

# Physiological mechanisms of the Endometrium, Implantation and Placentation

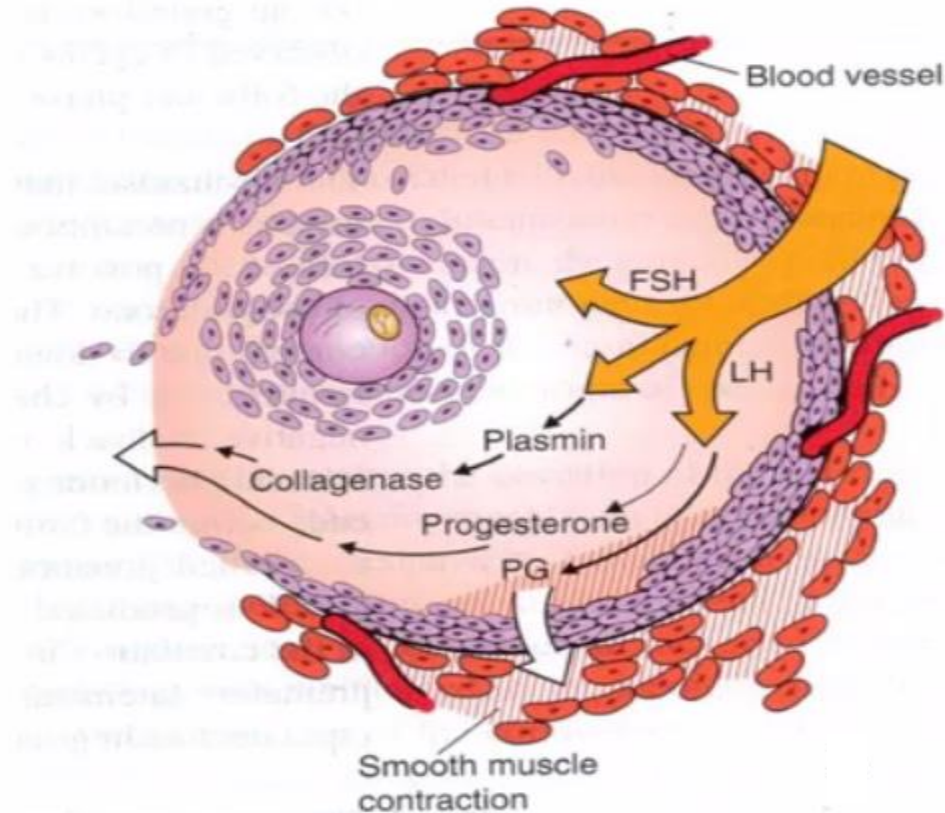
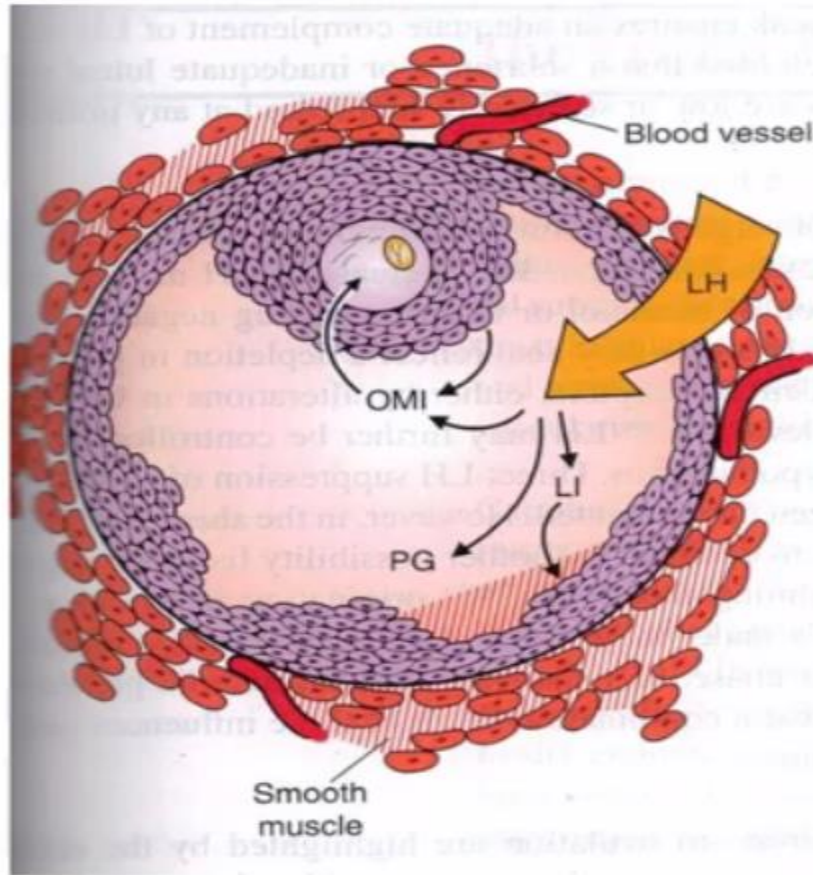
Lecture for the Academic Year 2018 – 2019  
Defined Learning Objectives

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# Learning Objectives

- Folliculogenesis and endometrium preparation
- Corpus Luteum and progesterone effect
- Conditions to implantation
- Junctional zone endometrium
- Endometrium evaluation by sonography
- Implantation and pinopodes
- Placentation – placenta structure and function
- Pregnancy hormones

# Ovarian follicle changes will differentiate the endometrium accordingly



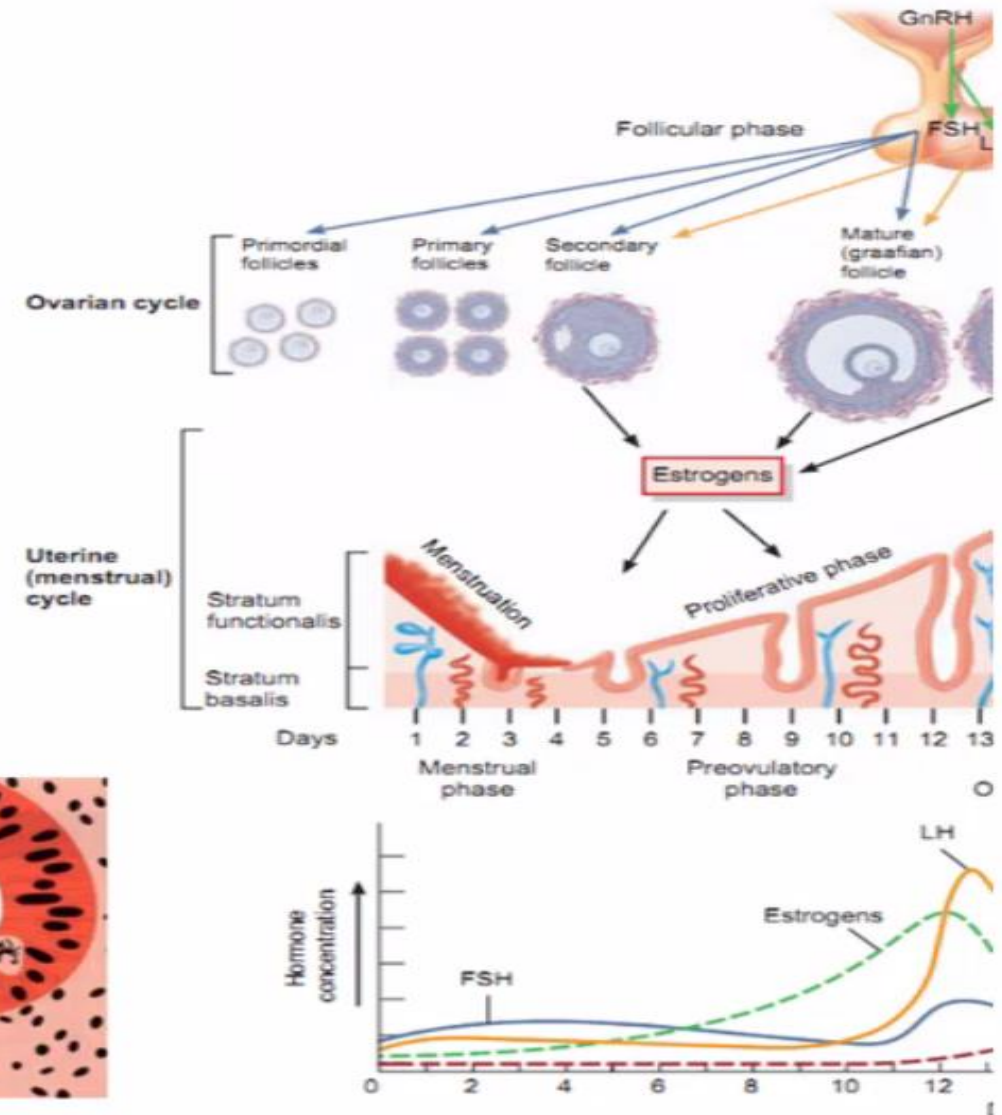
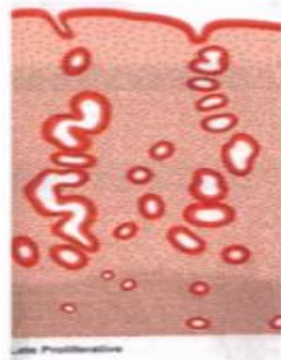
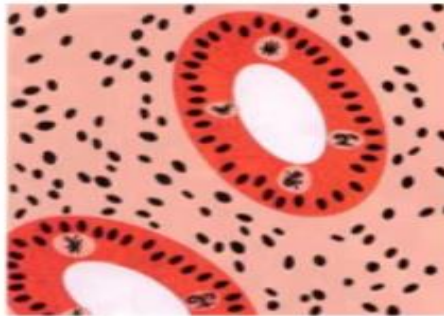
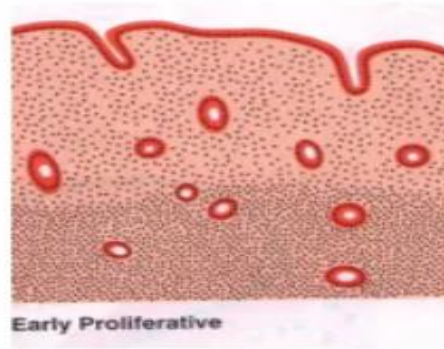


# Endometrial proliferative phase

Proliferative phase  
Stimulated by estradiol  
from the dominant follicle.

Stromal cell division,  
ciliated surface. Glands  
expand and become  
tortuous, increased  
vascularity,  
neoangiogenesis  
maximal cell division by  
days 12-14.

When endometrium  
>4mm induction of  
progesterone receptors  
and small muscular  
contractions of the  
myometrium.



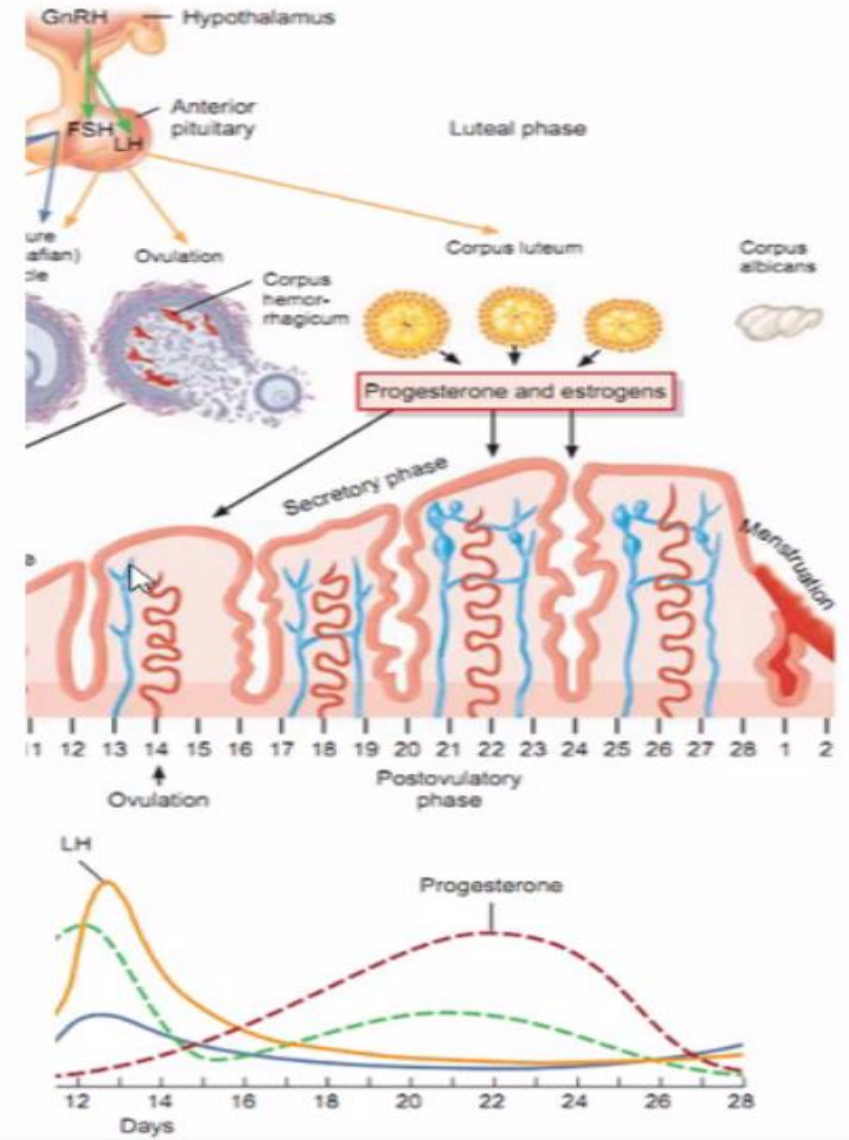
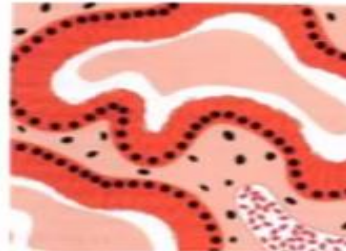
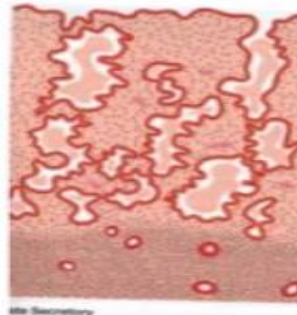
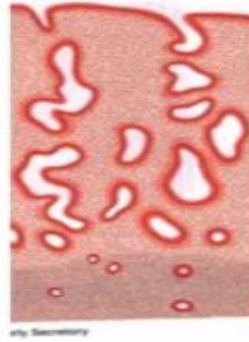
# Endometrial secretory phase

Secretory phase (luteal phase of ovary) 2-3 days after ovulation, the gradual rise in progesterone causes a reduction in cell division.

Glands increase in tortuosity and distend...secretion of glycoproteins and lipids commences.

Oedema, increased vascular permeability arterioles contract and grow tightly wound.

Myometrial cells enlarge and movement is suppressed blood supply increases.



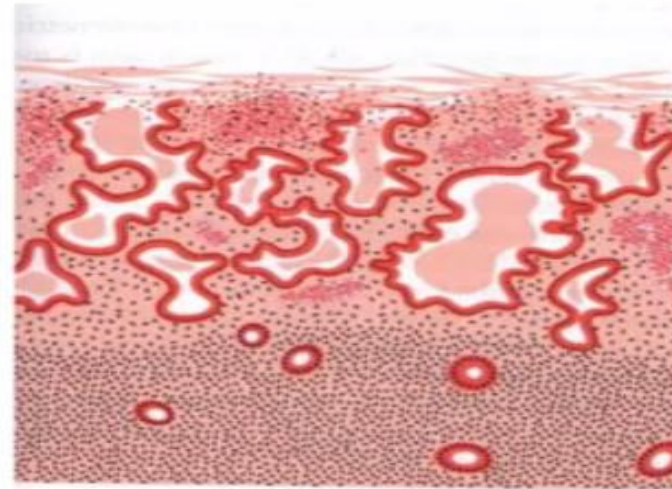


# Regression of the corpus luteum

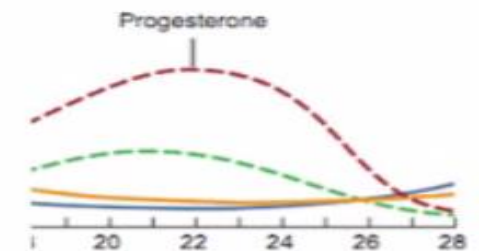
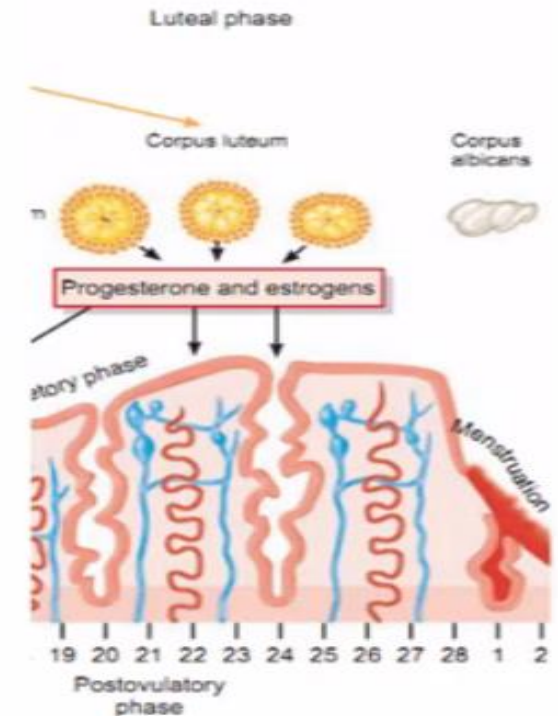
Corpus luteum stimulated by LH from pituitary during luteal phase.

The fertilised oocyte becomes a blastocyst and produces human chorionic gonadotrophin (hCG) which acts like LH ie on LH receptor, and 'rescues' the CL.

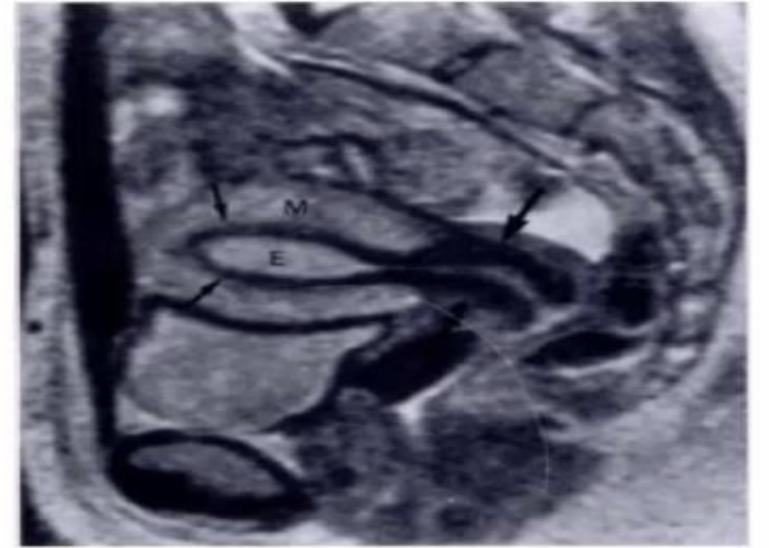
In the absence of this, falling levels of steroid from the CL results in menstruation.



Menstruation



# Junctional zone in MRI and 3D TVU

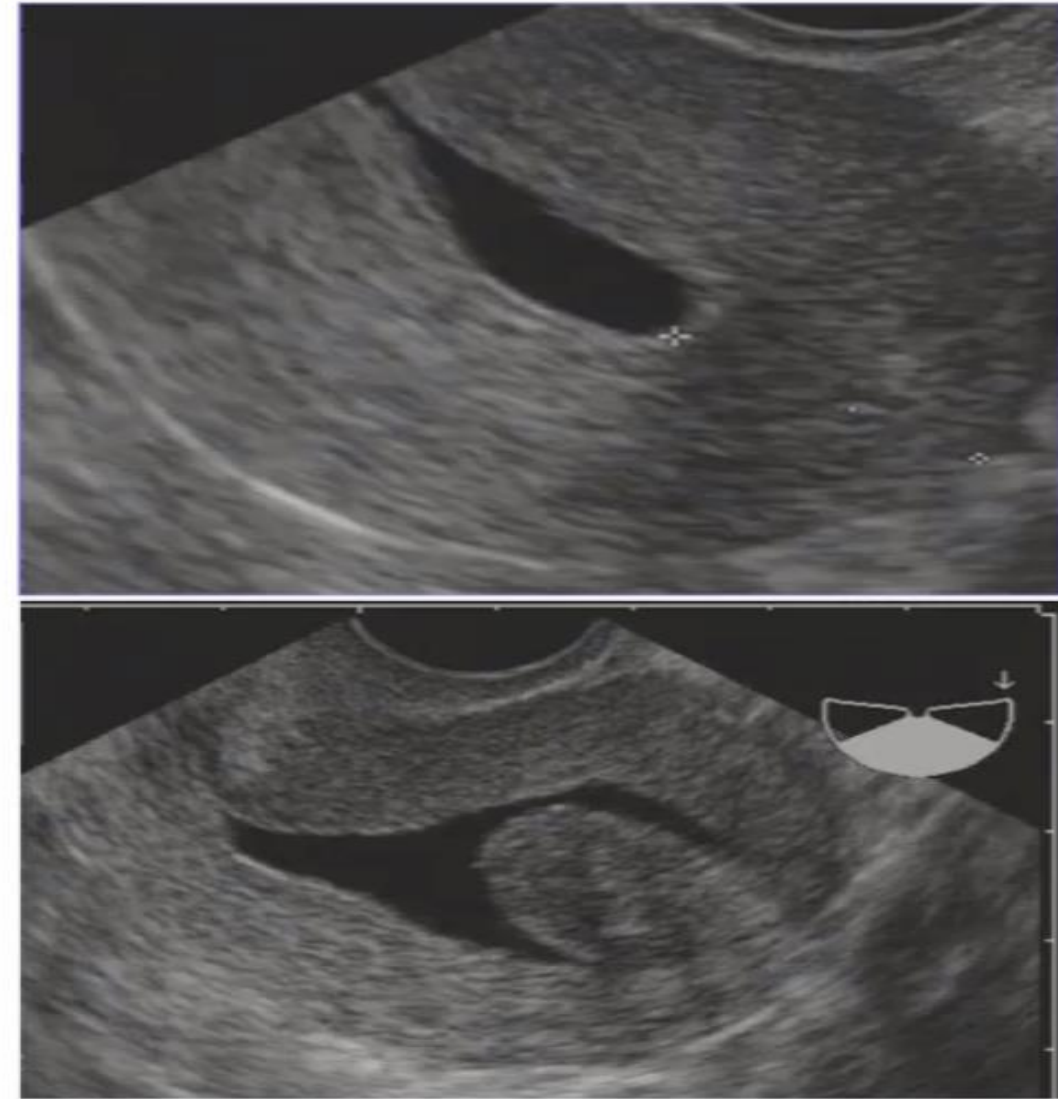


- The anatomically distinct segment of the uterus that represents the endometrial-myometrial transition
- The JZ is structurally and hormonally different from the other layers of the uterus
- Further research may elucidate its role in fertility and how disruption of this zone by fibroids can reduce implantation
- It is clearly seen in MRI section and most of the time in 3D TVU
- Images clarity depends on equipment specifications and technician experience



# Sonohysterography (HyCoSy and HyFoSy)

- sharply defines cavity contours and readily demonstrates even small intrauterine lesions
- sensitivity and specificity of HyCoSy exceeds that of TVU
- compares favourably with Hpy
- HyCoSy and endometrial Bxs is highly sensitive for final Dg of AUB
- Hysteroscopy offers both Dg & Tx of symptomatic intrauterine pathology





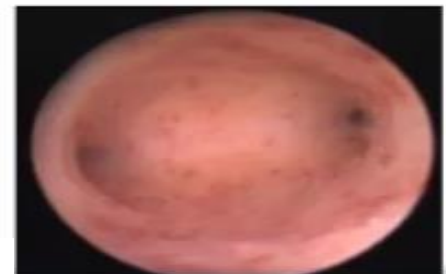
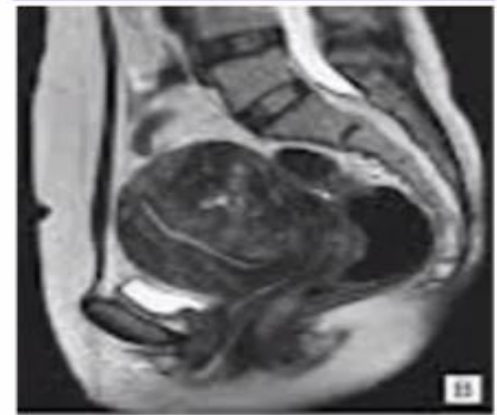
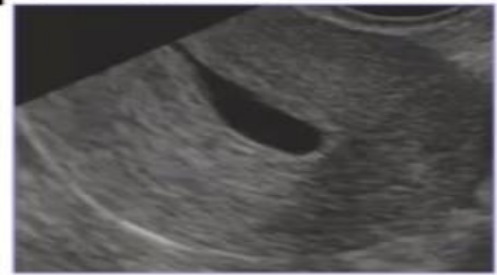
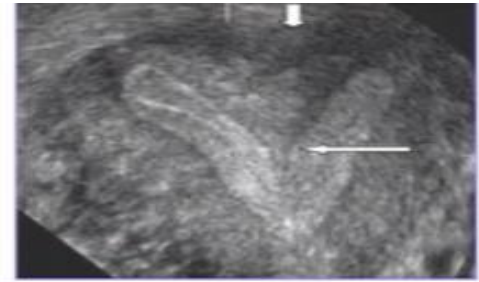
# Physical examination

- PS examination (vaginal or cervical lesions)
- define uterine size (normal or enlarged)
- contours (smooth and symmetrical or irregular)
- Consistency (firm or soft)
- tenderness
- Cervical smear (Pap test LBC)
- TVU



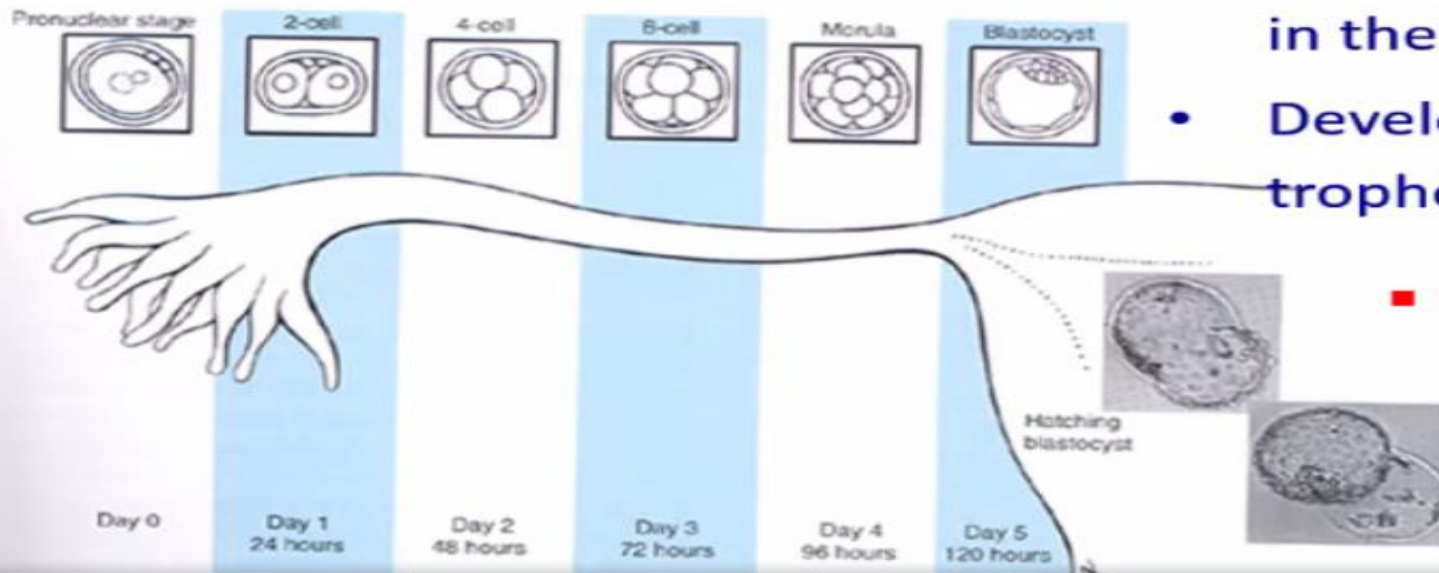
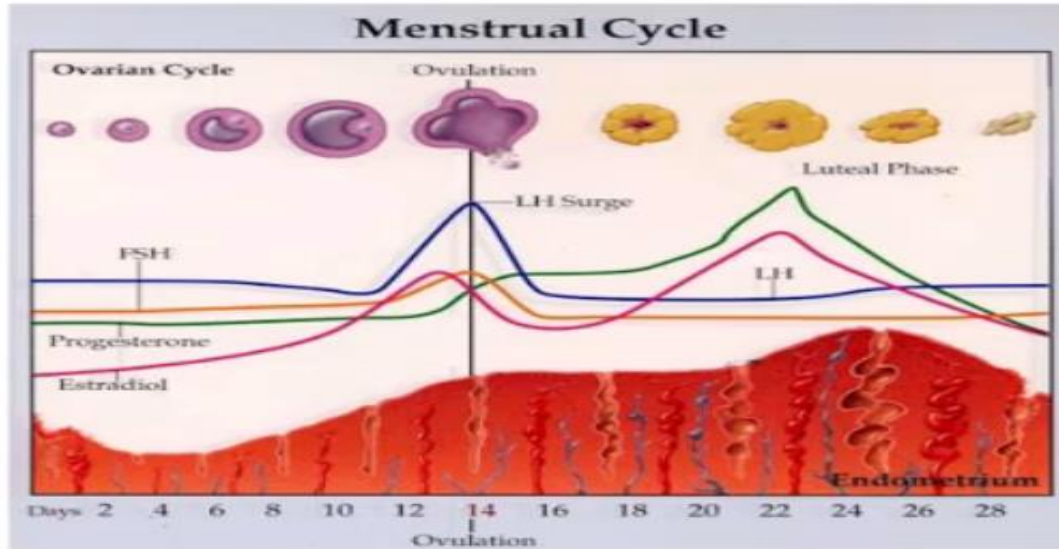
# Imaging

- Ultrasonography (standard Care)
  - 2D , 3D, HyCoSy, HyFoSy
- Magnetic resonance imaging (MRI)  
*highest reproducibility results* useful in obese when multiple myomas, location of lesion
- Hysteroscopy (Gold standard and method of choice to establish the diagnosis)





# Fertilization, embryo transportation, implantation

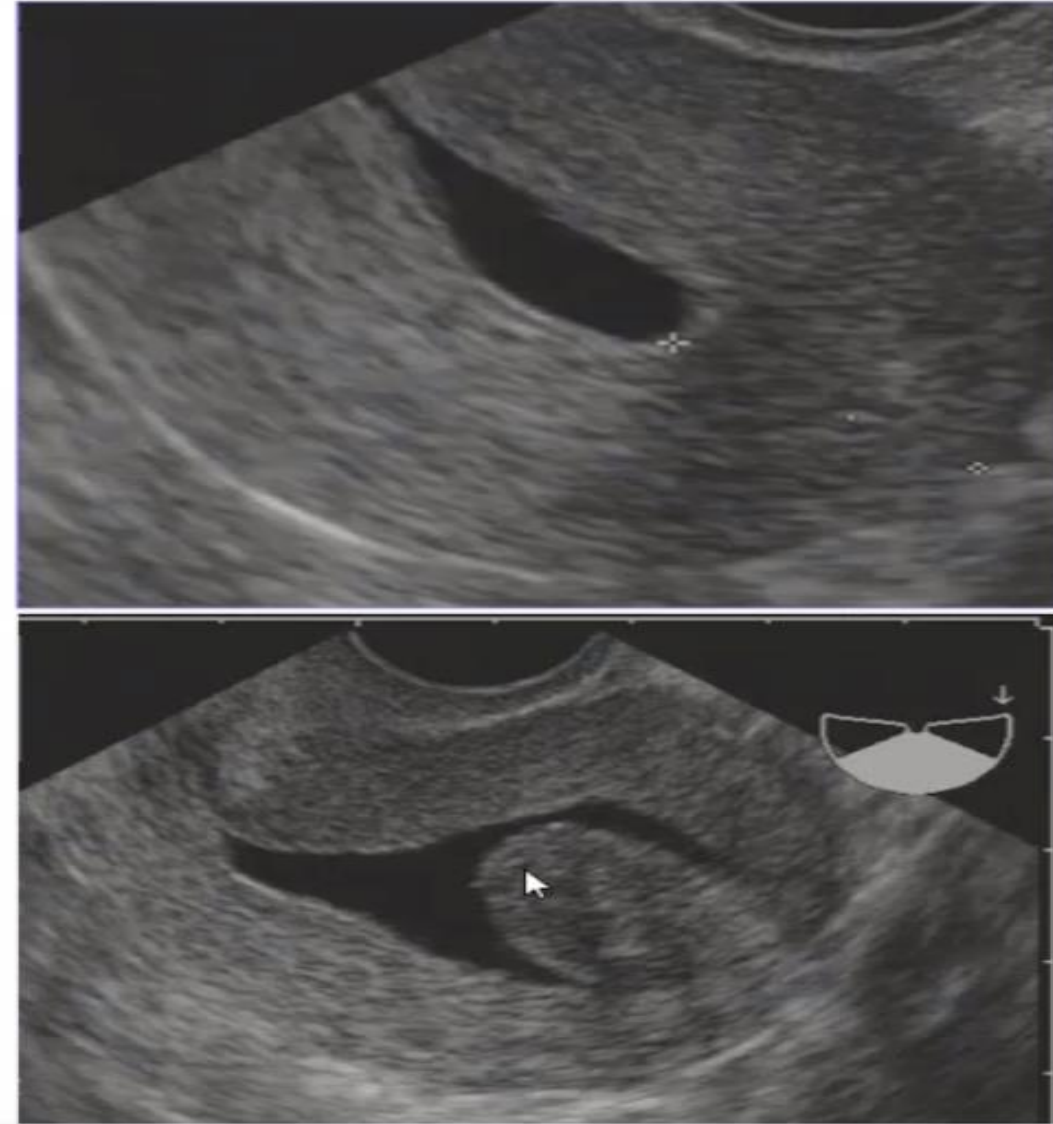


- Implantation
- Extra-embryonic structures development
- Hormone production essential for normal development and growth
- Differentiation of the trophoblast
- Trophoblastic invasion of decidua and myometrium
- Remodelling of the maternal vasculature in the utero-placental circulation
- Development of vasculature within the trophoblast

■ **blastocyst is about 72hrs in the uterine cavity before implanting**

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# Implantation

“implantation window” - specific period of time during which implantation is possible

**Day 5-6** - “window of implantation” (24-36 h)

- preparations in the endometrium  
biochemical and structural changes
- CL and Progesterone cause uterine contractility relaxation, enables embryo implantation

# Pinopodes (Uterodomes)

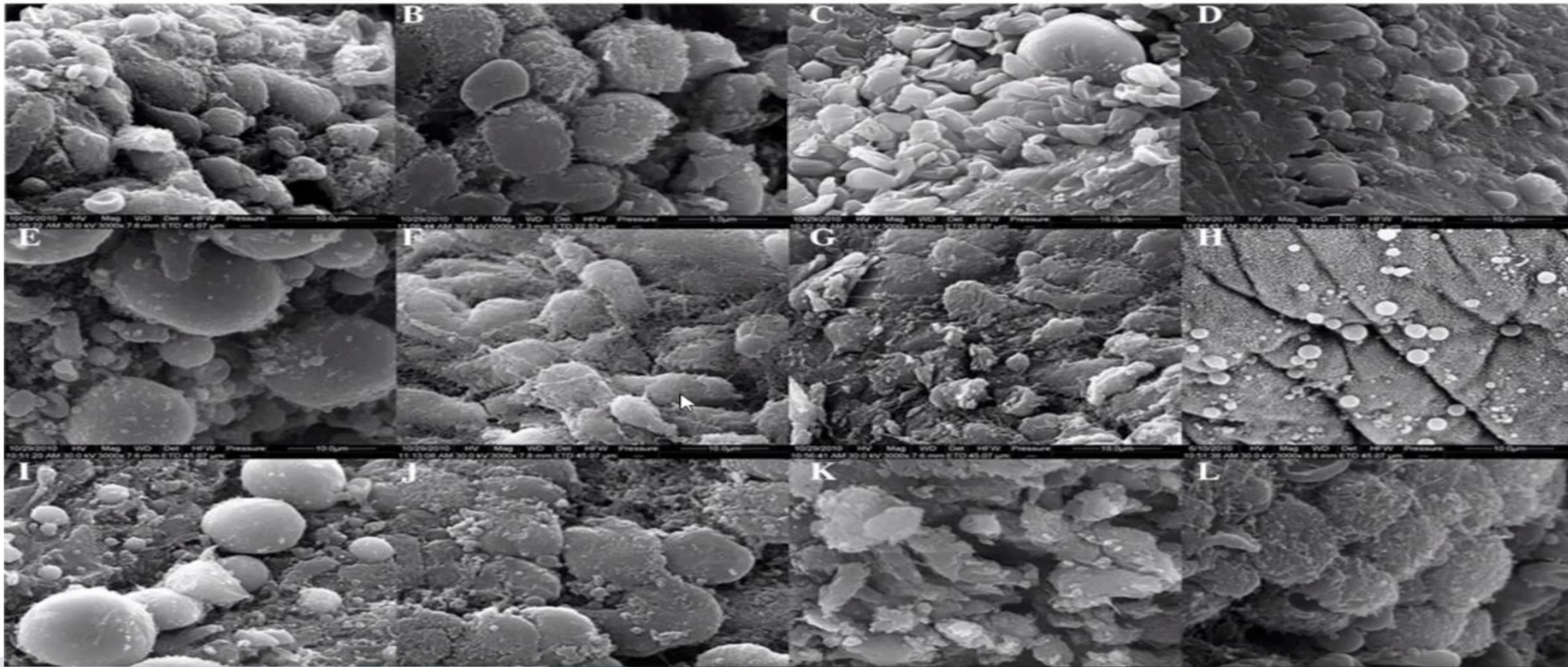
## as markers of implantation

- appear within the implantation window
- are several micrometers wide and project into the uterine lumen
- protrusions found on the apical surface of the endom. epithelium
- appear between day 19 and day 21 of gestational age
- approximately 5 to 7 days from fertilization age
- persist for only 2 to 3 days
- their development is enhanced by progesterone
- absorb fluid, most of it during the early stages of implantation
- assessment of endom. receptivity to optimize implantation rates
- nourishment relies on nutrients in ut. cavity, eg Fe, fat-soluble vits





# Pinopodes



# Predecidualization

- Endometrium is increased in thickness
- vascularization is increased (tortuous glands high activity)
- these changes reach their maximum about 7 days after ovulation

## Decidualization

- if pregnancy - predecidualization progress to Decidualization
- further developing the uterine glands, the *zona compacta*  
(the epithelium of decidual cells lining it)
- decidual cells become filled with lipids and glycogen  
(polyhedral shape characteristic for decidual cells)
- probably the blastocyst contributes to additional growing and sustaining of the decidua

# Decidua throughout pregnancy

- after implantation,
- the decidua remains at least through the first trimester
- Its function as a surrounding tissue is replaced by the definitive placenta

**Day 10** - trophoblast produces  $\beta$ HCG



# Mechanism of Implantation initiation

- blastocyst comes into contact with the uterine wall
- 3 stages: Apposition, adhesion and invasion
- blastocyst apposition, trophoblast cells adhere to the receptive endometrial epithelium
- blastocyst will anchor to the endometrial basal lamina and stromal extracellular matrix
- blastocyst penetration through the luminal epithelium
- invasion - implantation can only occur during a self-limited period
- between days 20 and 24 of a regular menstrual cycle  
(day LH + 7 to LH + 11)

# Implantation initiates Placentation

## Trophoblast

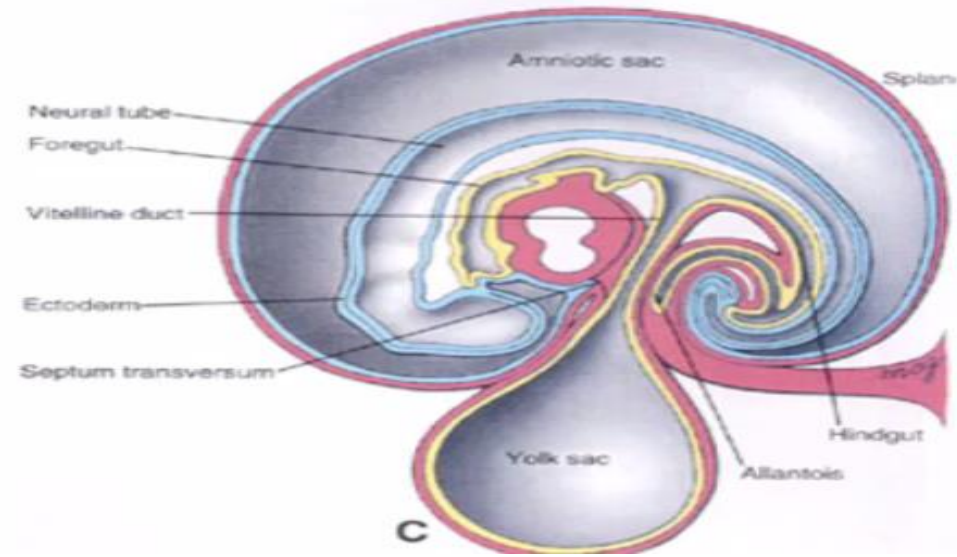
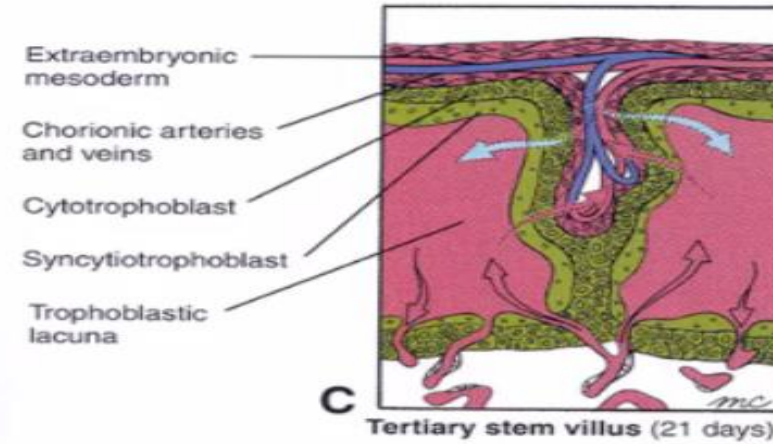
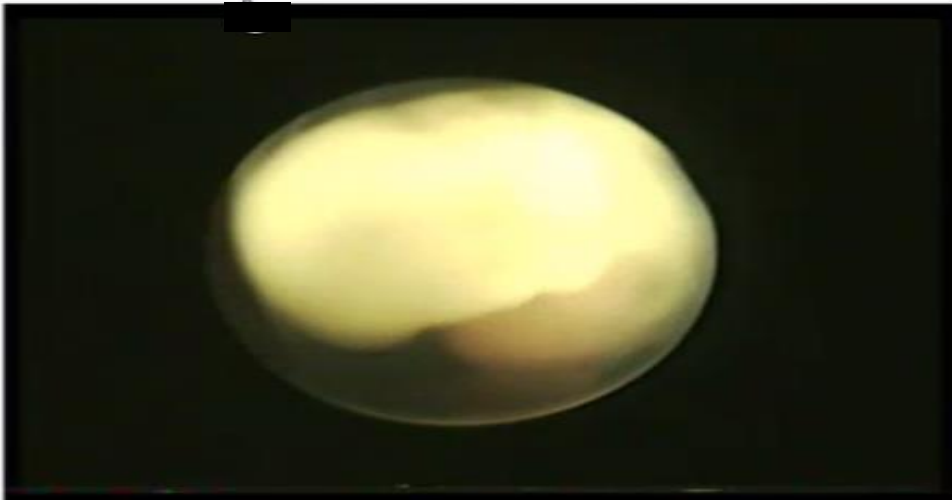
- cells of the blastocyst invade endometrium and myometrium (d 5-6)
- secrete  $\beta$ -hCG

## Chorion

- becomes the placenta

## Amnion

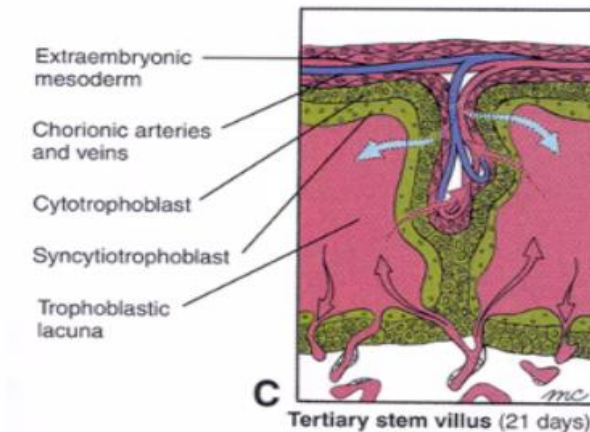
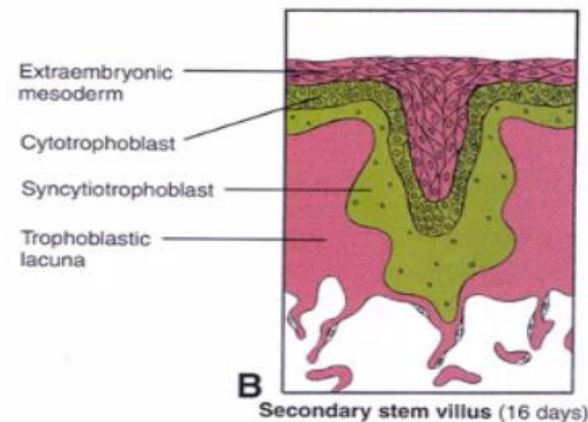
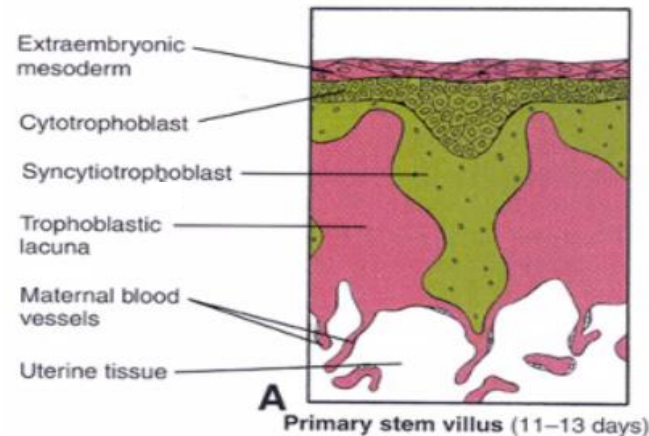
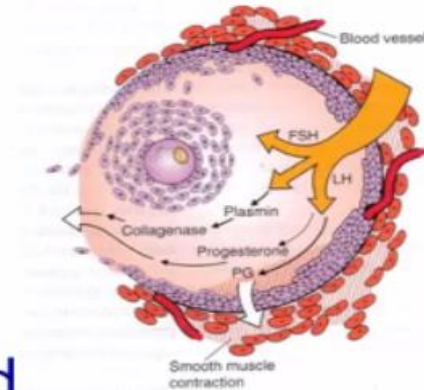
- layer that becomes the amniotic sac





# Immediate changes following implantation and placentation

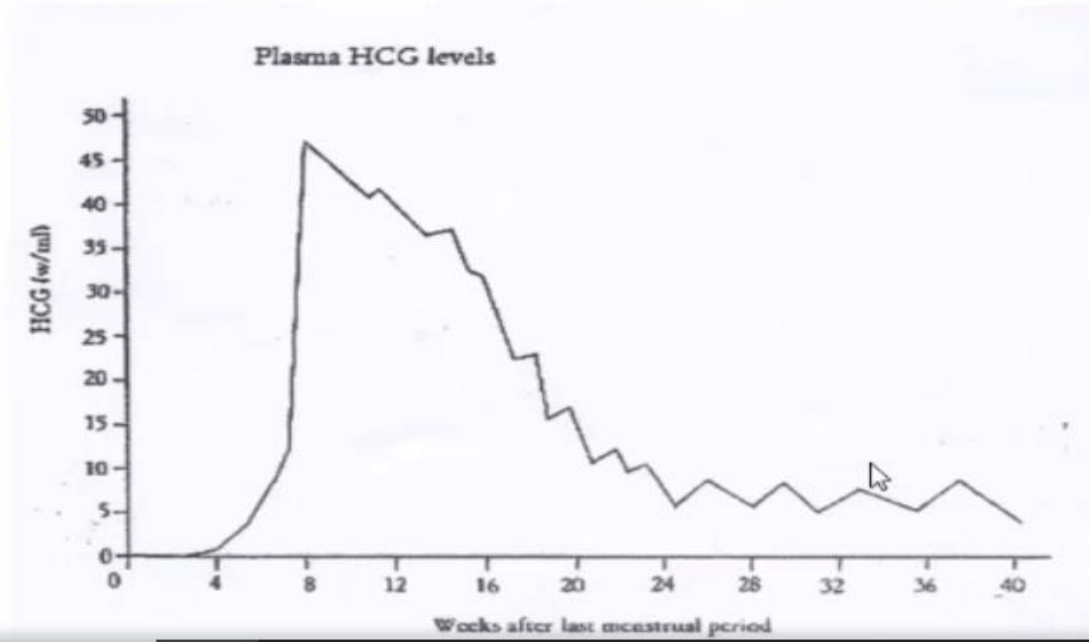
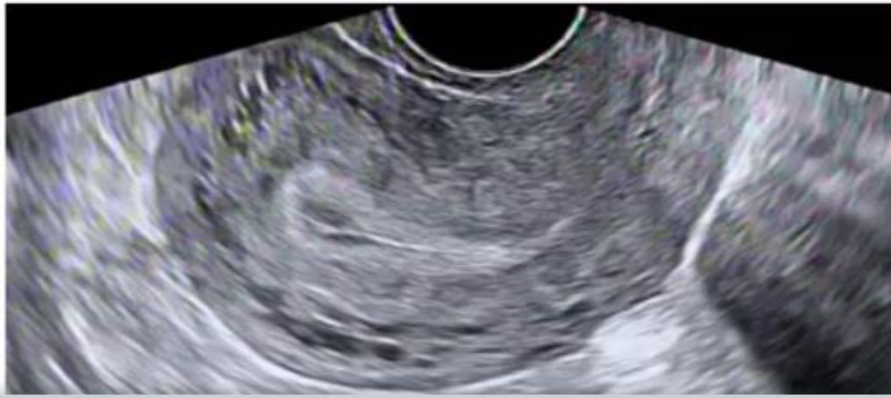
- **$\beta$ HCG** – a signal for recognition of pregnancy  
Maintenance of the **corpus luteum**  
– **Progesterone** production
- **Decidualisation** under progesterone
- Vital until **placental steroidogenesis** established



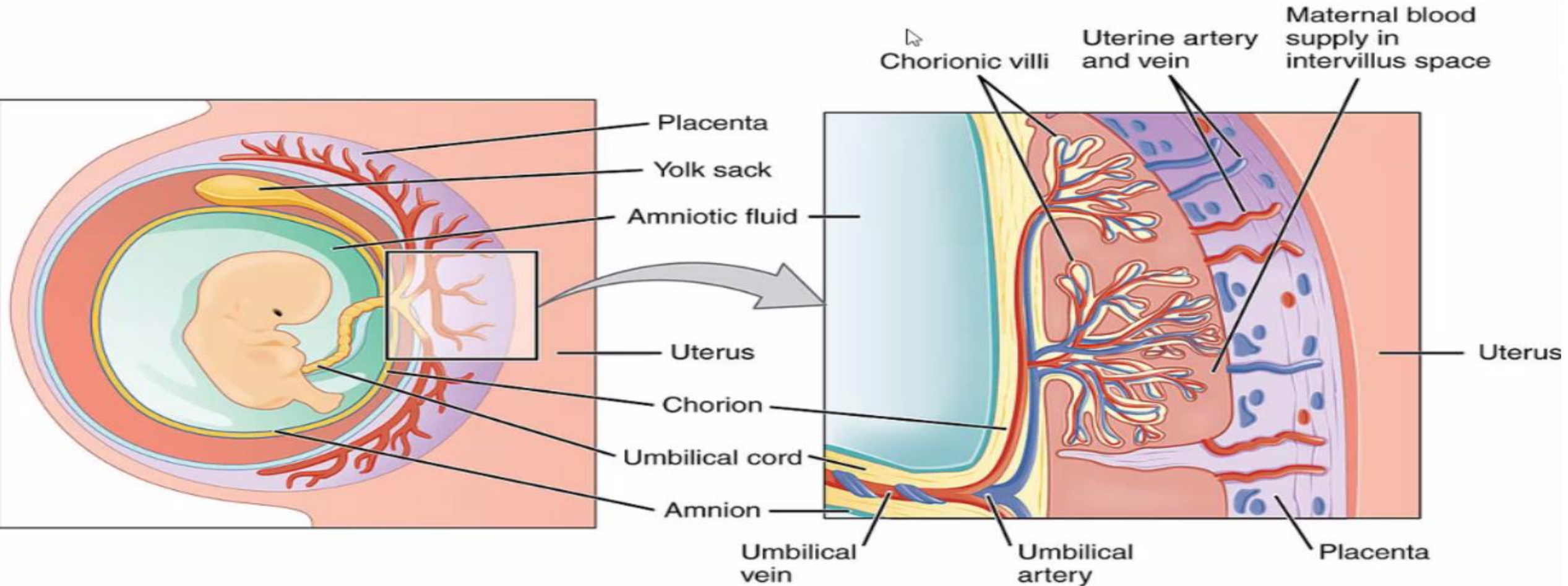


# $\beta$ HCG

- Basis of urinary pregnancy tests –  **$\beta$ -subunit** (qualitative)
- Maximal by 9 – 11 weeks
- Serum  **$\beta$ HCG** (quantitative) useful for monitoring early pregnancy complications e.g. ectopic pregnancy, miscarriage
- hCG amount doubles every 2 days at beginning of pregnancy
- Peak level 500,000-1.000.000 u
- Disappears 7-10d post partum

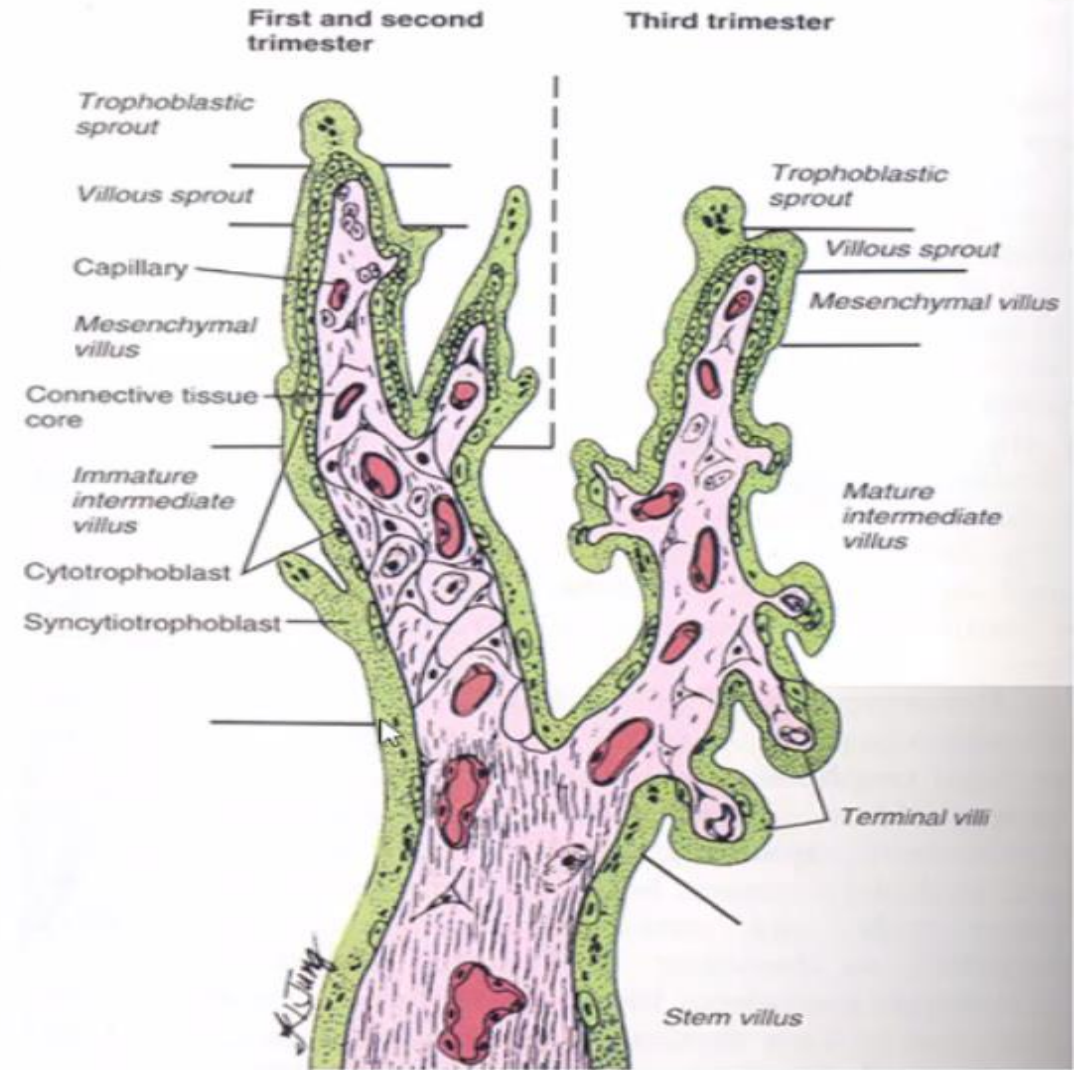
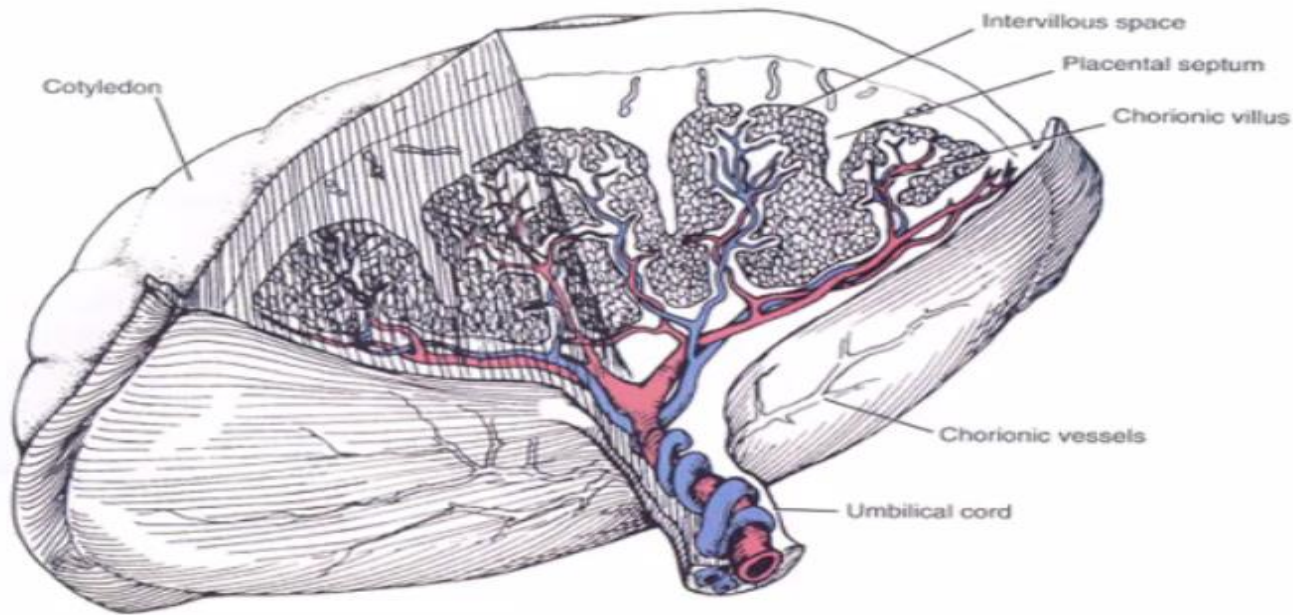


# Placentation during 1<sup>st</sup> trimester

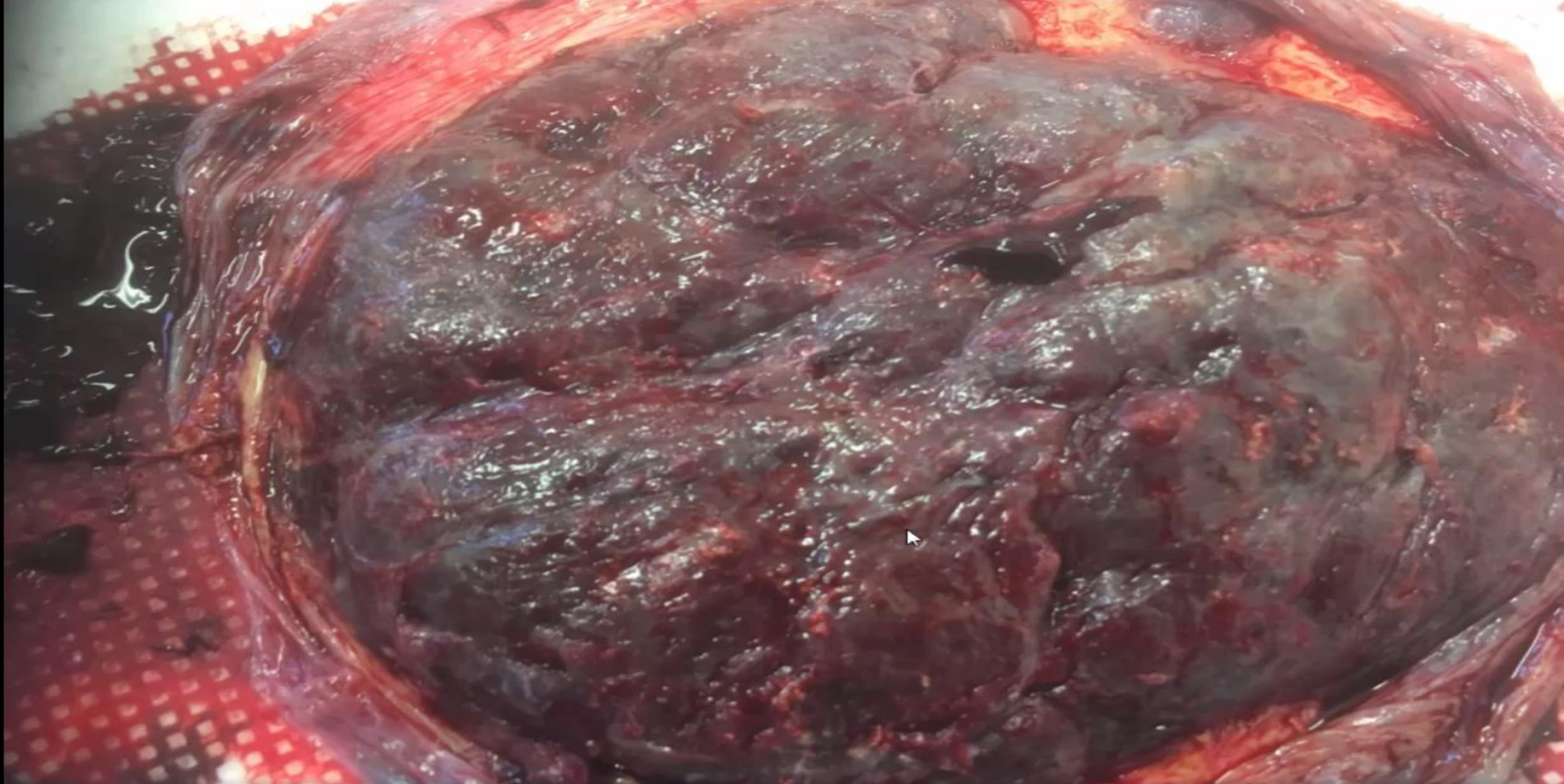




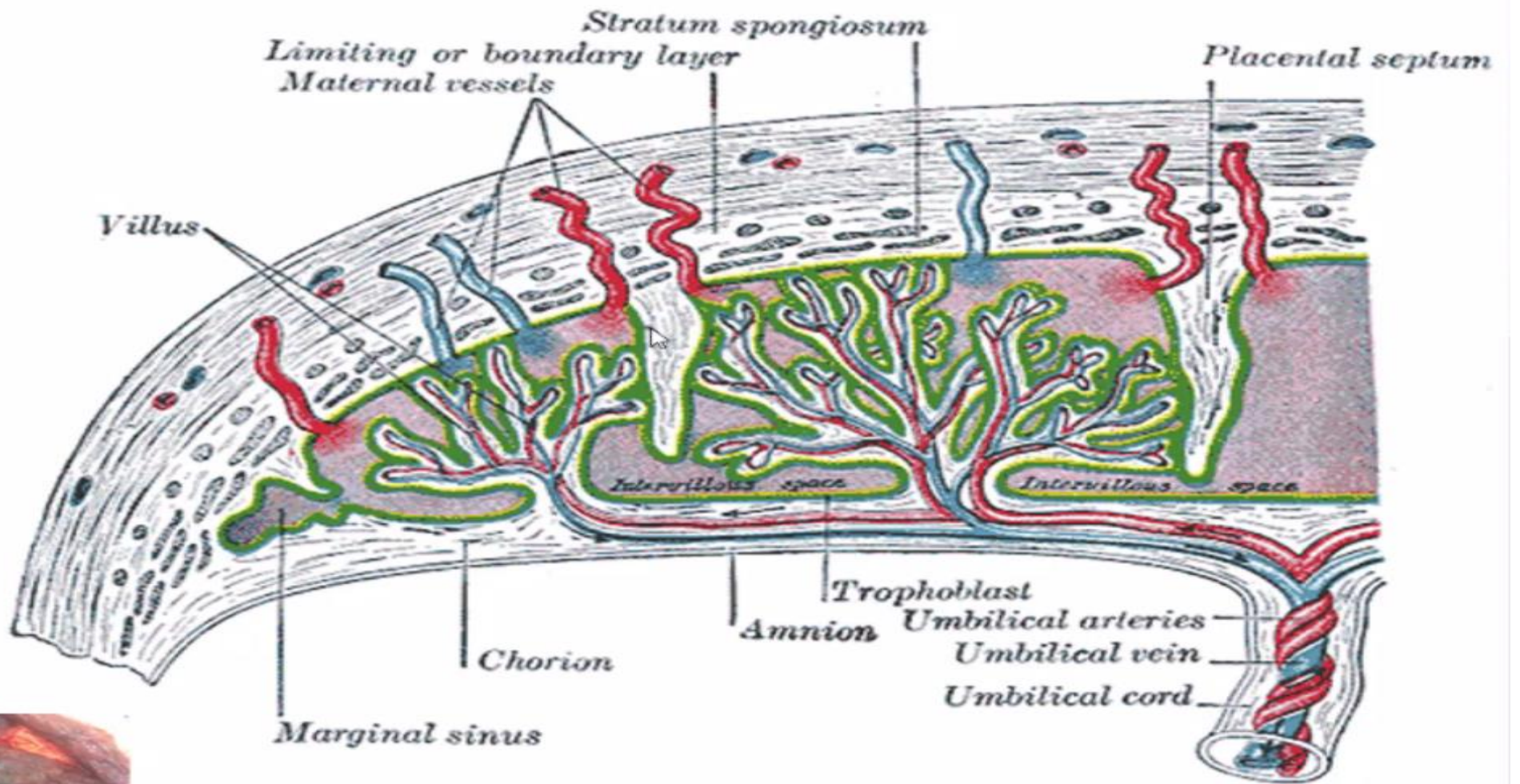
# Placentation 2<sup>nd</sup> and 3<sup>rd</sup> trimester





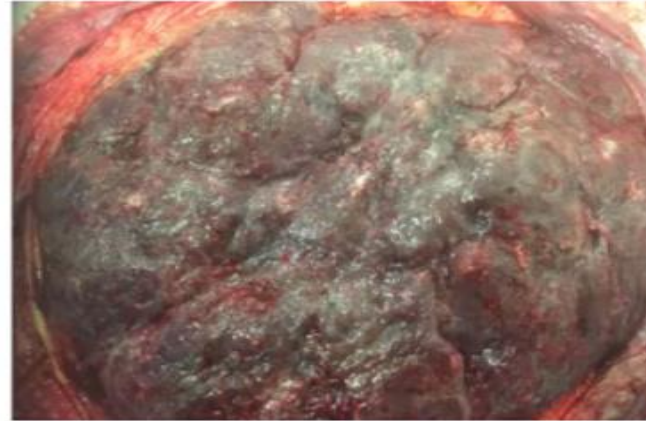






# Placenta function for fetus

- Respiration
- nutrient transfer and secretion
- hormone synthesis



## Placenta functions in general

- Steroidogenesis: oestrogens, Progesterone, HPL, cortisol
- Supplier: maternal  $O_2$ , CHO, fats, AA's, vitamins, minerals, antibodies
- Waste removal:  $CO_2$ , urea,  $NH_4$ , minerals
- Barrier: e.g. bacteria, viruses, drugs, etc

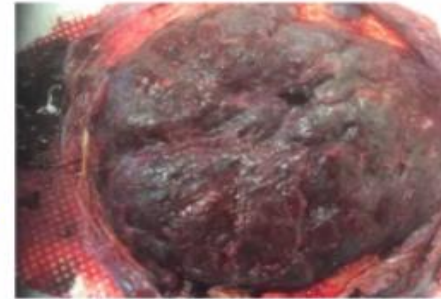


# Transport mechanism in placenta

- Passive transport - simple and facilitated diffusion
- Active transport - enzymatic reaction-expenditure of energy
- Placental metabolism comparable to that of liver or kidney

## Why the placenta is highly efficient

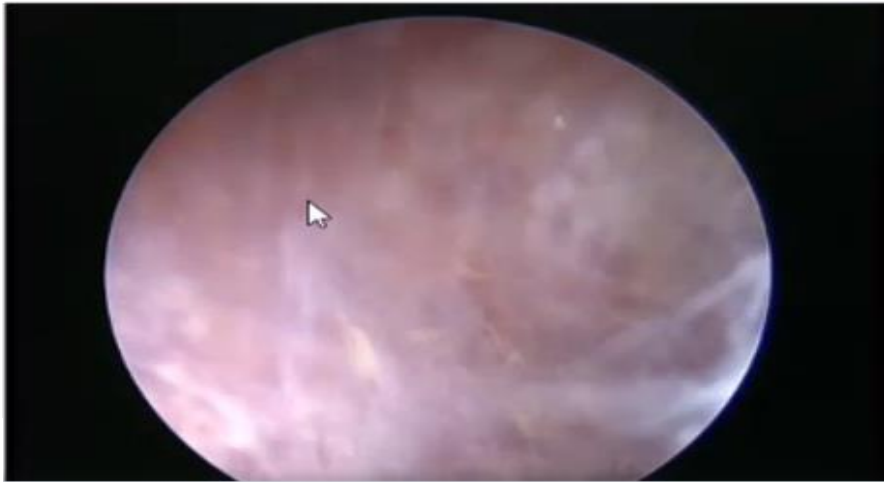
- Huge maternal uterine blood supply - low pressure
- Huge reserve in function
- Huge surface area in contact with maternal blood
- Highly adapted + efficient transfer system



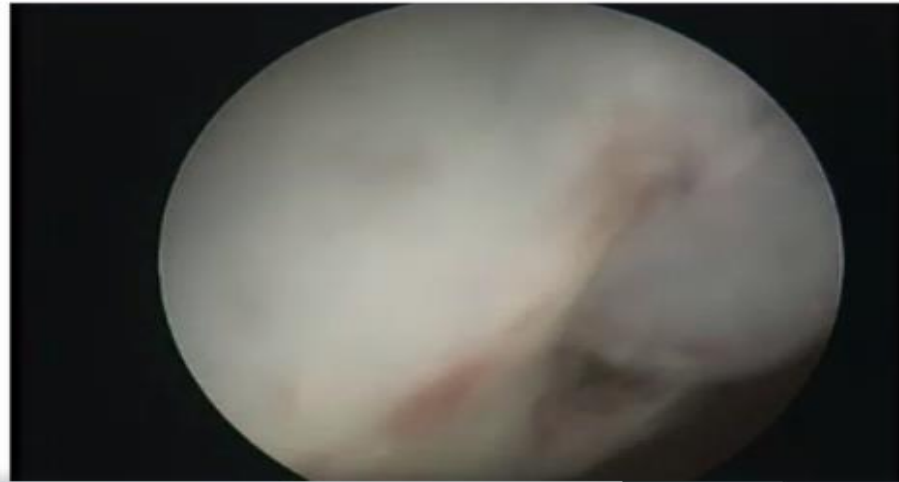
# Disorders of the Placenta

- Miscarriage - 15% (40% are due to placental abruption)
- Pre-eclampsia – 5-10% pregnancies
- Hydatidiform mole
- Placental Insufficiency / aging of the placenta
- Transfer of other substances - drugs, toxins, infections

**Abruption**



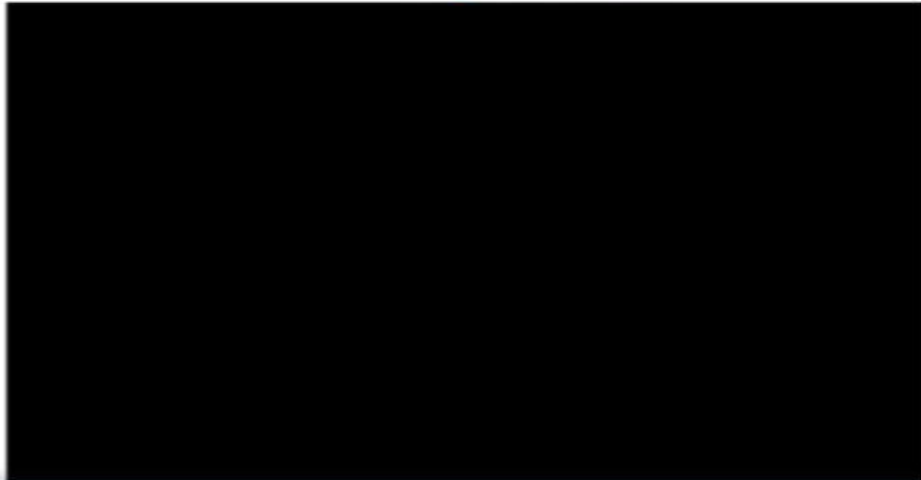
**Placenta Low insertion**



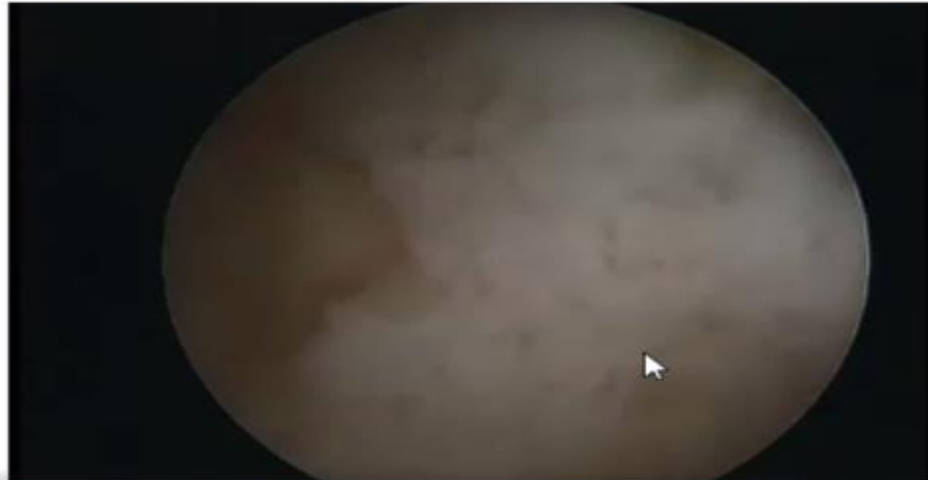
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**Abruption**



**Placenta Low insertion**





# Amniotic fluid

- Secreted by amniotic cells that lie over placenta
- 99% is water
- Increases during pregnancy
- Reduced near term
- Swallowed by fetus, absorbed by gut into fetal circulation  
most exchanged in placenta
- Transudation through fetal skin
- In late pregnancy fetal urination adds to amniotic fluid

# Function of the Amniotic Cavity

- Homeostasis - temperature, fluid, ions,
- Vital for development of certain structures e.g. limbs, lungs
- Protection - physical and barrier e.g. ascending infection

## Disorders of the Amnion

- Polyhydramnios
- Oligohydramnios
- Premature Rupture of Membranes

# Polyhydramnios

- Large placenta - multiple pregnancy, diabetes
- Fetal malformations prevent swallowing or absorption of amniotic fluid
- Duodenal atresia
- Anal atresia
- Anencephaly
- Spina bifida



# Oligohydramnios

- Renal tract malformations
- Intrauterine growth retardation
- Premature rupture of the membranes
- Pulmonary hypoplasia if rupture of membranes less than 20 weeks

# Placenta complication during Labour & Delivery

## *vasa praevia*





# Hormonal changes in pregnancy

- Maternal steroids
- Fetal steroids
- Placental steroids
- Placental peptide hormones

## Estrogens cause

- rise in cardiac output
- increasing the preload & stroke volume by 40–50%

## Progesterone

- Suppress maternal immunologic response to fetal antigens
- preventing maternal rejection of the trophoblast

# Protein hormones produced by placenta

- hPL, hCG, ACTH, GnRH, CRH, TRH
- aFP, prolactin, relaxin, somatostatin
- Growth hormone variant (hGH-V)
- Parathyroid hormone-related protein (PTH-rP)
- Growth hormone-releasing hormone (GHRH)
- Calcitonin, Relaxin, Inhibins Activins,
- Atrial natriuretic peptide,
- Hypothalamic-like releasing and inhibiting hormones



# Hormonal changes in pregnancy

## *General aspects*

- Many uncertain functions in human pregnancy
- Extremely complex interactions between mother, placenta and fetus
- Most hormones freely cross the placenta and found in high levels in maternal blood
- Changes in binding proteins as well

# Estrogen synthesis in pregnancy

## *General aspects*

- Requires intervention of fetus
- Placenta lacks specific enzymes for synthesis of estrogen from acetate and cholesterol
- Placenta secretes more oestriol (E3) than oestradiol (E2) or estrone (E1)
- $E3 > E2 > E1$
- E production relies on androgens from fetus and maternal adrenals
- development of uterine hypertrophy
- metabolic changes (insulin resistance)
- cardiovascular changes
- Breast development





# Hormonal changes in pregnancy

## *General aspects*

- Placental steroidogenesis (7 – 8 weeks)

### **Progesterone**

- Decidualisation (CL)
- Smooth muscle relaxation – uterine quiescence
- Mineralocorticoid effect – CVS changes

### **Prolactin:**

- Increases throughout pregnancy
- Breast development for lactation

# human Chorionic Gonadotropin

- rescues the CL from involution and maintains progesterone secretion by the ovarian granulosa cells
- diagnostic marker of pregnancy
- hCG gene expression in cytotrophoblast and syncytiotrophoblast,
- synthesized mainly in the syncytiotrophoblast
- maternal circulating hCG concentration, approximately 100 IU/L at the time of the expected but missed menses
- maximal level of about 100,000 IU/L at 8-10 weeks of gestation

## *clinical conditions - blood hCG titers are especially helpful*

- Trophoblastic disease (high b-hCG (3-100 x higher than normal preg
- ectopic pregnancies
- Tumors secreting hCG - teratoma



# Human Placental Lactogen (hPL)

- antagonizes insulin action
- associated with insulin resistance
- induces glucose intolerance, lipolysis and proteolysis in maternal system
- responsible for the GDM
- enhances insulin secretion and stimulates lipolysis
- increases circulating free fatty acids
- inhibits gluconeogenesis
- marked rise in maternal plasma IGF-1 close to term
- metabolic effects via IGF-I

# Progesterone

- During early pregnancy, the maternal levels of 17-OH Progesterone rise by CL support
- by 10<sup>th</sup> w 17-OH Prog returns to baseline levels indicating that placenta is not secreting Progesterone
- 32w there is a 2<sup>nd</sup>, more gradual rise in 17a-OH P due to placental utilization of fetal precursors  
*(prevention of preterm labor)*

# Progesterone effect on the genito-urinary system

- increase blood volume and vasculature causes increase in the size of the kidneys and ureter
- physiological hydro-nephrosis and hydro-ureter
- vasodilatation and increased blood flow to the kidneys
- GFR increases 50%, returning to normal 20 weeks postpartum
- GFR increases the excretion of protein, albumin, glucose
- increases urinary output and urinary frequency
- decreased motility of the ureters, stasis of the urine and increased risk of UTI





# Progesterone effect on the respiratory system

- respiratory rate does not change during pregnancy
- Increases respiratory minute volume (the amount of air breathed in and out of the lungs in 1 minute) by 40% in the first trimester
- $\text{CO}_2$  in the blood decreases and the [pH](#) of the blood becomes more alkaline (*i.e. the pH is higher and more basic*)
- maternal kidneys excrete [bicarbonate](#) to compensate for this change in pH
- decreased serum concentrations of both  $\text{CO}_2$  and bicarbonate
- increase blood pH (*to **7.44** as compared to 7.40 in the non-pregnant state*)

# Progesterone effect on the GIT

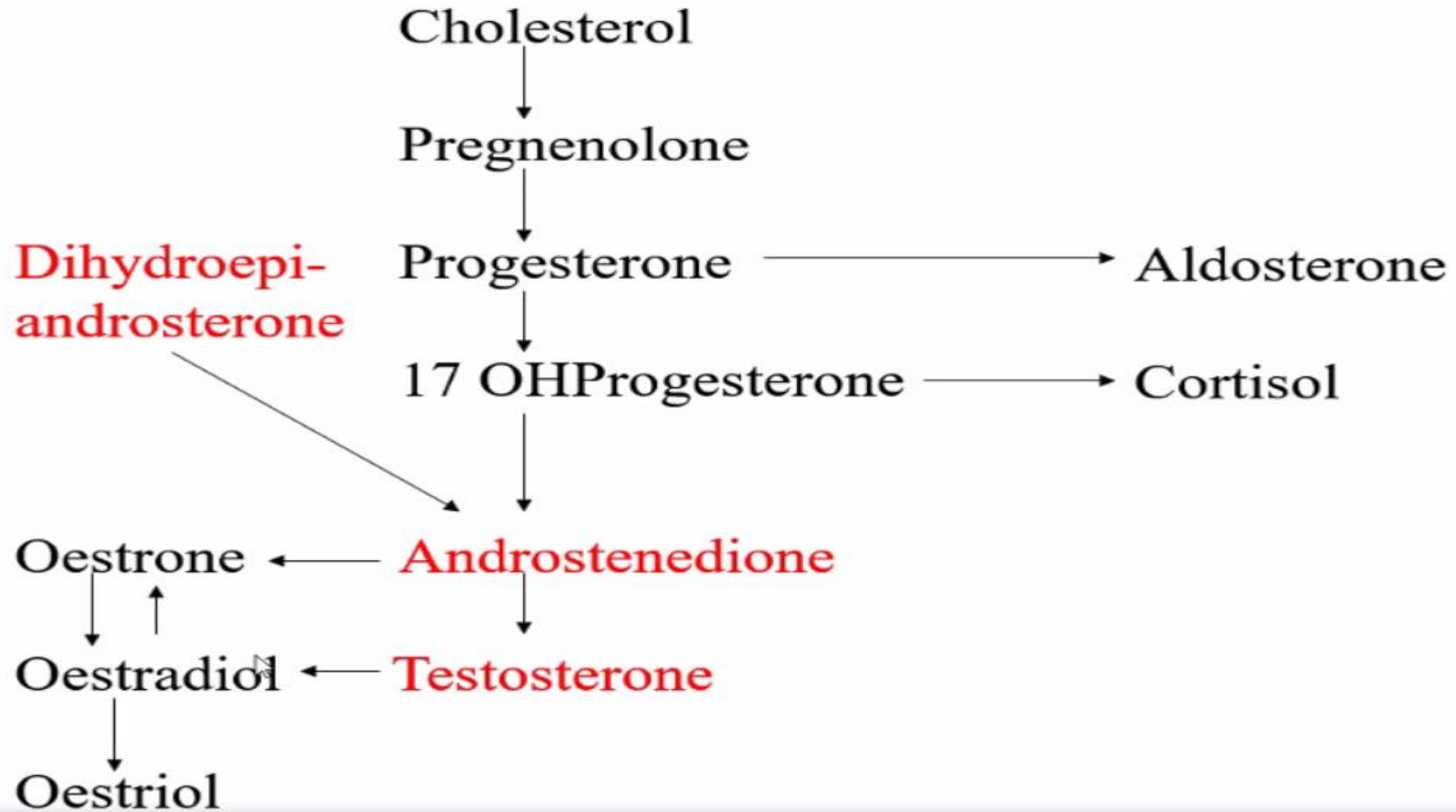
- Nausea and vomiting (hyperemesis gravidarum)
- correlates with the rise in the levels of hCG and Progesterone
- due to relaxation of smooth muscle of the stomach
  
- causes smooth muscle relaxation
- reduces GI motility and lower esophageal sphincter tone
- combined with increase in intragastric pressure
- leads to the gastroesophageal reflux
- inhibition of gallbladder contraction increases occurrence of gallstones
  
- **Constipation**
- narrowing of the colon as compression by the growing uterus
- increased absorption of water during pregnancy

# Trophoblast and Estrogen

- trophoblast lack 17-hydroxylase and cannot convert C21-steroids to C19-steroids, the immediate precursors of estrogen, thus
- DHA from the fetal adrenal is converted to estradiol-17 by trophoblasts
- placenta use precursors from either mother or fetus to circumvent its own deficiencies in enzyme activities
- Hormones act as catalysts for chemical changes at the cellular level that are necessary for growth, development and energy.
- Fetus lacks 3  $\beta$ -hydroxysteroid dehydrogenase-hence is unable to produce progesterone thus borrows from placenta
- fetus give placenta what it lacks (19 Carbon compounds) the precursor of estrogen



# Steroidogenesis



# Estrogen causes

- thyroid enlargement in the 1<sup>st</sup> trimester
  - increased GFR causes more iodide to be excreted
  - relative iodine deficiency and increase in thyroid size
  - increase in TBG
  - increase in total thyroxine (T4)
  - but FT3, FT4 remain normal
- 
- reduced biliary transportation of bile results in cholestasis

# Estrogen cause

- **Total cortisol** increases x 3, by 3<sup>rd</sup> trimester
- increase corticosteroid-binding globulin production
- adrenal gland produces more free cortisol
- contributes to insulin resistance and possibly striae
- pregnant does not exhibit Cushing syndrome or symptoms of high cortisol
- high progesterone levels act as an antagonist to the cortisol
- **aldosterone** increase x 8, but causes NO *hyper-aldosteronemia, NO hypo K or hyper Na or HBP*
- increase of Testosterone is buffered by E and increase in SHBG