

First trimester embryonic nutrition

Graham J Burton

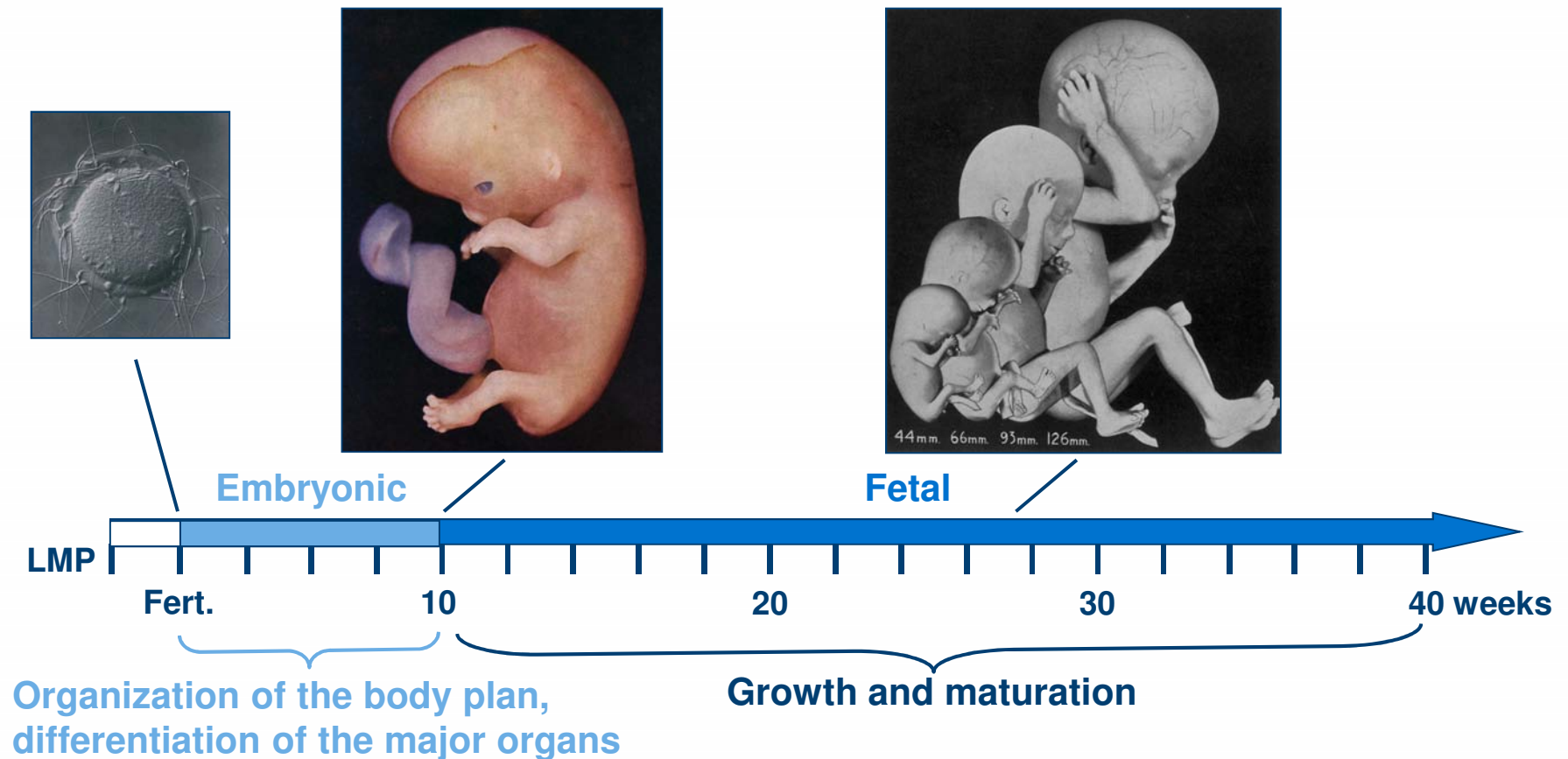
Centre for Trophoblast Research

Department of Physiology, Development and Neuroscience

Aims

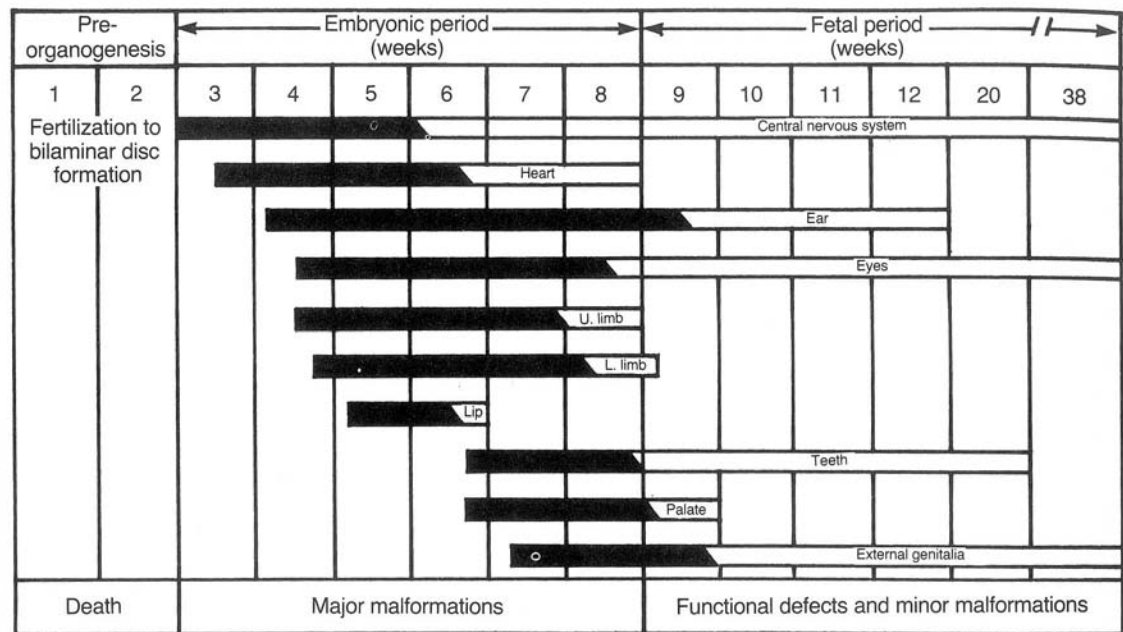
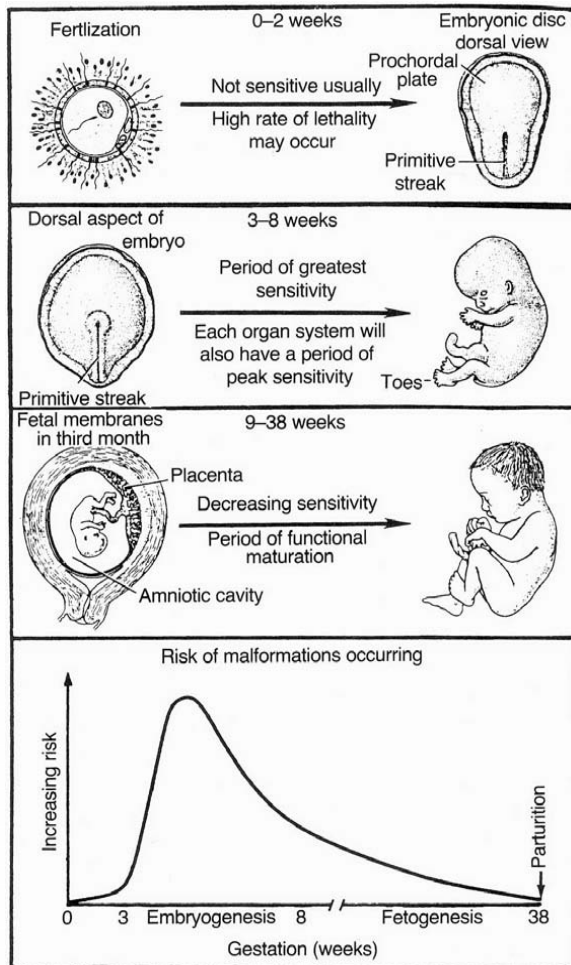
- To demonstrate that during the embryonic phase of development the human conceptus is supported by histiotrophic nutrition from the endometrial glands
- To present evidence that the yolk sac is important for the uptake of nutrients during embryogenesis
- To propose that the histiotrophic form of nutrition may protect the embryo from oxygen free radical mediated teratogenesis

Human pregnancy is traditionally separated in to the embryonic and fetal periods



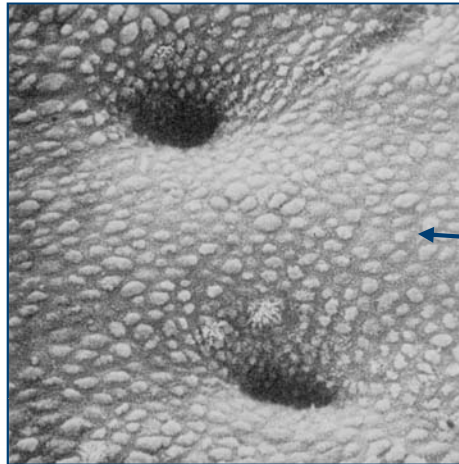
The teratogenic risk is greatest during the embryonic phase of development

Sadler

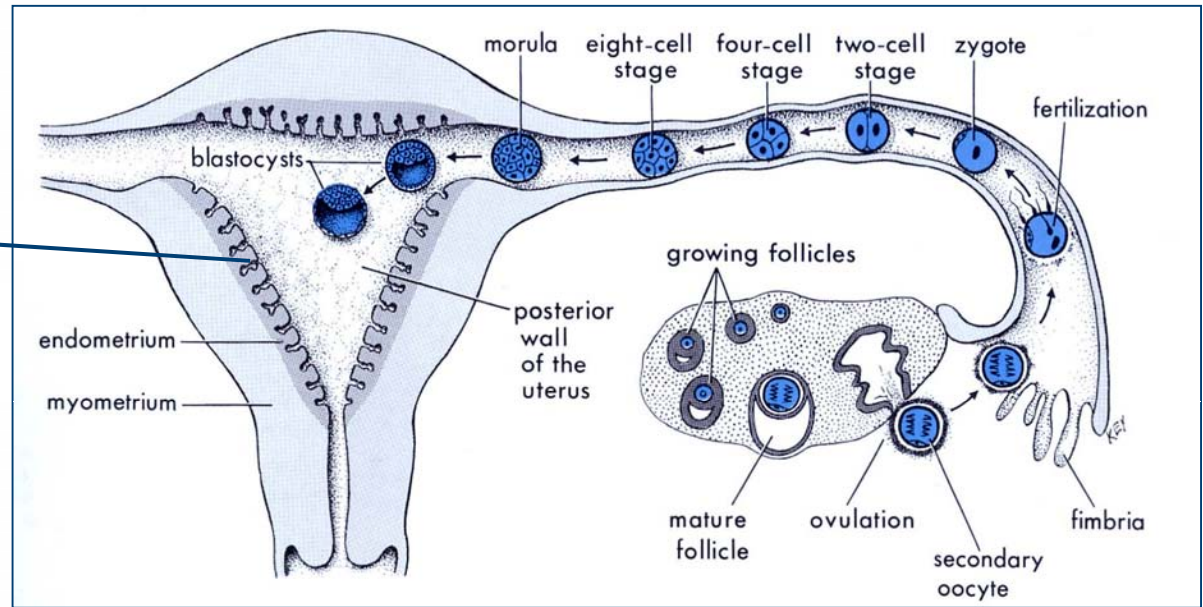


- Each organ system has a critical period depending on the timing of differentiation
- It is critical that the intrauterine environment is stable during the period of embryogenesis

The two sequential modes of nutrition for the conceptus

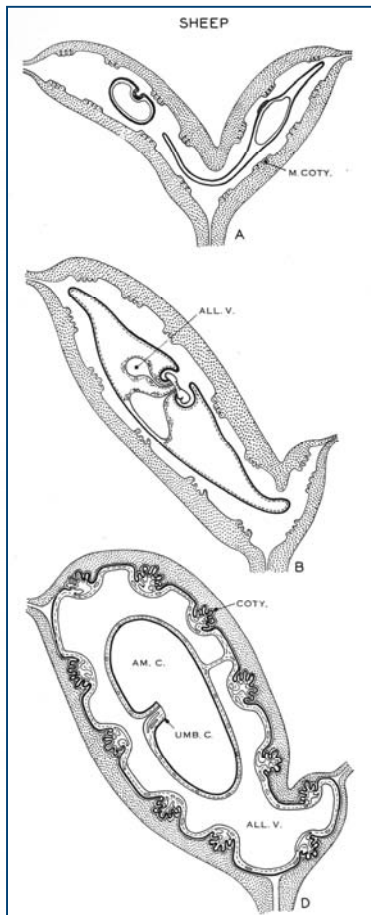


The human uterus has approximately 15 endometrial glands per mm²

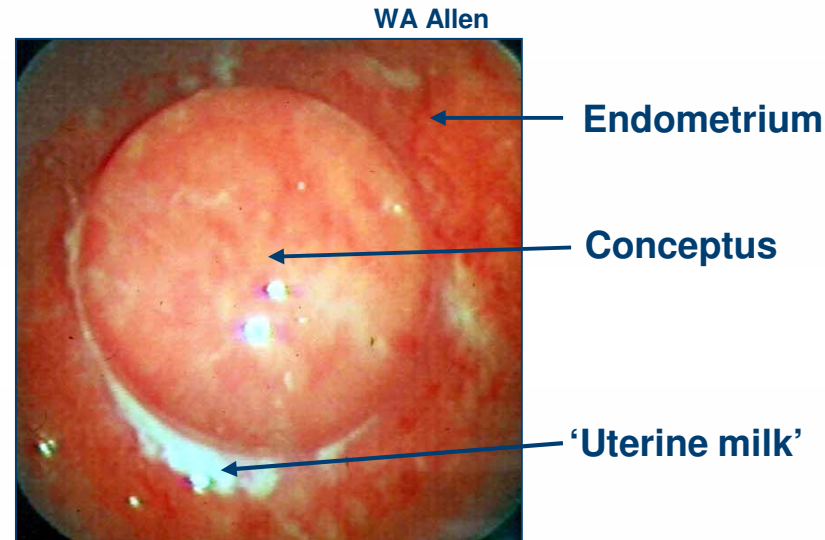


- Nutrition of the conceptus is initially histiotrophic in all species - the uptake of oviductal and uterine secretions by the trophoblast
- Later, in all mammals it switches to haemotrophic nutrition - exchange between the maternal and fetal circulations within the placenta

Histiotrophic nutrition in early pregnancy



Sheep, Cow
Horse, Pig

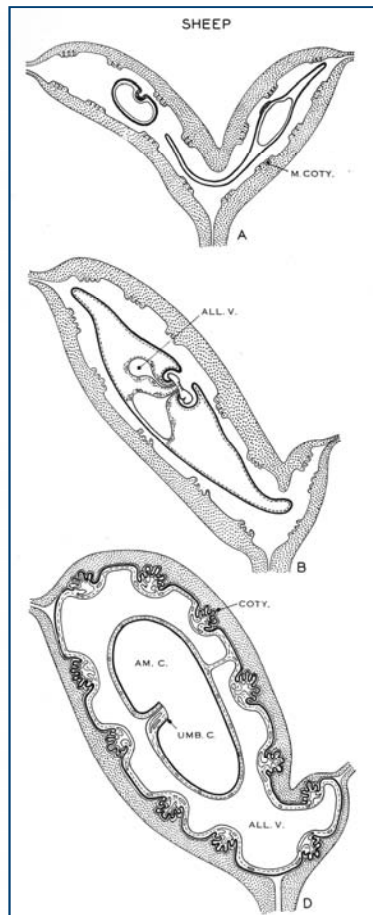


Endoscopic view of a horse conceptus at
approximately day 35 of pregnancy

- In the majority of species the conceptus remains within the uterine cavity and is supported during the embryonic period by glandular secretions, 'uterine milk', from the endometrium



Histiotrophic nutrition in early pregnancy



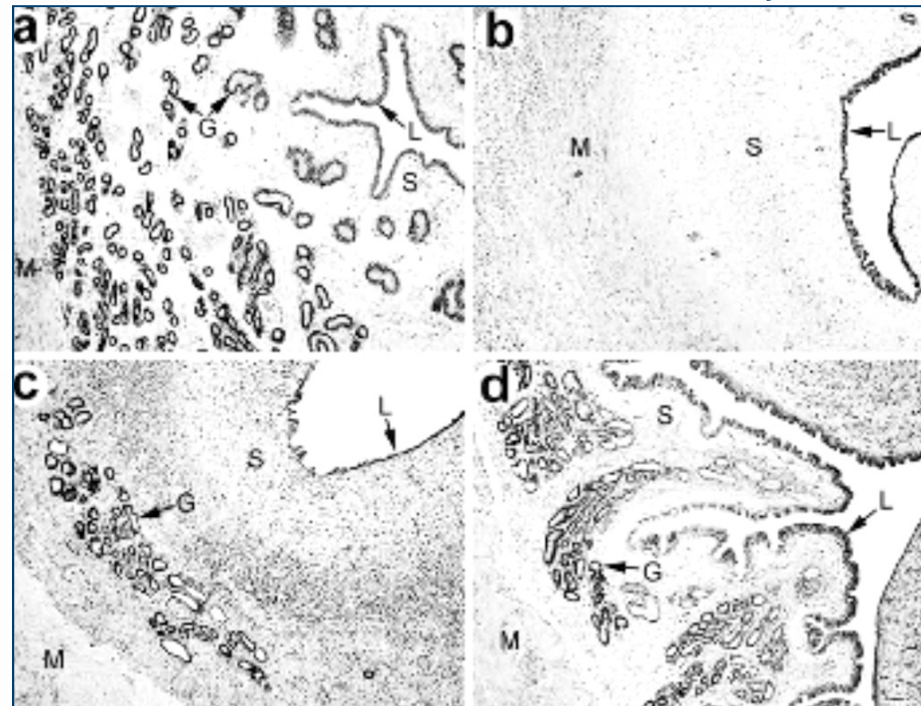
Sheep, Cow
Horse, Pig

Control

UGKO

Day 14 of pregnancy

Gray et al., 2001

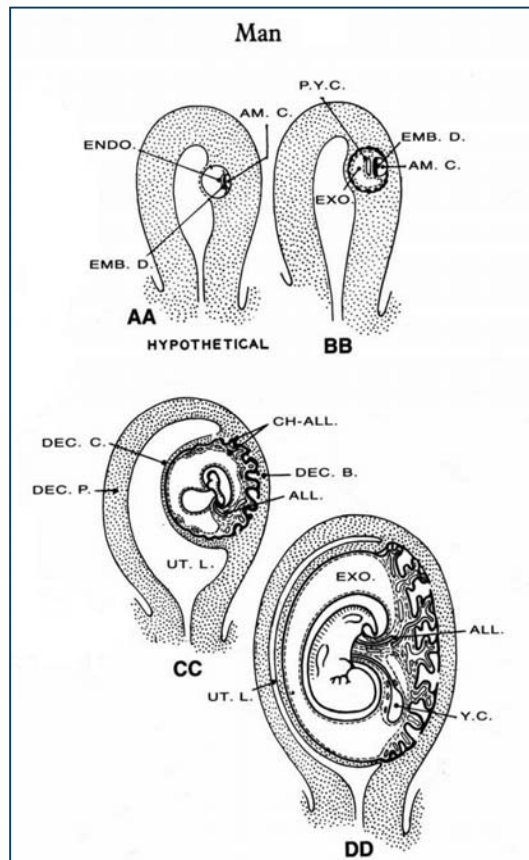


UGKO

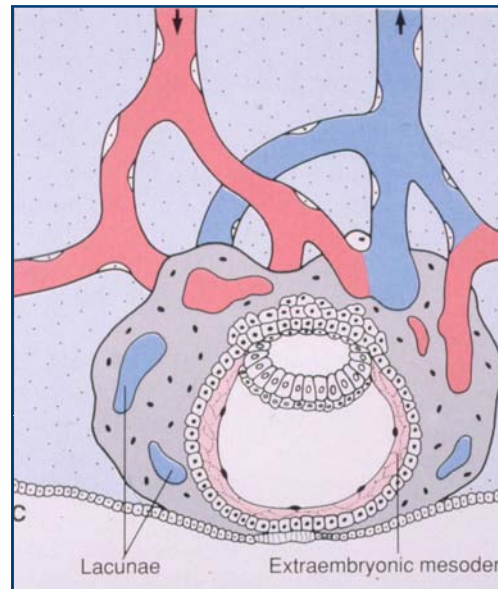
UGKO

- If development of the endometrial glands is suppressed experimentally in the sheep by high doses of oestrogens post-natally (UGKO), the conceptus fails to develop

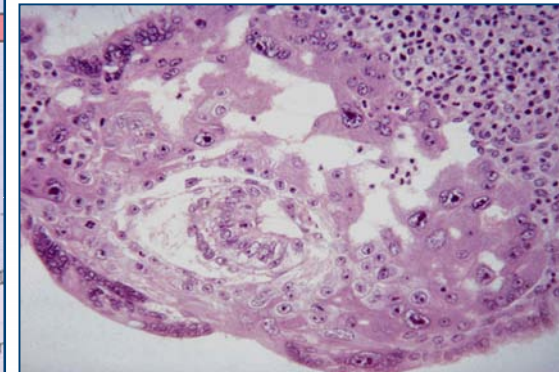
Histiotropic nutrition in early pregnancy



Human
Great apes



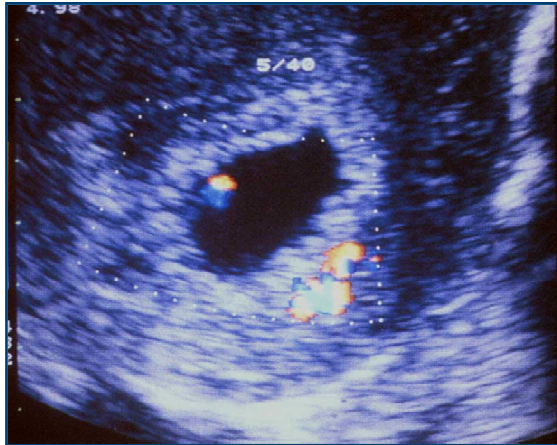
Day 9 post-fertilisation



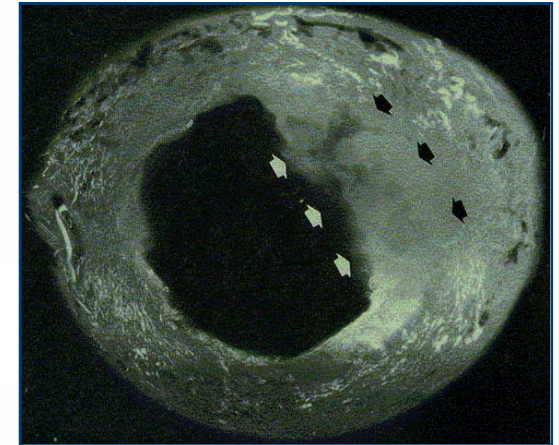
- By day 9 post-fertilisation, the unique invasive form of implantation displayed by the human conceptus has removed it from the uterine lumen
- Hence, the histiotrophic phase has always been considered to be brief

Changing concepts for the first trimester

8 - 9 weeks

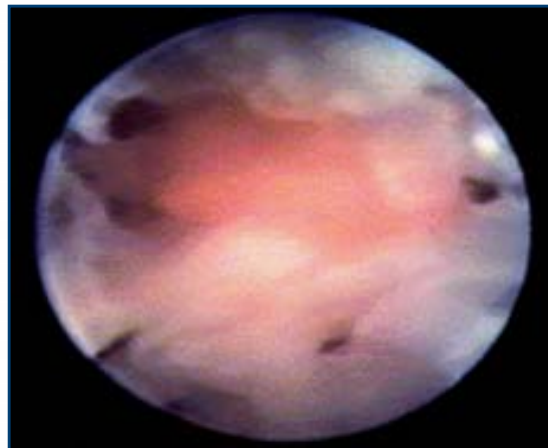


Hustin and Schaaps 1987-8



12 - 13 weeks

Doppler ultrasound, hysteroscopy, and perfusion of hysterectomy specimens all demonstrated an absence of significant maternal blood flow to the placenta prior to 10-12 weeks of pregnancy

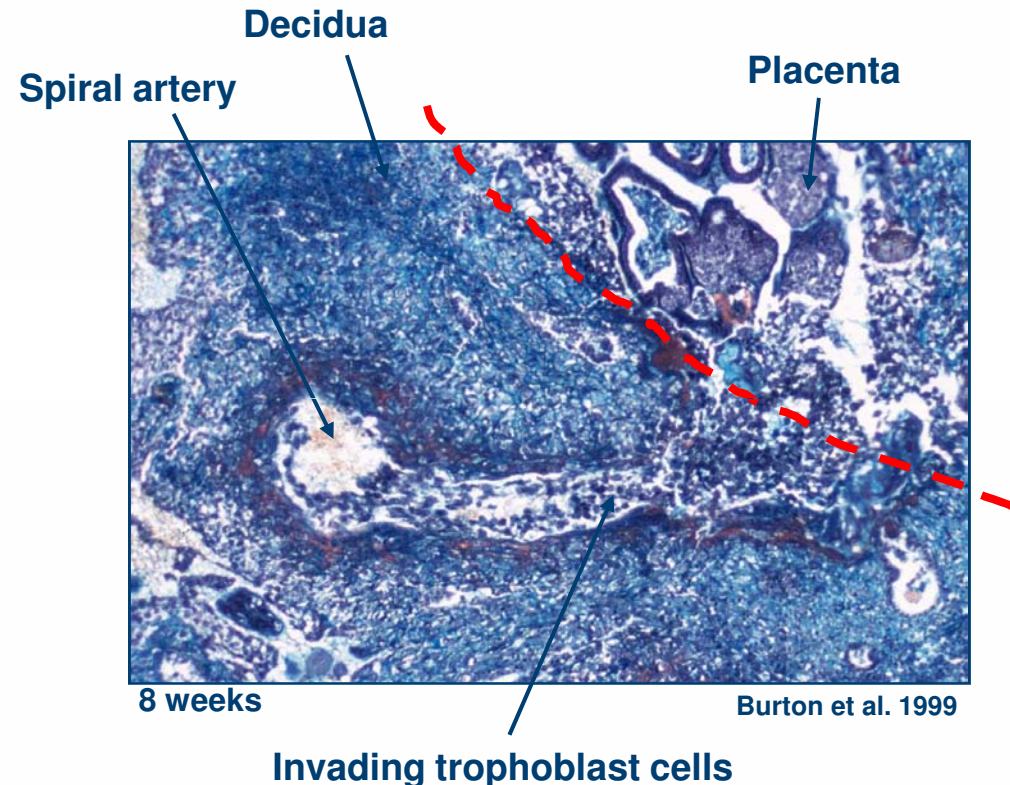
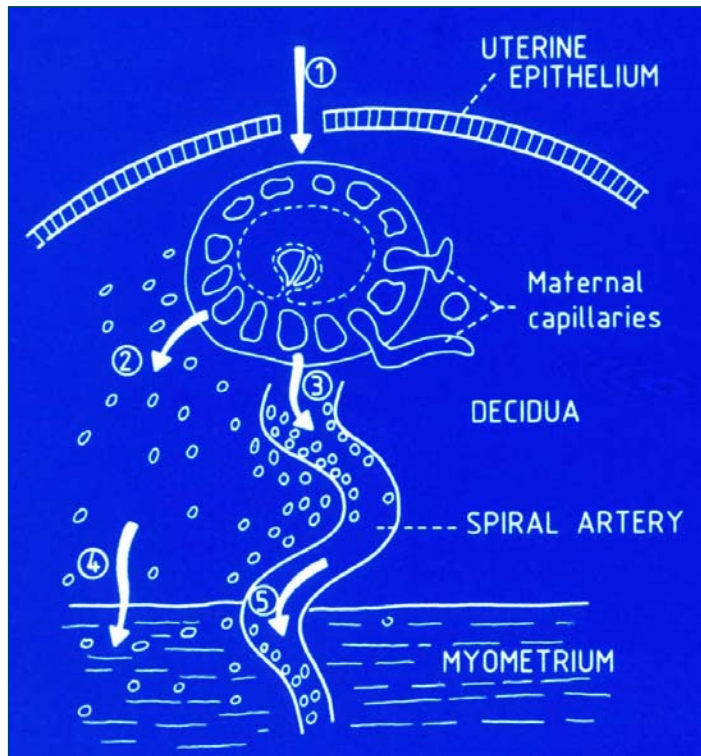


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Plugging of the maternal spiral arteries

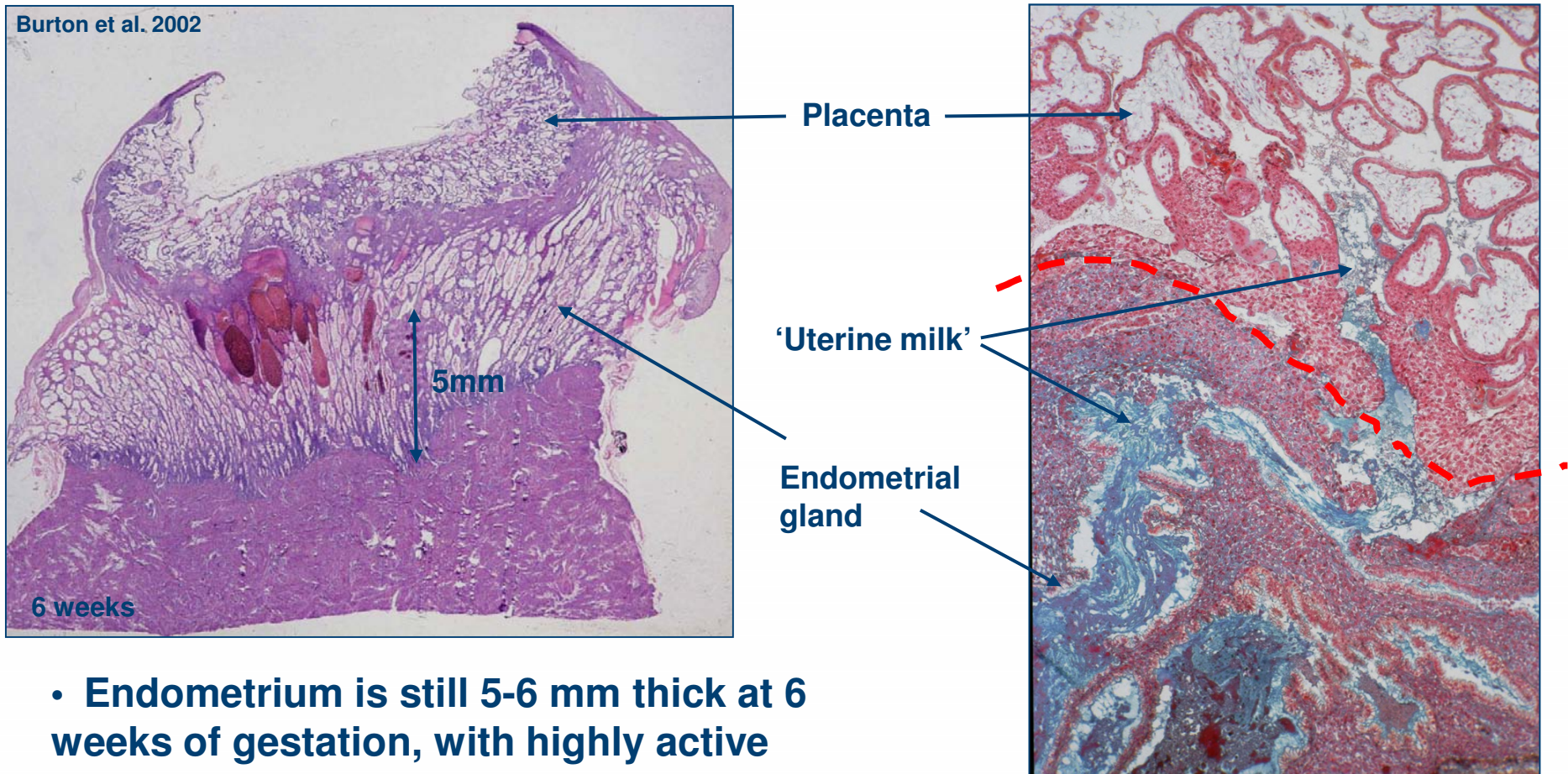
Pijnenborg



- During the first trimester the invading trophoblast cells plug the mouths of the maternal spiral arteries

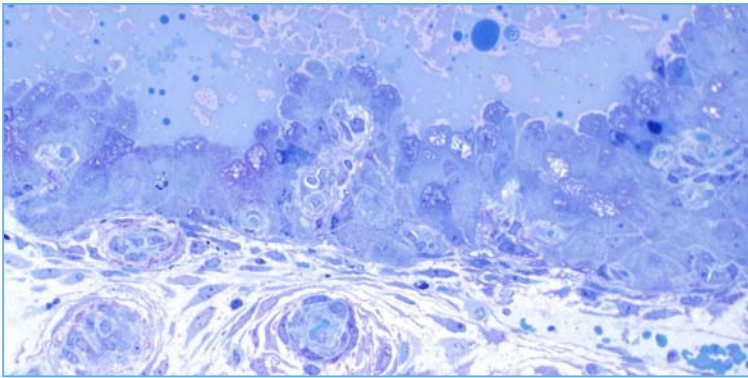


Endometrial glands during the first trimester

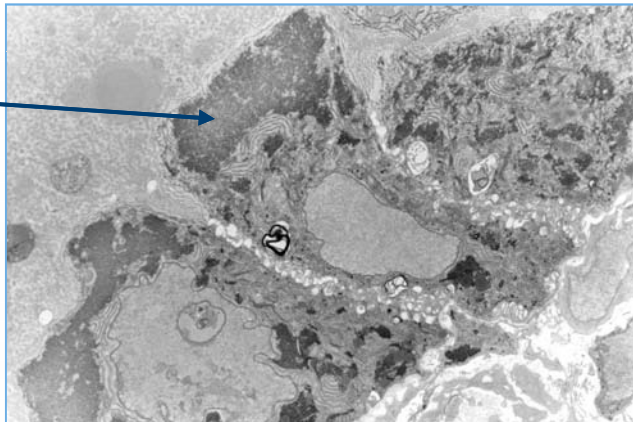


- Endometrium is still 5-6 mm thick at 6 weeks of gestation, with highly active glands that discharge into the placenta

Endometrial glands during the first trimester

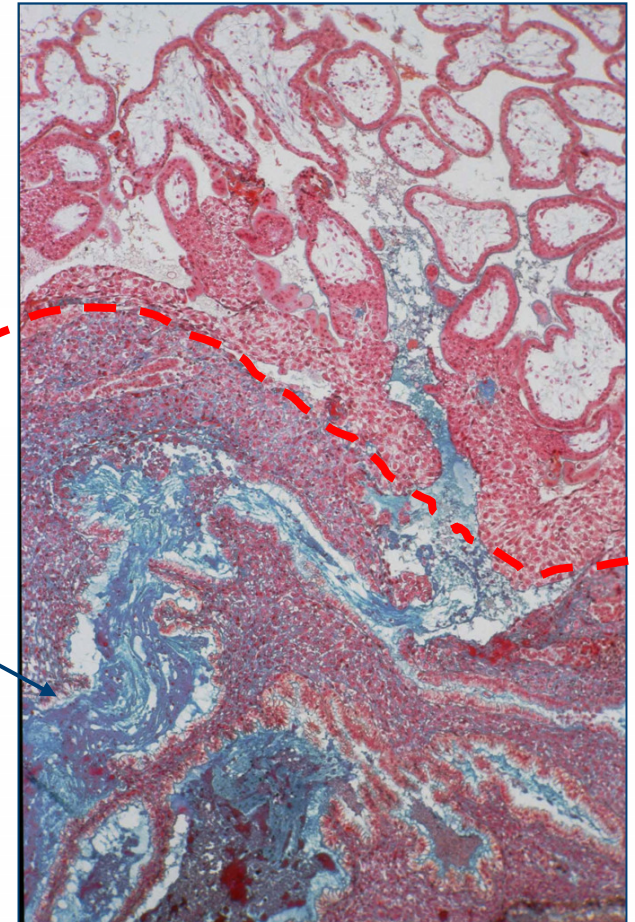


glycogen



6 weeks

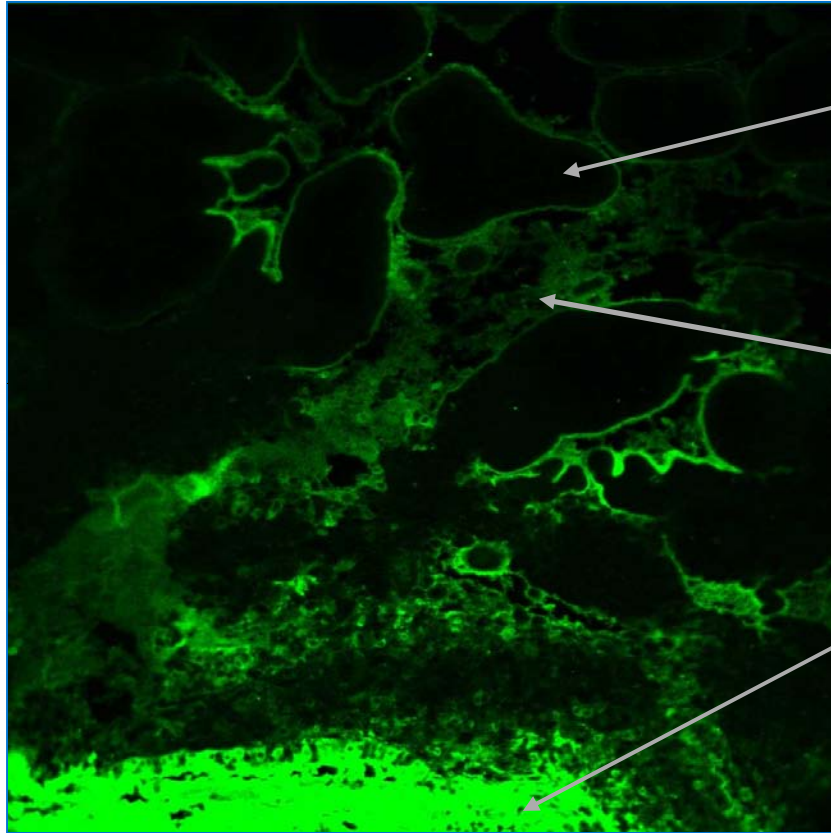
Endometrial gland



- At 6 weeks the gland epithelium is columnar, highly active, and similar morphologically to the secretory phase of the cycle

Endometrial glands during the first trimester

Burton et al. 2002

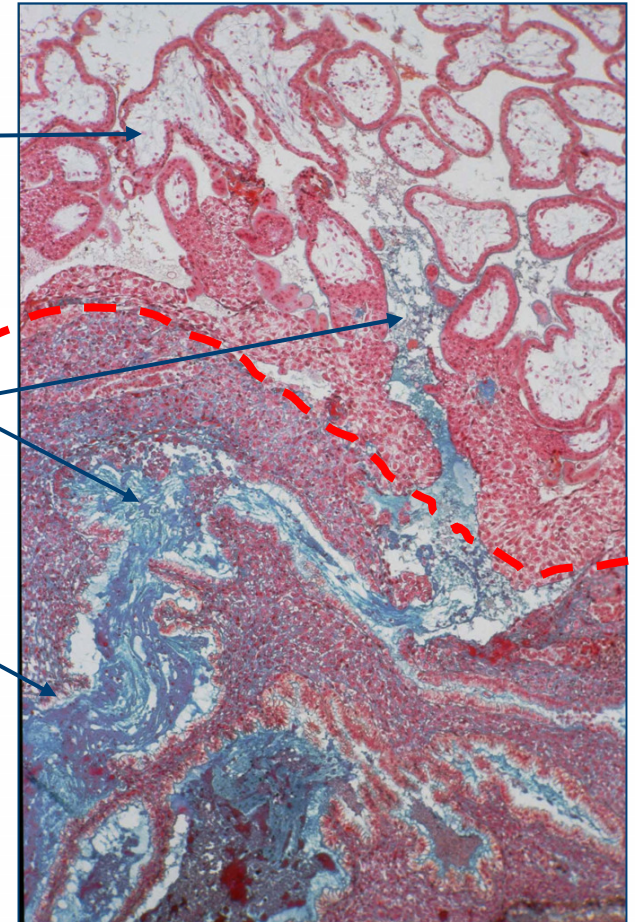


MUC-1

villus

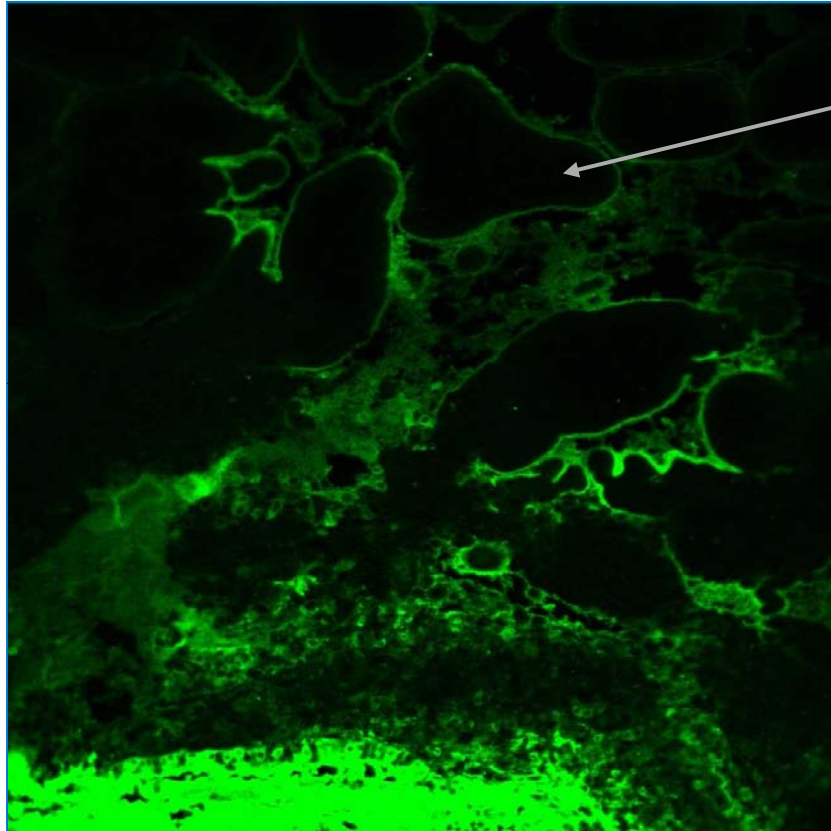
'Uterine milk'

Endometrial gland

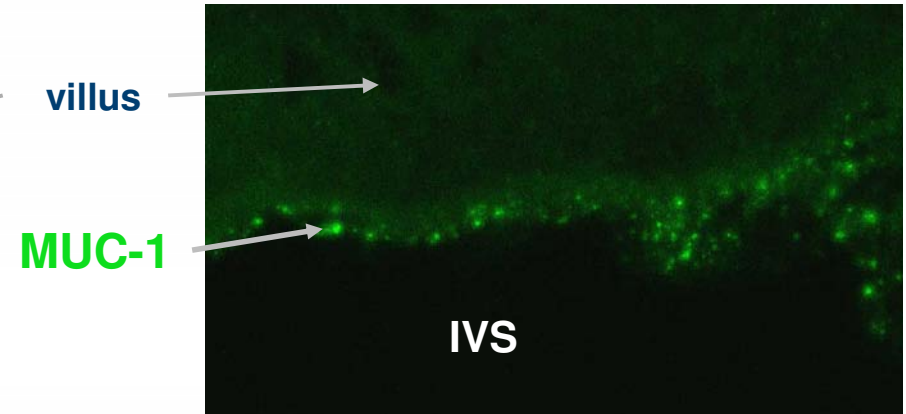


Endometrial glands during the first trimester

Burton et al. 2002



MUC-1



- Intense immunofluorescence for MUC-1 derived from the glands can be seen within the syncytiotrophoblast, suggesting phagocytic uptake
- Breakdown of these glycoproteins will release a rich supply of elements and amino acids



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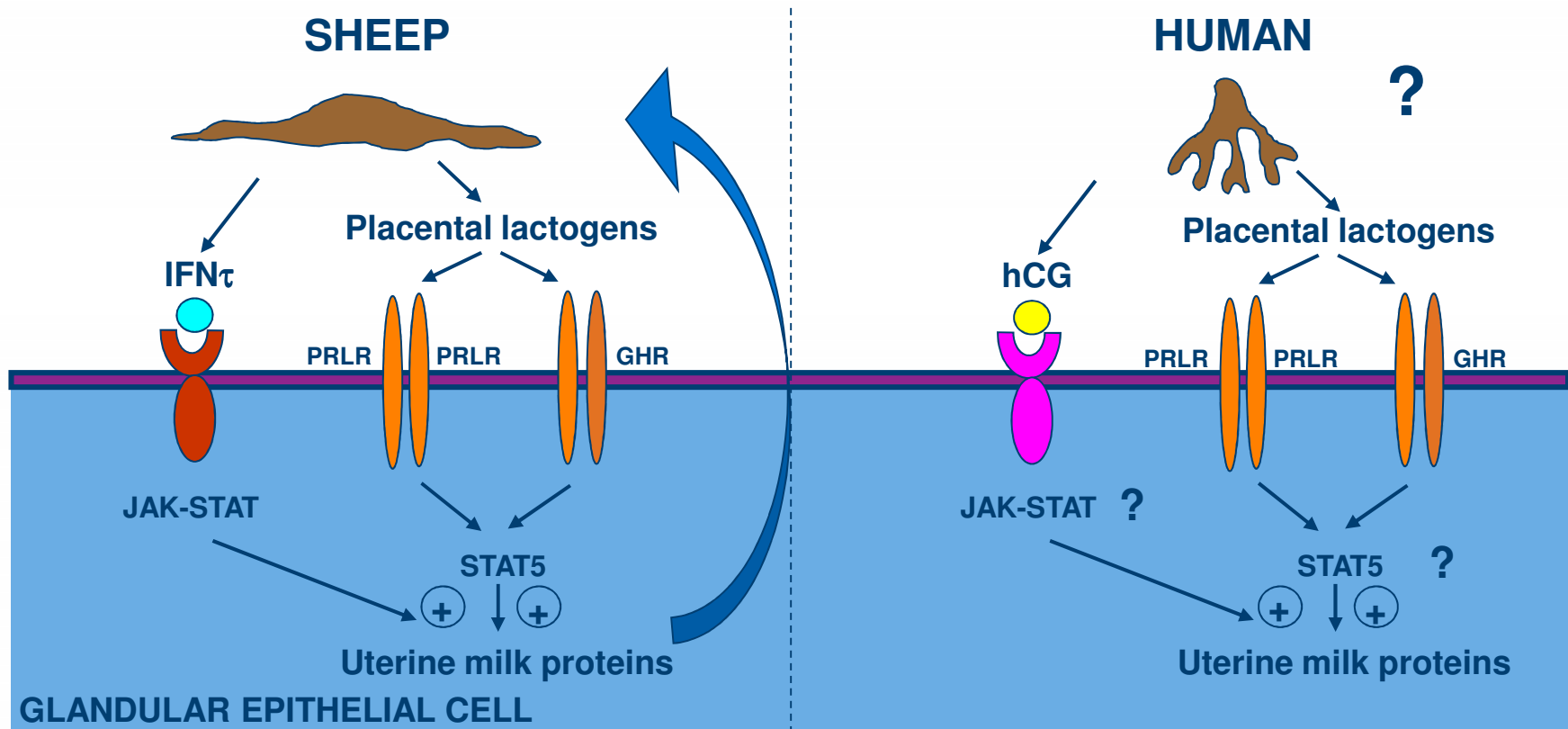
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Servomechanism regulating gland activity

Spencer et al. 2004

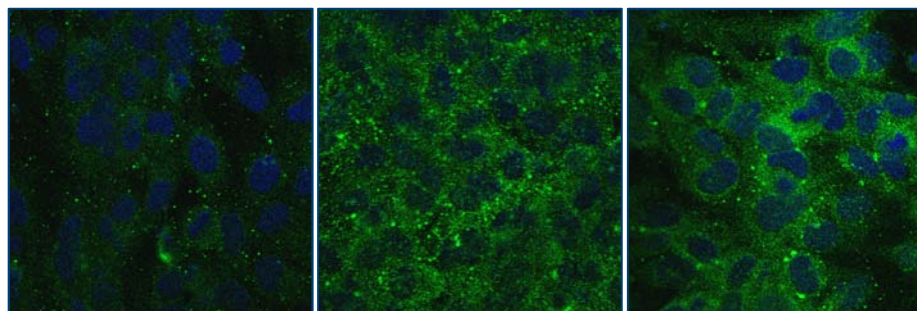
CONCEPTUS



Servomechanism regulating gland activity

CONCEPTUS

MUC-1



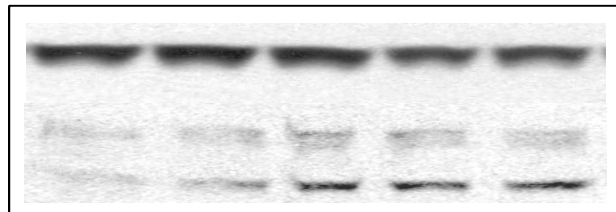
Vehicle control

1 ng/ml

100 ng/ml 3 hr

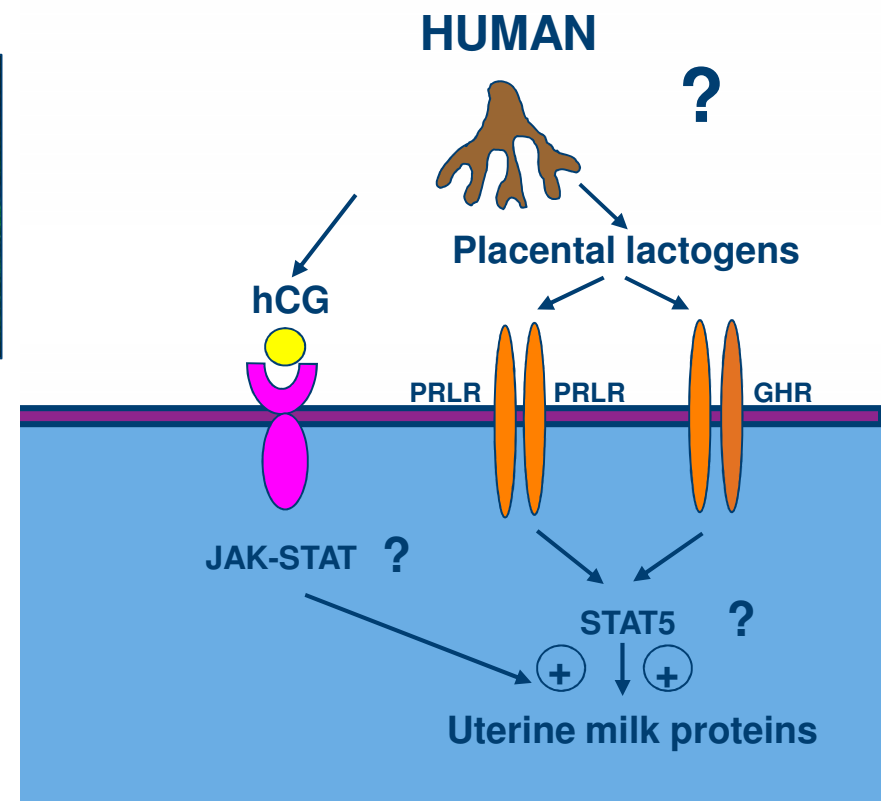
β -actin

MUC-1

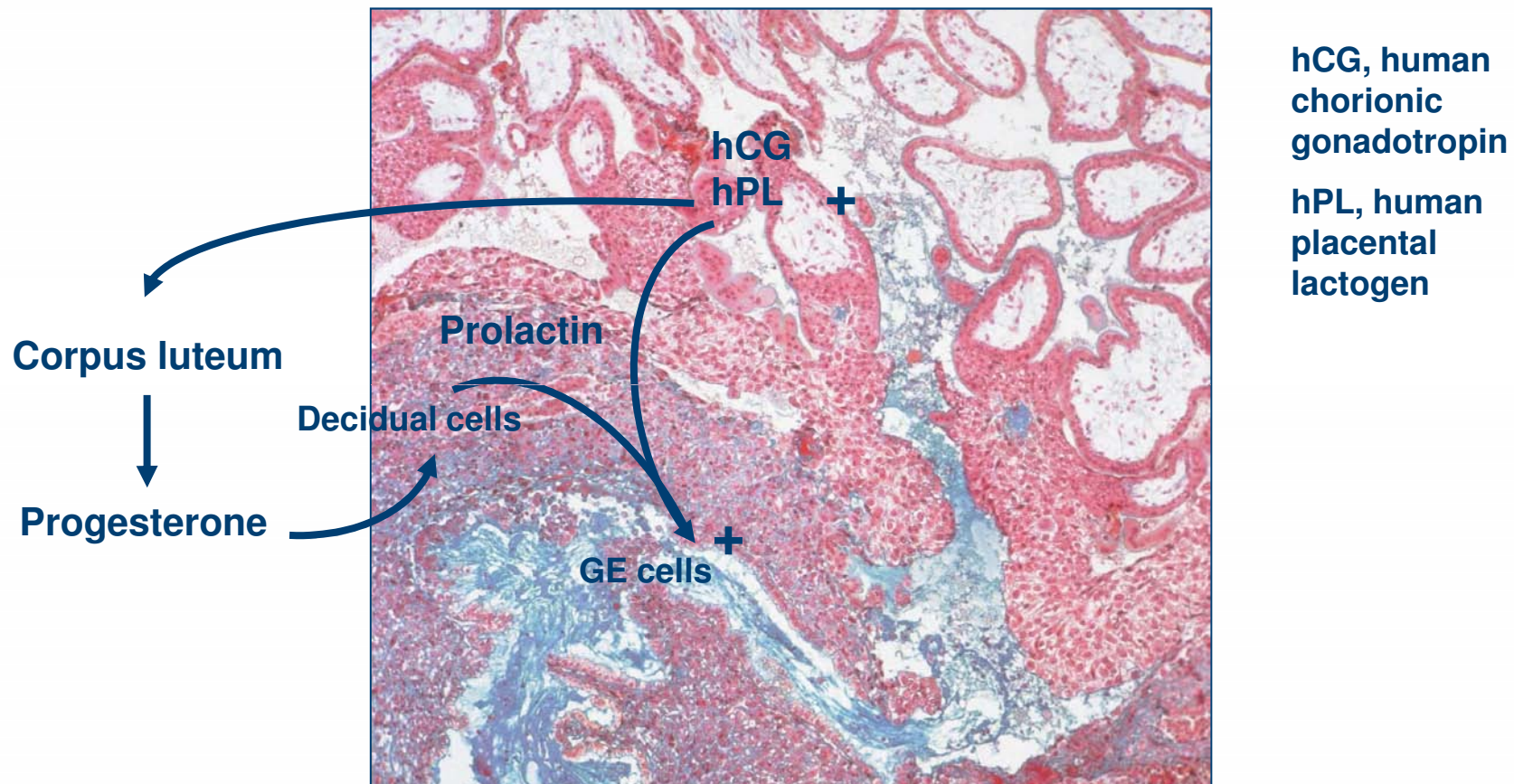


0 0.1 1 10 100
Prolactin (ng/ml)

- Addition of prolactin to a human endometrial gland cell line increases MUC-1, a 'milk protein' in a dose-dependent manner



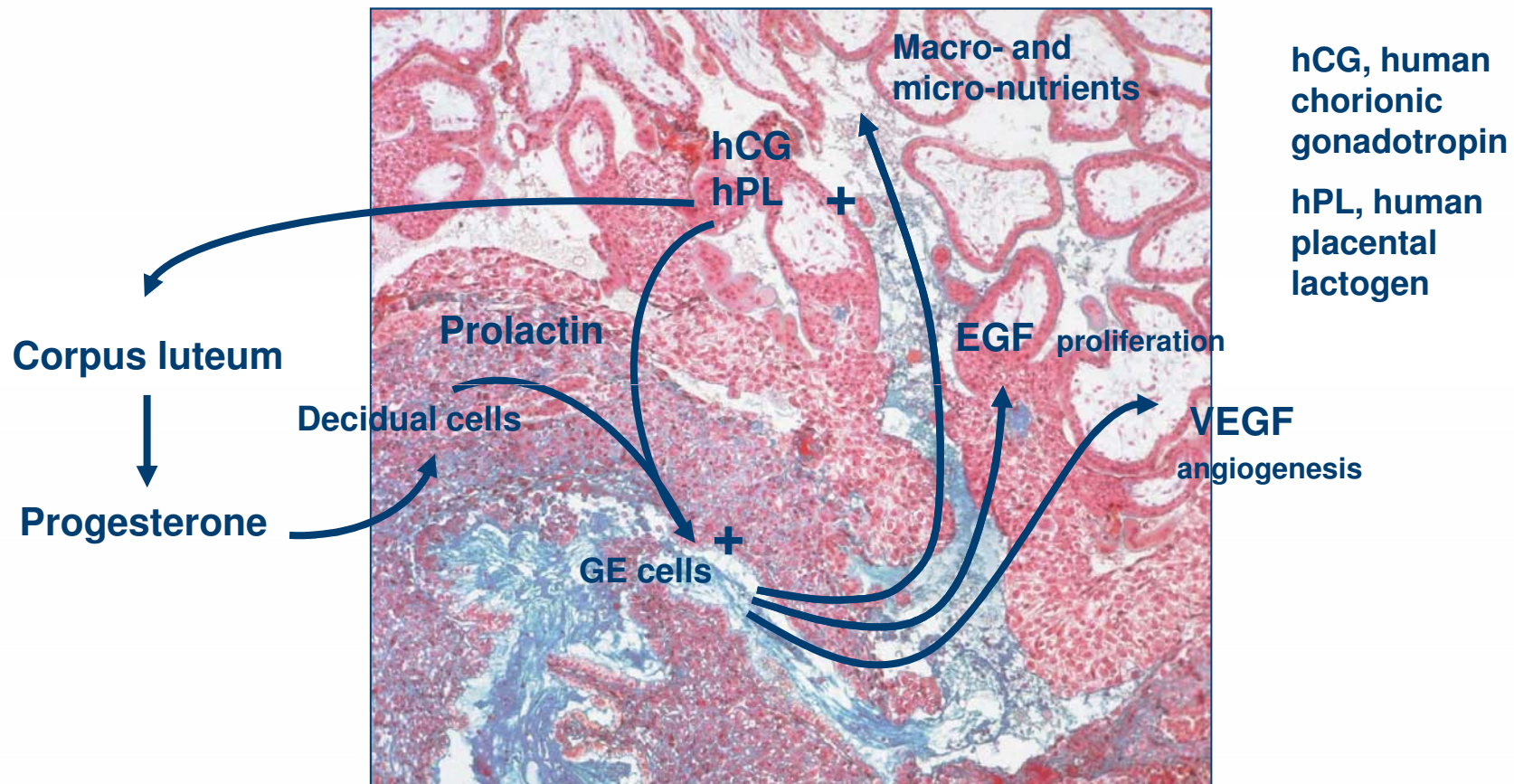
Potential servomechanism in the human



- hCG and hPL may stimulate the gland epithelial cells direct, or via prolactin secreted by the decidual cells in response to P4 from the CL



Potential servomechanism in the human

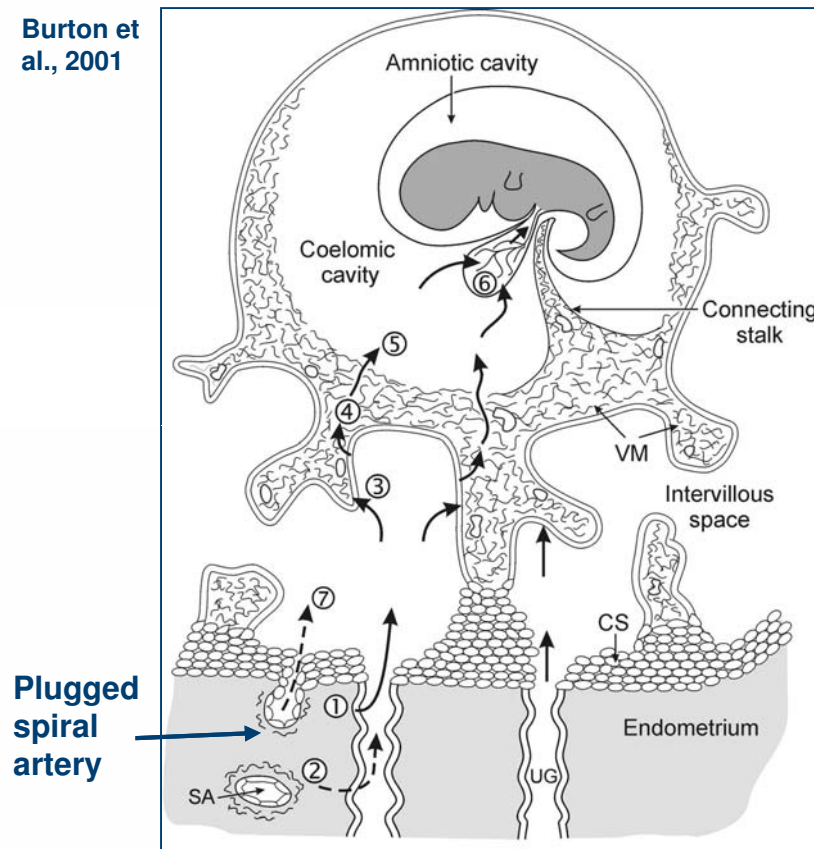


- In addition to nutrients, the glands also secrete an array of growth factors and cytokines that may regulate placental development



The pathway for nutrients during the first trimester

Burton et al., 2001



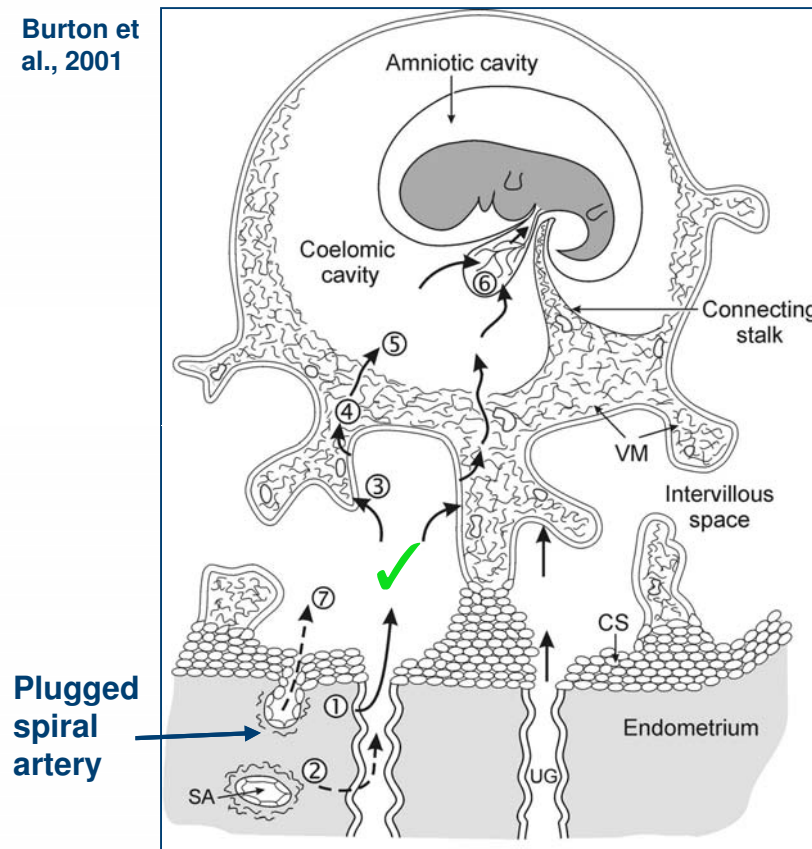
Proposed pathway

- The fetal circulation to the placenta is not established until around 8 weeks
- In all mammals the yolk sac is the first extraembryonic membrane to be vascularised
- In most mammals the yolk sac functions transiently in early pregnancy to transfer nutrients



The pathway for nutrients during the first trimester

Burton et al., 2001



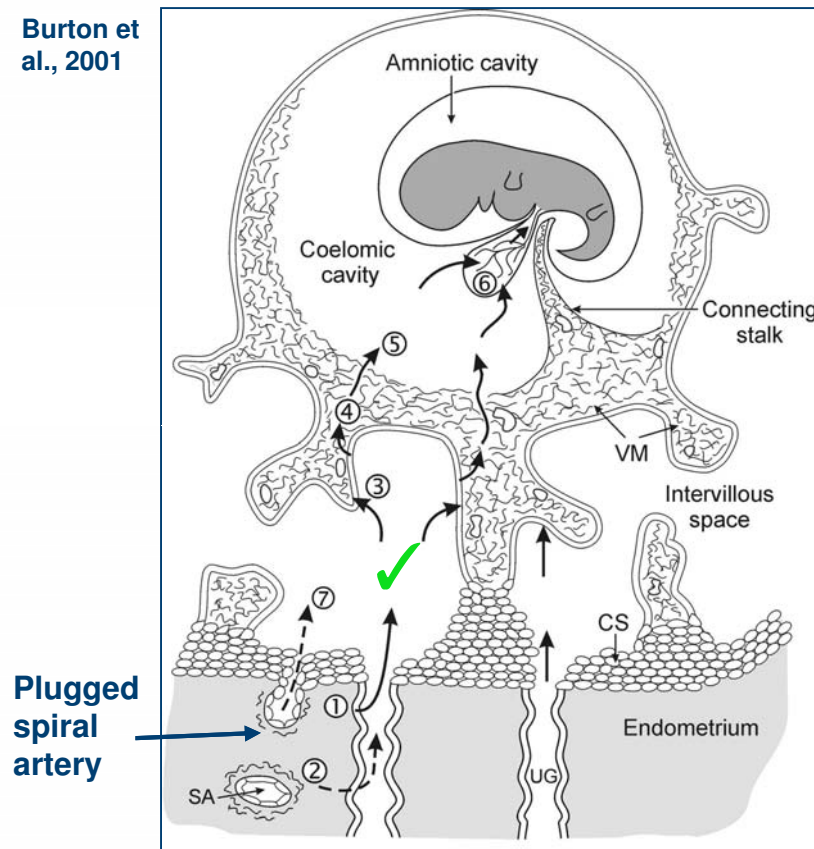
Proposed pathway

- The fetal circulation to the placenta is not established until around 8 weeks
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- In most mammals the yolk sac functions transiently in early pregnancy to transfer nutrients
- Can maternal nutrients reach the coelomic cavity?
- Can those nutrients be taken up by the yolk sac?

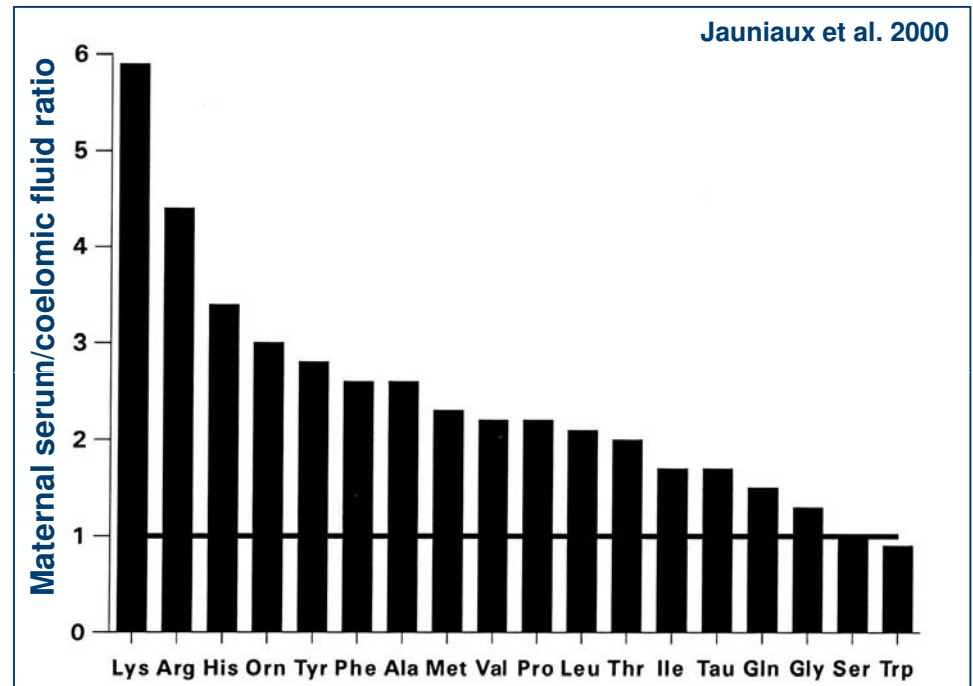


The pathway for nutrients during the first trimester

Burton et al., 2001



Jauniaux et al. 2000



- Amino acids accumulate in the coelomic fluid against a concentration gradient



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The pathway for nutrients during the first trimester

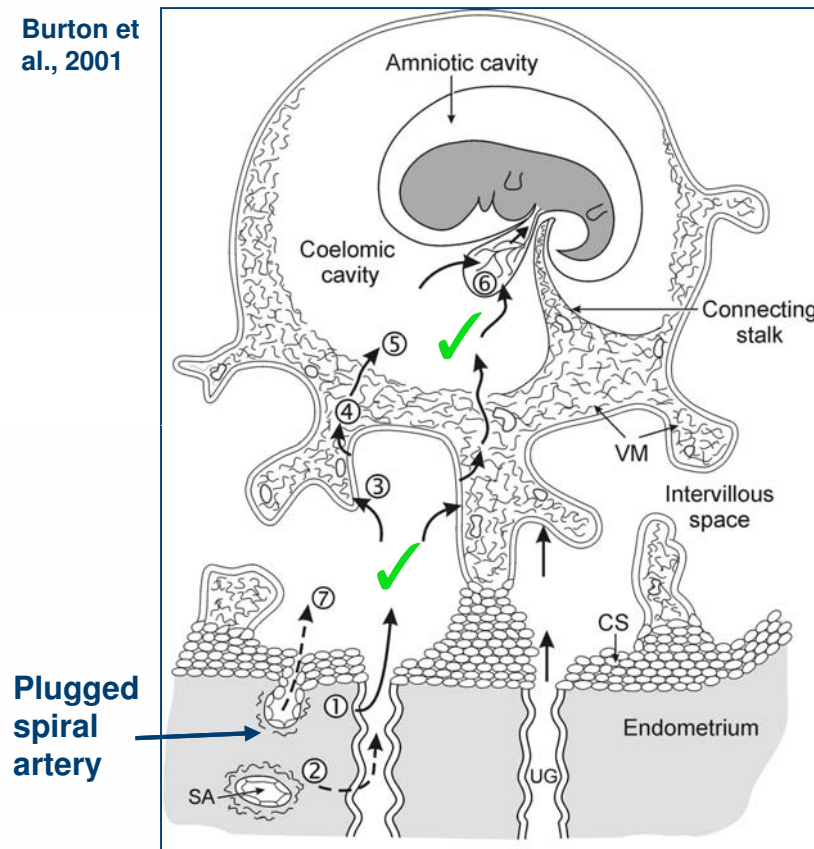
Molecules	Maternal Serum	Coelomic Fluid	Amniotic Fluid
Maternal Origin			
Total protein (g/L)	71.3	3.5	0.2
Urea (mmol/L)	7.2	8.3	7.2
Albumin (g/L)	45.5	1.7	ND
Thyroxine (nmol/L)	180	0.9	0.02
Glucose (mmol/L)	3.4	2.7	2.8
IGF-1 (µg/L)	233	41	38
Placental Origin			
Intact hCG (mIU/mL)	80193	105605	1057
Progesterone (pg/mL)	17	240	8
Oestradiol (pg/mL)	917	8469	1898
Inhibin B (pg/mL)	5.9	24.3	6.3
Lactate (mmol/L)	0.3	0.6	0.9
IGF-II (µg/L)	687	199	40
Decidual Origin			
Prolactin (mU/L)	709	371	40
Glycodelin A (µg/L)	642	4416	77
IGFBP-1 (µg/L)	76	150	16
IGFBP-2 (µg/L)	123	167	49

- Proteins of placental origin diffuse into the coelomic fluid, indicating free communication between these compartments
- Proteins of decidual origin e.g. glycodelin (originally referred to as PP14 as thought to be placental) accumulate in the coelomic fluid
- The coelomic fluid acts as a reservoir of nutrients for the embryo



The pathway for nutrients during the first trimester

Burton et al., 2001



Proposed pathway

- Can maternal nutrients reach the coelomic cavity?
- Can those nutrients be taken up by the yolk sac?



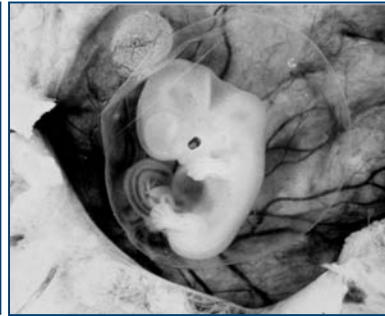
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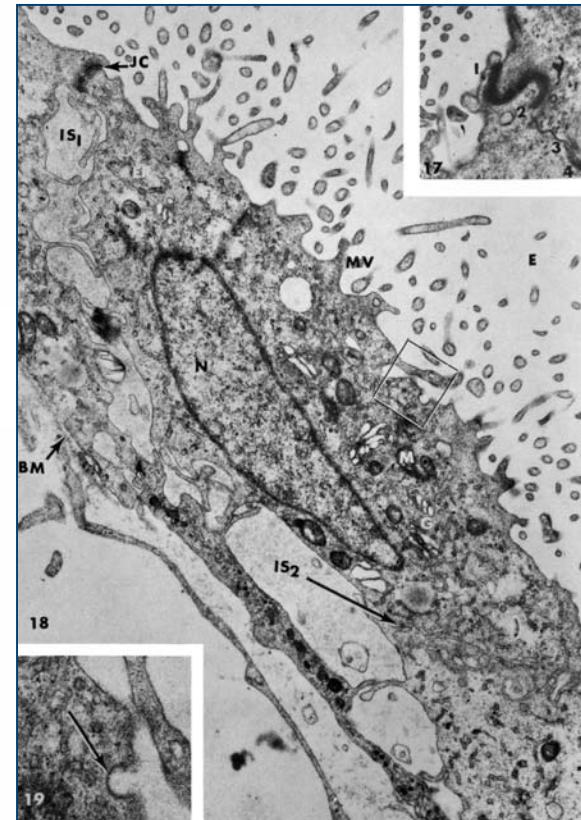
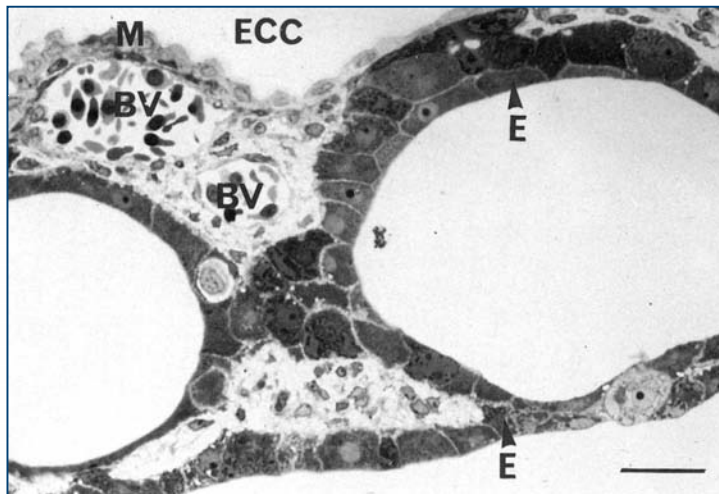


The pathway for nutrients during the first trimester

9 somites



8 weeks



- The outer mesothelial layer displays morphological features of an absorptive epithelium, with microvilli and coated pits

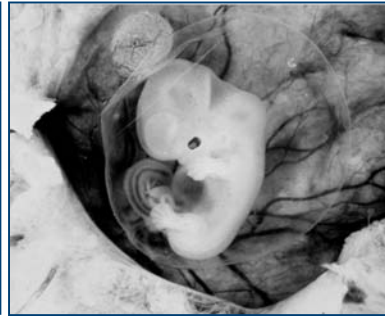


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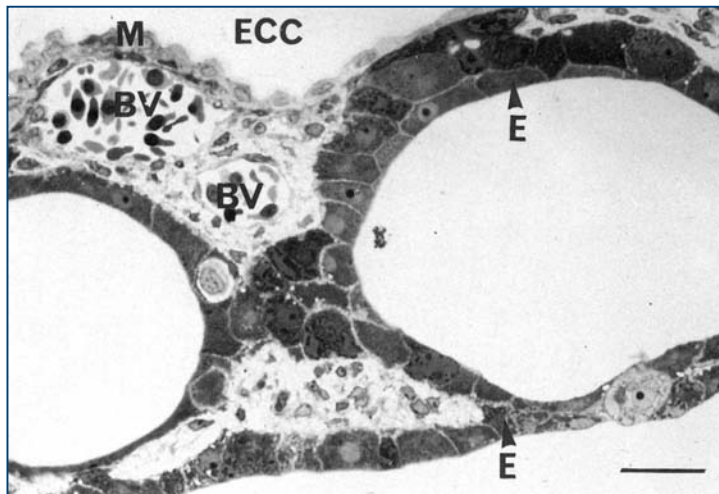


The pathway for nutrients during the first trimester

9 somites

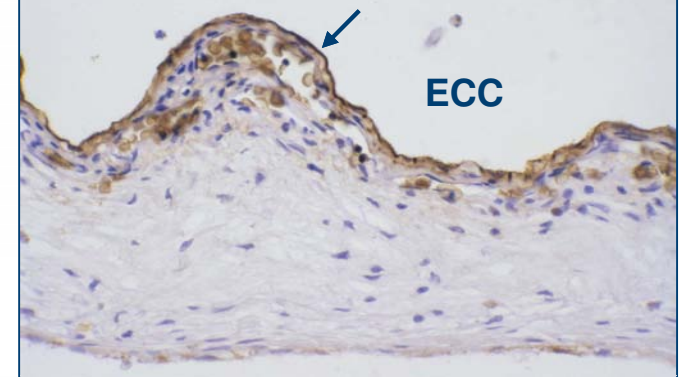


8 weeks

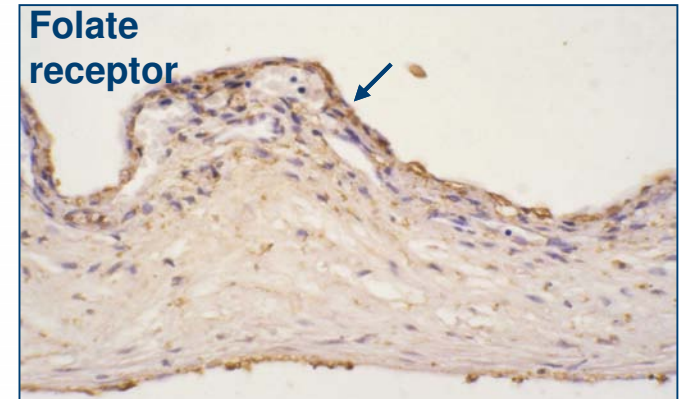


GLUT-1

10 weeks



Folate receptor



- The outer mesothelial layer is immunopositive for specific transporter proteins, such as GLUT-1 and the folate receptor



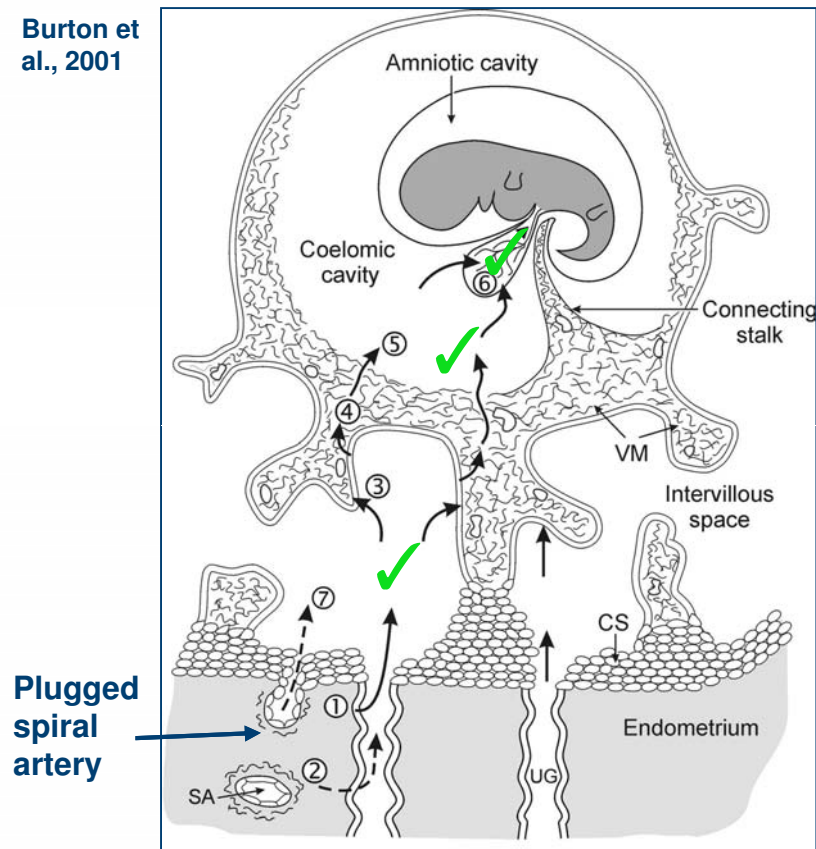
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The pathway for nutrients during the first trimester

Burton et al., 2001

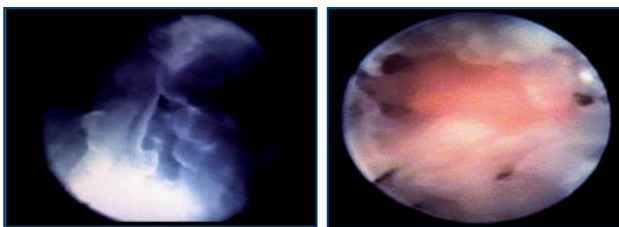
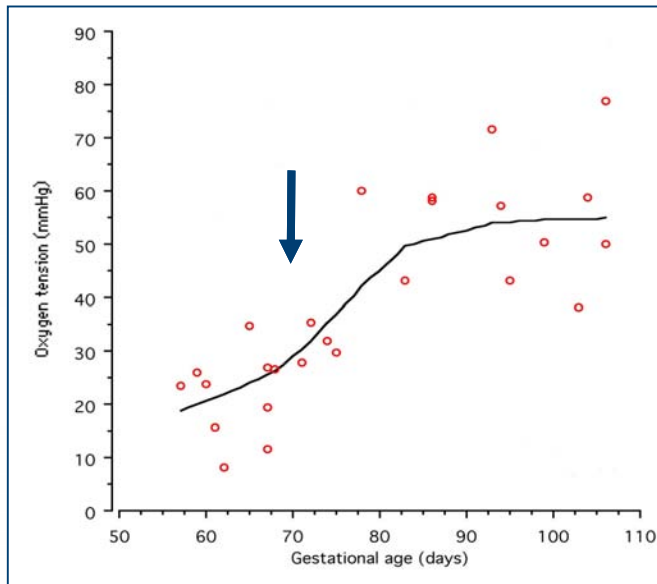


Proposed pathway

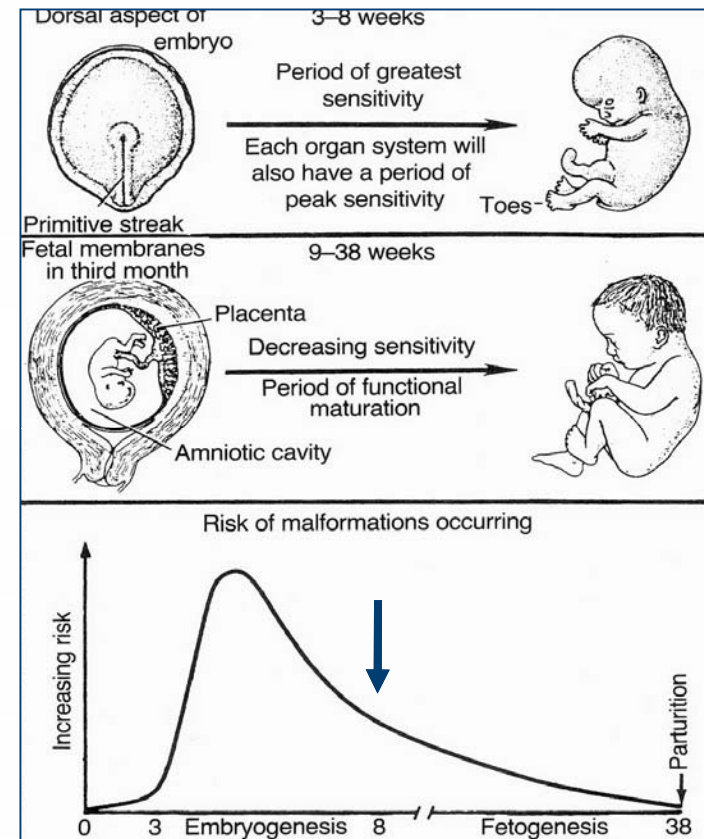
- Although there is no direct proof that the human yolk sac is involved in nutrient uptake, the relevant proteins are in the right place at the right time
- There are similarities with the rat/mouse in which 90% of amino acid transport during organogenesis is through protein uptake by the yolk sac and subsequent breakdown

Oxygen free radicals as teratogens

Jauniaux et al.,
2000

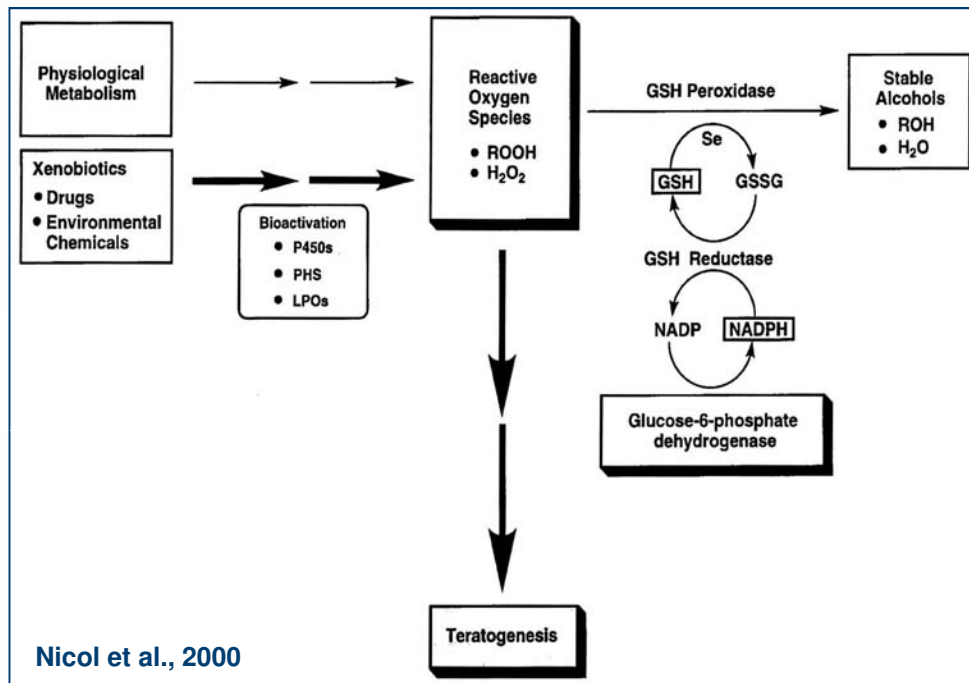


Sadler



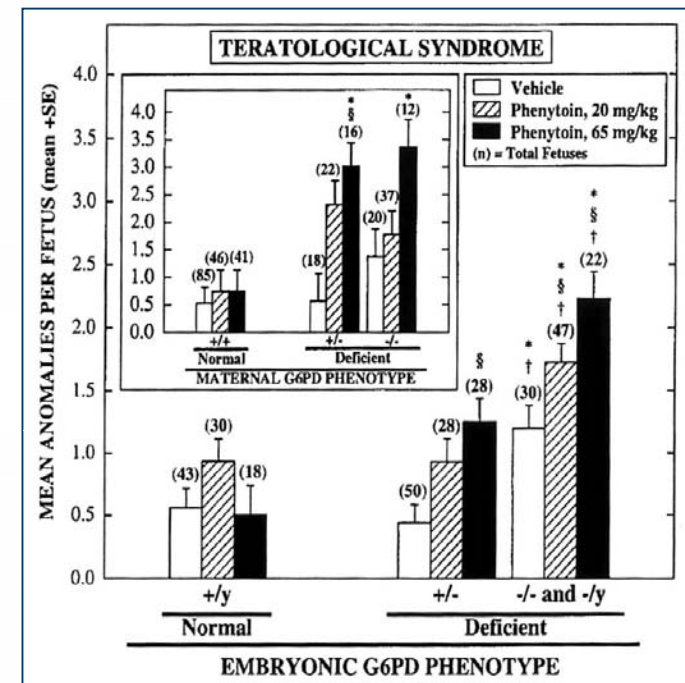
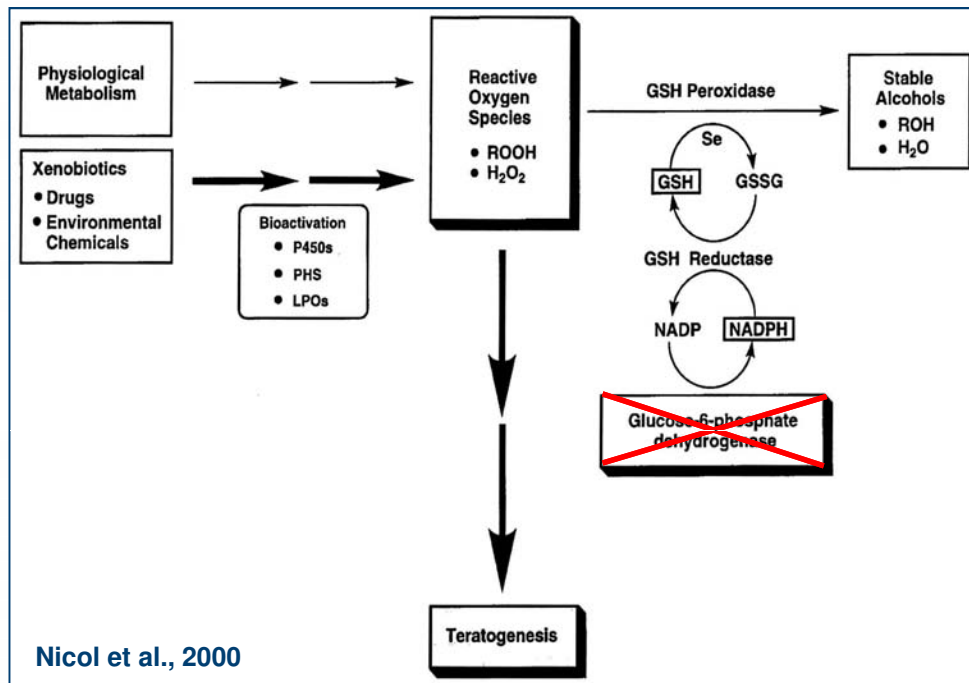
- There is a three-fold rise in intraplacental oxygen concentration with onset of the maternal circulation which coincides with the end of organogenesis

Oxygen free radicals as teratogens



- Oxygen free radicals are produced as a by-product of aerobic metabolism, and detoxified by anti-oxidant enzymes, including glutathione (GSH) peroxidase

Oxygen free radicals as teratogens



- Oxygen free radicals are produced as a by-product of aerobic metabolism, and detoxified by anti-oxidant enzymes, including glutathione (GSH) peroxidase
- In mice knock-out of G6PD leads to reduced activity of GSH peroxidase, and is associated with increased congenital malformations (cleft palate, microcephaly, omphalocele)
- Maintaining a low oxygen concentration during organogenesis may reduce the risk

Conclusions

1. The endometrial glands supply histiotrophic nutrition to the human conceptus during the first trimester, the period of organogenesis
2. There may be an endocrine servomechanism enhancing glandular activity in early pregnancy
3. Nutrients accumulate in the coelomic cavity
4. The outer mesothelial layer of the yolk sac is an absorptive epithelium containing specific transport proteins, and is likely to be involved in active uptake
5. Oxygen free radicals are teratogenic and maintaining the conceptus in a low oxygen environment during organogenesis will reduce the risk
6. The endometrium and its glands plays a more active role in maintaining an early pregnancy than previously realised



Acknowledgments

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Tommy's, The Baby Charity

Burton, G.J., Watson, A.L., Hempstock, J., Skepper, J.N. and Jauniaux, E. (2002) Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. *Journal of Clinical Endocrinology and Metabolism*, 87, 2954-2959.

Burton, G.J., Jauniaux, E. and Charnock-Jones, D.S. (2007) Human early placental development: potential roles of the endometrial glands. *Placenta*, 28 Suppl. A, S64-69.

Jauniaux E , Gulbis B. Fluid compartments of the embryonic environment. *Human Reproduction Update* 2000;6:268-78.

Jauniaux, E., Cindrova-Davies, T., Johns J., Dunster, C., Kelly, F., Hempstock, J. and Burton, G.J. (2004) Distribution and transfer pathways of antioxidant molecules inside the first trimester human gestational sac. *Journal of Clinical Endocrinology and Metabolism*, 89, 1452-1458.