The placenta, adverse pregnancy outcomes and long term consequences for cardiovascular health

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- I have no disclosures

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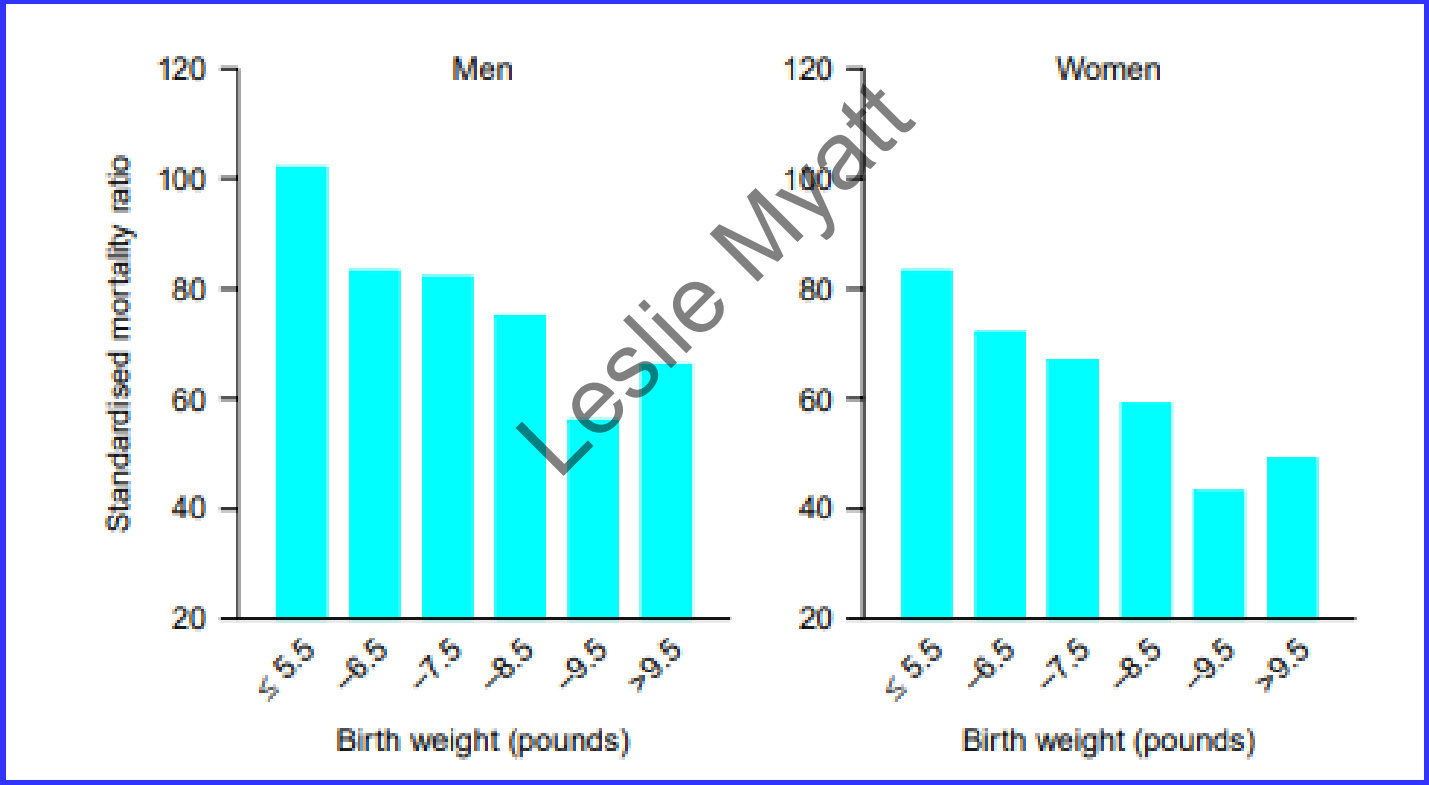
Mortality from Coronary Heart Disease in Hertfordshire



Barker DJP 1995

Programming of Cardiovascular Disease

- Main cause of mortality and morbidity in 21st century
- CVD accounted for 18.6 million deaths in 2019
- In utero and postnatal gene-environment interactions
- IUGR offspring have highest rate of CHD, myocardial dysfunction, type 2 diabetes, hypertension and stroke as adults.
- Incidence of ischemic heart disease and death 3x higher in men with low birth weight vs high birth weight.
- Dutch famine winter 1944/45 – association of maternal starvation, low birth weight and high incidence of hypertension and CHD as adults

Developmental (Fetal) Programming

(Barker Hypothesis)
(Fetal Origins of Adult Disease)
(Developmental Origins of Health and Disease [DOHaD])

- Life in utero determines risk of development of disease in adult life
  - Cardiovascular
  - Diabetes (Insulin resistance/Metabolic syndrome)
  - Obesity
  - Stroke
  - Osteoporosis
  - Obstructive Airway Disease
  - Cancer
  - Disordered HPAA axis
  - Behavioral abnormalities
- Sexual dimorphism in effect
- Epigenetic mechanisms
  - Histone modification, DNA methylation

Pregnancies with adverse outcomes

- Pregnancy-induced hypertension, preeclampsia - 5-7%
- Fetal growth restriction - 7%
- Macrosomia - 6-10%
- Pre-gestational diabetes - 1%
- Gestational diabetes - 2-10%
- Multifetal gestation - 3%
- Preterm birth - 11%
- Miscarriage - 10-20%
- Stillbirth - 0.6%
- Congenital malformation – 2-4%

Long Term Consequences of Adverse Pregnancy Outcome (Preeclampsia) - Mother

Increased risk of:

- Hypertension
- Coronary artery disease
- Stroke
- Type 2 diabetes mellitus

CVD risk in relation to time of occurrence

Preeclampsia at term - 2x risk

Preeclampsia <37 weeks) - 5x risk

Preeclampsia <34 weeks - 10x risk

Fetal growth restriction – 2x risk

Preeclampsia + FGR - 8x risk

? Pregnancy as a stress test (exposes subclinical disease)

? Does preeclampsia damage vascular system

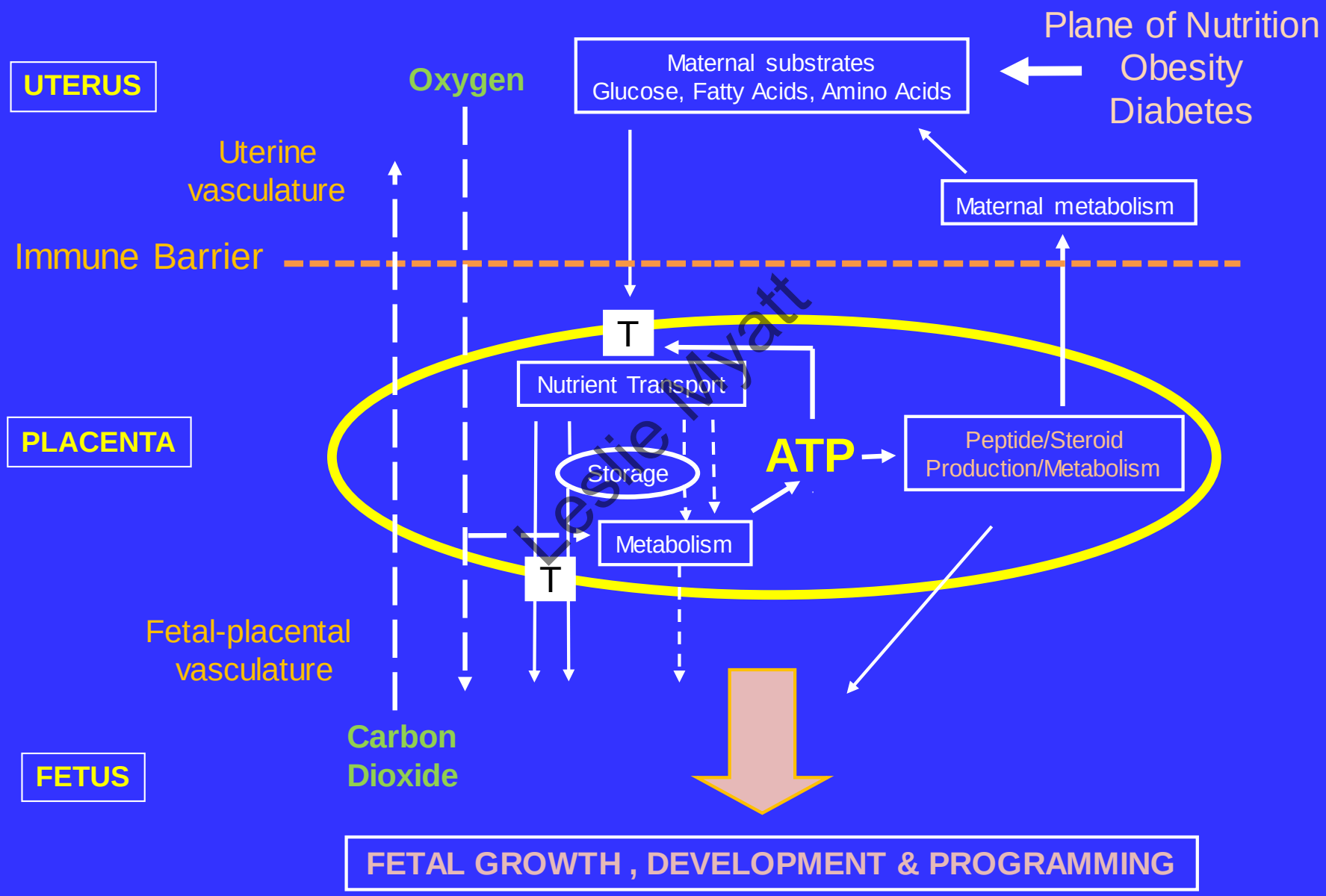
Long Term Consequences of Adverse Pregnancy Outcomes (Preeclampsia) - Offspring

Fetal programming for subsequent disease due to exposure to adverse intrauterine environment (Developmental Origins of Health and Disease, DOHaD)

At risk for subsequent development of

- Cardiovascular disease (↑BP, ↑cardiac wall thickness)
- Metabolic syndrome (↑BMI)
- Neurodevelopmental disorders (↑ASD [50%], ↑ADHD [28%])
- Congenital heart defects (↑50%)
- Epilepsy

Roles of the Placenta

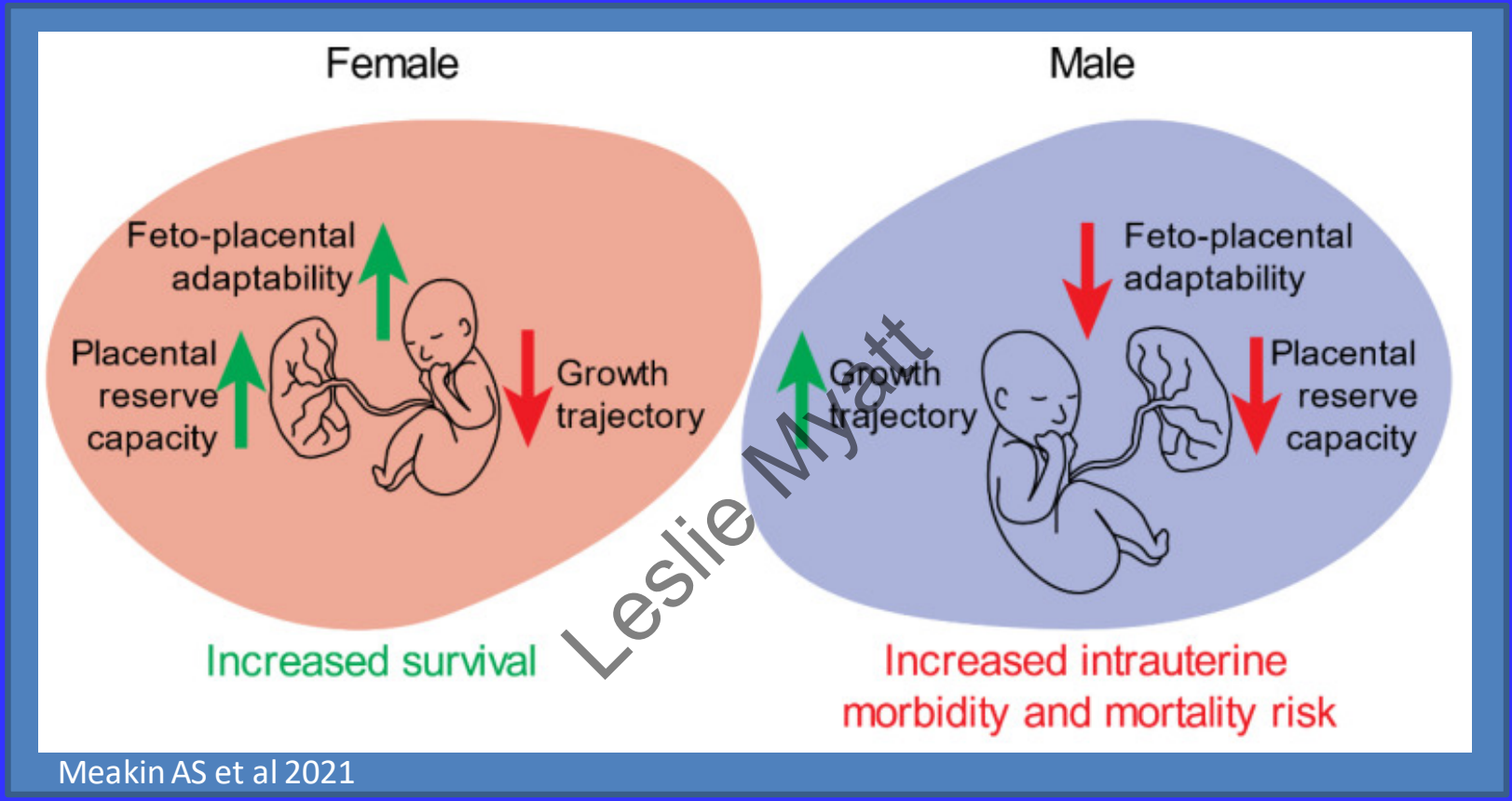


Placenta – Not Just a Conduit

- Second only to the brain in the number of gene transcripts
- In human placenta consumes 50% of oxygen and 30% of glucose supplied to uterus
- Metabolic activity 4-6 fold higher per unit weight than fetus
- One third of placental oxygen consumption used for de novo generation of peptides, one third to maintain cation gradient across membrane for transport
- Not simply a conduit, it regulates nutrient composition and supply from mother to fetus. Is it a selfish organ?

“Boys live dangerously in the womb”

Eriksson et al 2010



Meakin AS et al 2021

Different evolutionary strategies for males and females.
Male fetuses appear to keep growing, are larger but have more adverse outcomes due to less placental adaptability:

preterm birth, PPROM, placenta previa, preeclampsia, lagging lung development, macrosomia, late stillbirths, poorer maternal B cell function and increased risk of GDM.

Females adapt growth rate to optimize survival in a poor environment
Also reflected in differences in fetal programming males vs females

Evidence for Sexual Dimorphism in Placental Function

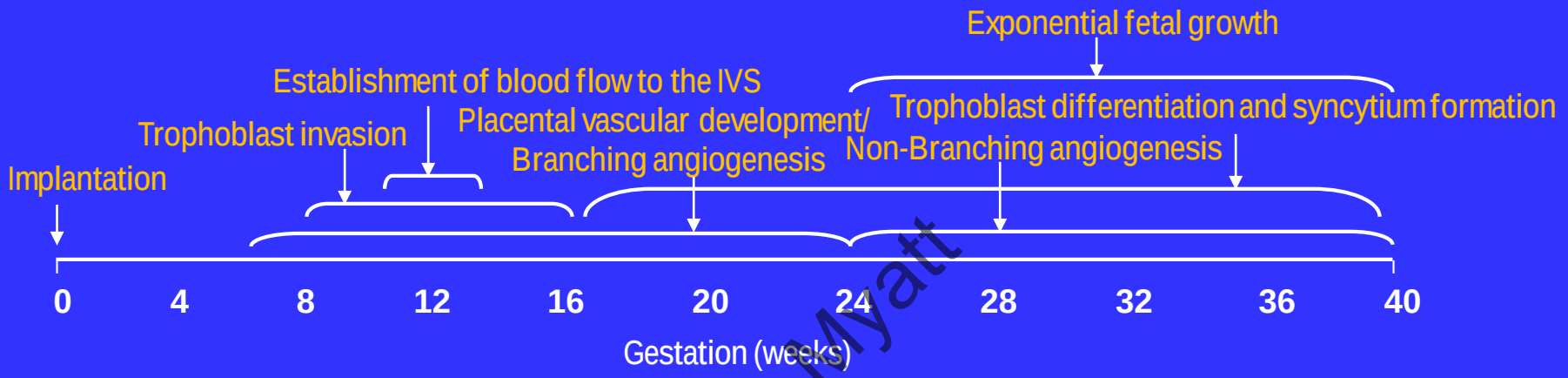
- Differences in gene expression, 1st trimester and term, linked to escape from X chromosome inactivation

- Inflammatory, hypoxia, apoptosis and autophagy responses
- Expression of antioxidant defense enzymes
- Fatty acid transporters
- Fatty acid oxidation
- Response to maternal adiposity and inflammatory status
- microRNA expression in normal pregnancy
- Steroid and peptide hormone synthesis
- All linked to difference in outcomes male vs female

Placental Growth and Development Throughout Gestation

	6 weeks	Term
Placental Weight (g)	6.0	470
Fetal Weight (g)	1.1	3500
Fetal/Placental Weight Ratio (efficiency)	0.18	7.23
Villous volume occupied by vessels (%)	2.7	28.4
Trophoblast Surface area (m^2)	0.08	12.5
Mean Trophoblast Thickness (μm)	18.9	4.1
Maternofetal Diffusion Distance (μm)	55.9	4.8

Critical periods during placental development



Placental development can be affected by type, severity, timing and duration of a challenge – clearly seen in animal models [structure/function].
An insult e.g. nutritional, applied at a specific time will have a specific effect on placental development /function.
The same insult at a different times may have different effect

E.g. IDDM plus LGA gives increased Glut 1 in BM and increased system A aa transporter, whereas GDM plus LGA no change in Glut 1 in BM but increased system A

Influences on placental development, function and programming

- Type and plane of nutrition
- Oxygen availability (altitude, anemia)
- Developmental timing, severity, duration of challenge
- Micronutrient availability
- Environmental toxicants - exposome
- Maternal stress

(Mal)adaptive responses of the placenta

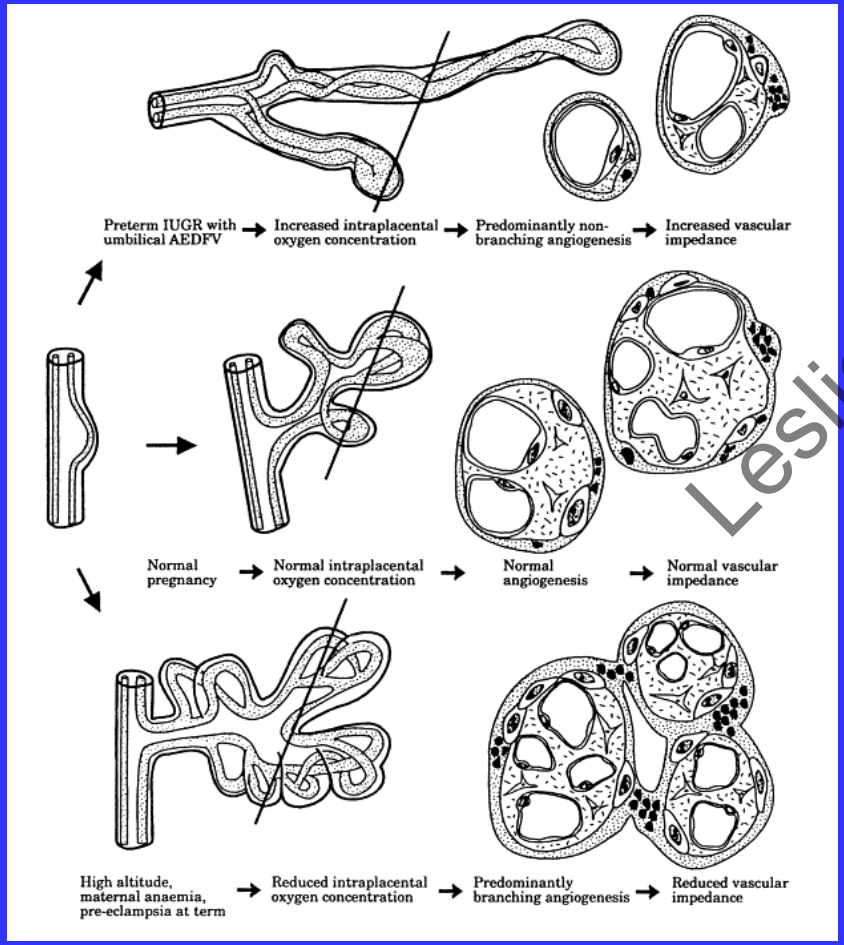
- Alteration in size, shape, surface area and structure
  - Vascularization (maternal, fetal)
  - Barrier surface area, thickness (diffusion distance)
- Epigenetic changes, gene expression
- Function
  - Hormone production
  - Expression of type and quantity of transporters
  - Buffering/storage/metabolism of nutrients to alter/limit transfer to fetus
  - Lipid accumulation, inflammation, oxidative stress
  - Barrier - metabolism of glucocorticoids

Seen with maternal obesity, gestational diabetes, preeclampsia, fetal growth restriction, large for gestational age, preterm birth

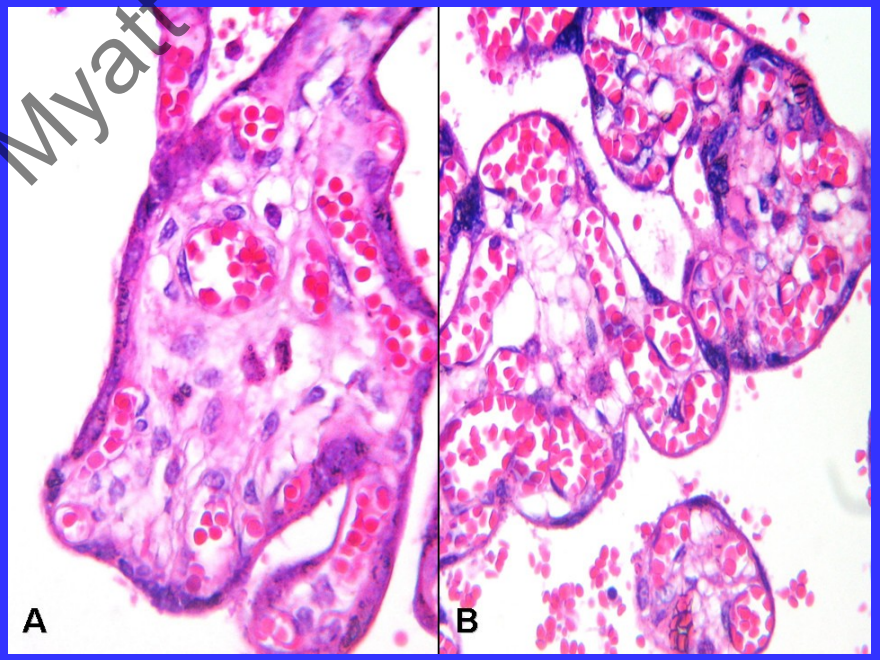
Fetal programming of the heart

- Direct correlation of oxygen and nutrient supply to fetus and cardiomyocyte development and function
- Cardiac remodeling – changes in size, shape, function resulting from cardiac load and injury
- Cardiac hypertrophy - globular shape, higher intraventricular septum thickness, increased pressure overload leading to systolic and diastolic dysfunction
- Signs of ventricular electrical remodeling
- Changes in cardiac gene expression *HIF-1α, PARP1, HSP70, PKCε, SIRT3, FOXO1*
- Genes and miRNA expression for energy metabolism
- Epigenetic changes - DNA methylation, histone modification

Villous angiogenesis in normal and IUGR pregnancy

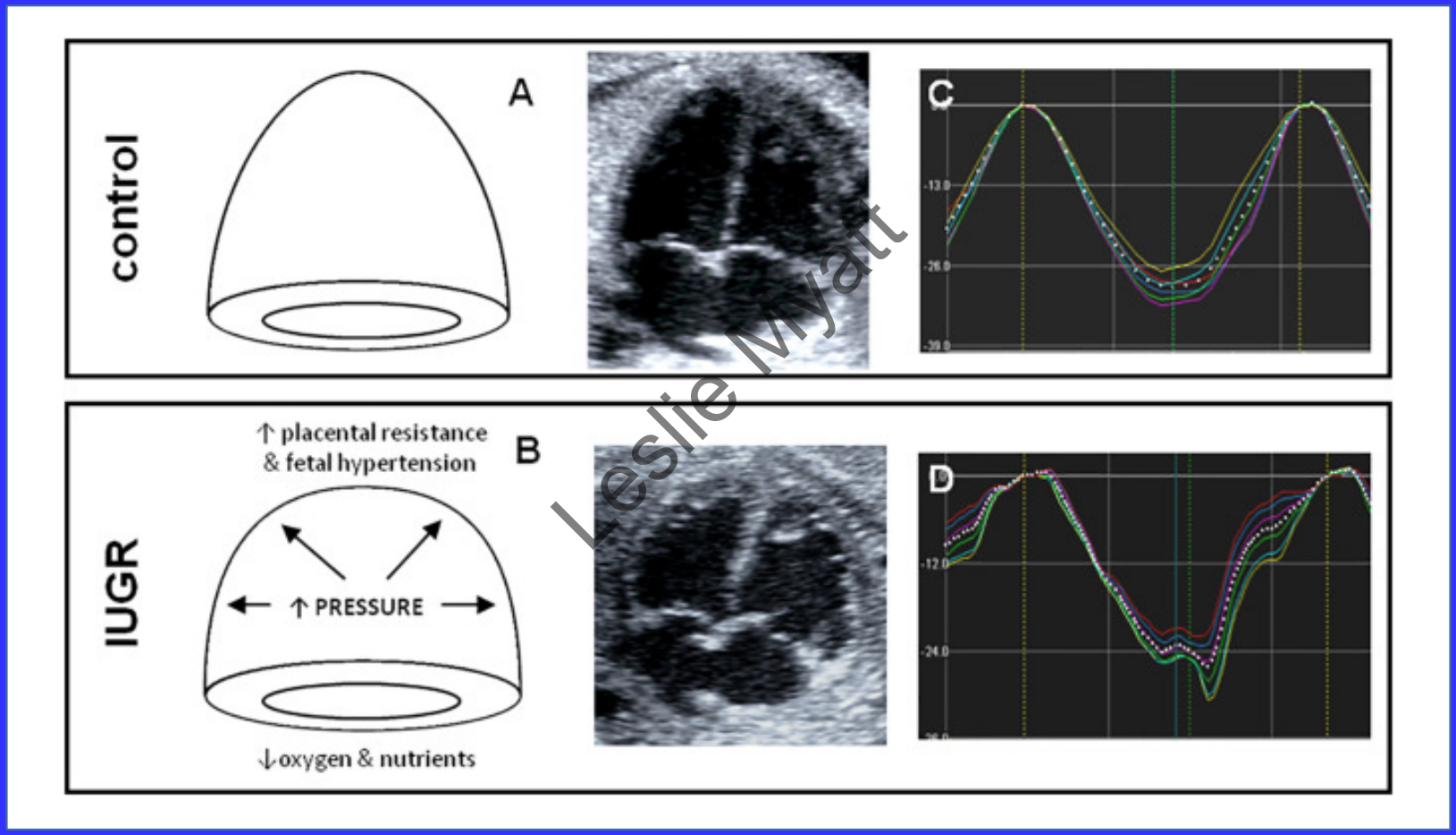


Kingdom et al 2000



Barut et al 2010

Cardiac Shape in Normal and IUGR Fetus



Crispi F et al 2018

Influence of Nutrition or the Metabolic Environment on Epigenetic Modifications

- Epigenetics – heritable changes in gene expression (active/inactive) that do not involve changes in DNA sequence but changes in physical structure (methylation/demethylation)
- Epigenome responds to changes in nutrients including methyl donors, folate supplementation, fat, glucose and caloric restriction
- Differences in DNA methylation reported in individuals exposed to the Dutch Hunger Winter
- Variations in DNA methylation associated with many aspects of diabetes mellitus and metabolic/inflammatory milieu of obesity

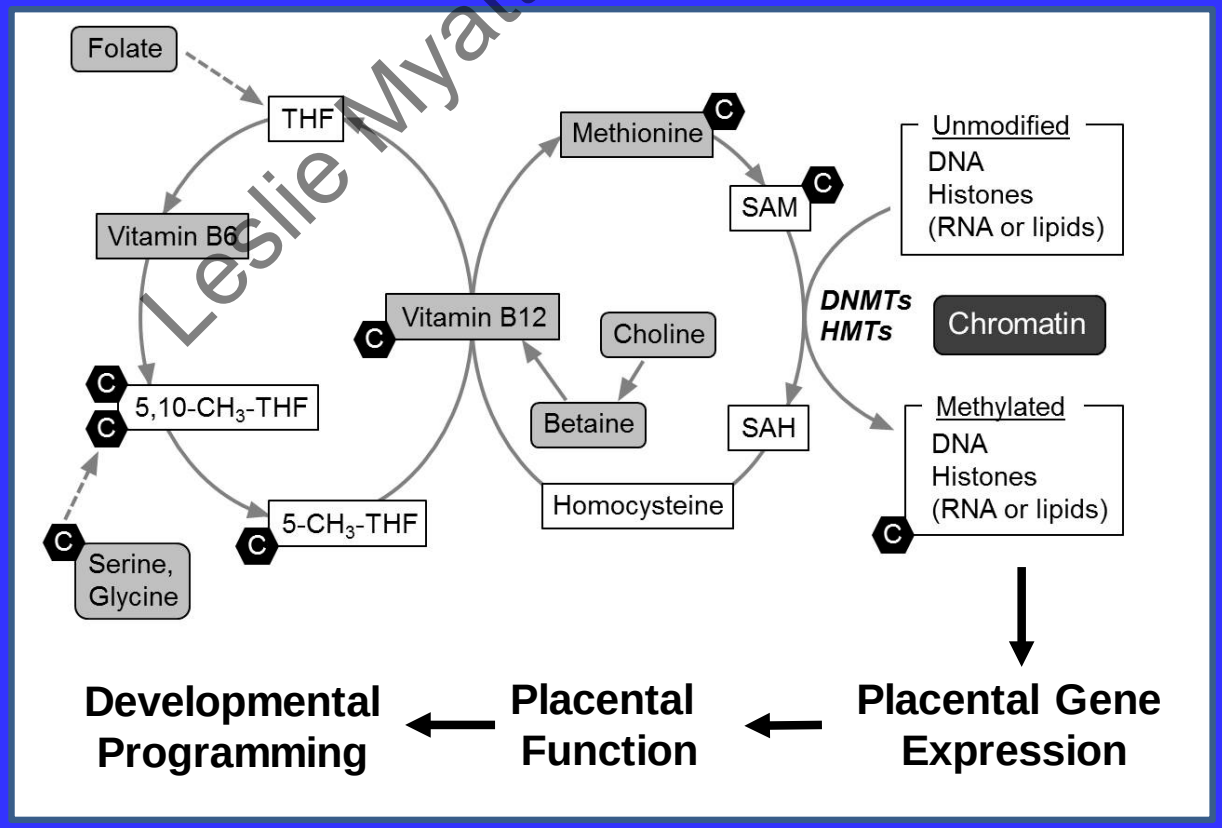
Micronutrients with a Role in the Placenta

- One carbon metabolism regulated by folic acid, choline, vitamin B12, and ω-3 fatty acids, results in biosynthesis of lipids, nucleotides, proteins, maintenance of redox status and methylation
- Transfer of zinc, iron, copper, calcium, selenium and Vitamins A, D and E may have a role in programming
- Micronutrient deficiency affects placental function,
  - see upregulation of transporters to maintain fetal supply and demand against concentration gradient e.g. Vit B6, B12, C, folate, iron, zinc
- Maternal iron restriction affects placental structure in rats, Zn deficiency can reduce trophoblast differentiation, placental weight and change protein expression
- Antioxidants, Zinc - Cu/ZnSOD, selenium – selenoproteins GPx, TrxR

Nutrients that affect Epigenetic Modification

Folate
Vitamin B12
Methionine
Choline
Betaine
Biotin
Niacin
Pantothenic acid
Resveratrol
Butyrate
Curcumin

Genestein
Polyphenols
Tea catechin



Maternal Metabolic Milieu with Obesity and GDM

- Insulin resistance
- Maternal hyperglycemia, hyperlipidemia
- Inflammation
- Oxidative stress
- Associated with adverse outcomes including stillbirth
- Both program the offspring for disease in later life
- Sexually dimorphic responses
- Increasing maternal adiposity associated with decreased placental mitochondrial respiration and further exacerbated with gestational diabetes.

  (Mele et al 2014, Muralimanoharan et al 2016)

Oxidative Stress In Pregnancy

- Antioxidants protect cells from oxidative stress which causes cellular damage of DNA, lipids and protein
- Normal pregnancy is a state of increased oxidative stress which is increased further in pathologic pregnancies e.g. PE, GDM
- The placenta is a source of oxidative stress due to its high metabolic activity with mitochondria being a major source
- The inflammatory conditions of obesity and gestational diabetes heighten oxidative stress and deplete antioxidant defenses often in a sexually dimorphic manner (Evans and Myatt 2017)
- Nutritional and supplemental sources of antioxidants
  - Vitamin C, Vitamin E, Resveratrol, N acetylcysteine (NAC), Omega 3 fatty acids, vegetables, selenium, zinc
-

Effect of Obesity on Placental DNA Methylation

Methylated regions identified by NimbleGen 2.1 M arrays (NimbleScan)

Number of methylated regions (peak score>3)	5mC	
	Normal	Obese
All tiled regions	12, 319	14,233
TSS1500 (1500 bp upstream to 500 bp downstream of TSS)	3,187	3,844
TSS100 (100 bp upstream - 100 bp downstream of TSS)	1,459	1,676
CpG islands	3,294	3,375
CpG island shores (2 kb flanking CpG islands)	3,127	3,774
CpG island shelves (2kb flanking shores)	1,502	1,764
Gene body	8,560	9,607
microRNA (-15 kb to +1 kb)	429	492

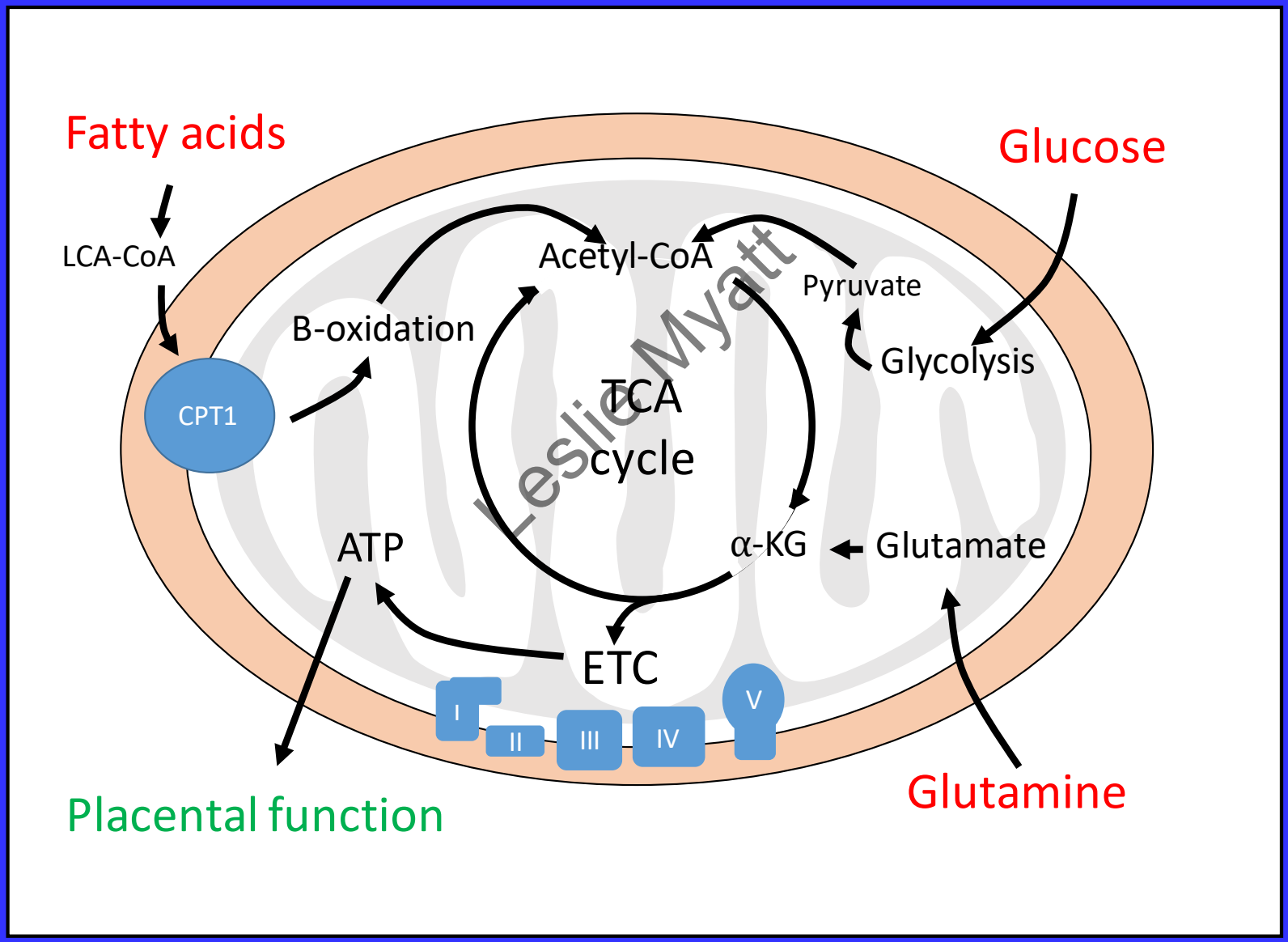
Mitsuya et al 2017

Genes showing significant differences in methylation in the region -100 to +100bp from TSS

Symbol	Locus	Gene
methylated in obese placentas (18 genes)		
MIA	19q13	Melanoma inhibitory activity
PSG1	19q13	Pregnancy specific glycoprotein
PSG4	19q13	
PSG5	19q13	
PSG8	19q13	
ABCG5	2p21	ATP-binding cassette, sub-family G
ABCG8	2p21	
BEST4	1p32	Bestrophin 4
HSPB3	5q11	Heat shock 27kDa protein 3
CSH2	17q22	Chorionic somatomammotropin hormone (placental lactogen)
CSH1	17q22	
GH1	17q22	Growth hormone 1
TET3	2p13	TET methylcytosine dioxygenase 3
ADAM6	14q32	ADAM metallopeptidase domain 6
ZFP92	Xq23	Zinc finger protein 92 homolog
NR1I3	1q23	Nuclear receptor subfamily 1
SEC16B	1q25	SEC16 homolog B (S. cerevisiae)
IL19	1q32	Interleukin 19
methylated in normal placentas (3 genes)		
CMTM1	16q22	CKLF-like MARVEL transmembrane domain containing
CMTM2	16q22	
SERPINB13	18q21	Serpin peptidase inhibitor

placental development (6)
cellular invasion (2)
cancer metastasis (2)
vascular remodeling (4)
increased BMI (1)
lipid transport (2)
energy metabolism (1)
immune and/or inflammatory responses (7)

Placental Fuel Substrates

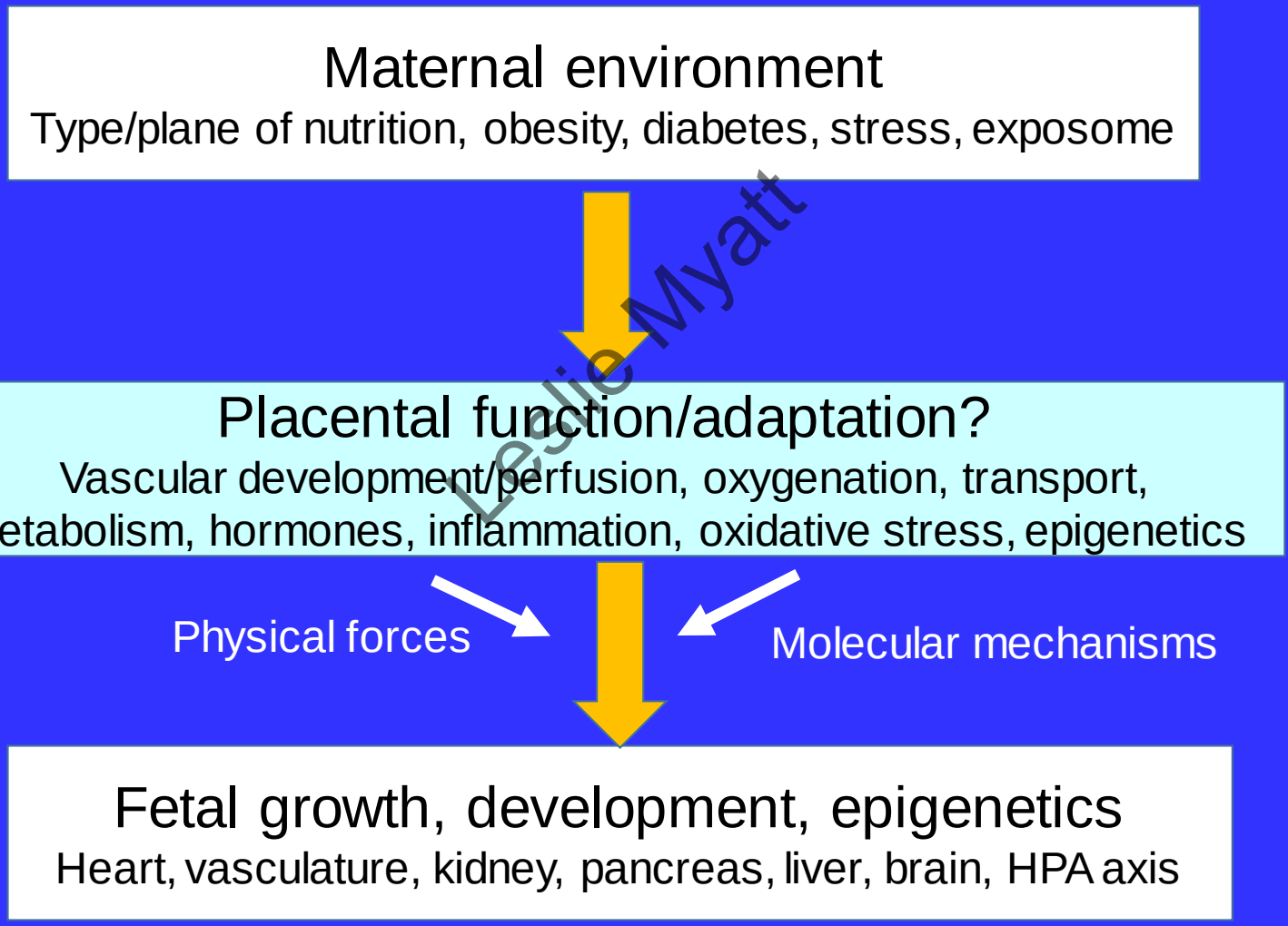


Effect of Obesity and GDM on Fuel Usage by Trophoblast

- In lean women there was no difference in dependency on or flexibility for these three fuels for baseline respiration between male and female trophoblast.
- With obesity and A2GDM (hyperglycemia and hyperlipidemia) we find increased dependency on glucose and fatty acids for baseline respiration but only in male placenta.
  - Accompanied by significantly decreased flexibility for both glucose and fatty acids, but also glutamine, i.e. male trophoblast cannot easily switch between fuels.
- Changes in placental metabolism may affect amount of each substrate available for transfer to fetus and hence fetal growth and development
- Is this related to the increased risk for adverse outcomes in males?

Wang et al JCEM 2019

Role of the placenta in fetal programming



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