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Patofyziologie reprodukce

Julie Dobrovolná

Opakování

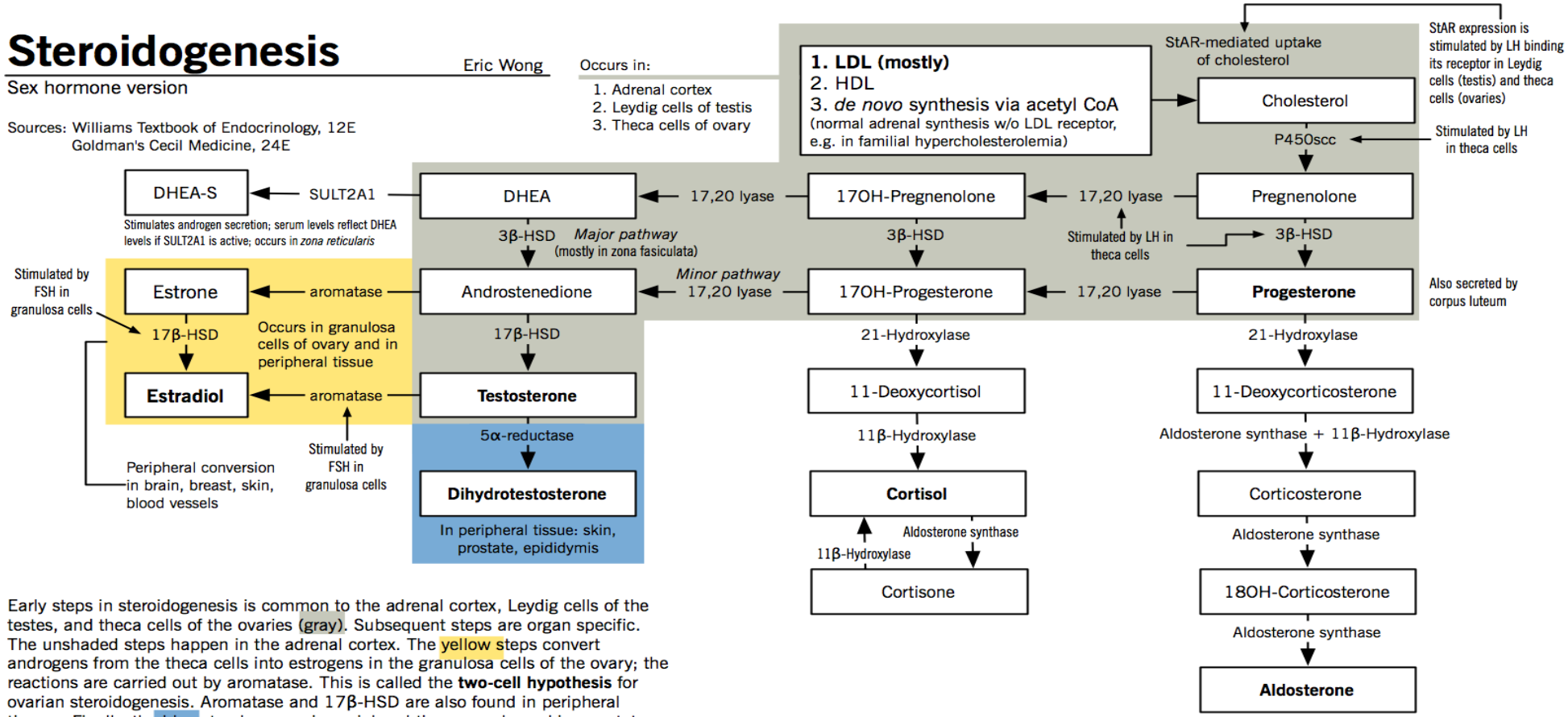
Steroidogenesis

Sex hormone version

Eric Wong

Sources: Williams Textbook of Endocrinology, 12E
Goldman's Cecil Medicine, 24E

Occurs in:
1. Adrenal cortex
2. Leydig cells of testis
3. Theca cells of ovary



Early steps in steroidogenesis is common to the adrenal cortex, Leydig cells of the testes, and theca cells of the ovaries (gray). Subsequent steps are organ specific. The unshaded steps happen in the adrenal cortex. The yellow steps convert androgens from the theca cells into estrogens in the granulosa cells of the ovary; the reactions are carried out by aromatase. This is called the **two-cell hypothesis** for ovarian steroidogenesis. Aromatase and 17β-HSD are also found in peripheral tissues. Finally, the blue step happens in peripheral tissues such as skin, prostate, and epididymis, where testosterone is converted into the more potent DHT.

Enzyme and gene names
P450scc = Cholesterol side-chain cleavage enzyme = CYP11A1
3β-HSD = HSD3B2
17,20 lyase = 17α-Hydroxylase = CYP17A1
21-Hydroxylase = CYP21A2
11β-Hydroxylase = CYP11B1
Aldosterone synthase = CYP11B2
17β-HSD = HSB17B
DHEA sulfotransferase = SULT2A1
Aromatase = P450aro

DHEA: dehydroepiandrosterone
StAR: steroidogenic acute regulatory protein

"Sex"
Androgen
Zona reticularis

"Sugar"
Glucocorticoid
Zona fasciculata
Regulation: HPA-axis

"Salt"
Mineralocorticoid
Zona glomerulosa
Regulation: RAAS

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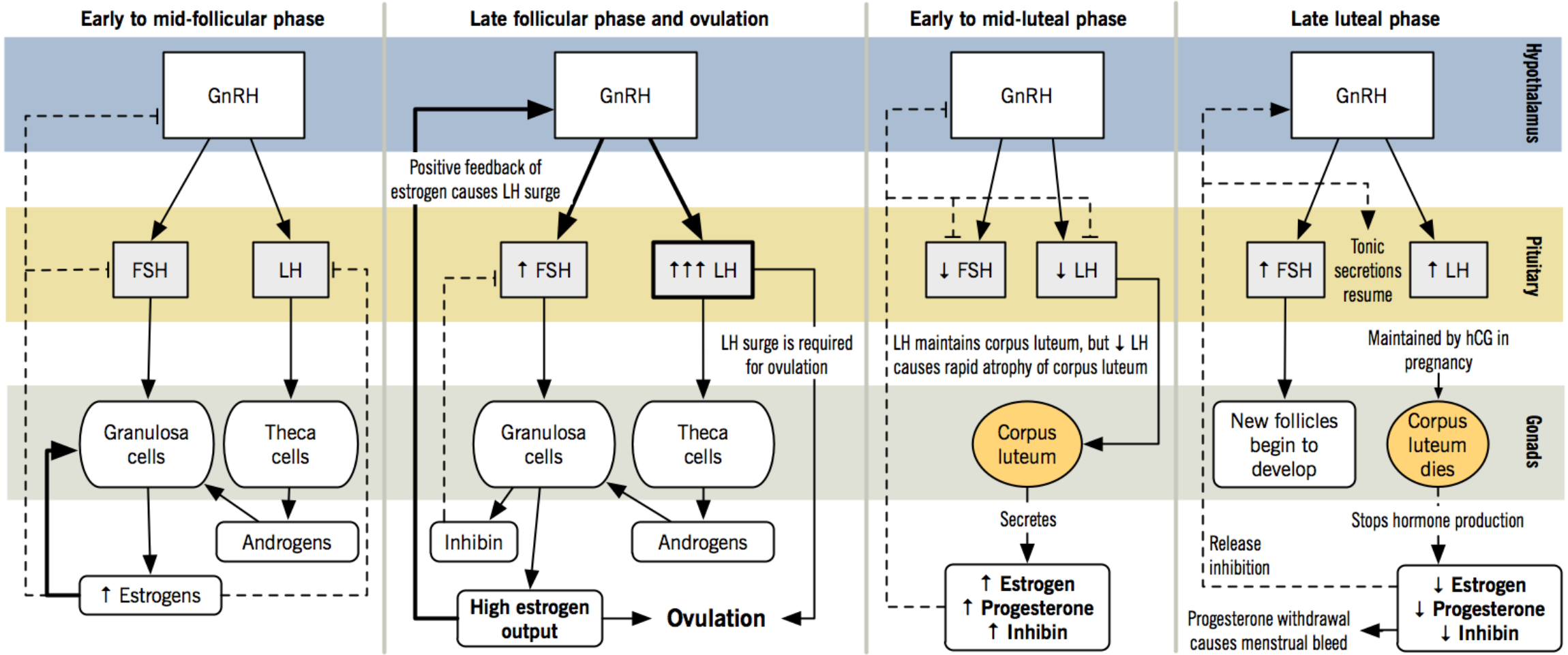
Hormonal regulation at various parts of the menstrual cycle

Eric Wong

Adapted from: Silverthorn Human Physiology 4E, figure 26-14



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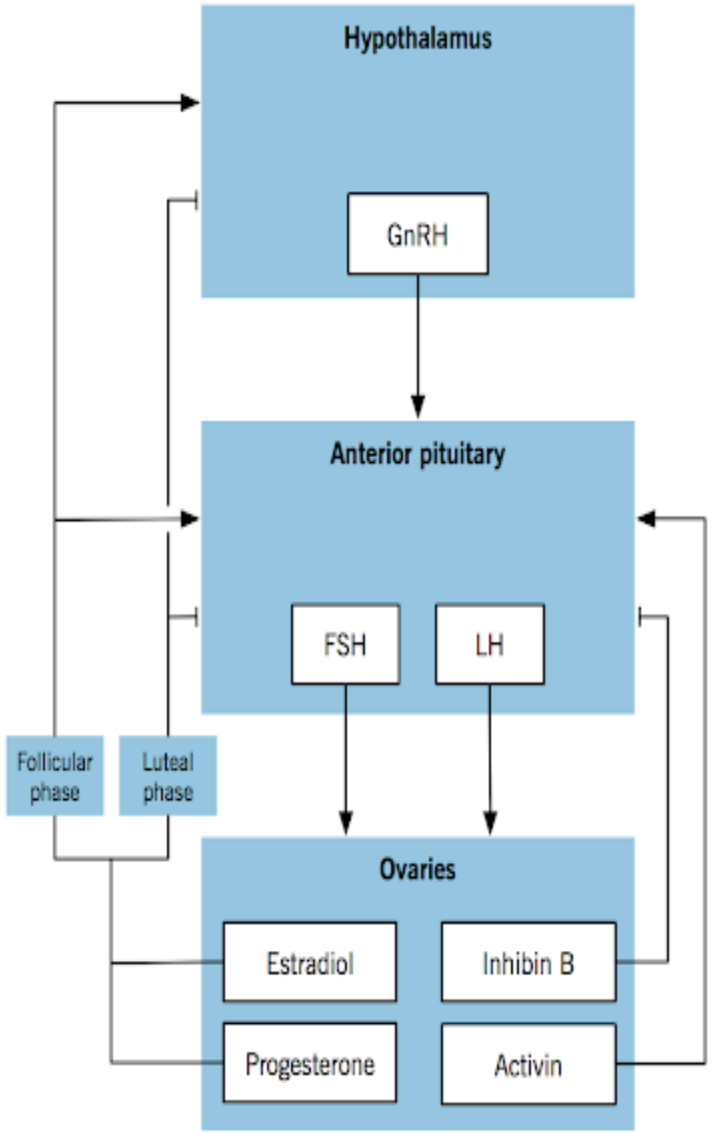
Premenopausal HPG axis

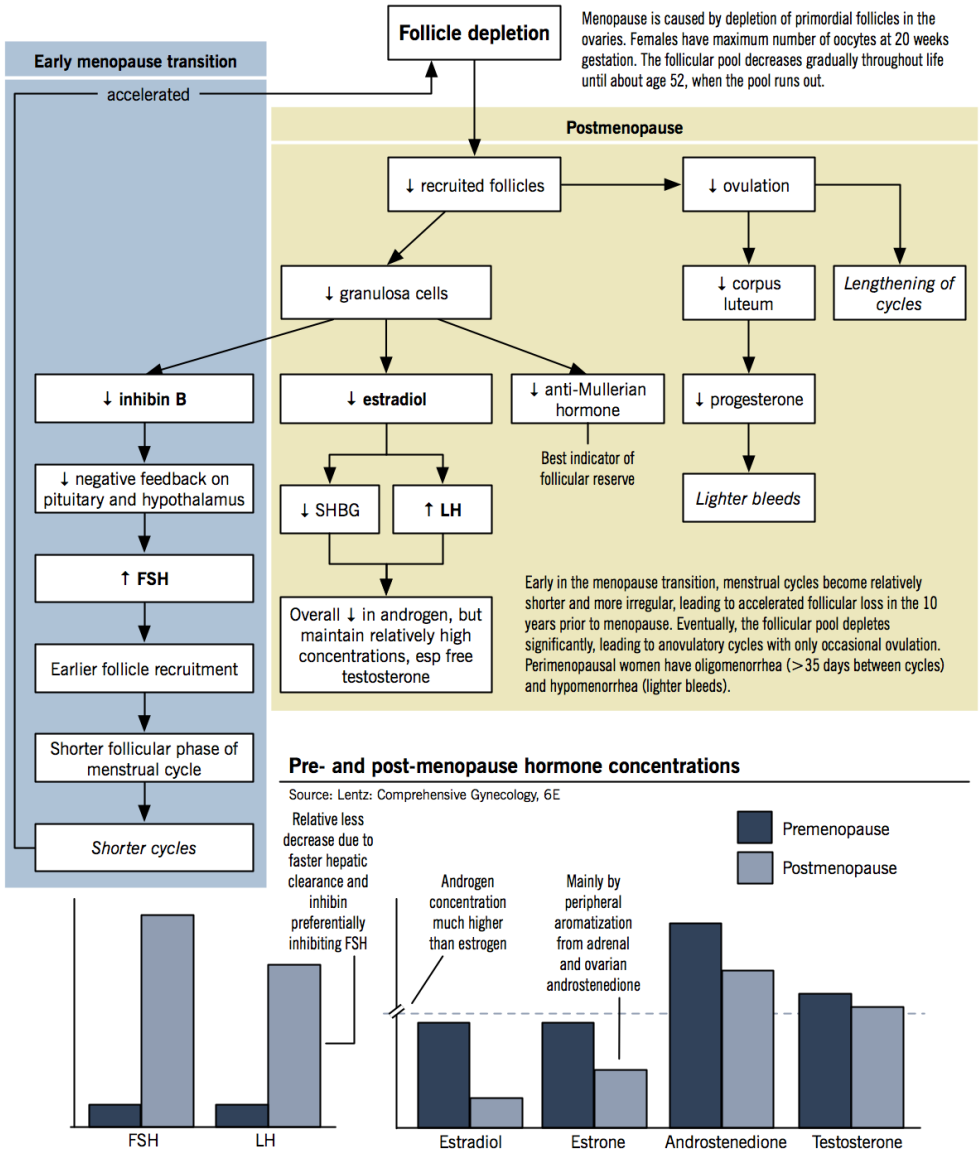
Anna Dul and Eric Wong



Pathophysiology of menopausal transition

Eric Wong

Source: Principles of Gender-Specific Medicine, 2E



Pre- and post-menopause hormone concentrations

Source: Lentz: Comprehensive Gynecology, 6E

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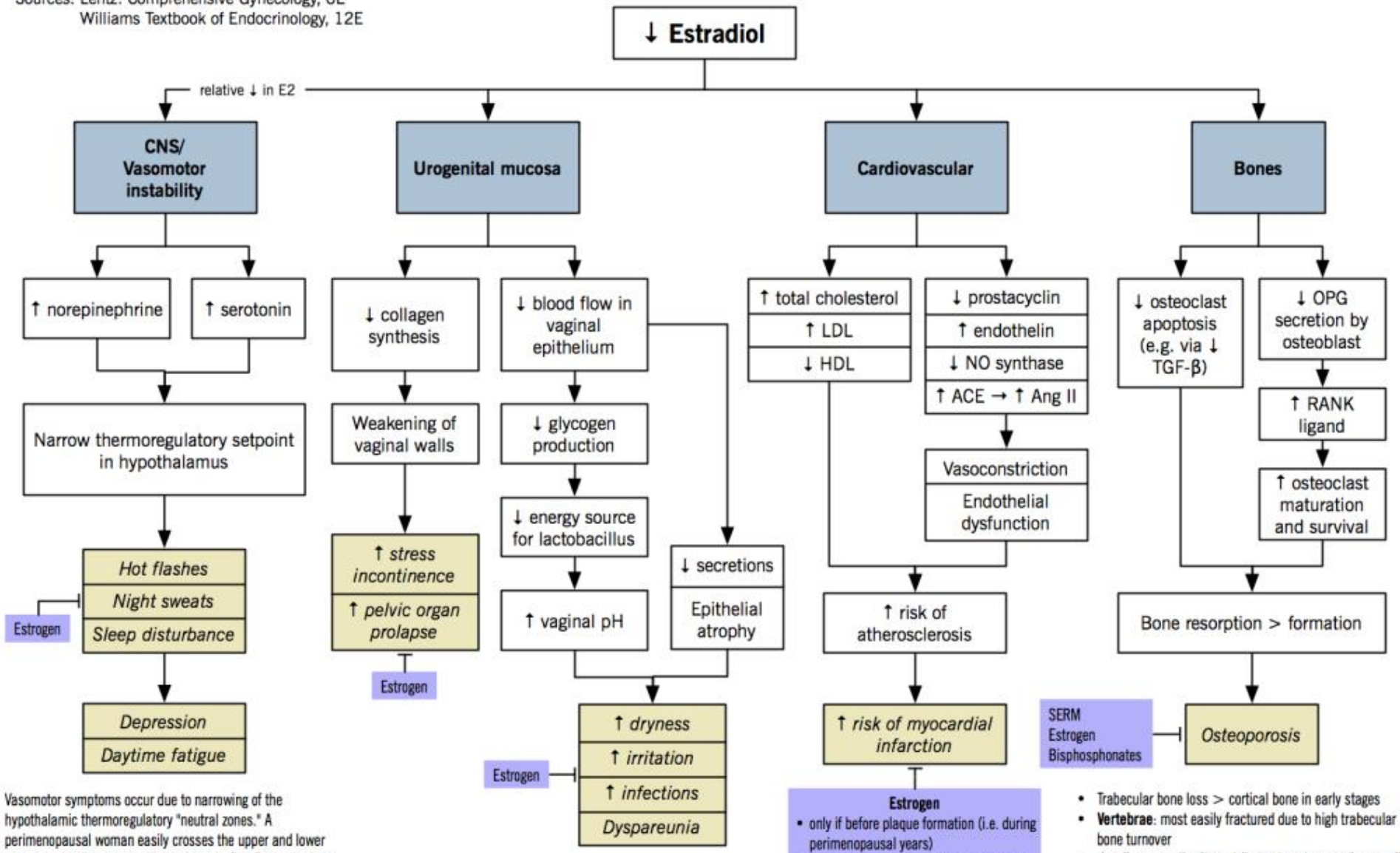
Pathophysiology of menopause organ changes

Eric Wong

Sources: Lentz: Comprehensive Gynecology, 6E
Williams Textbook of Endocrinology, 12E



Vasomotor symptoms occur due to narrowing of the hypothalamic thermoregulatory "neutral zones." A perimenopausal woman easily crosses the upper and lower setpoints, leading to vasodilation/sweats (hot flashes) when body is slightly warm and chills/shivers when slightly cool. The symptoms are worst at night, leading to frequent wakings and poor sleep quality. This effect is due to changes in estrogen level rather than absolute deficiency. Unlike other menopause changes, this will improve over time.

Estrogen

- only if before plaque formation (i.e. during perimenopausal years)
- once atherosclerotic plaques are formed, exogenous estrogen will destabilize plaques and lead to thrombus formation

- Trabecular bone loss > cortical bone in early stages
- **Vertebrae**: most easily fractured due to high trabecular bone turnover
- ↓ collagen synthesis contributes to osteoporosis as well
- Weight-bearing exercises, vitamin D, and calcium are important lifestyle factors in reducing osteoporosis

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Patofyziologie těhotenství

Fetoplacentární jednotka

Fetoplacentární jednotka:

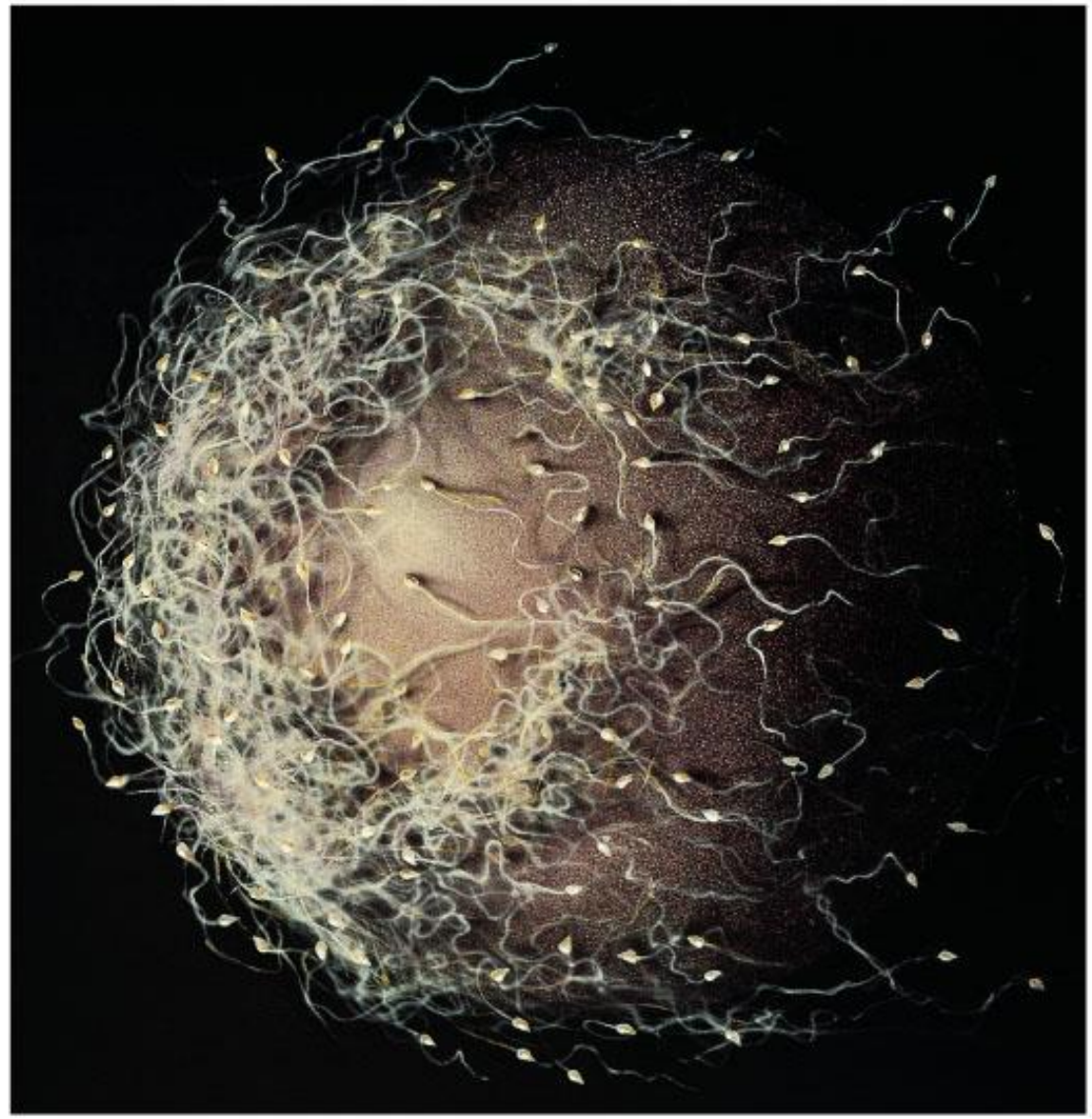
- se skládá **z placenty, nadledvin plodu a jater plodu**. Jedná se o interaktivní endokrinní entitu**.**

V této jednotce jsou nadledviny fétu primárním zdrojem dehydroepiandrosteronu. Ten je dále metabolizován fetálními játry a placentou na široké spektrum estrogenů.

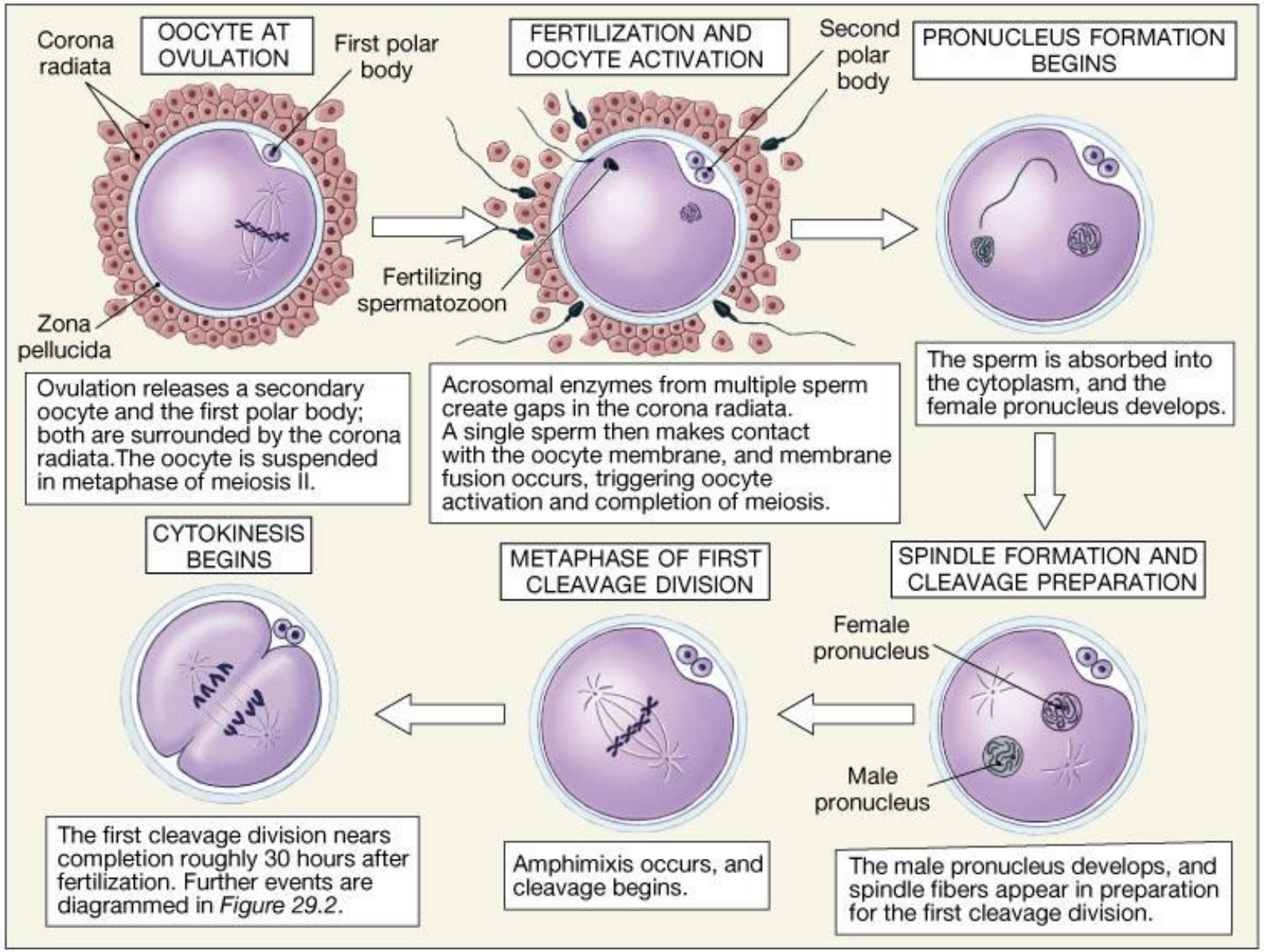
Existuje několik nemocí, které mohou postihnout fetální i mateřské nadledviny během těhotenství. Nejčastěji se jedná o deficit **steroid 21-hydroxylázy**, což vede k abnormalitám v sexuálním vývoji a může vést až k ohrožení života novorozence.

Těhotenství je poznamenáno akteracemi v několika endokrinních systémech, zejména systému renin-angiotenzin-aldosteron a systému hypothalamus-hypofýza-nadledvina.

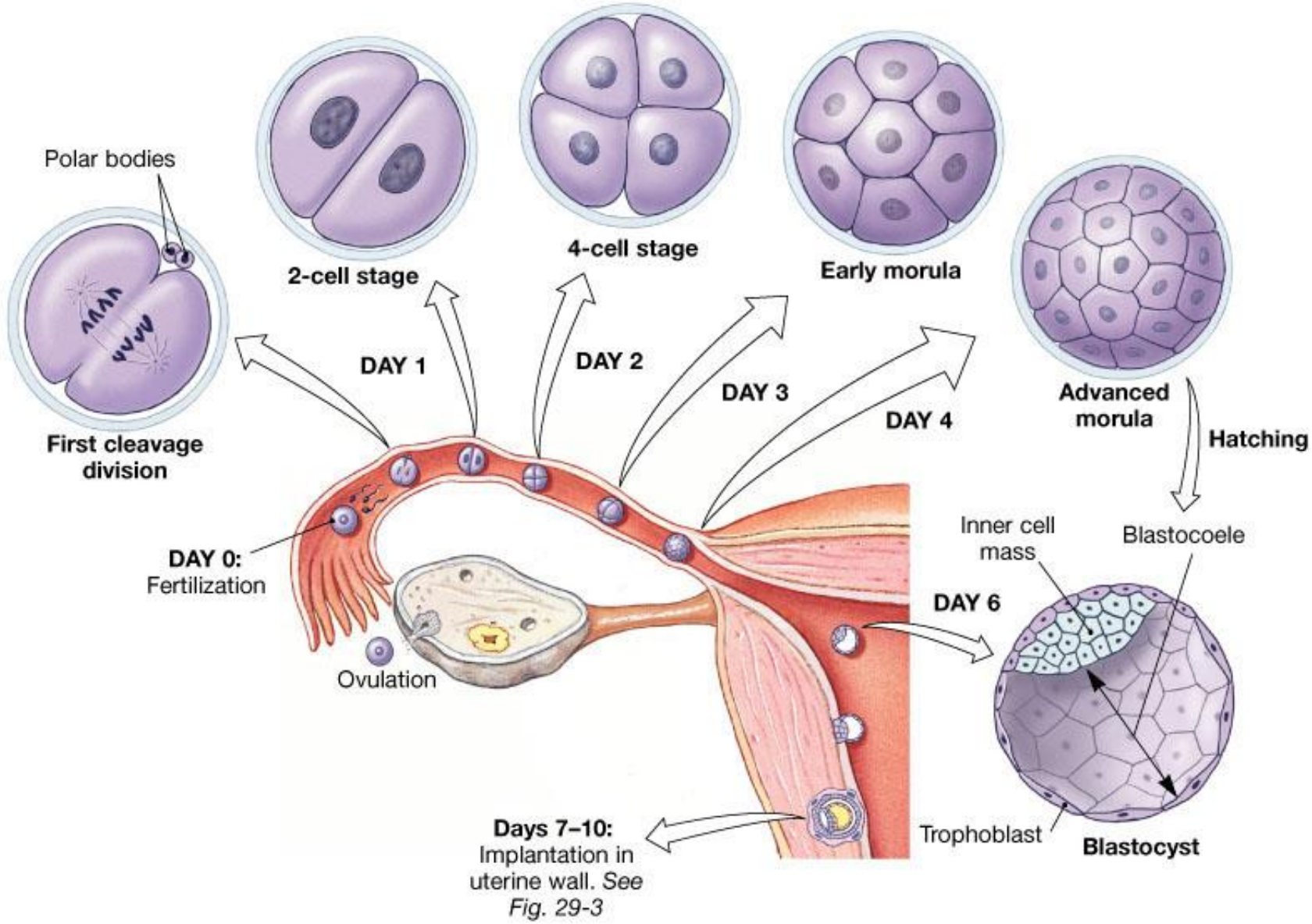
Maternální abnormality jsou asociovány s markantním rizikem maternální morbidity a mortality. Naštěstí jsou raritní.



(a)



https://embryology.med.unsw.edu.au/embryology/index.php/



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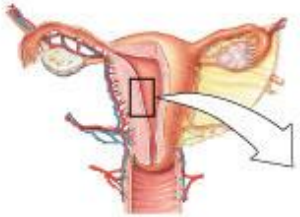
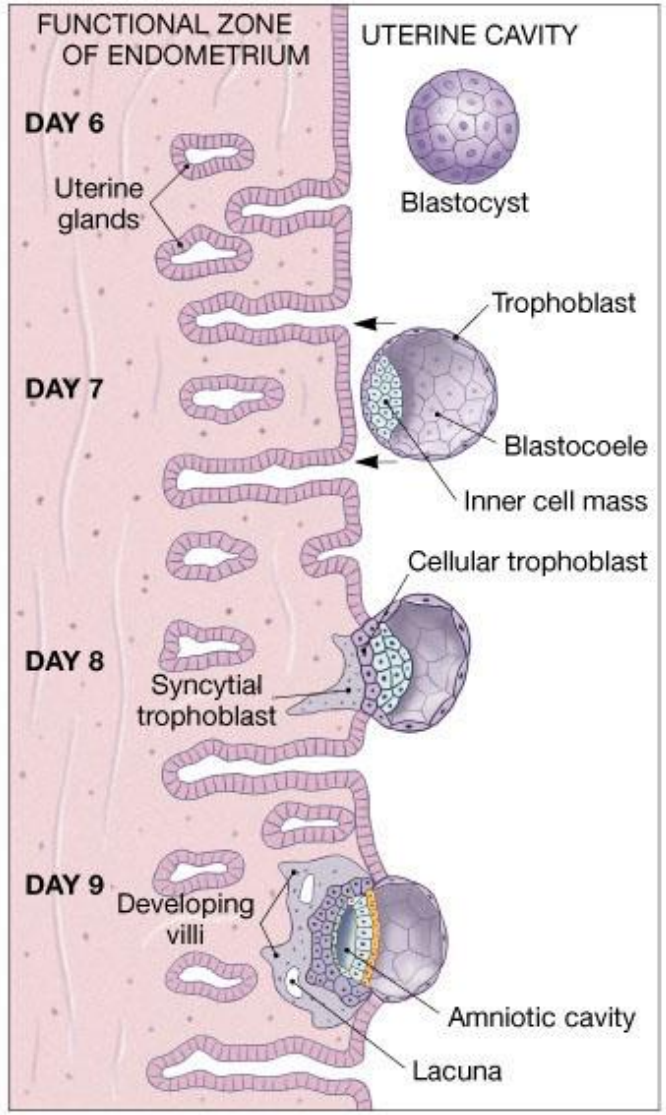
Implantace





Přibližně za 7 dní po oplození

Trofoblast se zvětšuje a šíří

Mateřská krev vtéká do otevřených lakun

Gastrulace

Embryonální terčík složený z následujících vrstev:

- Endoderm
- Mesoderm
- Ektoderm

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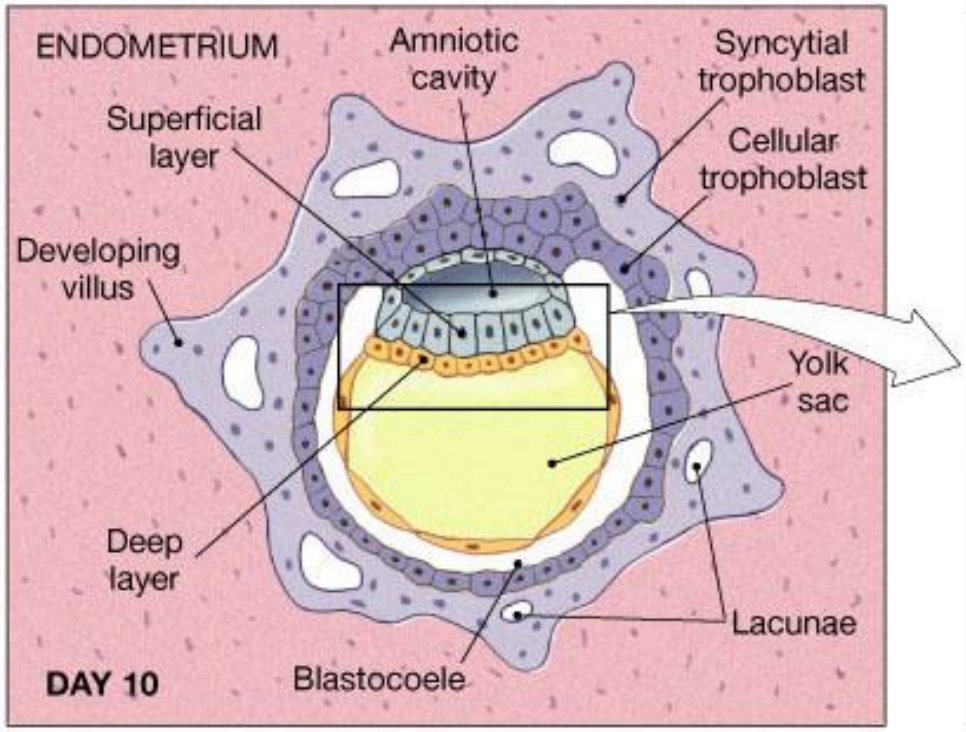
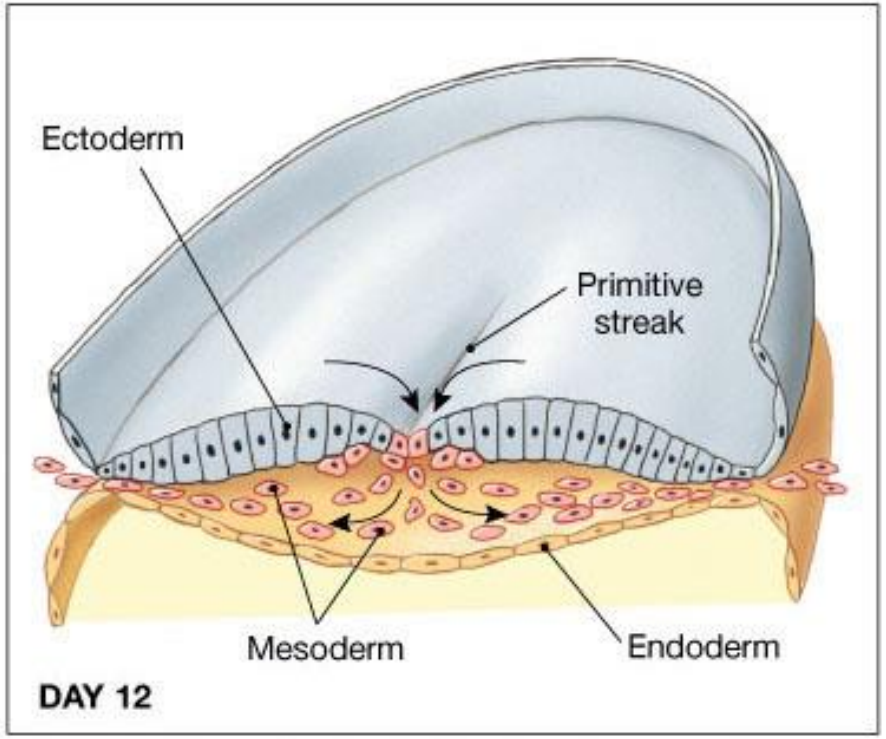
Vnitřní buněčná masa a gastrulace



The inner cell mass begins as two layers: a superficial layer, facing the amniotic cavity, and a deep layer, exposed to the blastocoele. Migration of cells around the amniotic cavity is the first step in the formation of the amnion. Migration of cells around the edges of the blastocoele is the first step in yolk sac formation.



Migration of superficial cells into the interior creates a third layer. From the time this process (gastrulation) begins, the superficial layer is called *ectoderm*, the deep layer *endoderm*, and the migrating cells *mesoderm*.

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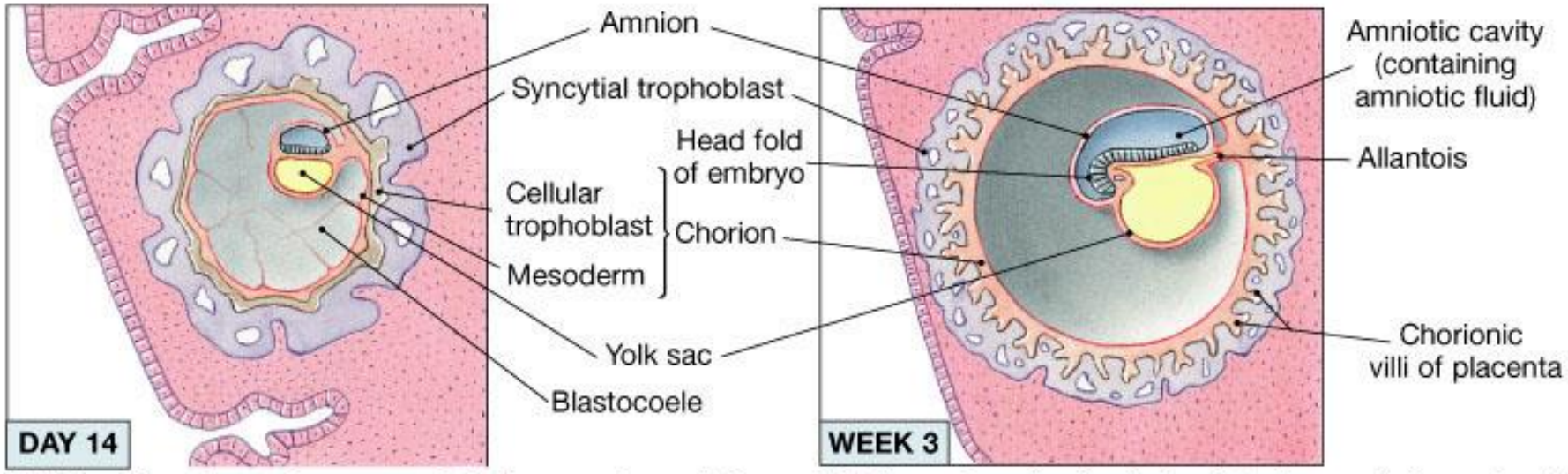
Extraembryonální membrány



(a) Migration of mesoderm around the inner surface of the trophoblast creates the chorion. Mesodermal migration around the outside of the amniotic cavity, between the ectodermal cells and the trophoblast, forms the amnion. Mesodermal migration around the endodermal pouch creates the yolk sac.

(b) The embryonic disc bulges into the amniotic cavity at the head fold. The allantois, an endodermal extension surrounded by mesoderm, extends toward the trophoblast.

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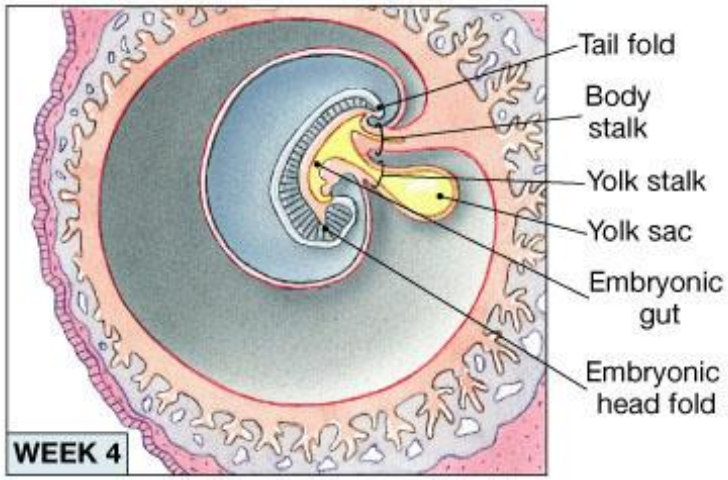
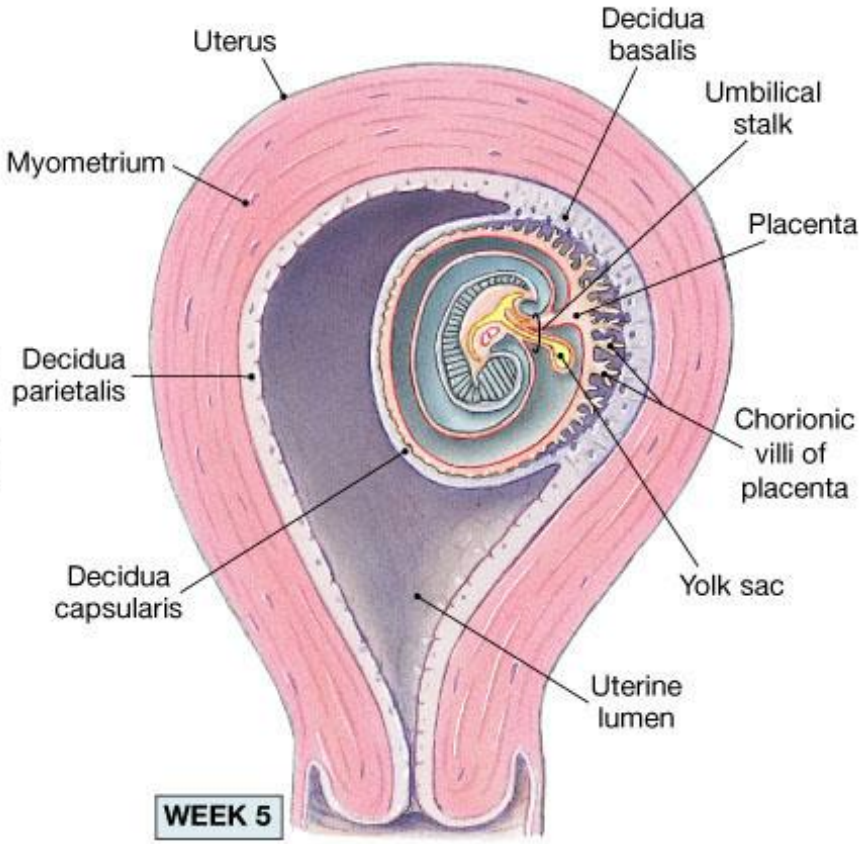
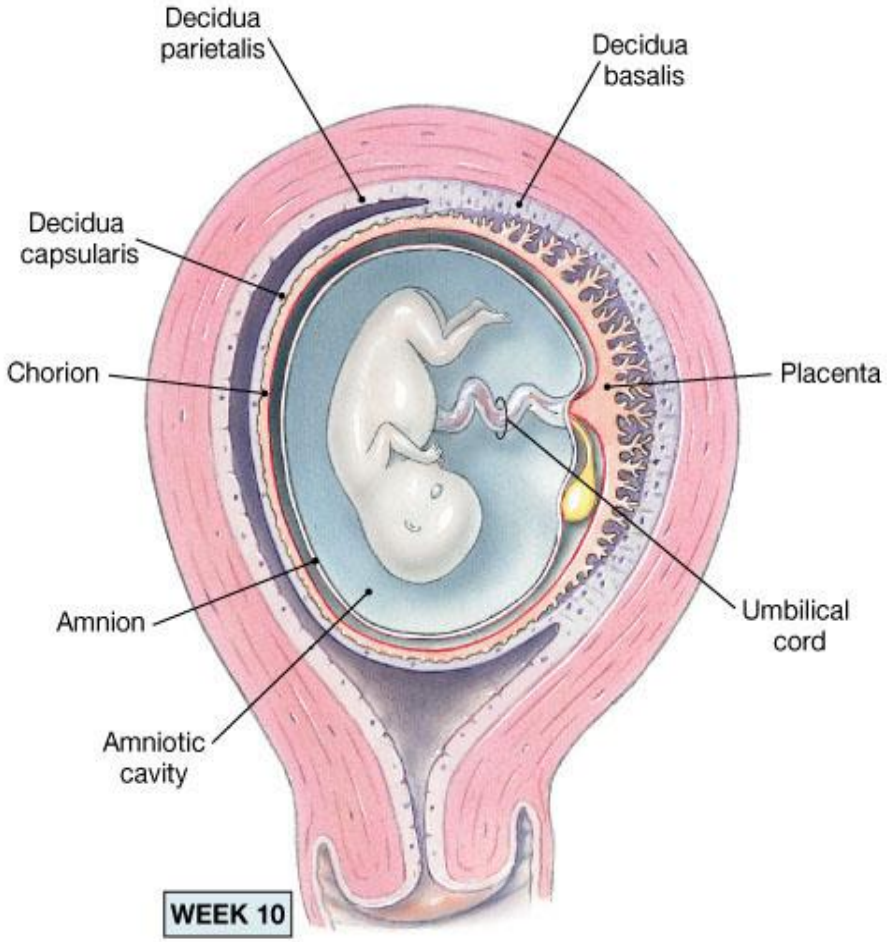
Tvorba placenty



(c) The embryo now has a head fold and a tall fold. Constriction of the connection between the embryo and the surrounding trophoblast narrows the yolk stalk and body stalk.



(d) The developing embryo and extraembryonic membranes bulge into the uterine cavity. The trophoblast pushing out into the uterine lumen remains covered by endometrium but no longer participates in nutrient absorption and embryo support. The embryo moves away from the placenta, and the body stalk and yolk stalk fuse to form an umbilical stalk.



(e) The amnion has expanded greatly, filling the uterine cavity. The fetus is connected to the placenta by an elongated umbilical cord that contains a portion of the allantois, blood vessels, and the remnants of the yolk stalk.

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Anatomie embrya

Žloutkový váček

Významné místo tvorby krevních buněk

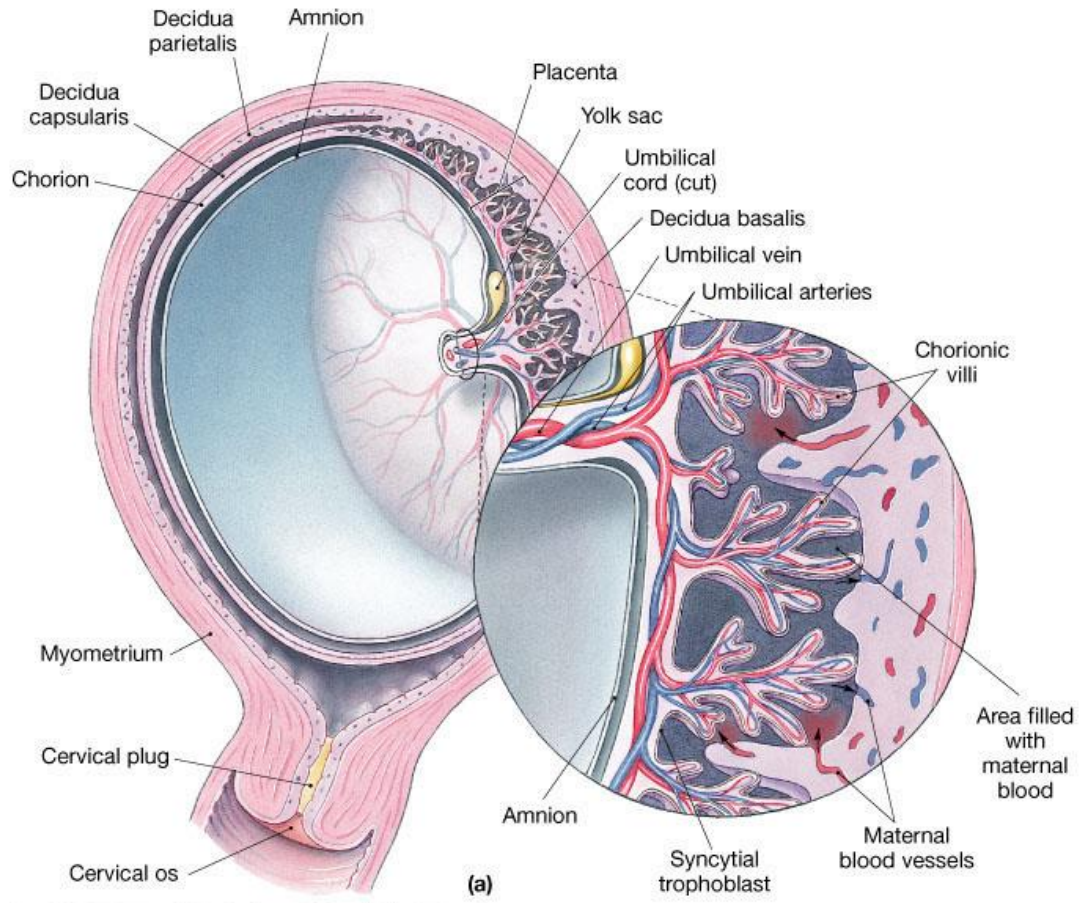
Amnion

Obklopuje tekutinu, která obklopuje embryo

Allantois

Močový měchýř

Chorion



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Charakteristické vlastnosti fetoplacentárního oběhu

- Paralelní uspořádání dvou arteriálních systému a odpovídajících komor
- Mísení venózního návratu a preferenčního toku krve.
- Vysoký odpor a nízký průtok plicní cirkulací
- Nízký odpor a vysoký průtok placentární cirkulací.
- Přítomnost shuntů (3 shunty
    - Ductus venosus
    - Foramen ovale
    - Ductus arteriosus

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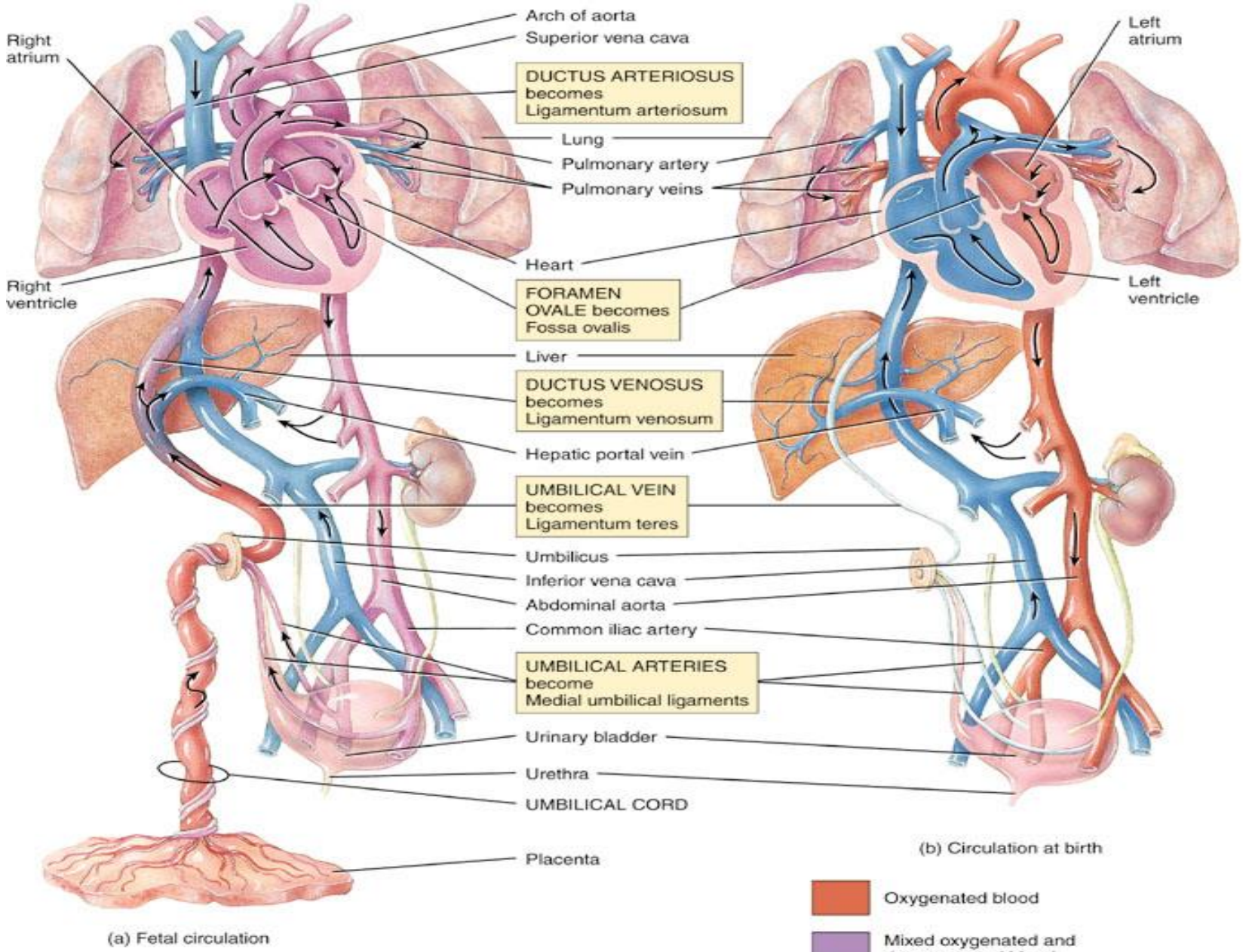

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Fetální krev

Fetální hemoglobin

Typ	Popis	Řetězce
Hemoglobin F	Fetální hemoglobin	2 alfa 2 gamma
Hemoglobin A	Metylací gamma řetězců se od 32-34. týdne gestace tvoří HbA	2 alfa 2 beta
Hemoglobin A_2	U zdravého plodu v malém množství, po porodu stoupá	2 alfa 2 delta

Disociační křivka kyslíku ve fetální a mateřské krvi

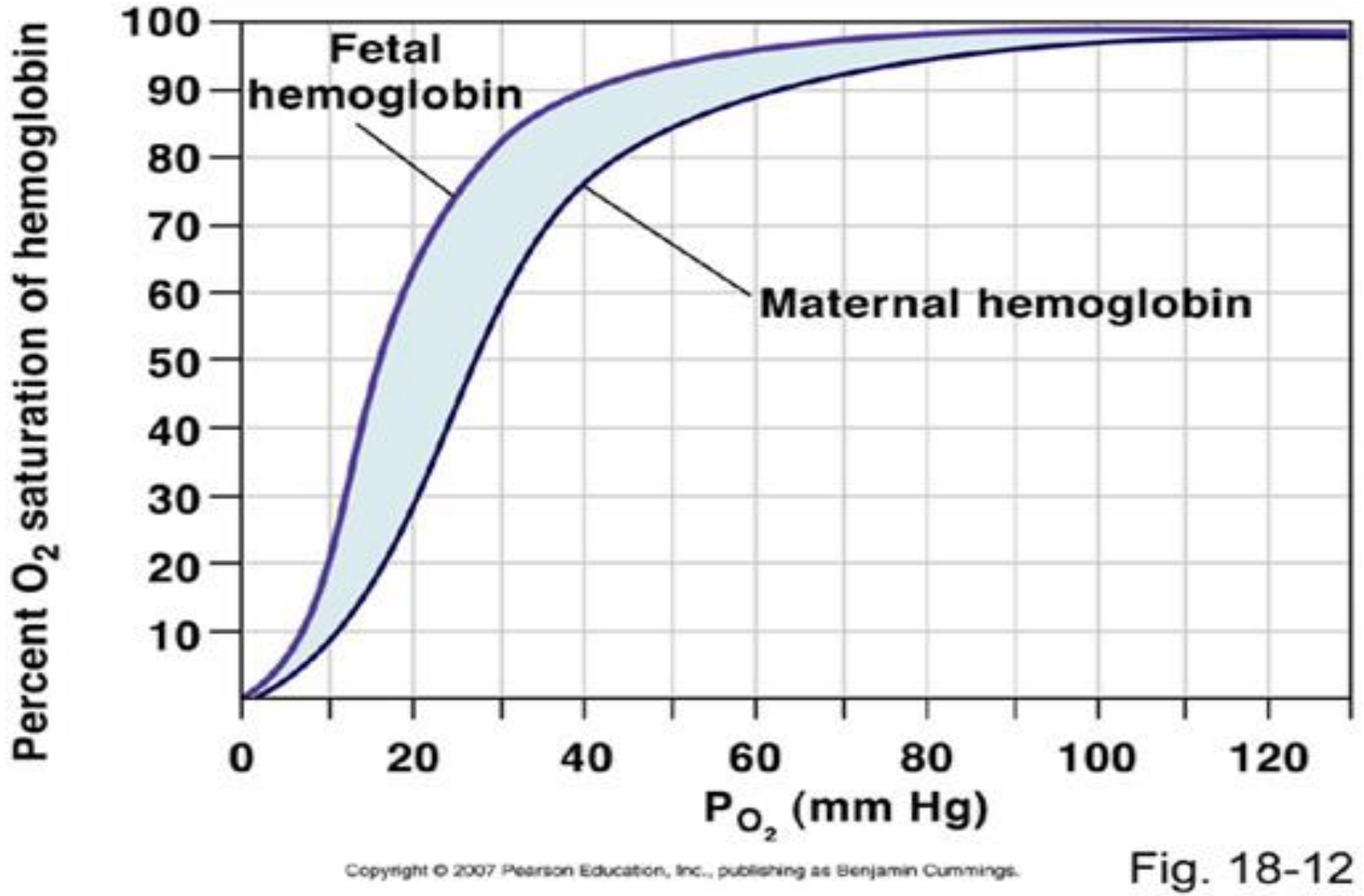
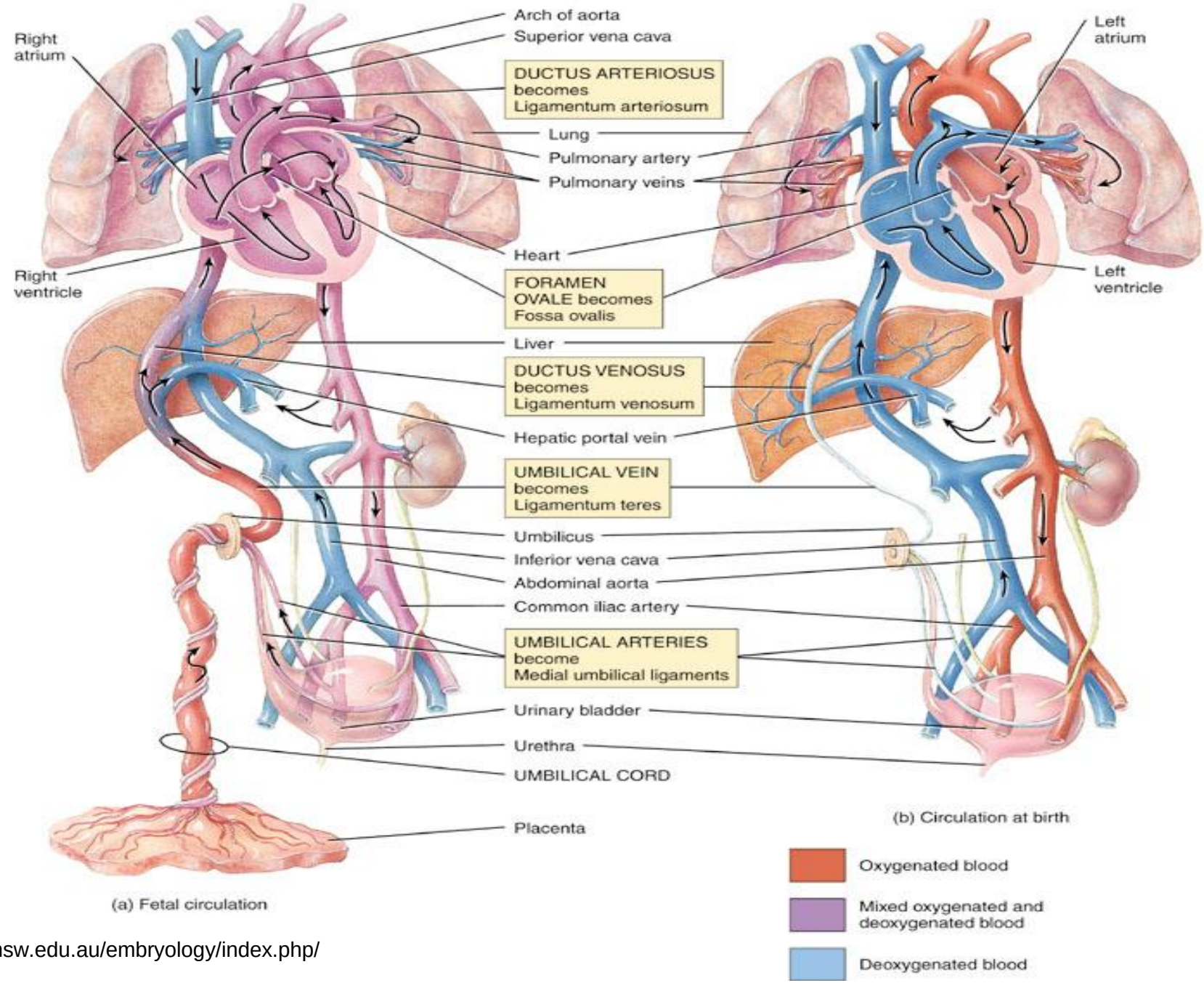


Fig. 18-12

Source: http://www.colorado.edu/intphys/Class/IPHY3430-200/image/18-12.jpg



https://embryology.med.unsw.edu.au/embryology/index.php/

Tok fetální krve I

Arterializace v **placentě** –

Cestou **v.umbillicalis** do těla plodu
Zčásti cestou **ductus venosus** obchvat jater (zbytek skrze játra)
Smísení s venózní krví z dolní poloviny těla (při vyústění do **vena cava inferior**) – **Pravá síň**
Skrze **foramen ovale** do **levé síně**
Levá komora, Aorta
Tepny hlavy a horní poloviny těla

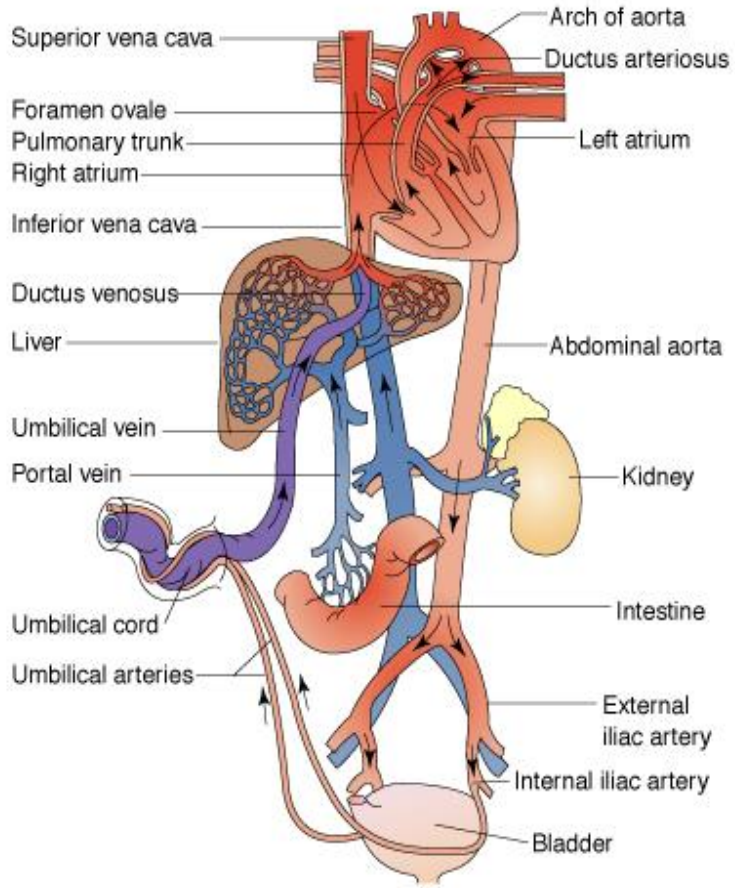


Figure 26-27 Fetal circulation.

ns & Wilkins. Instructor's Resource CD-ROM to Accompany *Porth's Pathophysiology: Concepts of Altered H*

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Tok fetální krve II

- Krev z horní poloviny těla **(vena cava superior)** do pravé síně
- **Pravá komora**
- 1/3 do plic (**truncus pulmonalis**, arteriae pulmonales)
- Zbylé 2/3 skrze **ductus arteriosus** do aorty

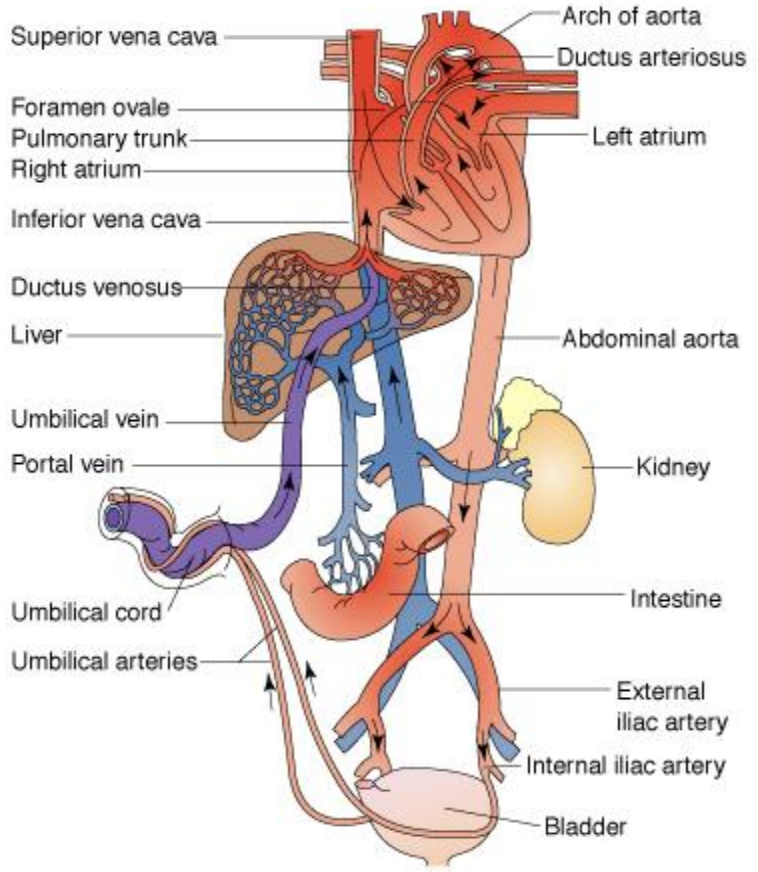

Figure 26-27 Fetal circulation.

ns & Wilkins. Instructor's Resource CD-ROM to Accompany *Porth's Pathophysiology: Concepts of Altered H*

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Tok fetální krve III

- **Ductus arteriosus** (venózní krev) vúsťuje do aorty až po odstupu velkých tepen

- Větší část cestou **a.umbillicalis** do placenty
- Zbytek do dolní poloviny těla
- Pravé a levé srdce zapojeny paralelně

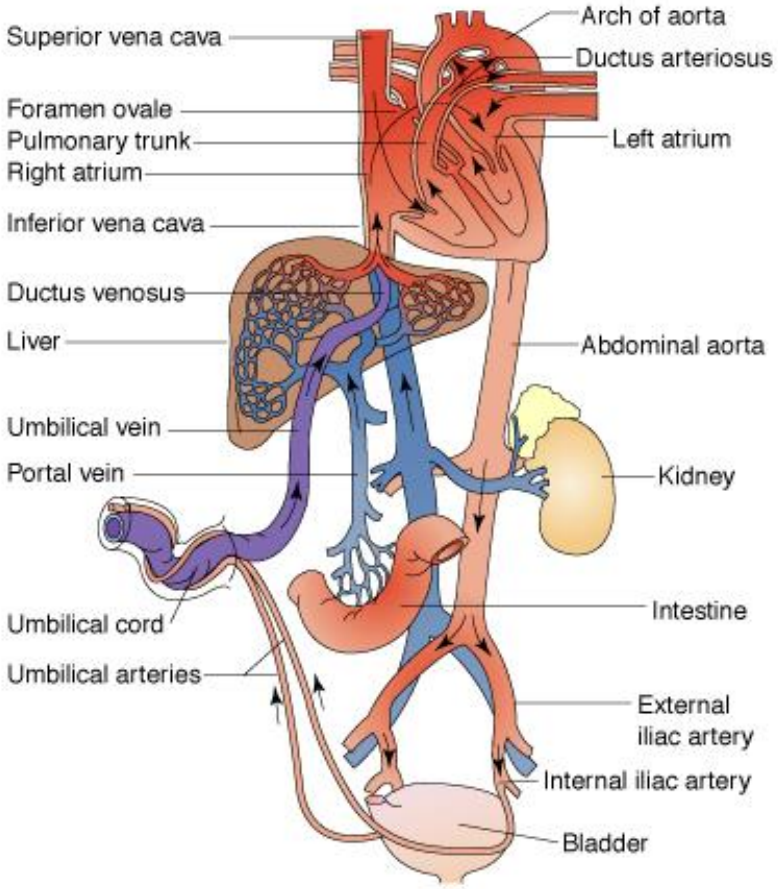

Figure 26-27 Fetal circulation.

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Uzávěr shuntů

Shunt	Funkční uzávěr	Anatomický uzávěr	Pozůstatek
Ductus arteriosus	10 – 96 hodin po porodu	2 – 3 týdnů po porodu	Ligamentum arteriosum
Formamen ovale	Několik minut po porodu	Rok po porodu	Fossa ovalis
Ductus venosus	Několik minut po porodu	3 – 7 dní po porodu	Ligamentum venosum

Umbilikální tepny – umbilikální ligamenta

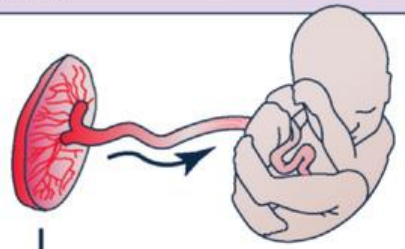
Umbilikální žíla → Ligamentum teres

Patofyziologie předčasného porodu

Patofyziologie předčasného porodu II

PRENATAL

Sleep development altered by:
- Preterm birth
- Infection/inflammation
- Hypoxia-ischaemia
- Intrauterine growth restriction (IUGR)



Placental hormones lost at birth - important for neurosteroid production, supporting:
- Neural development
- GABA neurotransmitter regulation and transition from excitatory to inhibitory
- Neuroprotection

Delayed sleep state maturation

Reduced glia and neuron production/maturation

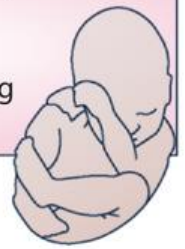
Impaired neural network connectivity

Impaired neurotransmitter function

POSTNATAL

Sleep development affected by:
- Gestational age at birth, IUGR, chronic inflammation
- Brain injury –impaired brain maturation
- Environmental/socioeconomic factors, parental input – sleep training
- Sleep position
- Sleep disordered breathing – obstructive sleep apnea, snoring

- Reduced sleep quantity and quality
- Delayed sleep onset
- Increased night waking
- Early chronotype?

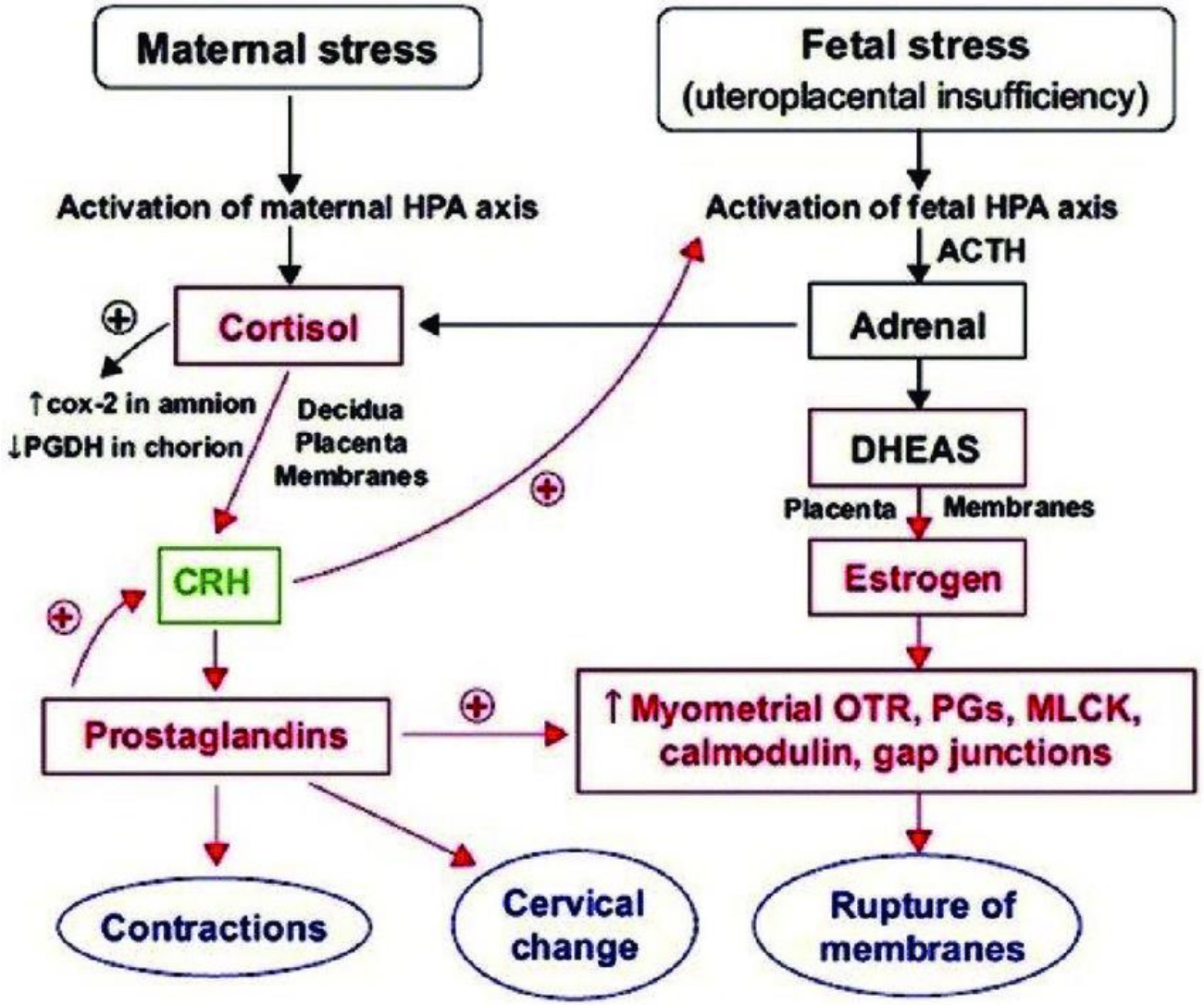


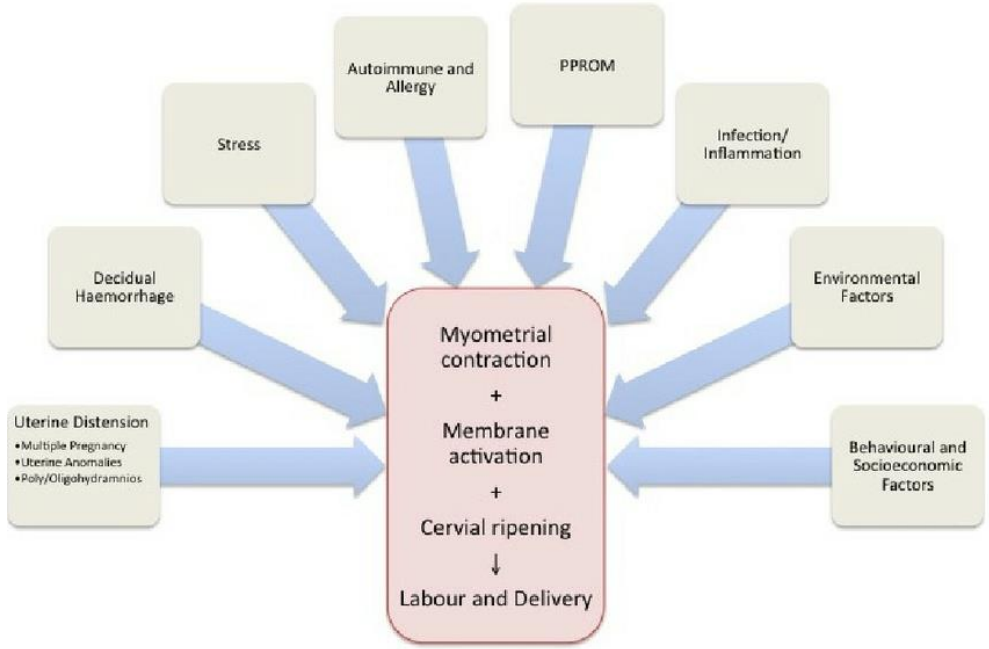
- Impaired learning, memory and cognition
- Behavioural and emotional difficulties

The Journal of Physiology

Waking up too early – the consequences of preterm birth on sleep development
Laura Bennet
David W. Walker
Rosemary S. C. Horne
First published: 24 April 2018
https://doi.org/10.1113/JP274950

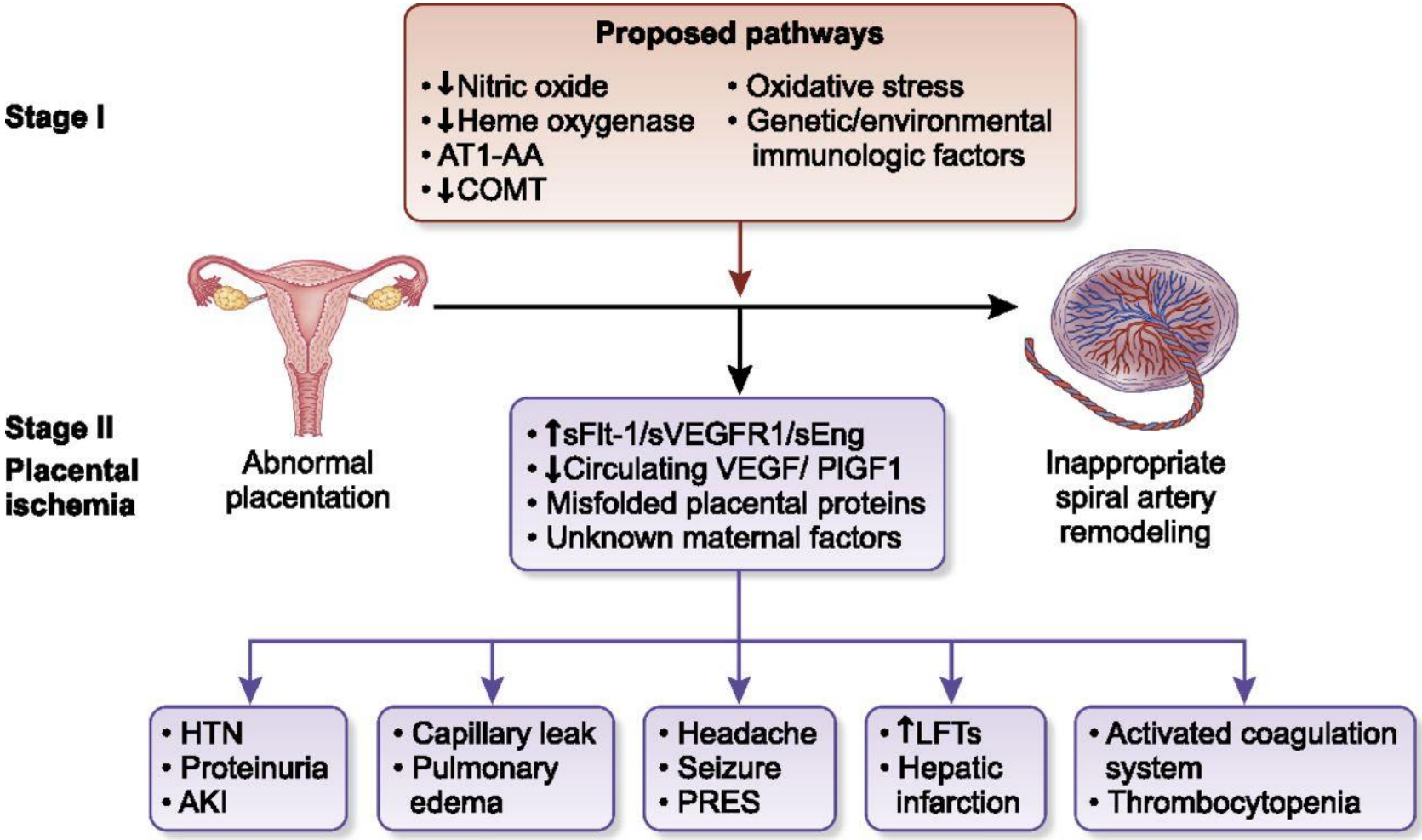
Patofyziologie předčasného porodu III





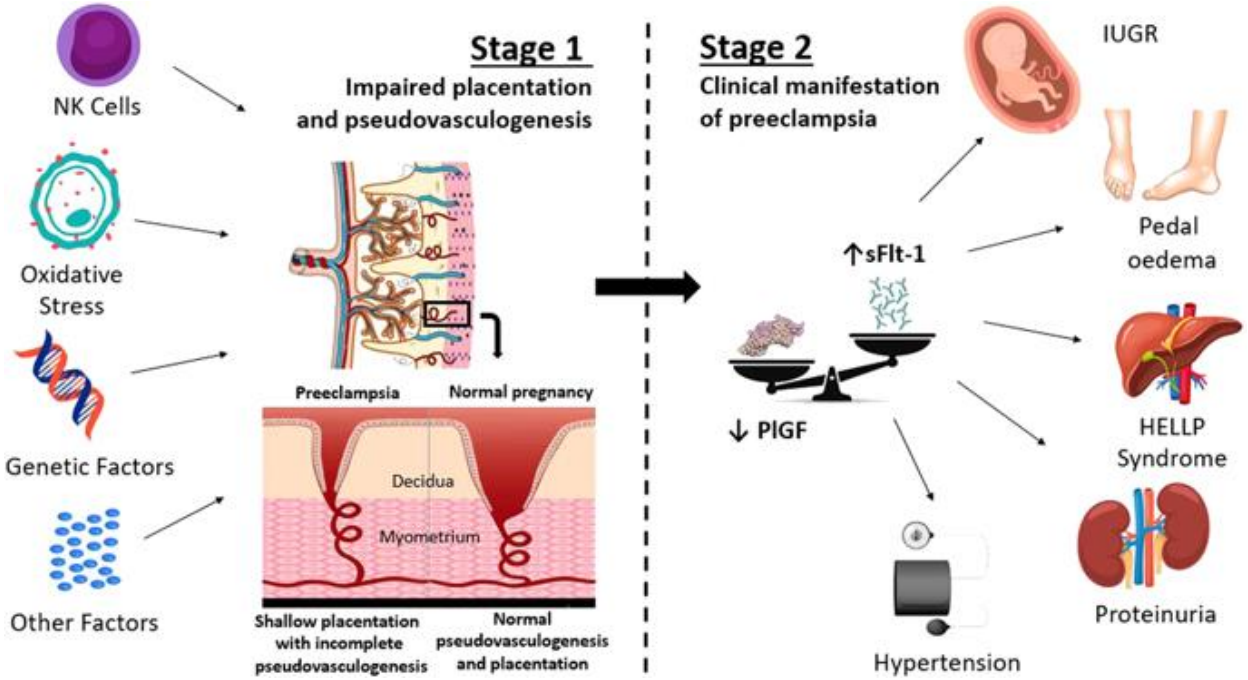
Low Birth Weight and Adverse Perinatal Outcomes
•November 2019
•DOI:
•10.5772/intechopen.89049

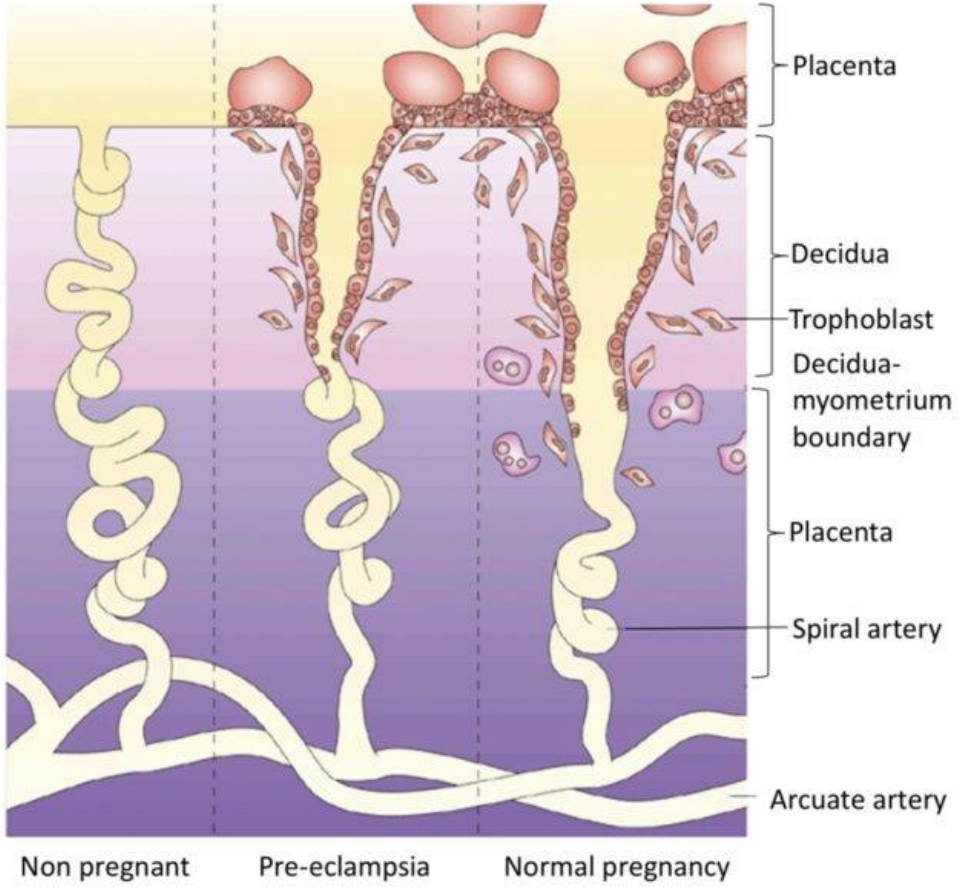
Patofyziologie preeklampsie



Elizabeth Phipps, Devika Prasanna, Wunnie Brima and Belinda Jim
CJASN June 2016, 11 (6) 1102-1113; DOI: https://doi.org/10.2215/CJN.12081115

Patofyziologie preeklampsie - II

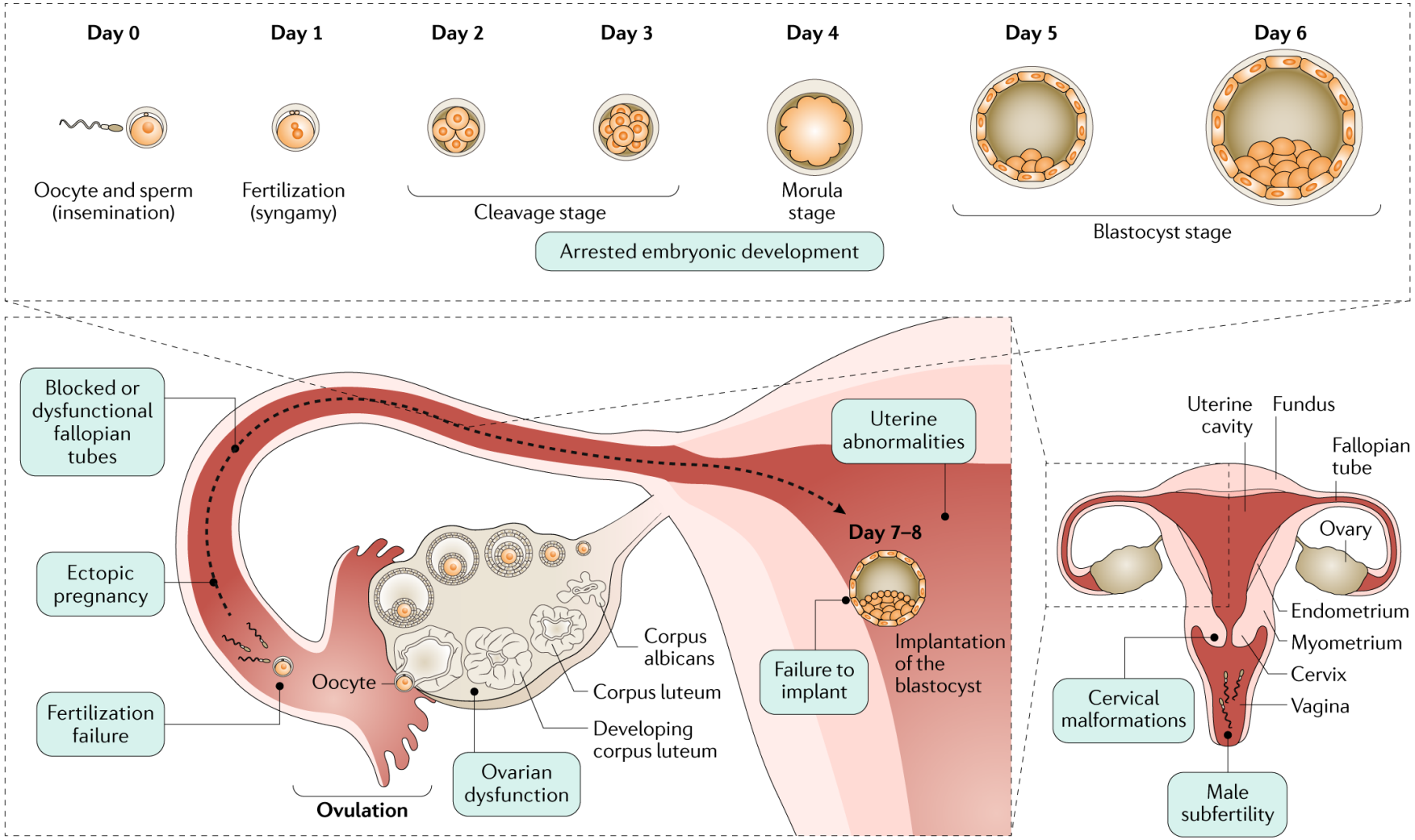




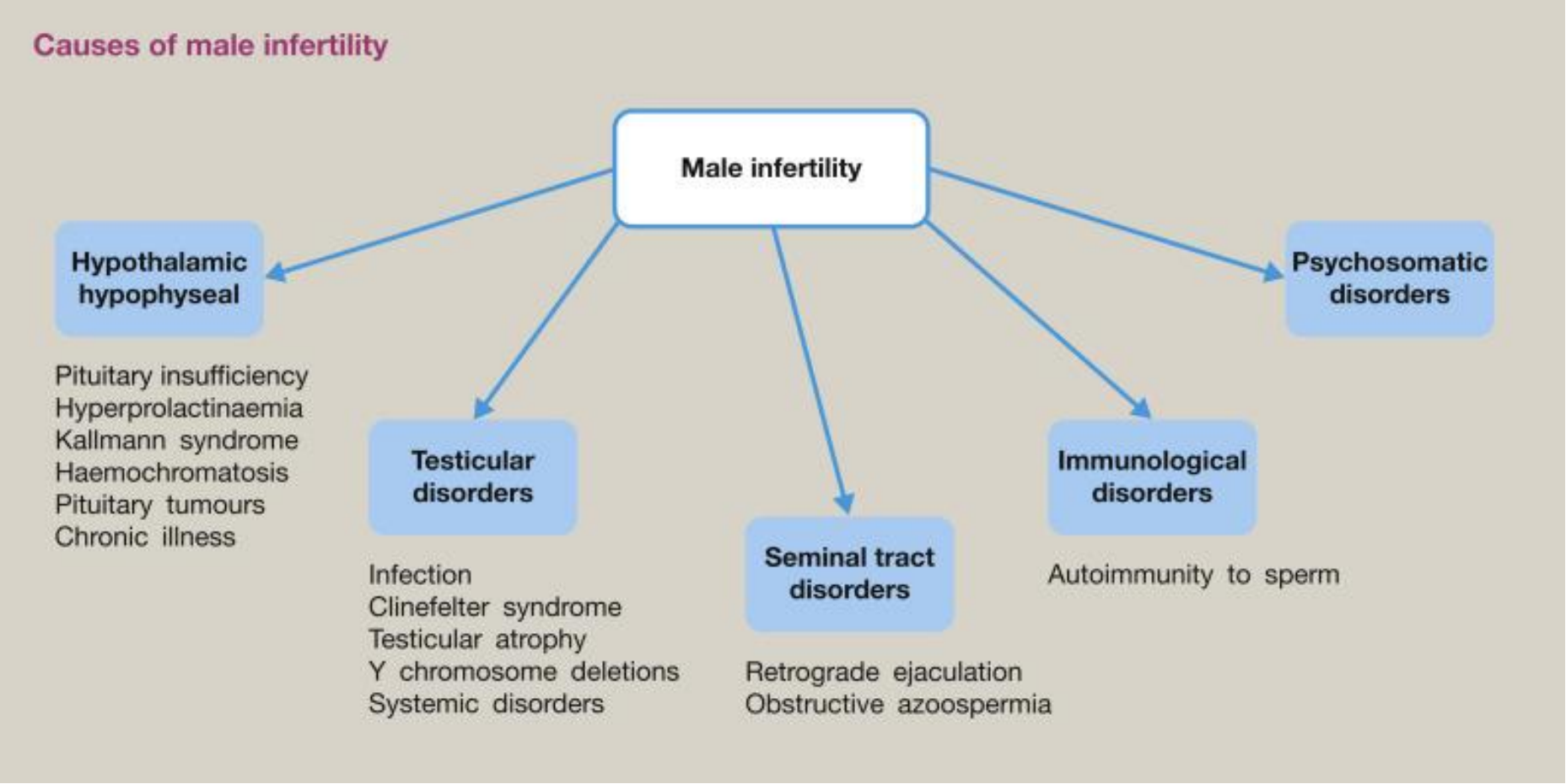
Aspirin in the **prevention** of **preeclampsia**: the **conundrum** of how, **who** and when.
Shanmugalingam R, Hennessy A, Makris A.
J Hum Hypertens. 2019 Jan;33(1):1-9. doi: 10.1038/s41371-018-0113-7.

Lina Bergman, Cerebral biomarkers in women with preeclampsia
October 2017 DOI: 10.13140/RG.2.2.30083.81445

Patofyziologie poruch koncepce – ženské faktory



Patofyziologie poruch koncepce – mužský faktor

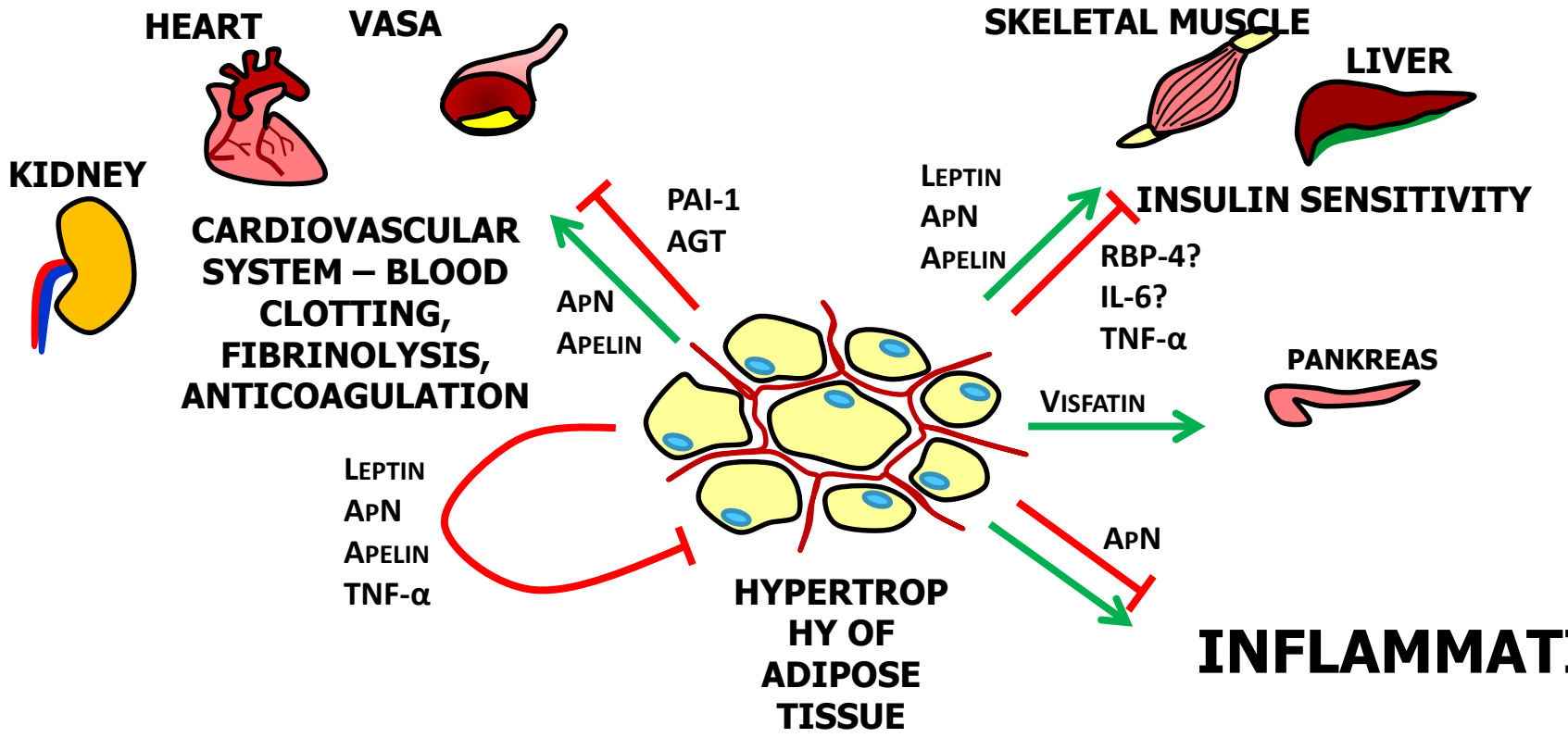


Úloha tukové tkáně v reprodukci

Bílá tuková tkáň (WAT)

Adipokiny:

- **Terminology overlap with cytokines, also referred to as „adipocytokines“:**
  - ***sensu stricto definition*: „cytokines produced in WAT“**
  - ***sensu lato*: „various substances, including cytokines and hormones, produced in WAT“**



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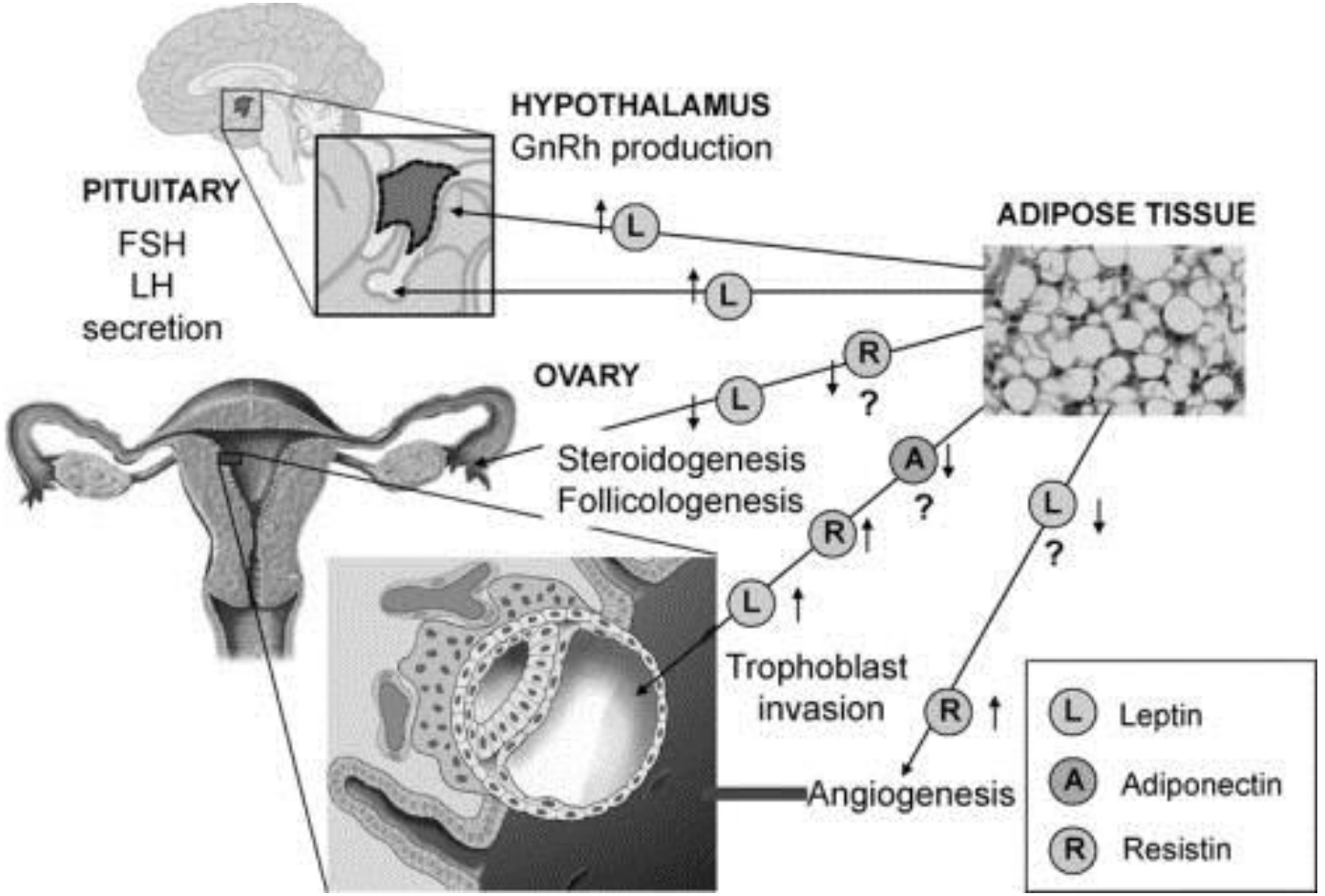
Známé účinky adipokinů v rámci řízení reprodukce u žen a v rámci rozvoje trofoblastu



Tersigni C. Obstet Gynecol Survey 2011

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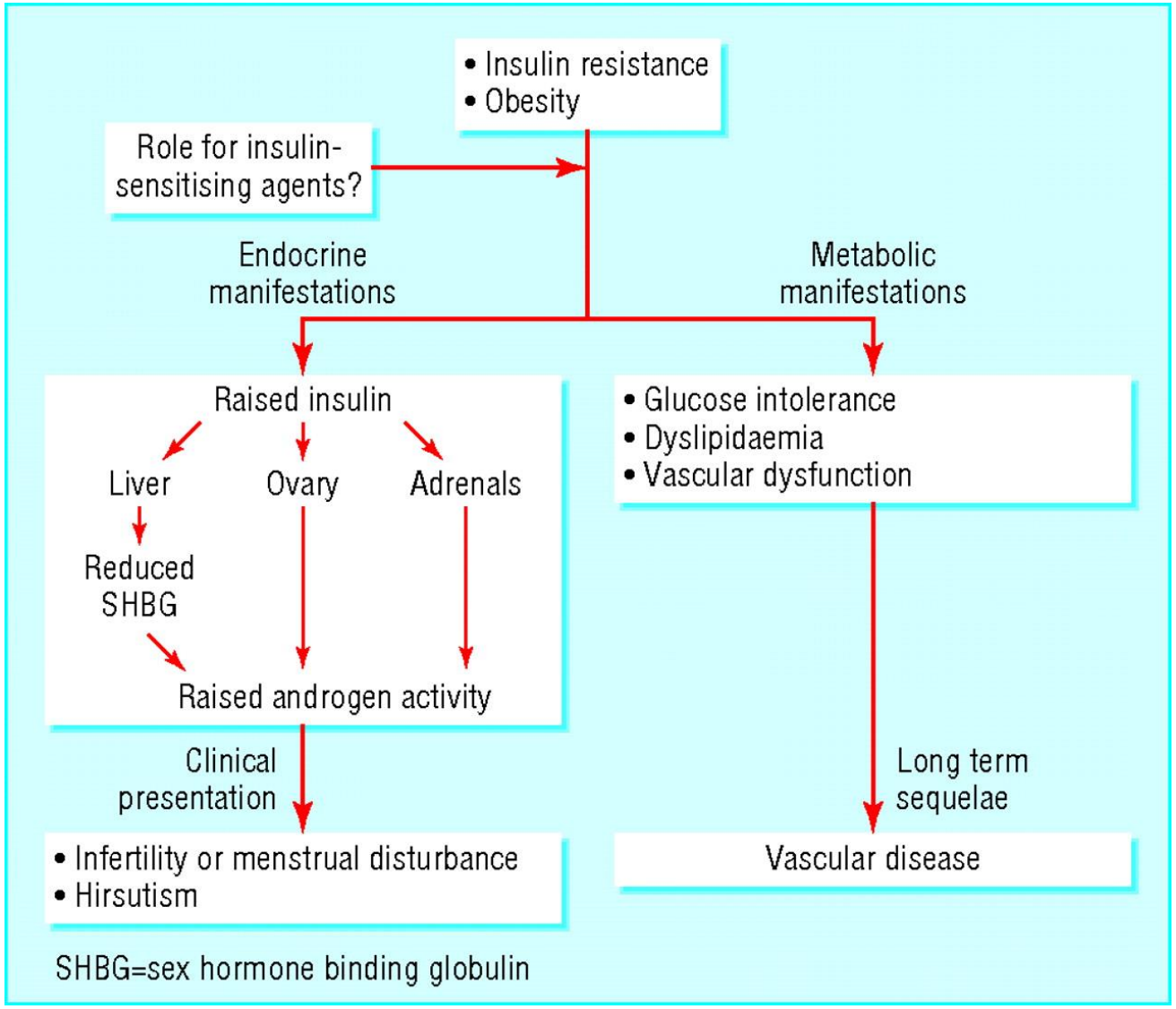
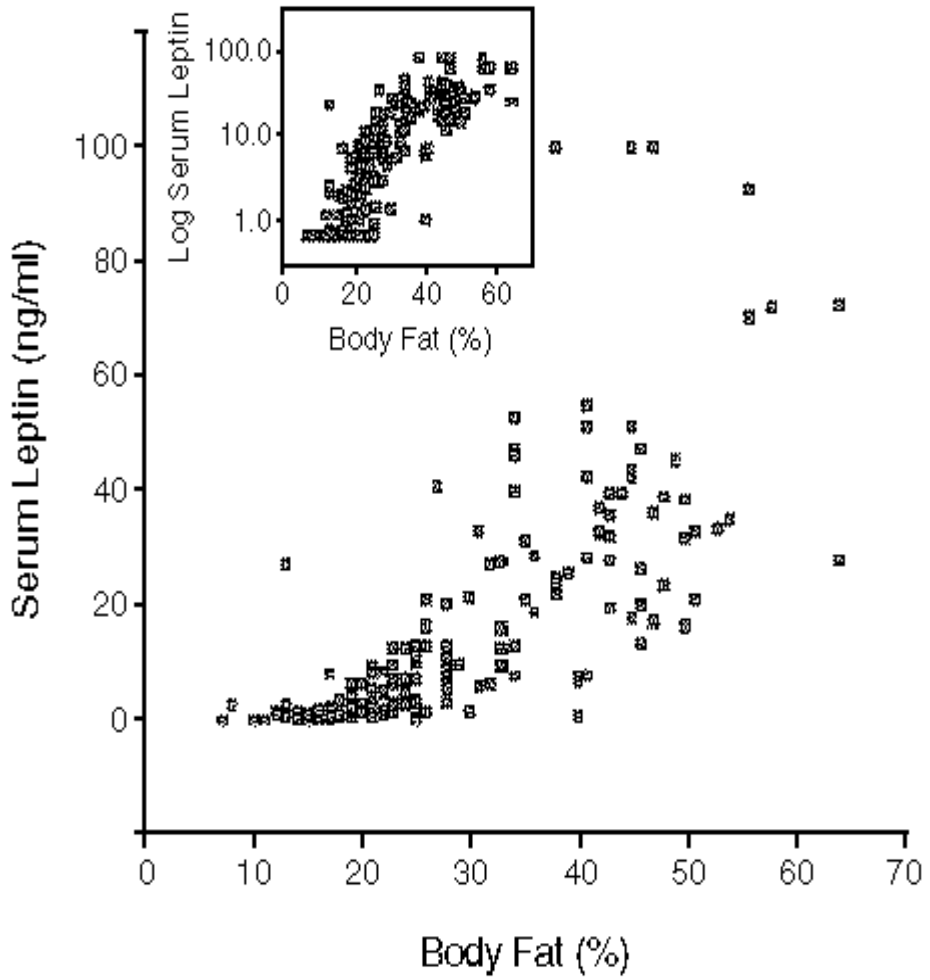
Známé účinky adipokinů v rámci obezity u žen

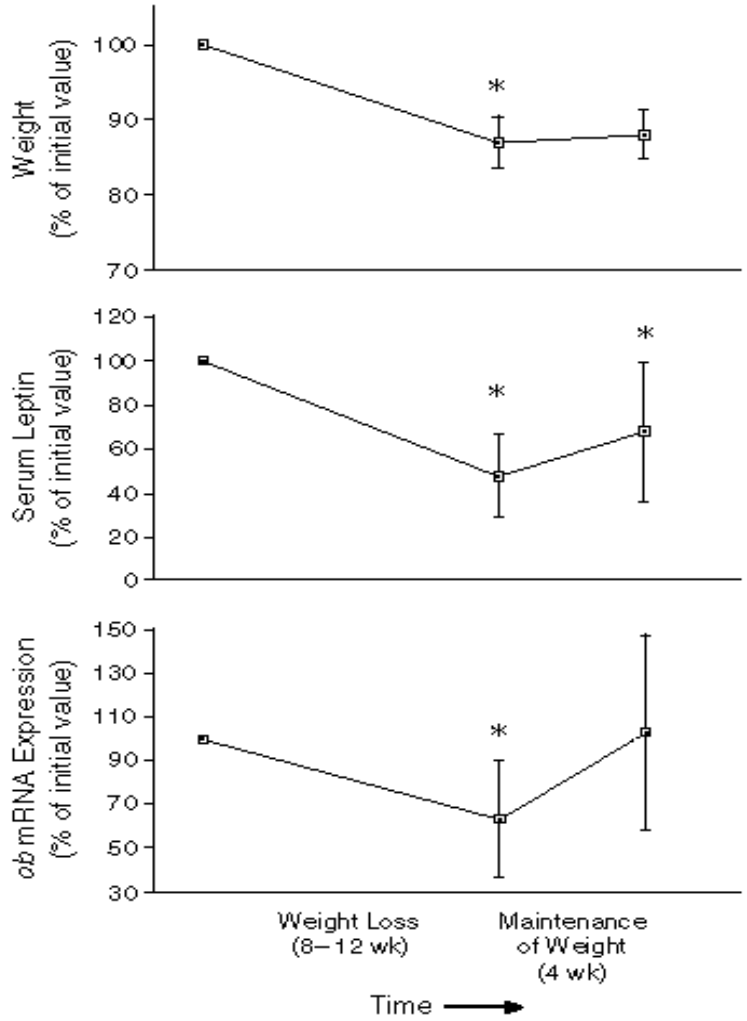


Ramsay, J. E et al. BMJ 2006

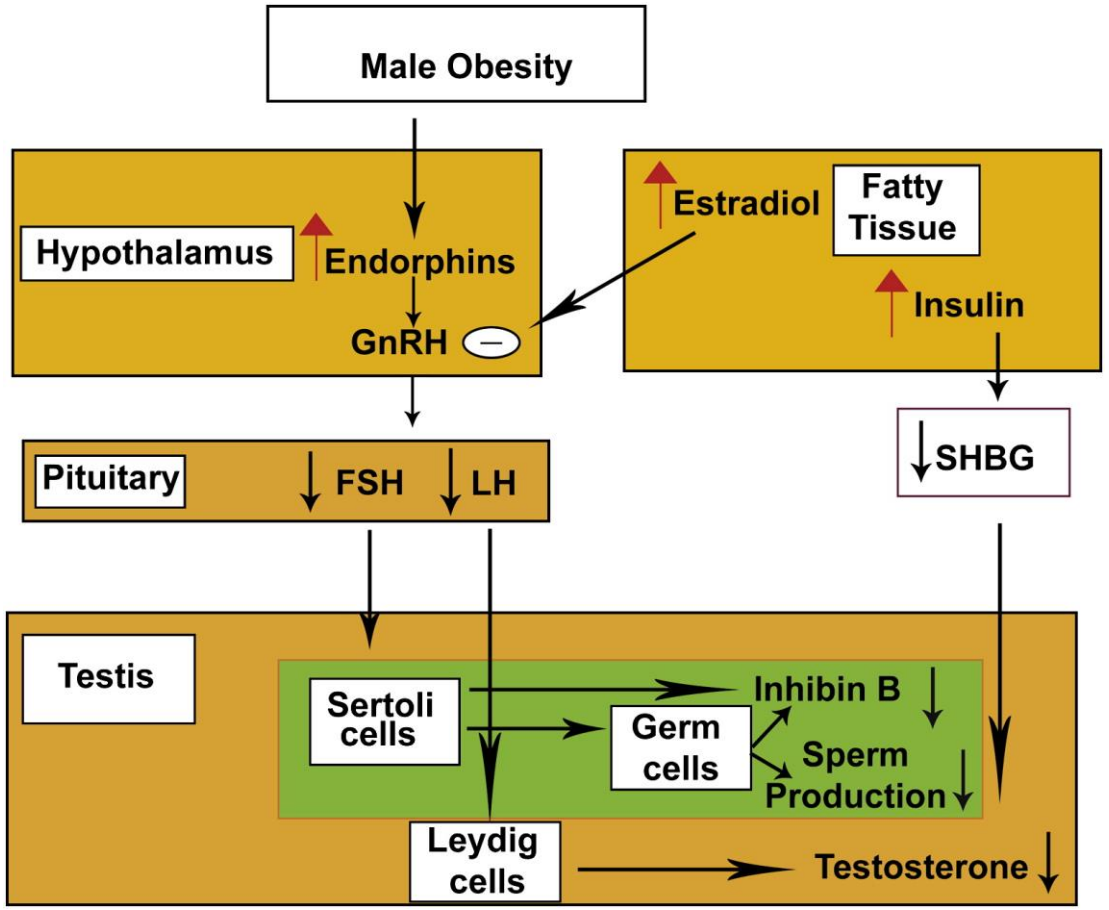
Sérové hladiny leptinu jako funkce % tělesného tuku

Considine RV. N Engl J Med 1996





Známé účinky adipokinů v rámci řízení reprodukce u mužů



Hammoud A. Fertil Steril 2008

Ještě něco? Cukr?

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Fetální programování?

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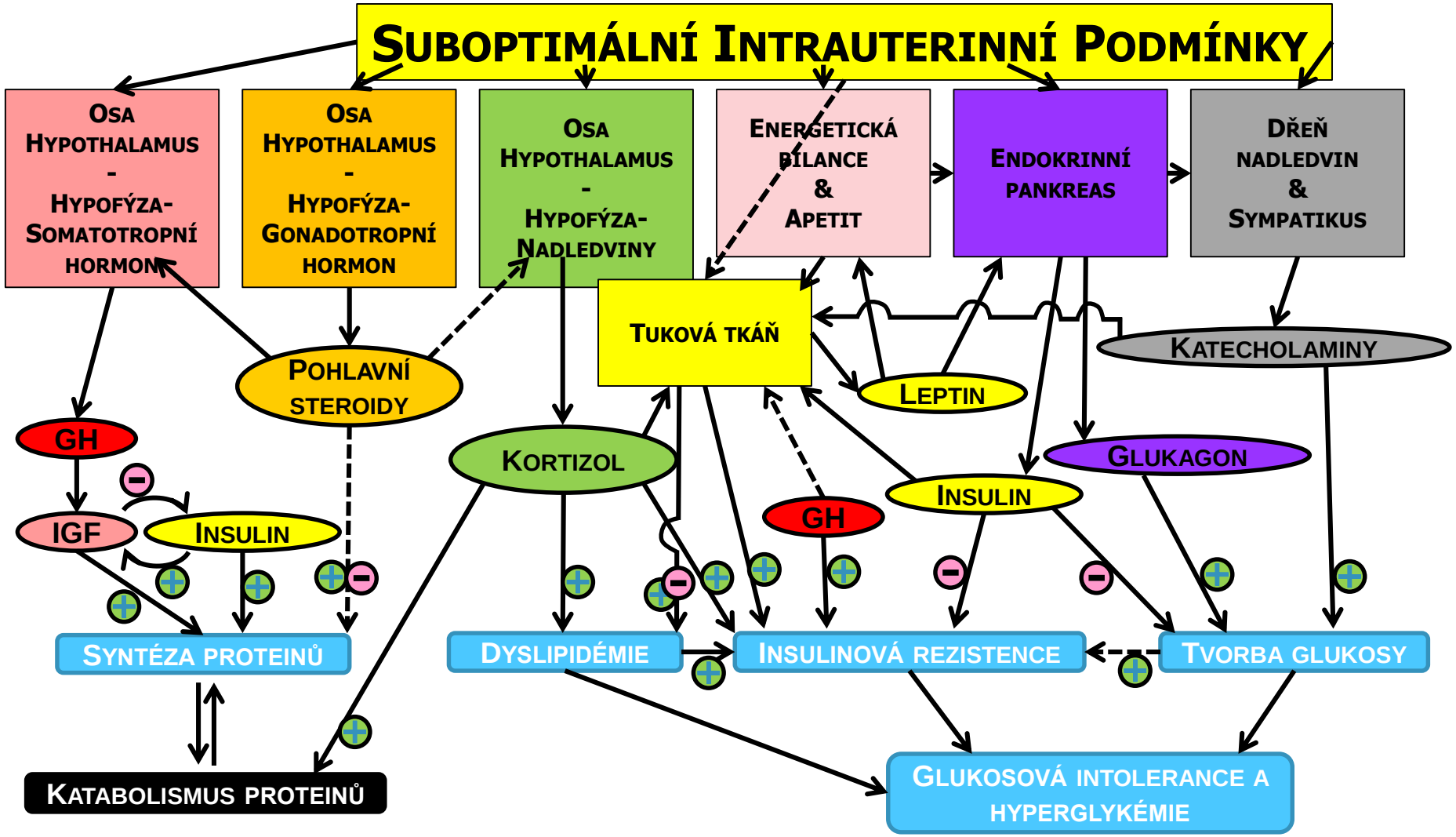
Fetální programování?



Fowden L et al. Endocrine and metabolic programming during intrauterine development. Early Human Development Volume 81, Issue 9, September 2005, Pages 723–734

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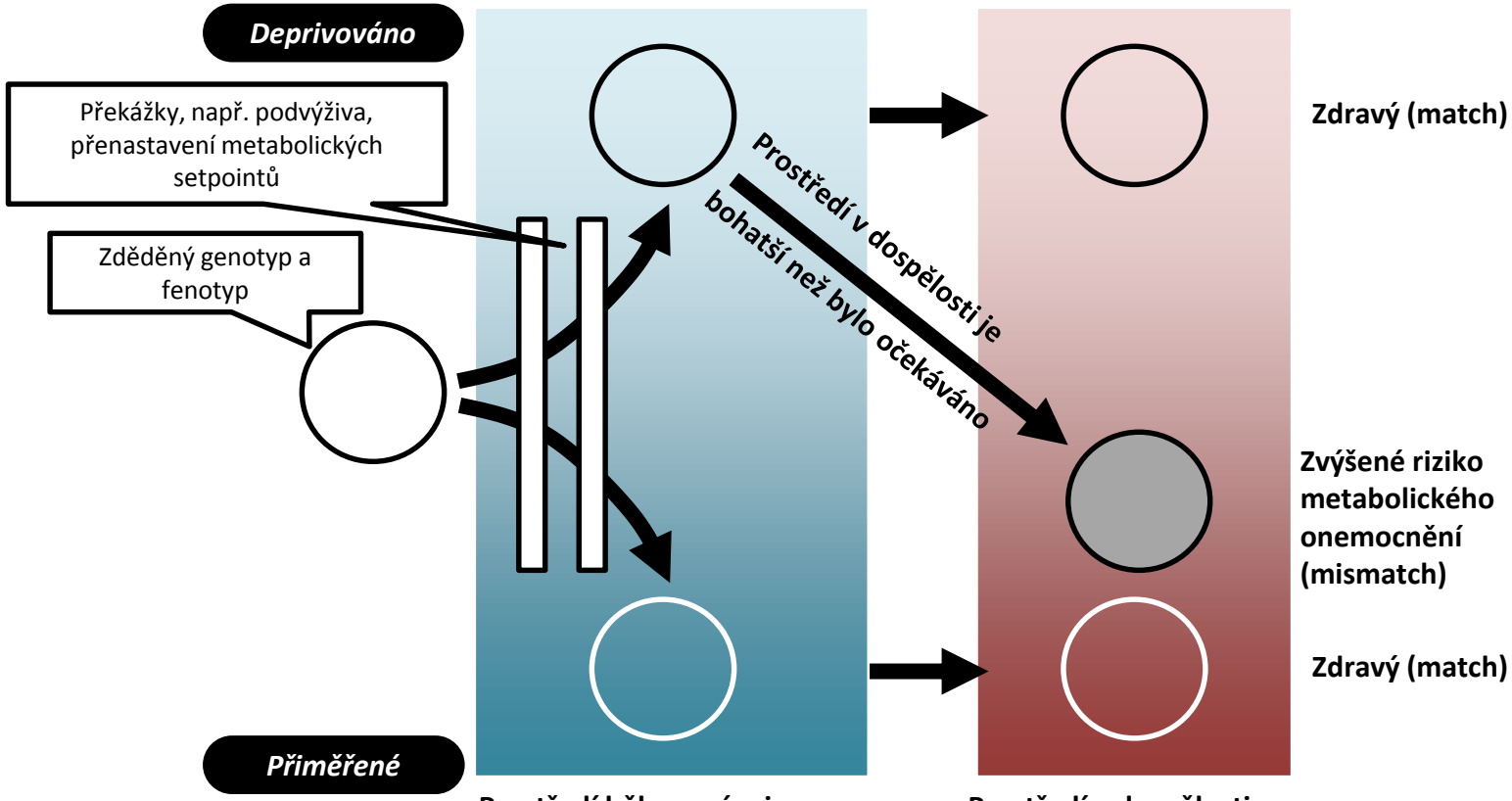
Vývojová plasticita?

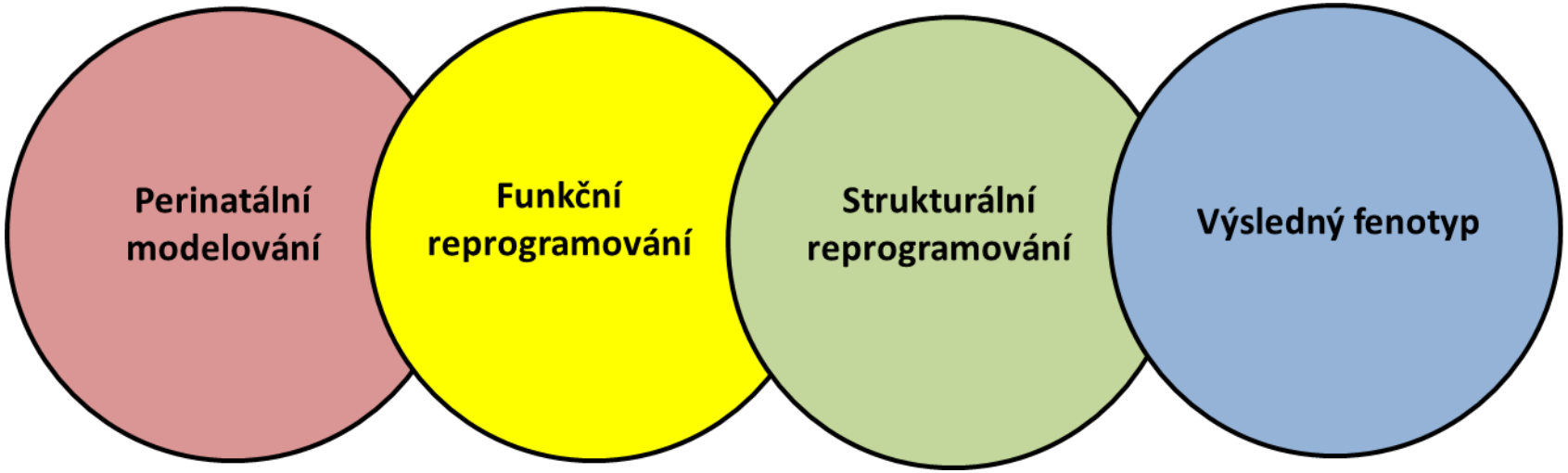


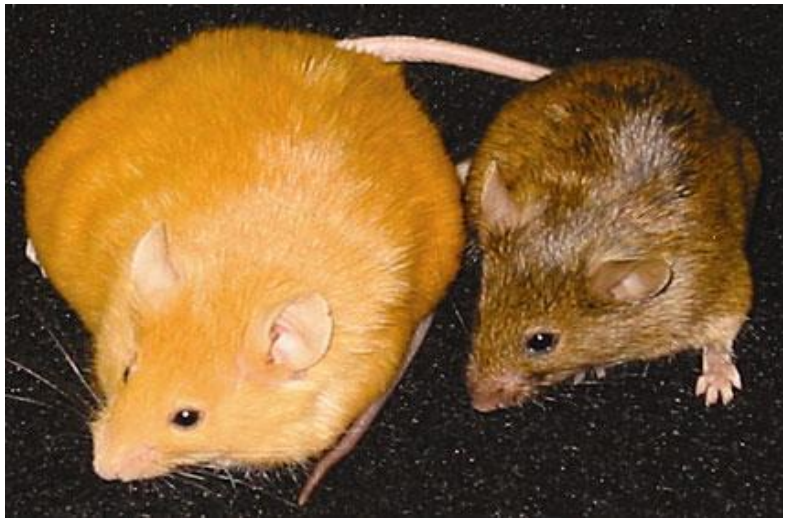
Hochberg Z et al. Endocrine Reviews 2011;32:159-224

ENDOCRINE REVIEWS

Vývojová plasticita – lze změnit vlohy?

Vývojová plasticita v čase





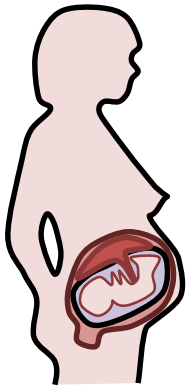
Braam B *et al.* (2007) Technology Insight: innovative options for end-stage renal disease—from kidney refurbishment to artificial kidney *Nat Clin Pract Nephrol* **3:** 564–572 doi:10.1038/ncpneph0600

nature CLINICAL PRACTICE NEPHROLOGY

DOHAD – Developmental Origins of Health and Disease

Faktory vnějšího prostředí

Programming

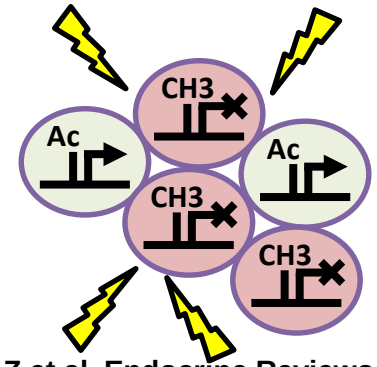


Konflikt s postnatálním prostředím

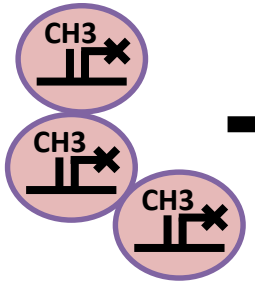
Nemoci v pozdější životě

- Ischemický choroba srdeční
- Obezita
- Diabetes 2. typu
- Hypertenze
- Rakovina
- Psychiatrická onemocnění

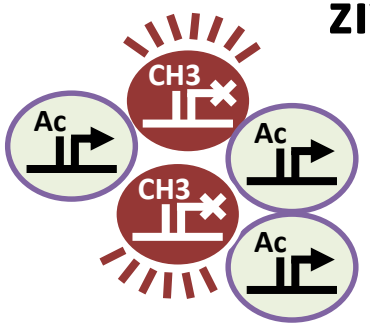
Epigenomické změny



Trvalé změny genové exprese



Vliv na fenotyp v pozdějším životě



Hochberg Z et al. Endocrine Reviews 2011;32:159-224

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Děkuji za pozornost

Vasku.julie@seznam.cz