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Pathophysiology of reproduction

Julie Dobrovolná

Revision

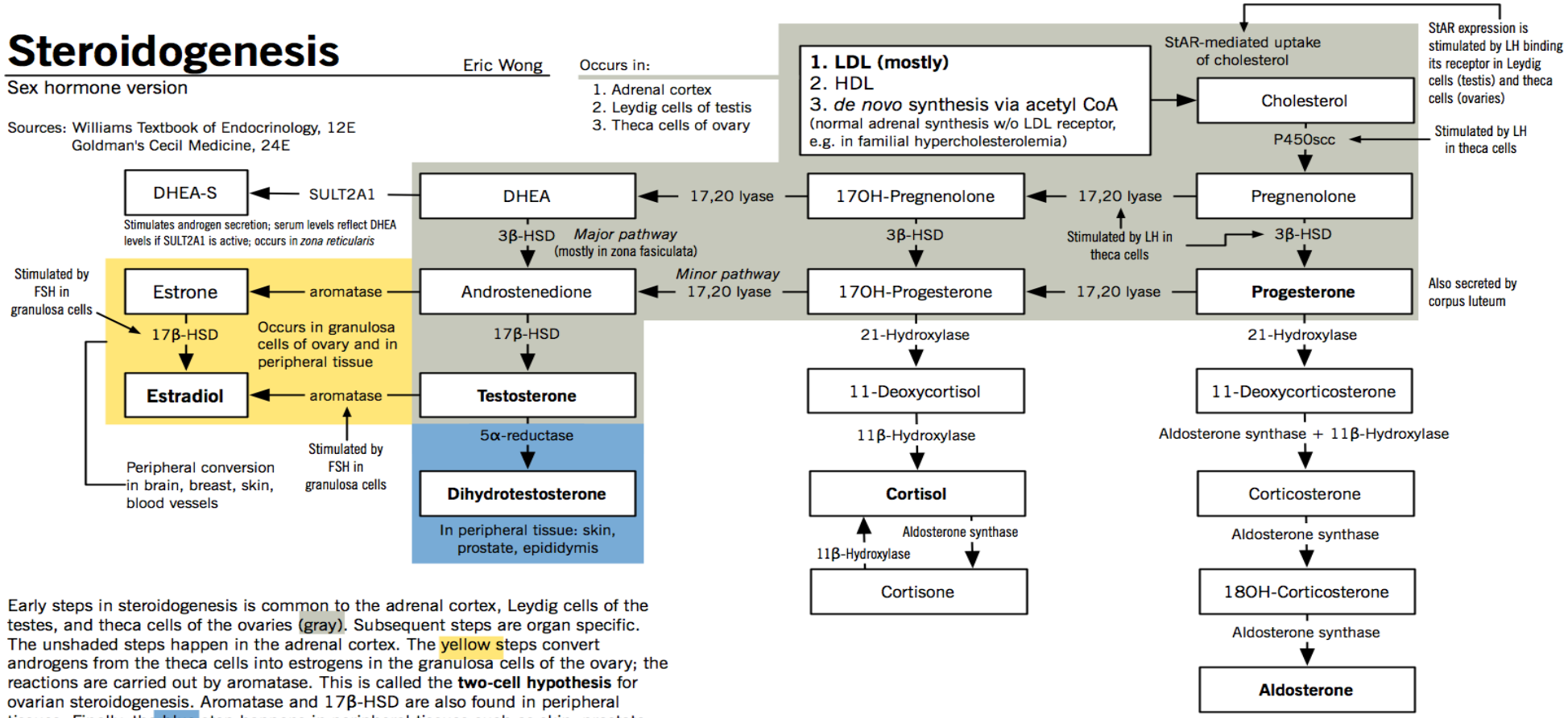
Steroidogenesis

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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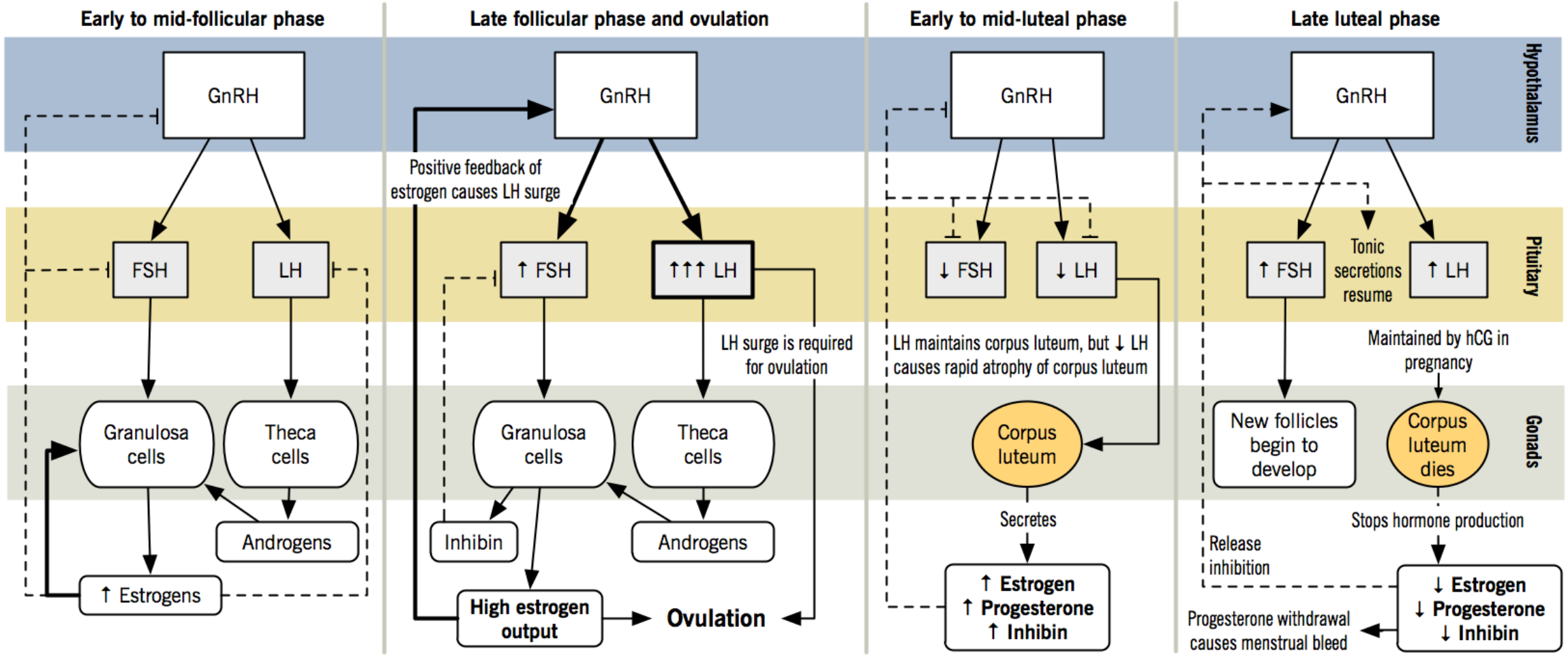
Hormonal regulation at various parts of the menstrual cycle

Eric Wong

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



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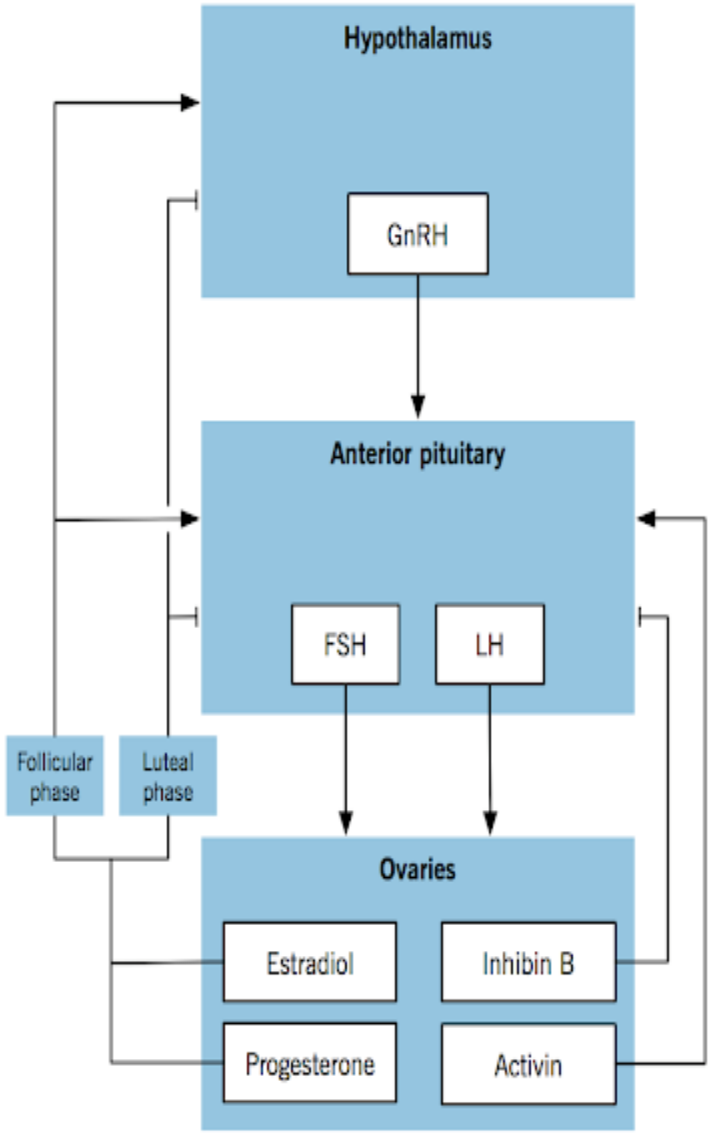
Premenopausal HPG axis

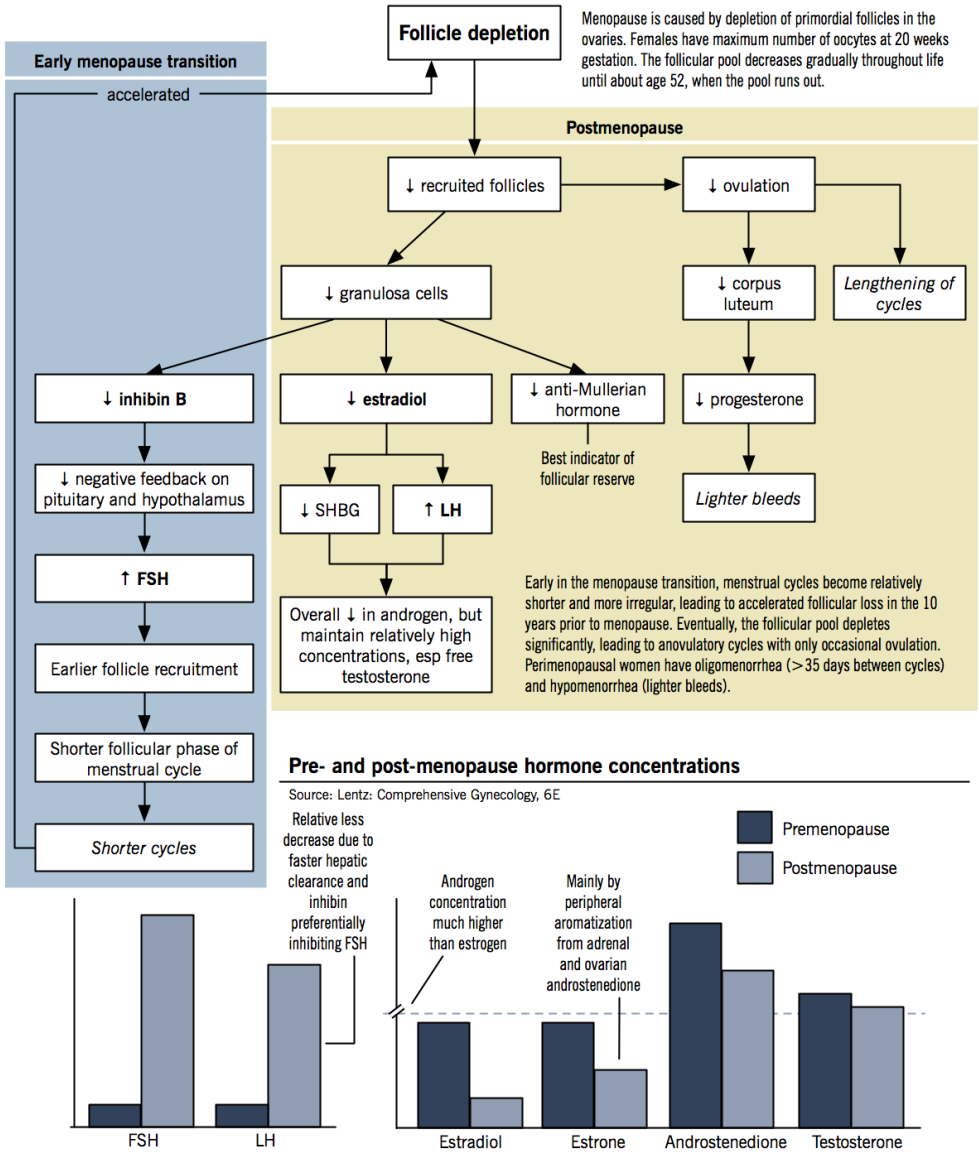
Anna Dul and Eric Wong



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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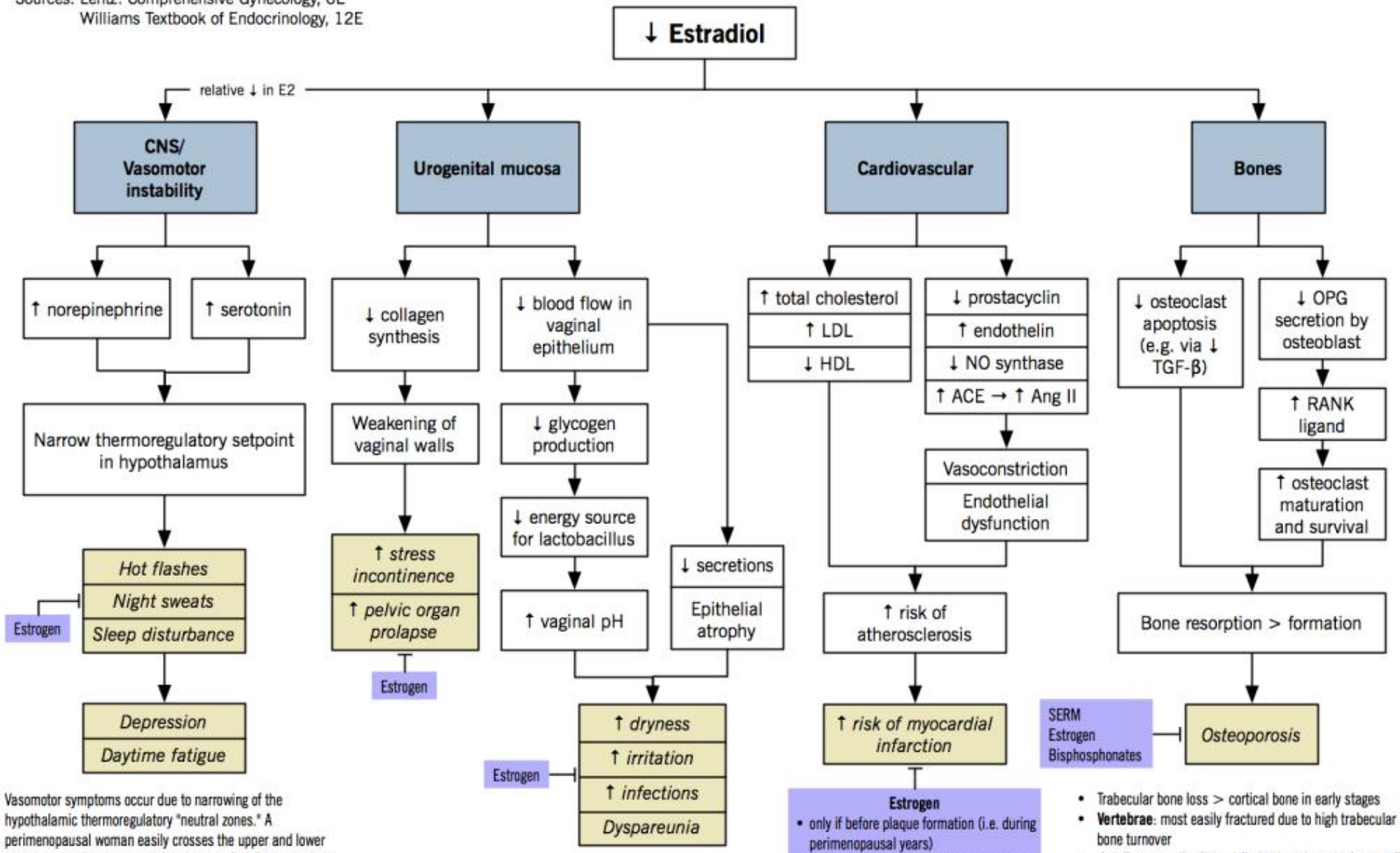
Pathophysiology of menopause organ changes

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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Pathophysiology of pregnancy

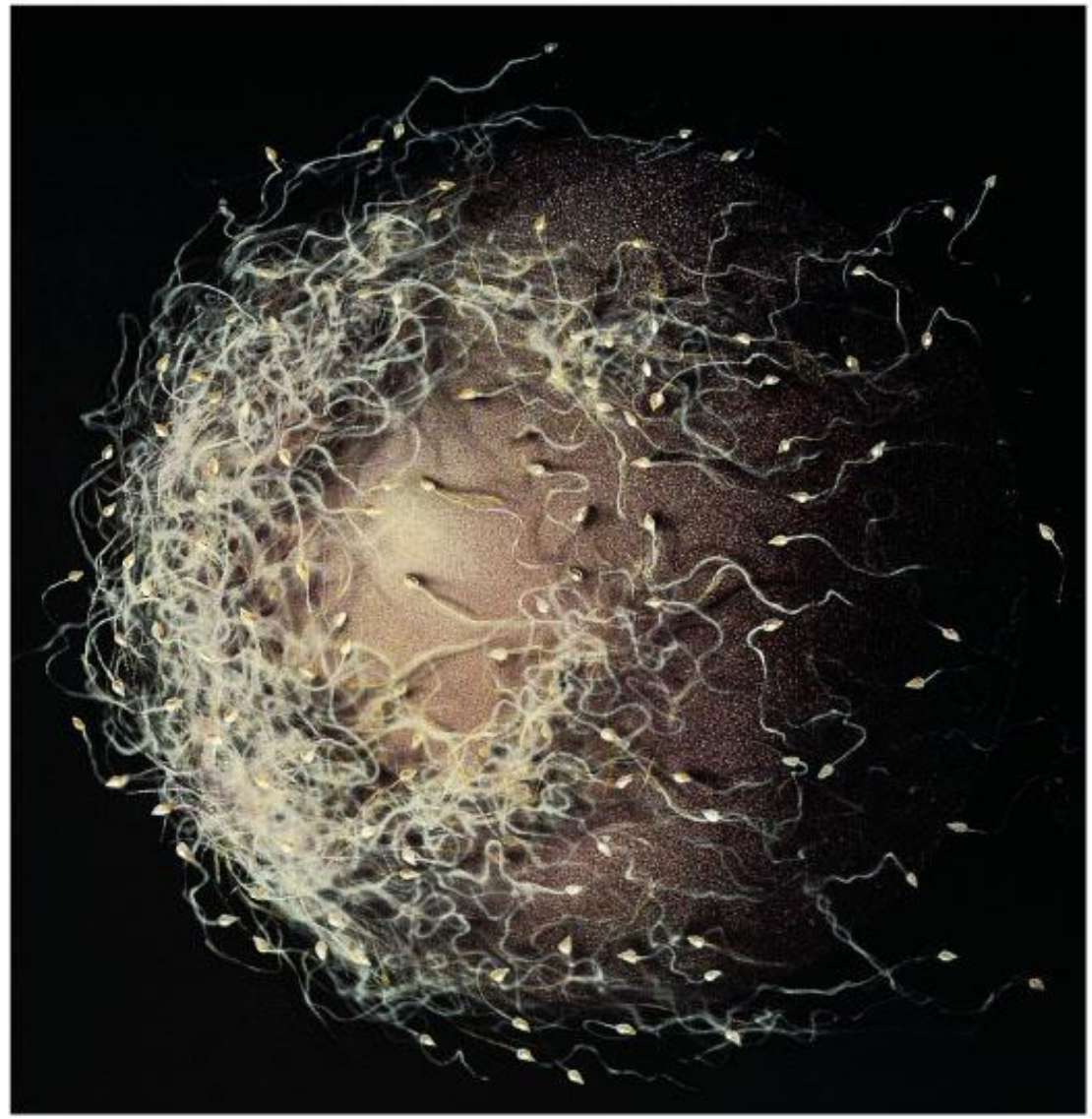
Fetoplacental unit

Fetoplacental unit:
- consists of **placenta, fetal adrenal gland and fetal liver**. In this unit, the fetal adrenal gland is the primary source of dehydroepiandrosterone. It is further metabolized by the fetal liver and placenta to a wide range of estrogens.

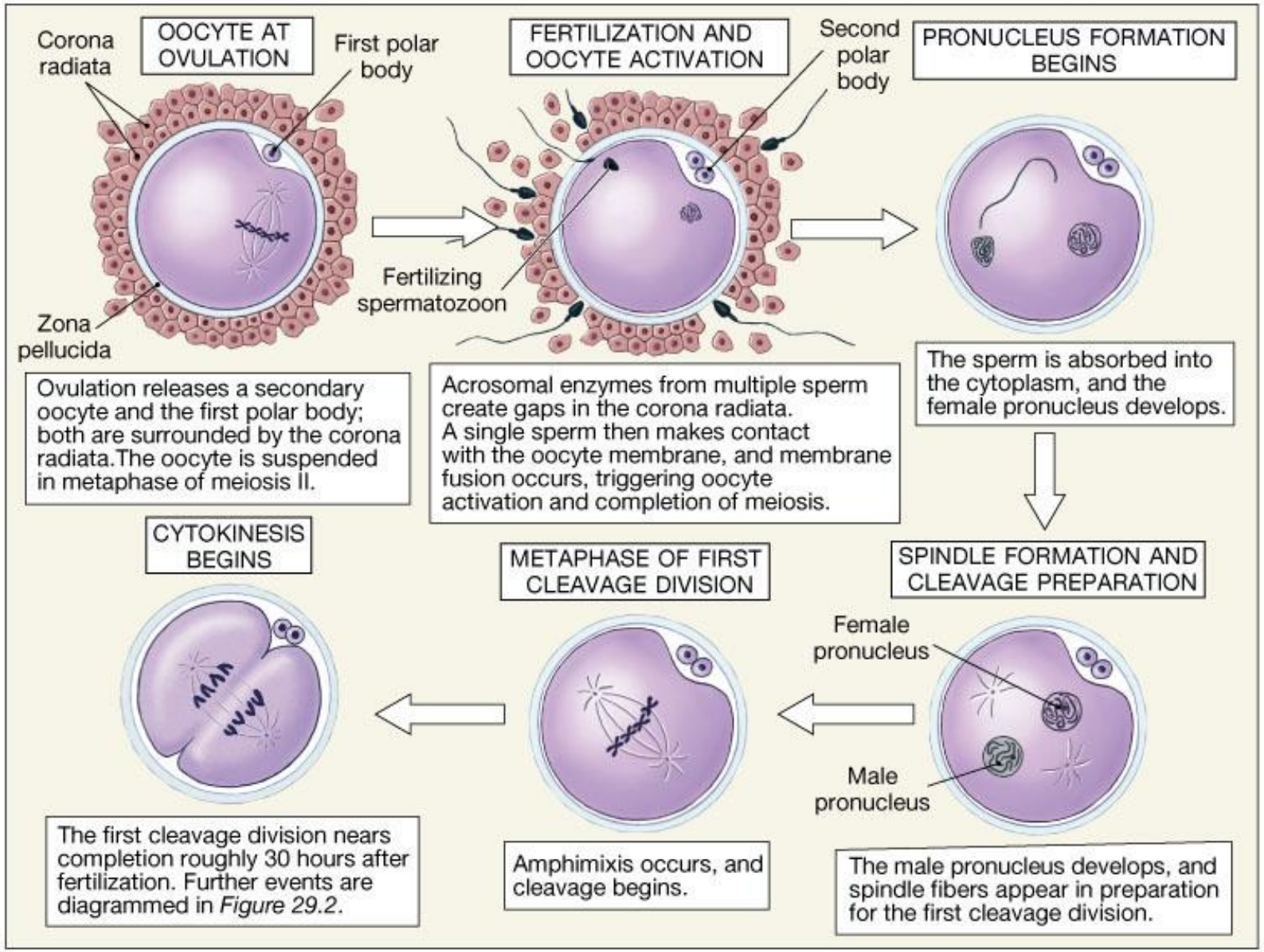
There are several diseases that can affect the fetal and maternal adrenal glands during pregnancy. Most often, it is steroid 21-hydroxylase deficiency, which leads to abnormalities in sexual development and may even endanger the life of the newborn.

Pregnancy is marked by accretions in several endocrine systems, particularly the renin-angiotensin-aldosterone system and the hypothalamus-pituitary-adrenal system.

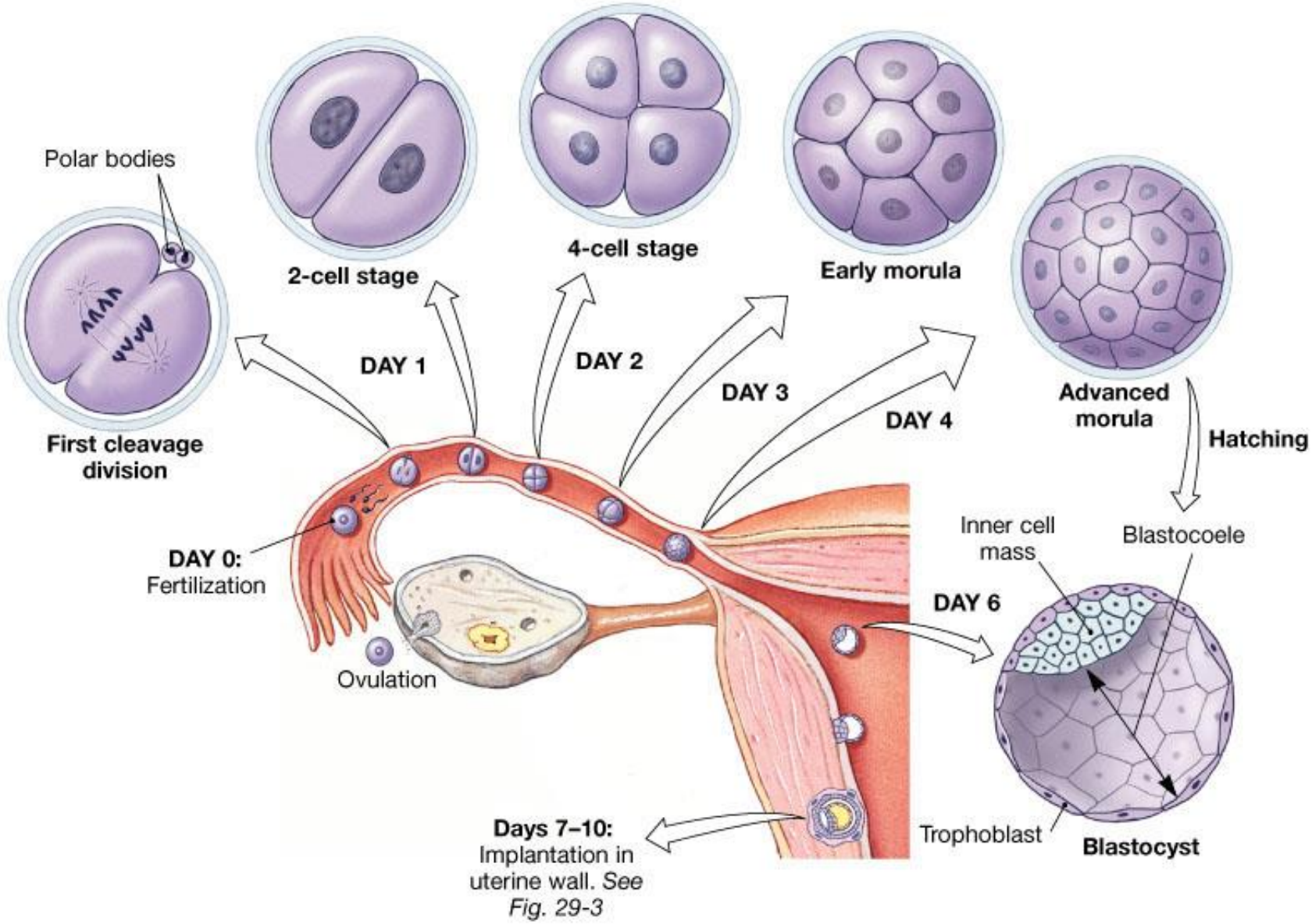
Maternal abnormalities are associated with a significant risk of maternal morbidity and mortality. Fortunately, they are rare.



(a)



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



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

Implantation

5-12 days after conception

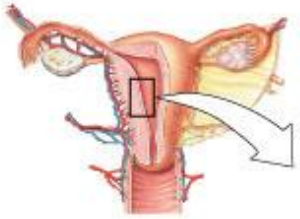
Trophoblast grows and spreads

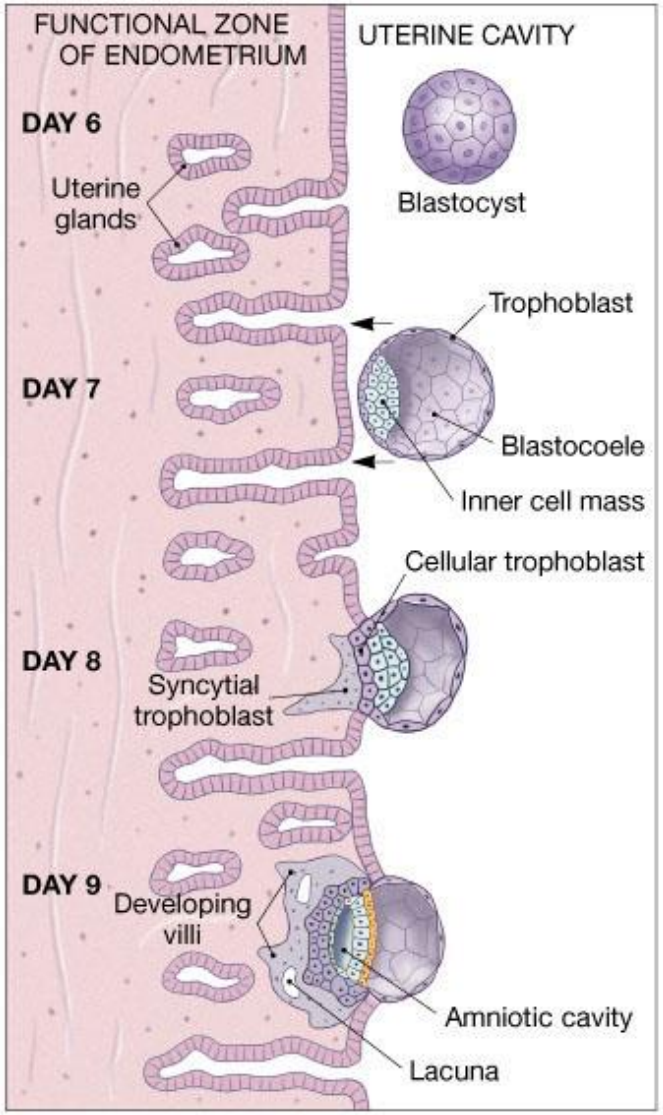
Maternal blood freely circulating in lacunes

Gastrulation

Embryonic target consists of:

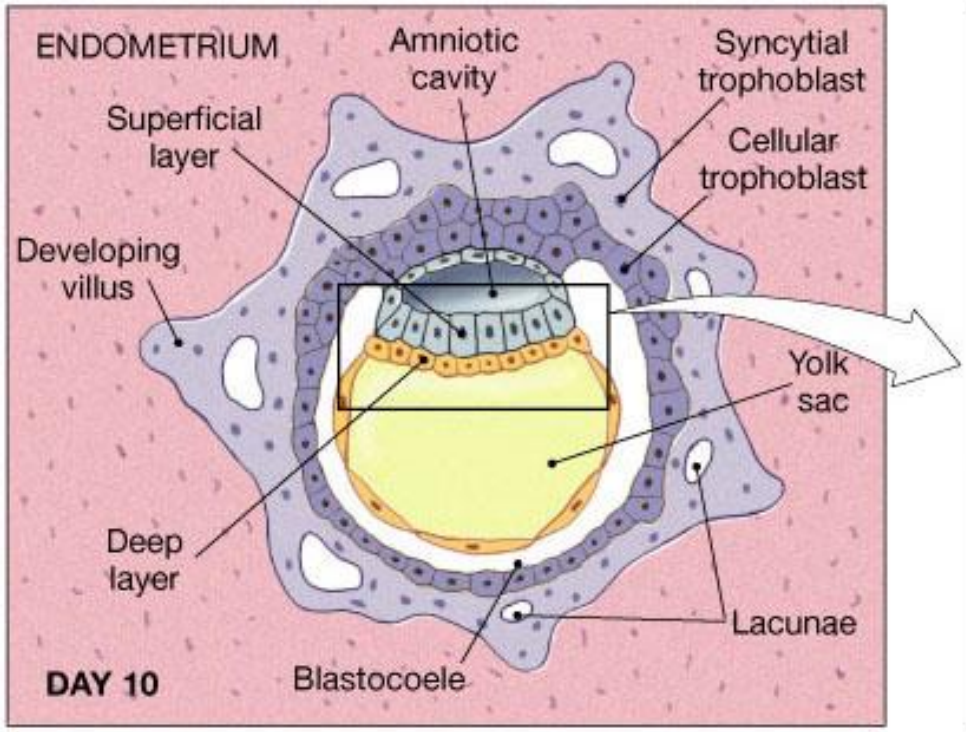
- Endoderm
- Mesoderm
- Ektoderm



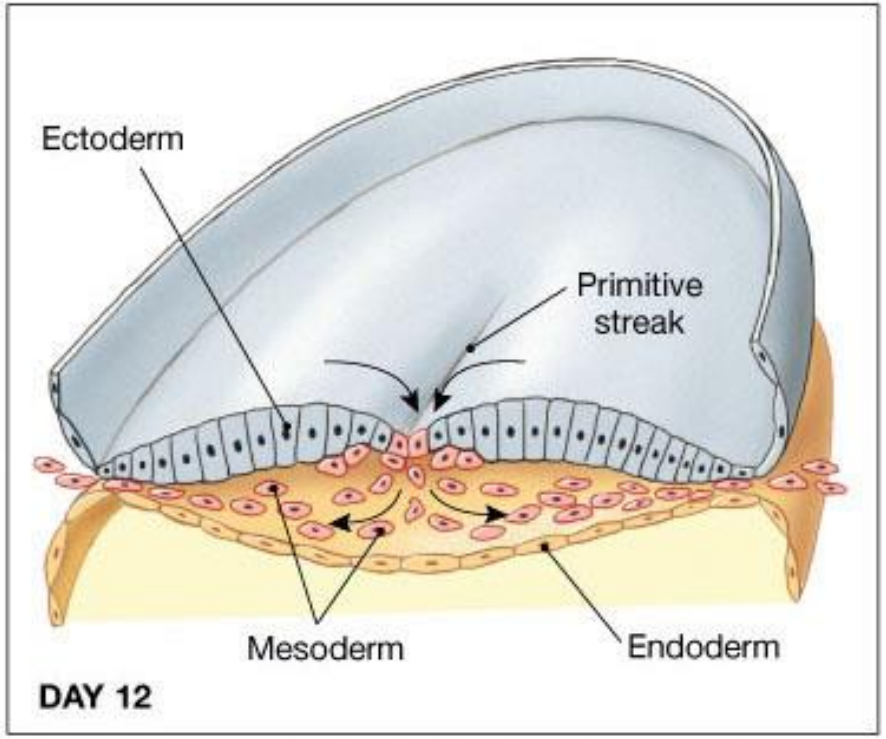


https://embryology.med.unsw.edu.au/embryology/index.php/

Internal cellular mass and gastrulation



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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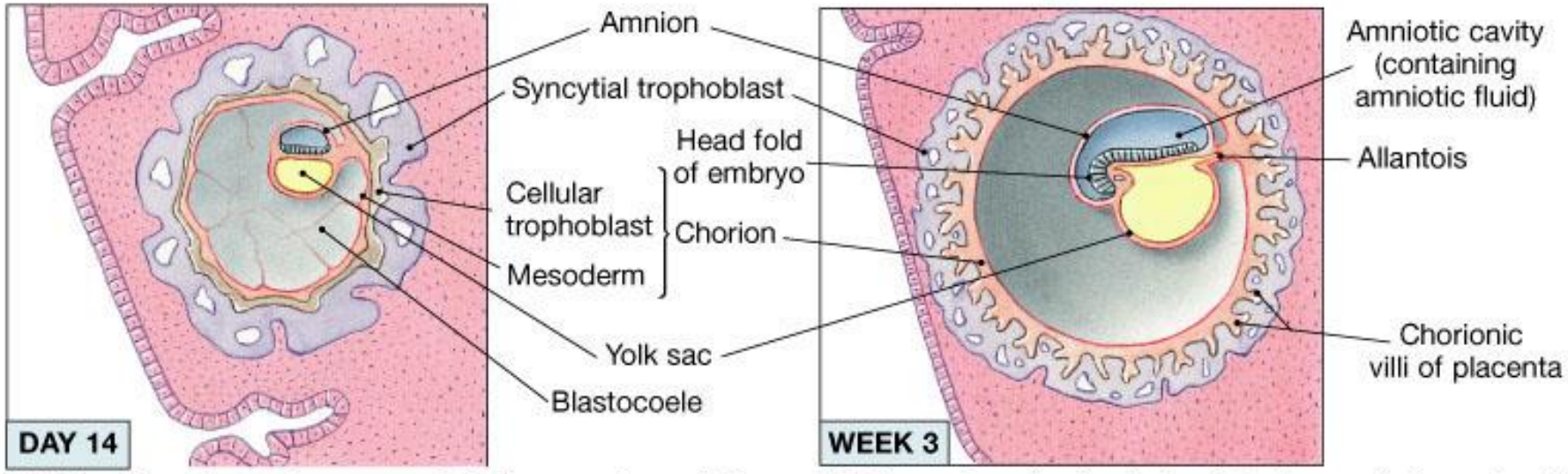
Extraembryonic membranes

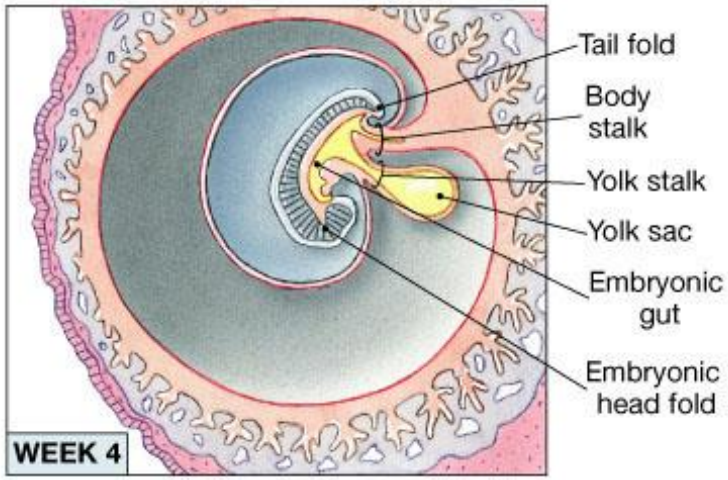


(a) Migration of mesoderm around the inner surface of the trophoblast creates the chorion. Mesodermal migration around the outside of the amniotic cavity, between the ectodermal cells and the trophoblast, forms the amnion. Mesodermal migration around the endodermal pouch creates the yolk sac.

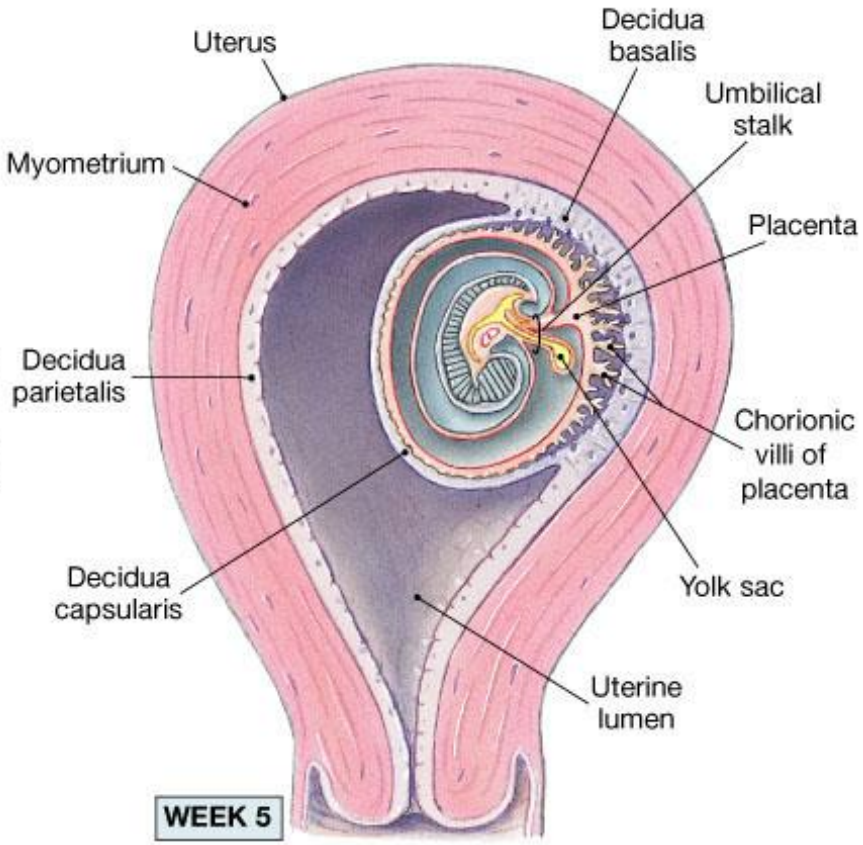
(b) The embryonic disc bulges into the amniotic cavity at the head fold. The allantois, an endodermal extension surrounded by mesoderm, extends toward the trophoblast.

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

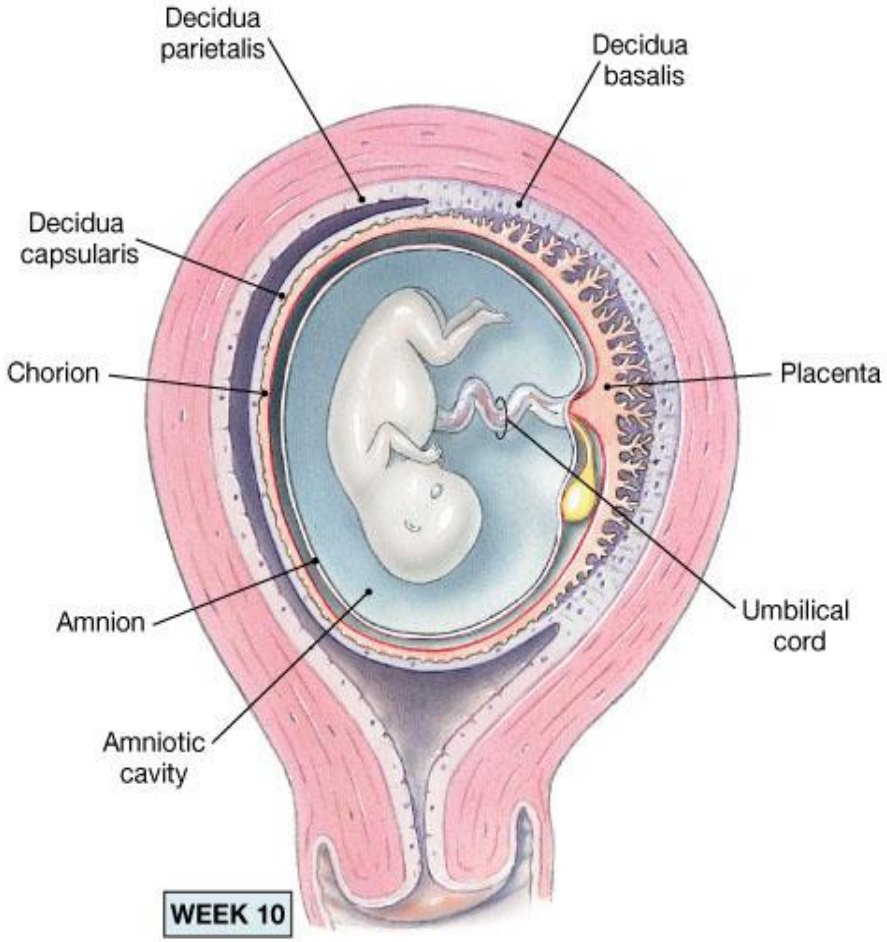
Placental development



(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.

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

Embryo anatomy

Yolk sac

Where blood cells are produced

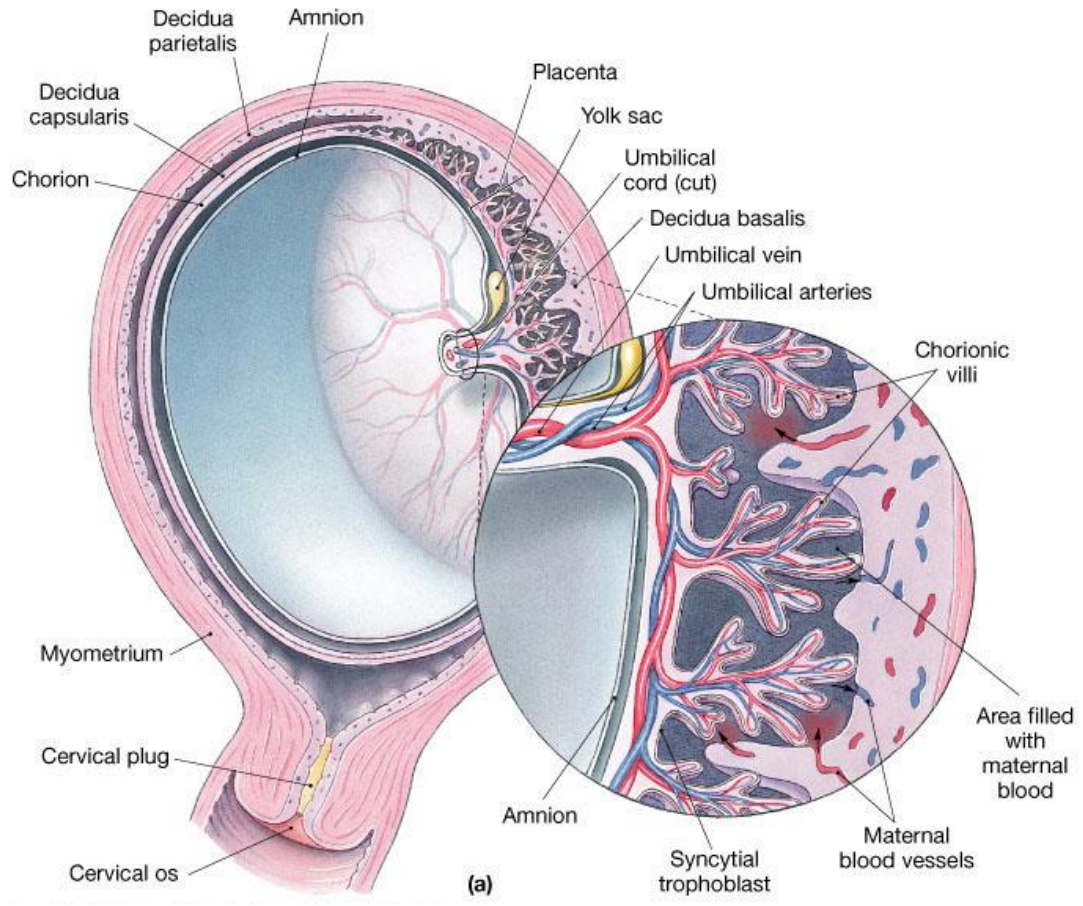
Amnion

Encompasses the fluid around embryo

Allantois

Bladder

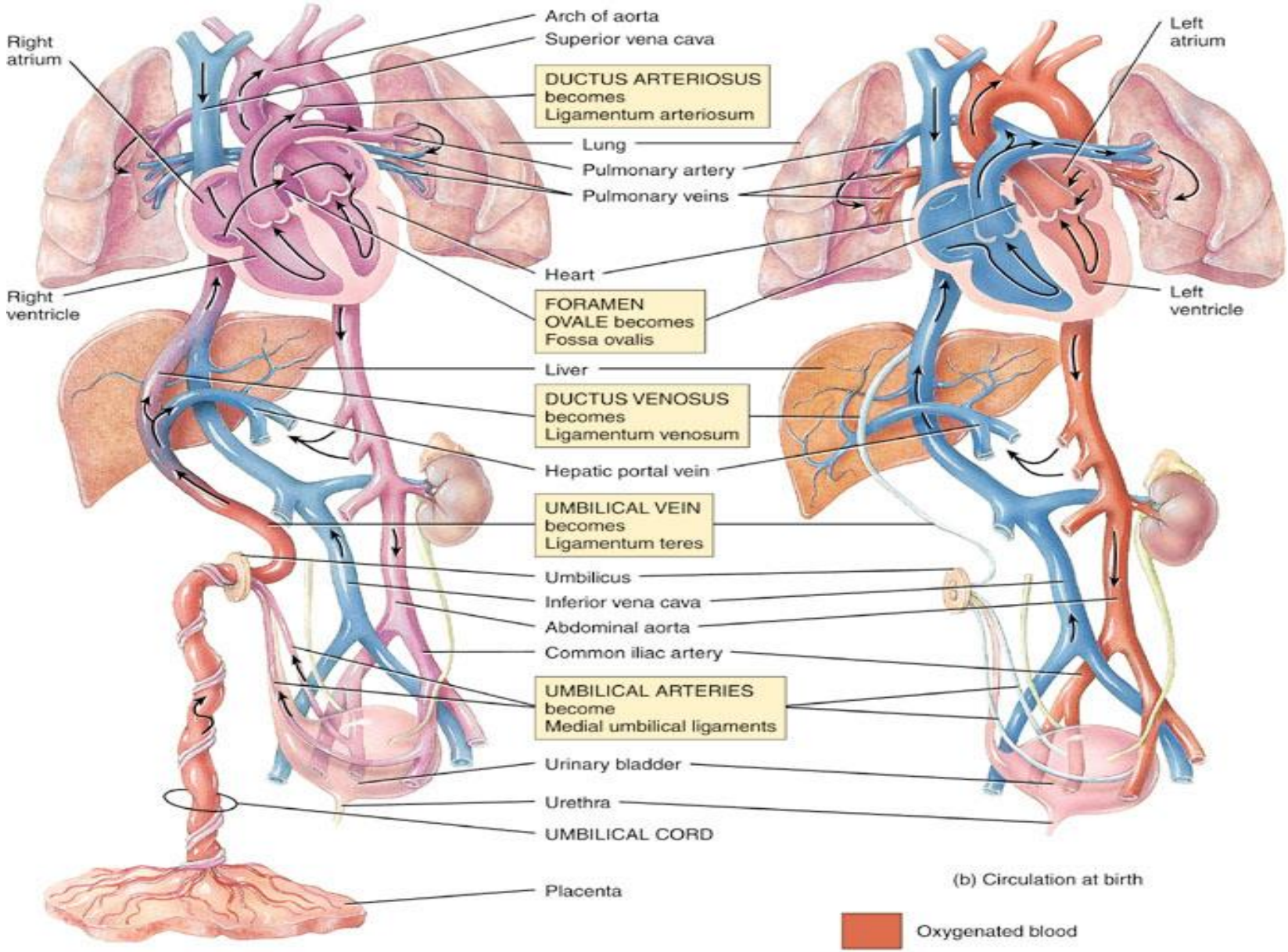
Chorion



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

Characteristic features of feto-placental circulation

- Parallel arrangement of two arterial systems and corresponding chambers
- Mixed venous return and preferential blood flow.
- High resistance and low real circulation in lung circuit
- Low resistance and high-flow circulation in placenta.
- Shunt presence (3 shunts
    - Ductus venosus
    - Foramen ovale
    - Ductus arteriosus



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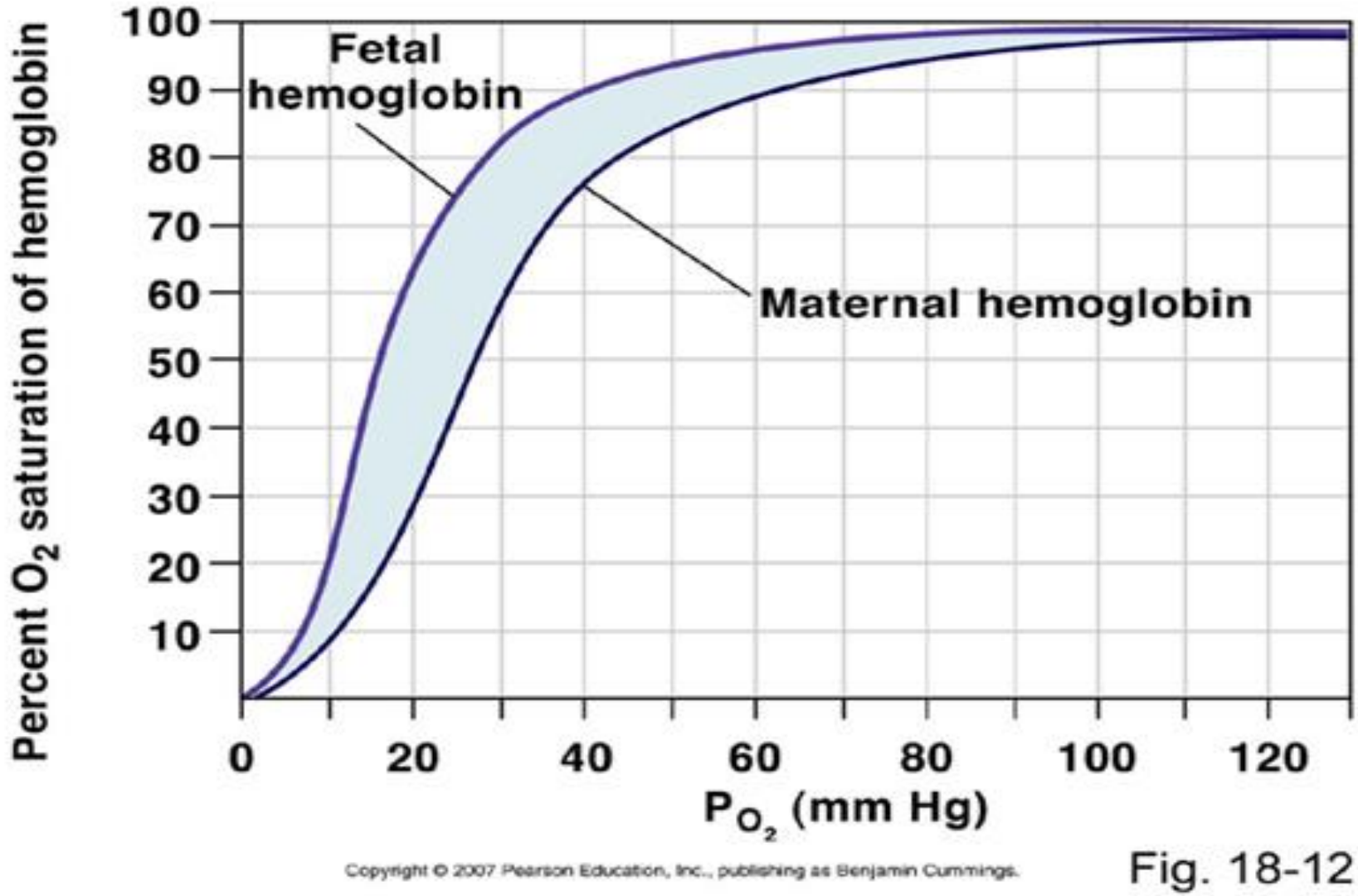
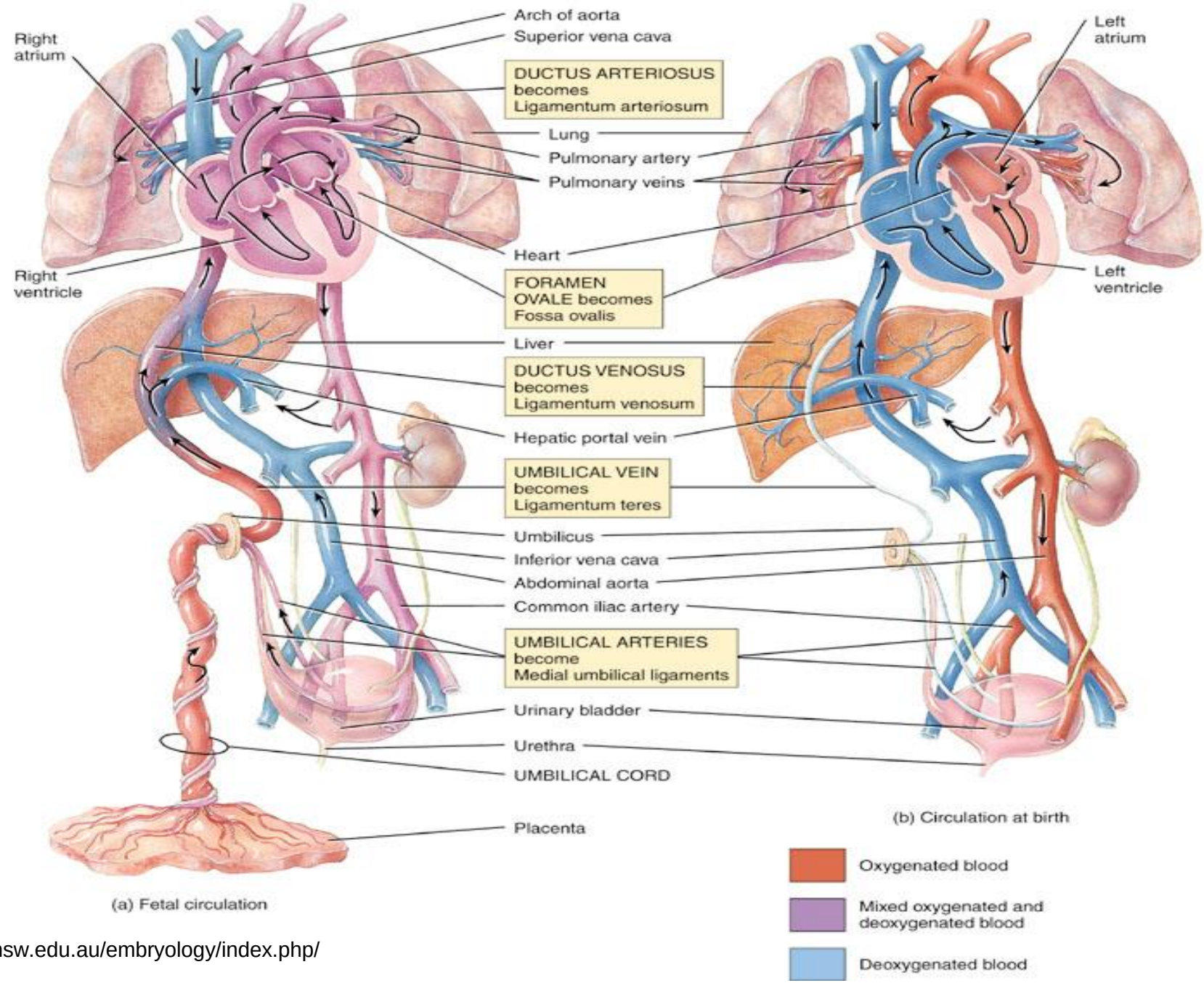


Fig. 18-12

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



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

Fetal blood flow I

When oxygenated blood from the mother enters the right side of the heart it flows into the upper chamber (the right atrium). Most of the blood flows across to the left atrium through a shunt called the foramen ovale.

From the left atrium, blood moves down into the lower chamber of the heart (the left ventricle). It's then pumped into the first part of the large artery coming from the heart (the ascending aorta).

From the aorta, the oxygen-rich blood is sent to the brain and to the heart muscle itself. Blood is also sent to the lower body.

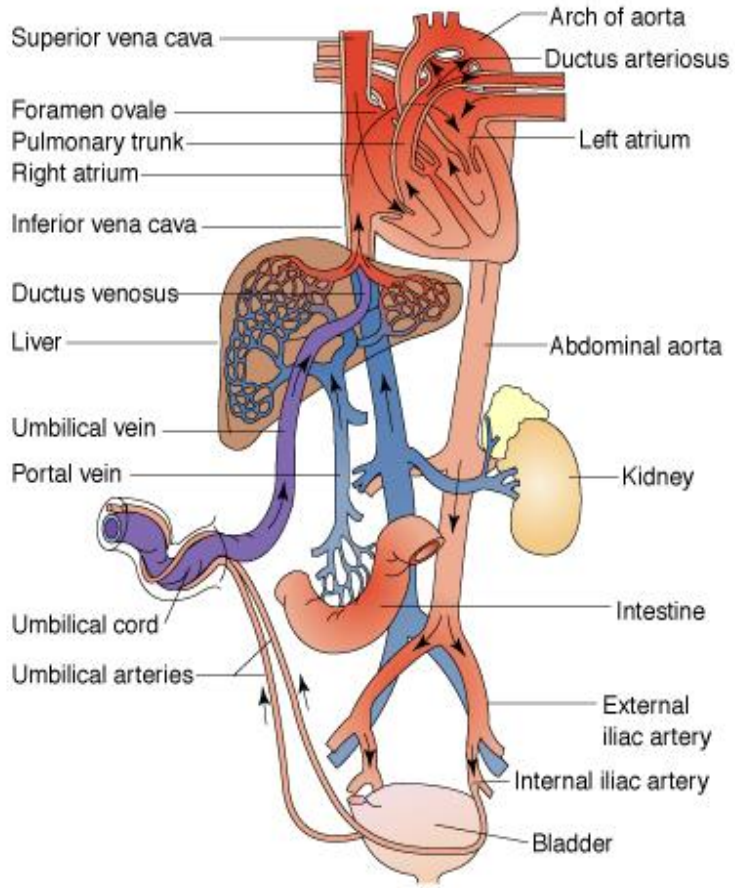


Figure 26-27 Fetal circulation.

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

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

Fetal blood flow II

Blood returning to the heart from the fetal body contains carbon dioxide and waste products as it enters the right atrium. It flows down into the right ventricle, where it normally would be sent to the lungs to be oxygenated. Instead, it bypasses the lungs and flows through the ductus arteriosus into the descending aorta, which connects to the umbilical arteries. From there, blood flows back into the placenta. There the carbon dioxide and waste products are released into the mother's circulatory system. Oxygen and nutrients from the mother's blood are transferred across the placenta. Then the cycle starts again.

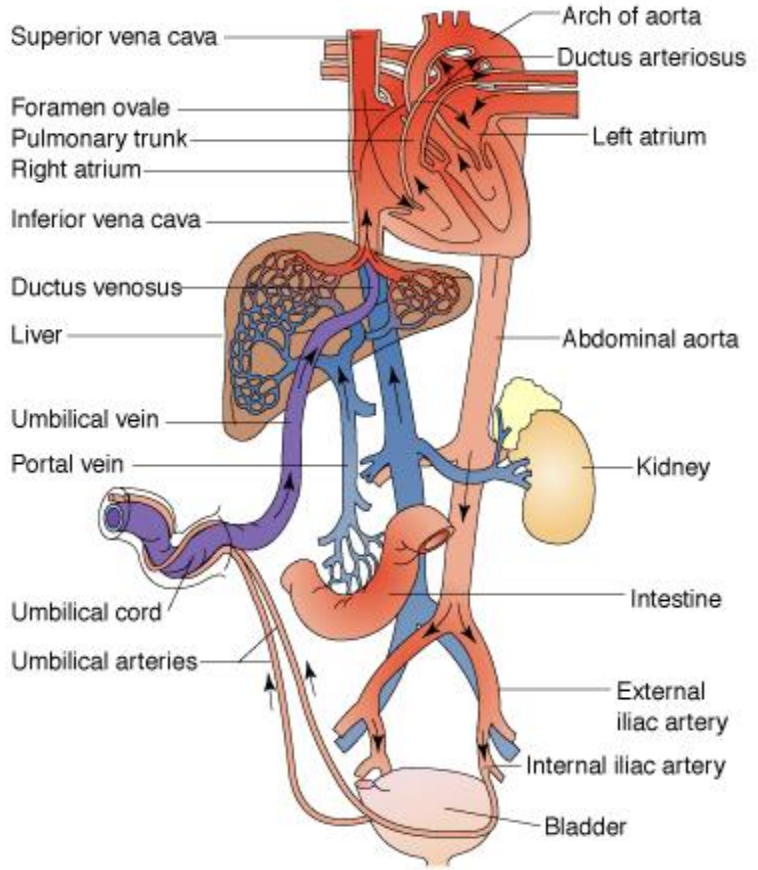


Figure 26-27 Fetal circulation.

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

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

Fetal blood flow III

At birth, major changes take place. The umbilical cord is clamped and the baby no longer receives oxygen and nutrients from the mother. With the first breaths of air, the lungs start to expand, and the ductus arteriosus and the foramen ovale both close. The baby's circulation and blood flow through the heart now function like an adult's.

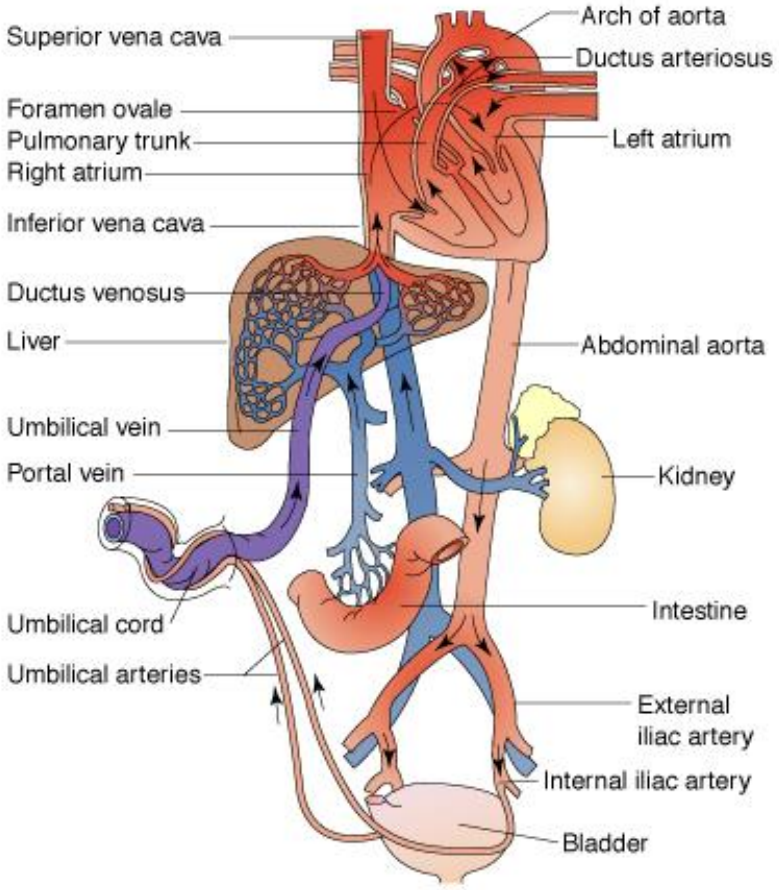


Figure 26-27 Fetal circulation.

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

Uzávěr shuntů

Changes After Birth: Closing of Shunts

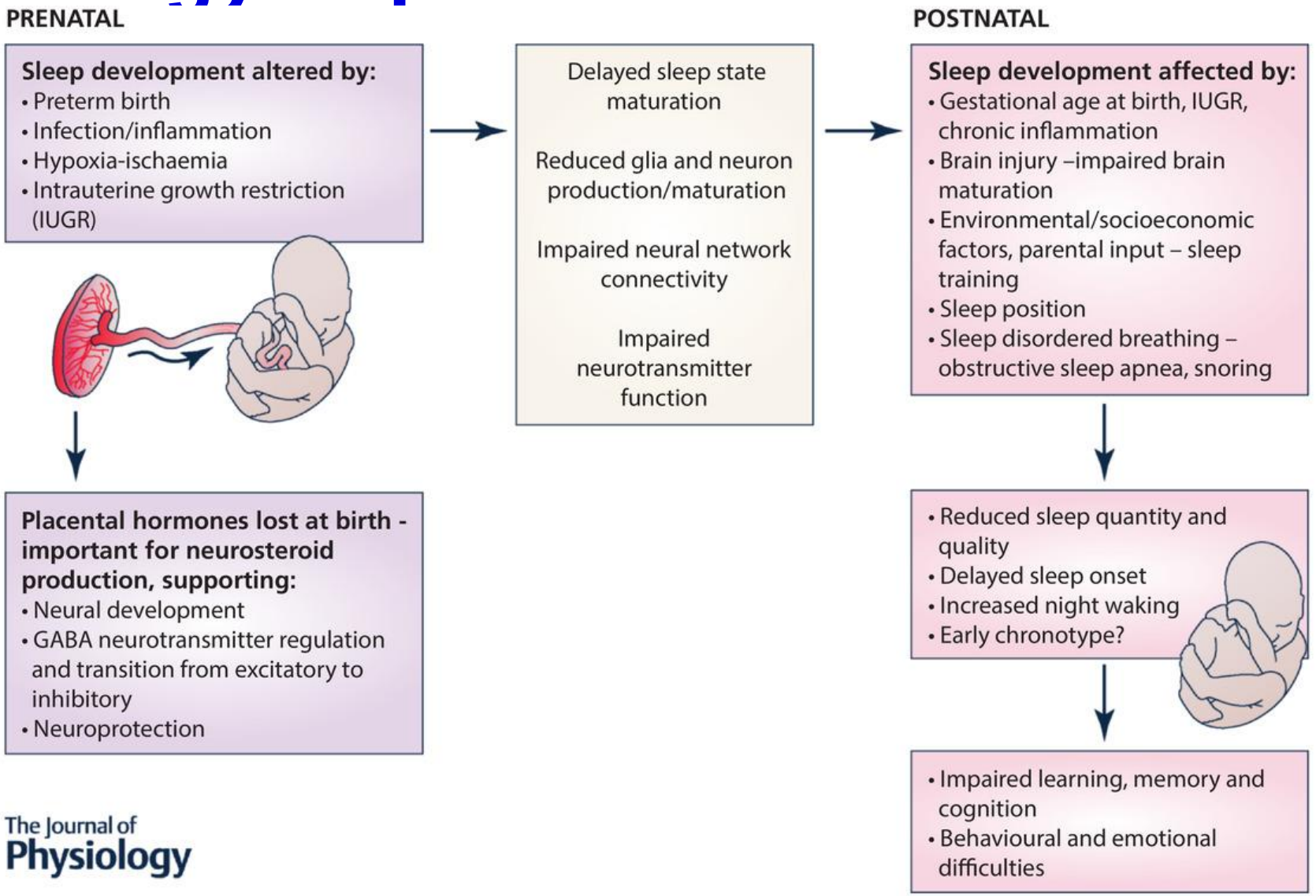
Shunt	Functional closure	Anatomical closure	Remnant
Ductus arteriosus	10 – 96 hrs after birth	2 – 3 wks after birth	Ligamentum arteriosum
Formamen ovale	Within several mins after birth	One year after birth	Fossa ovalis
Ductus venosus	Within several mins after birth	3 – 7 days after birth	Ligamentum venosum

Umbilical arteries → Umbilical ligaments

Umbilical vein → Ligamentum teres

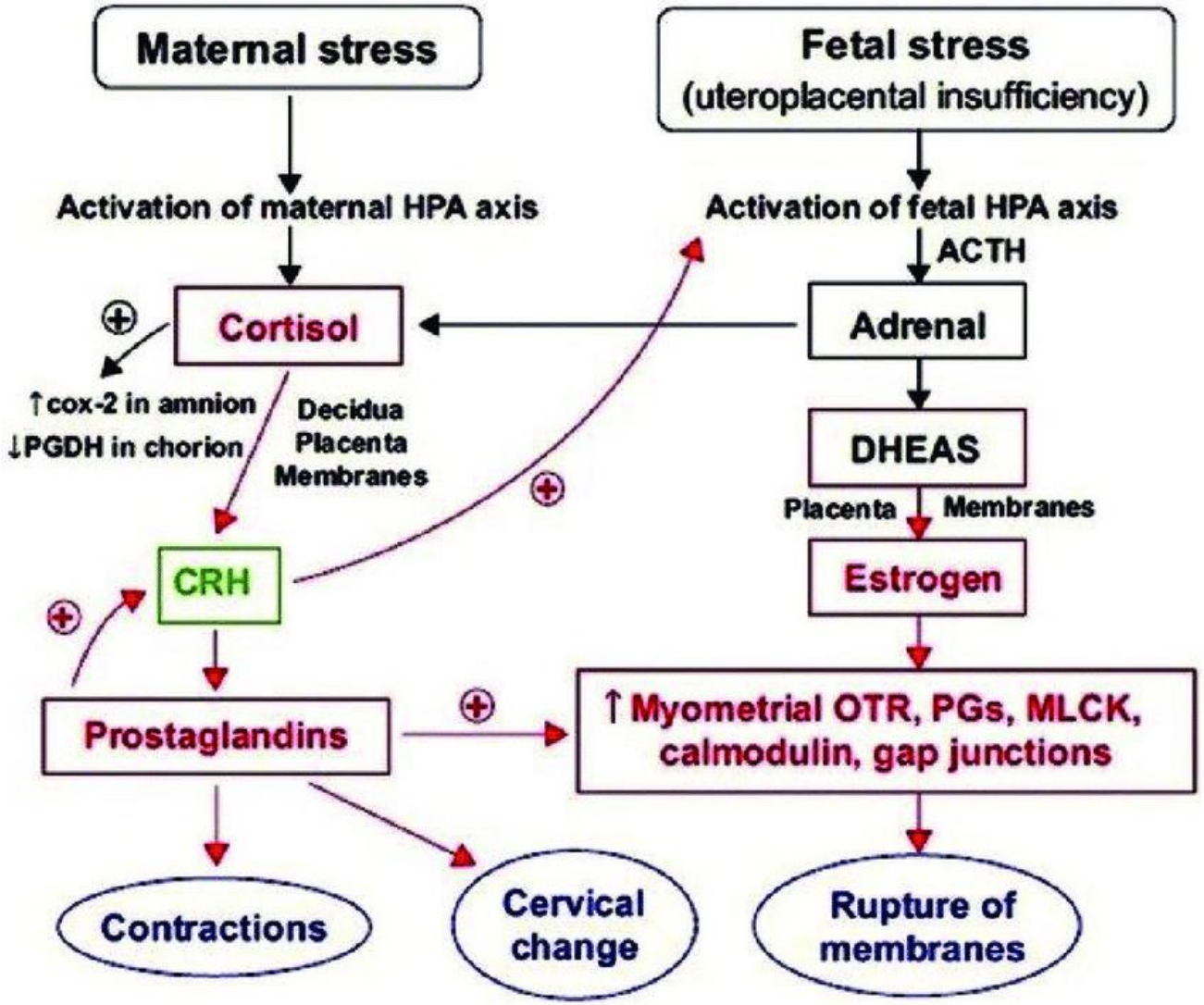
Pathophysiology of preterm birth

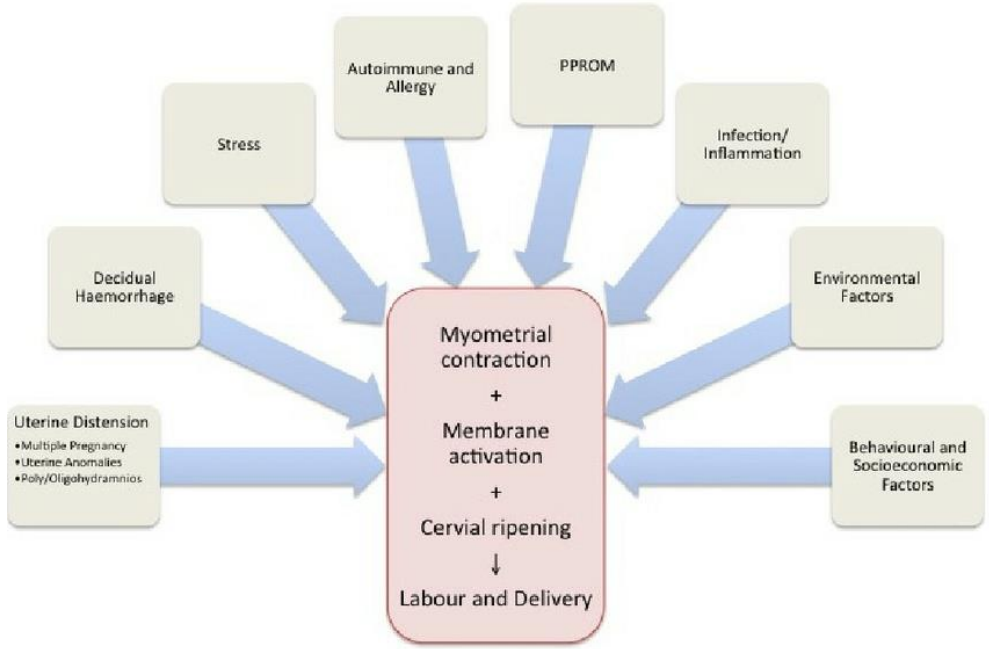
Pathophysiology of premature birth II



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

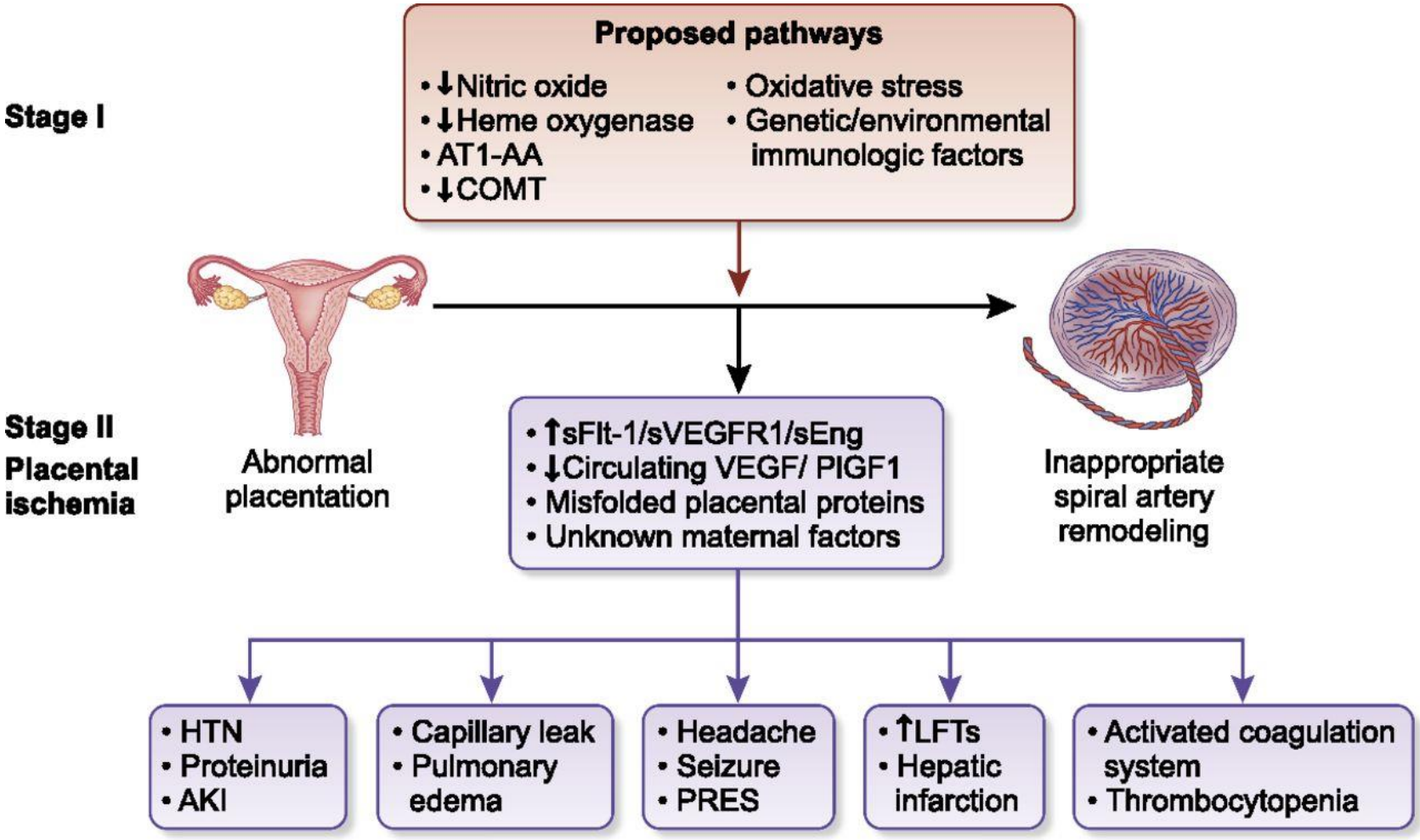
Pathophysiology of premature birth III





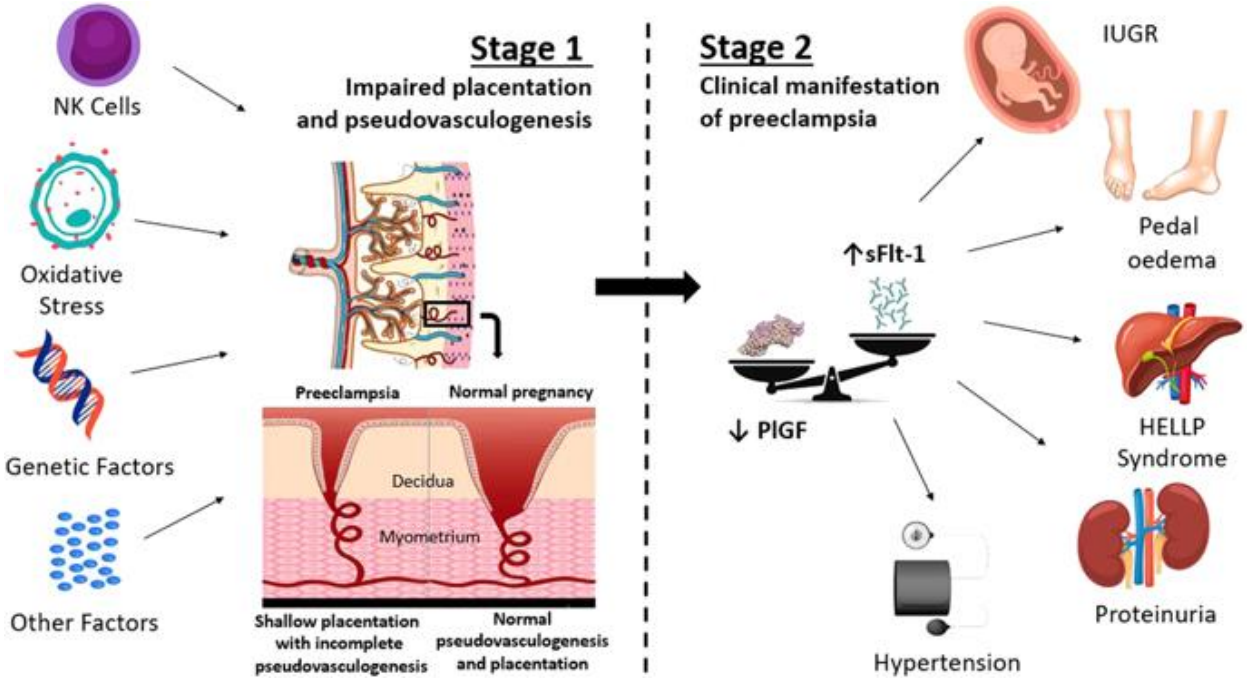
Low Birth Weight and Adverse Perinatal Outcomes
•November 2019 DOI: 10.5772/intechopen.89049

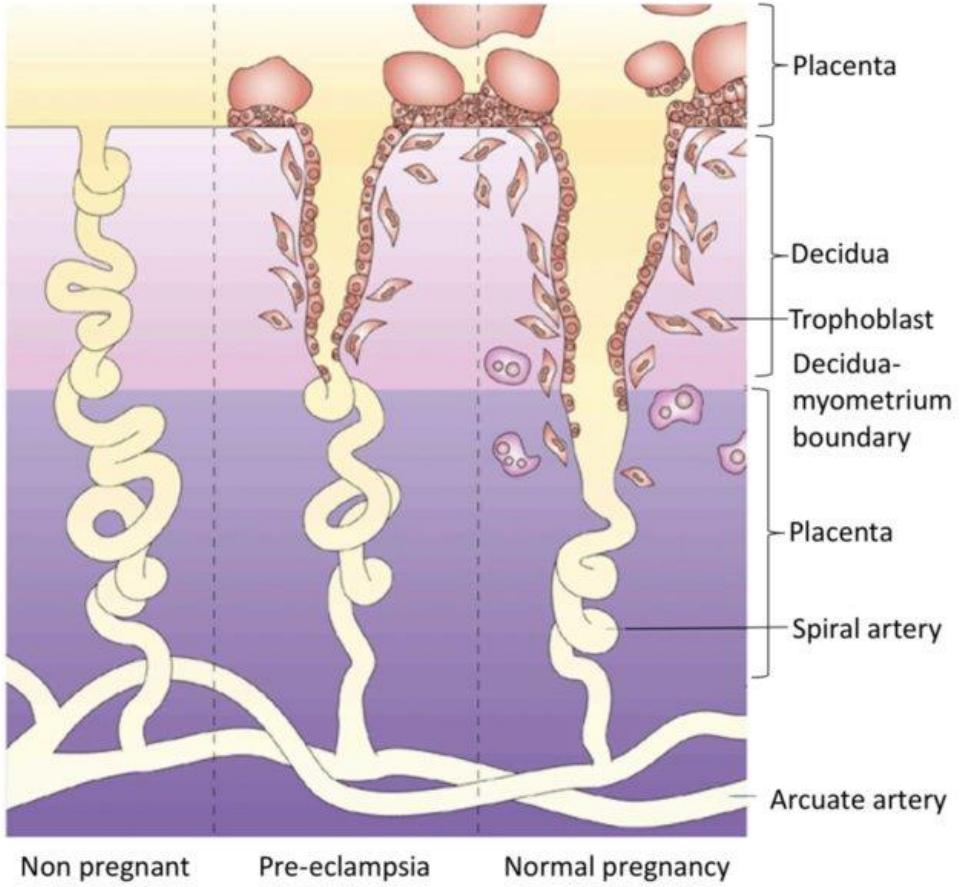
Pathophysiology of pre-eclampsia



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

Pathophysiology of pre-eclampsia - II

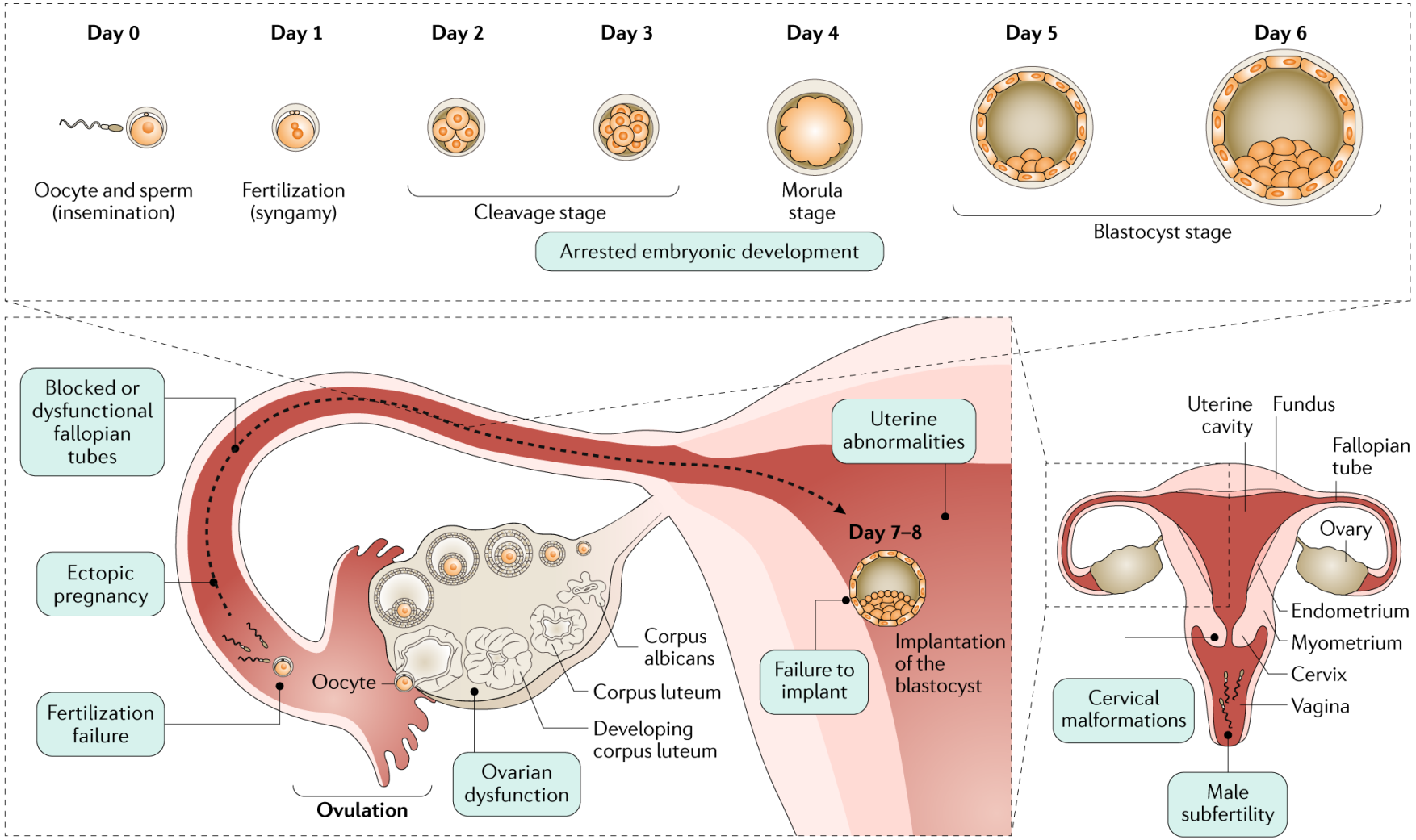




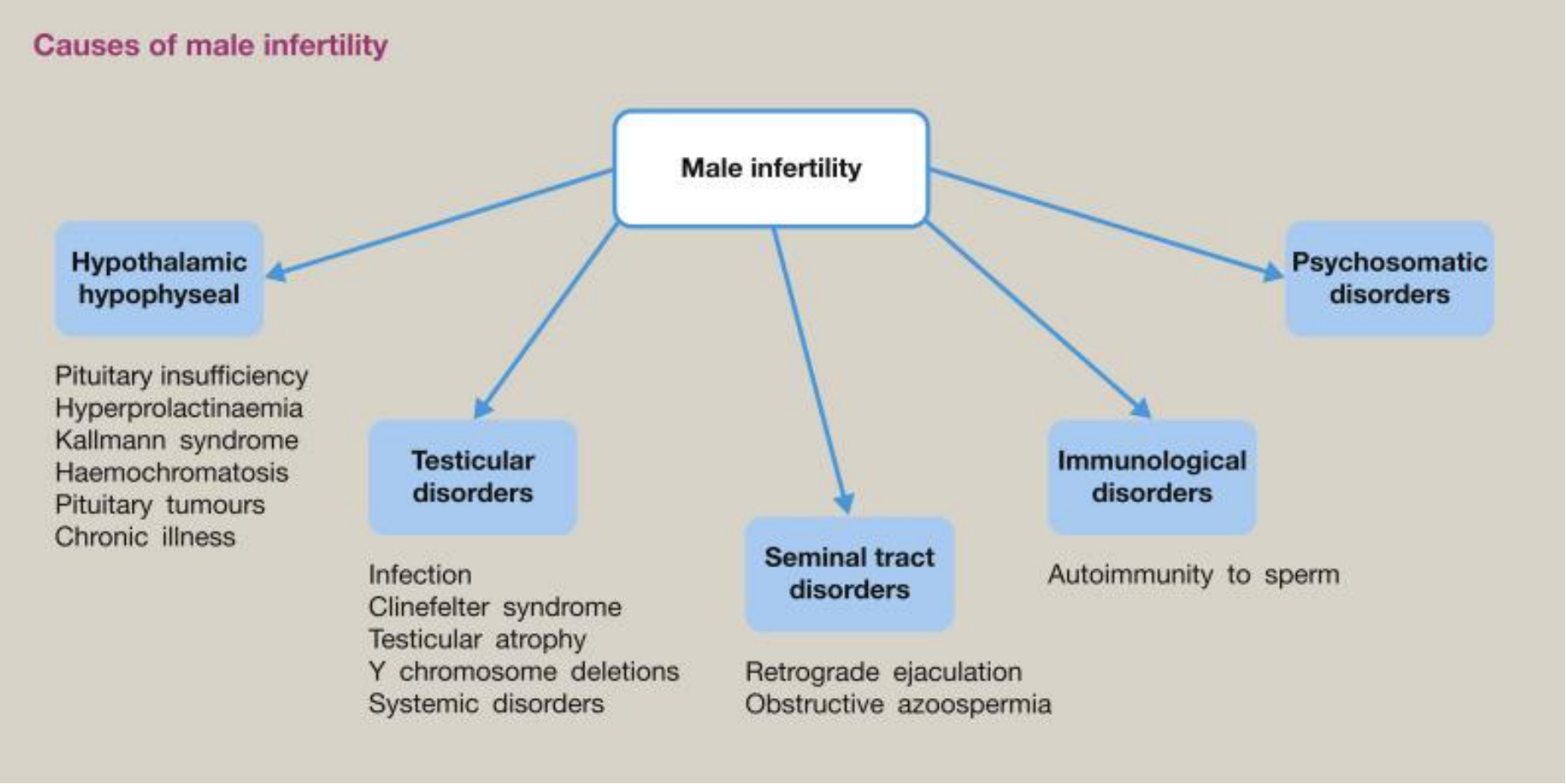
Aspirin in the **prevention** of **preeclampsia**: the **conundrum** of how, **who** and when.
Shanmugalingam R, Hennessy A, Makris A.
J Hum Hypertens. 2019 Jan;33(1):1-9. doi: 10.1038/s41371-018-0113-7.

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

Patophysiology of subfertility – female factors



Pathophysiology of subfertility – male factors

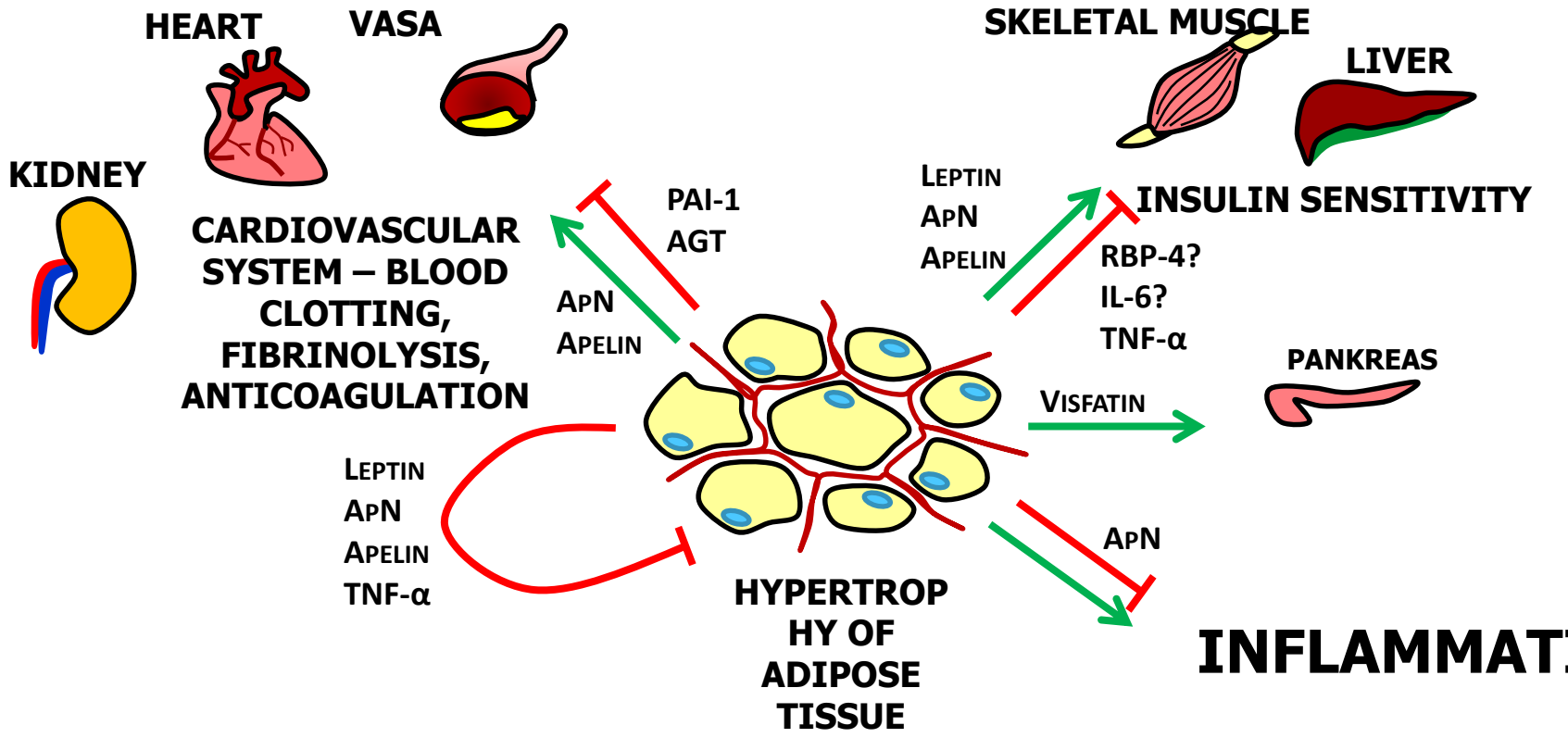


The role of adipose tissue in reproduction

White adipose tissue (WAT)

Adipokines

- 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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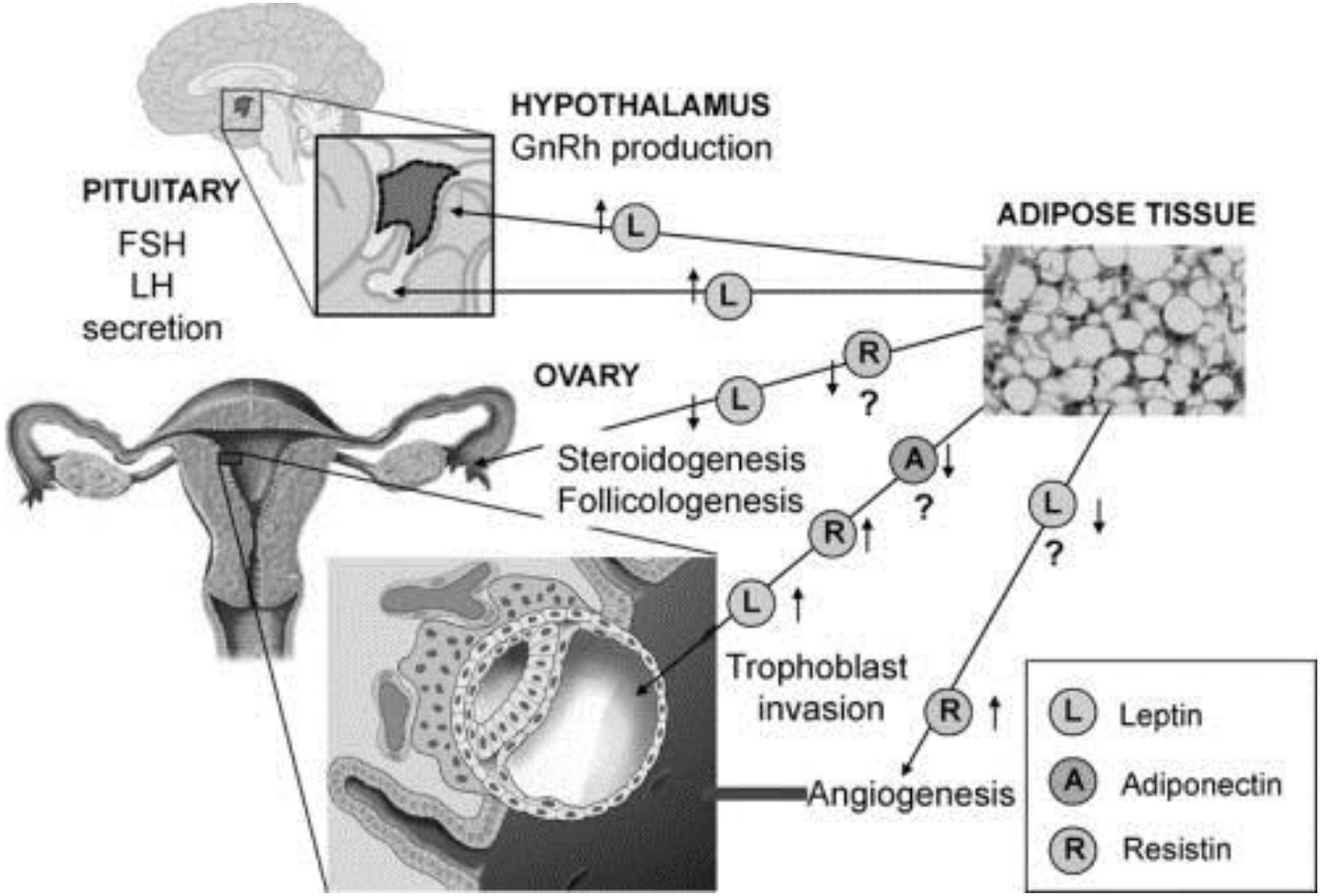
Adipokines in development of trophoblast



Tersigni C. Obstet Gynecol Survey 2011

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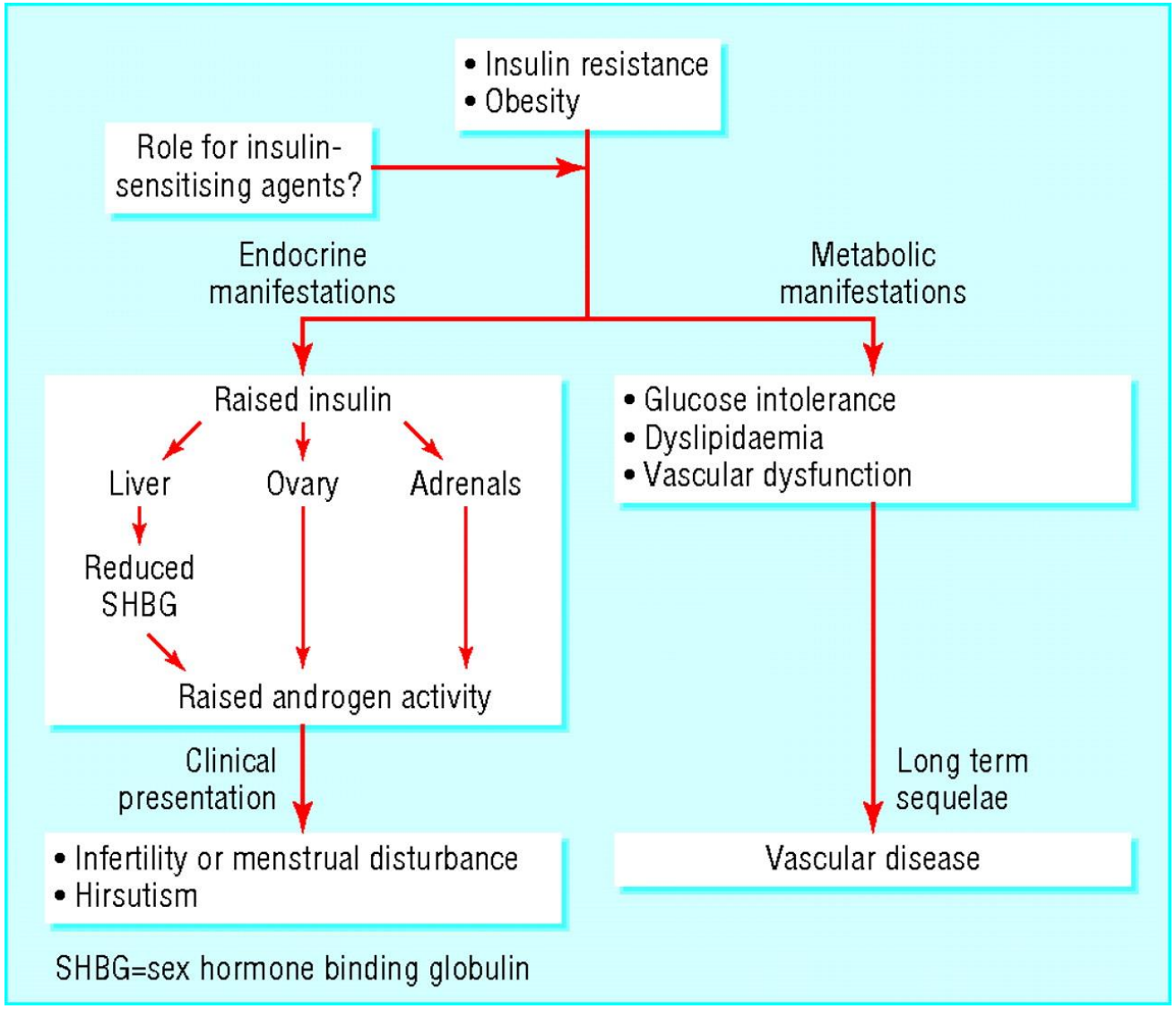
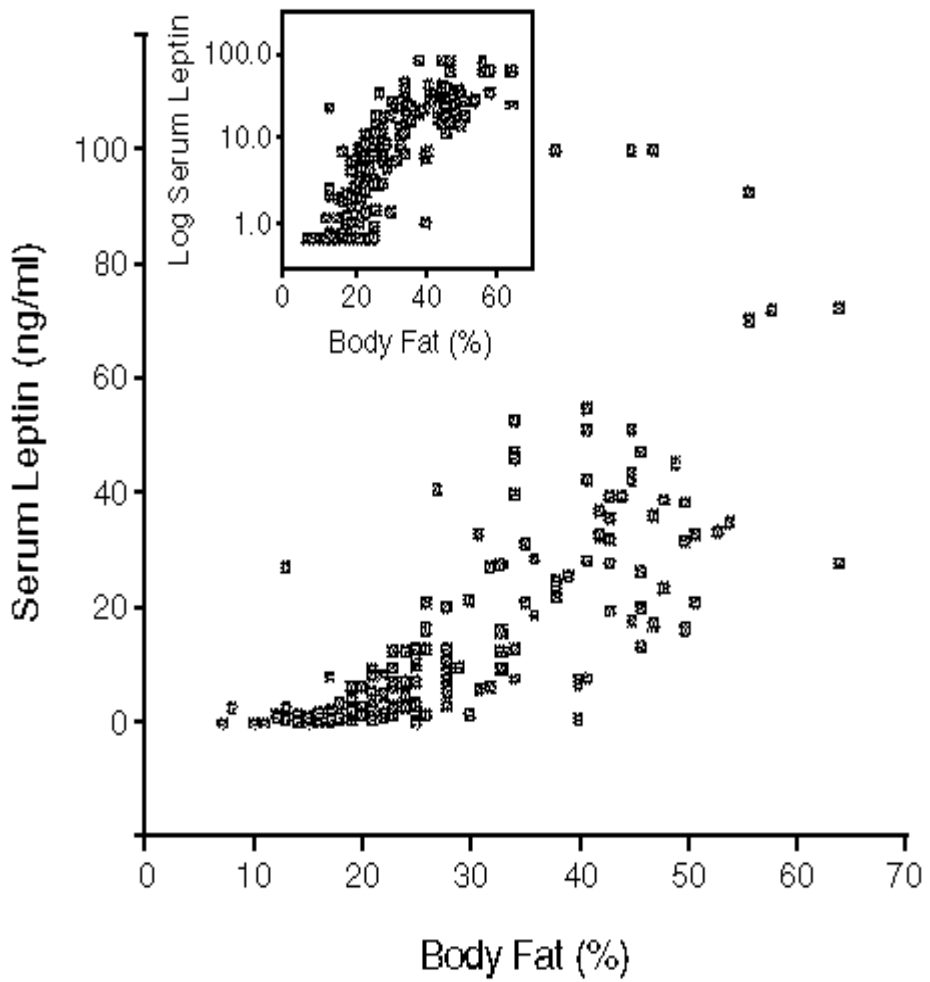
Adipokines, obesity and female fertility

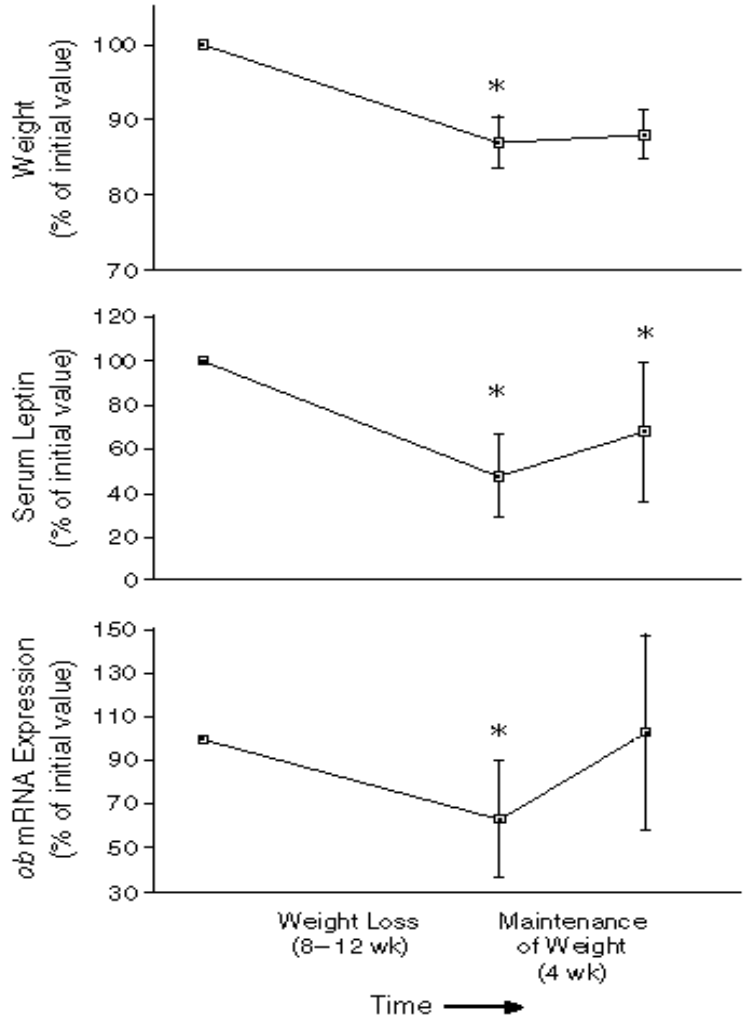


Ramsay, J. E et al. BMJ 2006

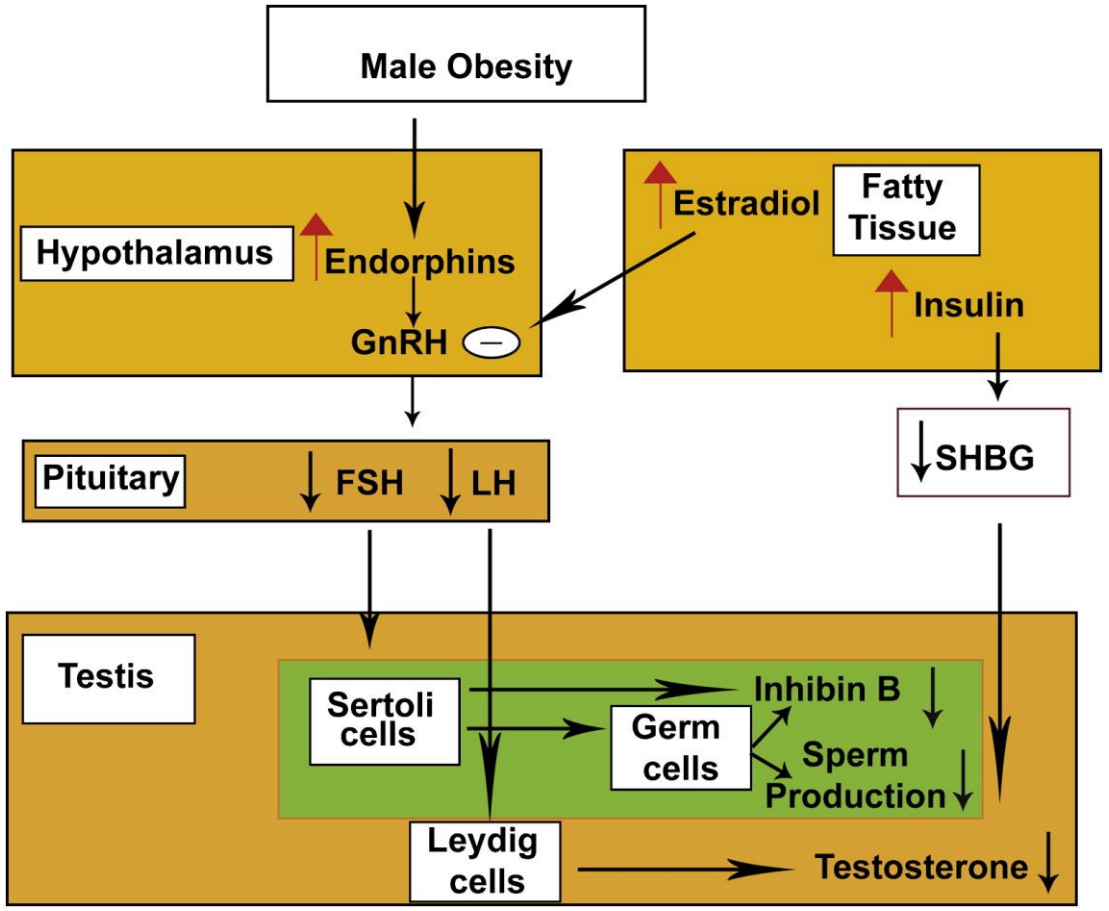
Serum levels of leptin as function of % body fat

Considine RV. N Engl J Med 1996





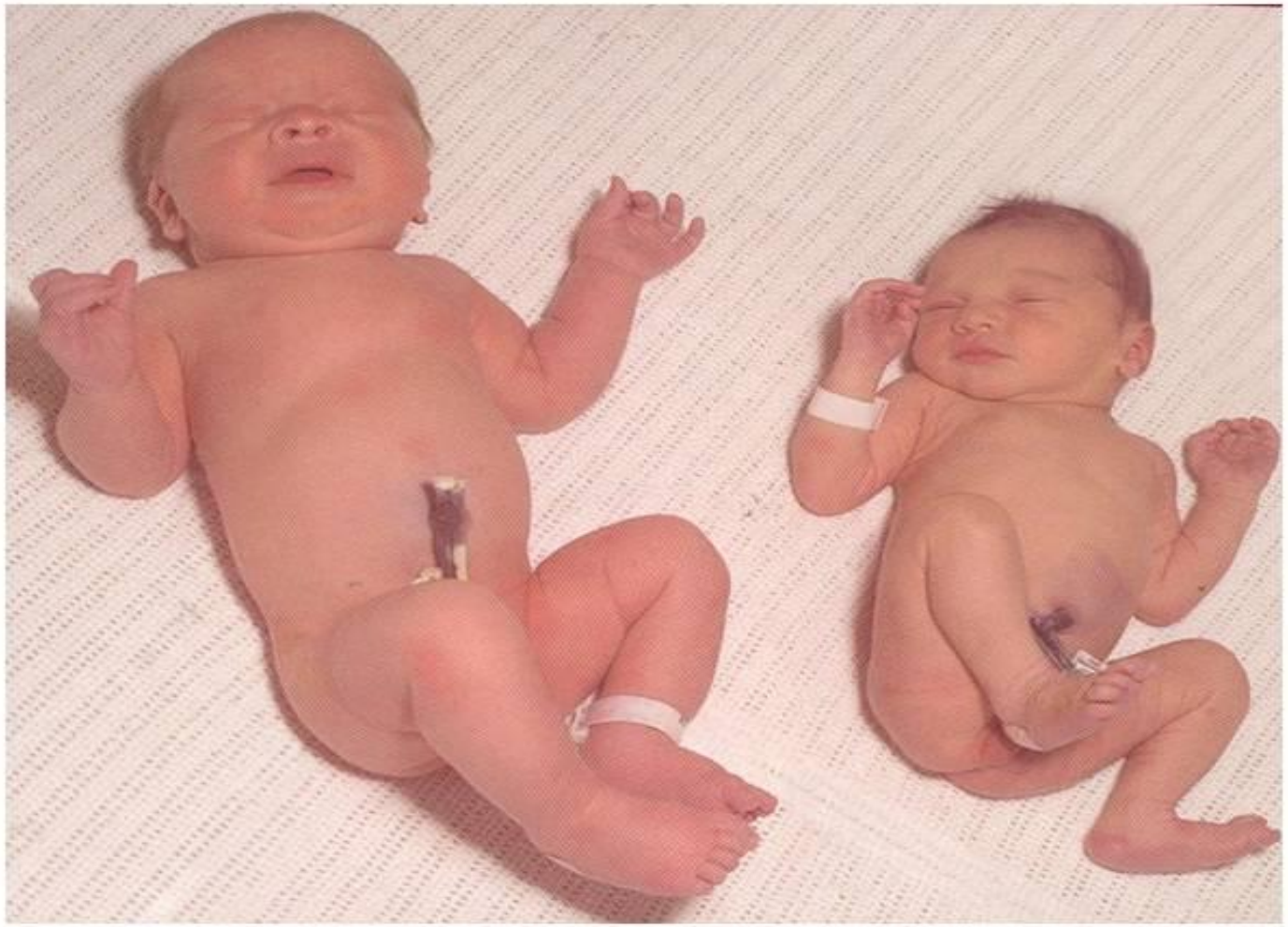
Adipokines in male fertility



Hammoud A. Fertil Steril 2008

What else? Sugar?

Fetal programming?



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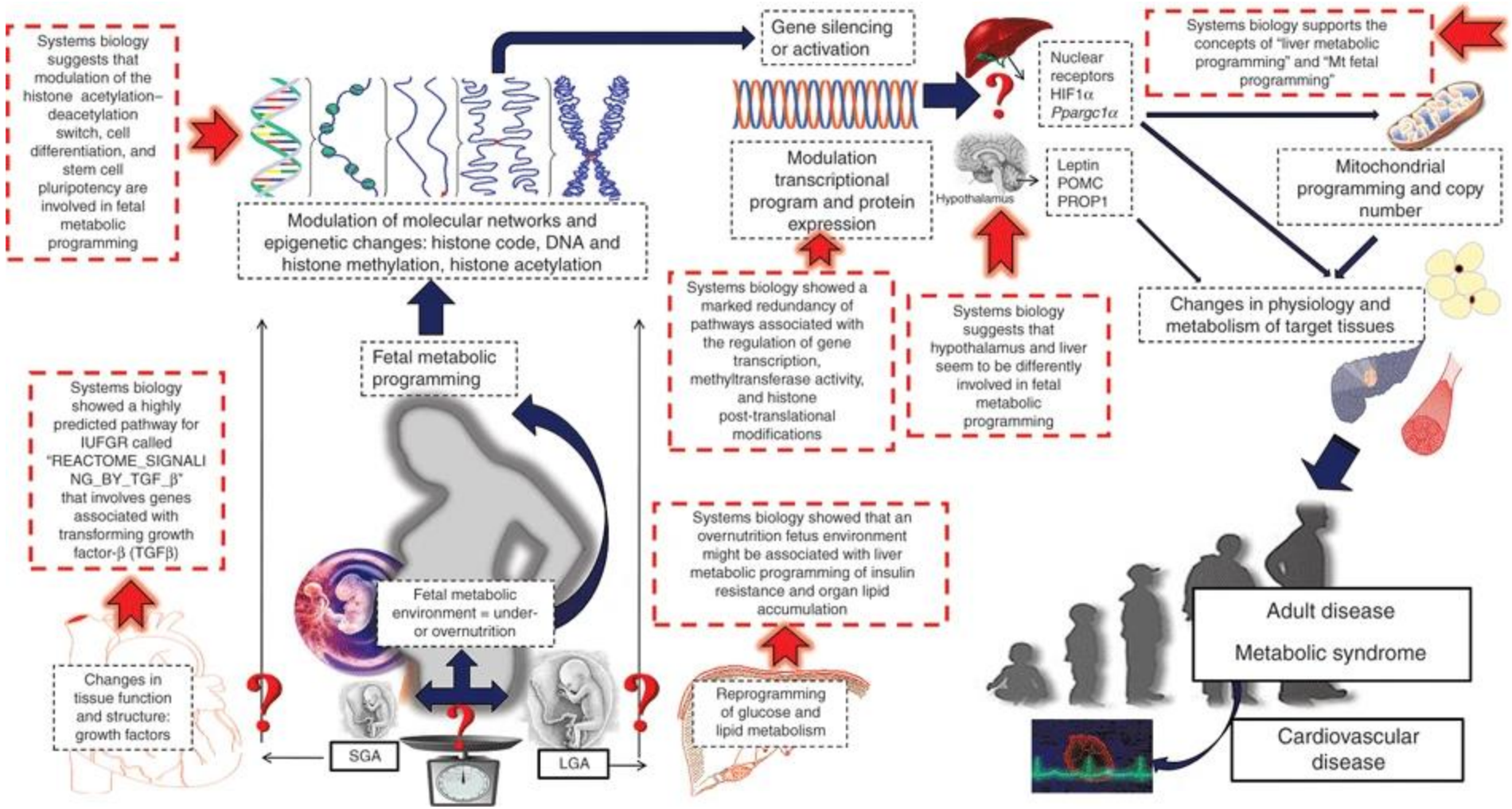
Fetal programming



Fetal metabolic programming and epigenetic modifications: a systems biology approach Silvia Sookoian, Tomas Fernández Gianotti, Adriana L. Burgueño & Carlos J. Pirola *Pediatric Research* **volume 73**, pages531–542(2013)

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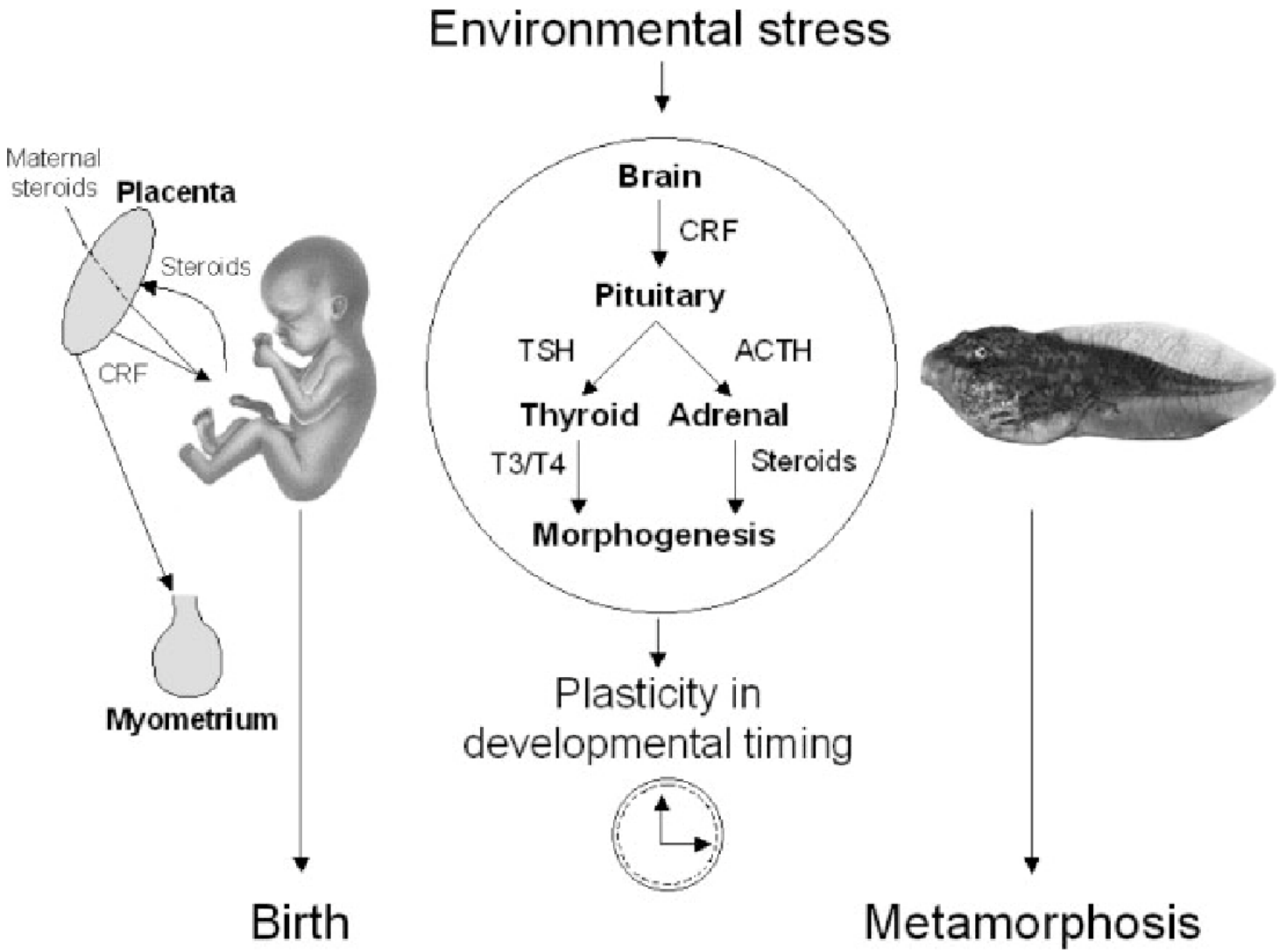
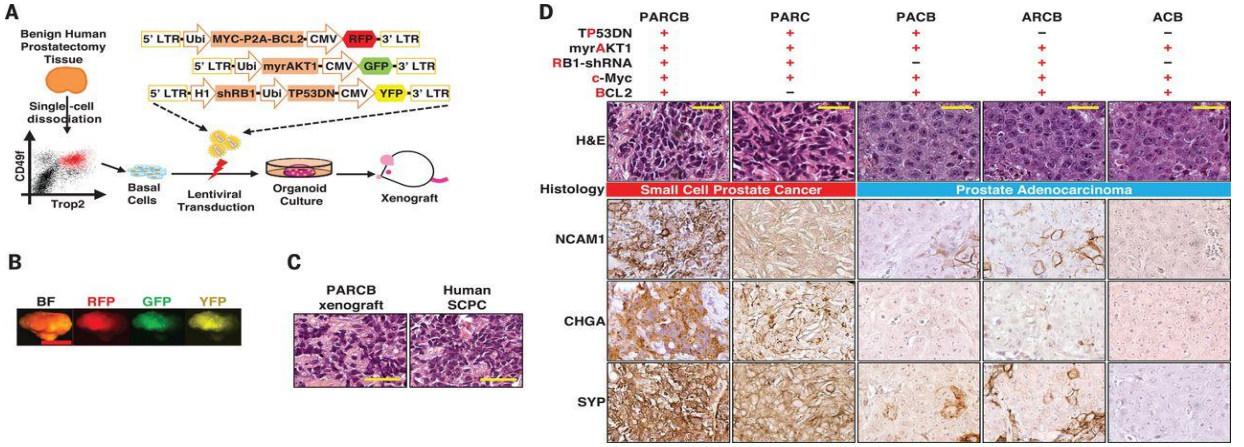
Developmental plasticity

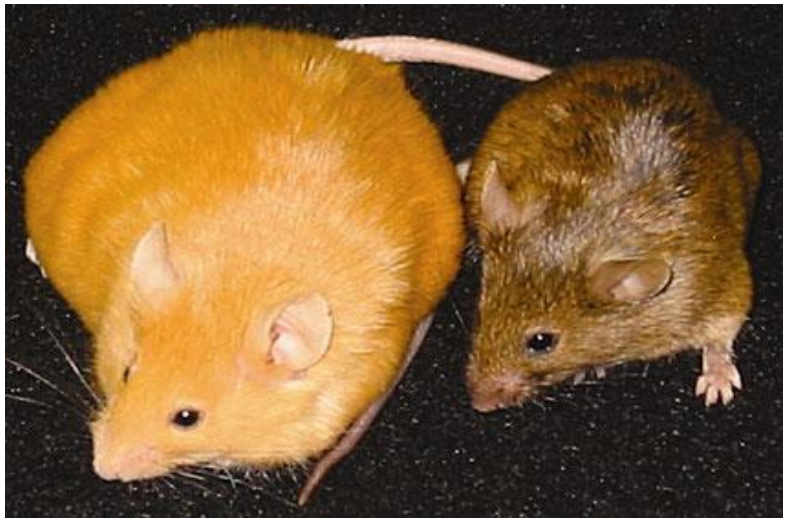


Ancient origins of **human developmental plasticity.**
Crespi EJ, Denver RJ.
Am J Hum Biol. 2005 Jan-Feb;17(1):44-54.

Developmental plasticity?

Developmental plasticity in time





Reprogramming normal human epithelial tissues to a common, lethal neuroendocrine cancer lineage

1.Jung Wook Park[1],
2.John K. Lee[2],
3.Katherine M. Sheu[3],
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Science 05 Oct 2018:

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

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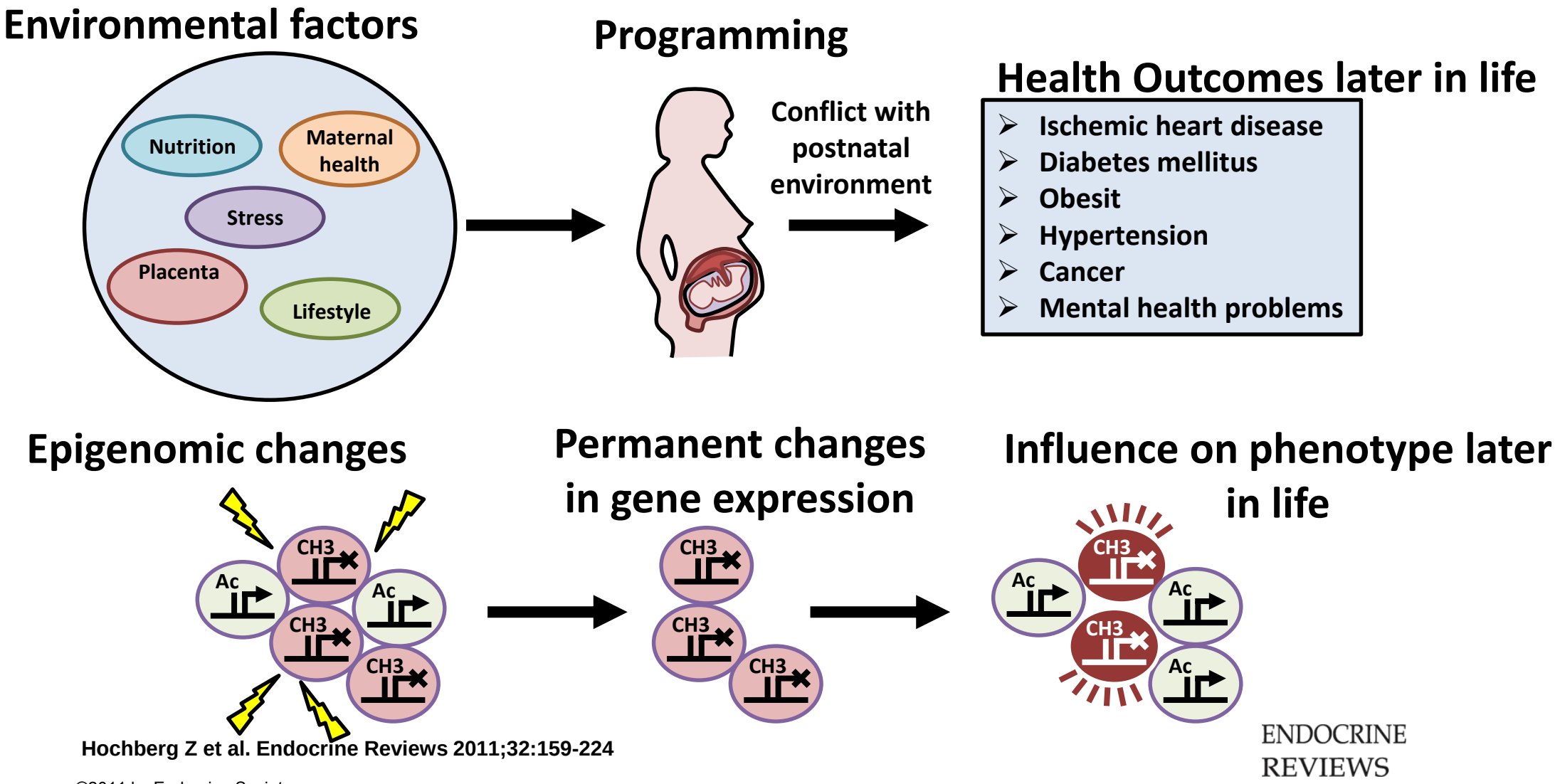

Hochberg Z et al. Endocrine Reviews 2011;32:159-224

ENDOCRINE REVIEWS

Thank you for attention,
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