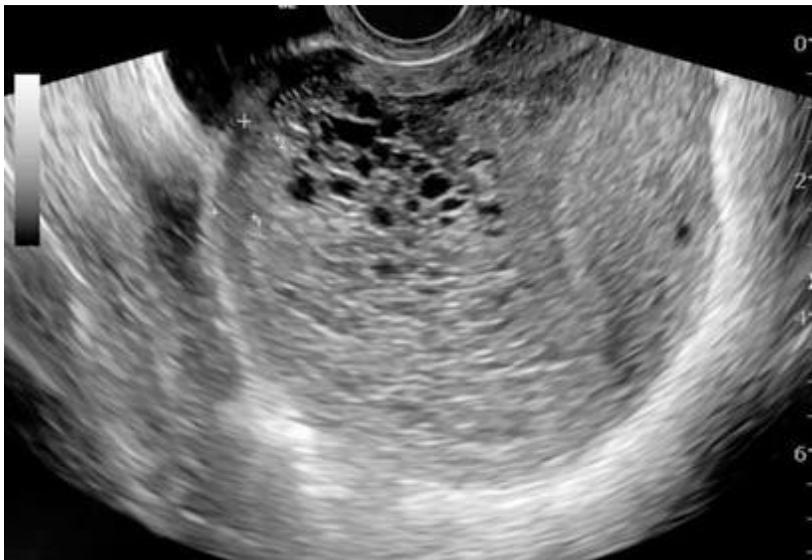
Clinical correlates: Placenta abruption



Placenta abruption: Separation of placenta from the uterus wall. Leading to bleeding.

- Decreases or block supply of oxygen and nutrients in fetus and subsequent hemorrhage in mother.
- Bleeding can cause **Trombin-induced myometrial contraction** to expel the placenta. Protective mechanism for mother.
- Blood within uterine wall can cause increase in resting tone of the uterus and possible blood clots which can make it difficult to make palpitations on the fetus and auscultation of fetal heart.

Clinical correlates: Molar pregnancy



Molar pregnancy or Hydatidiform moles:

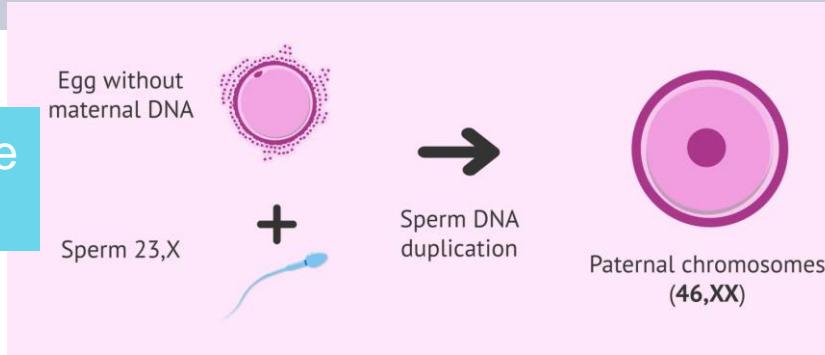
Overgrown of abnormal chorionic villi forming cystic clusters and resembles *cluster of grapes*.

- Tissue that was meant to become placenta overgrows becoming a mass of cysts.
- All molar pregnancies **end in miscarriage**, if there is an embryo it will not survive.
- Most common form of **Gestational trophoblastic disease (GTD)**.

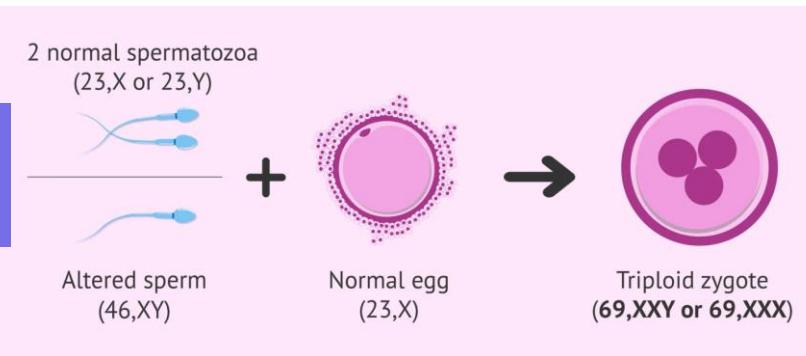
GTD is a group of rare diseases in which **abnormal trophoblast cells** grow inside the uterus after conception.

Clinical correlates: Molar pregnancy

Complete molar



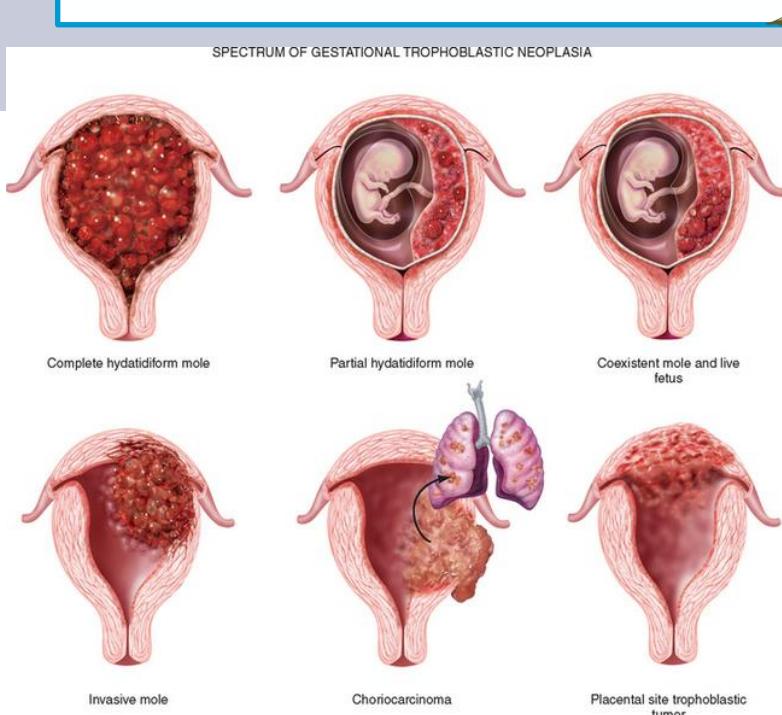
Partial molar



- **Caused by:** **Abnormal fertilisation** of an 'empty' egg (no maternal genome or inactive pronucleus) by **one or two sperms** OR a normal oocyte by **two sperm 'dispermy'**.

- **Genetic information for trophoblastic tissue** comes from **the paternal genome i.e male parent**.
- **Complete molar : no embryo**
- **Partial molar: Severely defective embryo**

Clinical correlates: Molar pregnancy

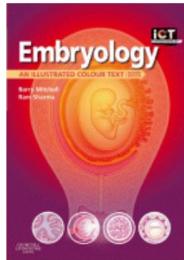


- Abnormal chromosomal mixing creates a ‘conceptus’ with **overdeveloped trophoblastic tissue with underdeveloped or missing embryo.**
- **Chorionic villi undergoes degeneration and vascular tissue is lost**, hence **creating cysts within the uterine wall**.
- Most GTD is benign, but some types can become malignant and spread to nearby tissues or even distant parts of the body.
 - Risk of becoming malignant ‘choriocarcinomas’ is about 3% to 5%.

Additional resource

- UNSW Embryology wiki:

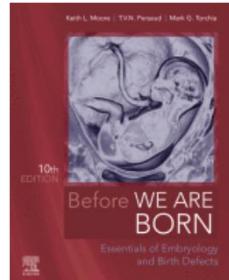
https://embryology.med.unsw.edu.au/embryology/index.php/Embryonic_Development



Embryology, Second Edition

Mitchell, Barry, BSc MSc PhD FIBMS FIBiol

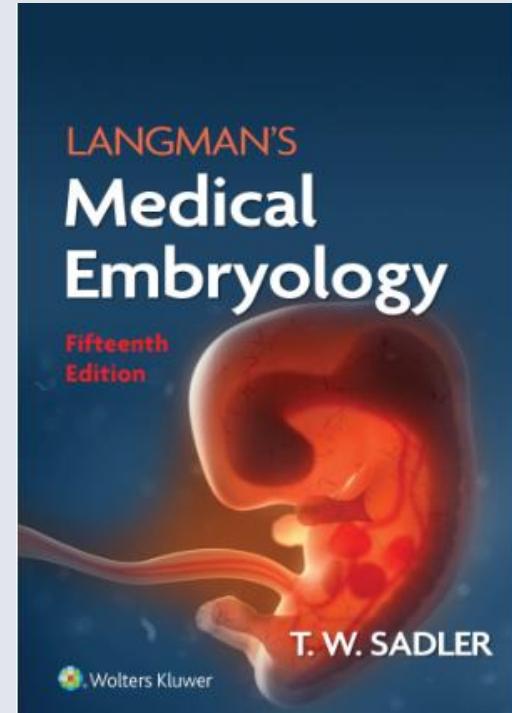
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Before We Are Born, Tenth Edition

Moore, Keith L., BA, MSc, PhD, DSc (OSU), DSc (WU), FIAC, FRSR, FAAA

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listening



Email:
mrajid@lancashire.ac.uk