

# Reproduction – fetal development, placenta and maternal physiology

Rudolf Cardinal, 22/24 Nov 1998

## Implantation and the decidual response

- Implantation in humans and some other species is **invasive** – the uterine surface epithelium is breached and the underlying stroma is invaded. (In yet other species, the epithelium remains intact with the fetal and maternal epithelia in close contact.)
- The blastocyst makes a signal (unknown) which induces a stromal response called **decidualization**. The stroma increases its vascular permeability, becomes oedematous, the matrix and stroma change composition and morphology and new capillaries grow. This prepares the major endometrial contribution to the placenta – the *decidua*.
- The decidual response depends on a uterus that has been exposed to progesterone (to synthesize secretory products) and also oestrogen (to stimulate the actual secretion of those products, and to make the uterine epithelium responsive to the blastocyst's signal).<sup>1</sup>
- Remember that the blastocyst also makes **hCG** to maintain the corpus luteum.

## Placental layers; haemotrophic support

- Following implantation, the surface epithelium under the conceptus is eroded. **Trophectodermal** processes invade this layer. Some fuse to form a syncytium (**syncytiotrophoblast**) while others remain cellular (**cytotrophoblast**), serving as a stem cell population for the syncytiotrophoblast.
- The uterine glandular tissue and the decidua adjacent to the trophoblast is destroyed, releasing large quantities of nutrients that are absorbed by the trophoblast and passed to the developing circulatory system to feed the embryo.
- The maternal blood in the human placenta comes from the *spiral arteries* and is drained by placental veins, but is not in blood vessels when it is in contact with the fetal tissue. The maternal capillaries are eroded to create **lakes of blood** which the trophoblast is in contact with.
- The placenta is composed of contributions from the conceptus and the endometrium.
- Human invasion is said to be *interstitial*, meaning that the conceptus invades so deeply that the surface epithelium is restored over it. The placenta is *discoid* in shape. The maternal *blood* is directly in contact with the conceptus and there is a *single layer* of chorionic trophoblast, making the human placenta *haemomonochorial*. (The path from fetal to maternal blood at its shortest is: fetal blood – capillary endothelium – capillary basement membrane – basement membrane of trophoblast – syncytiotrophoblast – maternal blood space.)
- See figures 9.7 and 9.8 of *Essential Reproduction – early development and structure of fetus/placenta*.
- **Haemotrophic support** allows much more efficient delivery of nutrients and removal of waste products and histiotrophic support. Exchange depends on *diffusion gradients*, *blood flow*, *diffusional barriers* and *special transport mechanisms*.
- Fetal and maternal blood is slowed on both sides of the placenta (having spiral arteries which dilate at the ends are two ways of slowing flow). This gives plenty of time for exchange of metabolites and may prevent the conceptus being dislodged by pulsatile flow in early pregnancy. Spiral arteries constrict in response to sympathetic stimulation – transient reductions in perfusion pressure are tolerated, but chronic reductions (esp. late in pregnancy) may lead to low birth weight.

## Hormones in pregnancy

- **Human chorionic gonadotrophin (hCG)**. Made by the conceptus within 2 weeks of fertilization. Maintains corpus luteum (immunising against hCG prevents pregnancy). Also stimulates fetal testis to make androgens. Most is made by the syncytiotrophoblast; some from the cytotrophoblast.
- **LH**. Pituitary LH supports the corpus luteum in (very) early pregnancy. Recall that hCG is structurally like LH – hCG supplements the low LH levels.
- **Transfer of endocrine support**. The corpus luteum remains active for the whole of pregnancy, but is not required after 4–5 weeks, because by this time the conceptus is also synthesizing all the steroidal hormones required for pregnancy. After 8 weeks, hCG levels fall – it is no longer needed.
- **Oestrogens**.
  - ❖ The primary oestrogen in pregnancy is oestriol (less potent than oestradiol 17 $\beta$ ).
  - ❖ The placenta makes progesterone; the fetal adrenal converts this to androgens (notably DHA); the placenta aromatizes these to oestrogens. The “feto-placental unit”.
  - ❖ (1) Priming agents – for example, induce progesterone receptors. (2) Assist in causing the growth of breasts and uterus. (3) Behavioural effects. (4) Feedback on hypothalamus. (5) Increase uterine blood flow.
- **Progesterone**.
  - ❖ The trophoblast makes progesterone, and is autonomous.
  - ❖ Acts together with oestrogens.
  - ❖ (1) Endometrial and myometrial growth. (2) Growth of mammary gland, though it prevents secretion. (3) Smooth muscle inhibitor – myometrium, vascular SM, GI SM. Inhibition of uterine contraction is obviously important in maintaining pregnancy! (4) Behavioural effects. (5) Negative feedback. (6) Stimulates respiratory centre.
- **Prolactin**. Pituitary prolactin stimulates breast development and inhibits ovulation. Release is stimulated by oestrogens.
- **Human placental lactogen (hPL; PLACENTAL)**. “Hijacks metabolism,” see “Nutrients” below. Weak effect on breast development. It has both GH and prolactin-like properties.

<sup>1</sup> In the rat, suckling young of a previous litter suppresses oestrogen secretion. In the absence of oestrogen, the blastocyst “hangs around” in the uterus and may stay there for many days. When oestrogen rises, implantation occurs. This is called *delayed implantation* and is probably useful for the rat – it delays the growth of the uterine litter until the previous litter have finished suckling (so they don't compete for milk). This is *facultative* delayed implantation – in other species, *obligatory* delayed implantation or *diapause* occurs – for example, some deer mate in summer and leave the conceptus as a blastocyst until January when it reactivates for delivery in May.

### *Fetal growth – snippets*

- Fetal growth is slow up to week ~20, accelerates to reach a peak at weeks 30–36 and then slows again. (There is also a postnatal growth peak at week 8).
- Growth is primarily determined by the fetal genome; IGFs are an important mediator. Fetal thyroid hormones stimulate growth in late pregnancy. The fetus makes GH but it is not effective in stimulating fetal growth.
- Maternal factors are clearly significant [crossbreeding horses...]. Nutrition, health, parity (first babies are smaller), smoking...
- Amniotic fluid volume increases until week 34, then declines.
- Placental size increases steadily (although the fetus grows faster, so the placental:fetal weight ratio falls).
- Red cell production shifts site (yolk sac → liver → marrow).
- Fetal HR = 120–140 bpm. Mean BP 40–50 mm Hg (66/35).
- See also next time...
- **Read about fetal development in more detail.**

### *Other changes in maternal physiology...*

- Maternal **cardiac output** ↑25–40% in pregnancy in response to the reduced peripheral load (HR 70→85 bpm, SV 60→70 ml).<sup>2</sup> **N.B. Placenta is a low-resistance shunt.**
- There is only a small increase in BP. Pathological increases occur in *pre-eclampsia*, a leading cause of maternal death.
- Oestrogens → increased transcortin<sup>3</sup> output from the liver. This results in increased blood levels of progesterone and cortisol. Remember that total levels ≠ active form!
- Progesterone → aldosterone (↑10×). In addition, oestrogens → angiotensinogen → aldosterone. Therefore **Na<sup>+</sup> and water retention**. Blood volume increases by up to 50% near term (20–30% increase in erythrocytes and 30–60% increase in plasma volume). GFR increases.
- Pulmonary ventilation ↑40% because progesterone stimulates ventilation. Despite the extra CO<sub>2</sub> from the fetus (see below), the increase in respiration causes a 25% decrease in maternal pCO<sub>2</sub> (with a corresponding fall in [bicarbonate] and a slight increase in pH). Respiration also affected by presence of the bulky uterus – which can also compress the IVC if the woman lies on her back.
- Renal tubular maximum for glucose decreases (high incidence of glycosuria) – plus diabetogenic influence of fetus (below).
- Pituitary size increases 30–50% (it's making prolactin; also ACTH and MSH<sup>4</sup>).<sup>5</sup>

/ PTO →

---

<sup>2</sup> A cardiac “flow murmur” is normally heard in >80% of healthy pregnant women, due to the increased blood flow.

<sup>3</sup> = corticosteroid-binding globulin (CBG)

<sup>4</sup> Permanent darkening of areolae and genital skin.

<sup>5</sup> Sheehan's syndrome: pituitary has a portal circulation, so vulnerable to hypoxia. Parturition → bleeding → shock → pituitary necrosis = Sheehan's.

## Placental function

**The placenta is a barrier between maternal and fetal circulations.**

Simple diffusional exchange occurs for *small* or *non-polar* molecules. This requires a *diffusion gradient*.

Other substances require *active transport*.

Exchange of a substance can be limited by *flow* (if diffusion occurs rapidly) or by *diffusion*.

### Fetal circulation

- **You must know this** and have covered it already. Oxygenated blood from the placenta arrives in the umbilical vein → ductus venosus → RA → foramen ovale → LA → LV → aorta → body and umbilical artery. Also RV → ductus arteriosus → aorta, again bypassing the lungs.

### Gas exchange

- Fetal oxygen stores are small (2 minutes' worth). Fetal consumption is high. O<sub>2</sub> diffuses readily across the placenta.
- Carbon dioxide diffuses even more readily (diffusion constant 20× that of O<sub>2</sub>).

	Maternal blood		Fetal blood		
	Arterial	Venous	Umbilical artery	Umbilical vein	
1	Oxygen tension (pO <sub>2</sub> ) (mmHg)	90	35	15	30
2	% O <sub>2</sub> saturation	95	70	25	65
3	Oxygen content (vol. %)	14	10	5	13
4	CO <sub>2</sub> tension (pCO <sub>2</sub> ) (mmHg)	30	35	53	40
5	pH	7.43	7.40	7.26	7.35

### Gas laws to remember

**Diffusion in tissue is proportional to the difference in gas partial pressure (tension).** This is Fick's law.

The partial pressure of a gas in a gas mixture is the total dry gas pressure multiplied by the fractional concentration of that gas (Dalton's law). For example, dry air is 20.93% O<sub>2</sub>. Air pressure at sea level is 760 mmHg, so the pO<sub>2</sub> is 159 mmHg.

The partial pressure of a gas in solution is its partial pressure in a gas mixture which is in equilibrium with the solution. We've just seen that diffusion depends on a difference in partial pressure, so a gas and solution in equilibrium must have the same partial pressure.

**The amount (concentration) of a gas in solution is its partial pressure multiplied by its solubility** (Henry's law).

- There is obviously a diffusion gradient for O<sub>2</sub> and CO<sub>2</sub> (90→15 and 53→30 mmHg respectively). Gradients vary with species. Large gradients caused by (1) placental O<sub>2</sub> consumption; (2) long diffusion path; (3) pattern of blood flow [concurrent flow → MV=FV; countercurrent flow → MA=FV]. Humans and other haemochorial mammals have small gradients.
- Though the pO<sub>2</sub> of fetal blood leaving the placenta is low, its oxygen content is not much less than that of maternal arterial blood. The fetal blood has **higher oxygen affinity**.<sup>6</sup>
- Why? Embryonic and fetal erythrocytes make different forms of haemoglobin, that have higher oxygen affinity than adult haemoglobin. Also, the fetus makes less 2,3-DPG and the embryonic/fetal Hb has fewer binding sites for it; recall that 2,3-DPG reduces O<sub>2</sub> binding.
- The **double Bohr effect** (see fig 11.2 of *Ess. Repro.*). The fall in pH of maternal blood as it passes through the placenta causes release of O<sub>2</sub>; the rise in pH of the fetal blood increases uptake of O<sub>2</sub>.
- As long as the blood supply is normal, perfusion (flow) is not the limiting factor; therefore the **rate of O<sub>2</sub> transfer** across the placenta varies simply with the pO<sub>2</sub> of umbilical blood – *the level of fetal oxygenation is regulated by the fetal requirement for oxygen*.
- **CO<sub>2</sub>**: there is a **double Haldane effect** (deoxygenated blood carries more CO<sub>2</sub>...).

### Water, electrolytes, nutrients

- **Water** exchange occurs at the placenta and at the non-placental chorion (where it touches the amnion). The placenta is probably the main route, but the amnion/chorion are permeable to water. Exchange is by simple diffusion. Since the placenta is very permeable to water, small osmotic pressure gradients could move large quantities of water. However, a hydrostatic pressure difference is more likely to be responsible for large water movement (maternal blood is at a higher pressure). This pressure difference is not large (or it would either collapse fetal vessels or dehydrate the fetus respectively).

<sup>6</sup> The *oxygen content* of the blood perfusing fetal tissues is therefore higher – this is *not* the same as the *rate* of O<sub>2</sub> transfer to the fetus! Note also that the fetal cardiac output per kg is ~4× the adult, so despite a relatively low pO<sub>2</sub> and %saturation, oxygen *delivery* to the tissues is good.

- **Sodium.** Fetus pumps  $\text{Na}^+$  out into the mother, making the fetus electronegative. It may use this to regulate fluid volume, but this also generates a gradient to drive other exchanges. **Potassium:** simple diffusion down electrochemical gradient. **Chloride:** active transport? **Iodide:** actively trapped.
- **Bilirubin.** Unconjugated and crosses by diffusion for the mother to excrete. (The fetus has no other way to get rid of it. The gut and urinary tract open into amniotic fluid, which the fetus drinks – indeed, fetal urination helps to maintain amniotic fluid volume. When the fetus is born, it must get rid of this toxic substance so it needs to start conjugating it, see next handout.)
- The fetus uses **carbohydrate** as its predominant energy source. Half its energy comes from glucose; the remainder is from amino acids and from lactate (formed from glucose in the placenta). It also needs material for anabolism – amino acids, fatty acids, vitamins, minerals.
- Metabolic rate: fetus 9 ml  $\text{O}_2/\text{kg}/\text{min}$ ; placenta 32 ml/kg/min!
- The fetus takes **glucose** from maternal blood. Early in pregnancy, progesterone stimulates appetites (→stores). **hPL switches maternal metabolism** via its GH-like actions: it mobilizes fatty acids stores for the mother to use, and renders maternal tissues *less sensitive to insulin*. This causes a rise in maternal glucose, which the fetus can capture. It is also a diabetogenic influence on the mother.<sup>7</sup> **Glucose transport is by facilitated diffusion.** So the fetal [glucose] is directly related to the maternal [glucose] – fetal mechanisms for regulating [glucose] are immature, though the *rate of utilization* of glucose by growing tissues is controlled by fetal insulin.<sup>8</sup> Storage occurs as hepatic glycogen and as fat (see also next week).
- **Lactate** makes up >25% of fetal fuel – the placenta makes it from glucose. This conversion maintains the glucose gradient.
- Maternal metabolism of **amino acids** becomes more efficient – the mother does not need to eat more protein, and non-pregnant females absorb >95% of dietary protein, but urea excretion falls so the AA are being used more efficiently. The effect is due to progesterone (reduced maternal hepatic AA deamination) and this provides the source for the fetus. There is **active transport** of amino acids into the fetus. Fetal urea diffuses passively back into the mother. 40% of amino acids are deaminated and used as fuel.
- **Iron** is actively transported across the placenta (a membrane iron transport protein). There is a net need of 550 mg in pregnancy (300 mg fetus, 50 mg placenta, 200 mg postpartum blood loss). Maternal intestinal absorption is enhanced. **Folic acids** (folate) and **vitamin B12** are provided for the fetus at the expense of the mother.<sup>9</sup> **Calcium** is also transported actively; there is a considerable demand for this (bone formation!); maternal  $\uparrow\text{PTH}$  (also as GFR increased, there's more urinary loss to be replaced) and maternal absorption becomes more efficient.
- Water-soluble vitamins are transported; fat-soluble vitamins (A,D,E,K) cross. But babies tend to be vit. K-deficient.

### The placenta as a barrier

- **Hormones** – peptides too large/polar. Catecholamines too polar. A bit of thyroxine in humans. Steroids mostly metabolised (sulphation/oxidation).
- **Steroids – conjugation.** The fetus sulphates steroids (in the liver/adrenals); the placenta desulphates. (Remember that sulphation is a form of conjugation.) Conjugated steroids are more water-soluble and less biologically active. This enables the fetus to be protected from high levels of steroids (e.g. high levels of weak androgens would masculinize a fetus) and still have the placenta make high levels for the maternal circulation to maintain pregnancy.
- **Immunological.** The fetus is antigenic and the mother can – and does – mount an immune response. (Indeed, a maternal immune reaction against paternal histocompatibility antigens may be *important* for pregnancy.<sup>10</sup>) However, the *quality* of the immune response may differ. In addition, the **trophoblast layer is antigenically 'neutral'**, perhaps because the syncytiotrophoblast lacks histocompatibility molecules, perhaps because it coats them somehow or perhaps because progesterone/corticosteroids/hCG are *local immunosuppressants*.
- Maternal **IgG can cross the placenta**, conferring passive immunity (see also next week). IgM is too large to cross. Immune cells are excluded.
- Why does the IgG not cause problems? Well, it does for Rhesus antigen. If the mother is Rh– and the fetus is Rh+, an IgG response is mounted, particularly at birth (fetal→maternal bleeding). Subsequent Rh+ pregnancies experience Rhesus haemolytic disease due to the IgG. But why not other antigens? Rh is only present on erythrocytes, but other antigens are present in solution (blood, amniotic fluid). Free antigen may 'mop up' any incoming IgG, leaving little left to cause significant problems.
- **Pathogens.** Some can cross and cause disease (including the TORCH diseases: Toxoplasma, Rubella, cytomegalovirus, hepatitis/HIV).
- **Drugs, toxins.**

<sup>7</sup> An example of maternal/fetal competition. See Ness & Williams (1994), *Evolution and Healing*. Benefits given to the fetus by the mother help only half her genes, so her optimum donation to the fetus is lower than the amount that is optimal for the fetus. She is also vulnerable to injury/death from the birth of a large baby. Most mothers can make enough insulin to counteract flooding with hPL. But gestational diabetes is a risk – and that's a risk to the fetus, which would do best to reduce hPL secretion in this case – but the fetus must play the odds.

<sup>8</sup> Therefore diabetic mother → high maternal glucose → high fetal glucose → high fetal insulin → big baby.

<sup>9</sup> Folate supplements in early pregnancy also reduce the risk of neural tube defects (e.g. spina bifida).

<sup>10</sup> If this is the case, what is the obvious benefit? What would the absence of such a reaction imply?