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VIETNAM - FRANCE - ASIA - PACIFIC
CONFERENCE ON OBSTETRICS AND GYNECOLOGY
Ho Chi Minh City, May 19th - 20th, 2016

16th

THERE IS A GENDER OF THE PLACENTA?

G.C. Di Renzo, MD, PhD, FACOG, FRCOG, FICOG
University of Perugia , Italy

PREMISES

Gender aspects and ethnicity

Sex ratio (male vs female) at birth is on average 1.06

Asian or Pacific Island newborns, as a group, had the highest male/female ratio (1.06). The gender ratio for Hispanic newborns (1.04) was intermediate between non-Hispanic white newborns (1.05) and non-Hispanic black newborns (1.03). American Indian newborns had the lowest gender ratio (1.028). European studies reported a male/female ratio of approximately 1.05.

Lancet 1997

Sex ratio related to the lenght of pregnancy

An extremely high sex ratio (male to female) was found in fetuses born after very short duration (16-19 weeks): 248:100. This ratio fell very steeply to 130:100 around the 20th week, remained almost at this level among premature births up to the 36th week, and stabilized at term around equity: 100:100.

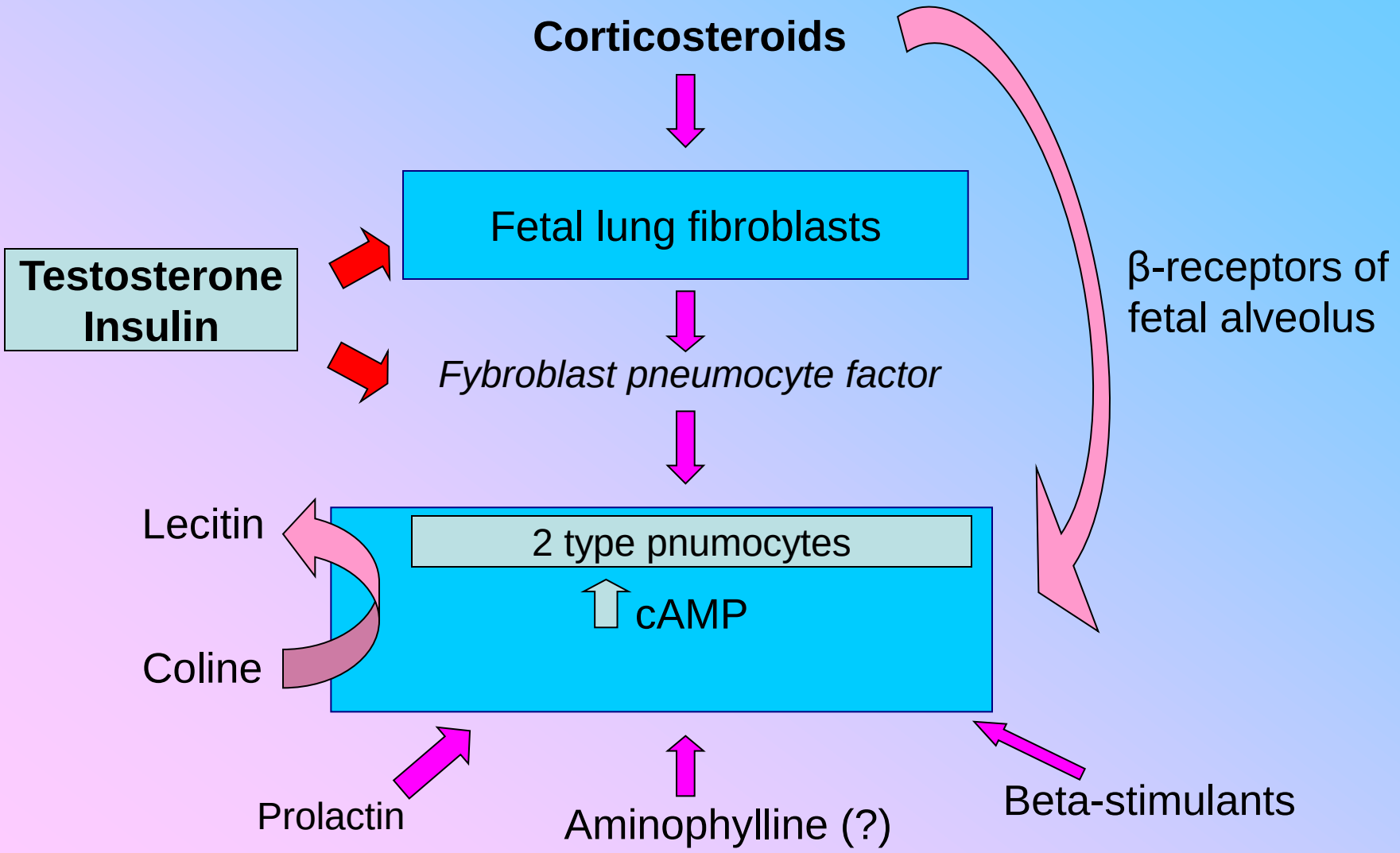
Jongbloet , Am J Obstet Gynecol 2005

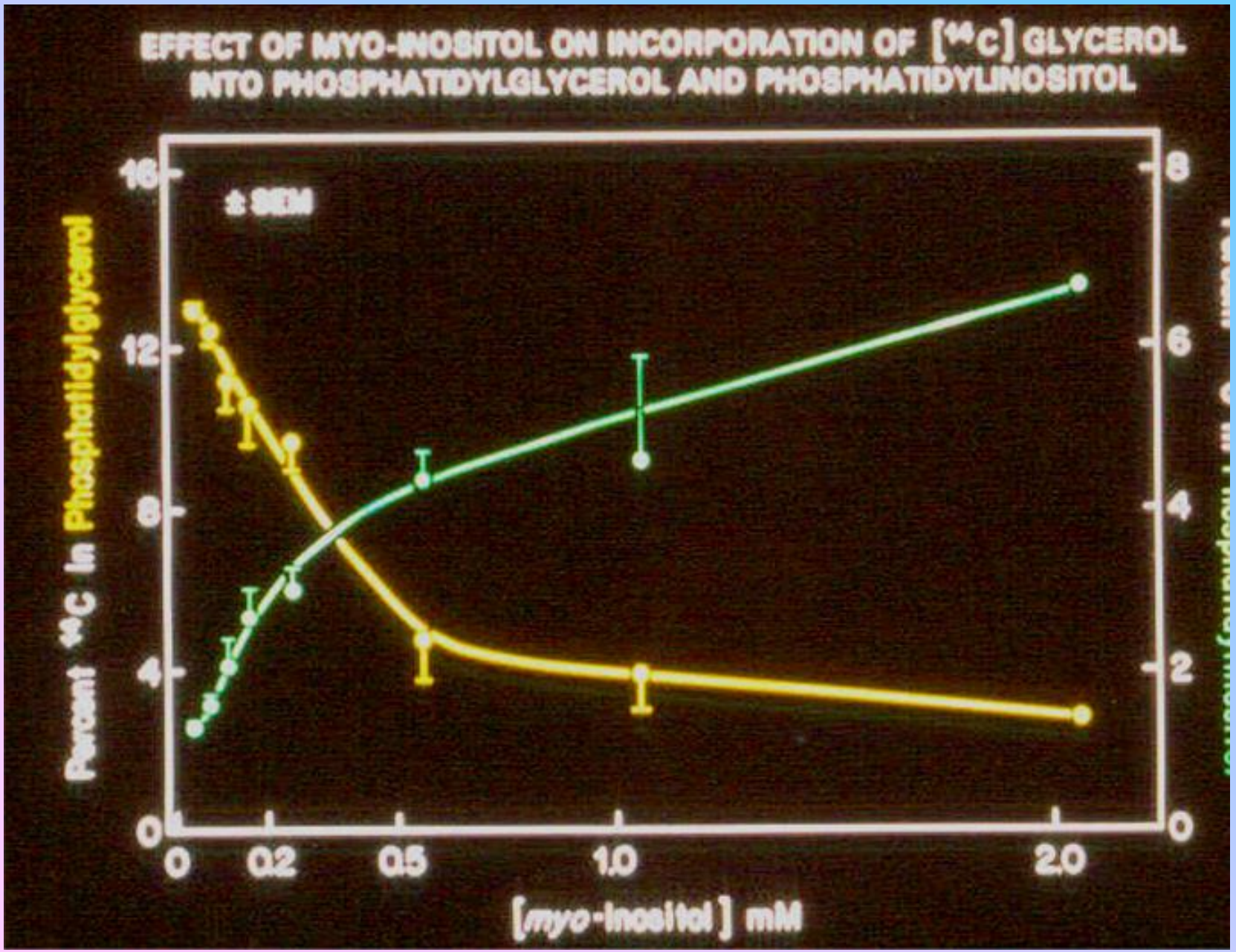
Gender aspects of preterm birth

National figures from Sweden show that boys are more likely to be delivered prematurely, accounting for 55-60% of all newborns between 23 and 32 gestational weeks. Neonatal deaths in these gestational weeks are also more common among boys. In 1993, the overall 1-year mortality rate (including all gestational weeks) in Sweden was 5.4% for boys and 4.1% for girls. The difference in infant mortality (within 1 year) is most pronounced at extremely early birth (23-24 gestational weeks) being 62% for boys compared with 38% for girls.

BJOG 2003

CORTICOSTEROIDS & RDS: MECHANISMS OF ACTION




EFFECT OF MYO-INOSITOL ON INCORPORATION OF [14C] GLYCEROL INTO PHOSPHATIDYLGLYCEROL AND PHOSPHATIDYLINOSITOL
± SEM
Percent 14C In Phosphatidylglycerol
16
12
8
4
0
8
6
4
2
0
0
0.2
0.5
1.0
2.0
[myo-Inositol] mM

Multiple logistic regression analysis to assess the independent effects of gestational age, gender, and IUGR on mortality rate, bronchopulmonary dysplasia, and intraventricular hemorrhage revealed that gestational age was the most significant contributor to all three outcome variables; IUGR contributed to an increased mortality rate, and male gender contributed to the occurrence of bronchopulmonary dysplasia.

Chen et al., J Pediatr. 1993

Differences of perinatal outcome according to fetal gender (% on 12,000 deliveries, Perugia University Hospital)

	Male (%)	Female (%)	*p*<
Gestational diabetes	5.0	2.8	0.01
Preeclampsia	3.8	2.0	0.05
IUGR	3.0	4.0	0.05
Preterm birth (<32 wks)	**1.7**	**0.9**	**0.05**
Neon compos morbid	35.6	25.2	0.01
Malformations (excluded chromosomal)	0.7	0.4	0.05
IUFD	0.4	0.3	>0.05

GENDER DIFFERENCES AND PREGNANCY OUTCOME

- Gender specific differences in fetal growth and fetal and neonatal morbidity and mortality.
- Greater mortality of males than females in both the number of stillbirths and neonatal deaths.
- Different birthweight range of males and females: males generally larger than females and females more likely to be growth reduced.
- Different gender ratio: more males were delivered than females rather than an expected 1:1 ratio.
- Significant effects of fetal gender on pregnancy outcome and the development of pregnancy-related complications:
  - preterm birth,
  - premature preterm rupture of membranes,
  - gestational diabetes mellitus,
  - fetal macrosomia,
  - failure to progress during the first and second stages of labor,
  - cord prolapse,
  - nuchal cord and true umbilical cord knots,
  - frequent Cesarean section among male neonates.

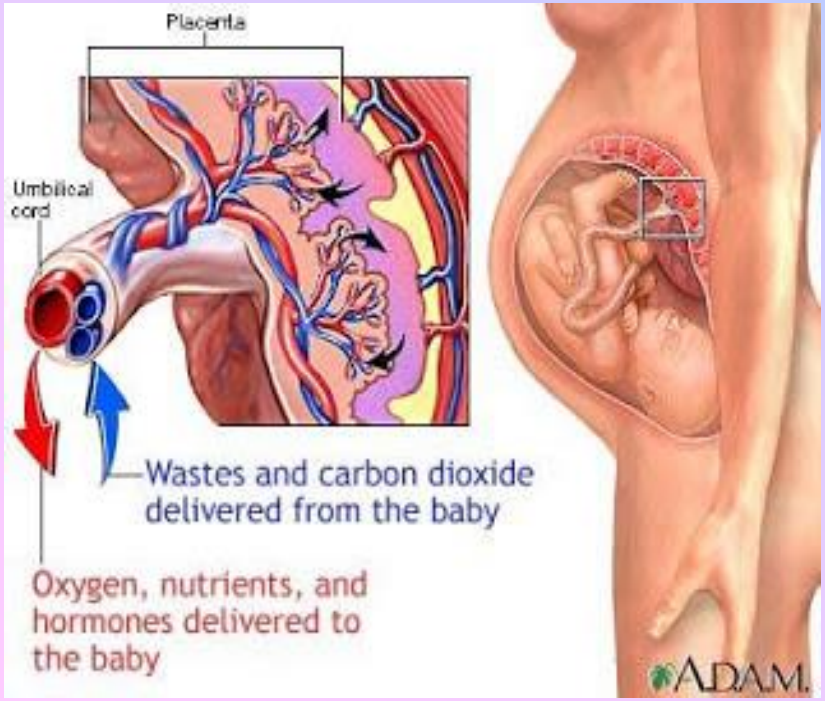
Vatten 2004; Di Renzo 2007; Engel 2008; Papageorgiou 1981; Stevenson 2000; Clifton 2010

GENDER DIFFERENCES AND DEVELOPMENTAL ORIGINS OF ADULT DISEASES (DOHaD)

- **Differential sex-dependent pattern of placental pathology** amongst high-risk pregnancies with severe placental dysfunction, defined by delivery before 33 weeks' of gestation.
- More **velamentous umbilical cord insertions and chronic deciduitis** in males, while higher rate of villous infarction in females.
- Association of male born from complicated pregnancies with:
  - adult hypertension
  - unfavorable lipid profiles as young adults
  - higher death rate of ischemic heart disease
  - increased risk of stroke
  - higher incidence of coronary heart disease
  - subclinical atherosclerosis
  - myocardial infarction

PLACENTA IN FETAL AND MATERNAL PHYSIOPATHOLOGY

- Although several factors contribute to the risk of adult cardiovascular disease, including smoking and elevated body mass index, many epidemiologic studies suggest that there are "fetal origin" that predispose adults to these disorders.
- Furthermore, several pregnancies disorders are associated with placental pathology.

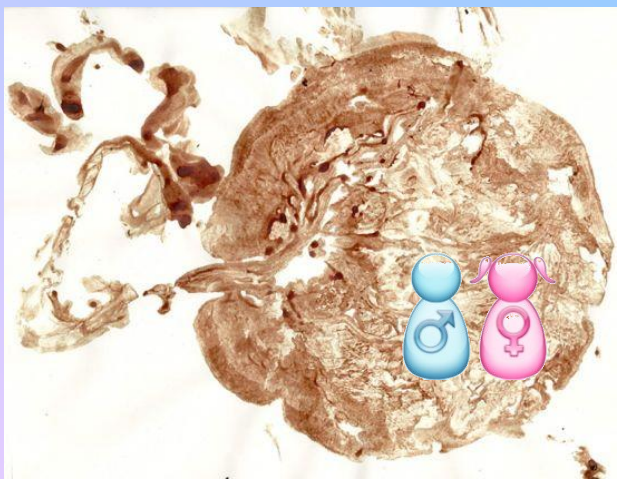


- The placenta is a temporary organ that performs the functions of several adult organs for the growing fetus.
- The placenta is designed for exchange of oxygen, nutrients, antibodies, hormones and waste products between the mother and fetus and may carry valuable information about the pregnancy.
- The investigation of placenta may provide valuable insights into placental functions and help identify molecular mechanisms that have both immediate and long lasting effects on health of the fetus.

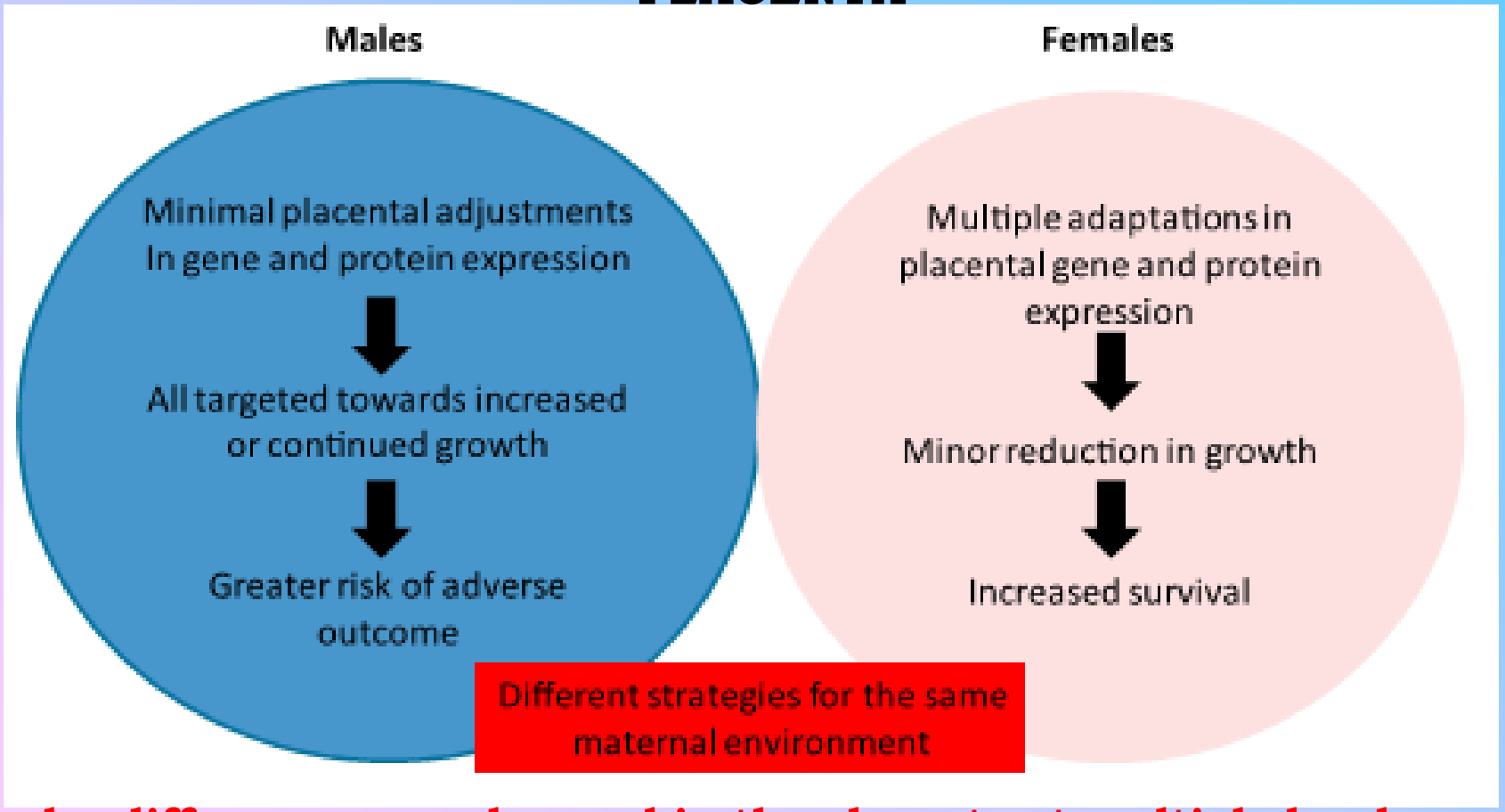
THE ROLE OF PLACENTA

- The placenta has traditionally been considered **an asexual organ** and therefore, many studies focusing on the placenta have not taken the sex of the embryo into account.
- But given it s extraembryonic in origin, the placenta **has a sex**: that of the embryo it belongs to and numerous developmental origins of adult diseases (DOHaD) studies indicate that sex differences can originate early in development and in particular in the placenta.
- There is an effect of sex chromosome « dosage » on placental size in mice, with XY placentas being **significantly larger** than XX placentas and that such differences are **independent of androgen** effects.

Although the possession of one X chromosome rather than two leads to an increase in placental size, the underlying mechanism is still to be determined.



MOLECULAR ASPECTS OF GENDER DIFFERENCES IN PLACENTA



Gender differences are observed in the placenta at multiple levels:

- gene expression
- protein expression
- epigenetic modification of DNA
- immune function
- SNPs

GENE EXPRESSION

- **Global gene changes in the human placenta have been analyzed**

- There are sex specific differences in placental gene expression not limited to just X and Y linked genes but also to autosomal genes related to immune pathways including JAK1, IL2RB, Clusterin, LTBP, CXCL1 and IL1RL1 and TNF receptors: these are expressed at higher levels in female than male placentae.
- The differences in **immune gene expression** may contribute to gender differences in the fetal **response to infection or inflammation.**
- There are significant individual differences in placental gene expression which exemplifies the diversity of the human population and suggests that each individual placenta may therefore exhibit a **unique molecular adaptation to the same maternal environment**.

Placenta expresses anti-Müllerian hormone and its receptor: Sex-related difference in fetal membranes

R. Novembri [a], L. Funghi [a], C. Voltolini [a], G. Belmonte [b], S. Vannuccini [a], M. Torricelli [a], F. Petraglia [a, *]

[a] Obstetrics and Gynecology, Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy
[b] Department of Biomedical Sciences, Applied Biology, University of Siena, Siena, Italy

Placenta. 2015 Jul;36(7):731-7

Highlights:
- Term placenta and fetal membranes express AMH and AMHRII mRNA and peptide.
- Semi-quantitation of IHC shows a more intensive staining in male fetal membranes.
- In placental tissues were not differences between male and female sex.
- Immunofluorescence showed an intense co-localization of AMH and AMHRII.

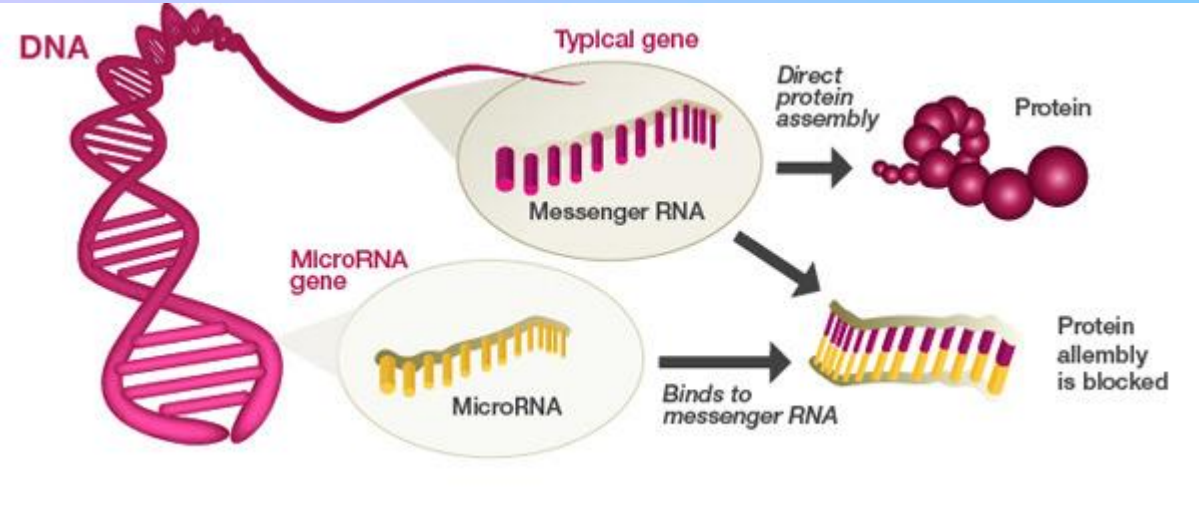
The Human Placental Sexome Differs between Trophoblast Epithelium and Villous Vessel Endothelium

Silvija Cvitic[1], Mark S. Longtine[2], Hubert Hackl[3], Karin Wagner[4], Michael D. Nelson[2], Gernot Desoye[1], Ursula Hiden[1]*

The key findings of our study are: (i) all four cell types analyzed *in vitro* varied in the extent of sex-biased gene expression, despite the fact that these cells originate from the same organ; (ii) transcripts of male fetuses prevailed in the epithelial compartment, represented by cytotrophoblasts and syncytiotrophoblasts, whereas the endothelial compartment, represented by arterial and venous endothelial cells, showed more female-biased genes; (iii) sex-biased genes in both the epithelial and endothelial compartments clustered with groups of genes linked to distinct biological functions and molecular pathways.

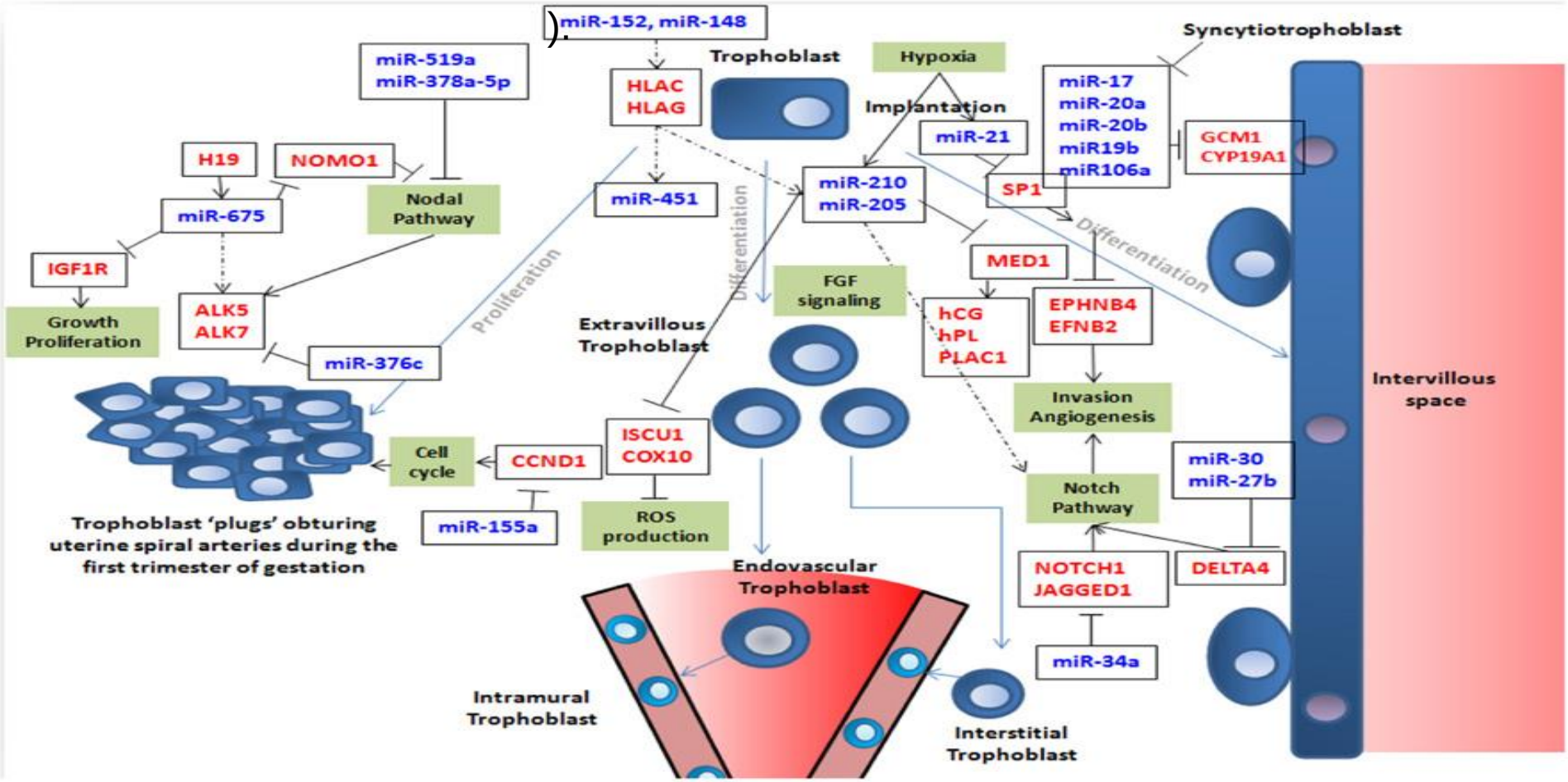
MiRs EXPRESSION

- MicroRNAs (MiRs), a class of small non-coding RNAs involved in posttranscriptional regulation of protein coding mRNA, may play a role in regulating sex specific gene expression.



- A PubMed search for the keywords “MiRs” and “trophoblast” or “placenta,” yielded 137 results, the first paper having been published in 2006.
- One seminal study that set the *de novo* landscape of miRNA-regulation in cells of the trophoblast lineage, was published in 2012 by Morales-Prieto et al. (2012). Authors screened 762 human miRNAs for their expression level in term and first trimester cytotrophoblasts.

MiRs EXPRESSION



Identification of clusters of placenta-specific miRNAs: C19MC, 54 miRNAs on chr 19, C14MC, 34 miRNAs on chr 14, and another minor cluster on chr 19

MiRs EXPRESSION

Preliminary data of Osei-Kumah at the International Federation Placental Association in Adelaide (2009) report female placentae of normal pregnancies have different mIR expression relative to male placentae.

There are now some published papers examining gender specific differences in placental MiRs

- **Effect of preeclampsia on placental function: influence of sexual dimorphism, microRNA's and mitochondria.**
Myatt L[1], Muralimanoharan S, Maloyan A.
Adv Exp Med Biol. 2014;814:133-46

- Sexual dimorphism in miR-210 expression and mitochondrial dysfunction in the **placenta** with maternal obesity.
Muralimanoharan S, Guo C, Myatt L, Maloyan A.
Int J Obes (Lond). 2015 Aug;39(8):1274-81.

Osei-Kumah A, Hodyl N, Kong W-C, Owens J, Clifton VL. Sex specific differences in human placental microRNA expression. Placenta 2009.

MiRs EXPRESSION

There are presently no published papers examining gender specific differences in placental MiRs but preliminary data report female placentae of normal pregnancies have **different mIR expression** relative to male placentae.

Osei-Kumah et al Placenta 2009.

EPIGENETIC MODIFICATION OF DNA

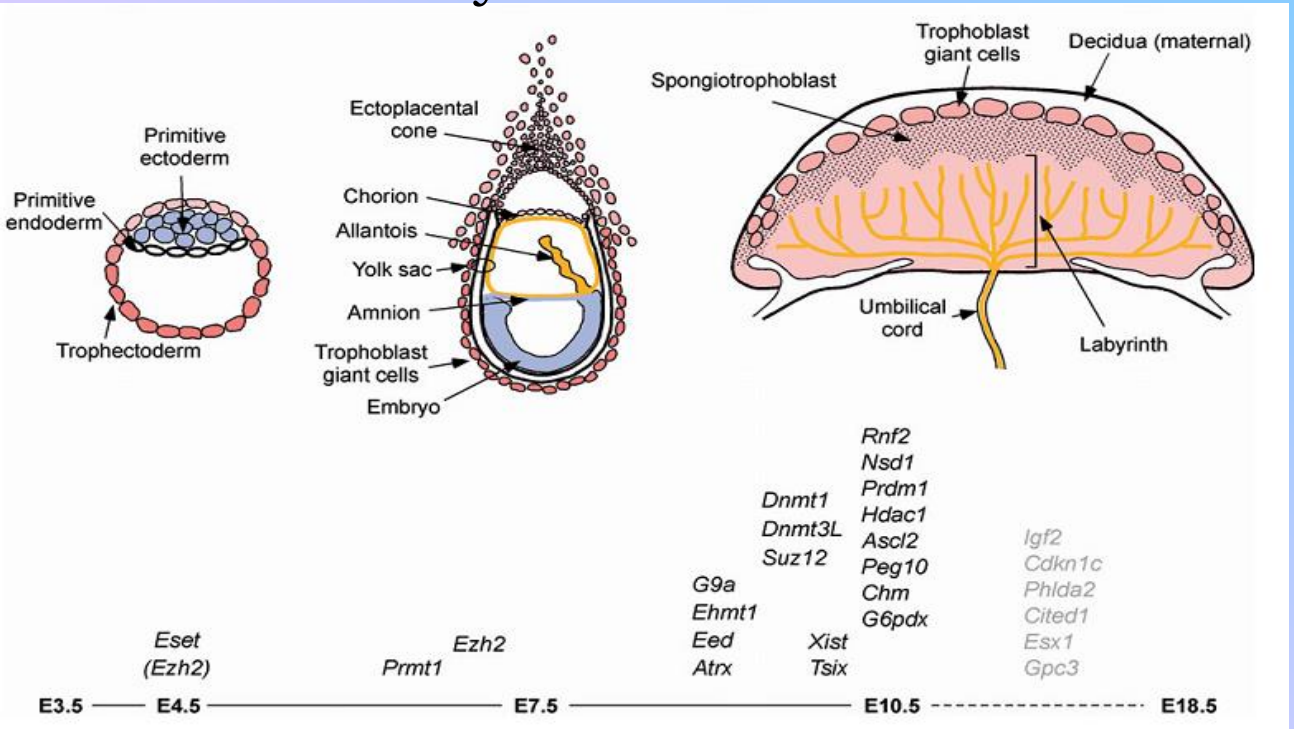
- Epigenetic changes are modifications of DNA which occur without any alteration in the underlying DNA sequence and can control whether a gene is turned on or off and how much of a particular message is made.
- Every cell in our body has the same DNA sequence but different genes are turned on or off to make our different tissues, such as muscle or liver.
- As a gateway to the fetus the placenta is affected by numerous environmental factors including **nutrient status and tissue oxygenation, which may modify epigenetic marks and gene expression within the placenta** and therefore placental development and function.
- The resulting changes in epigenetic marks may alter cell fate decisions, the ensuing growth and development of tissues and organs, and subsequently be responsible for inadequate responses to later challenges such as an **hyperglicemic environment in a sex- specific manner.**

EPIGENETIC MODIFICATION OF DNA

- The sex of the placenta and the environment have an influence on its epigenomes, and hence on the epigenomes of the developing fetus. In all adult tissues examined to date, including the gonads and brain, the expression of many genes is modulated in a sex-specific manner.
- Chromatin structure and epigenetic marks differ between male and female samples in brain and liver.
- However, even with recent developments in this field, we still know little about the mechanisms underlying the early sex-specific expression of genes and gene networks resulting from epigenetic regulation in the placenta.
- Most DOHaD studies have reported sex-specific transmission and/or effects, but very few have tackled the sex-specific epigenetic mechanisms involved, and especially in the placenta.
- DNA methylation profiling highlights the unique nature of the human placental epigenome for genomic imprinting and placenta-specific gene-associated methylation. **Placental cell types have a pattern of genome methylation that is significantly different from that in somatic tissues, with low methylation at some, but not all, repetitive elements.**

EPIGENETIC MODIFICATION OF DNA

In mouse placenta, global DNA methylation is also **sexually dimorphic** in animals fed the control diet, with **lower methylation levels in the placentas of male offspring than in those of female offspring** . Under high fat diet, hypomethylation was observed only in the female placenta. Consistent with this observation, expression of the gene encoding the **DNA methyl-transferase cofactor Dnmt3l was downregulated in females** only.



Given the importance of genomic imprinting in the placenta, this observation provides new clues for further investigations of **sexual dimorphism in the placenta.**

Gabory *et al. Biology of Sex Differences* 2013, **4**:5
http://www.bsd-journal.com/content/4/1/5

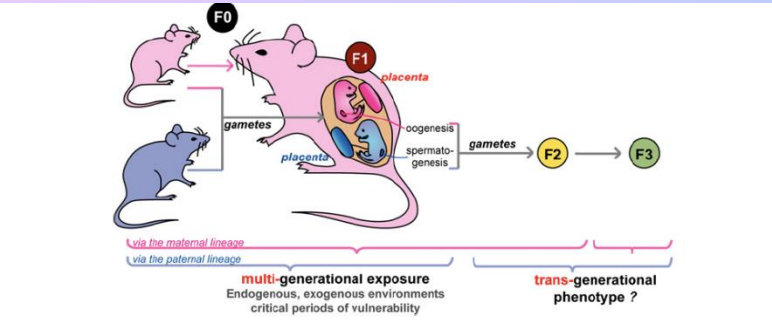
BIOLOGY OF SEX DIFFERENCES

REVIEW Open Access

Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics

Anne Gabory[1], Tessa J Roseboom[2,3], Tom Moore[4], Lorna G Moore[5] and Claudine Junien[1,6*]

Sex-specific outcomes of the effects of placental growth on fetal programming



This figure shows how such influences to subsequent generation(s), and illustrate the central role of the placenta on the sex specificity of these parent-of-origin effects.

It is important to know the role played by the placenta and the possible maternal and or paternal epigenetic imprints carried by the gametes forming the zygote.

- Female and male placentas have different optimal transcriptomes that may affect fetal growth and later disease susceptibility or health trajectory;
- Differences in how male and female placentas cope with stressful conditions indicate that this tissue should also be taken into account if we want to understand how it contributes to sexual dimorphism later in life.
- Finally, unravelling the epigenetic marks and mechanisms underlying these sex differences in physiological trajectories and in response to environmental changes represents a major health challange.

IMMUNE FUNCTION

- Sex differences of the fetal-placental immune system have been investigated in relation to preterm delivery.
- Histological examination of placentae of males delivered less that 32 weeks gestation had **more severe lesions of chronic inflammation** than placentae from matched females.
- The sites of chronic inflammation were **areas of interaction between interstitial trophoblast and maternal decidua** rather than within placental villi or membranes suggesting the maternal immune system induces an inflammatory response in the placenta via the decidua.

Acta Obstet Gynecol Scand 2005: 84: 547–550
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Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL ARTICLE

Histologic placental lesions in women with recurrent preterm delivery

ALESSANDRO GHIDINI AND CAROLYN M. SALAFIA

IMMUNE FUNCTION

- Male neonates were more likely to have an infected placenta then female neonates with greater decidual lymphoplasmacytic cell infiltration.
- Male placentae have higher toll-like receptor-4 (TLR-4) expression and a more enhanced endotoxin induced tumor necrosis factor (TNF)-a response relative to placentae from females.
- There is a greater population of placental macrophages in males relative to females of normal pregnancies: the enhanced TNF- a response may be derived from **a sex difference in immune cell populations.**

Sex difference in cytokine production may contribute to the increased incidence of preterm delivery in males.

IMMUNE FUNCTION

- These data demonstrate that placental immune function is at least partially sex specific and suggests **the placenta responds to maternal inflammatory status in a sex specific manner**.
- These findings have implications for understanding the impact of maternal viral, bacterial and parasitic infections during pregnancy such as HIV, pneumonia and malaria on fetal growth and survival.
- It also has relevance to understanding the impact of maternal inflammatory states that can complicate pregnancy including obesity, rheumatoid arthritis, asthma and Crohn's disease. Preeclampsia has been identified as an inflammatory state and may also influence placental immune function in a sex specific manner.
- Since the placental immune system plays a role in regulating apoptosis, prostaglandin synthesis, vascular permeability and programming of the fetal immune system, it is possible that **all these mechanisms are sexually dimorphic.**

SNPs

- In recent years, numerous studies have focused the attention on the role of **genetic polymorphisms such as Single Nucleotide Polymorphisms (SNPs)** in influencing the development of disease or the response to pathogens, chemical agents or drugs.
- The human genome contains about 10 million SNPs, some of which are involved in immunoregulatory mechanisms (endocrine, metabolic and apoptotic), and some of these may also predispose to adverse pregnancy outcomes, such as preterm birth (PTB).
- Some SNPs of genes responsible for inflammation, such as polymorphisms in the genes for cytokines, have been widely studied: TNF-alfa nucleotide 308, interleukin-1ß (IL-1ß) nucleotides 3953 and 3954, and IL-6 nucleotide 174, highlighting their **involvement in predisposing to delivery before term.**

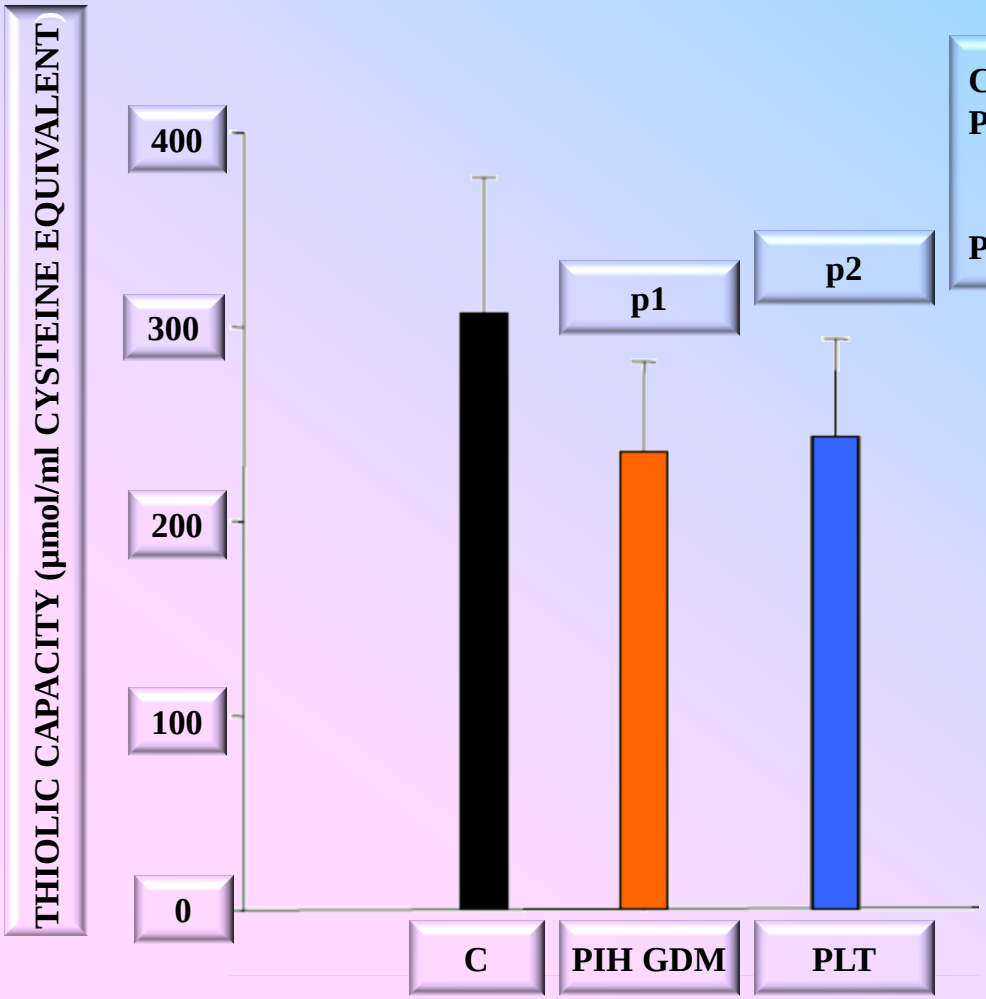
SNPs AND PRETERM BIRTH

- In addition to inflammation, oxidative stress and apoptotic process have been thought to play a key role in the induction of placental tissue degeneration, leading to the outbreak of childbirth.
- In pregnancy, both pre-term contractions when labour starts, and the imbalance between reactive oxygen species (ROS) and antioxidants may result in an **excessive oxidative stress that triggers trophoblast apoptosis.**
- The Mst3 (human counterpart of the protein serine / threonine kinase present in the yeast Ste20) is expressed in the human placenta and plays an important role in TB, mediating trophoblast apoptosis induced by oxidative stress and placental degeneration.
- The trophoblastic apoptosis mediated by Mst3 is induced by the activation of MAP kinase pathway including JNK (c-Jun N-terminal kinases) or Mapk8, in turn regulated by TNF alpha, which is a known regulator of MMP-9. This pathway has as final target the **Caspase 3, which is apparently the effector caspase of placental apoptosis during labor.**

TOTAL ANTIOXIDANT CAPACITY IN PREGNANCY AND IN CORD BLOOD

Alberti & Di Renzo *J Matern Fetal Neonatal Med*. 2002

TOTAL ANTIOXIDANT CAPACITY (TAC)

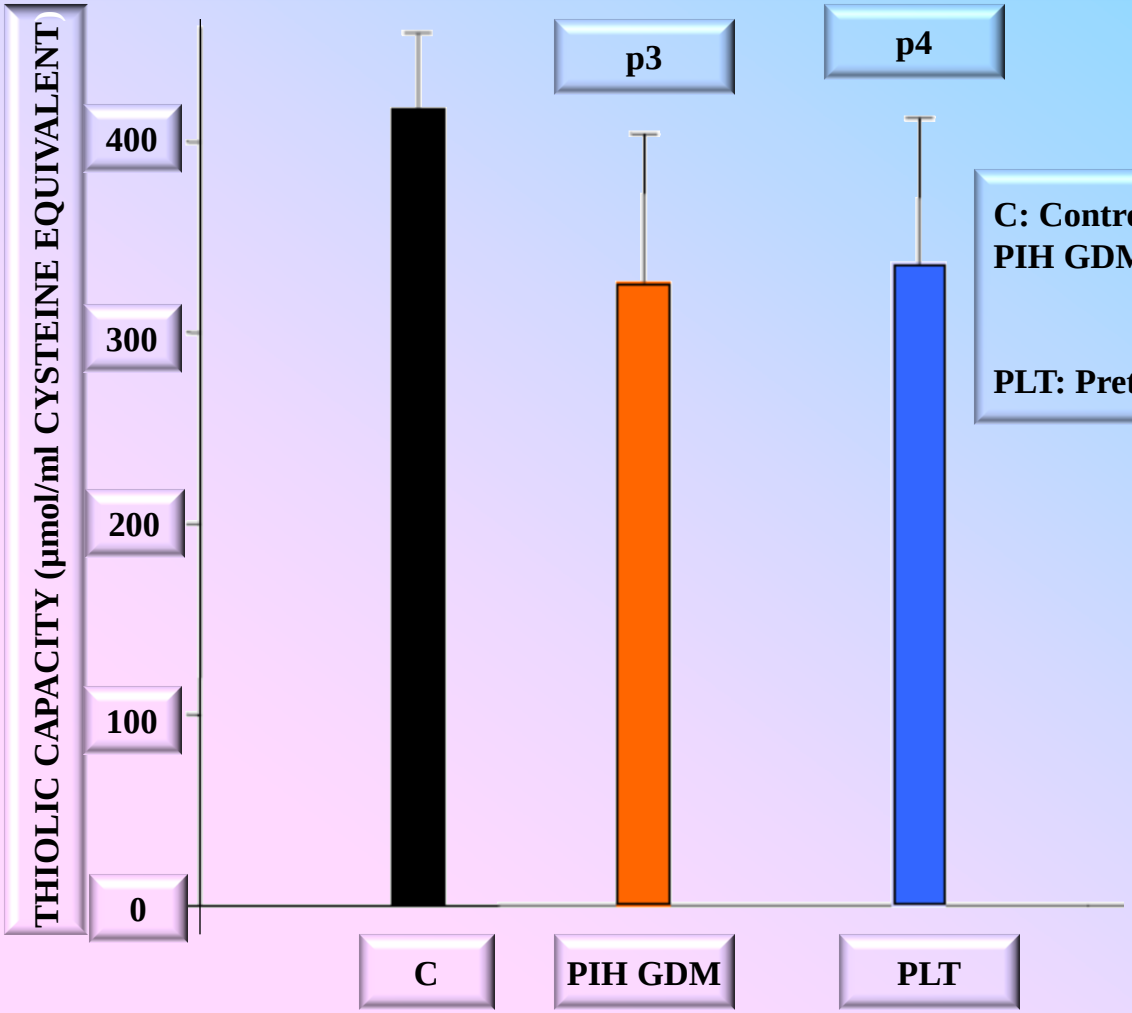


C: Control group
PIH GDM: Pregnancy Induced Hypertension (PIH) and Gestational Diabetes Mellitus (GDM) group
PLT: Preterm Labor Threat group

p1=0.0086 (p1<0.05) PIH GDM vs C
p2=0.0479 (p2<0.05) PLT vs C

Di Renzo et al, JOG 2011

THIOLIC CAPACITY (TC)

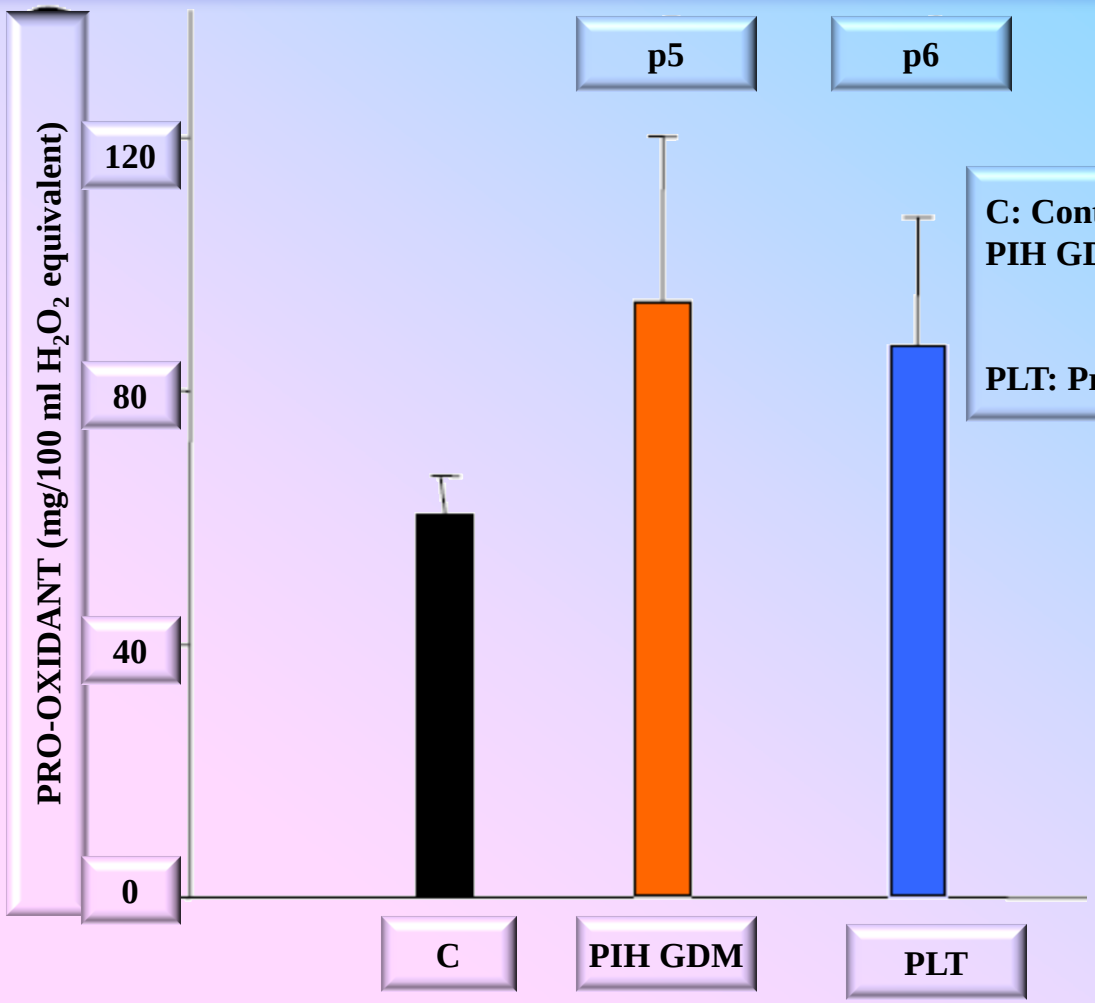


C: Control group
PIH GDM: Pregnancy Induced Hypertension (PIH) and Gestational Diabetes Mellitus (GDM) group
PLT: Preterm Labor Threat group

p3=0.0029 (p3<0.05) PIH GDM vs C
p4=0.0084 (p4<0.05) PLT vs C

Di Renzo et al, JOG 2011

PRO-OXIDANT CAPACITY (TC)

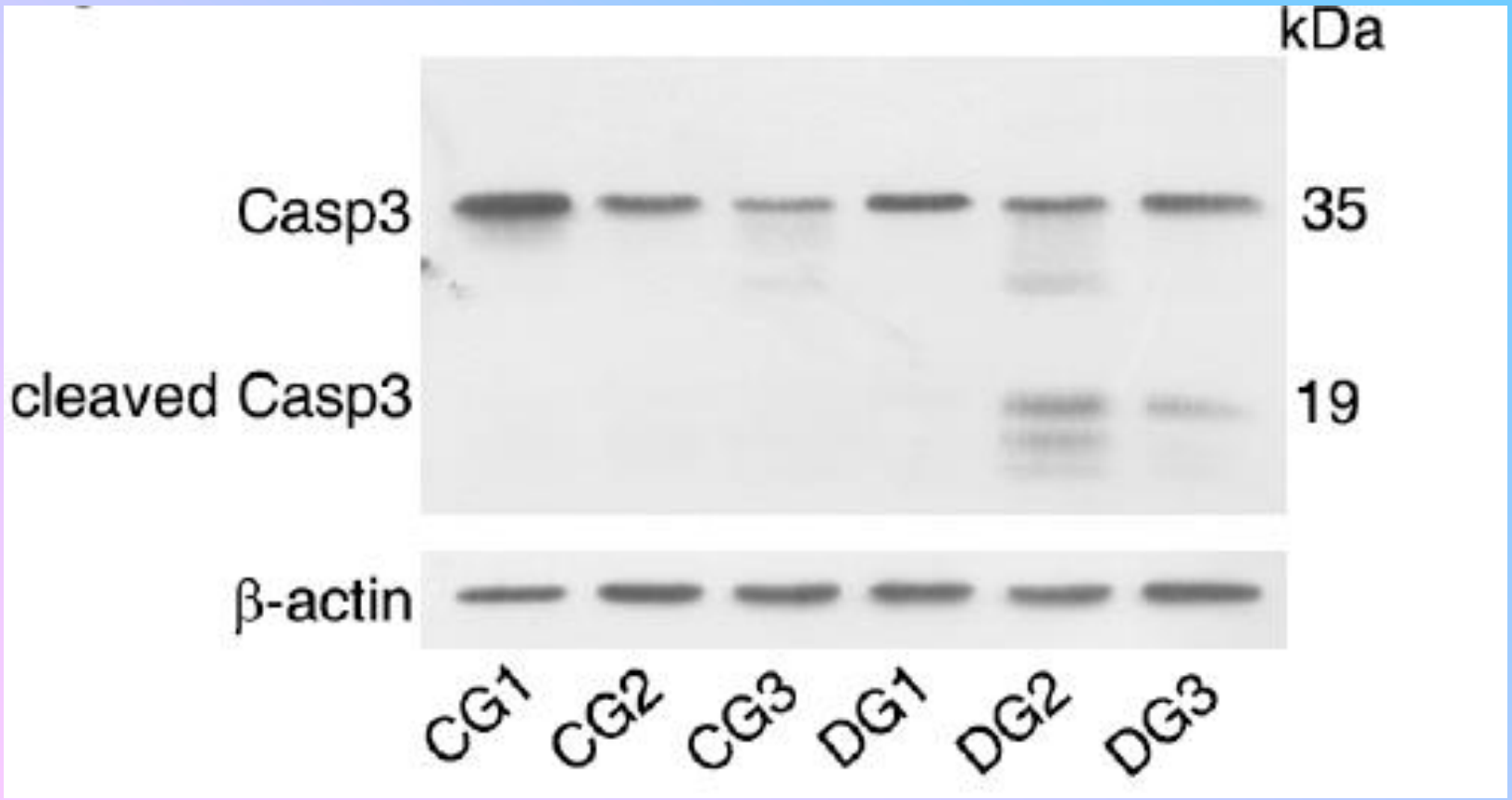


C: Control group
PIH GDM: Pregnancy Induced Hypertension (PIH) and Gestational Diabetes Mellitus (GDM) group
PLT: Preterm Labor Threat group

p5=0.00034 (p5<0.05) PIH GDM vs C
p6=0.00044 (p6<0.05) PLT vs C

Di Renzo et al, JOG 2011

ANALYSIS of Caspases 3



CG1,2,3 **CONTROLS**

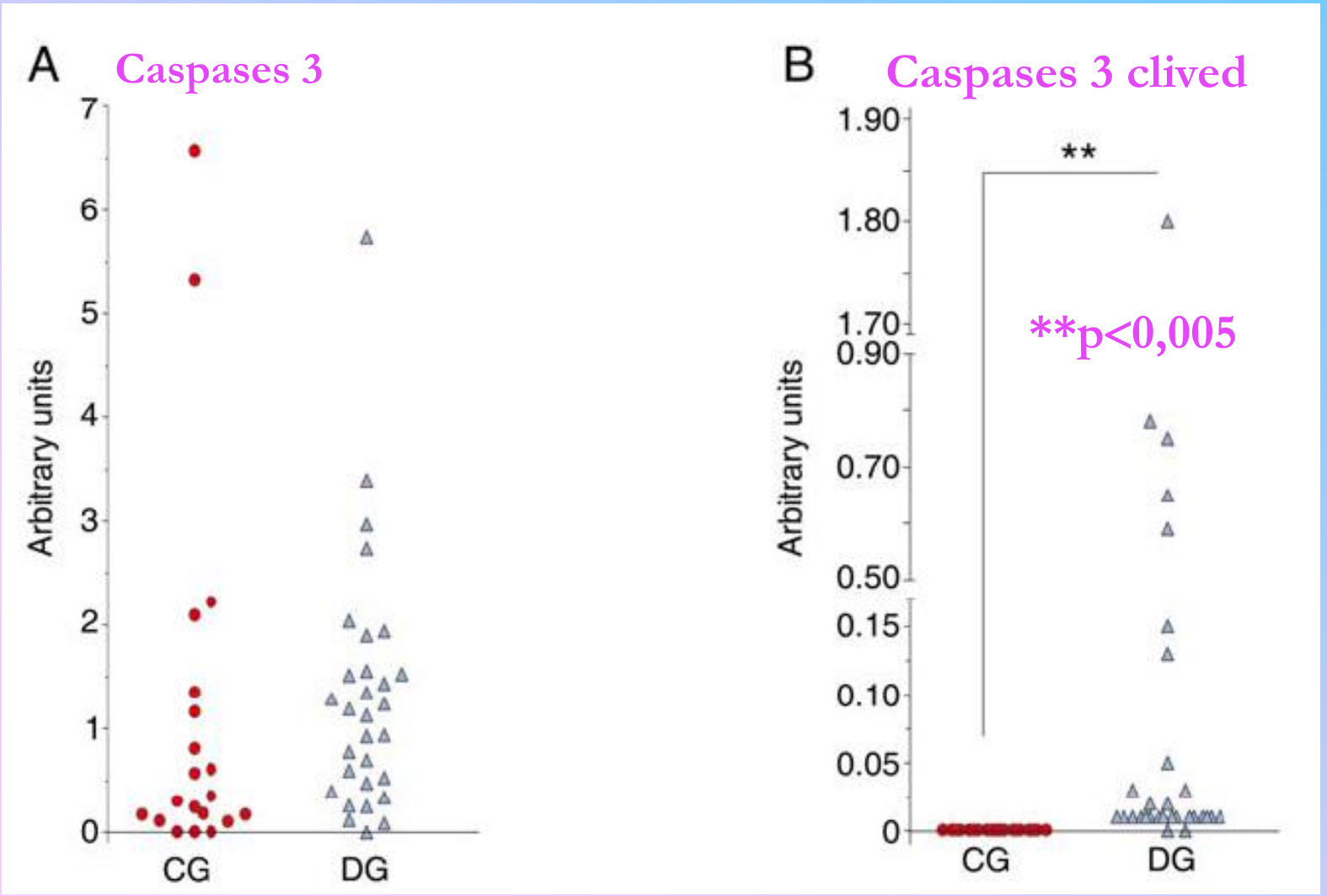
DG1,2,3 **DIABETIC PREGNANT PATIENTS**

Band 35kDa Caspasi 3

Band 19 kDa Caspasi 3 clived

β-actina **Control**

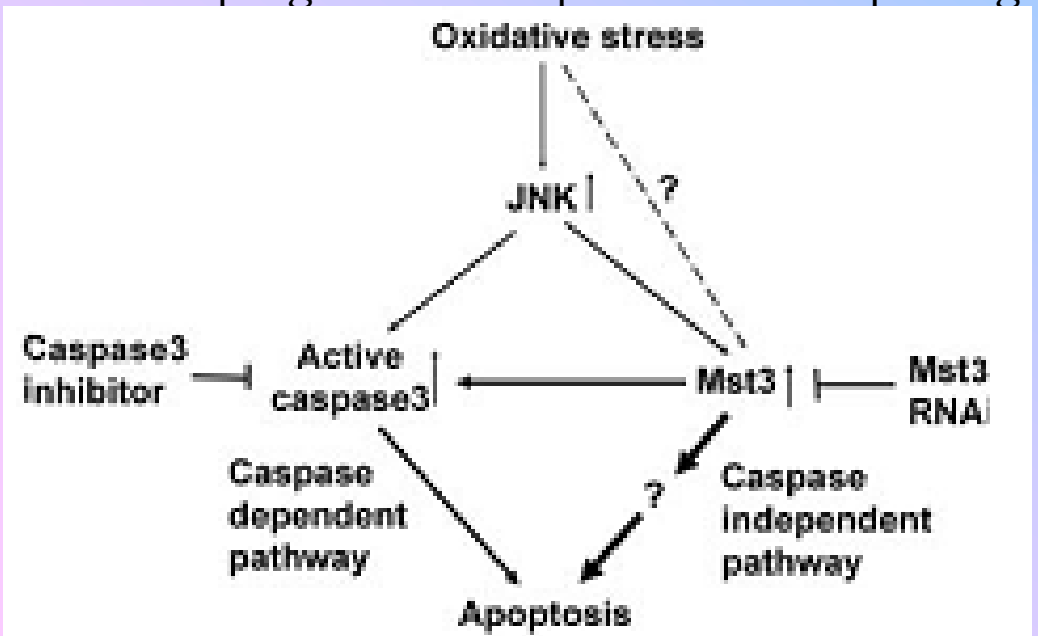
EXPRESSION OF CASPASES 3 AND CLIVED CASPASES 3



SNPs, PRETERM BIRTH AND GENDER DIFFERENCES: OUR EXPERIENCE

Introduction

- Since gender differences are involved in several placental pathologies, our study aimed to investigate its influence in preterm birth.
- **1st phase:**
  polymorphisms of genes involved in the apoptotic pathway triggered by oxidative stress (TNF alpha, JNK, Mst3, Caspase 3) were analyzed in 400 placental samples (300 at term and 100 preterm) to evidence differences between male and female pregnancies in preterm birth pathogenesis.
- **2nd phase:**
  polymorphisms of TNF alpha, JNK, Mst3, Caspase 3 genes were analyzed in 948 blood samples (914 at term and 34 preterm) to evidence differences between male and female pregnancies in preterm birth pathogenesis.



SNPs, PRETERM BIRTH AND GENDER DIFFERENCES: OUR EXPERIENCE

1st phase results

- No significant differences between term (controls) vs. spontaneous preterm birth (sPTB)

	Neonatal sex	
	Female	Male
Controls	163 54,9%	134 45,1%
sPTB	32 57,1%	24 42,9%
	p=0,755	

- Significant differences between female and male sex in SNPs genotyping of CASP3 and MST3 determined in placenta samples

	CASP3 pl				MST3 pl				JNK pl				TNFA-1 pl				TNFA-2 pl			
	0	1	2		0	1	2		0	1	2		0	1	2		0	1	2	
Female sex Count	70	7	112	**p=0,052**	77	44	67	**p=0,018**	75	20	94	p=0,820	19	2	53	p=0,929	28	12	34	p=0,335
%	37,0%	3,7%	59,3%		41,0%	23,4%	35,6%		39,7%	10,6%	49,7%		25,7%	2,7%	71,6%		37,8%	16,2%	45,9%	
Male sex Count	67	12	72		82	20	49		60	13	78		19	2	46		33	7	27	
%	44,4%	7,9%	47,7%		54,3%	13,2%	32,5%		39,7%	8,6%	51,7%		28,4%	3,0%	68,7%		49,3%	10,4%	40,3%	

Legend

SNPs	**(ALLELE 1/ALLELE 2)**
TNF A	G/T
CASP3	G/A
MST3	A/C
JNK	G/T

SNPs	
HOMOZIGOUS ALLELE 1	1
HOMOZIGOUS ALLELE 2	2
HETEROZIGOUS ALLELE 1/ALLELE 2	0

SNPs, PRETERM BIRTH AND GENDER DIFFERENCES: OUR EXPERIENCE

2nd phase results

- Increasing the number of analyzed subjects, a significant difference between term (controls) vs. spontaneous preterm birth (sPTB) is observed.
- sPTB is more frequent among male pregnancies vs. female pregnancies.

	Neonatal sex	
	Female	Male
Controls	448	466
	49,0%	51,0%
sPTB	10	24
	29,4%	70,6%

p= 0,038

- Results of SNPs genotyping are under statistical analysis.

PRETERM BIRTH AND…OXIDATIVE STRESS

frontiers in IMMUNOLOGY

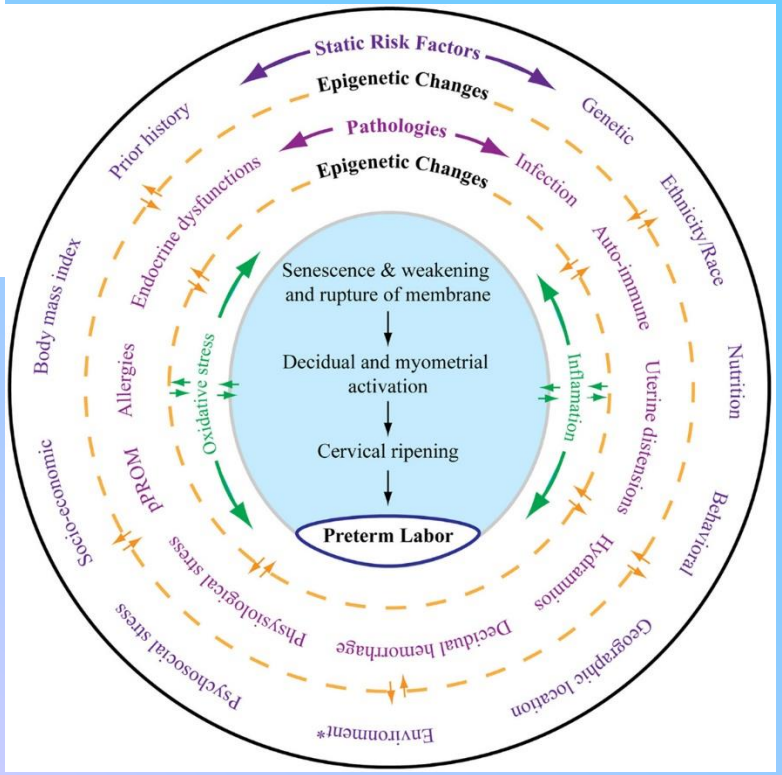
REVIEW ARTICLE

Oxidative stress damage as a detrimental factor in preterm birth pathology

Ramkumar Menon*

Department of Obstetrics and Gynecology, School of Medicine, The University of Texas Medical Branch Galveston, TX, USA

Normal extrauterine environment is markedly hypoxic as compared to the extrauterine environment. During pregnancy, the fetus gradually prepares for transition to the relatively oxygen-rich extrauterine environment, as is shown by the substantial increase in antioxidant enzyme levels during the last weeks of pregnancy. If preterm delivery occurs (particularly before 32 weeks), this preparation is not completed, and the fetus is susceptible to environmental factors such as elevated oxidative stress (OS).
The imbalance between ROS and antioxidants is present in both maternal and placental compartment and interactions between these two compartments result in the clinical manifestations of preterm birth.



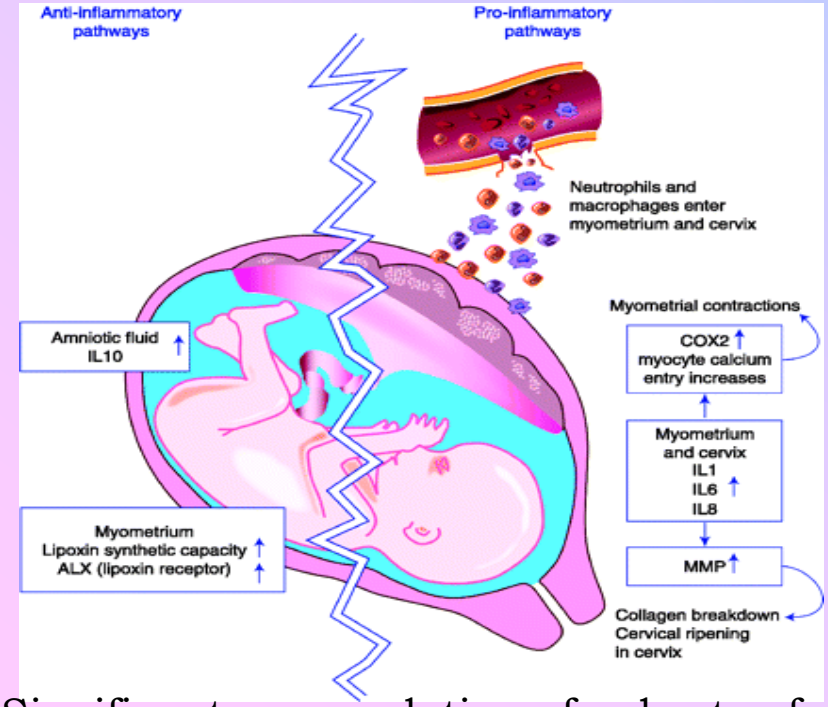
Preterm labor (the innermost circle) is an end result of multitudes of complex interacting pathologies and pathophysiologic pathways

Static and dynamic risk factors produce pathways and pathophysiologies depicted in the inner circle with a unique biomarker profile contributing to labor-inducing changes, resulting in PTB or pPROM. The final effector pathways culminating in labor and delivery include inflammation and oxidative stress (OS). In normal pregnancies, these are generated by various fetal and maternal factors that signal the end of pregnancy. In PTB, the maternal–fetal signals and their causal origins are still unclear as they arise from complex etiologies and redundant pathways.

PRETERM BIRTH, OXIDATIVE STRESS AND…INFLAMMATION

The placenta is a key regulator of the intrauterine environment mediating maternal-fetal interaction. Maternal physiological or phatological signals are translated into the placenta and can affect fetal programming.

Adequate placentation and fetal development also depend on levels of important hormones such as placental leptin and adiponectin. Increased leptin levels have been found in fetuses and placentas from diabetic mothers, while decreased adiponectin levels have been seen in their children at birth. Adipokine levels in early developmental stages possibly play a significant role in programming the body composition of individuals. In humans, hyperleptinemia states have been seen in obesity, metabolic syndrome, and cardiovascular disease



The placenta, however, is known to represent a critical source of ROS in both normal and pathophysiologic pregnancy. Placental oxidative stress may be initiated by direct changes in placental oxygenation and/or local inflammatory reactions in the placenta. Given that preterm birth frequently results from intrauterine inflammation, increased exposure of the fetus to excess placental ROS production is likely in these pregnancies, with increased production of ROS thought to contribute significantly to the development of conditions that complicate preterm birth.

Significant accumulation of subsets of macrophages has been shown in placentas resulting in production of pro-inflammatory cytokines including IL-6, TNFa, and TLR-4.

PRETERM BIRTH, OXIDATIVE STRESS, INFLAMMATION AND…FETAL GENDER

Several studies report significant effects of fetal sex on pregnancy outcome and the development of pregnancy-related implications. Placental development seems to be sensitive to fetal sex, and the maternal-fetal interaction may therefore be reflected in specific measures of placental pathology.

	Adipokine		ROS	Cytokine		
	Adiponectina	Leptina	GPX	TNFA	NFKB	TLR4
Males vs.females	=	↑	↓	↓	↓	↑
	Gui Y, 2004		*Stark M J , 2011*	*Myatt L, 2016*		*Yeganegi M, 2009*

Adiponectin/Leptin: Maternal leptin and adiponectin plasma levels lead to placental regulation of nutrient transport to the fetus. In male mice, plasma leptin increased, whereas adiponectin levels were constant.

Glutathione peroxidase: GPX activity was found to be lower in placentae of males compared to females resulting in a increased oxidative stress seen in preterm infants.

Tumor Necrosis Factor alpha: TNF-α decreases trophoblast mitochondial respiration in a sexually dimorphic manner. The effect is seen only in trophoblasts of a female placenta and is mediated by the transcription factor NFκB1.

Nuclear factor kappa-light-chain-enhancer of activated B cells: the inflammatory intrauterine environment induces an NFκ B1-mediated increase in miR-210 in a fetal sex dependent manner, leading to inhibition of mitochondrial respiration and placental dysfunction in the placentas of female fetuses.

Toll Like Receptor-4: TLR-4 is expressed at a greater abundance in placental trophoblast cells of male fetuses and it may contribute to the heightened inflammatory response observed in these fetuses. This in turn could also contribute to the increased incidence of preterm birth, sepsis, and poorer outcome during fetal and neonatal periods.

www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(2):e040246
doi: 10.7363/040246
Received: 2015 Sept 22; accepted: 2015 Oct 10; published online: 2015 Oct 26

Review

Is there a sex of the placenta?

Gian Carlo Di Renzo, Elena Picchiassi, Giuliana Coata, Graziano Clerici, Eleonora Brillo

- The long-term effects of the same environmental insult, such as maternal unbalanced nutrition or maternal stress, can have various phenotypic effects on male and female offspring. *Bale, 2011; Aiken and Ozanne, 2013*

- The sex specificity of the adult-onset phenotype is therefore already partly shaped *in utero* and the placenta is at stake in this sex-specific feature.

- Gender differences occur in many adult diseases, including metabolic diseases, hypertension, cardiovascular disease, psychiatric and neurological disorders and cancer. For example, men are more predisposed to cardiovascular disease while women are more predisposed to obesity.

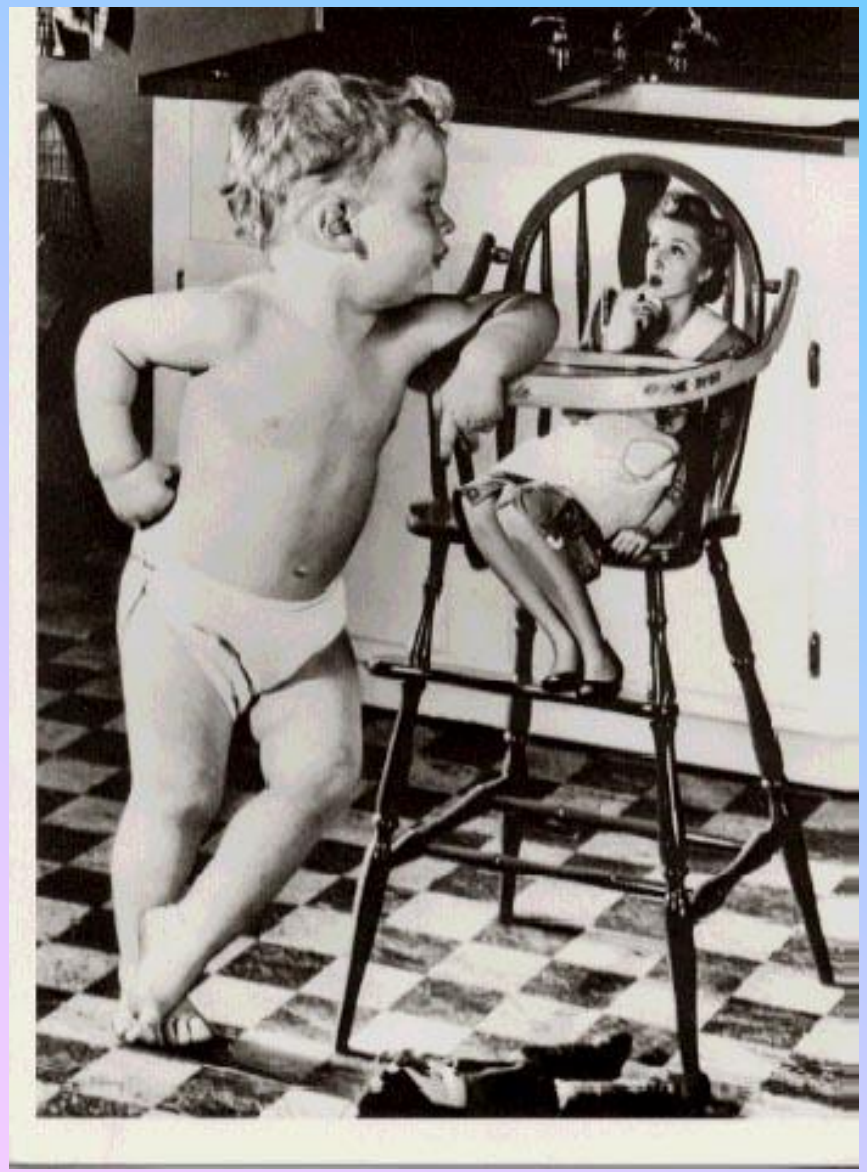
- Explaining the sex-specific causal variables and how males versus females respond and adapt to environmental perturbations should help physicians and patients anticipate disease susceptibility.

CONCLUSIONS

- **Female and male placentas have different routes to maximize fitness** and therefore the two sexes have different optimal transcriptomes that may affect fetal growth and later disease susceptibility or health trajectory.
- **The male strategy** for responding to an adverse maternal environment is a **minimalist approach** with few gene, protein or functional changes instituted in the placenta which ultimately ensures continued growth in a less than optimal maternal environment.
- This male response is associated with a greater risk of either intrauterine growth restriction, preterm delivery or death in utero if another adverse event occurs during the pregnancy.
- The **female placenta** responds to an adverse maternal environment with **multiple placental gene and protein changes** that result in a decrease in growth without growth restriction (>10th centile).
- These female adjustments in placental function and growth ensure survival in the presence of another adverse event which may further compromise nutrient or oxygen supply.

CONCLUSIONS

- The **placenta** may therefore be seen as an **ideal system** to study the **sensing**, by the fetus, of stresses, starvation, endocrine disruption and obesity-prone diets or lifestyles, in a **sex-specific manner**.
- Thus if we are going to use the placenta as an indicator of what occurred in utero, it is crucial to understand how, in addition to sex-specific differences in the endocrine and immune systems, **sex- specific genetic architecture also influences placental growth and specific functions,** both under normal conditions or severe placental dysfunction that may induce adverse pregnancy outcomes,
such as preterm birth.



Fetal or Maternal perspective?

EPICRISIS

There is evidence that females have an advantage over males with a better outcome in the perinatal period, particularly after preterm birth. The gender difference seems to persist throughout life, particularly regarding age-related degenerative changes in the brain. Although there are gender differences originating from the period early after conception, the exact mechanisms responsible for the continued differences later in life remain to be determined…..

Author Maureen Dowd asks if men are even necessary anymore. To add fuel to the fire, some pundits predict the death of the Y-chromosome within the next 125,000 years and believe it won't be such a devastating loss – because we'll be able to continue the human race through technology quite satisfactorily, perhaps even manufacturing people to precise and carefully determined specifications.

Dowd M. *Are men necessary? When sexes collide*. New York,NY: GP Putnam's sons; 2005:338
Sykes B. *Adam's curse: a future without men*. New York,NY: WW Norton & Co,Inc; 2006:310

FETAL MALE SEX (AND PLACENTA) IS AN INDEPENDENT RISK FACTOR FOR PRETERM BIRTH

TAKE HOME MESSAGE


♀♂?
I am ok!

Grazie **Gracias**

Danke **Thank you**