PATHOPHYSIOLOGY OF FETOPLACENTAL UNIT

VLA

April 3, 2018

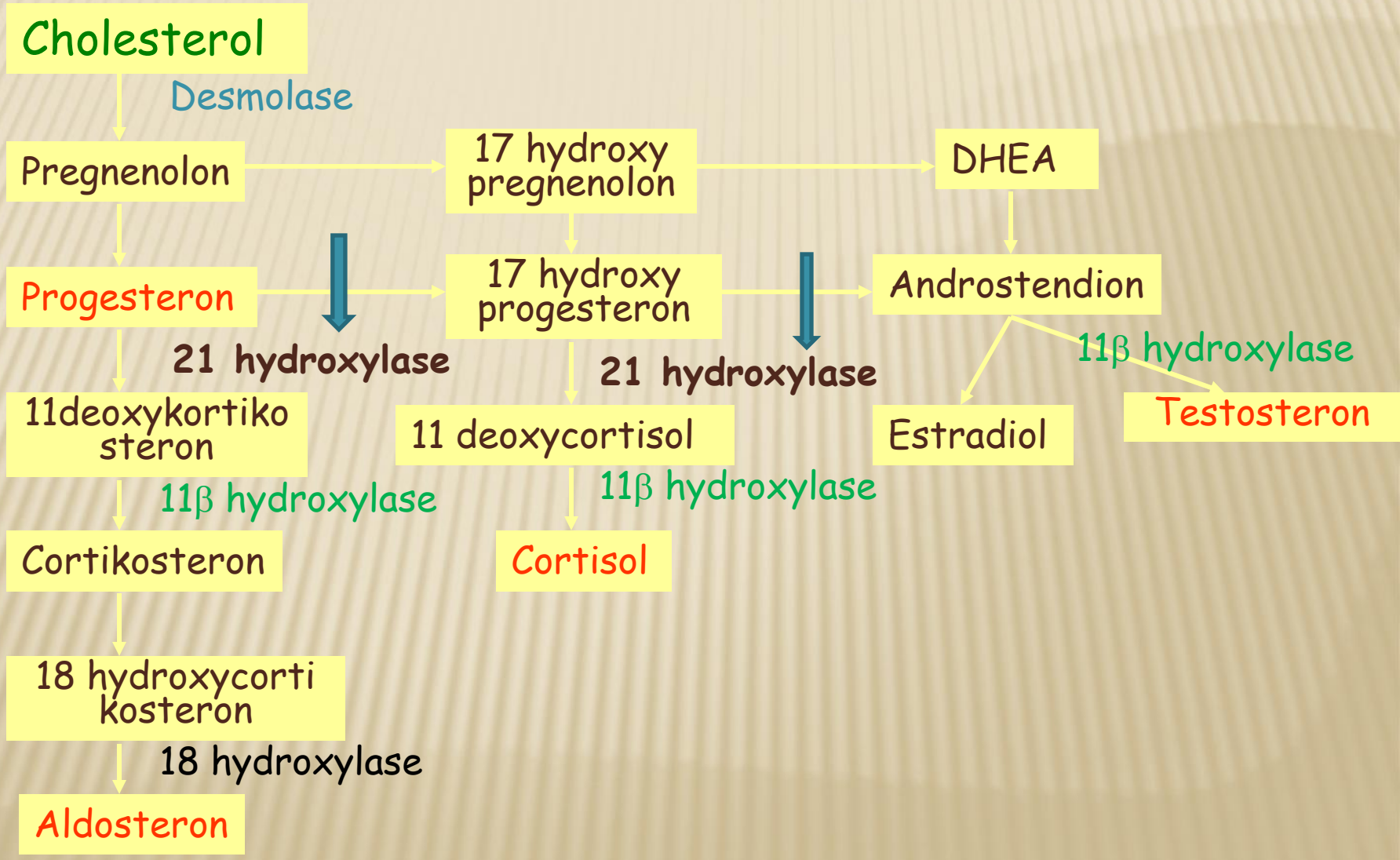
PREGNANCY

- Pregnancy is marked by **alterations** in a number of endocrine systems, including activation of **the renin–angiotensin–aldosterone system** and **the hypothalamic–pituitary–adrenal axis**.
- Although rare, maternal adrenal disorders are associated with considerable maternal mortality and morbidity if not promptly recognized and treated.

FETOPLACENTAL UNIT

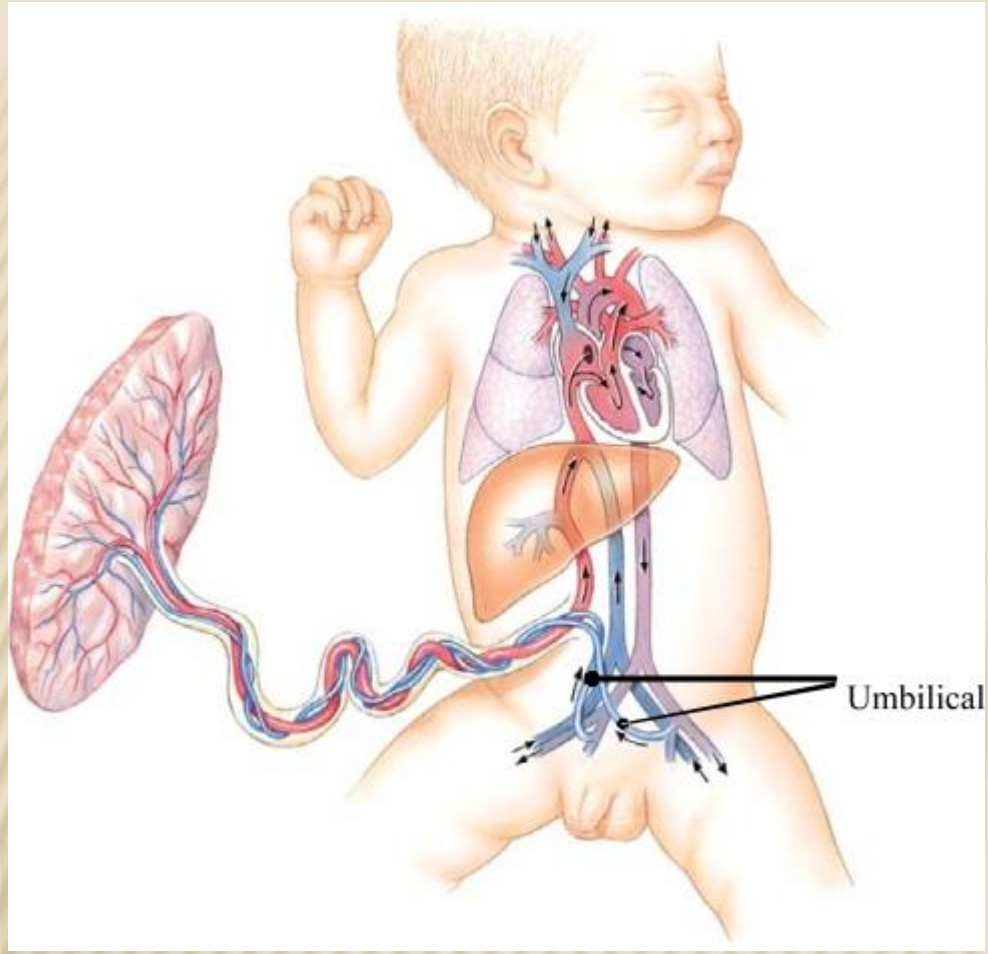
- The **placenta, the fetal adrenal glands and the fetal liver** constitute an interactive endocrine entity, known as the **fetoplacental unit.**
- In the fetoplacental unit, the fetal adrenal glands are the primary source of dehydroepiandrosterone sulphate (DHEAS), which is further metabolized by the fetal liver and placenta to produce a variety of estrogens.

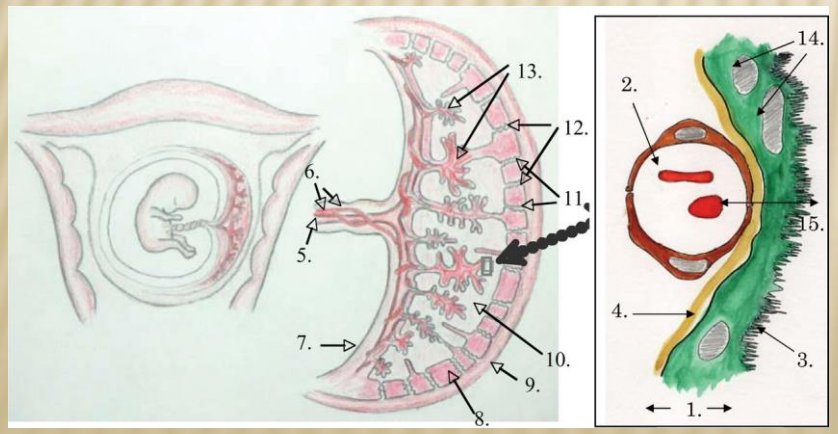
Steroidogenesis in adrenal glands



STEROID HORMONS

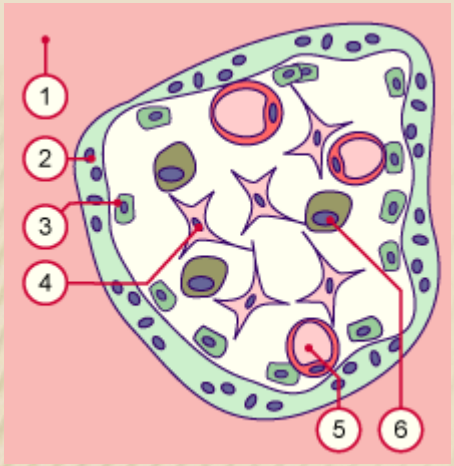
Suprarenal gland	Aldosteron Cortisol Reproductive hormons
Testes	Testosteron
Ovaries	Progesteron Estrogens
Placenta	Estrogens Progesteron





1, Syncytiotrophoblast; 2, fetal capillary with erythrocytes; 3, MVM; 4, BM; 5, umbilical vein; 6, umbilical arteries; 7, chorion plate; 8, decidua; 9, myometrium; 10, intervillous space with maternal blood; 11, veins; 12, spiral arteries; 13, villus tree; 14, syncytiotrophoblast cell nuclei; 15, diffusion distance between maternal and fetal blood.

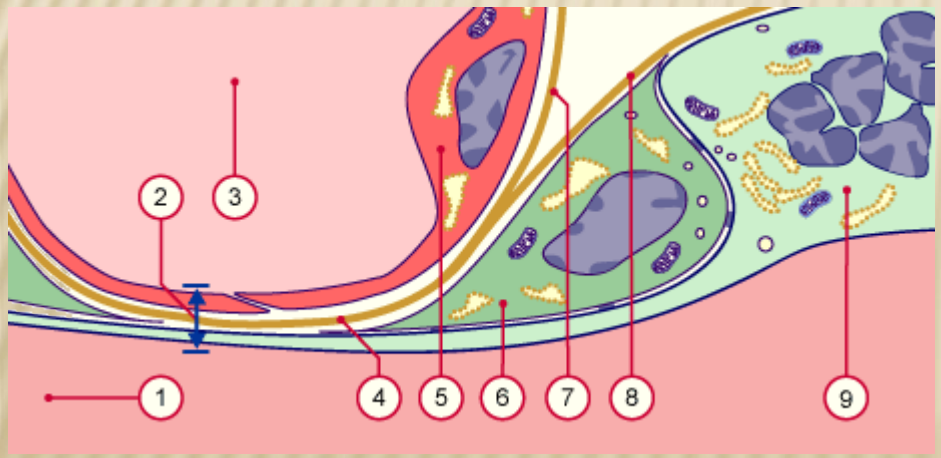
Placental Barrier



1 Intervillous space
2 Syncytiotrophoblast
3 Cytotrophoblast
4 Villus mesenchyma
5 Fetal capillaries
6 Hofbauer macrophages

First trimester: the villus has an intact syncytio- and cytotrophoblast layer. In the villus interior there are mesenchymal cells with macrophages and fetal capillaries.

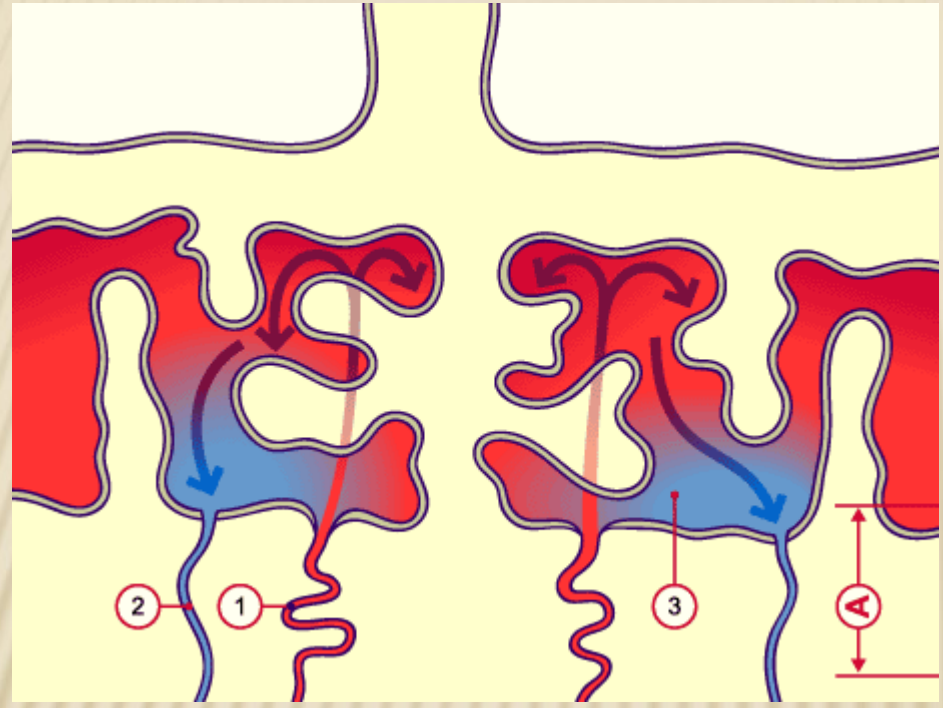
In **the middle third** of the pregnancy the capillaries migrate to the villus surface. The cytotrophoblast layer disappears slowly and the syncytiotropho-blast layer becomes thinner.



1 Intervillous space (with maternal blood)
2 Placental barrier of a terminal villus
3 Fetal capillaries
4 Merged basal membranes of the fetal capillary and of the syncythiothrophoblast
5 Endothelial cells
6 Rare cytotrophoblast cells
7 Basal membrane of the capillaries
8 Basal membrane of the trophoblast portion
9 Syncytiotrophoblast with proliferation knots (nuclei rich region)

During the 6th month the nuclei of the syncytiotrophoblast group together in the so-called proliferation knots. The other zones of the syncythiothrophoblast lack nuclei and are adjacent to the capillaries (exchange zones).

Maternal circulation system



1 Spiral arteries
2 Uterine veins
3 Intervillous spaces
A Basal plate

Maternal blood arrives at the intervillous space via arteries that open directly into the intervillous space. At the placental level, it thus finds itself temporarily outside the vessel network.

STRESS SYSTEM AND THE FEMALE REPRODUCTIVE SYSTEM

- The actions of the stress system and the female reproductive system are bidirectionally interrelated.
- ACTH inhibits the secretion of gonadotropin hormone-releasing hormone (GnRH) from the arcuate nuclei of the hypothalamus.
- Glucocorticoids inhibit both GnRH secretion and render resistance to sex hormone tissues that are normally sensitive to them.
- Half estrogen-responsive elements have been shown on the promoter area of the human CRH gene, while estrogens have been shown to directly regulate the expression of the human CRH gene.
- A reciprocal relationship exists between the HPA axis and the immune/inflammatory reaction. A dysregulated HPA response to stressors in women might contribute to autoimmune phenomena, which are more frequent in them.
- The epithelial cells of human endometrium produce CRH throughout the menstrual cycle, while the stroma needs to undergo decidualization in order to produce CRH. CRH-R1 alpha is present on both epithelial and stromal cells of the human endometrium, and the human myometrium contains CRH-R1 receptors.

MATERNAL HPA AXIS IN PREGNANCY

- Pregnancy has been explored from the immunological point of view, since it can be considered as a semiallograft situation. In this context, locally produced embryonic and endometrial CRH plays a role in both the aseptic inflammatory process of implantation and the antirejection process that protects the fetus from the maternal immune system.
- It has been suggested that CRH of fetal and maternal origin regulates FasL production, thus affecting the invasion process through a local autoparacrine regulatory loop of cytotrophoblast cells and regulating their own apoptosis. More particularly, CRH decreases FasL expression in embryonic trophoblast and maternal decidua, and promotes apoptosis of activated T lymphocytes.

MATERNAL HPA AXIS IN PREGNANCY

- During pregnancy, circulating immunoreactive CRH in plasma increases exponentially up to a thousand times its nonpregnant level, from the eighth to tenth week of gestation onward. This increase is the result of CRH production by the placenta, decidua, and fetal membranes rather than of hypothalamic origin.
- Placental CRH secretion is promoted by cortisol and supressed by estrogens.
- The CRHbp (bound to protein) plasma concentrations in pregnant women remain similar to levels of nonpregnant women until the third trimester of pregnancy. At that time its values fall to roughly one-third the levels of earlier pregnancy or those of the nonpregnant state. Amniotic fluid CRHbp levels also fall approaching term.
- The unbound fraction of CRH stimulates maternal ACTH secretion.
- CRH can induce vasodilation in the uterine arteries, and may regulate the placental blood flow. Placental CRH does not exhibit a circadian rhythm.

MATERNAL HPA AXIS IN PREGNANCY

- Although during pregnancy the maternal pituitary gland enlarges by about one-third (due to lactotroph cell hyperplasia), its functions remain intact.
- The circadian rhythm of maternal ACTH plasma levels is maintained during pregnancy, probably due to AVP secreted by the parvicellular paraventricular nuclei. However, overall pituitary ACTH secretion and plasma ACTH levels rise (remaining, though, within normal limits) and follow in parallel the rise of plasma-free and total cortisol levels. **This rise of maternal ACTH levels is due to circulating unbound placental CRH.**
- ACTH concentration in amniotic fluid rises during pregnancy, peaking at the beginning of the third trimester, and then showing a decline of the plasma levels of this hormone.

MATERNAL HPA AXIS IN PREGNANCY

- Elevated estrogen levels in pregnancy lead to a doubling of corticosteroid-binding globulin (CBG) levels, resulting in low catabolism of cortisol by the liver and a doubling of cortisol's half-life in plasma. Moreover, during pregnancy maternal adrenal glands gradually become hypertrophic as cortisol production in the adrenal zona fasciculata is increased, because of the relatively increased maternal ACTH secretion. Consequently, a steady rise in total and free plasma cortisol is noted, peaking during the third trimester at about two and three times nonpregnant values, respectively. These peak cortisol levels are comparable to those observed in Cushing's disease, severe depression, anorexia nervosa, and in athletes doing strenuous exercise.
- Thus, pregnancy is a transient, but physiologic, period of relative hypercortisolism for the normal woman. The diurnal variation of plasma cortisol levels is maintained in pregnancy. During pregnancy, amniotic fluid cortisol levels follow the plasma levels of this hormone.

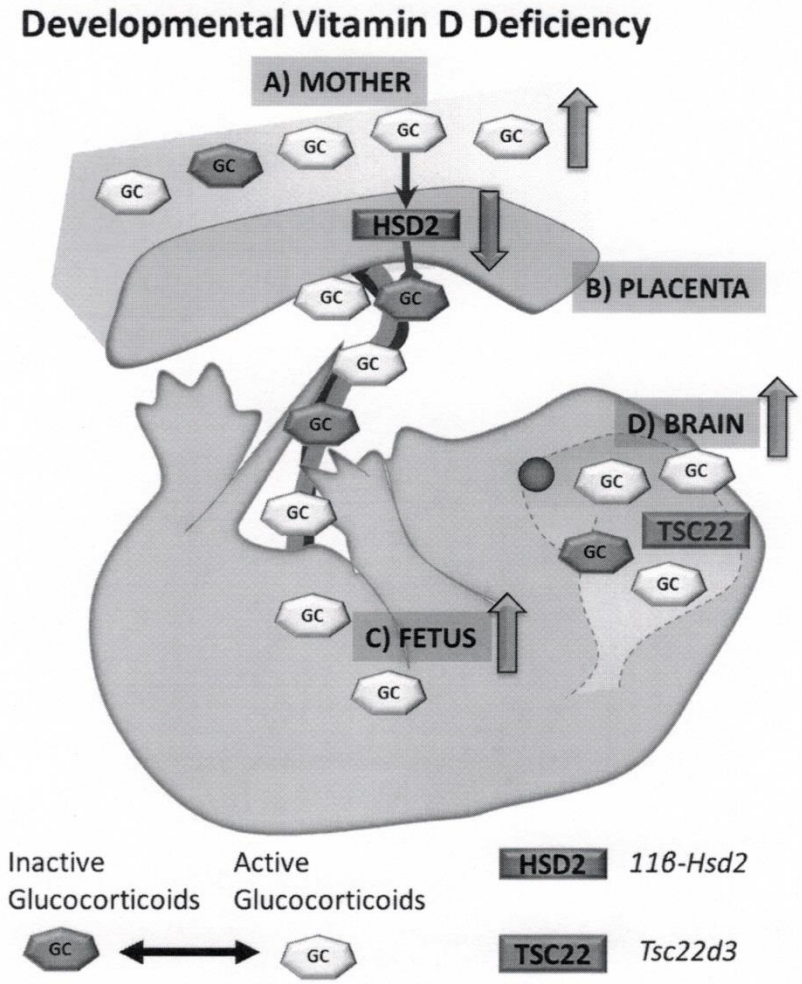


Figure 2. Proposed effects of developmental vitamin D deficiency on glucocorticoid metabolism and levels in the mother and fetus. A) In gestational vitamin D deficiency, maternal circulating active glucocorticoids (GCs) and GC release in response to stress is elevated, likely increasing placental GC exposure and transport. B) In the placenta, 11β-HSD2 (a key enzyme that inactivates GCs), is decreased by vitamin D deficiency, which decreases the conversion of active GCs to inactive forms. C) In the fetus, the combination of increased maternal GC levels and decreased GC inactivation due to vitamin D deficiency leads to increased fetal GC exposure. D) Ultimately, vitamin D deficient fetuses exhibit a likely increase in GC exposure in the brain, as indicated by increases in the GC-responsive gene Tsc22d3.

189x212mm (150 x 150 DPI)

Yates N, Crew RC, Wyrwoll C.
Vitamin D deficiency and impaired placental function: potential regulation by glucocorticoids
Reproduction. 2017 Jan 30. pii: REP-16-0647. doi: 10.1530/REP-16-0647. [Epub ahead of print]
?

MATERNAL HPA AXIS AND PARTURITION

- During normal labor in humans, transient increases in maternal plasma CRH, ACTH, and cortisol are observed, the levels of which drop to prepartum values within 1–4 days postpartum.
- Interestingly, neither correlation has been shown between maternal ACTH and cortisol levels at this stage, nor between maternal ACTH levels and parity, weight of the newborn, or duration of the delivery.
- Primiparous women with uneventful pregnancies that deliver spontaneously vaginally, show elevated ACTH levels when their labor is not progressing satisfactorily.

MATERNAL HPA AXIS AND PARTURITION

- It has been proposed that the HPA axis during pregnancy functions as a biological clock, "counting" from the early stages of gestation. In this model, placental CRH is the timing starter, determining the course of pregnancy and culminating, accordingly, in a preterm, term, or postterm labor.
- CRH-R 1 is considerably up-regulated at the time of labor in the human myometrium and the fetal membranes. In the final hours before birth the fetal adrenal cortisol production exceeds the CBG binding capacity, leading to a sudden increase in fetal free cortisol concentration. Cortisol competes with the action of progesterone in the regulation of placental CRH gene at the end of gestation. Moreover, cortisol may also act as an endogenous inhibitor of progesterone action on prostaglandin-inactivating enzymes, thus playing a role in regulating the timing of parturition.
- The fetal adrenals (at the level of the glands' fetal zone) respond to pituitary ACTH and placental CRH with DHEAS production. The latter is aromatized in the placenta to estrogen. An increase in local concentration of estrogen (and more particularly in amniotic fluid) or of the estrogen to progesterone ratio promotes myometrial contractility.

MATERNAL HPA AXIS IN THE POSTPARTUM PERIOD

- In the postpartum period, maternal plasma cortisol levels show a decline toward normal levels, as the HPA axis gradually returns to its prepregnant dynamic state. Immediately after parturition, the maternal HPA axis is mildly suppressed. Dynamic testing of the HPA axis shows transiently suppressed hypothalamic CRH secretion at 3 and 6 weeks postpartum, and normal responses after 12 weeks. Although suppressed ACTH responses are noted in the postpartum period, the total plasma cortisol levels are within normal range.

MATERNAL HPA AXIS IN THE POSTPARTUM PERIOD

- Healthy lactating women show blunted HPA responses to physical stress. In these women, estrogen levels were lower and prolactin levels were higher compared to nonlactating women.
- The HPA axis seems to influence the mother's psychological status and the mother-infant relationship/bonding. More particularly, among first-time mothers, those with higher plasma cortisol levels recognize, in the early postpartum period, their own infants' odors more easily and are more attracted to them than women with low plasma cortisol levels.

THE HPA AXIS IN PREGNANCY AND THE POSTPARTUM PERIOD: PATHOPHYSIOLOGIC CONSIDERATIONS

- The HPA axis is involved in the response of pregnant women to psychosocial stress; high plasma levels of ACTH and cortisol have been measured in pregnant women.
- Prenatal maternal stress is associated with premature birth. Since the latter is also associated with elevated maternal plasma CRH, it can be hypothesized that the timing of birth can be modified via HPA axis activation. Increased levels of corticosteriods (following physical or emotional stress) can promote placental CRH secretion and culminate in premature labor.
- ACTH-like products from the fetoplacental unit, may—very rarely—induce Cushing's syndrome, which may even resolve postpartum.

THE HPA AXIS IN PREGNANCY AND THE POSTPARTUM PERIOD: PATHOPHYSIOLOGIC CONSIDERATIONS

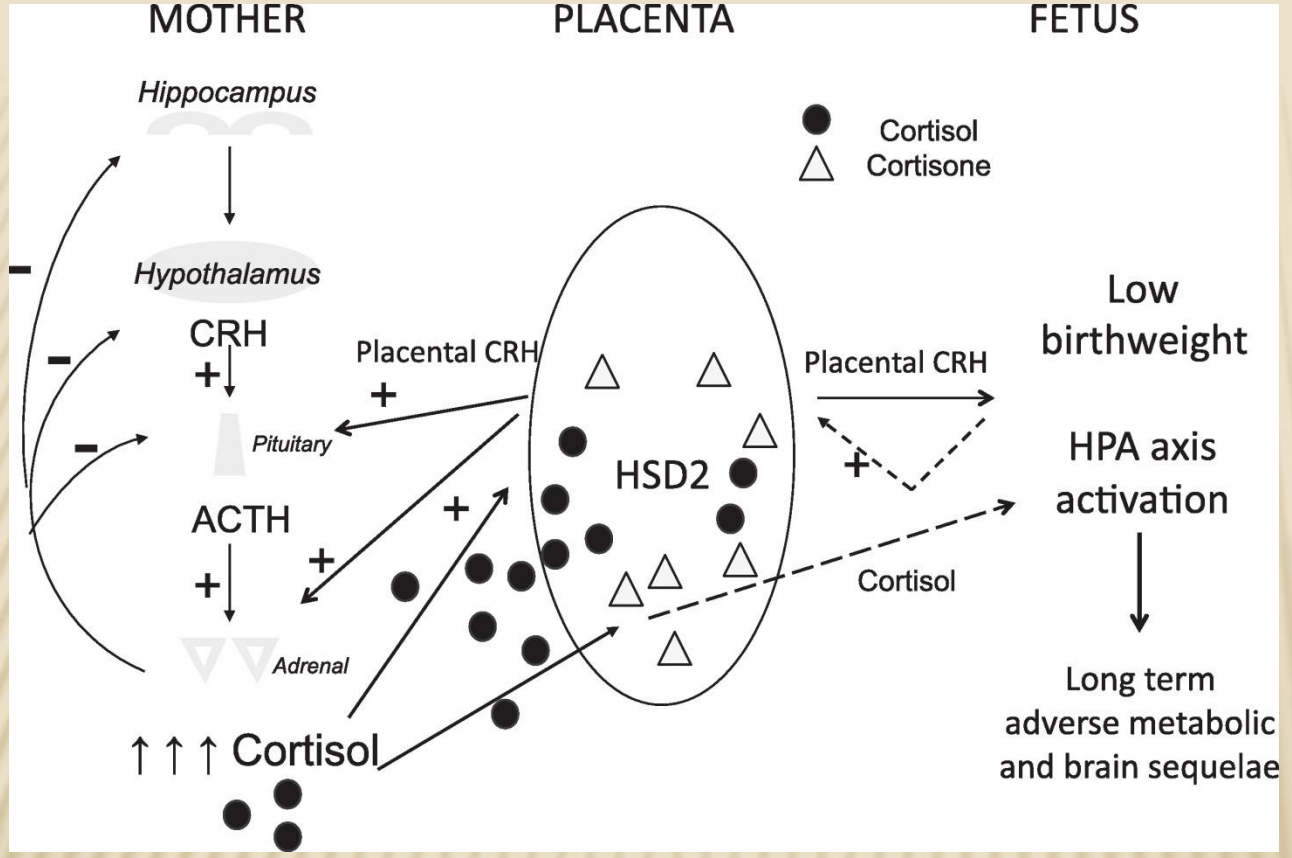
- Almost half of postpartum women develop a short-lived dysthymic disorder, called the "postpartum blues," while overt postpartum depression is common and occurs in up to 18% of newly delivered mothers.
- Mood disorders after pregnancy can last up to a year postpartum.

THE HPA AXIS IN PREGNANCY AND THE POSTPARTUM PERIOD: PATHOPHYSIOLOGIC CONSIDERATIONS

- During pregnancy cell-mediated immune function and Th1 cytokine production (e.g., IL-12, interferon-gamma) are suppressed, and humoral immunity and Th2 cytokine production (e.g., IL-4, IL-10) are enhanced. These cytokine patterns are reversed in the postpartum period.
- Thus, opposite Th1/Th2 cytokine profiles characterize pregnancy and the postpartum period. Convincing evidence exists to indicate that changes in the production of cortisol (as well as in progesterone and estrogen) play major roles in modulating the balance between Th1 and Th2 cytokines.
- In women with rheumatoid arthritis, pregnancy has an ameliorating effect on disease activity, while the disease tends to flare in the postpartum period. The prevalence of postpartum thyroiditis is 5–7%. The increased postpartum vulnerability to such autoimmune diseases could be attributed to the steroid withdrawal syndrome, the suppressed hypothalamic CRH secretion, and the subsequent changes in cytokine profiles.

FETAL-NEONATAL HPA AXIS

- The actions of the fetal HPA axis (in concert with those of the placenta) are essential in fetal development, maturation, and homeostasis, and eventually prepare for the survival of the neonate.
- The fetal pituitary matures first, with fetal HPA activity beginning at midgestation. Fetal hypothalamic and placental CRH lead to fetal pituitary ACTH secretion. The latter controls adrenocortical functional development, including angiogenesis and expression of steroidogenetic enzymes.
- The fetal adrenal gland is characterized by the presence of the fetal zone, which is the principal localization of DHEAS synthesis, the substrate for placental estrogen synthesis. Also in the fetal adrenal the definitive zone is the main site of mineralocorticoid synthesis, while the transitional zone synthesizes cortisol *de novo* after the 28th week of pregnancy. Although about one-third of variations in fetal cortisol levels are attributable to maternal cortisol levels, fetal stress responses are independent of maternal responses.



Psychoneuroendocrinology
38 (1), January 2013, Pages 1–11

Glucocorticoid signalling between mother, placenta and fetus. Figure shows interaction between maternal, placental and fetal compartments during pregnancy leading to overexposure of the developing fetus to glucocorticoids. Activation of the maternal HPA axis during pregnancy leads to increased circulating levels of cortisol (filled circles). Placental CRH also directly stimulates the maternal pituitary and adrenal to further increase cortisol levels, while maternal cortisol also stimulates placental CRH production. Maternal cortisol passes through the placenta where it is broken down by the enzyme HSD2 into inactive cortisone (grey triangles). The fetus can also signal to the placenta to increase production of placental CRH when fetal metabolic demands increase. Overexposure of the developing fetus to excess cortisol leads to fetal HPA axis activation which is associated with low birthweight and long term adverse programmed outcomes including metabolic and brain sequelae. CRH – corticotropin releasing hormone, ACTH – adrenocorticotropin hormone, HSD2 – 11β hydroxysteroid dehydrogenase type 2.

FETAL-NEONATAL HPA AXIS

- Birth is a very stressful situation for the neonate, and the adequate adrenocortical secretion of steroids (mainly of cortisol) enables adaptation to extrauterine life.
- Preterm and low-weight infants have adequate pituitary function; however, they show decreased baseline cortisol levels or low adrenocortical reserve after ACTH stimulation. Cortisol precursors are elevated in these infants, pointing to reduced steroidogenic enzymes' activity due to adrenal immaturity. In these infants, an inability to "recognize" stress or a failure of the hypothalamus to secrete CRH in stressful situations has been hypothesized.

PREGNANCY

- Pregnancy is a physiological state with a complex anatomical and functional interaction between mother and fetus. When this interaction is not a success, the mother, the fetus, or both exhibit functional impairments.
- Complications of pregnancy are important causes of maternal mortality, where gestational diabetes mellitus (GDM) and obesity of the mother in pregnancy (OP) are major obstetric pathologies. Fetal-maternal interaction could result in metabolic disturbances leading, for example, to placental and endothelial dysfunction.
- Endothelial dysfunction in pregnancy is defined as an altered capacity of the endothelium to take up and metabolize the cationic amino acid L-arginine, the substrate for nitric oxide (NO) synthesis via endothelial NO synthases (NOS). Interestingly, it is reported that GDM and OP are pathological conditions associated with altered L-arginine transport and NO synthesis (i.e., the "L-arginine/NO signalling pathway"), probably due to altered uptake and metabolism of adenosine, an endogenous nucleoside acting as vasodilator in most vascular beds.

FETAL PROGRAMMING

- These pathophysiological characteristics are considered key in the establishment of a "programmed state" of the developing fetus (i.e., "fetal programming"). This concept refers to the impact of abnormal intrauterine conditions on the development of diseases in adulthood and becomes a key mechanism associated with future development of chronic diseases including cardiovascular disease (CVD), diabetes mellitus, and metabolic syndrome (a concept globalizing clinical association of obesity, type II or non-insulin-dependent diabetes mellitus, hypertension, and dyslipidaemia) .
- Interestingly, GDM is a condition that also increases the risk of obesity in children and adolescents , a phenomenon leading to high incidence of type 2 diabetes mellitus (T2DM). OP is also related to neonatal metabolic compromise, which is already apparent in the offspring at birth, characterized by reduced insulin sensitivity and higher concentrations of inflammatory markers .

FETAL PROGRAMMING

- Adverse influences during fetal life alter the structure and function of distinct cells, organ systems or homeostatic pathways, thereby 'programming' the individual for an increased risk of developing cardiovascular disease and diabetes in adult life.
- It can be caused by a number of different perturbations in the maternal compartment, such as altered maternal nutrition and reduced utero–placental blood flow.
- Perturbations in the maternal environment must be transmitted across the placenta in order to affect the fetus. In IUGR (intrauterine growth restriction) pregnancies, the increased placental vascular resistance subjects the fetal heart to increased work load, representing a possible direct link between altered placental structure and fetal programming of cardiovascular disease.

FETAL PROGRAMMING

- The placenta appears to function as a nutrient sensor regulating nutrient transport according to the ability of the maternal supply line to deliver nutrients. By directly regulating fetal nutrient supply and fetal growth, the placenta plays a central role in fetal programming. Furthermore, perturbations in the maternal compartment may affect the methylation status of placental genes and increase placental oxidative/nitrative stress, resulting in changes in placental function.
- A decreased activity of placental 11β-HSD-2 (type 2 isoform of 11β-hydroxysteroid dehydrogenase) activity can increase fetal exposure to maternal cortisol, which programmes the fetus for later hypertension and metabolic disease.

GESTATIONAL DIABETES MELLITUS (GDM) AND OBESITY IN PREGNANCY (OP)

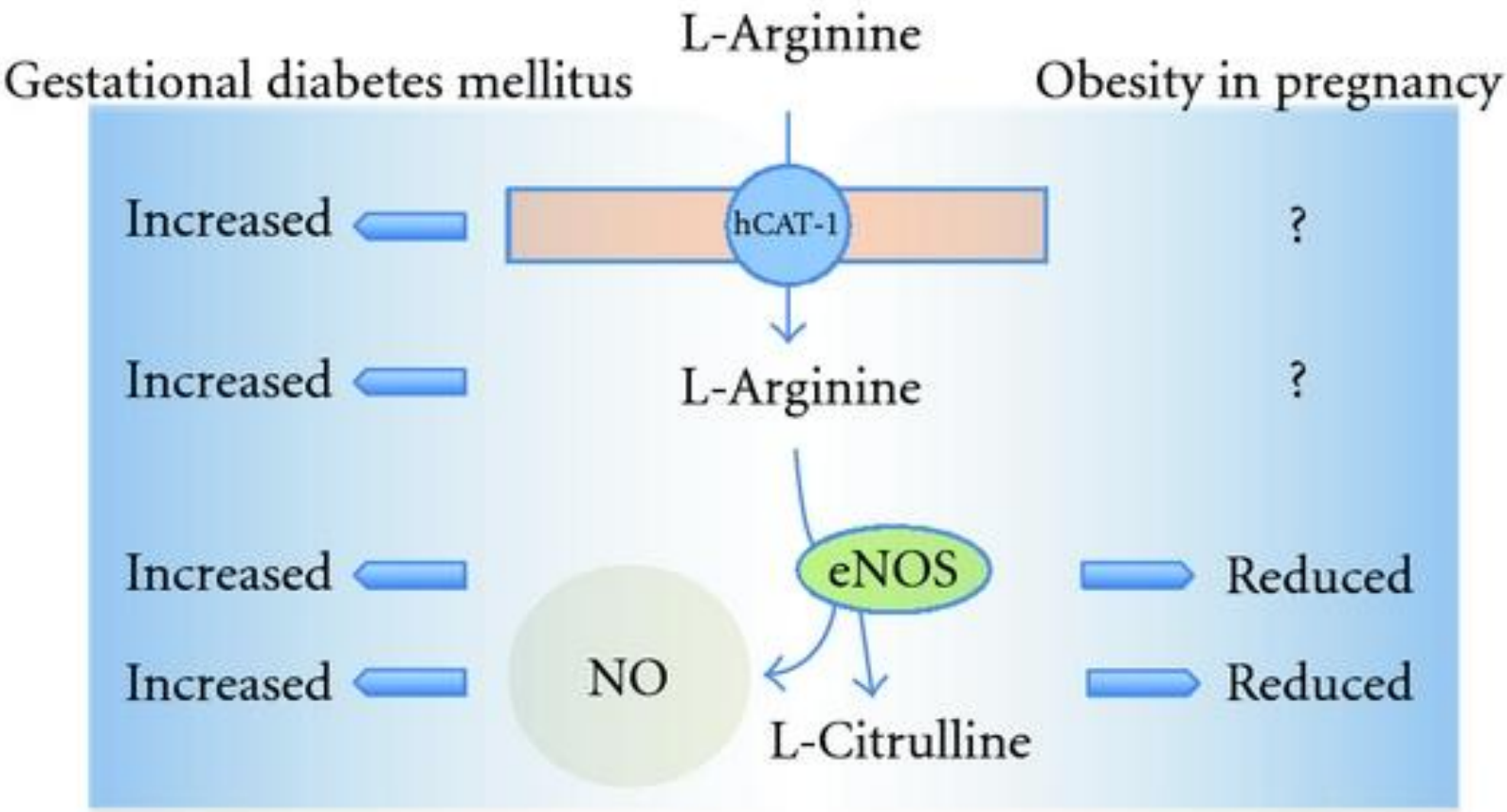
- are pathological conditions associated with placenta vascular dysfunction coursing with metabolic changes at the fetoplacental microvascular and macrovascular endothelium. These alterations are seen as abnormal expression and activity of the cationic amino acid transporters and endothelial nitric oxide synthase isoform.
- GDM and OP prone placental endothelium to an "altered metabolic state" leading to fetal programming evidenced at birth, a phenomenon associated with future development of chronic diseases, such as cardiovascular disease, obesity, diabetes mellitus (including gestational diabetes), and metabolic syndrome.

GESTATIONAL DIABETES MELLITUS

- Gestational diabetes mellitus (GDM) is a syndrome characterized by glucose intolerance leading to maternal hyperglycaemia first recognized during pregnancy.
- GDM is associated with abnormal fetal development and perinatal complications, such as macrosomia and neonatal hypoglycaemia .
- Alterations associated with GDM result from a change in the amount of D-glucose available to the fetus due to alterations in the physiology of the placenta (e.g., increased D-glucose transplacental transport) or by hormone-induced dysfunction (e.g., altered insulin signalling), phenomena that could lead to abnormal growth of the fetus (macrosomia) and perinatal complications.

GESTATIONAL DIABETES MELLITUS (GDM)

- Gestational diabetes mellitus (GDM) is a syndrome compromising the health of the mother and the fetus.
- Endothelial damage and reduced metabolism of the vasodilator adenosine occur and fetal hyperinsulinemia associated with deficient insulin response is characteristic for this pathology. These phenomena lead to endothelial dysfunction of the fetoplacental unit.



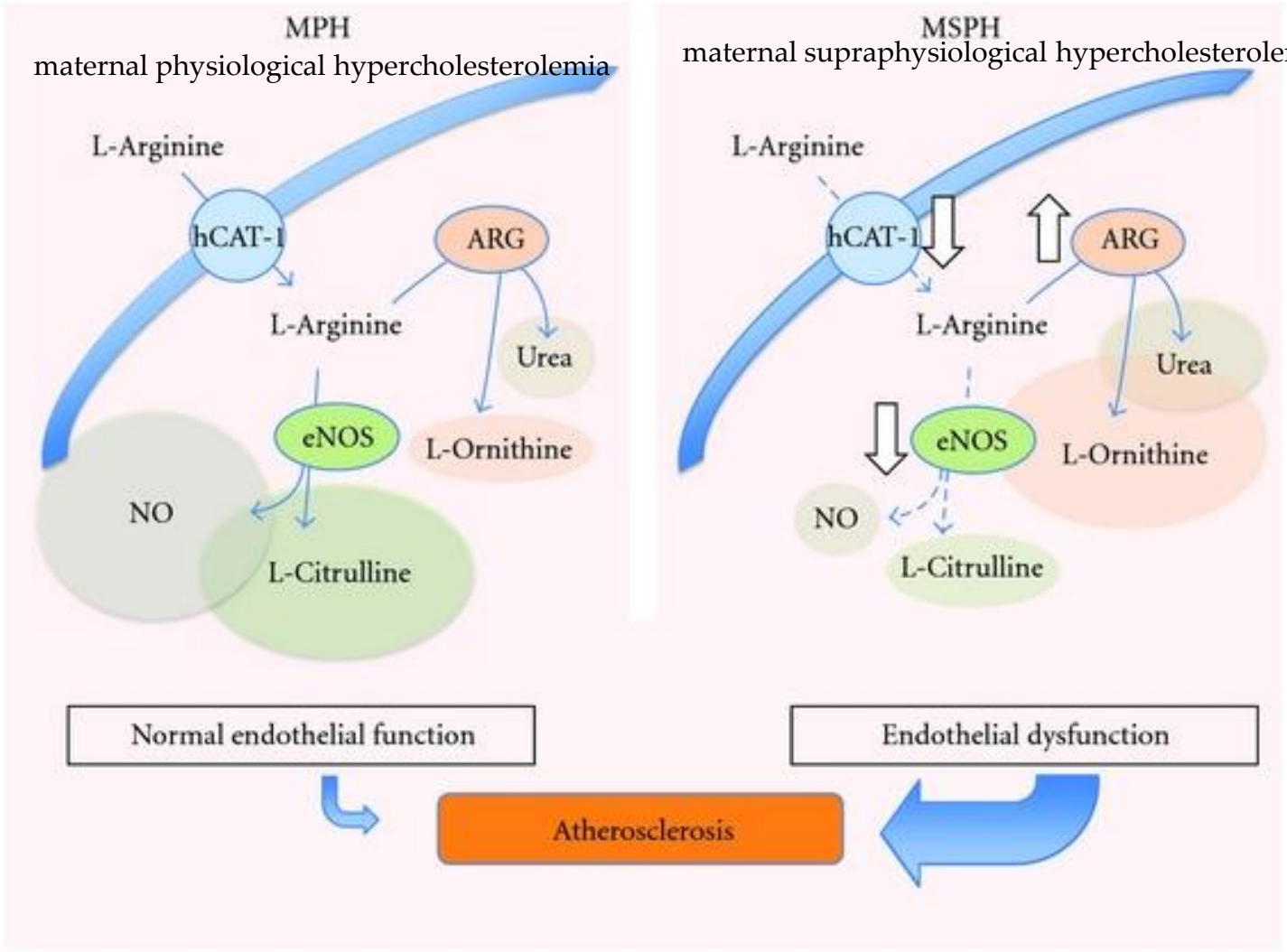
Endothelial L-arginine/NO signalling pathway in gestational diabetes mellitus and obesity in pregnancy. In human endothelial cells L-arginine is taken up via cationic amino acid transporters 1 (hCAT-1) accumulating this amino acid in the intracellular compartment

HYPERTRIGLYCERIDEMIA IN PREGNANCY

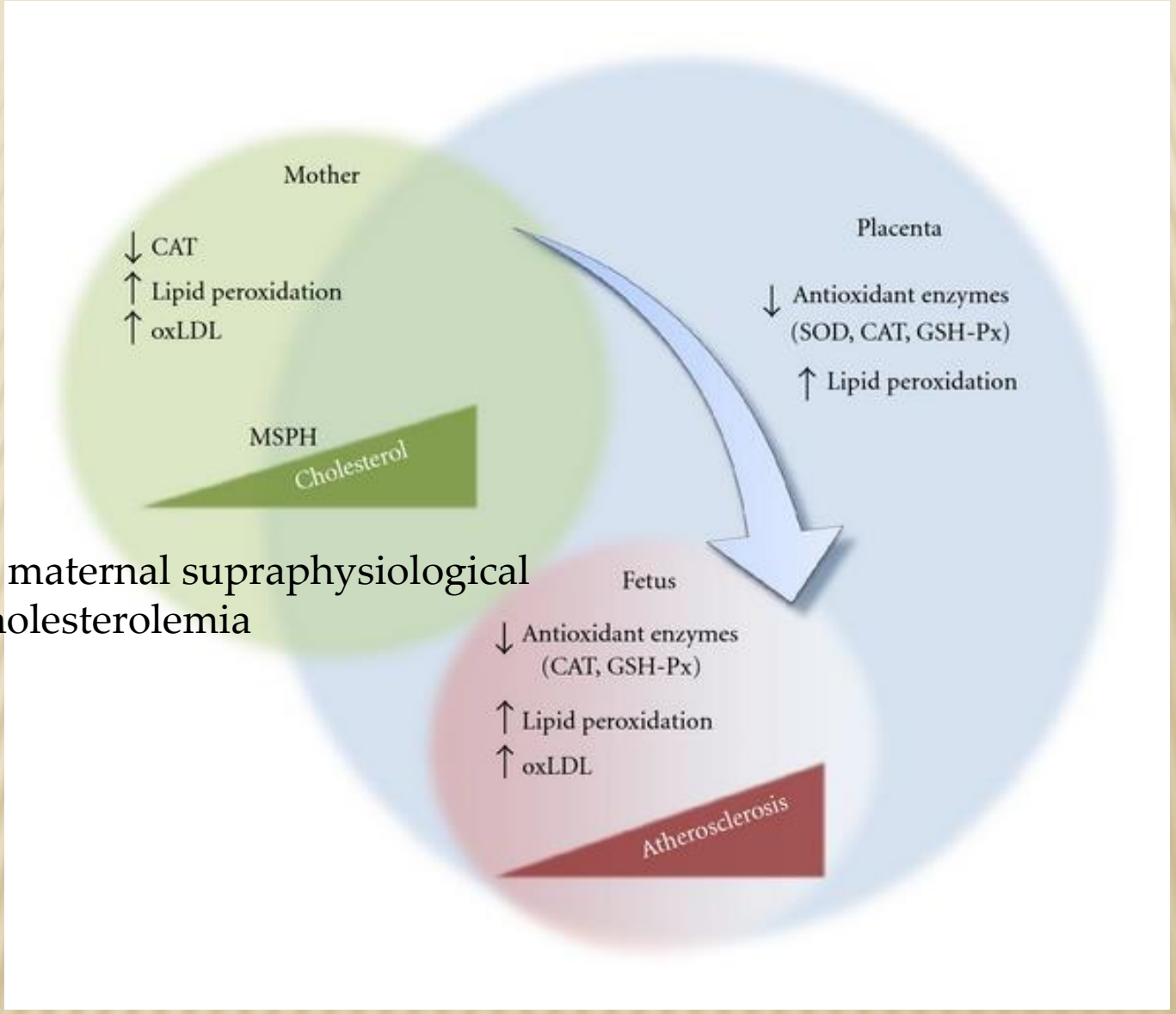
- Pregnancy is a physiological condition characterized by a progressive weeks of gestation-dependent increase (reaching 100–200%) in the maternal blood level of triglycerides.
- These changes promote accumulation of maternal fat stores in early and mid pregnancy, so to metabolize and use it in late pregnancy.

DYSLIPIDEMIA

- GDM is a pathological condition also characterized by maternal dyslipidaemia, alteration directly affecting fetal development and growth.
- Dyslipidaemia is defined as elevated levels of triglycerides (hypertriglyceridemia) and total blood cholesterol (hypercholesterolemia), including increased low-density lipoprotein (LDL) and reduced high-density lipoprotein (HDL) levels.
- Dyslipidaemia is the main risk factor for development of CVD later in life in mother.
- GDM is a risk factor to fetal programming due apparently to metabolic syndrome and, thus, predisposes to an accelerated development of CVD in adult life.



L-Arginine metabolism in hypercholesterolaemia. In human endothelial cells, L-arginine is taken up via cationic amino acid transporter 1 (hCAT-1) which is then metabolized by either the endothelial nitric oxide synthase (eNOS) into L-citrulline and nitric oxide.



MSPH= maternal supraphysiological hypercholesterolemia

Potential pathophysiological interaction between the mother, the placenta, and the fetus in fetal atherosclerosis. Maternal factors, including reduced (↓) catalase (CAT) activity, increased (↑) lipid peroxidation, and oxidized low density lipoproteins.

PREECLAMPSIA

- Preeclampsia is a multi-system disorder of pregnancy, which is characterized by new onset hypertension (systolic and diastolic blood pressure of ≥ 140 and 90 mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of ≥ 300 mg in a 24 h urine collection, or a dipstick of ≥ 2+), that develop after 20 weeks of gestation in previously normotensive women
- Dependent on the systemic involvement, several other symptoms, such as edema, disturbance of haemostasis, renal or liver failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) also complicate the clinical picture.

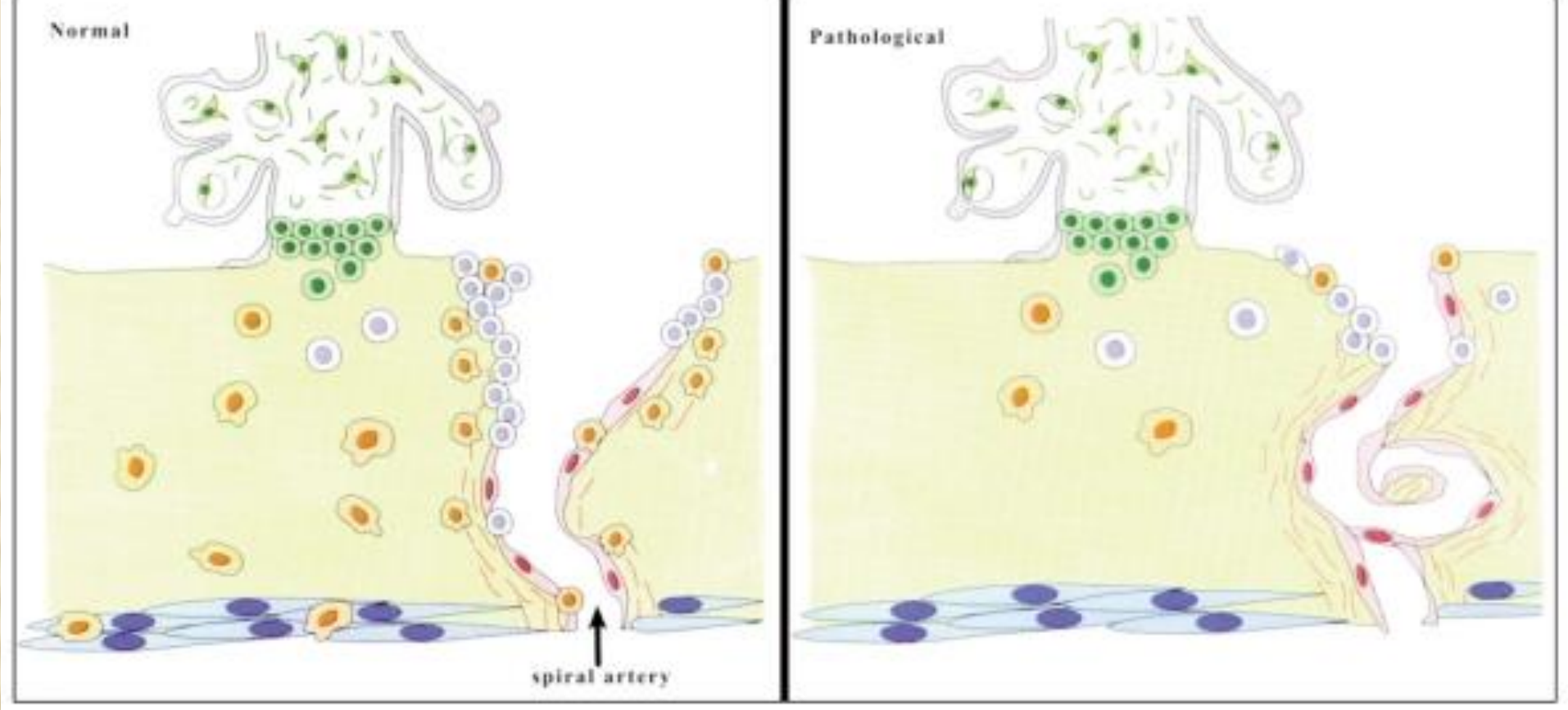
PREECLAMPSIA

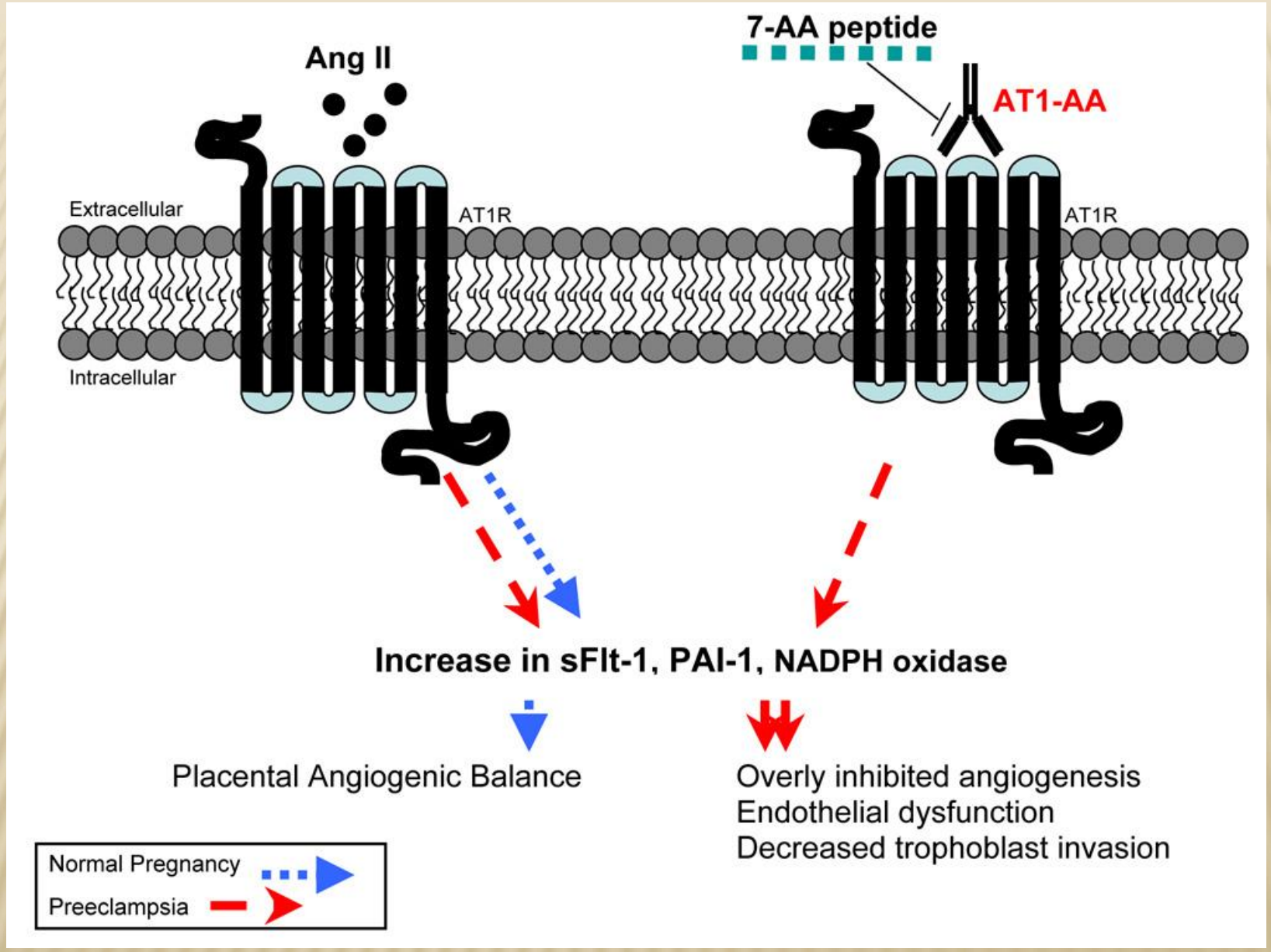
- Preeclampsia can have an early onset (preeclampsia starting before 34 weeks of gestation) or late onset (preeclampsia starting after 34 weeks of gestation),
- can show mild or severe symptoms (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, proteinuria >5 g/24 hours, oliguria, neurological symptoms, other clinical symptoms such as deranged liver function, thrombocytopenia < 100 000 mm3, HELLP syndrome)
- can evolve in eclampsia in the most severe cases.
- it can manifest as a maternal disorder only, with an appropriate fetal growing, or
- it can present itself with a growth restricted fetus (intrauterine growth restriction (IUGR)) or sudden fetal distress.

PREECLAMPSIA

It is the main cause of maternal morbidity and mortality, and fetal metabolic disturbances in developed and developing countries.

- Fetal complications in preeclampsia have been related with lower placental blood flow. The placenta lacks of innervation, thus vascular tone regulation depends on endothelial release of vasoactive molecules such as **adenosine and nitric oxide (NO)**. Information about NO synthesis and its action in the fetoplacental vasculature in preeclamptic pregnancies is controversial.
- A high plasma level of adenosine has been reported in umbilical vein from preeclampsia compared with normal pregnancies. Since this nucleoside is mainly involved in the regulation of vascular tone and angiogenesis, perhaps through the modulation of potassium channels, it is suggested that it would be involved in the maintenance of normal fetoplacental function. A potential adenosine-mediated, NO-dependent mechanism is hypothesized accounting for the feto-placental reduced blood flow exhibited in preeclampsia.


Normal
Pathological
spiral artery


7-AA peptide
Ang II
AT1-AA
Extracellular
AT1R
AT1R
Intracellular
Increase in sFlt-1, PAI-1, NADPH oxidase
Placental Angiogenic Balance
Overly inhibited angiogenesis
Endothelial dysfunction
Decreased trophoblast invasion
Normal Pregnancy
Preeclampsia

ANGIOTENSIN II TYPE I RECEPTOR AGONISTIC AUTOANTIBODY

- **AT_1-AA interact with AT_1 receptors on trophoblasts which synergistically act with ANG II to impair placentation**
- Normal RAS function and AT_1 receptor activation is imperative for normal placental development. AT_1-AA, found in the serum of preeclamptic women, functions as ANG II by activating AT_1 receptors to increase production of sFlt-1, PAI-1 and NADPH oxidase in trophoblast cells. The 7-AA peptide corresponds to a sequence on the second extracellular loop of the AT_1 receptor. AT_1-AA-mediated effects can be neutralized by 7-AA. AT_1-AA: Angiotensin II type I receptor agonistic autoantibody (AT1-AA). This autoantibody can induce many key features of the disorder and upregulate molecules involved in the pathogenesis of preeclampsia.

POSTNATAL OUTCOME IN OFFSPRING IN OBESITY IN PREGNANCY

- Prepregnancy obesity and excessive gestational weight gain have been implicated in an intergenerational "vicious cycle" of obesity, since overweight or obese women give birth to macrosomic girls, who are more likely to become obese themselves and deliver large-sized neonates.
- Gestational weight gain and birth weight were directly associated with the body mass index and the risk of obesity in adolescence. The relationship described was independent of parental characteristics, potentially mediating peripartum factors, child obesogenic behaviour, and weight at birth, suggesting a role of the intrauterine environment on long-term offspring weight regulation.

POSTNATAL OUTCOME IN OFFSPRING IN OBESITY IN PREGNANCY

- Interestingly, an association between weight gain of the mother during pregnancy and increased risk of greater adiposity in the offspring has been shown at ages of infancy as early as 7 or 3 years old. Considering the high prevalence of OP and its potential association with GDM, there is an increasing interest in considering a potentially negative influence of maternal overnutrition and raised birth weight on the risk of disease in childhood and adulthood.

POSTNATAL OUTCOME IN OFFSPRING IN OBESITY IN PREGNANCY

- Children of obese women exhibiting increased risk of diabetes in pregnancy are more likely to develop insulin resistance later in life.
- Women gaining more than recommended weight during gestation have been found to be more prone to have offspring with greater body mass index, waist, fat mass, leptin, systolic blood pressure, C-reactive protein, and interleukin-6 levels, but lower HDL cholesterol and apolipoprotein A levels than women with a physiological weight gain.

POSTNATAL OUTCOME IN OFFSPRING IN OBESITY IN PREGNANCY

- Additionally, greater prepregnancy weight was independently associated with greater offspring adiposity and adverse cardiovascular risk factors.
- OP increases the incidence of metabolic syndrome in children . Interestingly, OP is related to neonatal metabolic compromise already apparent at birth, characterized by reduced insulin sensitivity and increased serum inflammatory markers. Since OP effect on the susceptibility to obesity in offspring is apparently independent of GDM, as obese women with normal blood glucose have babies with increased adiposity , OP and excessive maternal weight gain during pregnancy are independent factors leading to increased risk of obesity, insulin resistance, and early markers of CVD in the offspring.
- All this evidence shifts our attention towards the gestational period as an extremely key interventional target in the prevention of obesity and associated consequences such as insulin resistance and cardiovascular risk.

MECHANISMS OF ADVERSE POSTNATAL OUTCOME

- During normal intrauterine life, maternal insulin does not cross the placenta, whereas maternal D-glucose is actively transferred to the fetus. The developing fetal pancreas responds to a D-glucose load by increasing synthesis and release of insulin, which acts as a fetal growth hormone. This is the basic concept of the "**Pedersen's hyperglycaemia-hyperinsulinism hypothesis"** (where fetal overgrowth due to hyperinsulinemia in response to increased transplacental D-glucose transfer is proposed, explaining observations showing that offspring of diabetic mothers exhibit high birth weight.

MECHANISMS OF ADVERSE POSTNATAL OUTCOME

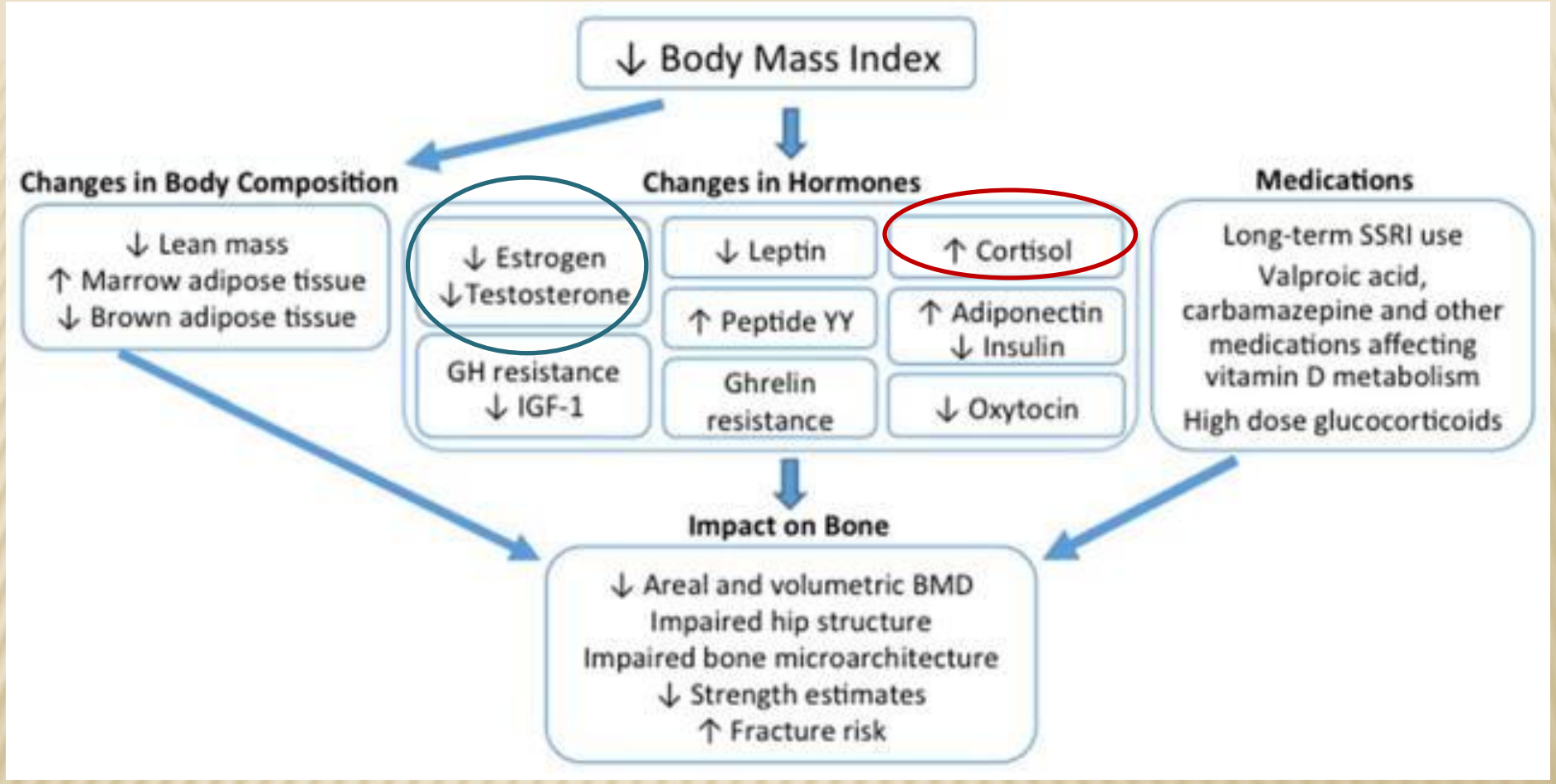
- Maternal overnutrition produces hyperglycaemia, which leads to increased fetal insulin secretion in a similar manner as seen in GDM. Thus, secondary fetal hyperinsulinemia is believed to be involved in the intrauterine programming of obesity and diabetes.
- Prospective studies indicate that at birth and at 6 years old the greatest increase in weight to height relation (relative obesity) was seen in children who experienced the greatest exposures to insulin in uterus (as judged by amniotic fluid insulin concentration) .

MECHANISMS OF ADVERSE POSTNATAL OUTCOME

- Leptin is also implicated in programming obesity.
- In humans, leptin is increased in OP and maternal diabetes and is reduced in intrauterine growth restriction. Although the placental transfer of leptin has been demonstrated *in vivo*, it is believed that umbilical blood level of this circulating peptide is a marker of neonatal adiposity more than a relevant modulator of fetal growth.

MECHANISMS OF ADVERSE POSTNATAL OUTCOME

- Additionally, several inflammatory cytokines levels are elevated in obese pregnant women , changes that are proposed as potential mediators of metabolic programming.
- Thus, altered metabolic phenotypes, such as obesity and insulin resistance seen in offspring in OP, could partially be explained by the involvement of multiple mediators. Probably, a multifactorial contribution of nutrient- (e.g., D-glucose, fatty acids, amino acids) and hormone-(e.g., insulin, leptin) triggered signals between the obese mother and the developing fetus would better describe the involved mechanisms.



Changes in hormone levels in anorexia

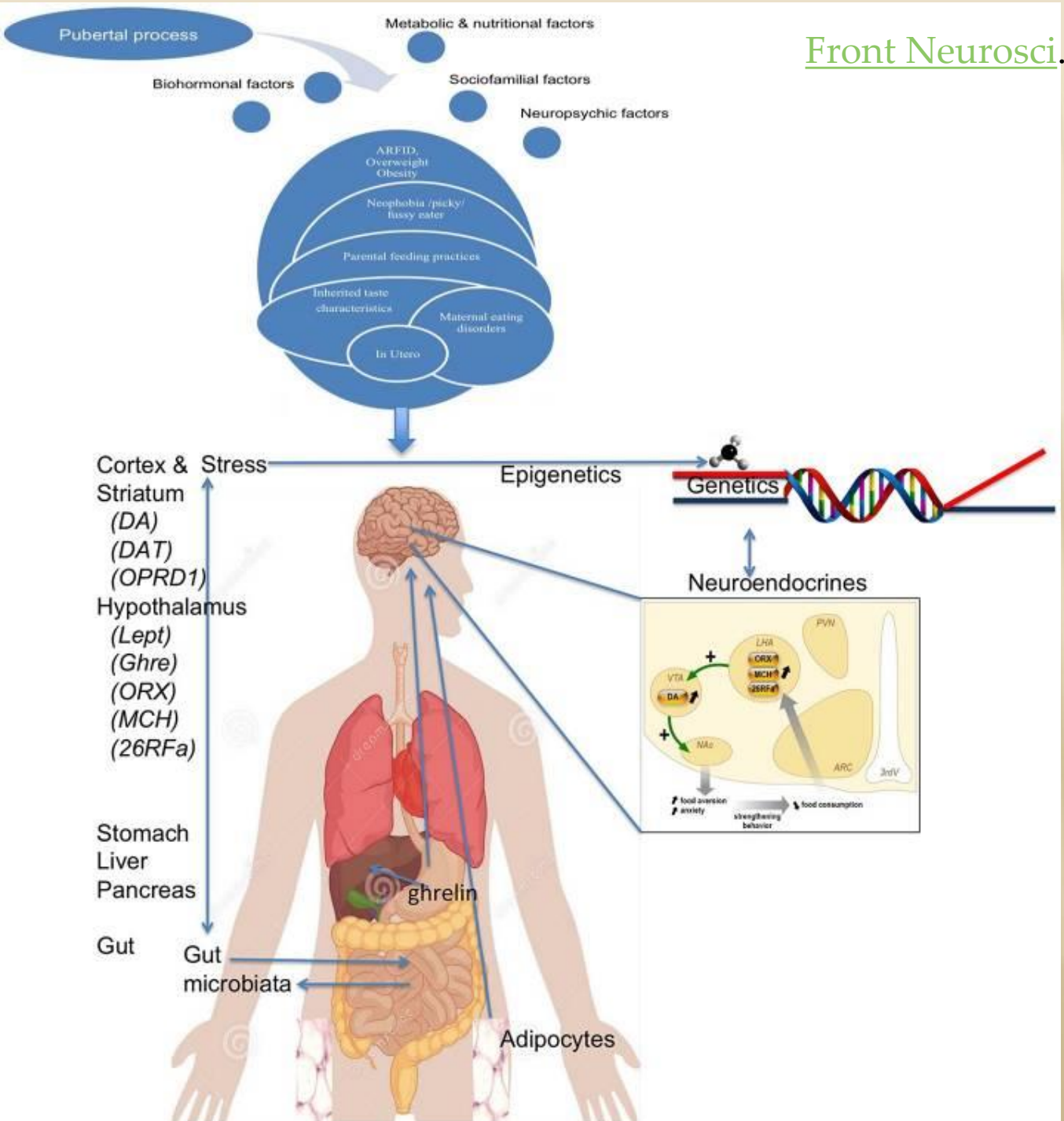
Int J Eat Disord. 2016 Mar; 49(3): 276–292.

ANOREXIA NERVOSA AND PREGNANCY

- AN, a state of severe energy deprivation, leads to changes in many endocrine axes. Which is not functioning as necessary, is
- (1) energy conservation (through suppression of the hypothalamic-pituitary-gonadal axis, thus avoiding energy utilization in activities such as procreation)
- (2) activation of pathways that
- (a) cause an increase in energy intake (though an increase in appetite stimulating hormones and a decrease in appetite inhibiting hormones), or
- (b) mobilize substrates to increase energy availability for vital functions (such as through activation of the glycogenolytic and lipolytic pathways by cortisol and growth hormone respectively).

ANOREXIA NERVOSA AND PREGNANCY

- **Hypothalamic-Pituitary-gonadal (HPG) Axis**
- The state of low energy availability in AN has an inhibitory effect on the HPG axis, resulting in varying degrees of menstrual dysfunction, the most extreme being a state of amenorrhea.
- Hypogonadism leads to low levels of the gonadal steroids, estrogen and testosterone.



Front Neurosci. 2016; 10: 256

PATHOPHYSIOLOGY OF AN

- An integral pathophysiological scenario that fits to the natural history of AN with the following steps an be porposed:
- (1) enhanced vulnerability to stress (genetic, epigenetic, or environmental factors);
- (2) major stressing events activating the stress-axis, increased intestinal permeability, and increased virulence of the microbiota;
- (3) bacterial proteins (e.g., ClpB) challenge the immune response and due to molecular mimicry, cause increased production of Igs cross-reactive with neuropeptides (e.g., α-MSH);
- (4) this results in altered food intake, anxiety, gastrointestinal discomfort and other consequences of altered central and peripheral melanocortin signaling;
- (5) global malnutrition and some specific macro- and micro-nutrient deficiencies contribute to the perpetuation of gut barrier and immune dysfunction as well as behavioral symptoms.

Front Neurosci. 2016; 10: 256

OREXIGENIC NEUROPEPTIDES

- Orexigenic neuropeptides including ghrelin, orexins and 26RFa are up-regulated in AN and it is thought that this orexigenic profile reflects an adaptive mechanism of the organism to promote food intake and thus to counteract undernutrition. However, this adaptive mechanism is ineffective in increasing food consumption leading to the concept of a global resistance of AN patients to orexigenic signals.
- We can speculate that a chronic increase of the activity of LHA orexigenic neurons expressing orexins, MCH, or 26RFa could reinforce dopamine-induced anxiety in the reward system of AN patients and thus the aversion to ingest food.

Front Neurosci. 2016; 10: 256

THANK YOU FOR YOUR ATTENTION