

Human Placental Structure and Development

Graham J Burton

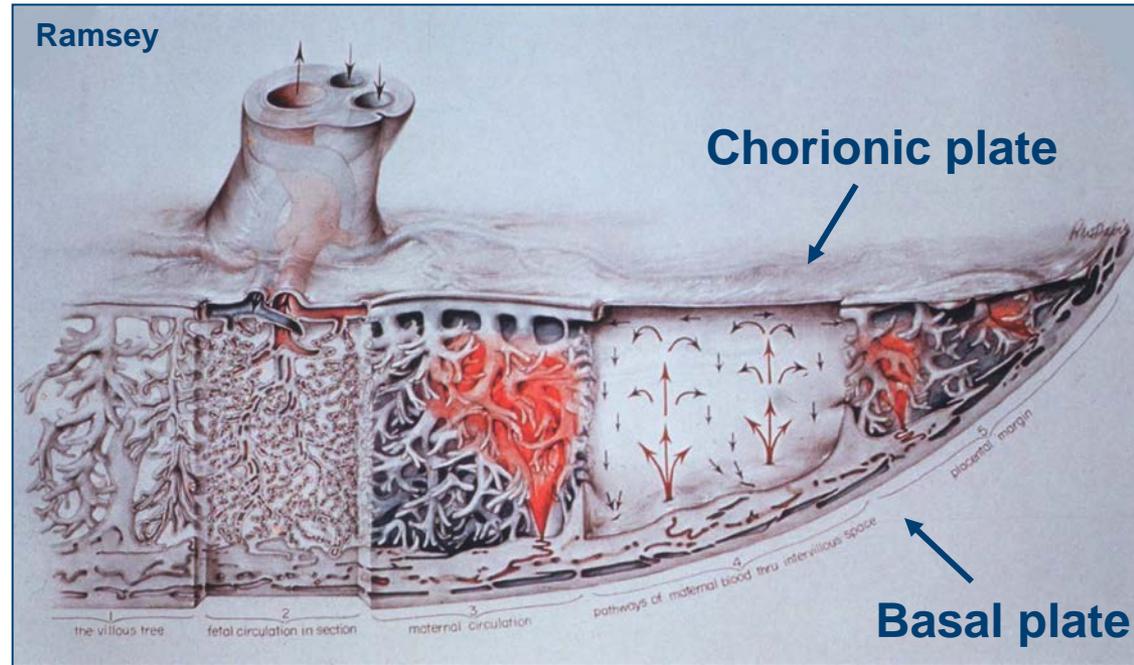
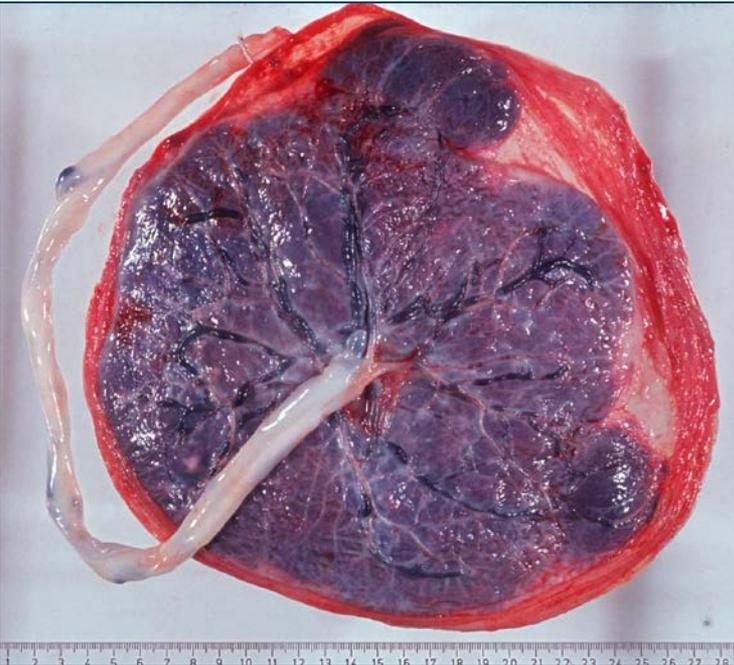
Human Placenta Project, May 27th 2014

Centre for Trophoblast Research (www.trophoblast.cam.ac.uk)

Aims

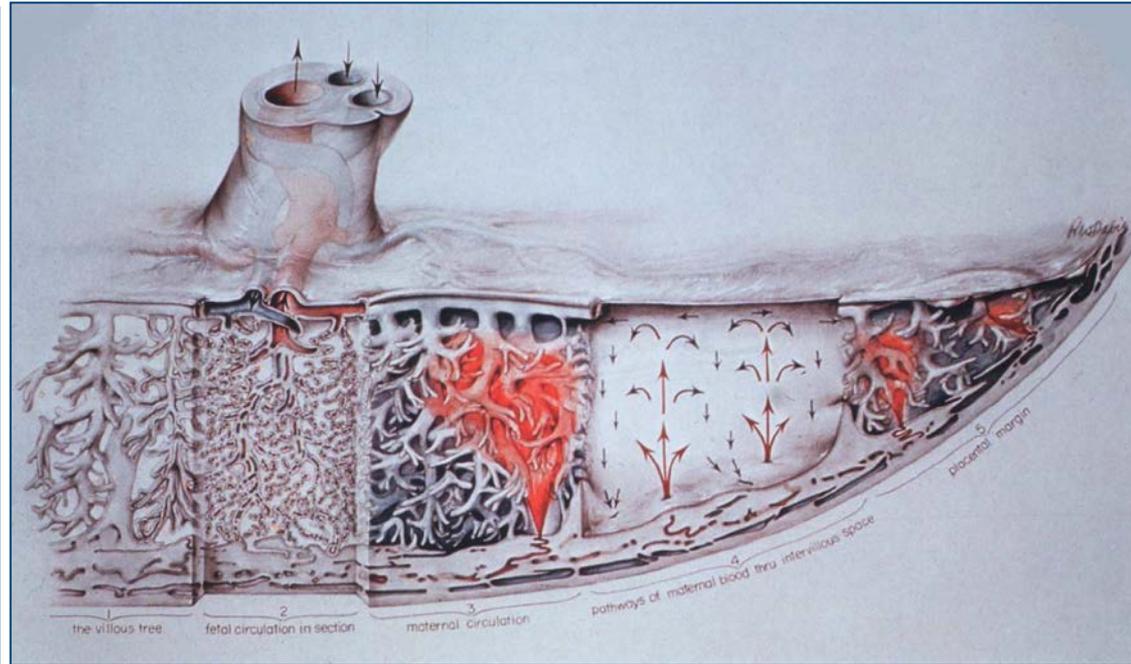
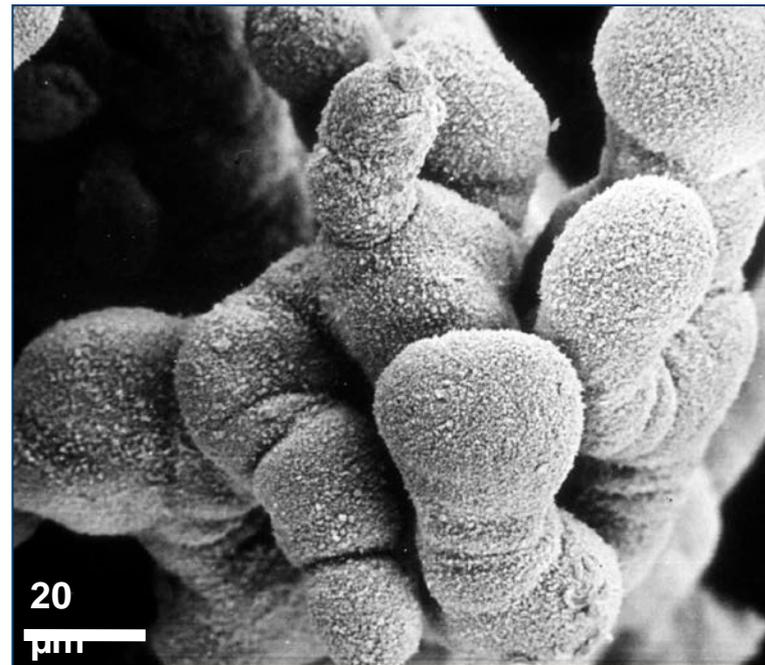
- **To outline the structure of the mature placenta**
- **To outline development of the placenta**
 - **elaboration of the villous trees**
 - **the intrauterine environment during the first trimester**
 - **establishment of the maternal circulation to the placenta**
- **To consider remodelling of the early placenta and formation of the smooth membranes**

The mature human placenta



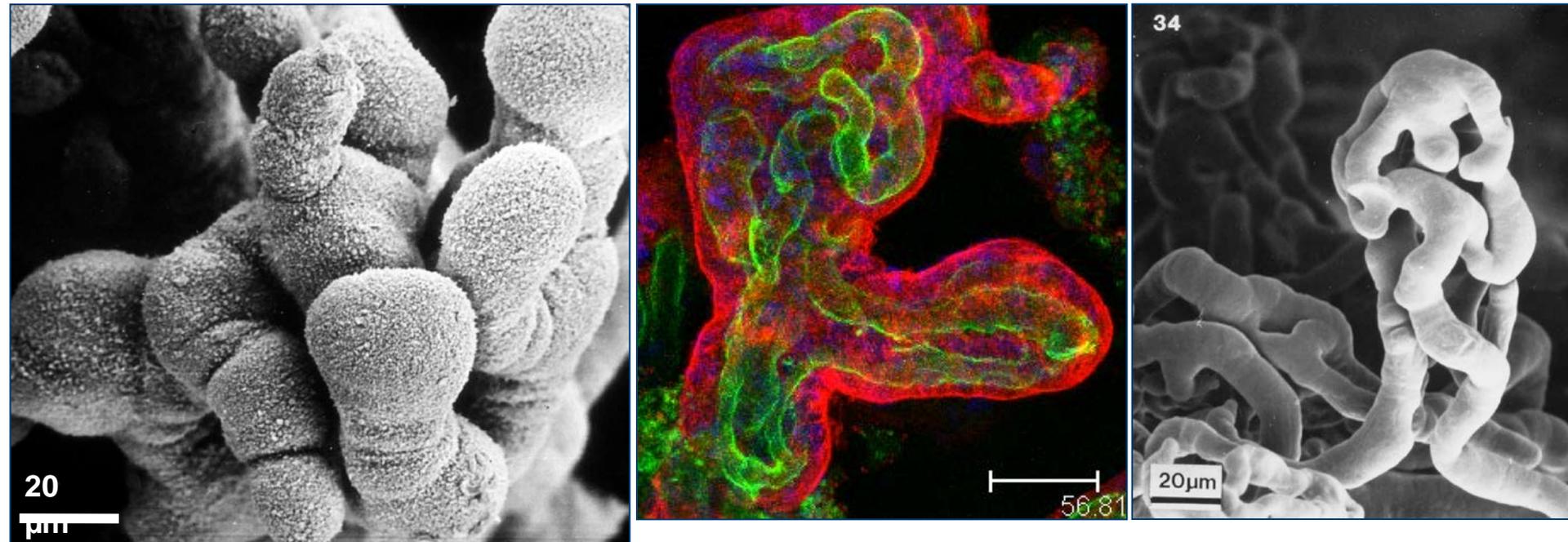
- The mature human placenta is a discoid organ 20-25 cm in diameter, 3 cm thick and weighing 400-600g
- Internally it consists of a fetal villous tree bathed directly by maternal blood, at least during the second and third trimesters

The mature human placenta



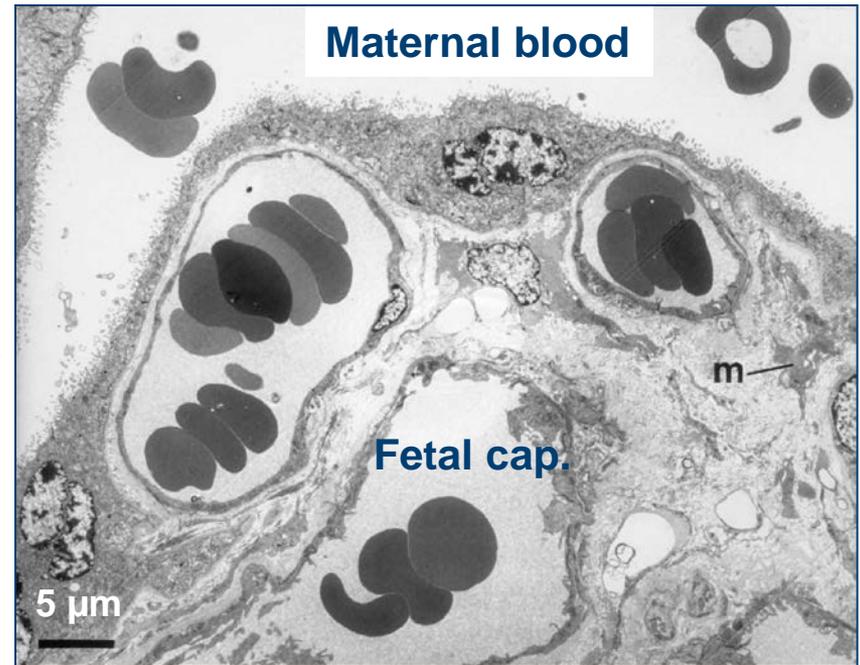
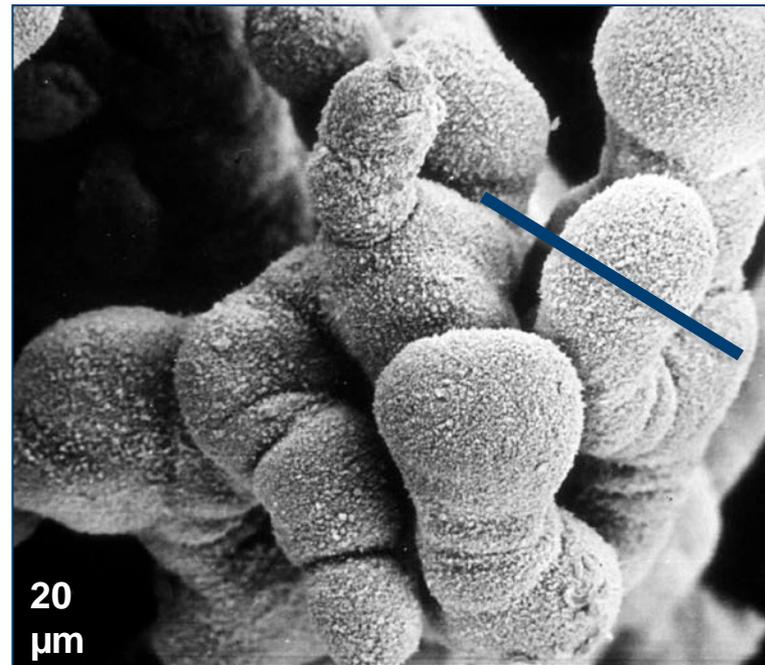
- To enhance diffusional exchange a large surface area and a thin membrane between the maternal and fetal circulation is needed
- The villous trees branch repeatedly to generate a surface area of 12-14 m²

The mature human placenta



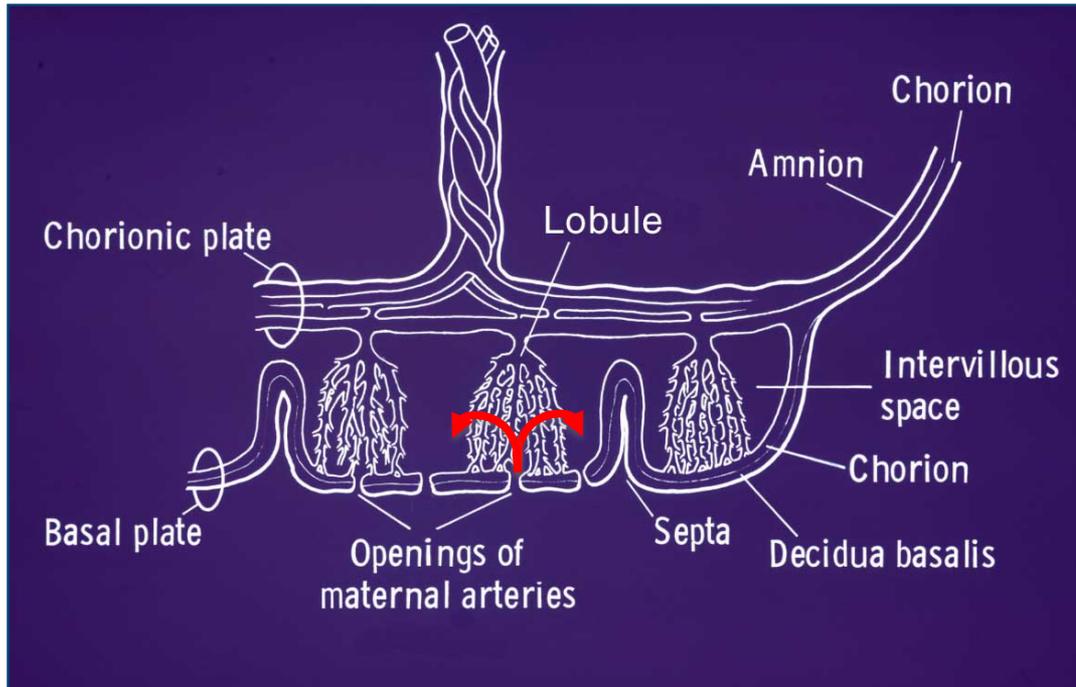
- Inside each villus is a complex network of fetal capillaries
- The capillaries are irregular in diameter, with dilated regions often at the points of bends

The mature human placenta



- The dilations bring the capillaries into close contact with the epithelial covering, the trophoblast, which is locally thinned
- At these vasculo-syncytial membranes the diffusion distance may be reduced to 2-3 μm

The lobular arrangement of villi

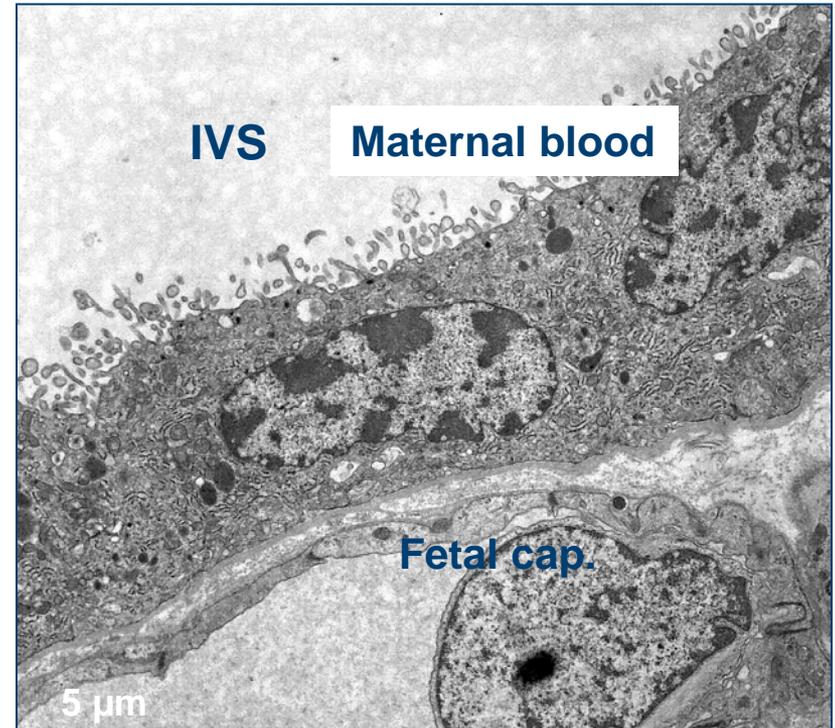


Vascular cast showing fetal vasculature in white and the maternal arterial blood in red

- The villi are arranged into a series of 30-40 lobules, each centred over the opening of a spiral artery
- Each lobule acts as an independent maternal-fetal exchange unit

The placenta is more than a gas exchanger

- Secretion of steroid and peptide hormones, cytokines and growth factors
- Endocytosis and catabolism of maternal proteins
- Active transport of amino acids and other nutrients
- Metabolic regulation and ionic homeostasis
- Excretion of waste products
- Antithrombotic activity



- The trophoblast is highly metabolically active and accounts for ~40% of oxygen consumption by the feto-placental unit

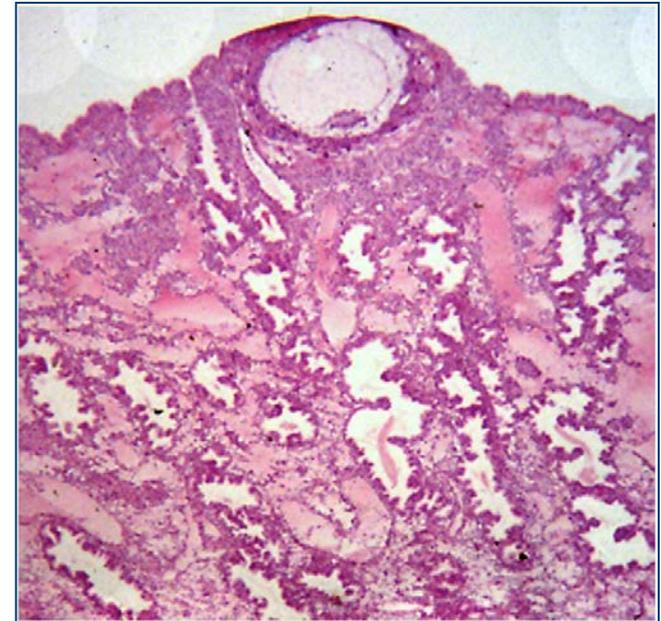
Aims

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- **To outline development of the placenta**
 - **elaboration of the villous trees**
 - **the intrauterine environment during the first trimester**
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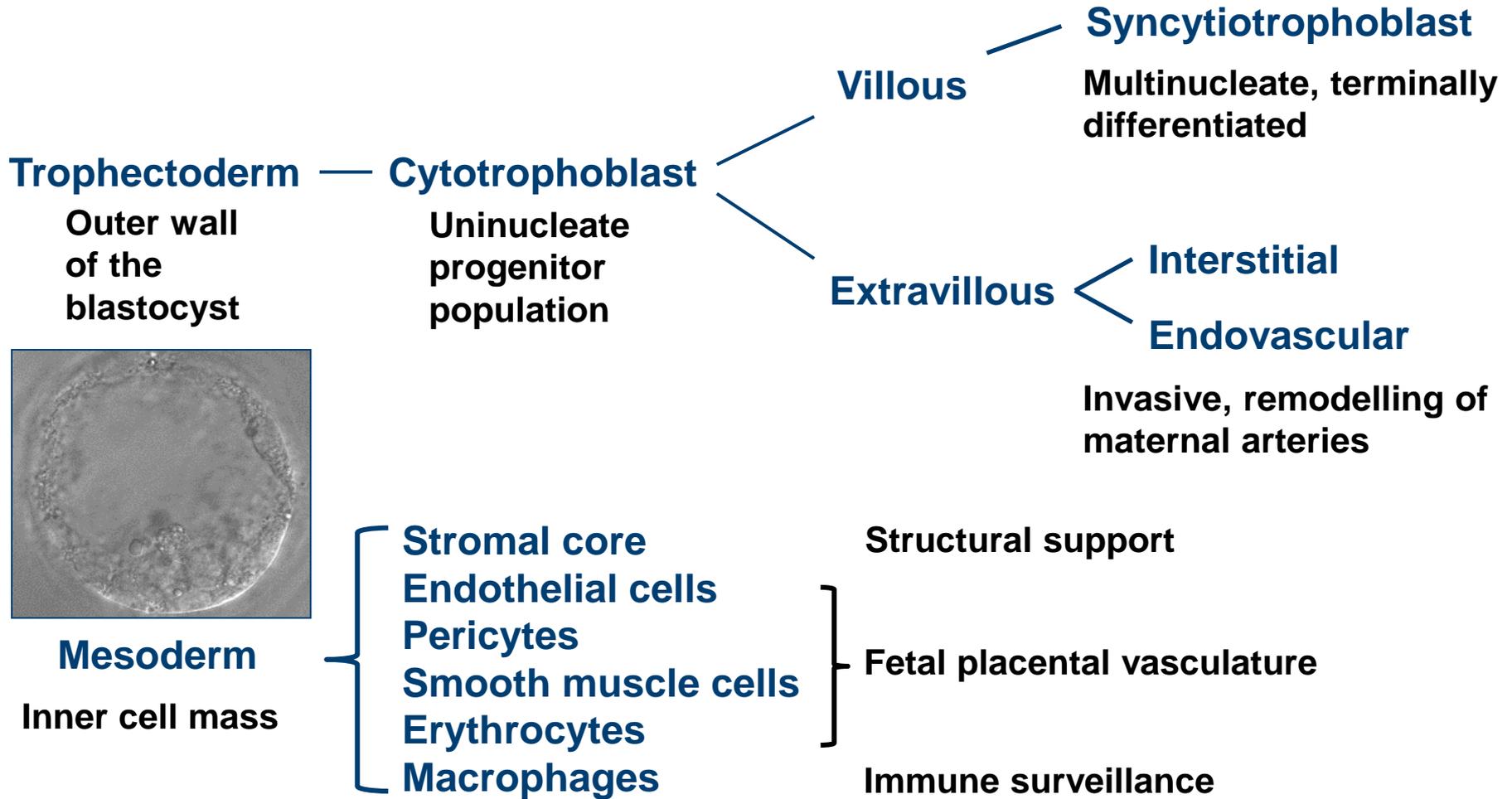
Placental development

There are two main players that interact closely:

- **The conceptus**
- **Provides the cells for elaboration of the villous trees**
- **The endometrium**
- **Nutritional support and growth factor stimulation**
- **Maternal arterial circulation**

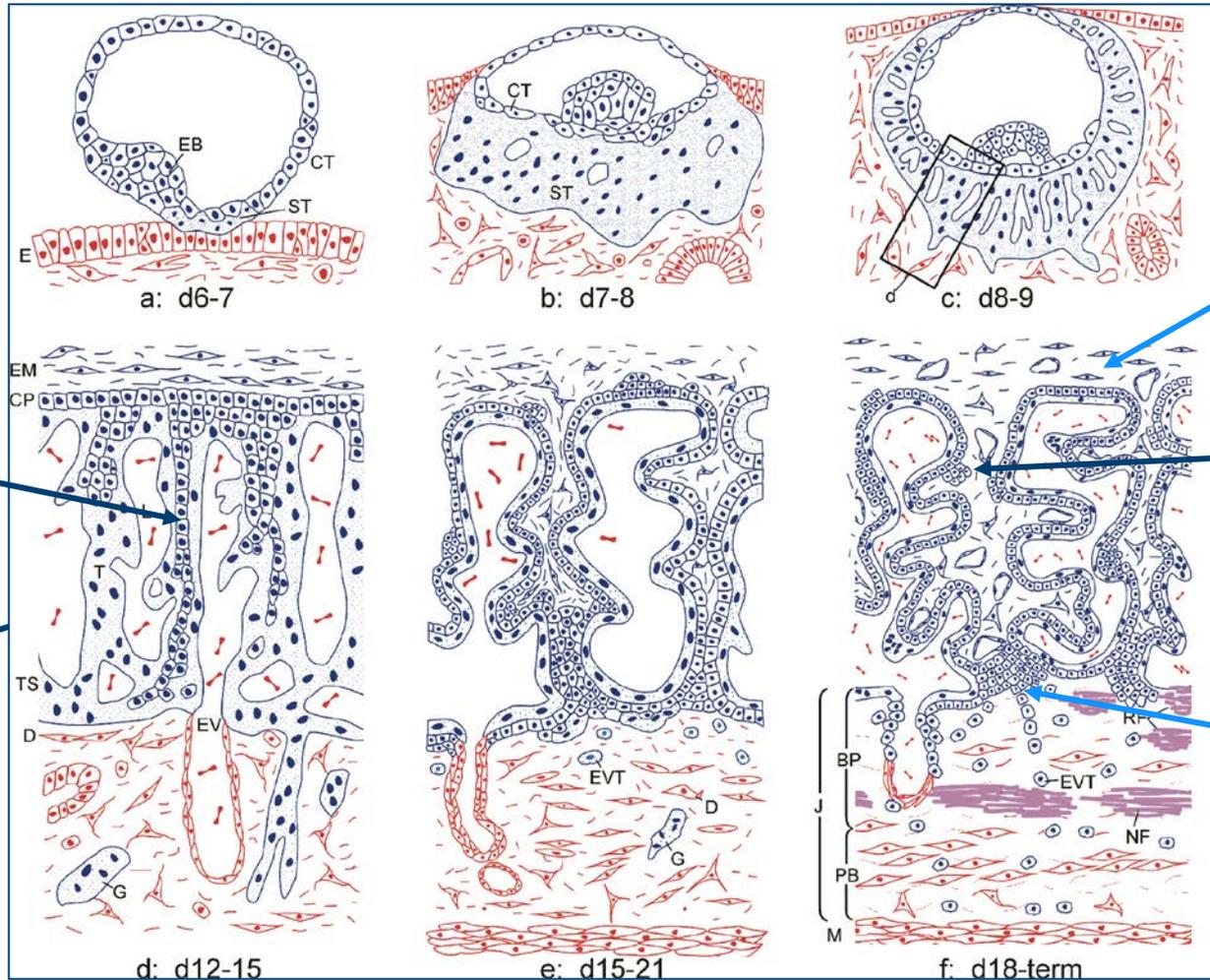


The placental cell types



Summary of villus formation

Benirschke et al.



Chorionic plate

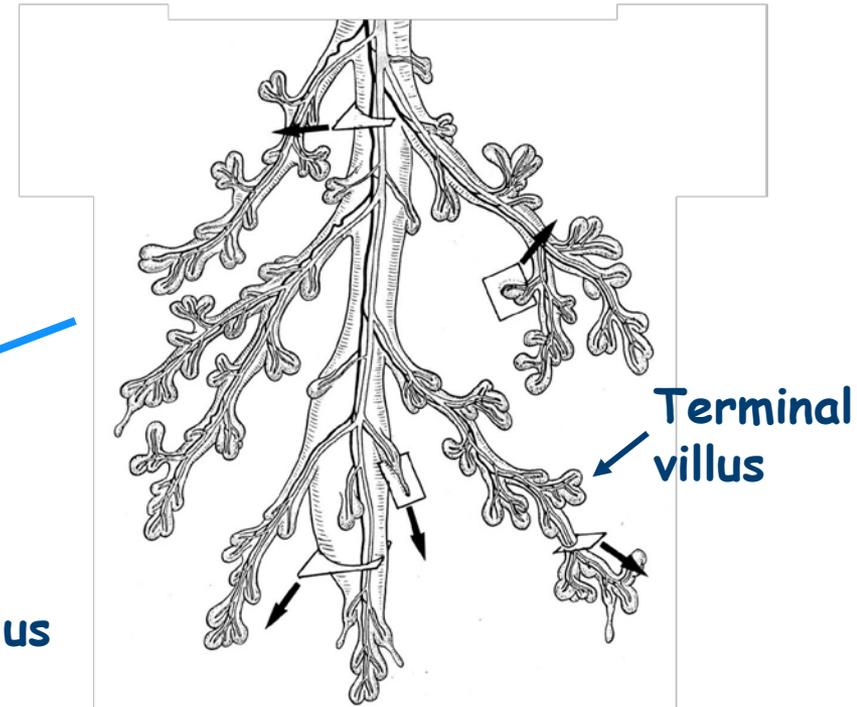
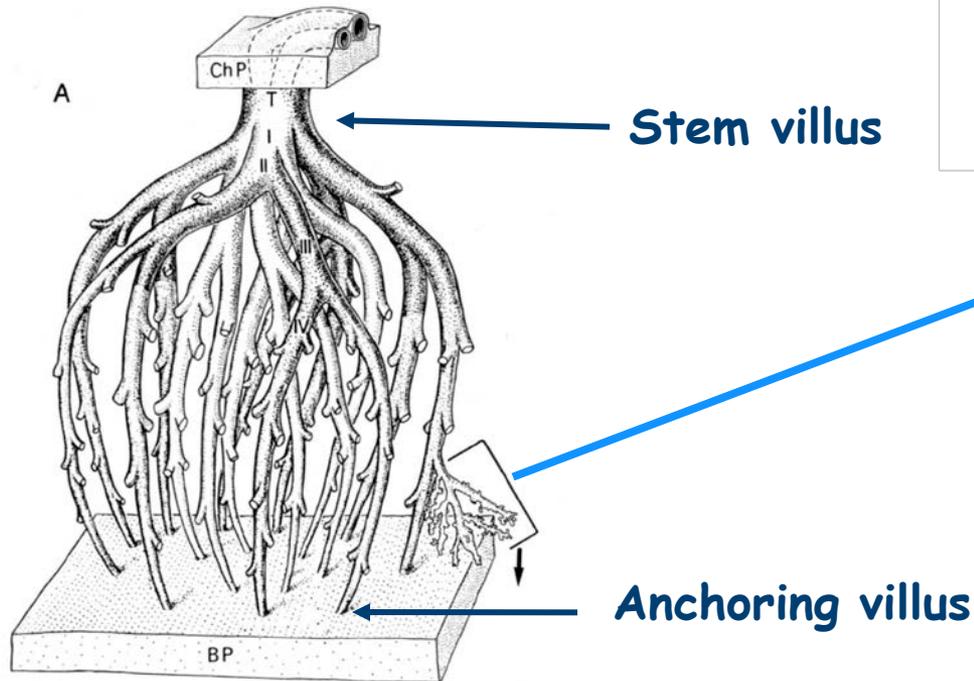
3. mesoderm

Basal plate

2. cytotrophoblast cells

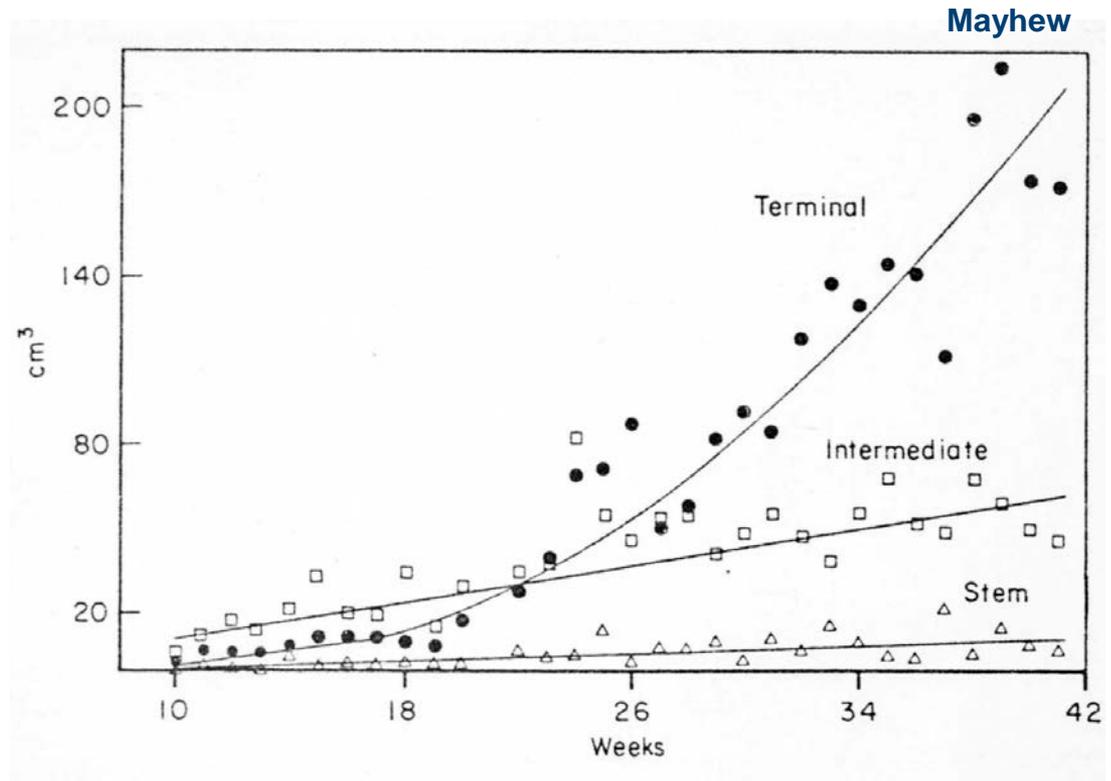
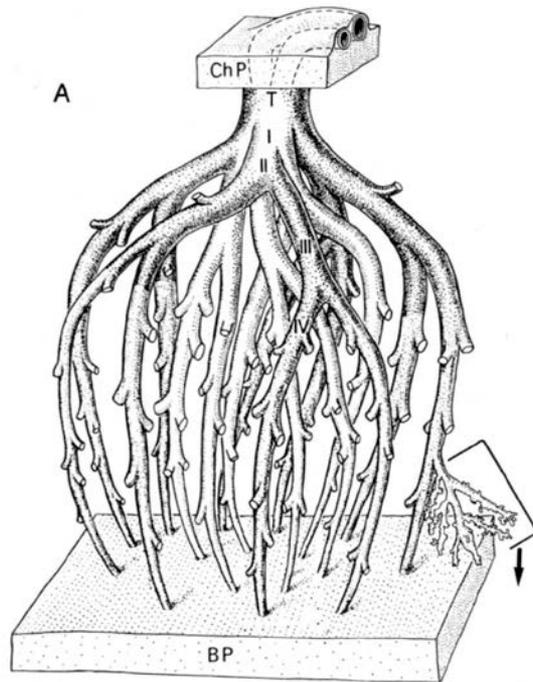
1. trabeculum of STB

Elaboration of the villous trees



- The proximal part of the original trabeculum becomes the main stem villus attaching to the chorionic plate
- The more distal parts become the anchoring villi attached to the basal plate

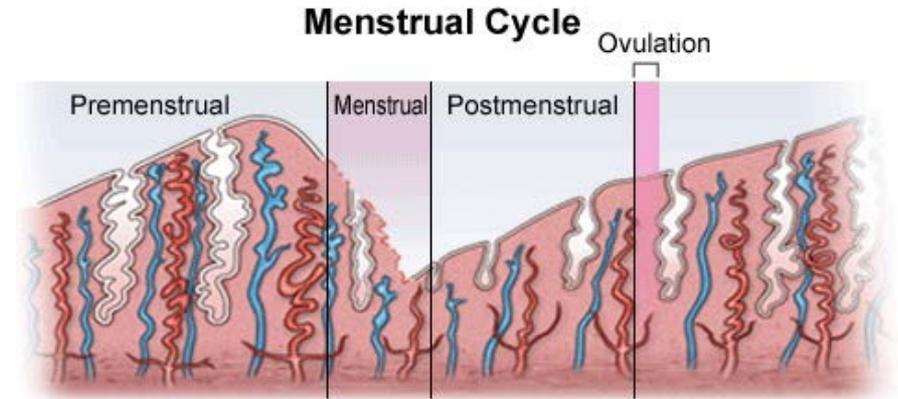
Elaboration of the villous trees



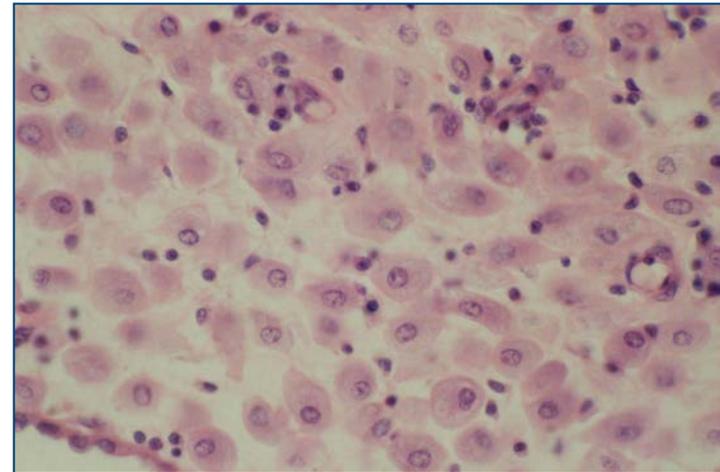
- Terminal villi are the principal sites of M-F exchange, and are elaborated primarily after 20 wks of gestation, continuing until term

The endometrium

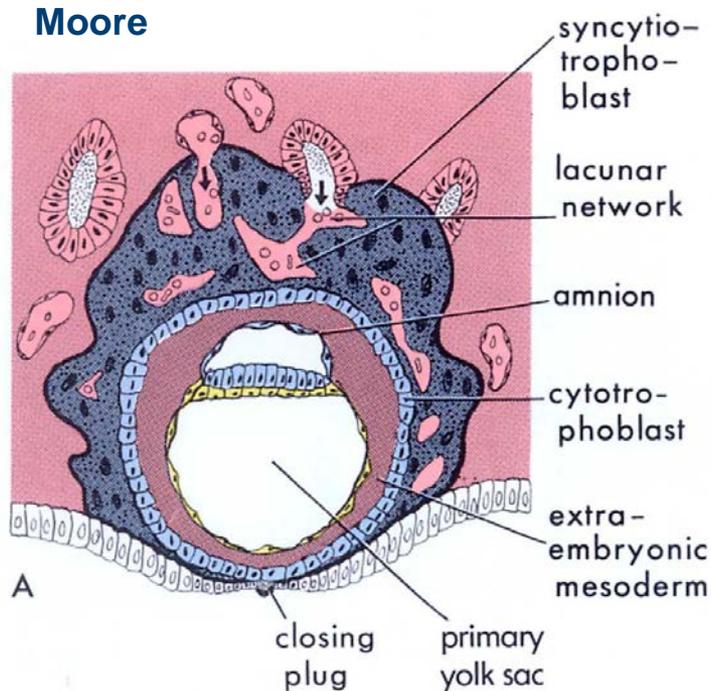
- 1. The uterine glands**
Increase in size and activity prior to pregnancy. Provide nutrient and growth factor support during first trimester.



- 2. The decidual cells**
Endometrial stromal cells undergo transformation into highly secretory decidual cells in early pregnancy. Poor decidualisation related to complications of preg.



During implantation both endometrial capillaries and uterine glands are eroded

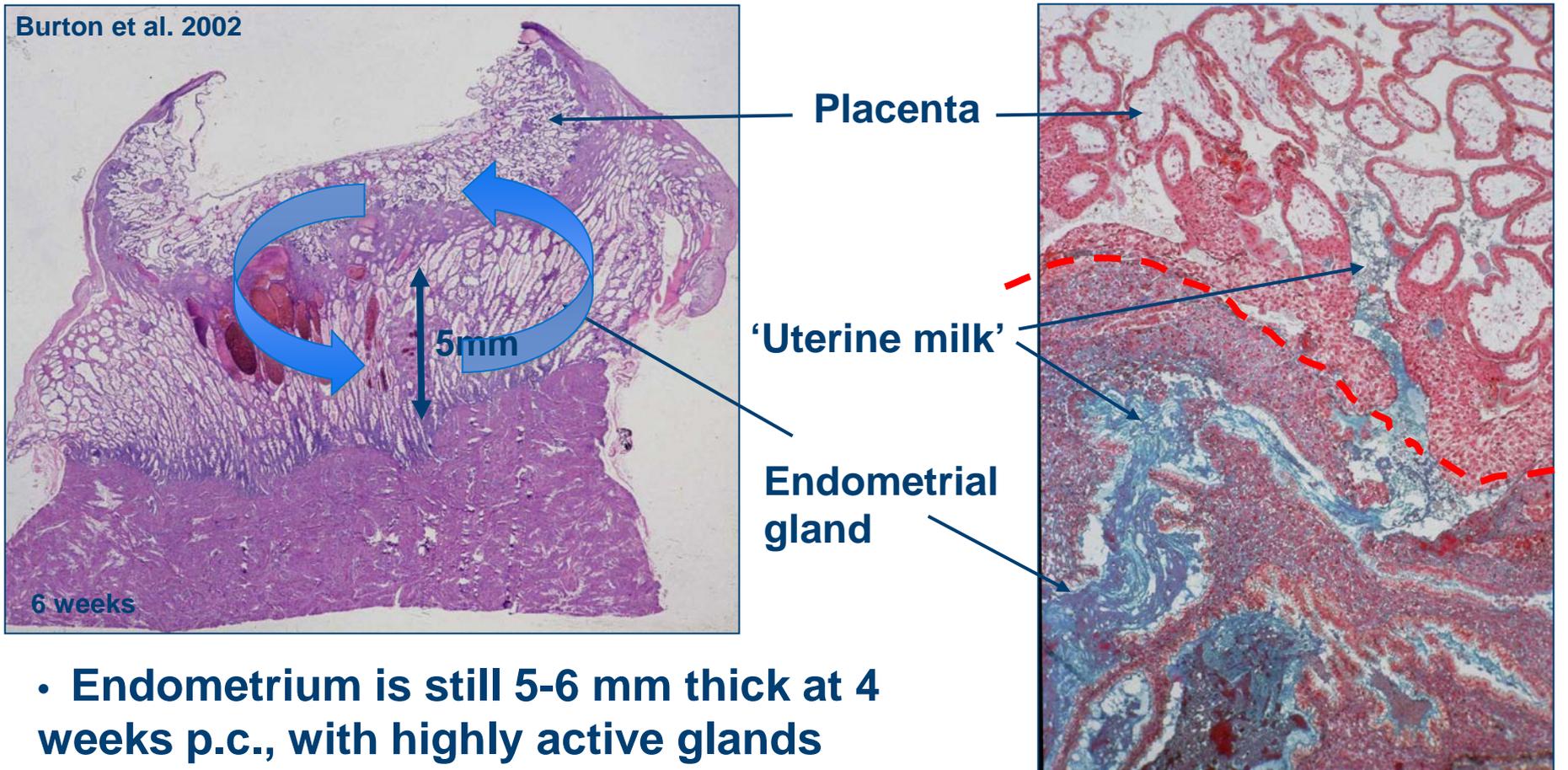


Carnegie collection



- After implantation both maternal capillaries and endometrial glands are eroded by the invading syncytiotrophoblast

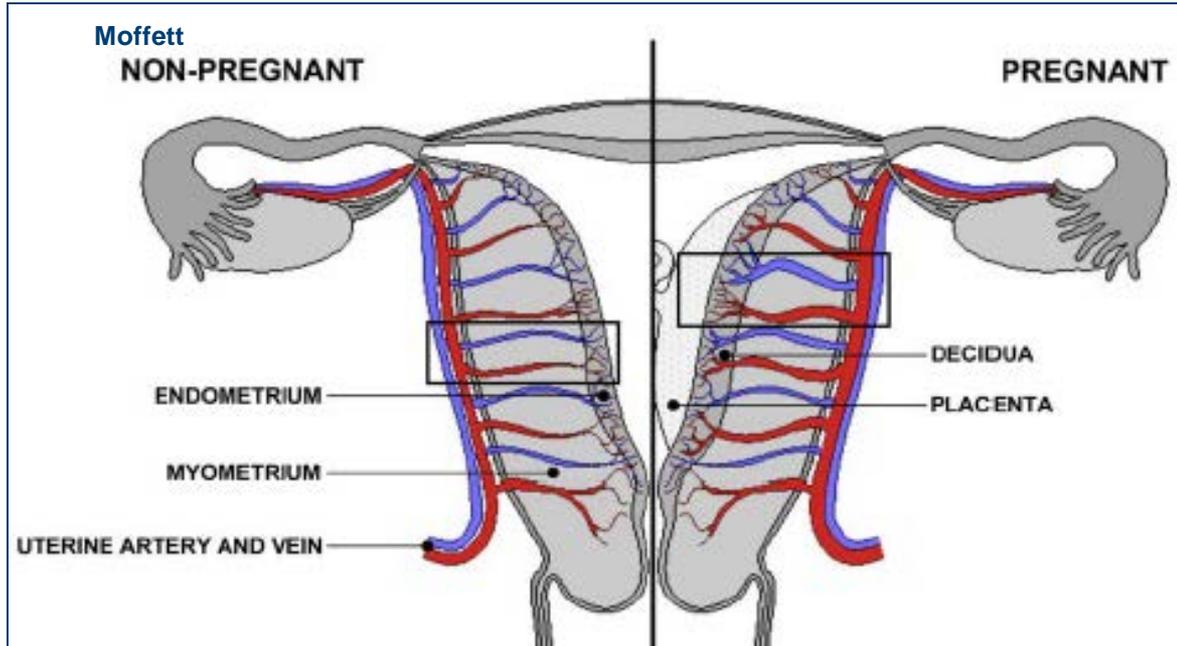
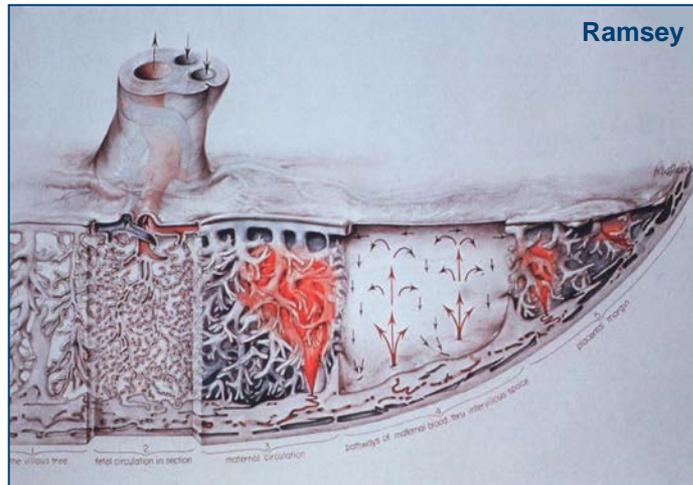
Secretions from the endometrial glands support the conceptus during the first trimester



- Endometrium is still 5-6 mm thick at 4 weeks p.c., with highly active glands that discharge into the placenta

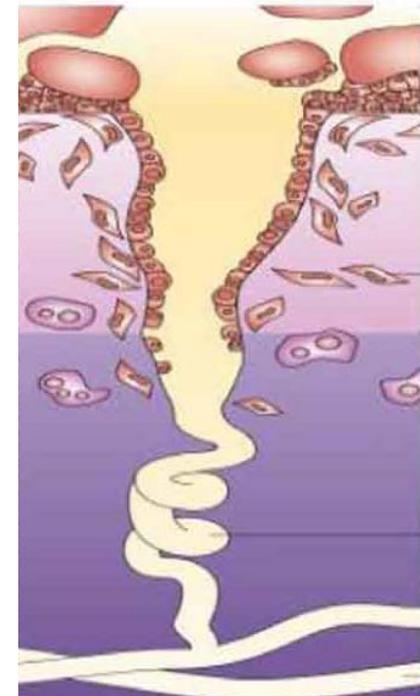
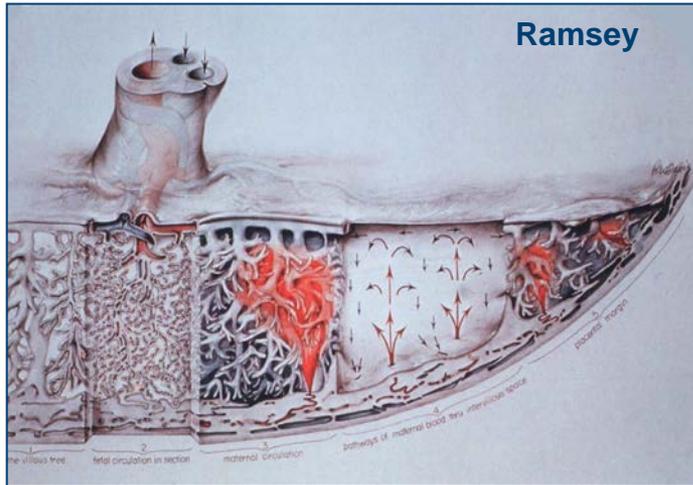
Maternal arterial blood supply to the placenta

Burton et al. 2009



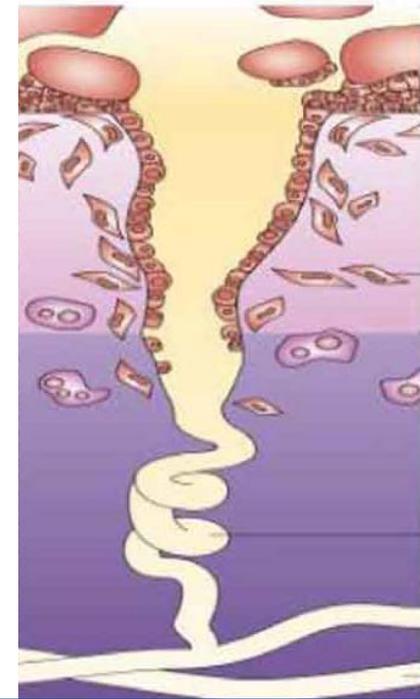
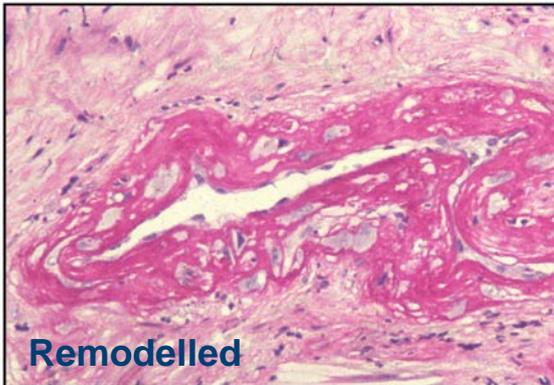
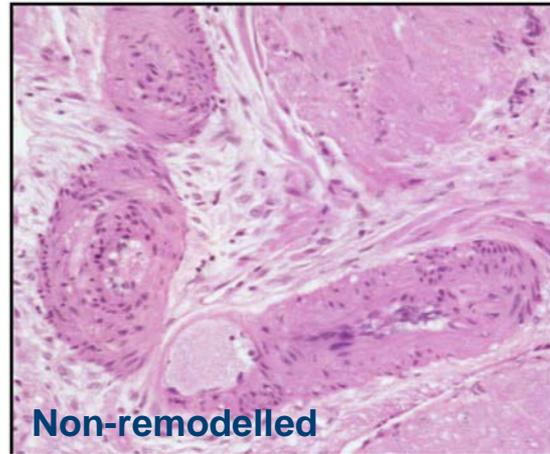
- As it invades, the placenta taps into the spiral arteries in the wall of the uterus
- This is potentially dangerous due to the high maternal blood pressure, and so the arteries undergo major remodelling

Deficient maternal spiral artery remodelling



- Remodelling of the spiral arteries during early pregnancy involves loss of the smooth muscle in their walls and dilation of the mouths

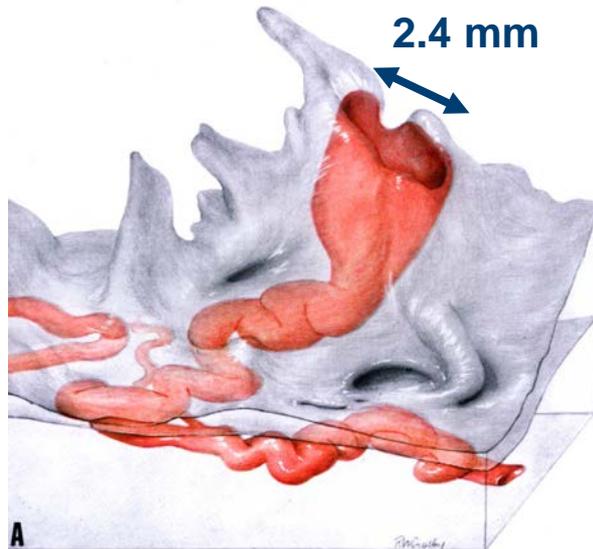
Deficient maternal spiral artery remodelling



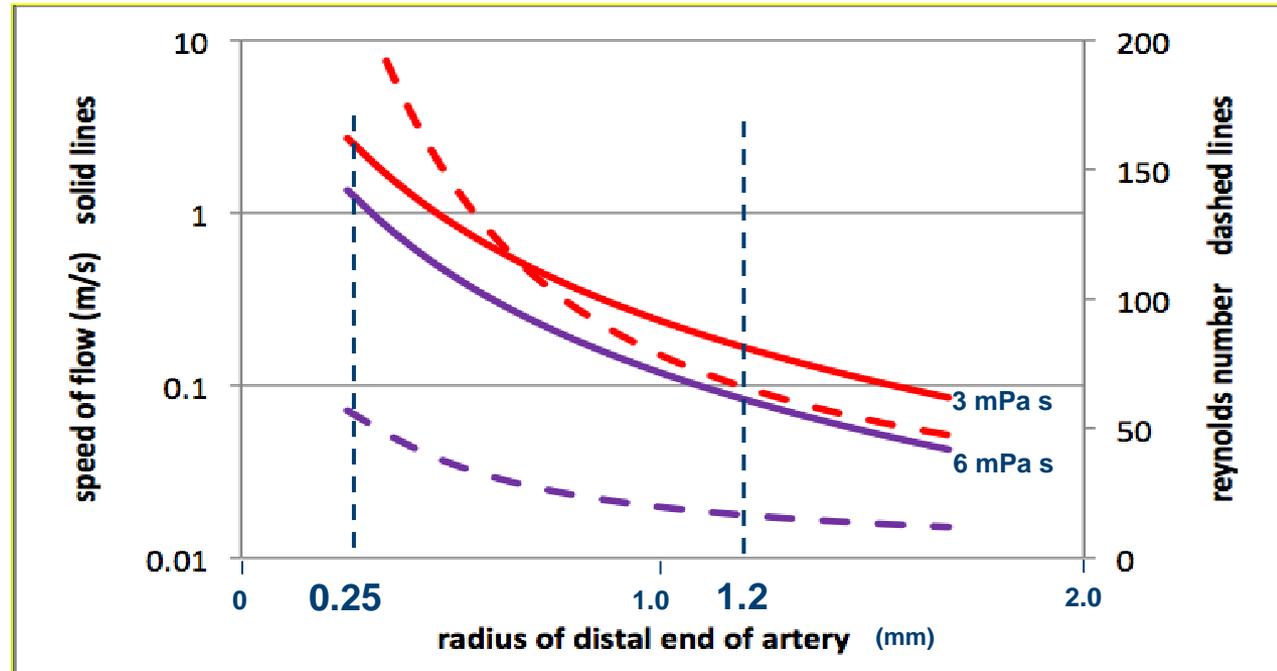
- Remodelling is dependent on endocrine priming and the presence of extravillous trophoblast cells, which release proteases and elastases

Haemodynamic consequences of conversion

Harris and Ramsey 1966



Burton et al. 2009

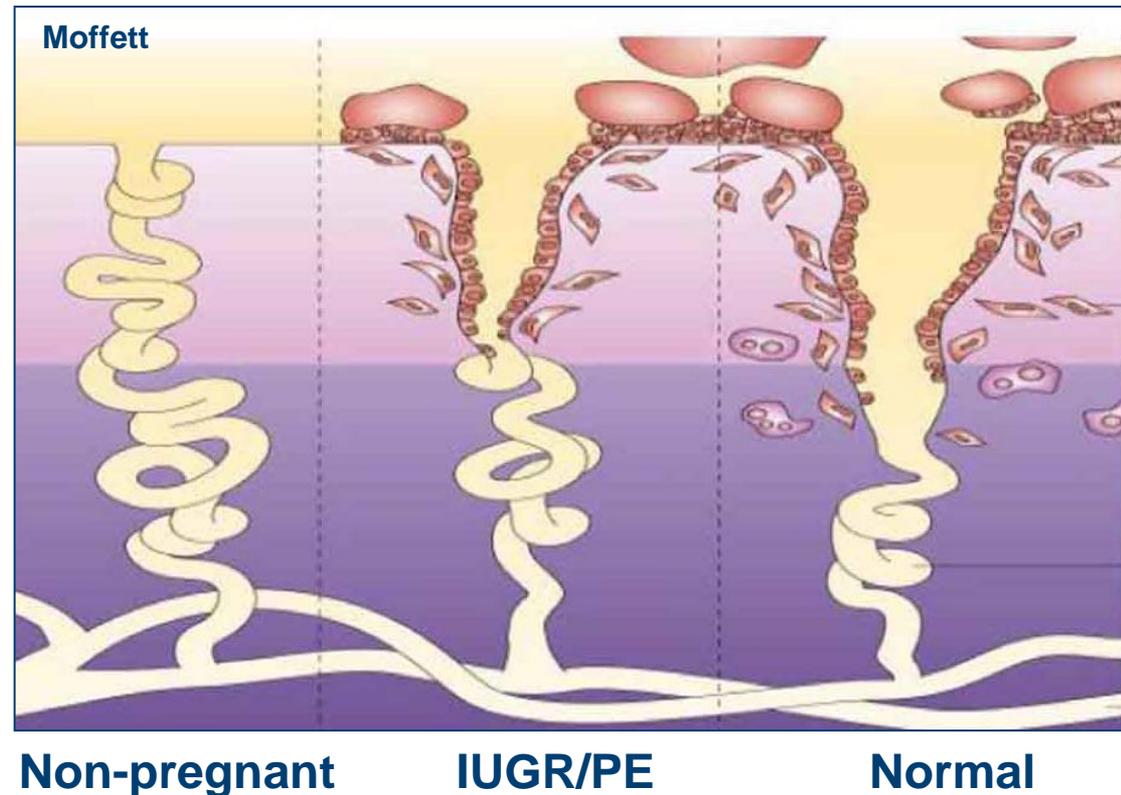


- Dilation of the mouth of the artery reduces the speed of flow by an order of magnitude, from 2-3 m/s to approximately 0.1 m/s
- The lower Reynolds number indicates less tendency for turbulent flow

Deficient maternal spiral artery remodelling

- Failure of remodelling is associated with growth restriction, pre-eclampsia, and premature delivery
- Reflected in the uterine arterial waveform
- High velocity or fluctuating maternal flow thought to cause placental oxidative stress

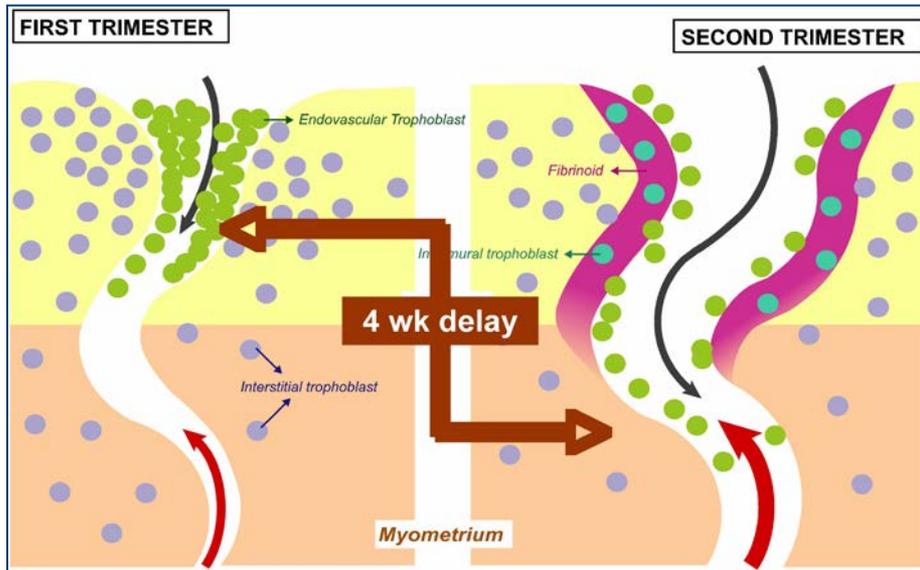
Why should remodelling be deficient in some cases?



Onset of the maternal arterial placental circulation starts at 10-12 weeks

Pijnenborg et al. 2006

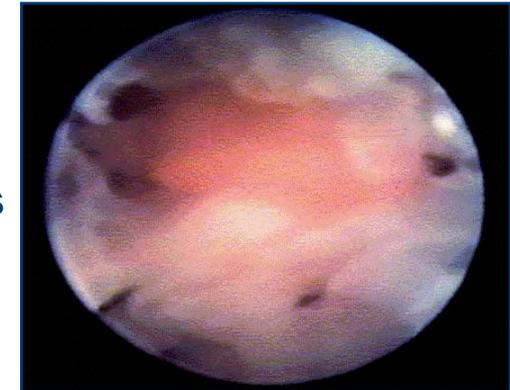
Hustin & Schaaps 1987



8 - 9 weeks



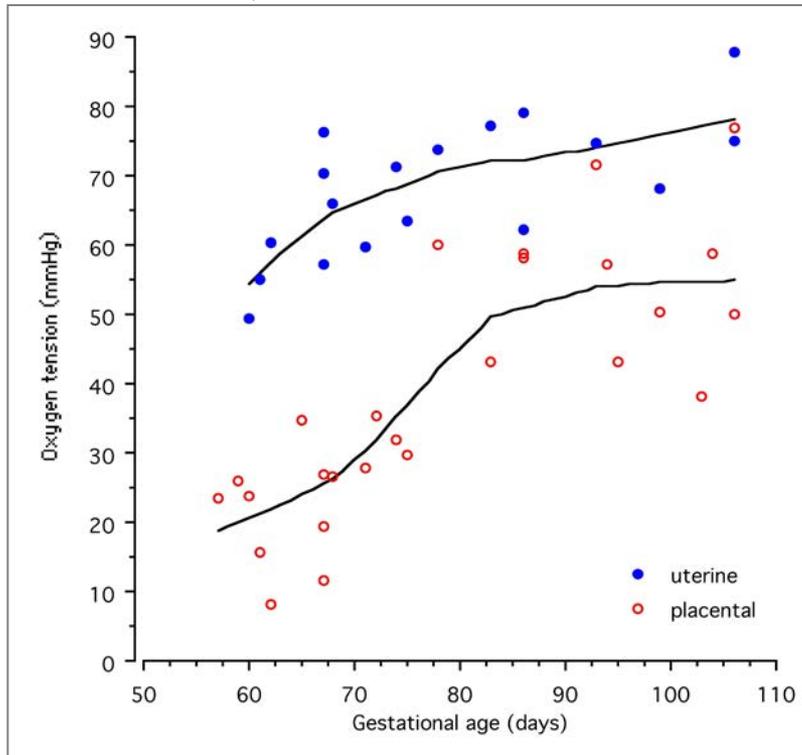
12 - 13 weeks



- During the first trimester the maternal spiral arteries are plugged by invading endovascular trophoblast, and the intervillous space is filled with a clear fluid

Oxygen and the first trimester environment

Jauniaux et al., 2000

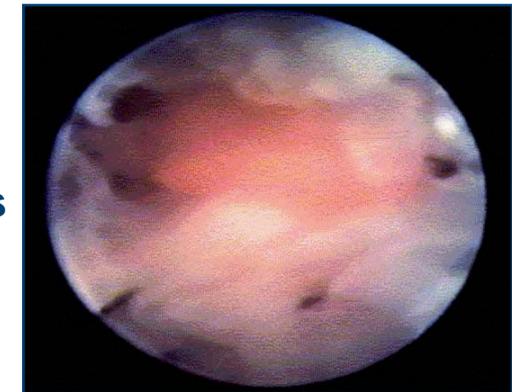


Hustin & Schaaps 1987

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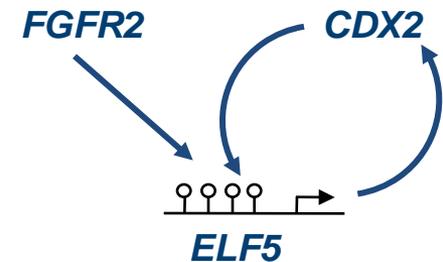
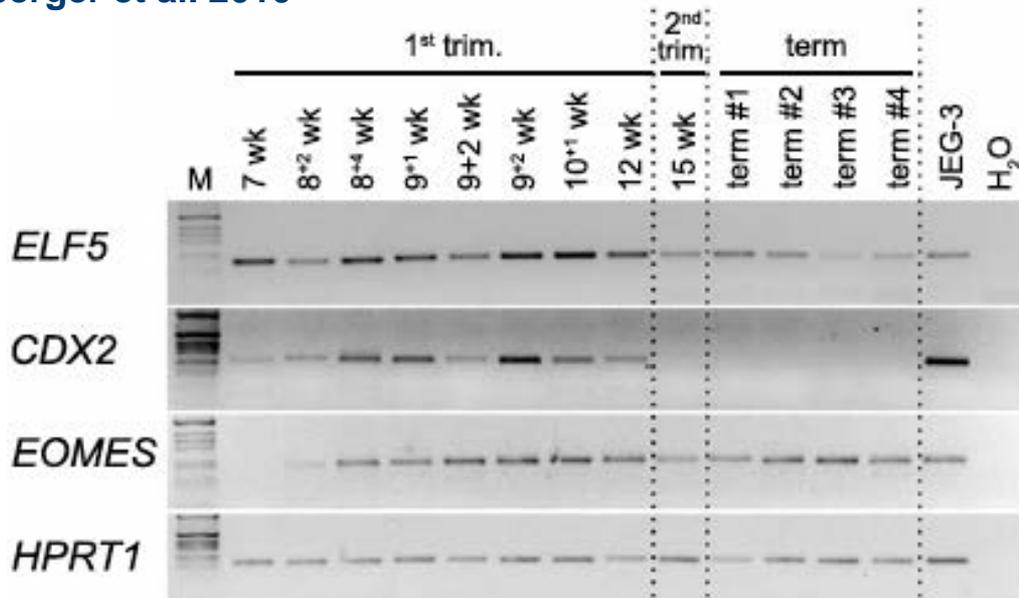
12 - 13 weeks



- The absence of a placental maternal arterial circulation means that the oxygen tension within the placenta is low during the first trimester

Markers of trophoblast proliferation decline at the end of the first trimester

Hemberger et al. 2010



***ELF5*, the gatekeeper of trophoblast lineage specification**

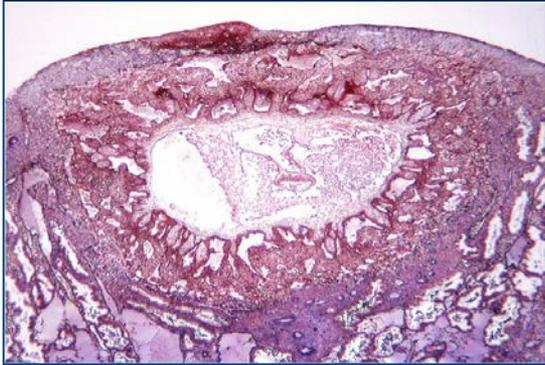
- There is a dramatic reduction in markers of trophoblast stemness, *ELF5* and *CDX2*, after the end of the first trimester
- This may reflect loss of growth factors from the glands and/or increased oxygen concentration

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Regression of villi and formation of the smooth membranes

3 weeks



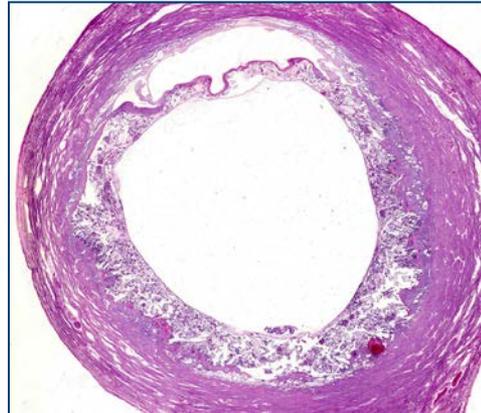
38 weeks



6 weeks



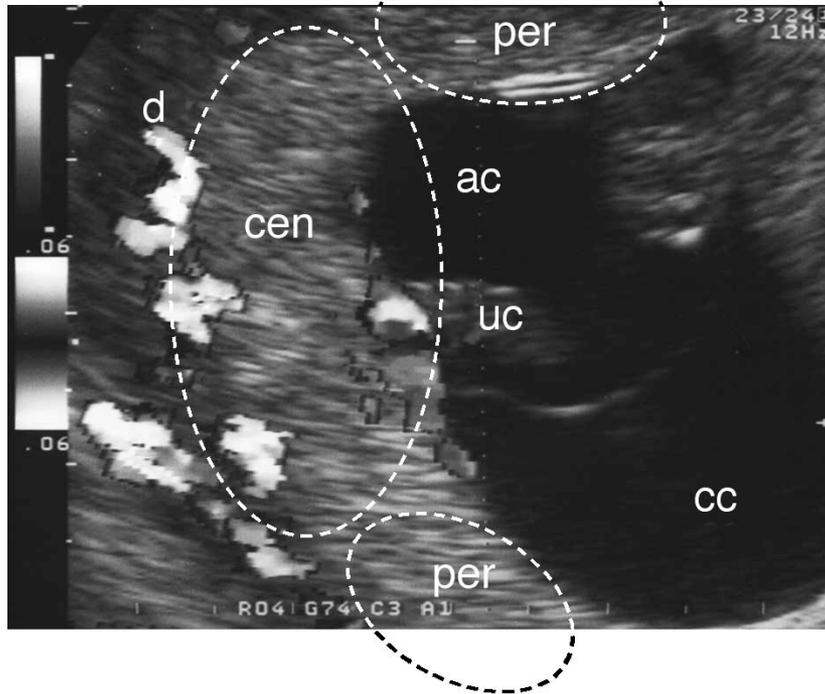
8.5 weeks



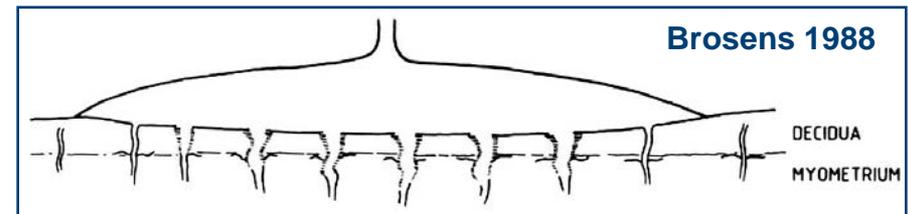
- Initially, villi form over the entire chorionic sac, but later regress over the superficial pole to leave the discoid placenta and the smooth membranes

Maternal arterial circulation starts in the periphery

Jauniaux et al., 2003



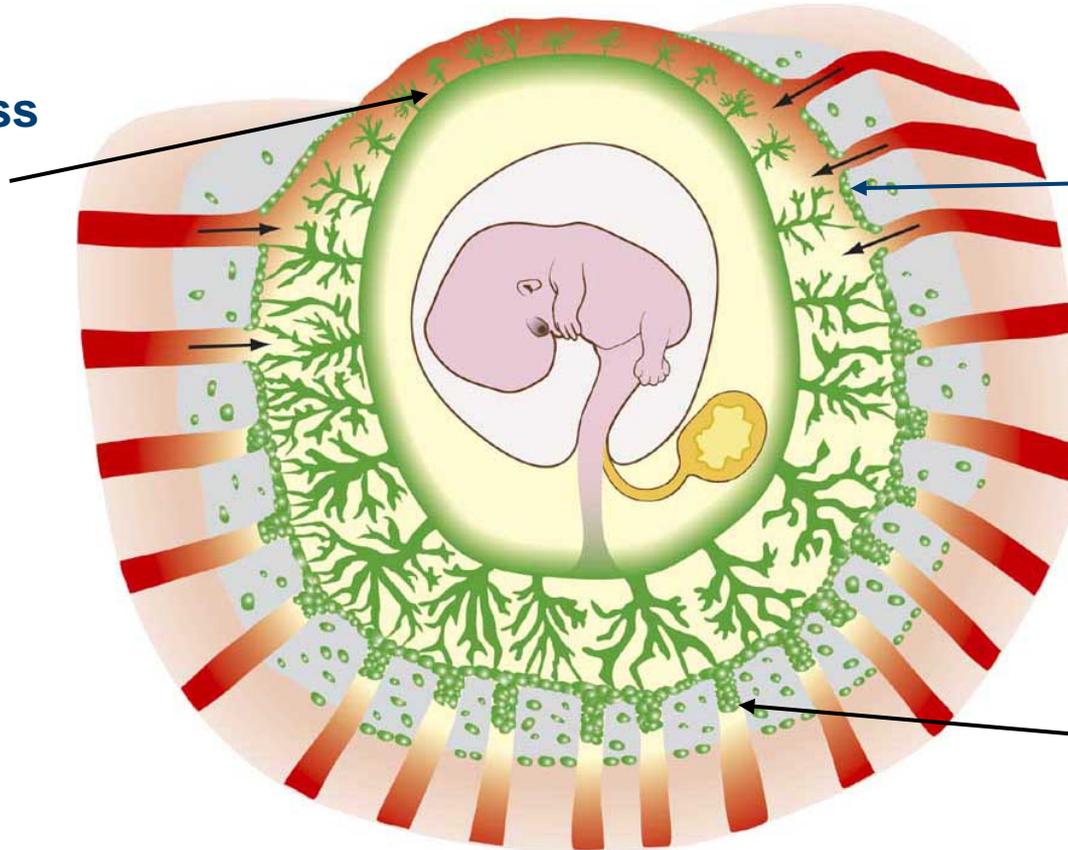
Gestational age (weeks)	Normal		
	C	P	C & P
8-9 (n=25)	1	5	3
10-11 (n=20)	2	7	3
12-13 (n=20)	3	7	8



- Onset of the maternal circulation starts in the periphery and extends to the centre of the placenta, reflecting the degree of trophoblast invasion across the implantation site

Summary

↑ Oxidative stress
↑ Apoptosis
↓ proliferation



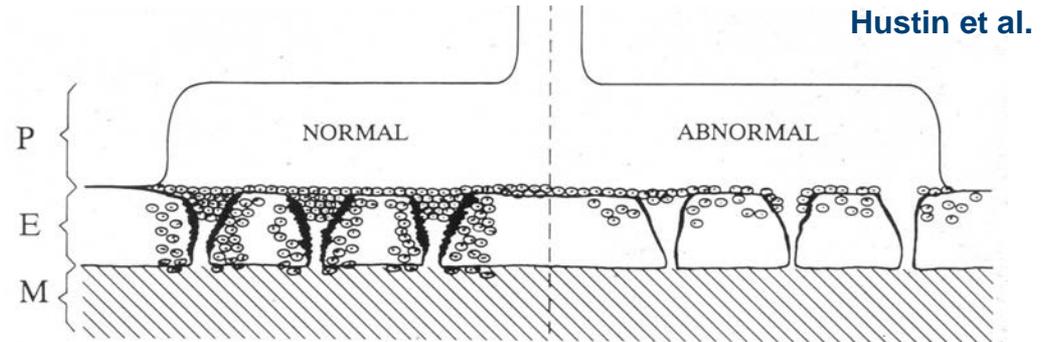
Plugs less extensive or absent

Arterial plugs

Jauniaux et al. 2004

- Elevated levels of oxidative stress in the peripheral regions of normal pregnancies leads to villous regression and formation of the chorion laeve

Abnormal onset of the maternal circulation in missed miscarriage



Gestational age (weeks)	Normal			Abnormal			χ^2
	C	P	C & P	C	P	C & P	
8-9 (n=25)	1	5	3	9	1	12	14.4*
10-11 (n=20)	2	7	3	4	2	14	10.0*
12-13 (n=20)	3	7	8	2	1	8	6.1*

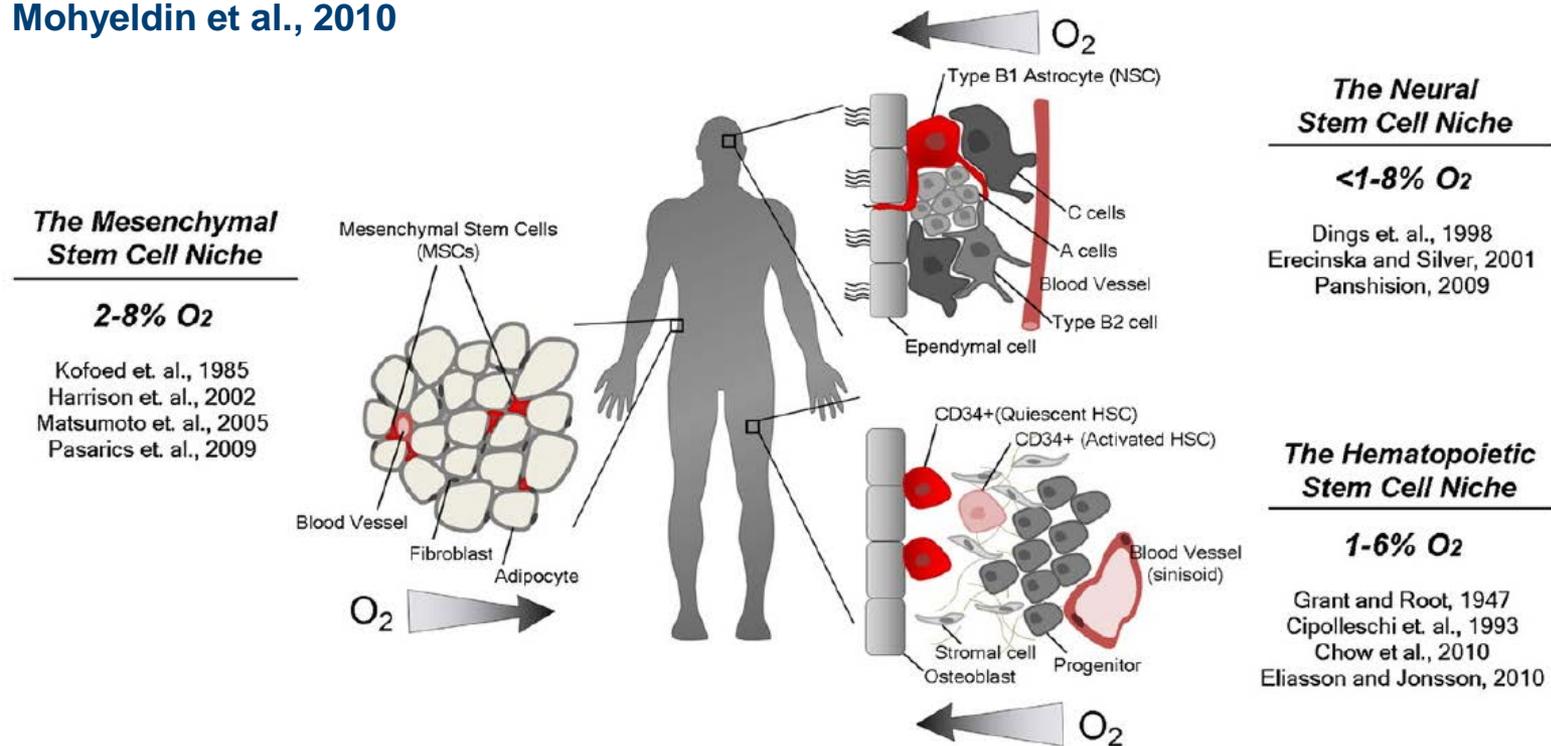
- Missed miscarriage is associated with early and disorganised onset of the maternal arterial circulation, even when karyotypically normal

Conclusions

- **The mature placenta presents a large surface area and thin membrane to facilitate diffusion**
- **During the first trimester the placenta develops in a low oxygen environment, stimulated by the endometrial glands**
- **Onset of the maternal circulation at the start of the second trimester is associated with formation of the discoid placenta and smooth membranes**
- **Remodelling of the maternal spiral arteries by placental cells is a key event in early pregnancy, and deficiency is associated with the 'Great Obstetric Syndromes'**

Oxygen and the maintenance of stem cells

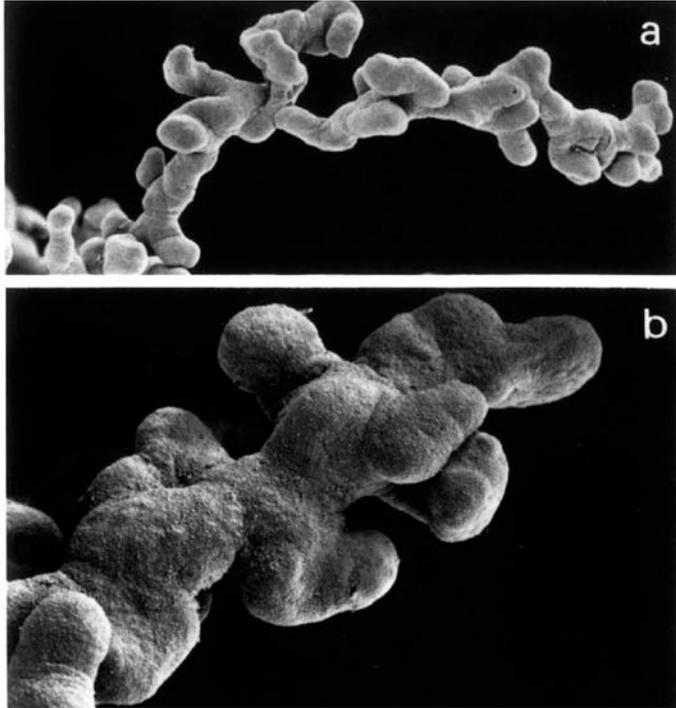
Mohyeldin et al., 2010



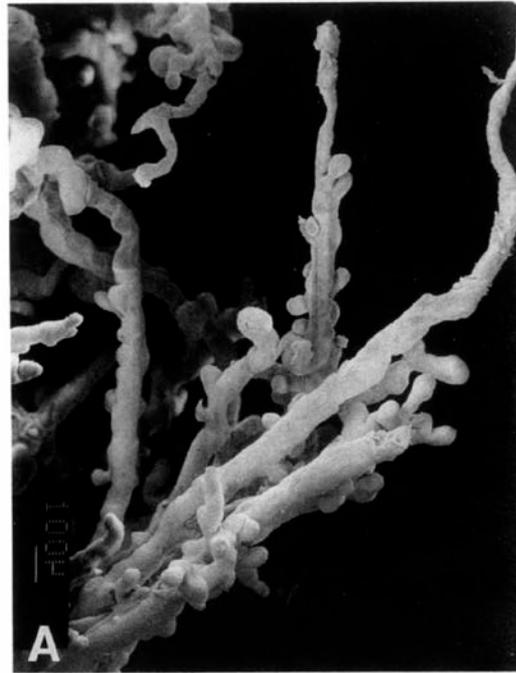
- Low oxygen concentration may favour placental and fetal stem cells, as many adult stem cells are found in low oxygen niches, with stemness maintained through HIF-dependent pathways

Abnormal villous growth in complicated pregnancies

Normal



IUGR



Kaufmann



- Impoverished formation of terminal villi is often associated with abnormal placental shape, and may be due to high velocity of maternal blood flow secondary to the deficient remodelling

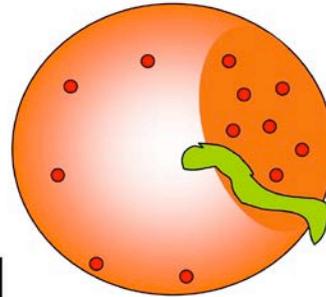
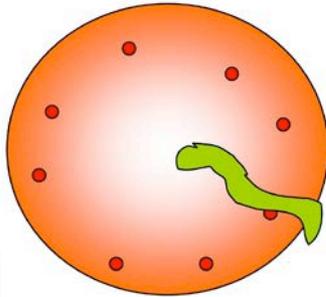
Abnormal villous regression in complicated pregnancies

Burton et al. 2010

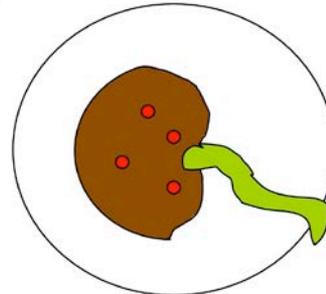
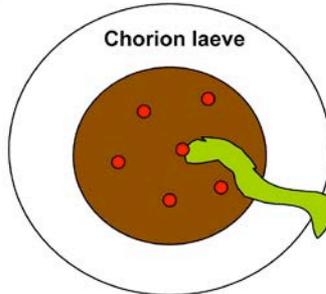
Periphery-centre
onset of flow

Regional aberration
in onset of flow

1st
trimester



term



normal

Abnormal shape with
eccentric cord insertion

- Unplugged spiral artery
- Oxidative stress

- Abnormal regional onset of the maternal circulation, due to locally reduced trophoblast invasion and arterial plugging, may lead to excessive regression
- This may result in small, abnormally shaped placentas with eccentric cord insertions