MUNI
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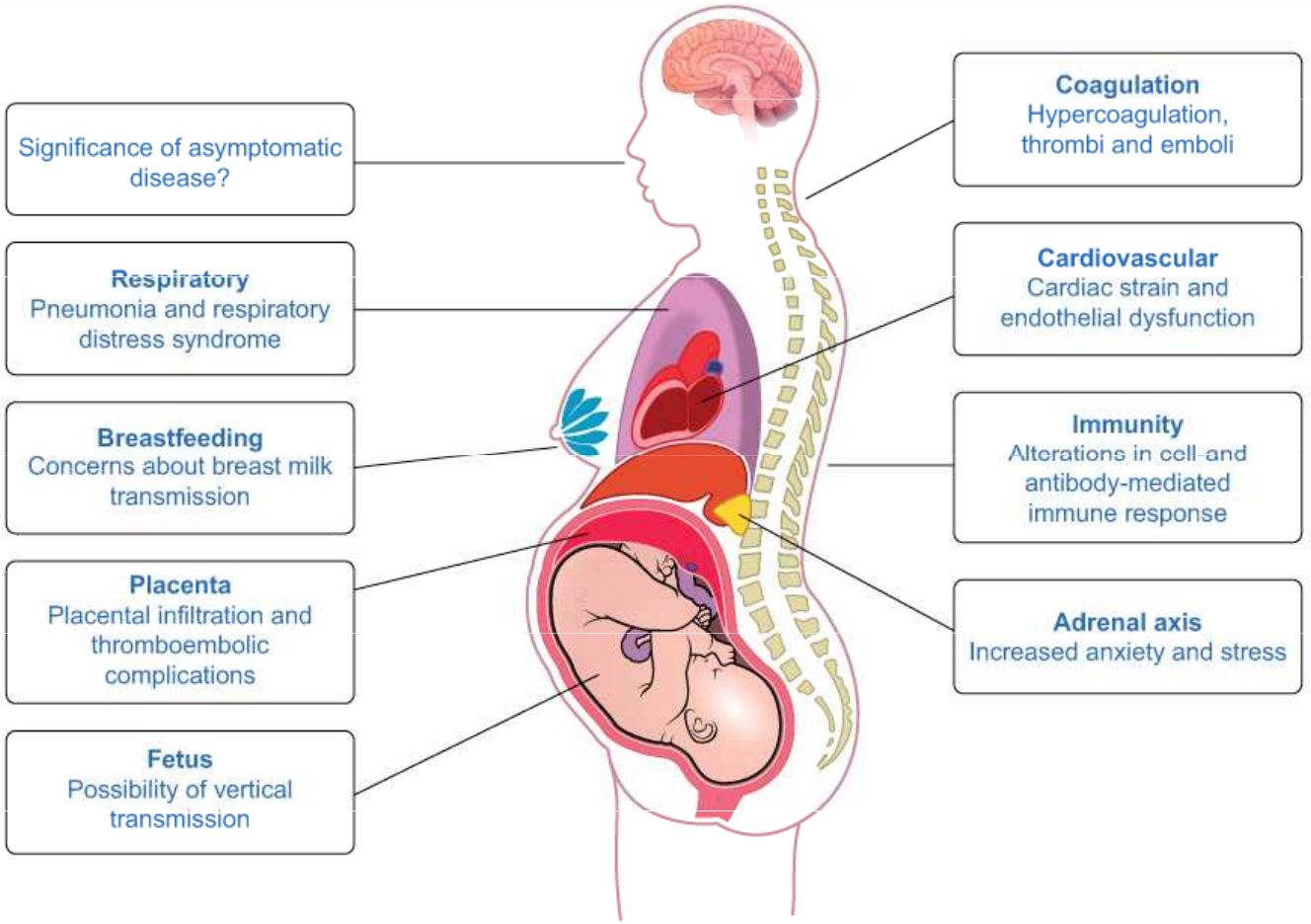
Pathophysiology of reproduction II

Julie Dobrovolná

Pathophysiology of pregnancy



Fetoplacental unit

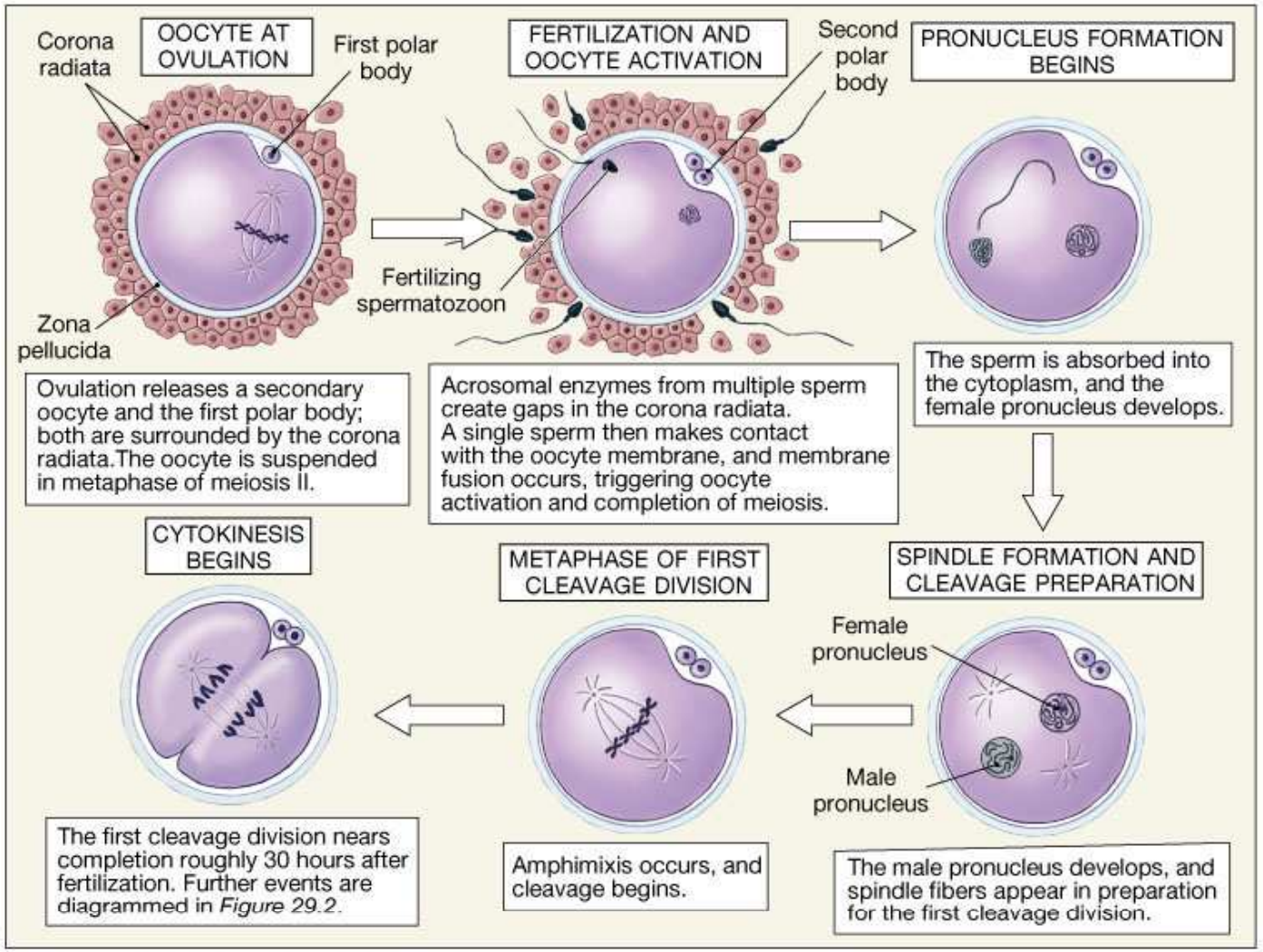
Fetoplacental unit:
- consists of **placenta, fetal adrenal gland and fetal liver**. In this unit, the fetal adrenal gland is the primary source of dehydroepiandrosterone. It is further metabolized by the fetal liver and placenta to a wide range of estrogens.

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.

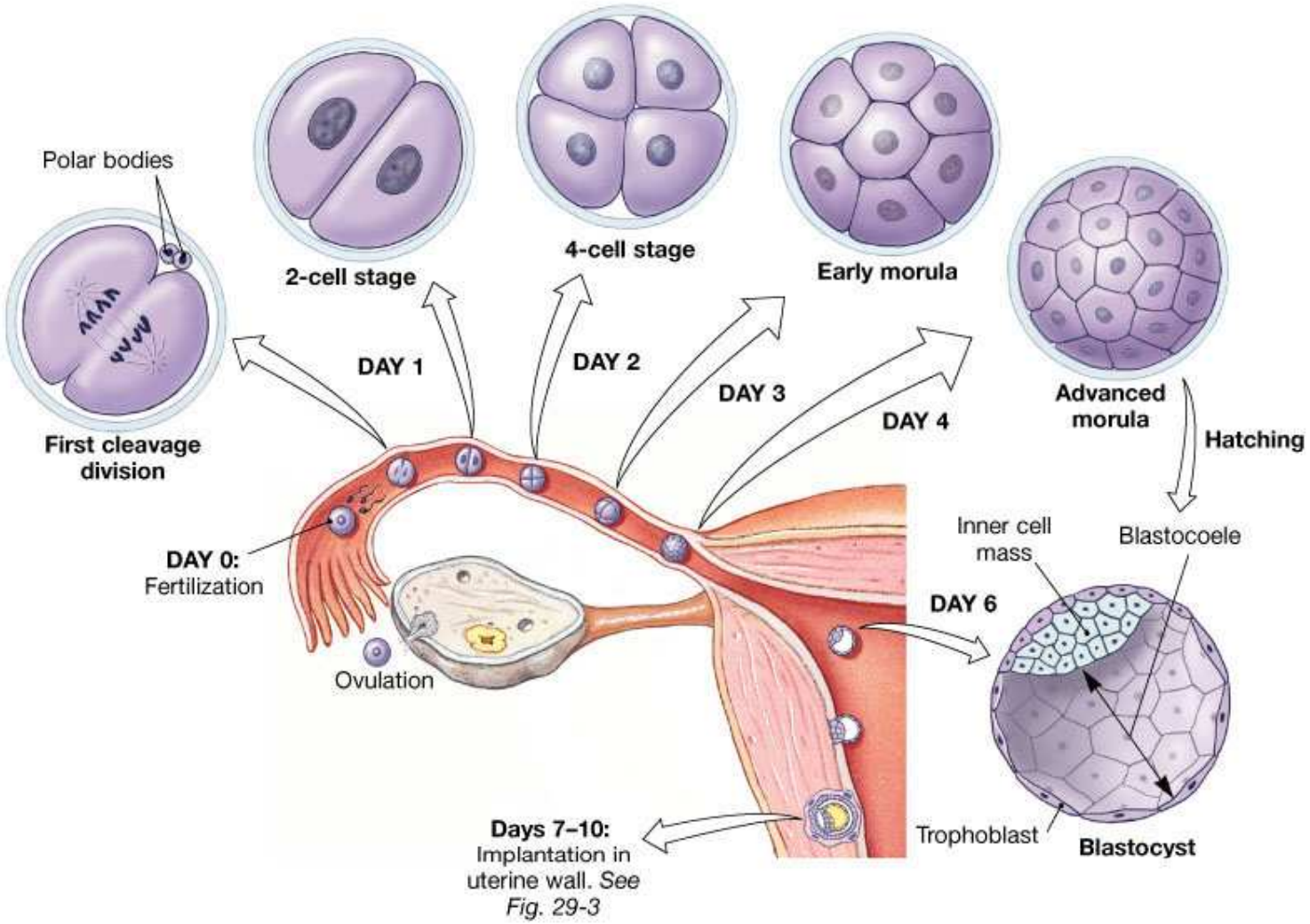
Pregnancy is marked by accretions in several endocrine systems, particularly the renin-angiotensin-aldosterone system and the hypothalamus-pituitary-adrenal system.

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

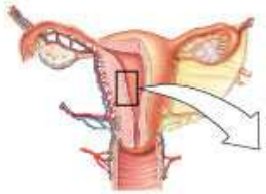
Trophoblast grows and spreads

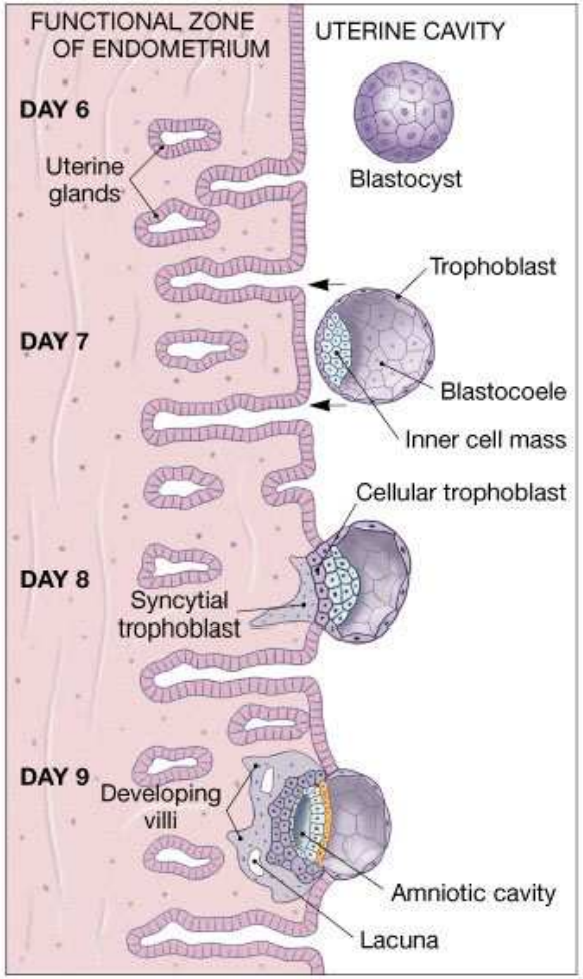
Maternal blood freely circulating in lacunes

Gastrulation

Embryonic target consists of:

- Endoderm
- Mesoderm
- Ektoderm





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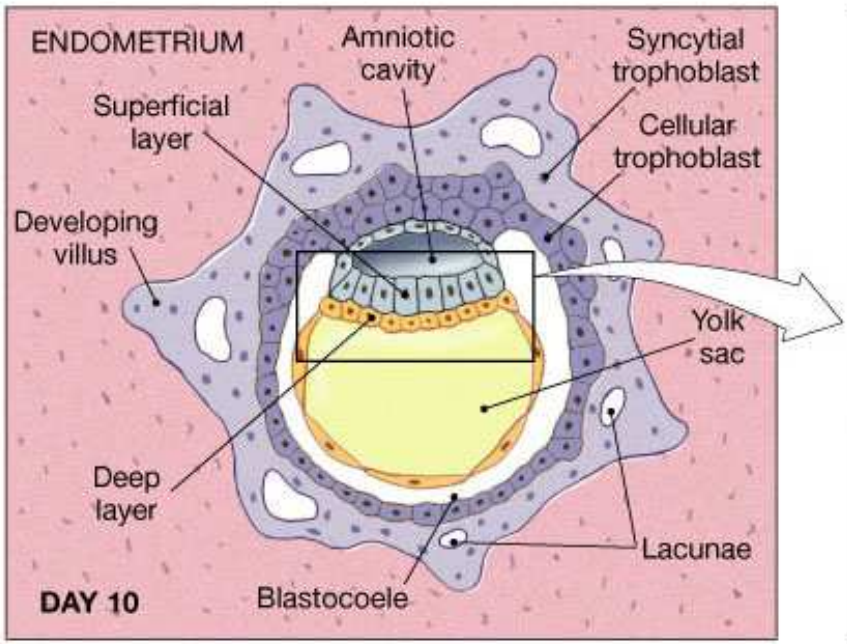
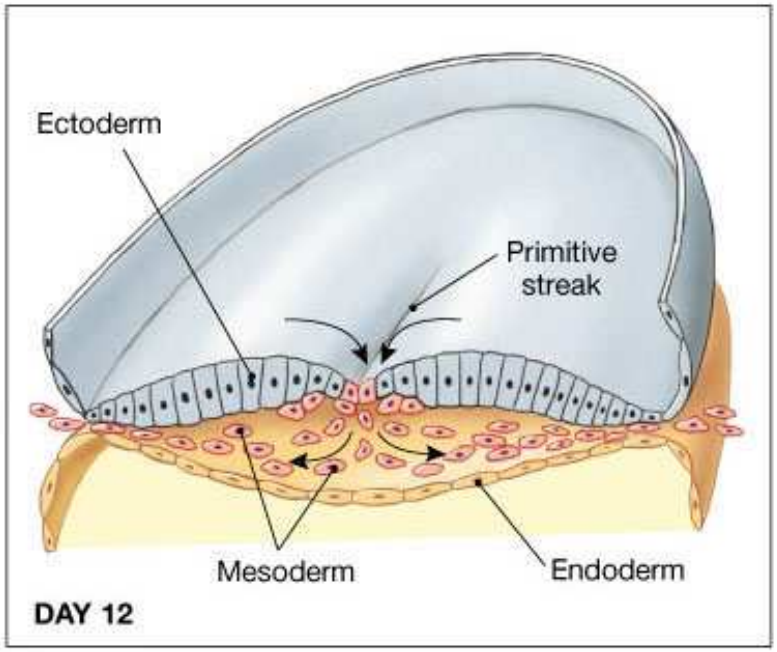
Internal cellular mass and gastrulation



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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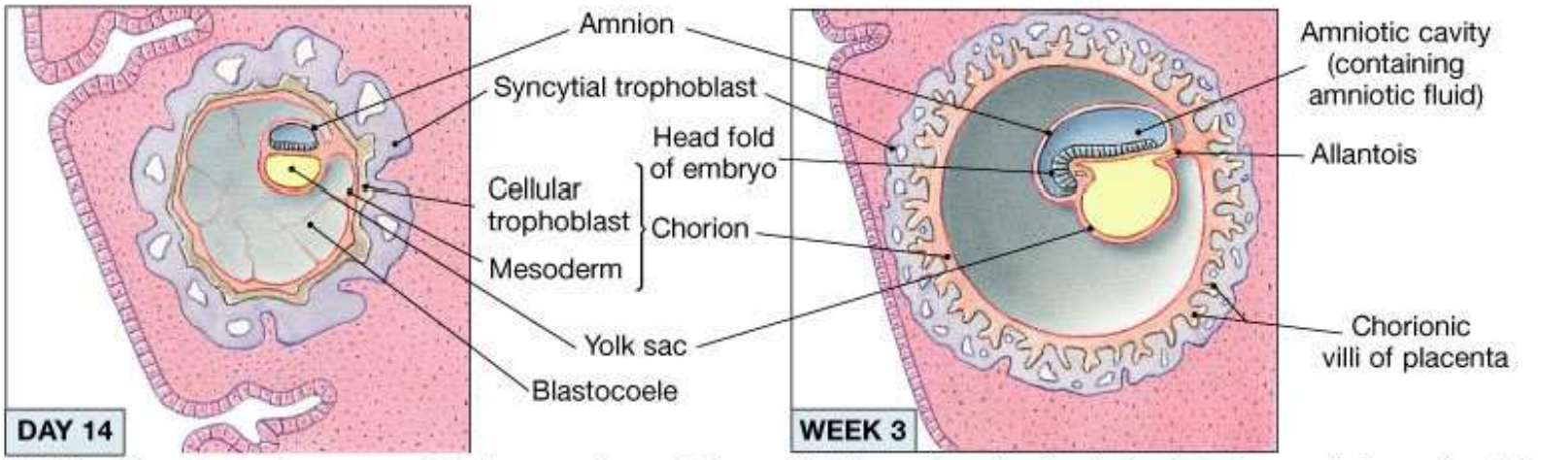
Extraembryonic membranes

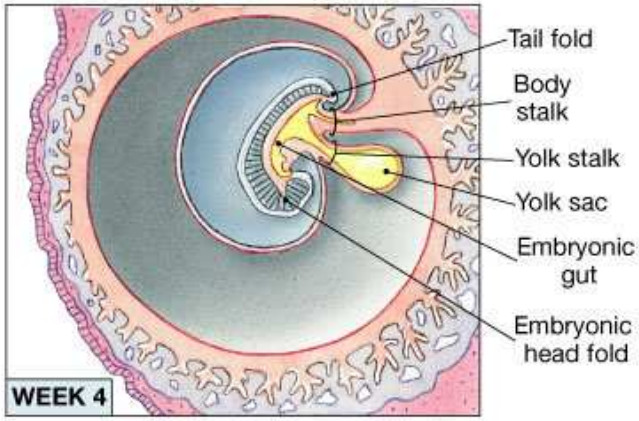


(a) Migration of mesoderm around the inner surface of the trophoblast creates the chorion. Mesodermal migration around the outside of the amniotic cavity, between the ectodermal cells and the trophoblast, forms the amnion. Mesodermal migration around the endodermal pouch creates the yolk sac.

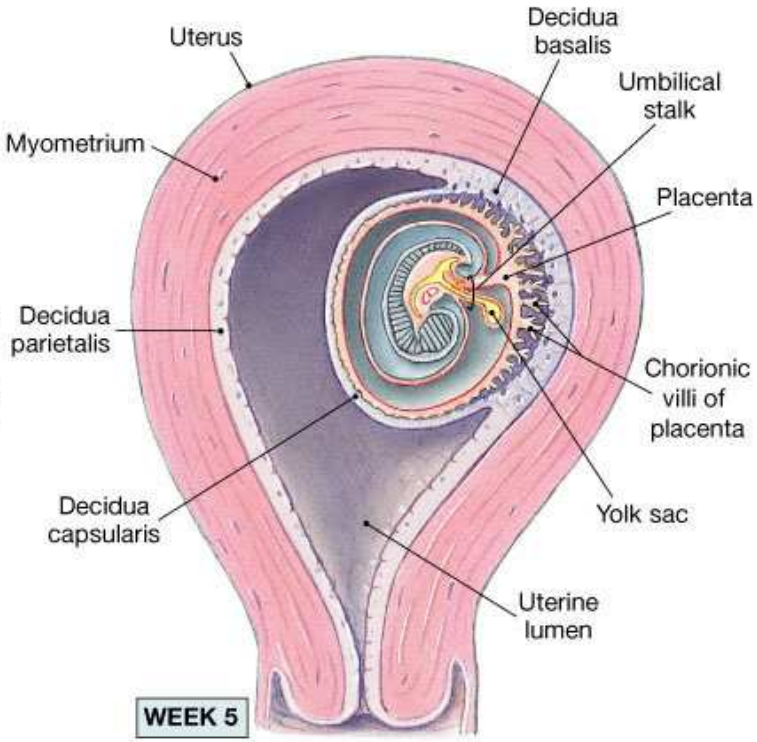
(b) The embryonic disc bulges into the amniotic cavity at the head fold. The allantois, an endodermal extension surrounded by mesoderm, extends toward the trophoblast.

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

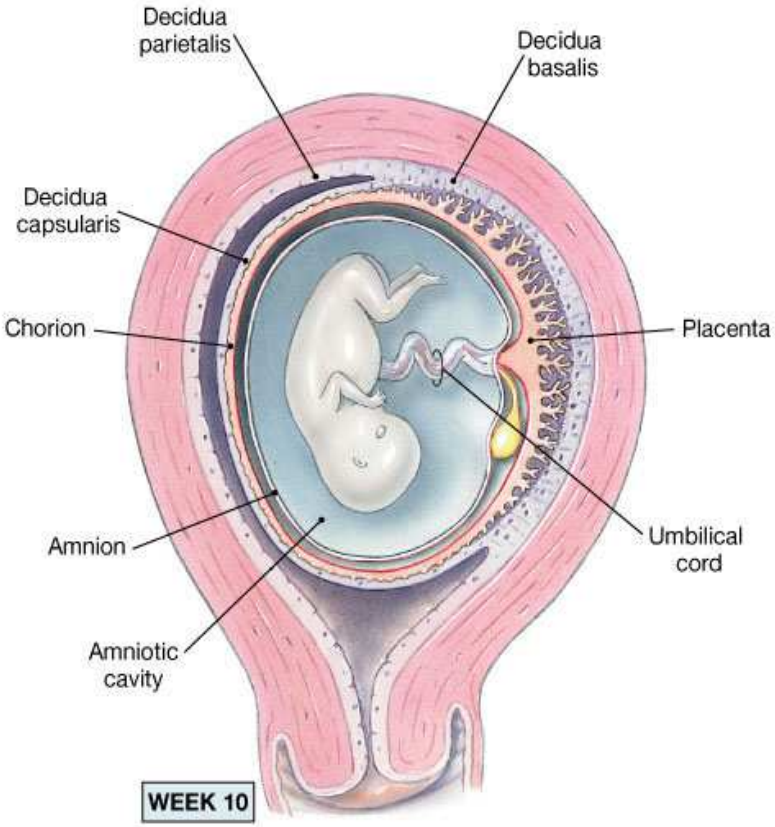
Placental development



(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.

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Embryo anatomy

Yolk sac

Where blood cells are produced

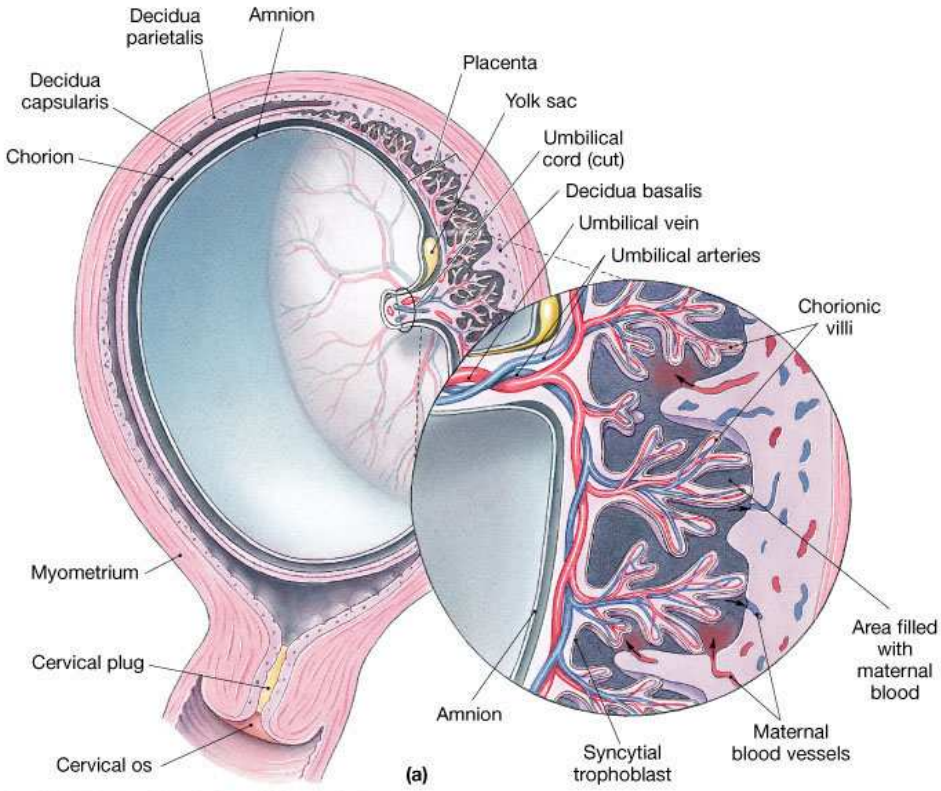
Amnion

Encompasses the fluid around embryo

Allantois

Bladder

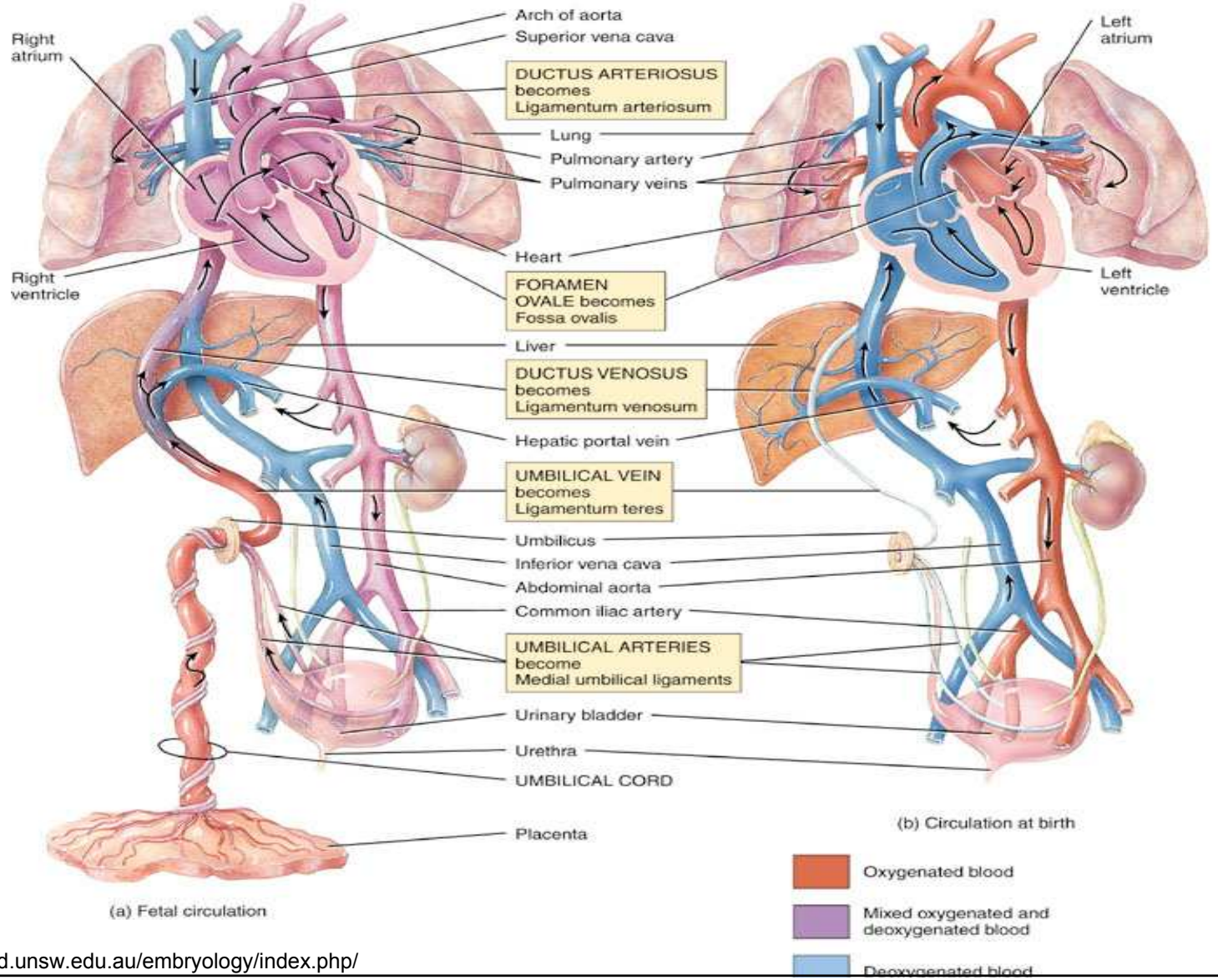
Chorion



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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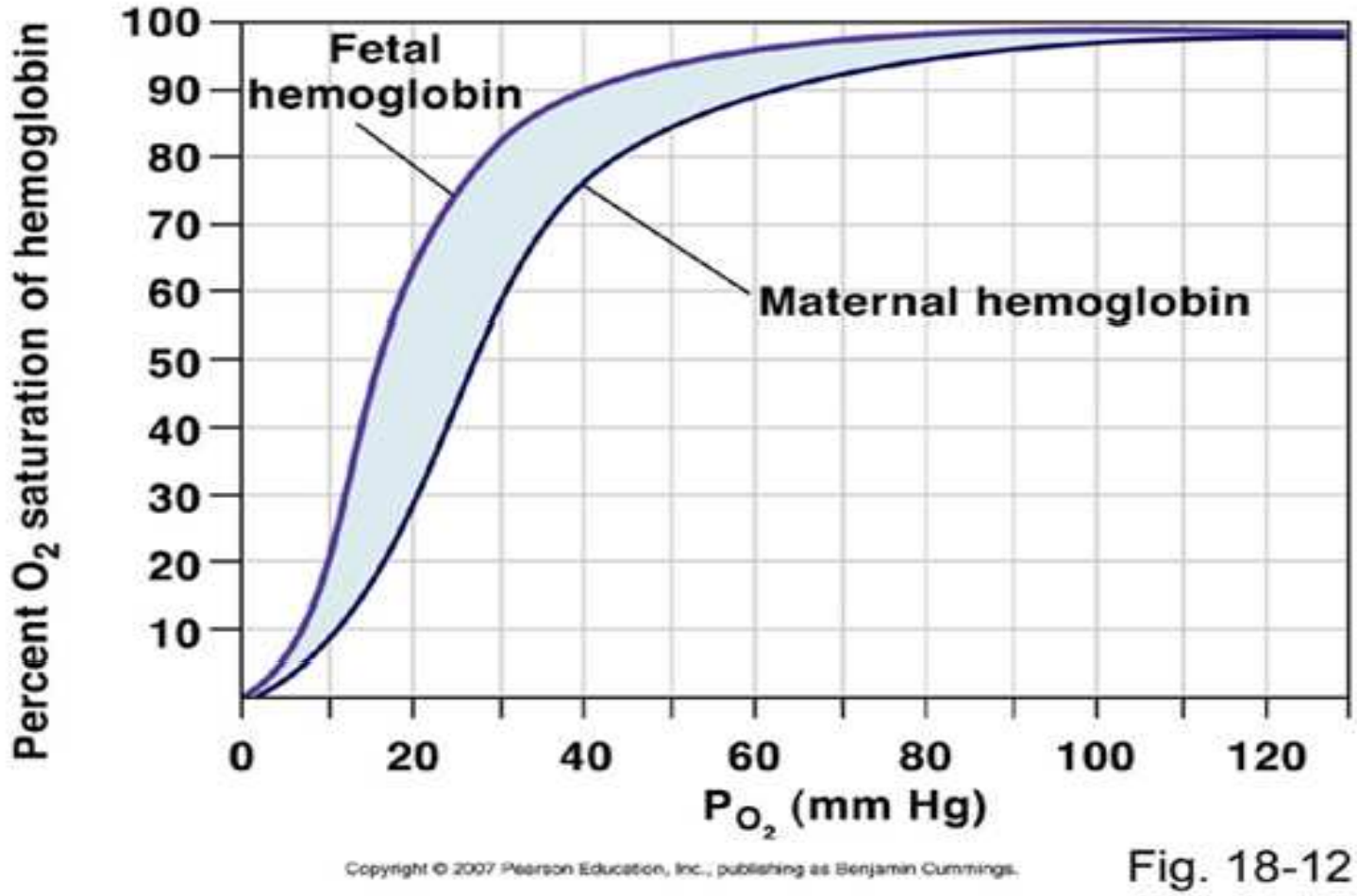
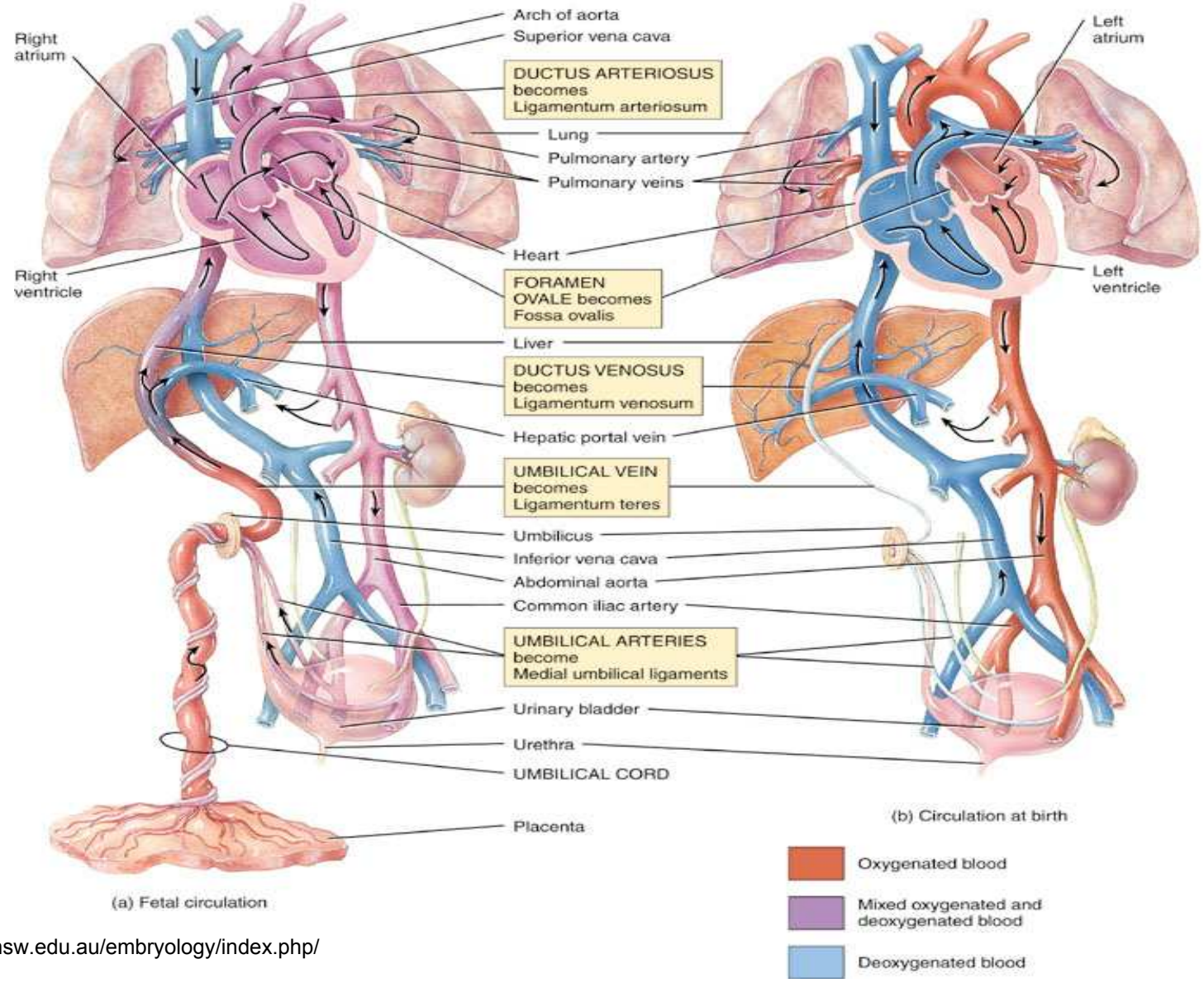


Fig. 18-12

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



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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.

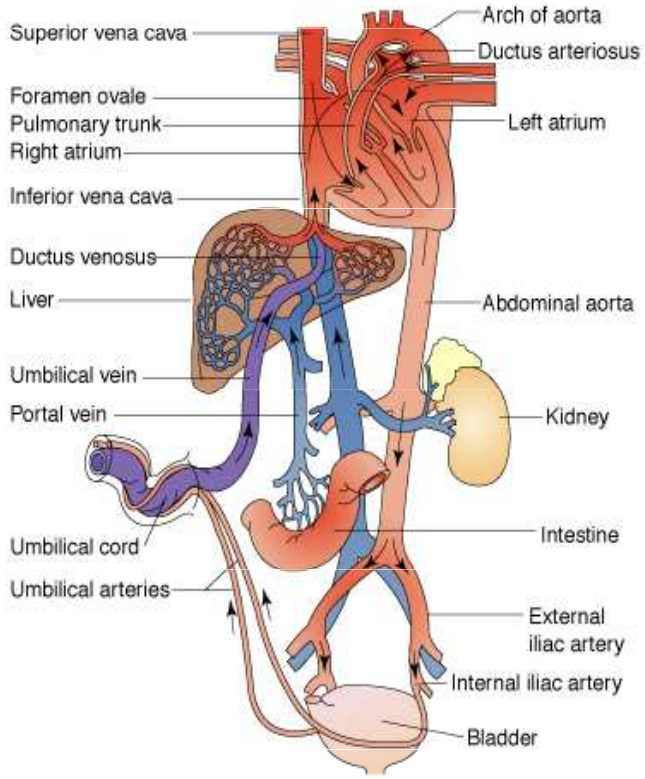

Figure 26-27 Fetal circulation.

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.

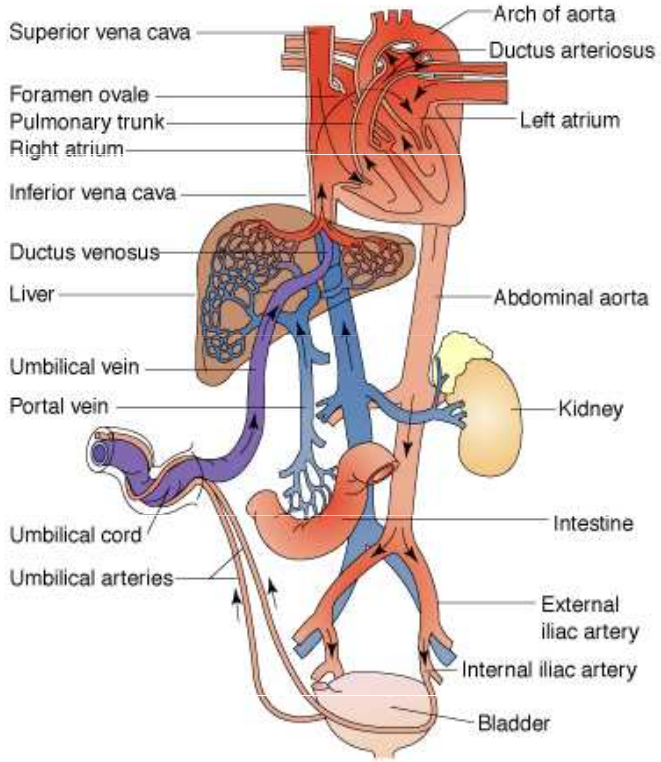

Figure 26-27 Fetal circulation.

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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.

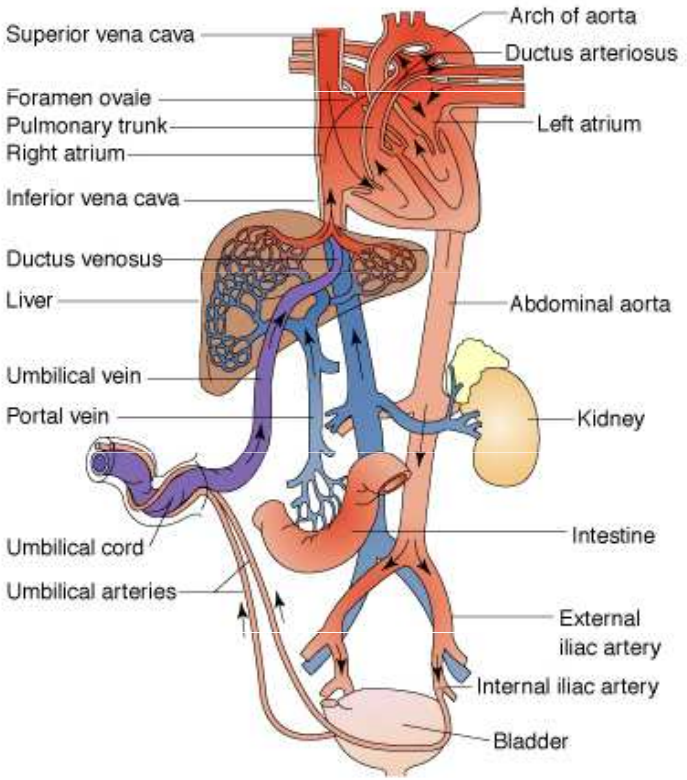

Figure 26-27 Fetal circulation.

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

Pathophysiology of preterm birth

Preterm Labor

- Preterm labor is defined as the onset of uterine contraction of adequate strength and frequency to cause progressive dilatation and effacement of cervix between 20 and 37 weeks of gestation[1]

- Preterm labor is one of the leading cause of perinatal morbidity and mortality[2]

- Preterm delivery effects almost 23% pregnancies in developing countries like India[3]

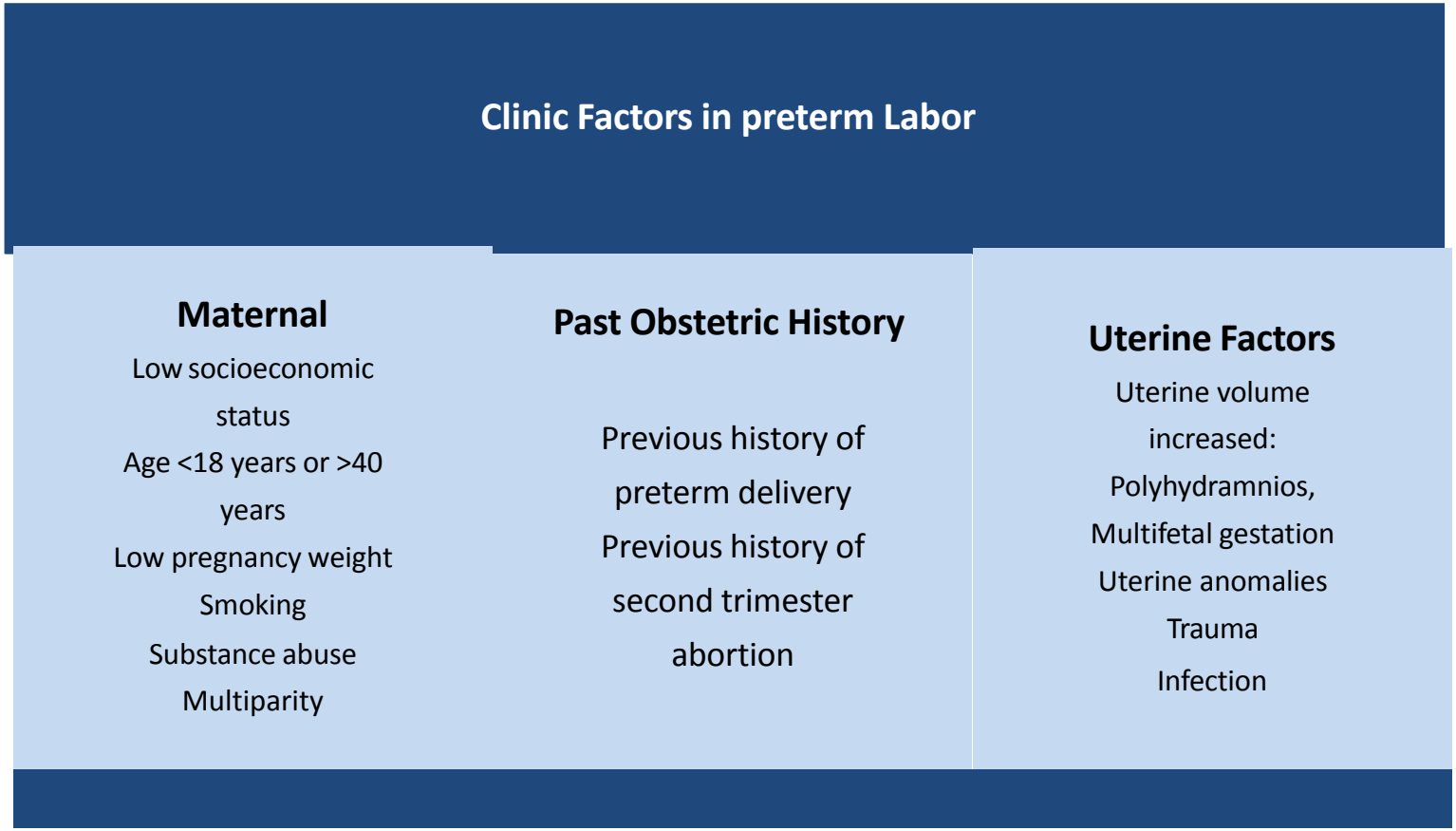
1. Revisiting the use of Isoxsuprine in Preterm Labor – Indian Consensus Document by ISSRF
2. BJOG. Volume 120, Issue 13 December 2013 Pages 1588–1598
3. International Journal of Basic and Applied Medical Sciences ISSN: 2277 : An Open Access, Online International Journal2015 Vol. 5 (3) September

Clinical Circumstances Associated with Preterm Birth

- Spontaneous preterm labor with intact membranes

- Preterm PROM
- Indicated preterm delivery
  - Maternal (e.g. pre-eclampsia)
  - Fetal (e.g. SGA/fetal compromise)

Risk Factors

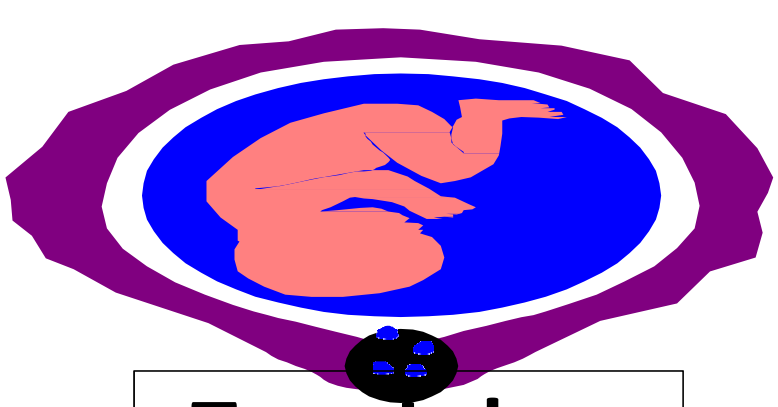


Mechanism of Preterm Labor

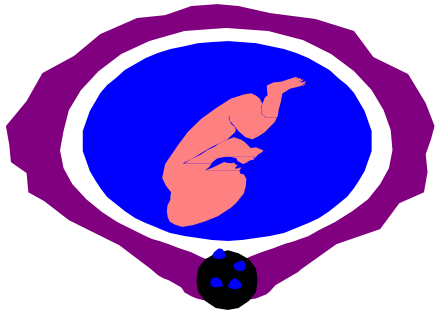
Causes	Mechanism
• Stress •Premature activation of physiological effectors	Activation of maternal-fetal HPA-axis •CRH → Fetal adrenal androgens •Placental estrogen and progesterone
• Inflammation and infection	• Pro-inflammatory cytokines • Fetal inflammatory response syndrome
• Ischemia or hemorrhage	• Thrombin activation
• Pathological Uterine distension	•Increased gap junction along with contraction associated protiens and upregulation of prostaglandins and oxytocin receptors

Common Uterine Features of Term and Preterm Labor

- Increased myometrial contractility
- Cervical ripening (dilatation and effacement)
- Decidual/membrane activation



Term Labor



Preterm Labor

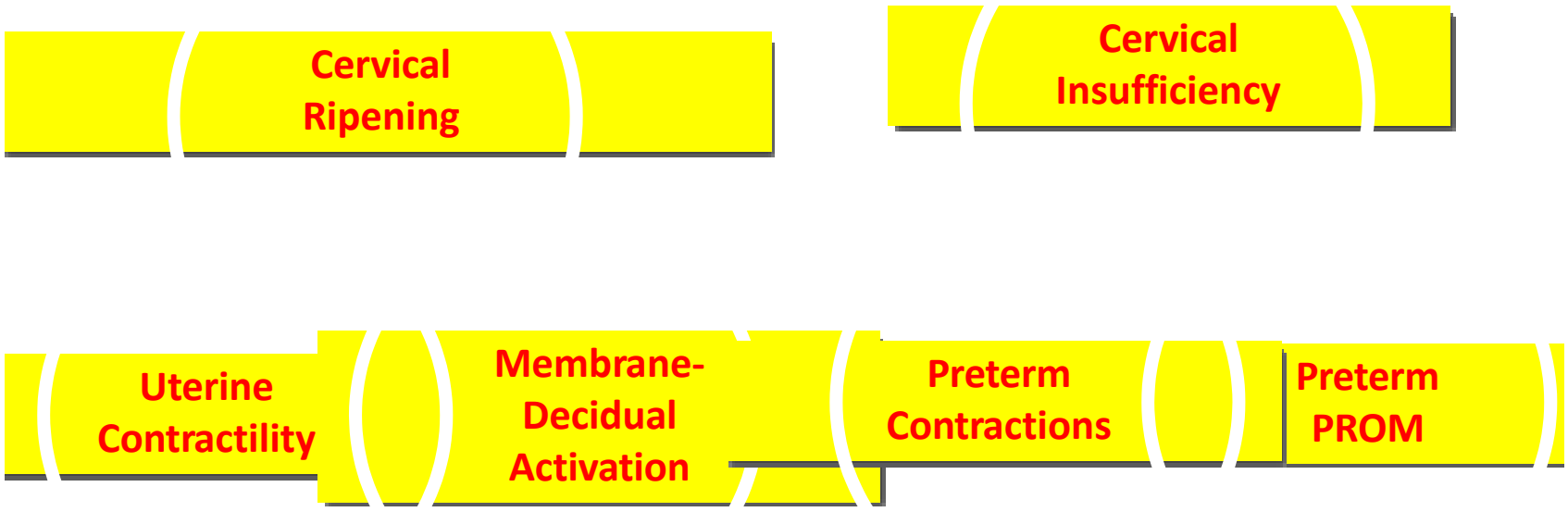
Romero R, Mazor M, Munoz H et al: The Preterm Labor Syndrome. Ann NY Acad Sci 1994;734:414

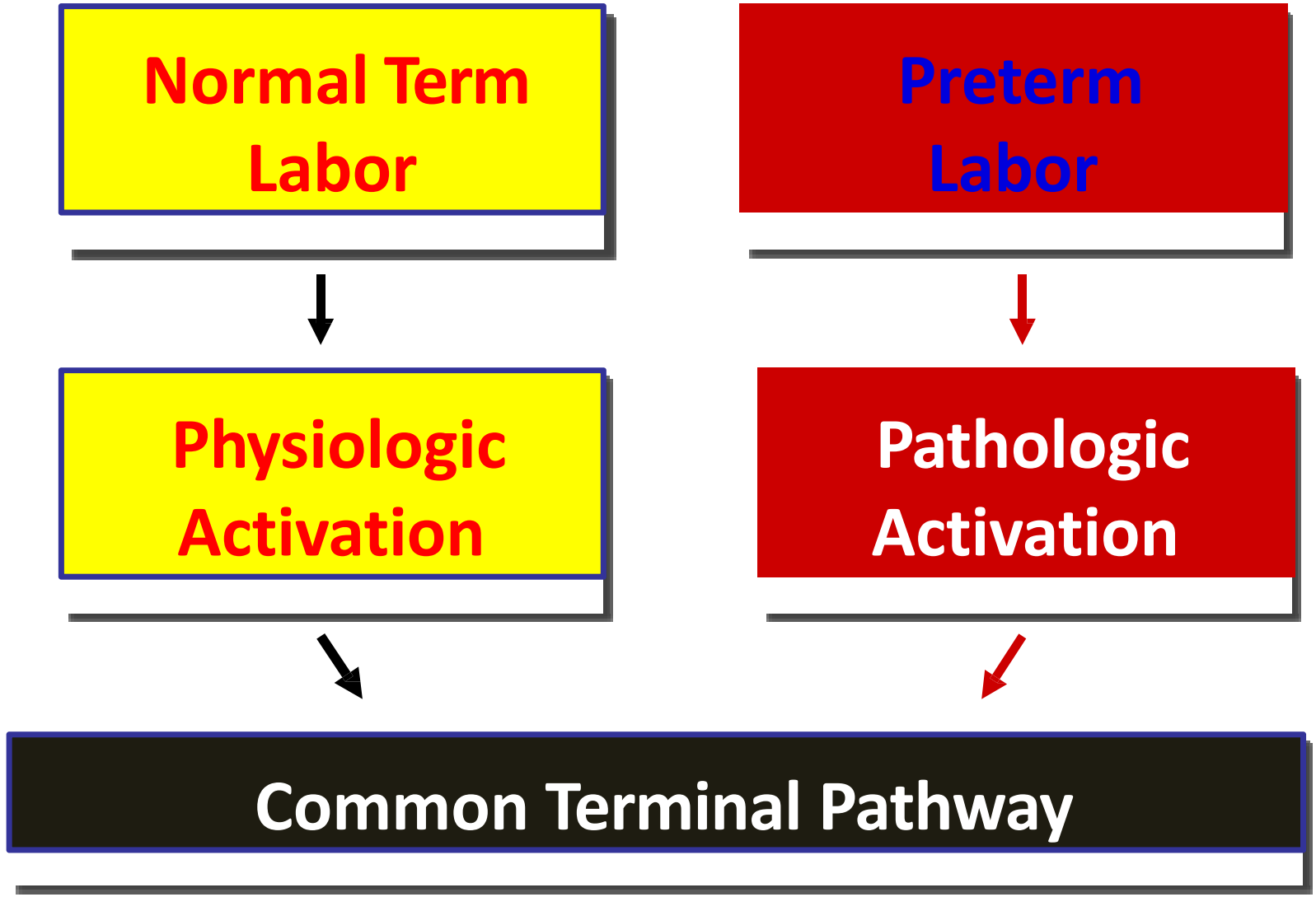
Common Pathway of Parturition

- Anatomic, physiologic, biochemical, endocrinologic, immunologic, and clinical events in the mother and/or fetus in both term and preterm labor

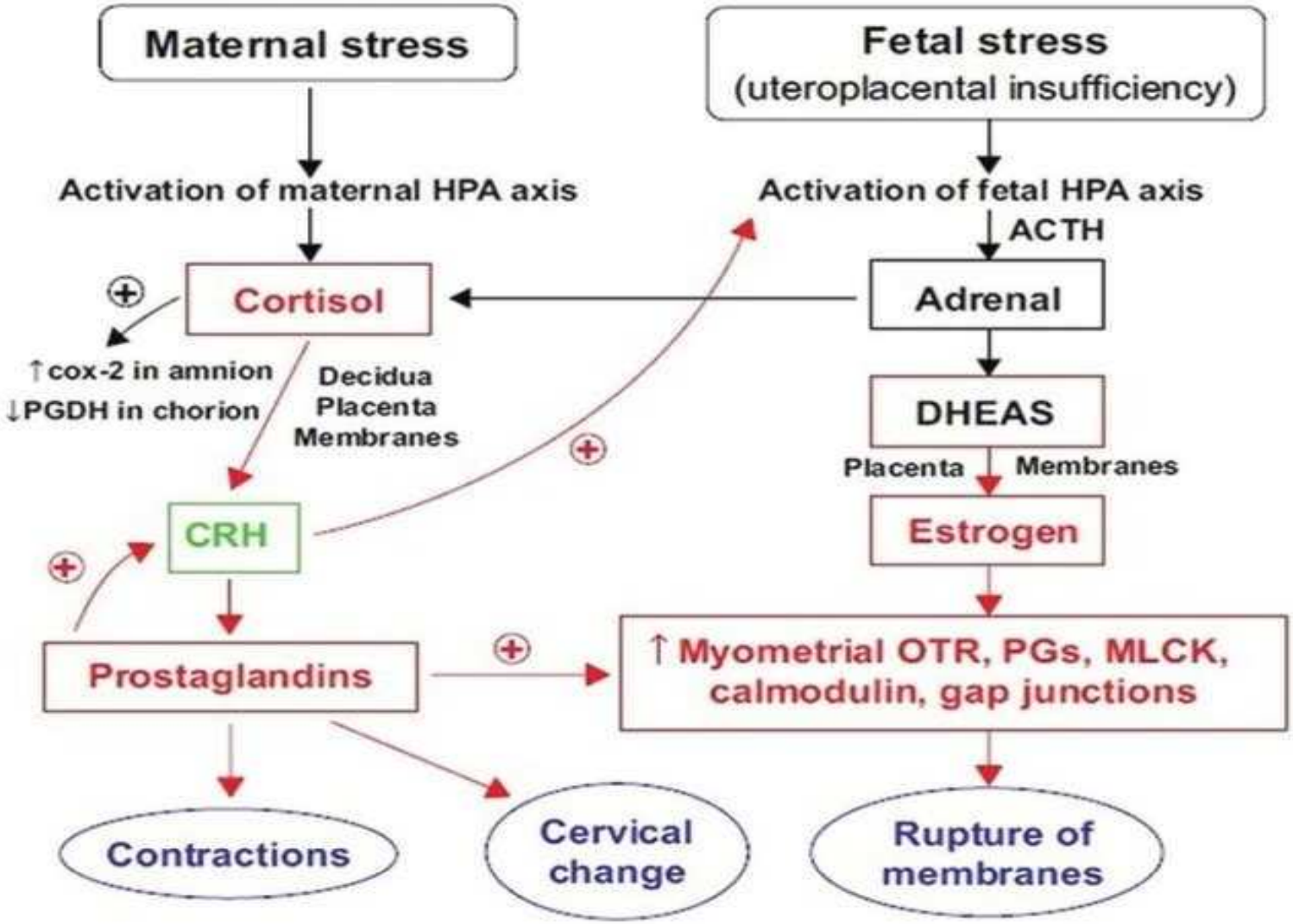
Romero R, Mazor M, Munoz H et al: The Preterm Labor Syndrome. Ann NY Acad Sci 1994;734:414

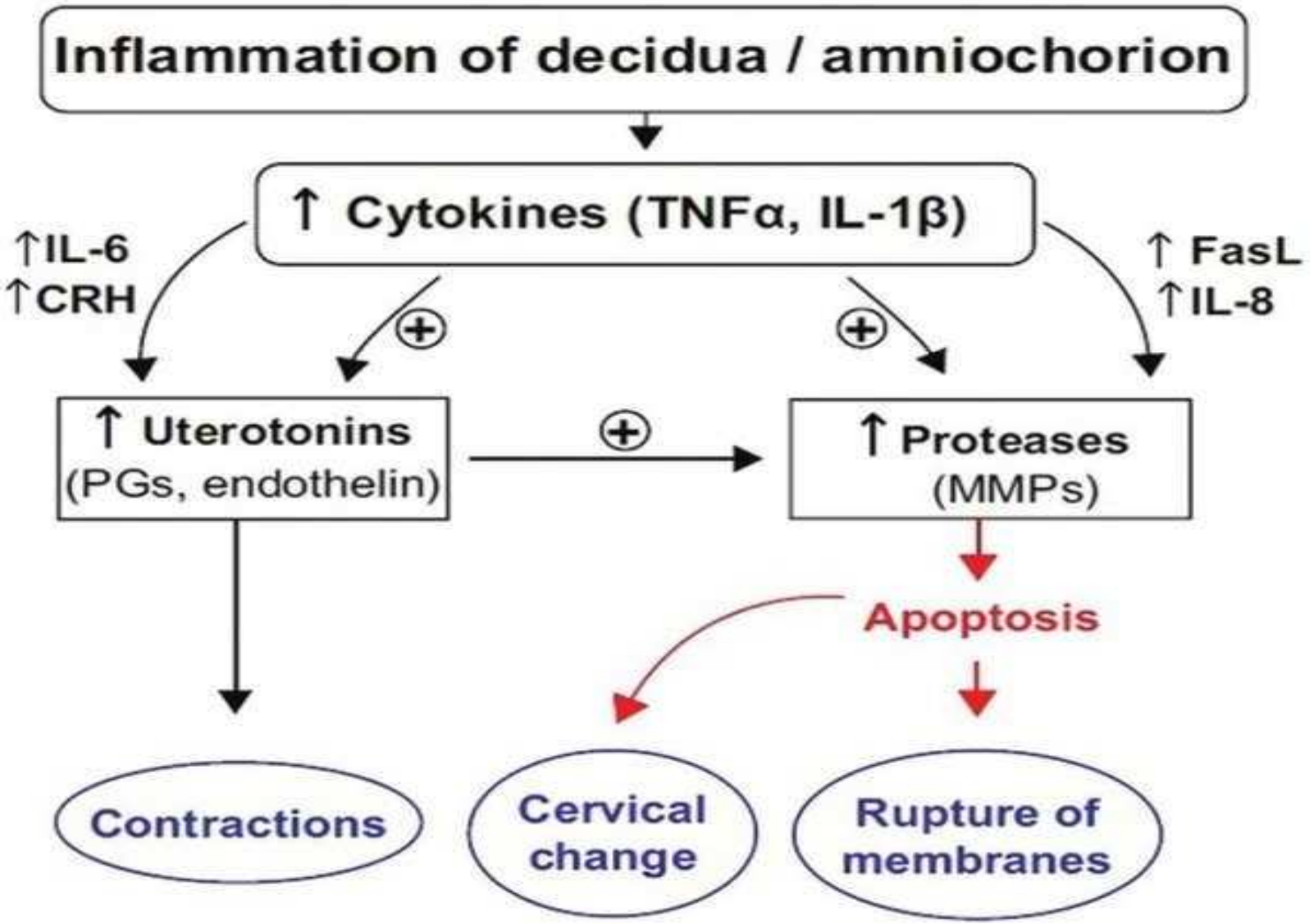
Synchronous and Asynchronous Activation of Labor



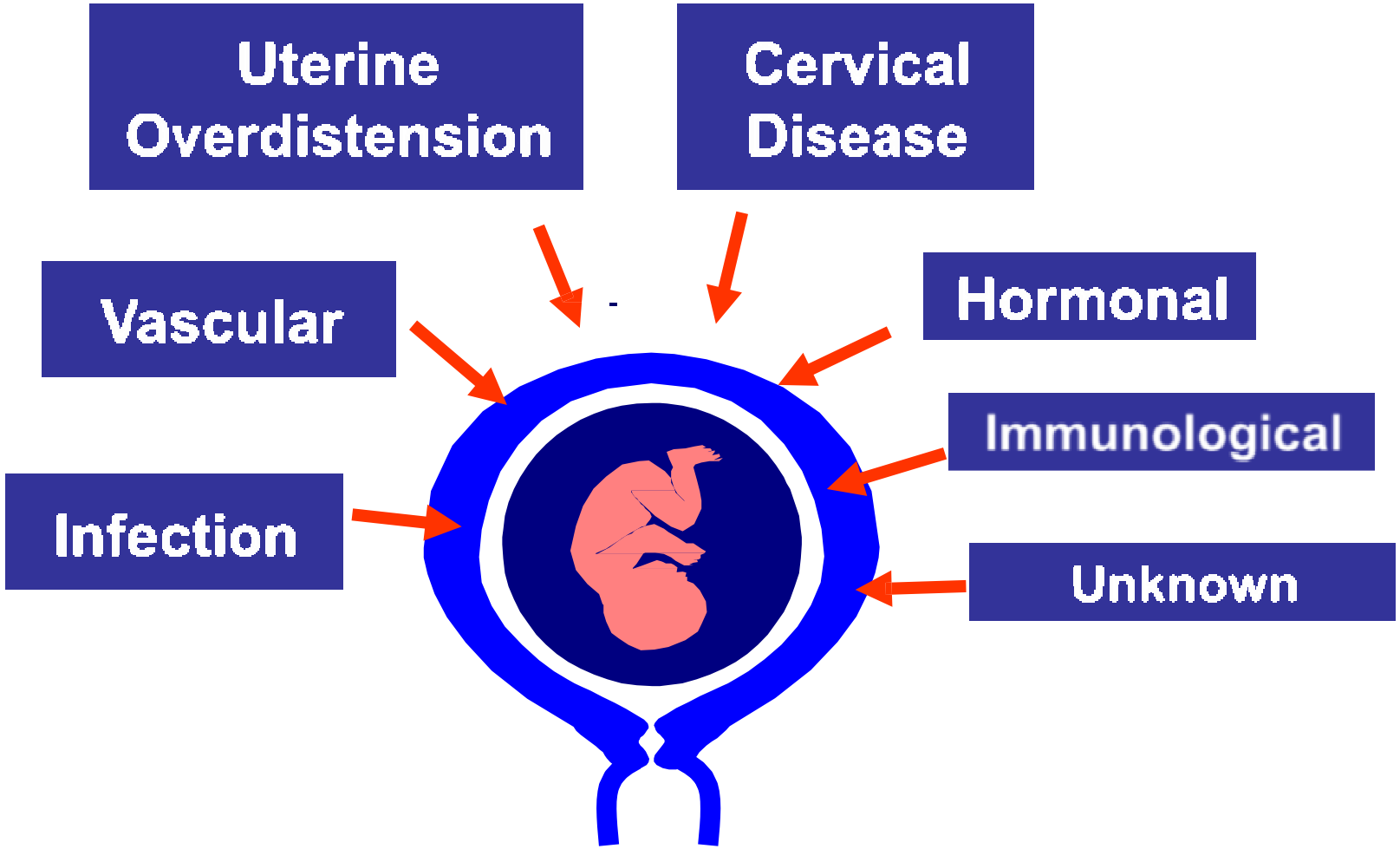

Normal Term Labor
Preterm Labor
Physiologic Activation
Pathologic Activation
Common Terminal Pathway

What causes pathologic activation of the pathway ?


Maternal stress
Fetal stress
(uteroplacental insufficiency)
Activation of maternal HPA axis
Activation of fetal HPA axis
ACTH
Cortisol
Adrenal
↑cox-2 in amnion
↓PGDH in chorion
Decidua
Placenta
Membranes
DHEAS
Placenta
Membranes
CRH
Estrogen
Prostaglandins
↑ Myometrial OTR, PGs, MLCK, calmodulin, gap junctions
Contractions
Cervical change
Rupture of membranes


Inflammation of decidua / amniochorion
↑ Cytokines (TNFα, IL-1β)
↑IL-6
↑CRH
↑ FasL
↑IL-8
⊕
⊕
⊕
↑ Uterotonins
(PGs, endothelin)
↑ Proteases
(MMPs)
Apoptosis
Contractions
Cervical change
Rupture of membranes

The Preterm Parturition Syndrome



Intrauterine infection

- Frequent: 25 % (at presentation)
- Sub-clinical
- Fetal disease
- FIRS
- Host defense

Subclinical infection

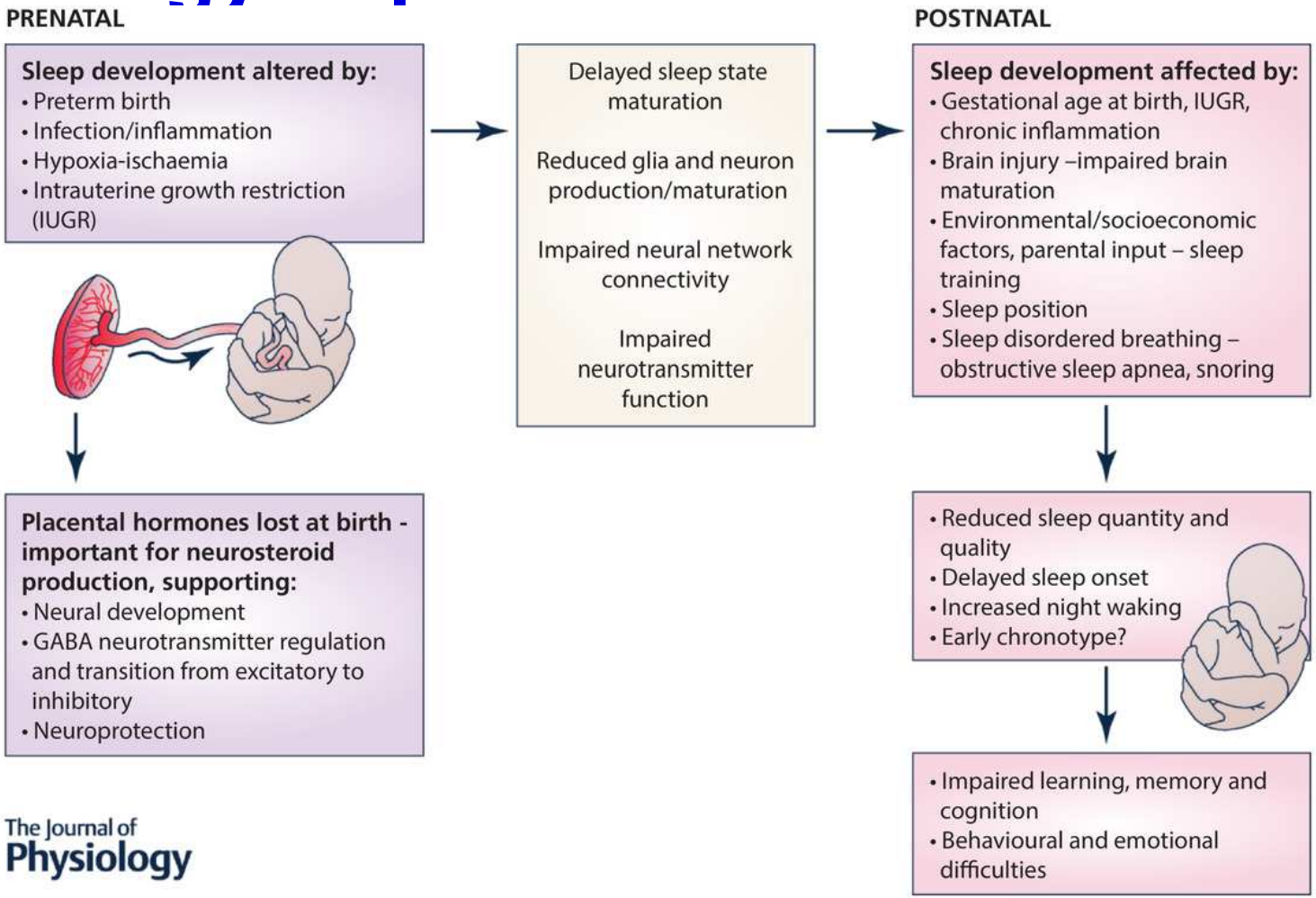
Clinical Chorioamnionitis

- **12% of preterm labor**
- **20% of preterm PROM**

Fetal inflammatory response syndrome

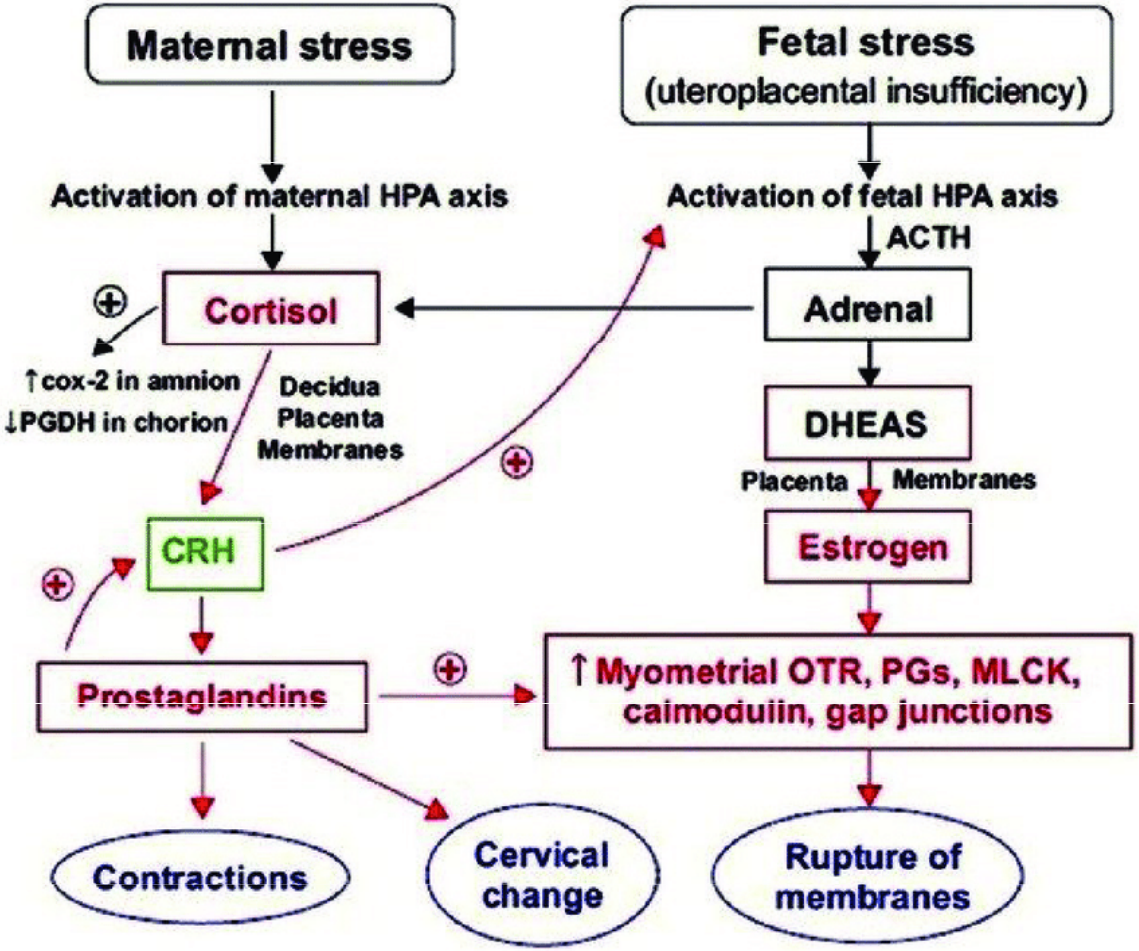
- Hematologic Abnormalities
- Endocrine System
- Cardiac Dysfunction
- Pulmonary Injury
- Renal Dysfunction
- Brain Injury (PVL)

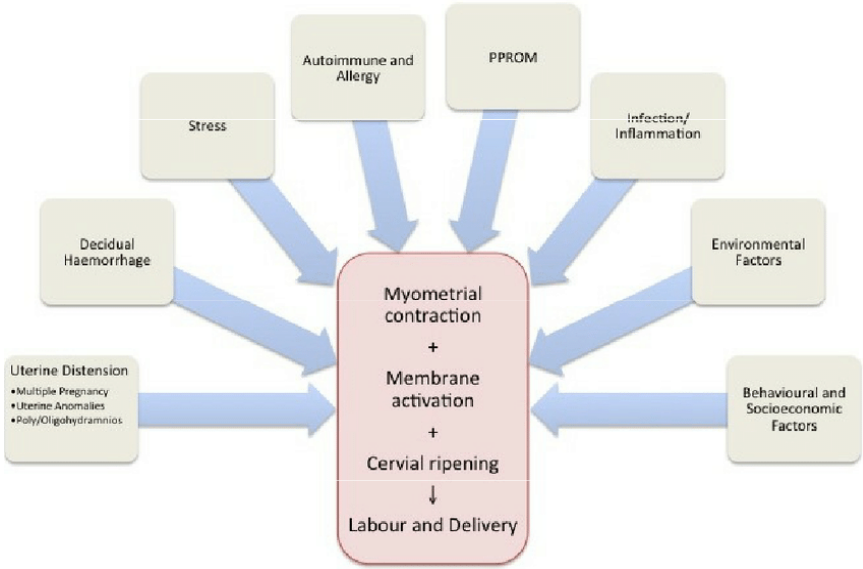
Pathophysiology of premature birth II



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



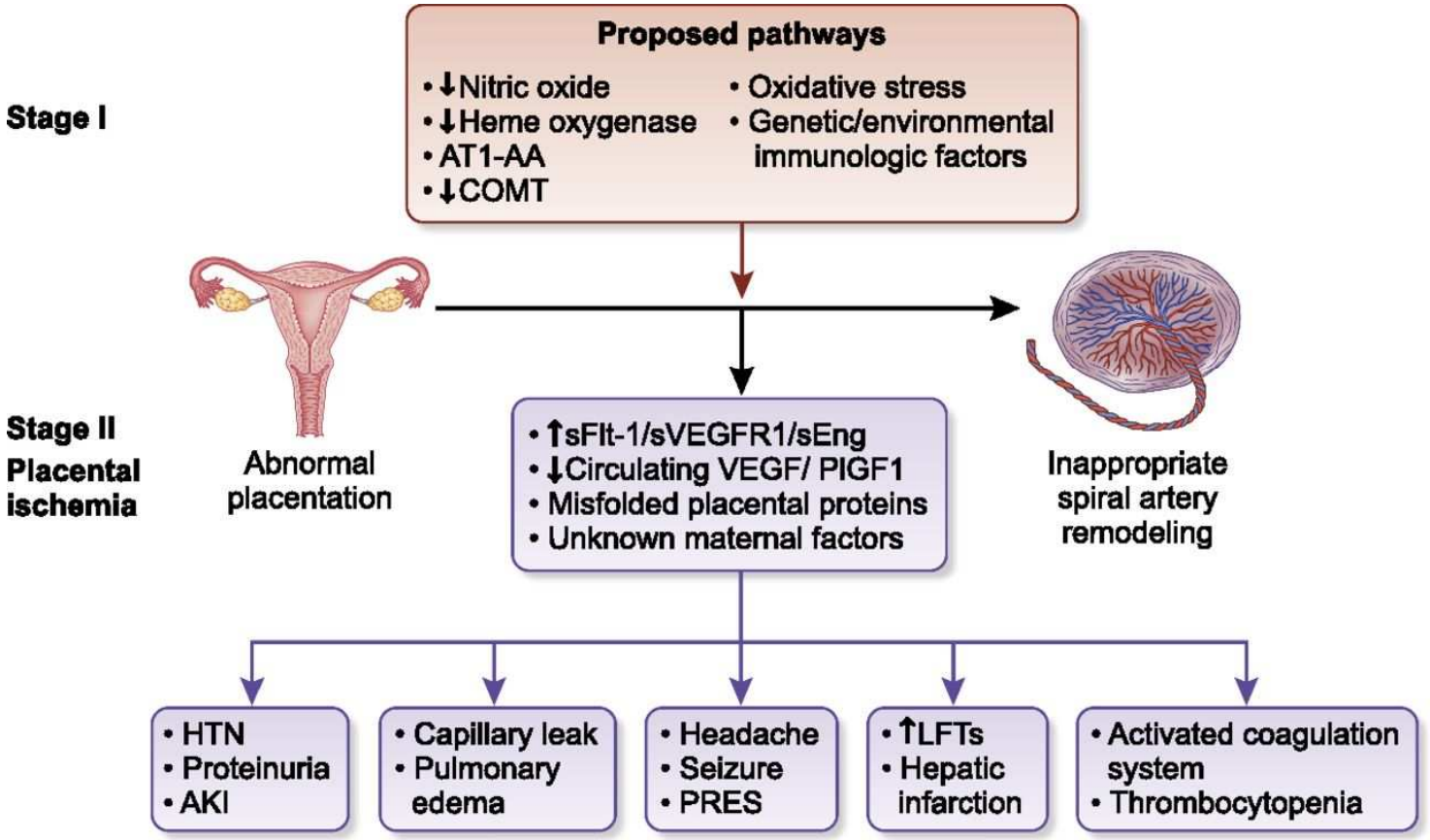


Low Birth Weight and Adverse Perinatal Outcomes
•November 2019 DOI: 10.5772/intechopen.89049

Hypertensive disorders of pregnancy

- They are divided into four categories :
- 1-gestational hypertension
- 2-chronic hypertension
- 3-chronic hypertension with superimposed preeclampsia
- 4- preeclampsia-eclampsia

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

Epidemiology

- Hypertensive disorders of pregnancy complicate nearly 10 % of pregnancy and their incidence is increasing
- Preeclampsia causes 50000 – 60000 deaths per year worldwide
- In addition to causing significant maternal and fetal morbidity in hundreds of thousands of others
- Some of these outcomes can be prevented or improved upon through implementation of the updated recommendations in clinical practice

Preeclampsia

- Preeclampsia is a multi-system progressive disorder characterized by the new onset of hypertension and proteinuria, or hypertension and end-organ dysfunction with or without proteinuria, in the last half of pregnancy or postpartum
- The disorder is caused by placental and maternal vascular dysfunction and always resolves after delivery
- Although most affected pregnancies deliver at term or near term with good maternal and fetal outcomes, these pregnancies are at increased risk for maternal and/or fetal mortality or serious morbidity.
- In addition, women with preeclampsia are at increased risk for future cardiovascular disease.

Diagnostic Criteria for Preeclampsia (ACOG, 2013)

Blood Pressure	• ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic one 2 occasions at least 4 hrs apart not more than 1 wk apart after 20 wks GA in women with a previously normal BP • ≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic, confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
And	
Proteinuria	• ≥ 300mg per 24-hr urine collection (or this amount extrapolated from a timed collection) **Or** • Protein/creatinine ratio ≥ 0.3 mg/dL • Dipstick reading of ≥ 1+ (used only if other quantitative methods not available) **on at least two occasions at least 4 hours apart but no more than 1 week apart**
Or in the absence of proteinuria, new-onset hypertension with the new onset of one or more of the following:	
Thrombocytopenia	• Platelet count < 100,000/μL
Renal insufficiency	• Serum creatinine > 1.1 mg/dL or a doubling of the serum creatinine in the absence of other renal disease
Impaired liver function	• Elevated blood levels of liver transaminases to twice normal concentrations
Pulmonary edema	
Cerebral or visual symptoms	

No longer in use are the criteria of

- Increase in blood pressure above baseline measurements of 30 mmHg systolic, 15 mmHg diastolic, or 20 mmHg mean arterial pressure.
- Edema is a common finding in the gravid patient, occurring in approximately 50% of women. Lower extremity edema is the most typical form of edema.

Severity Of Preeclampsia

ABNORMALITIES	NONSEVERE *(mild)*	SEVERE
Blood pressure	≥140/90mmHg but <160/110mmHg	≥160/110mmHg
Proteinuria	≤2+	≥3+
Oliguria	Absent	<400ml/day
Headache	Absent	Present
Visual disturbances	Absent	Present
Platelet count	Normal	Thrombocytopenia (100,000/mm^3)
HELLP syndrome	Absent	May be present ALT,AST >70 IU/L LDH>600 IU/L Bilirubin >1.2g/L
Serum transaminases(AST,ALT)	Normal (<40 IU/L)	Elevated
Epigastric pain	Absent	Present
Fetal growth restriction	Absent	Obvious
Pulmonary oedema	Absent	present

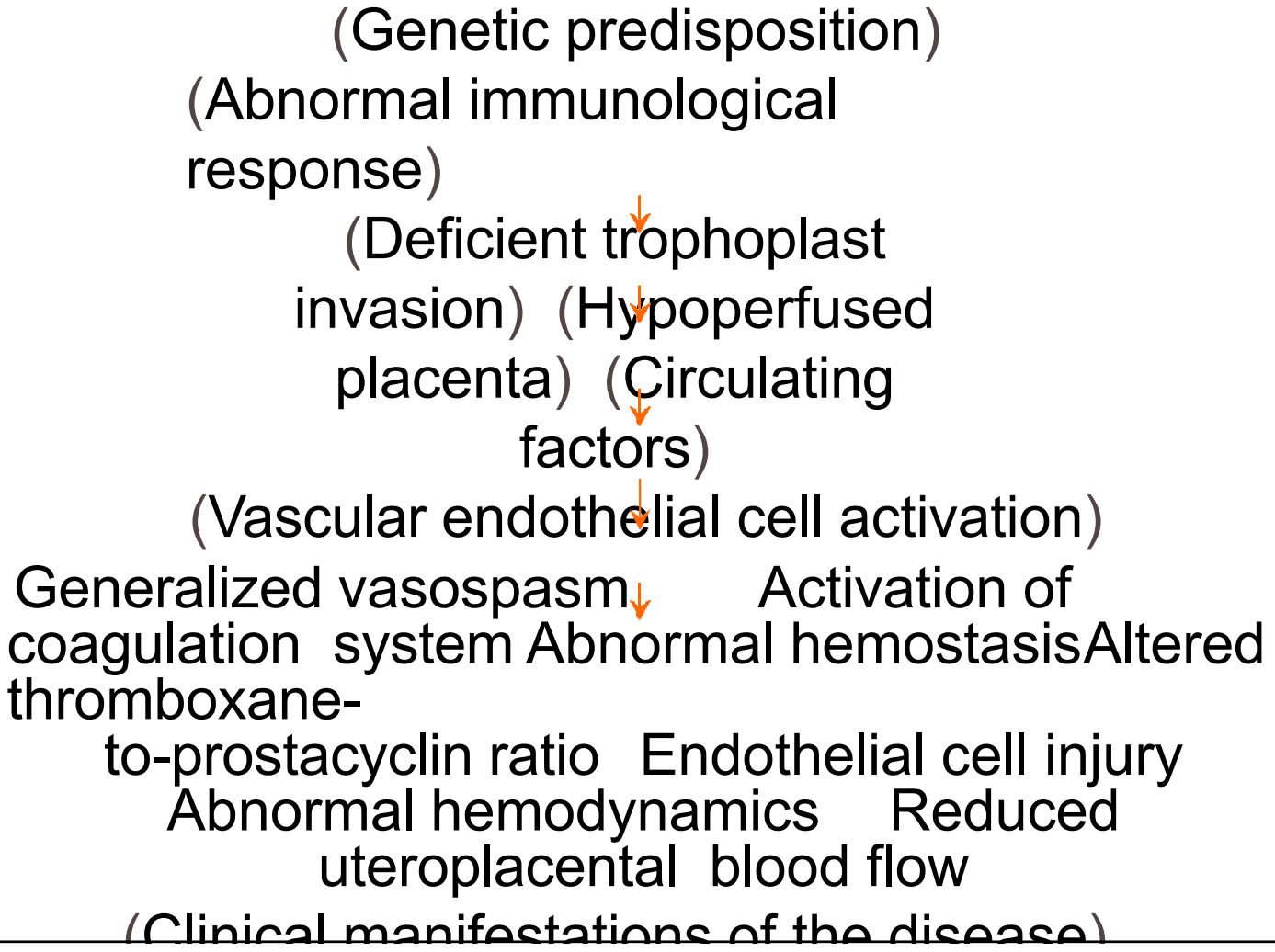
HELLP Syndrome

- A particularly severe and serious form of preeclampsia is HELLP syndrome characterized by hemolysis, elevated liver enzymes, and low platelets.
- Prompt recognition is vital to improving outcomes.
- Due to the different number of assays used to measure liver enzymes, clinicians should be familiar with the upper limit values used in their own laboratory.
- Criteria for HELLP syndrome are:
- LDH > 600 IU/L (more than 2 times the upper limit of normal values) or
- bilirubin > 1.2 mg/dL,
- AST > 70 IU/L (more than 2 times the upper limit of normal values), and
- platelets < 100,000/μL.(Sibai, 2004)
- Proteinuria may or may not be present with HELLP syndrome

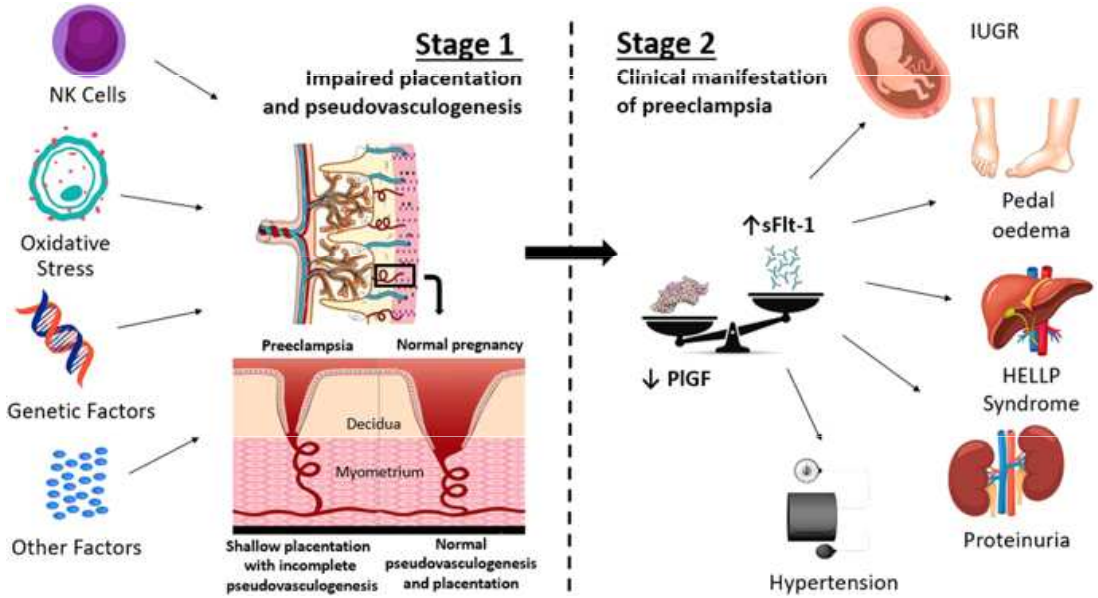
Pathophysiology

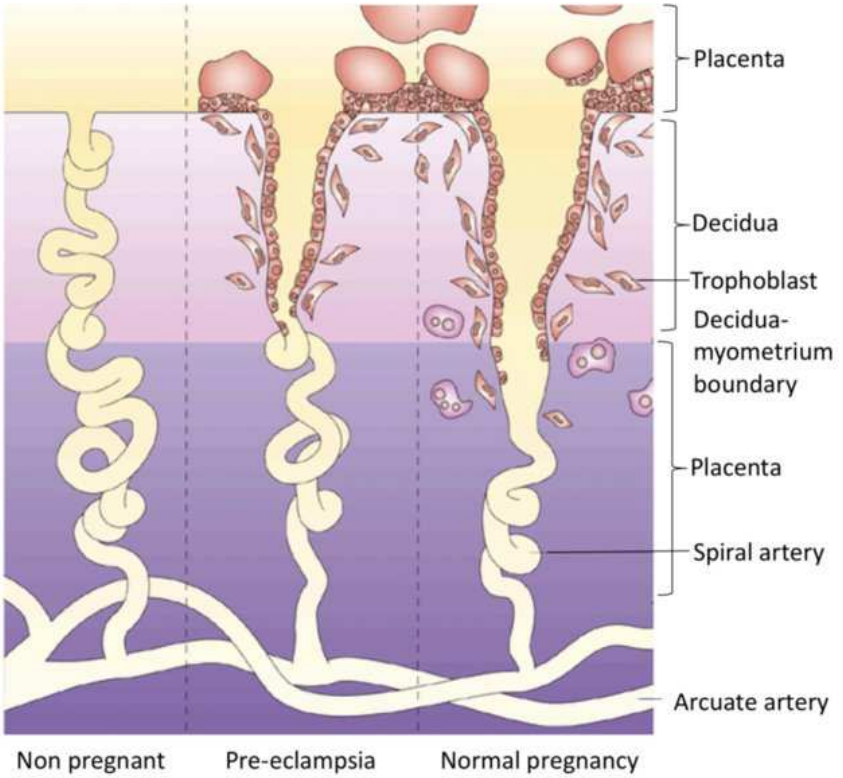
- The precise mechanism for the development of preeclampsia is unknown
- The pathophysiology of preeclampsia likely involves both maternal and fetal/placental factors.
- A major component in the development of preeclampsia is the excessive placental production of antagonists to both vascular epithelial growth factors(VEGF) and transforming growth factorB (TGF-B)
- These antagonists to VEGF and TGF-B disrupt endothelial and renal glomerular function resulting in edema , hypertension and proteinuria
- In addition there appears to be a heritable component and oxidative stress and abnormal placental implantation can further increase the risk of developing the disease

Aetiology of preeclampsia



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.

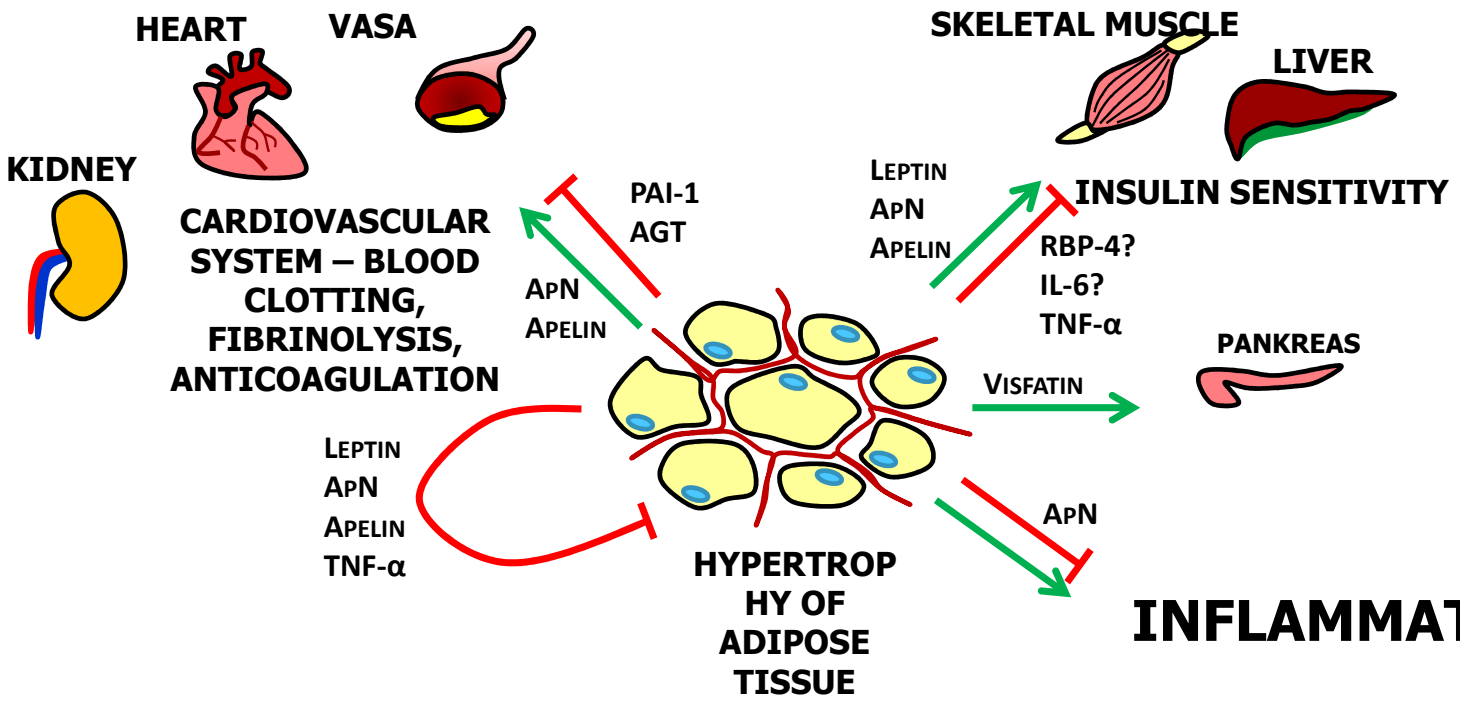
Lina Bergman, Cerebral biomarkers in women with preeclampsia
October 2017 DOI: 10.13140/RG.2.2.30083.81445

Context?

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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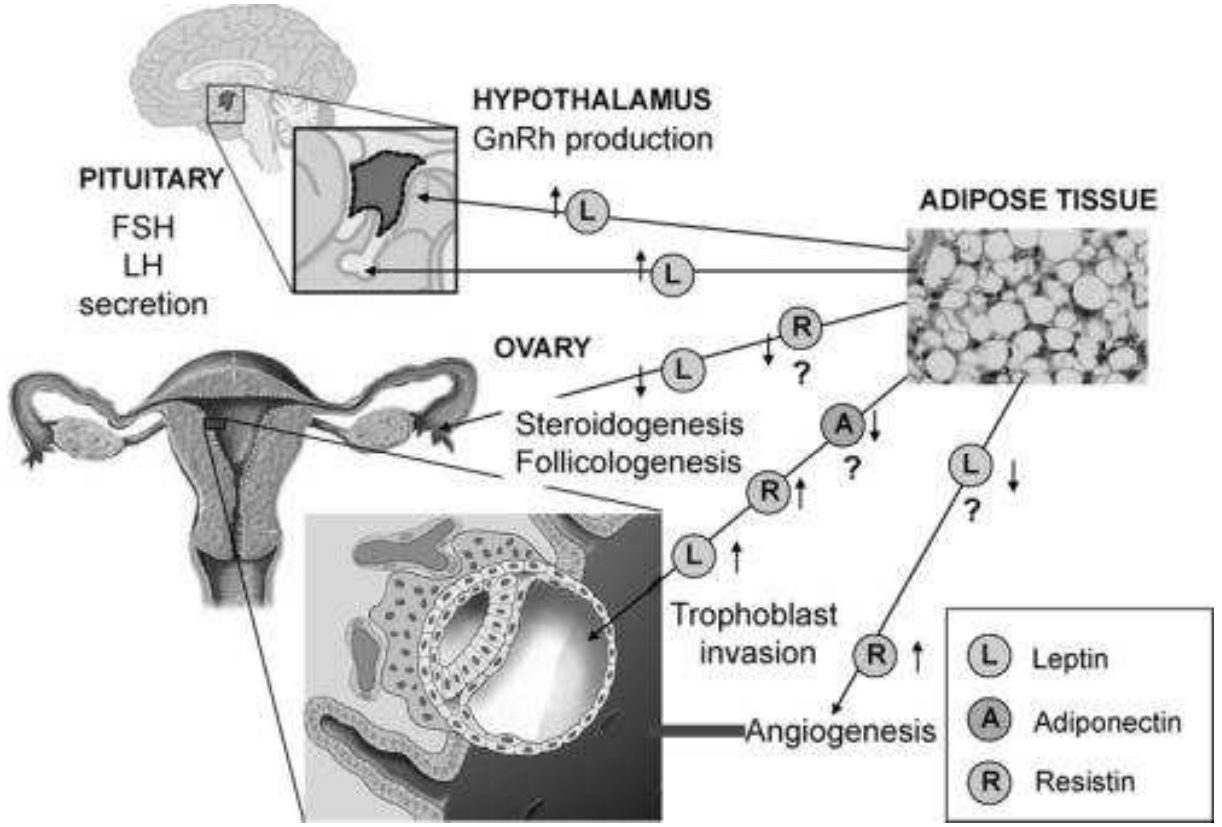
Adipokines in development of trophoblast



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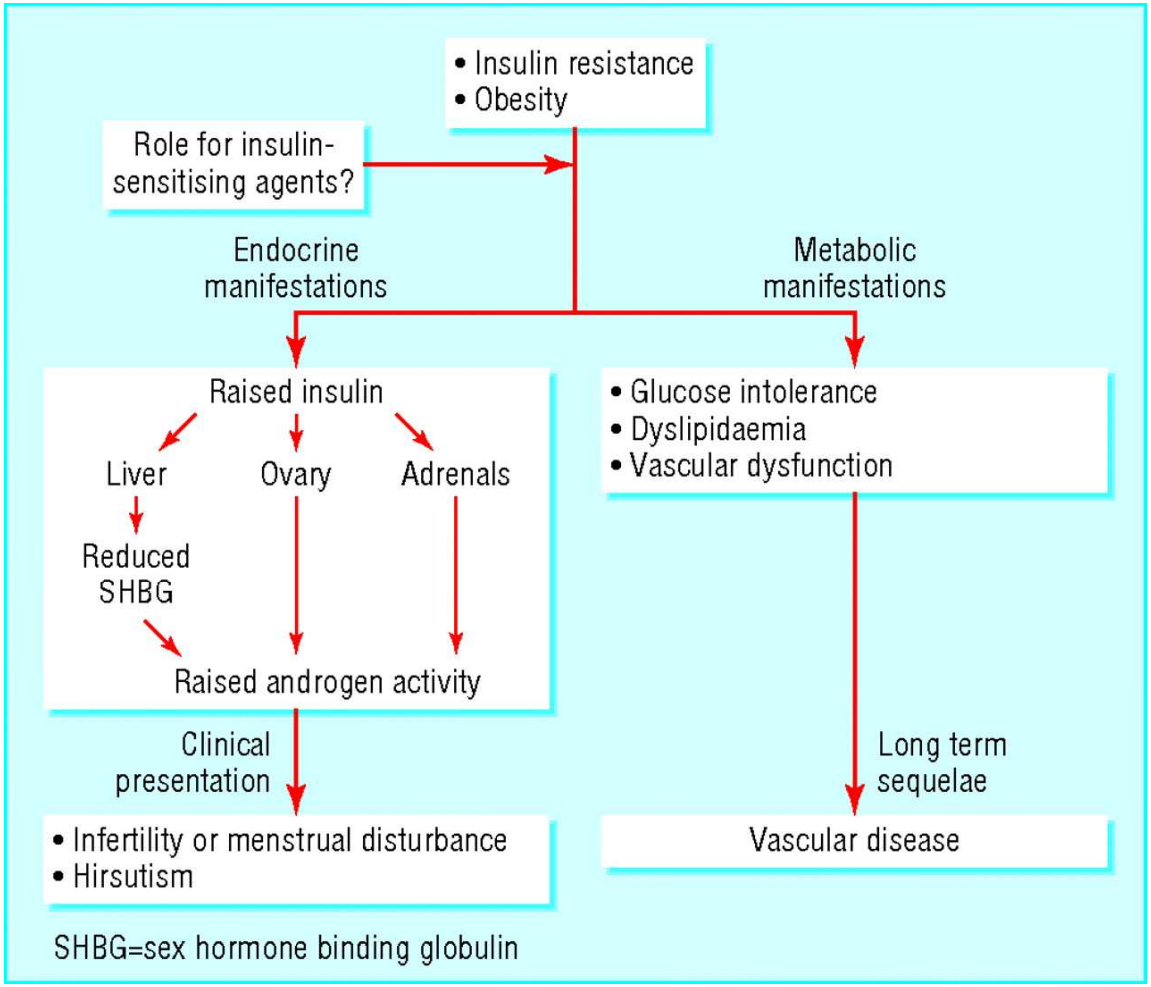
Adipokines, obesity and female fertility



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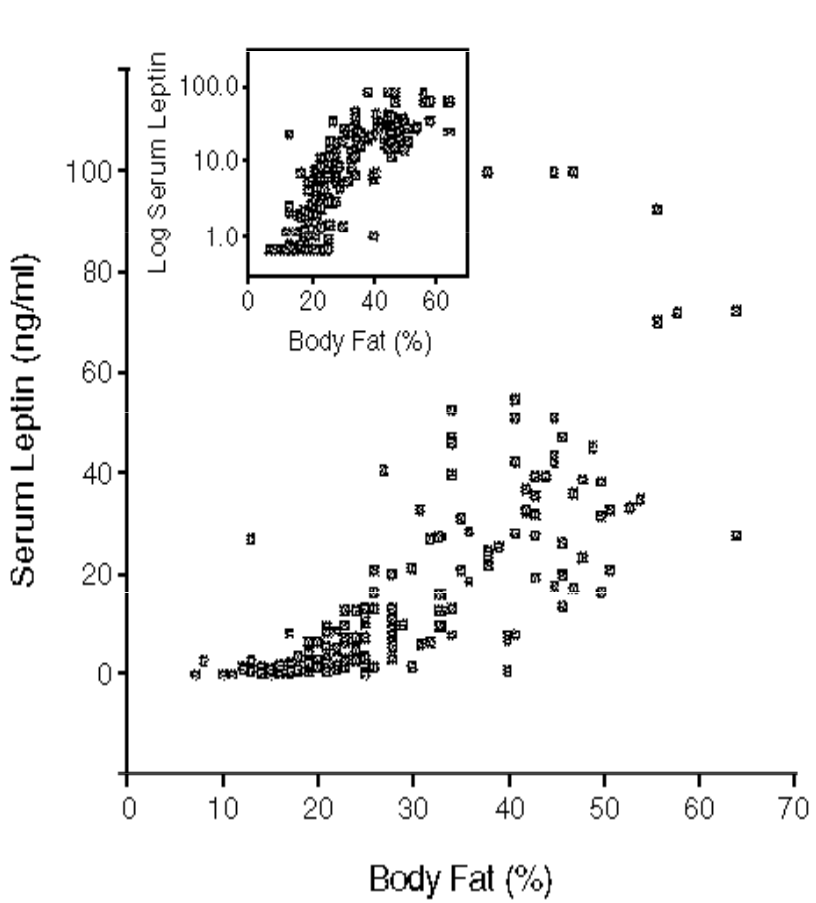
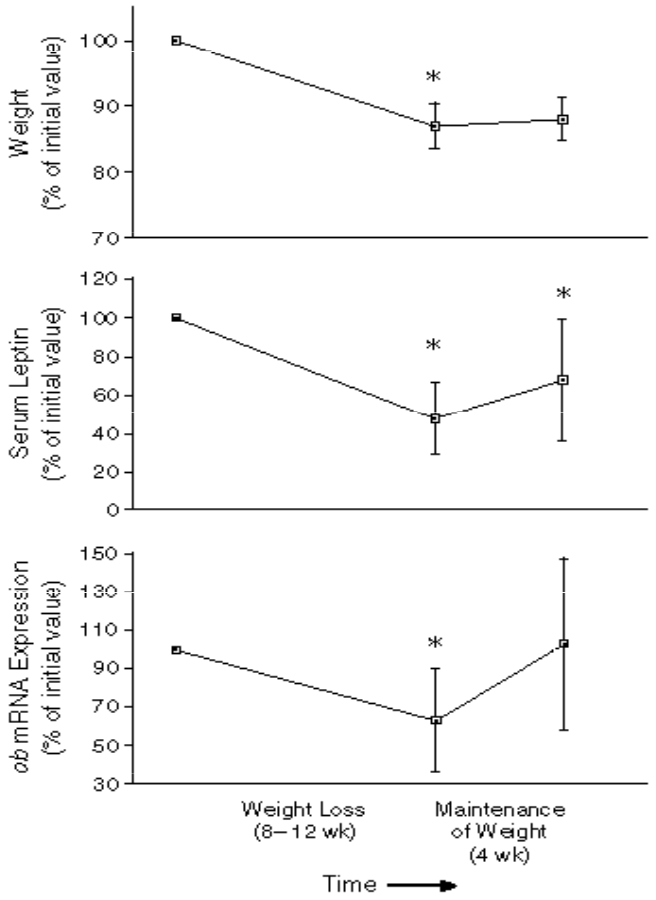
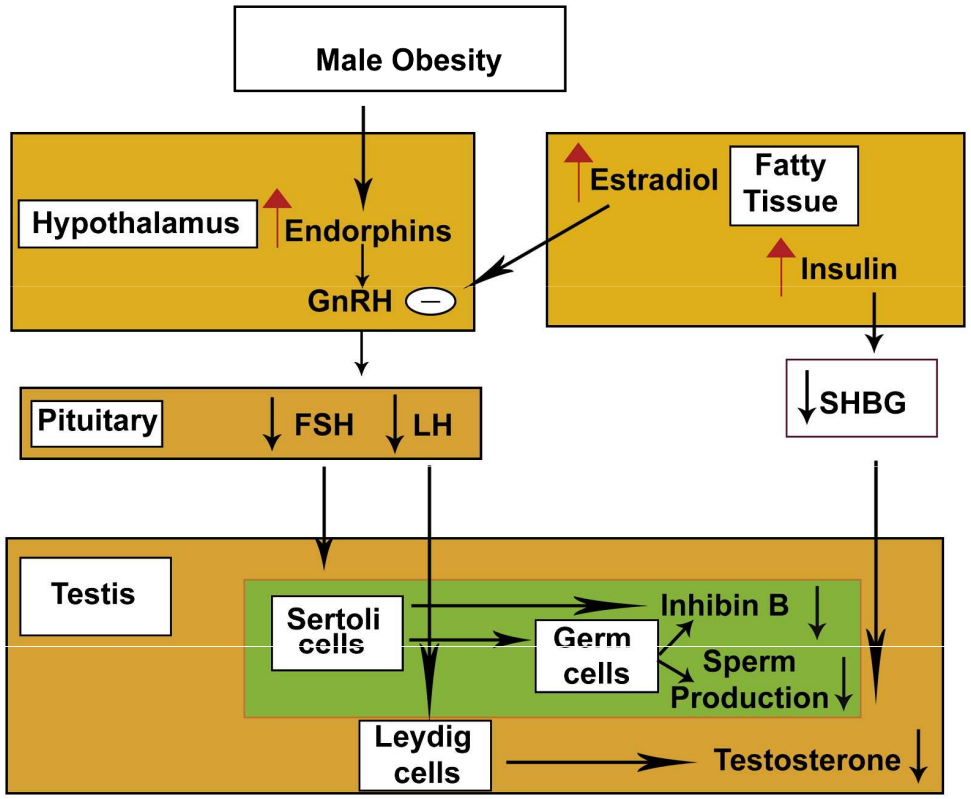
Considine RV. N Engl J Med 1996





Adipokines in male fertility



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What else? Sugar?

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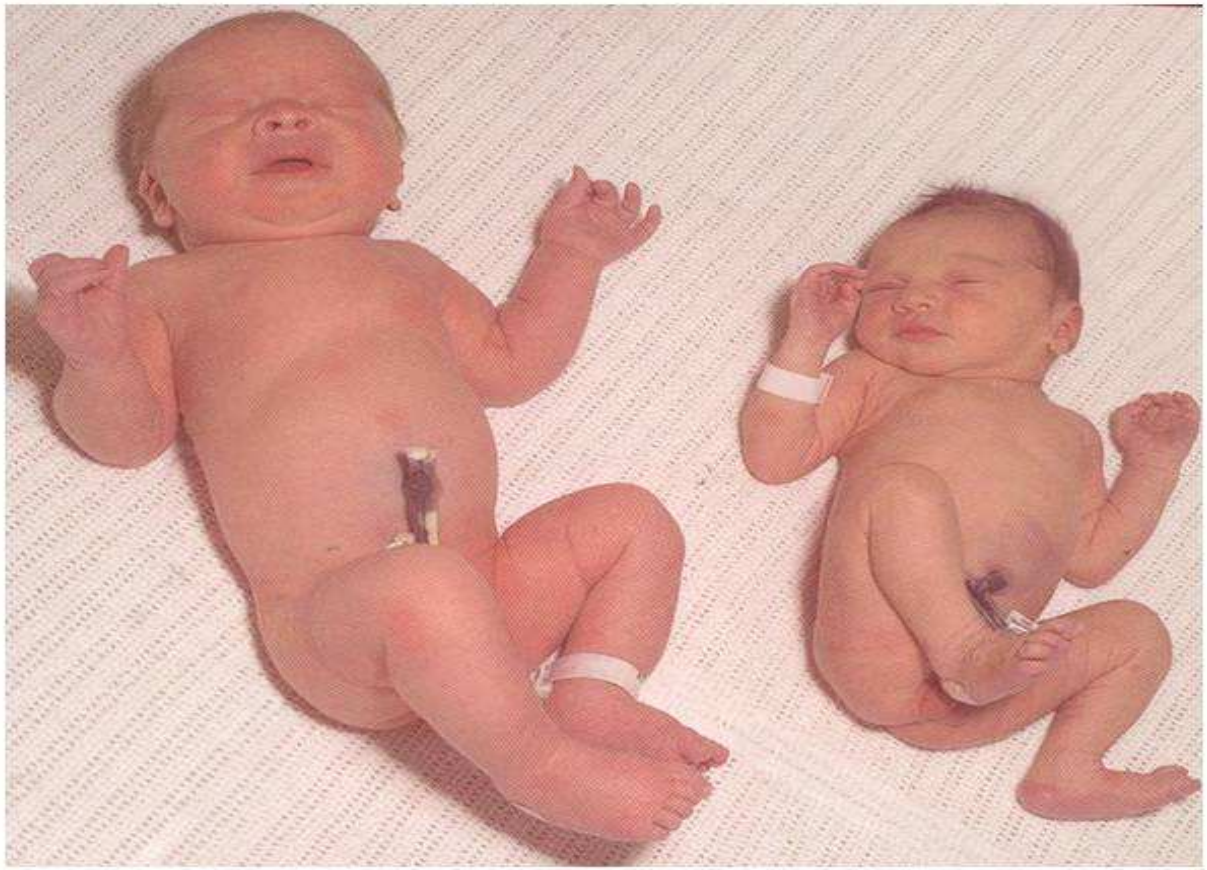
Fetal programming?



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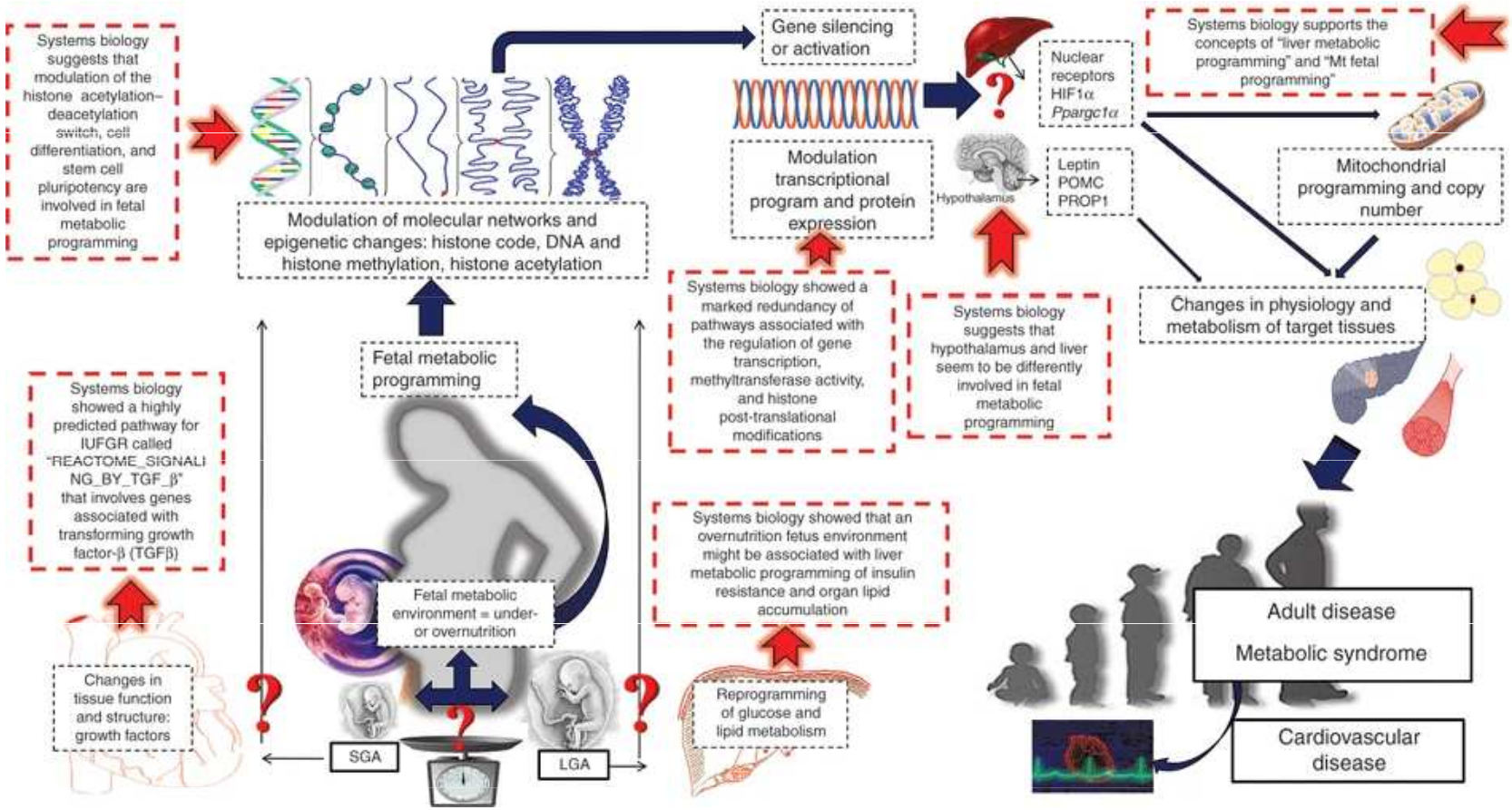
Fetal programming



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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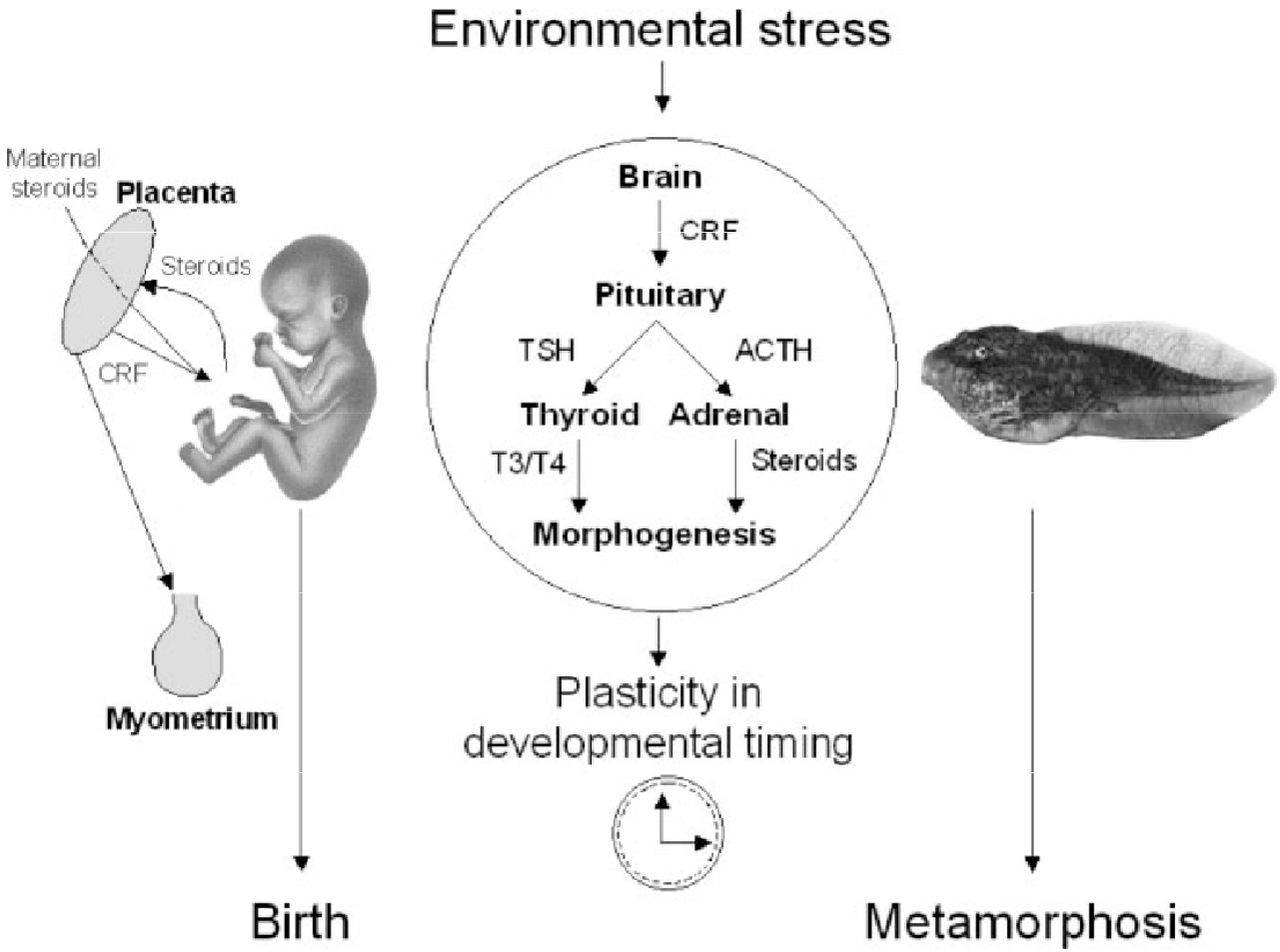
Developmental plasticity



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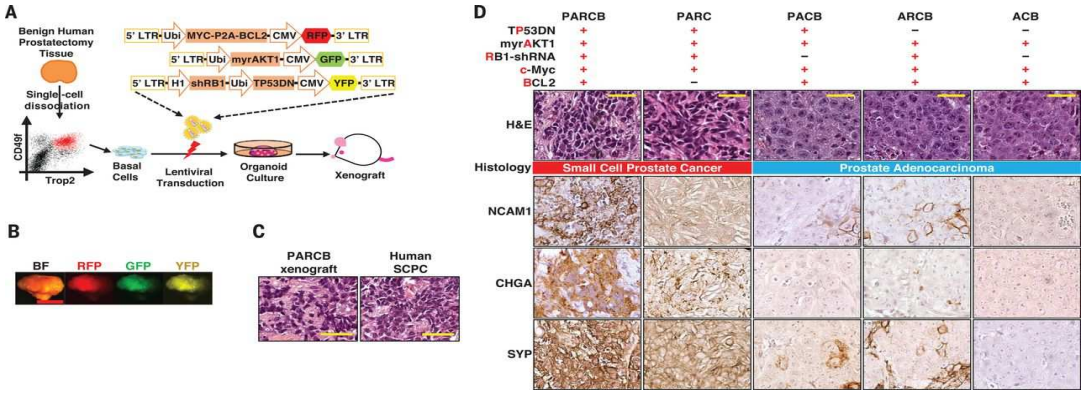
Am J Hum Biol. 2005 Jan-Feb;17(1):44-54.

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],
4.Liang Wang[1],
5.Nikolas G. Balanis[3],
6.Kim Nguyen[4],
7.Bryan A. Smith[1],
8.Chen Cheng[5],
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14.Owen N. Witte[1,3,7,8,9,*]
See all authors and affiliations

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

nature CLINICAL PRACTICE NEPHROLOGY

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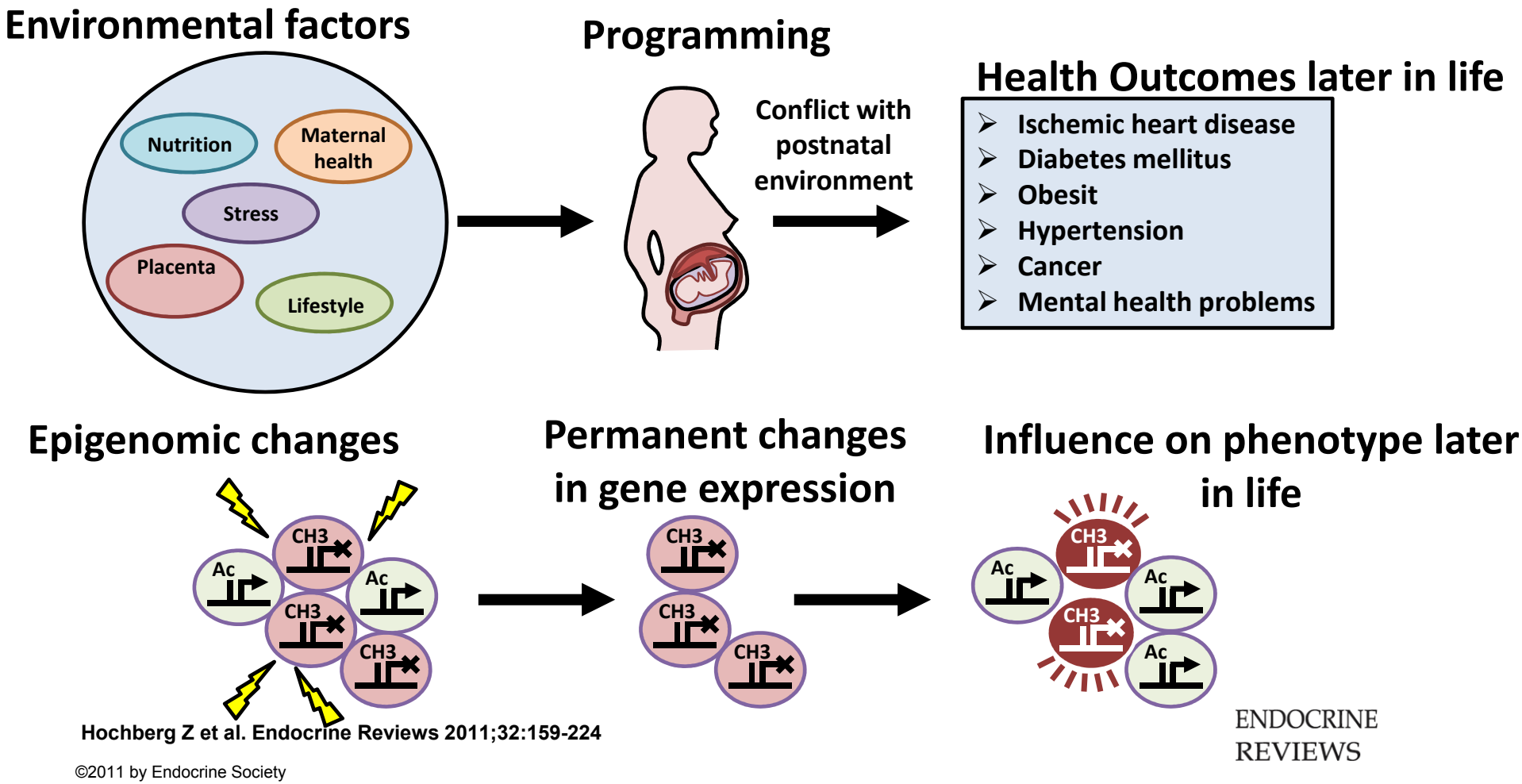

Hochberg Z et al. Endocrine Reviews 2011;32:159-224

ENDOCRINE REVIEWS

Thank you for attention,
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