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

- 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

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

- **Trophectoderm**: Outer wall of the blastocyst
- **Cytotrophoblast**: Uninucleate progenitor population
  - **Villous**: Multinucleate, terminally differentiated
  - **Extravillous**: Invasive, remodelling of maternal arteries
    - **Interstitial**
    - **Endovascular**

**Mesoderm**
- Stromal core
- Endothelial cells
- Pericytes
- Smooth muscle cells
- Erythrocytes
- Macrophages

**Inner cell mass**
- Structural support
  - Fetal placental vasculature
  - Immune surveillance

**Fetal placental vasculature**
- Structural support
Summary of villus formation

1. trabeculum of STB

2. cytotrophoblast cells

3. mesoderm

Chorionic plate

Basal plate

Benirschke et al.
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
• Terminal villi are the principal sites of M-F exchange, and are elaborated primarily after 20 wks of gestation, continuing until term
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.
3. The maternal immune cells
   A mix of macrophages, T cells and Natural Killer cells.
   NK cells most numerous and accumulate prior to implantation.

4. The spiral arteries
   Highly muscular.
   Will supply the placenta but do not penetrate into superficial endometrium.
During implantation both endometrial capillaries and uterine glands are eroded

- 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.
Servomechanism in early pregnancy

- hCG and hPL from the placenta, and Prl from the decidua may stimulate gland activity
- Growth factors from the glands may stimulate proliferation of placental cells
Maternal arterial blood supply to the placenta

- 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.
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?
Deficient maternal spiral artery remodelling

- Invading EVT come into close contact with the Natural Killer (NK) cells of the maternal innate immune system.
- Recent genetic data indicate that certain combinations of fetal HLA-C haplotypes on the EVT and maternal KIR (Killer Immunoglobulin-like Receptor) on the NK cells predispose to complications of pregnancy, although mechanism still uncertain.
Onset of the maternal arterial placental circulation starts at 10-12 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
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

• 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

- 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

- 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

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<tr>
<th>Gestational age (weeks)</th>
<th>Normal</th>
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<td>8-9 (n=25)</td>
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<td>10-11 (n=20)</td>
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<td>12-13 (n=20)</td>
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Elevated levels of oxidative stress in the peripheral regions of normal pregnancies leads to villous regression and formation of the chorion laeve.
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’
• 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

- 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

- 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

Burton et al. 2010

Unplugged spiral artery
Oxidative stress