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

16th

PREIS SCHOOL

Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

PRETERM BIRTH:

A GREAT OBSTETRICAL SYNDROME

GC DI RENZO, MD, PhD, FACOG, FRCOG, FICOG

University of Perugia, Italy

"No period in an individual's life is as critical in determining his or her future health and propensity to disease as the "*periconceptional period*"

" The early identification and correction of fetal or neonatal abnormalities may prevent not only early death but also chronic disease"

Romero, Di Renzo 2009, J Matern Fetal Neonatal Med

The Journal of Maternal-Fetal and Neonatal Medicine, August 2009; 22(8): 633–635

EDITORIAL

The Great Obstetrical Syndromes

GIAN CARLO DI RENZO, M.D., Ph.D.

Department of Obstetrics and Gynecology, Centre for Perinatal and Reproductive Medicine, University of Perugia, Perugia, Italy

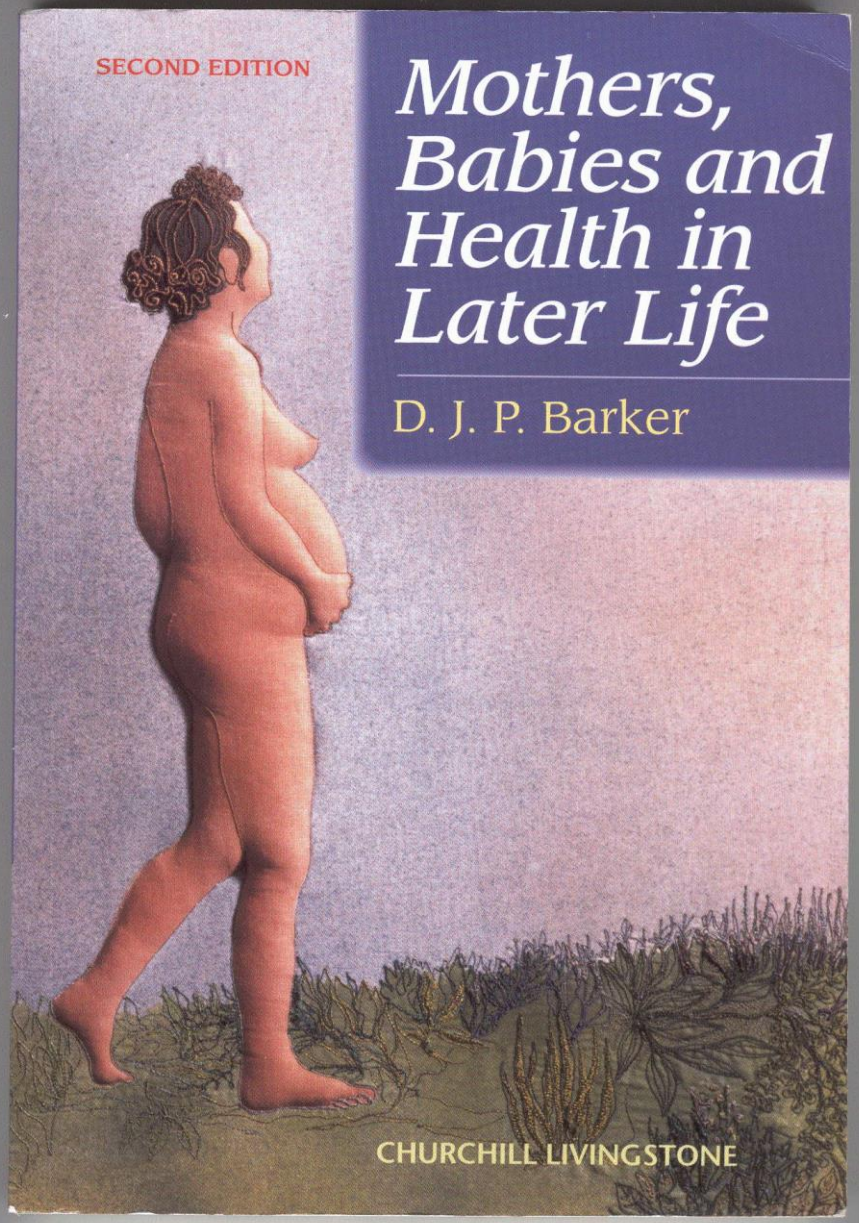
The Journal of Maternal-Fetal and Neonatal Medicine, August 2009; 22(8): 636–639

The "Classic Editorial" that coined the term "The Great Obstetrical Syndromes" published over 10 years ago

Prenatal medicine: The child is the father of the man*

ROBERTO ROMERO

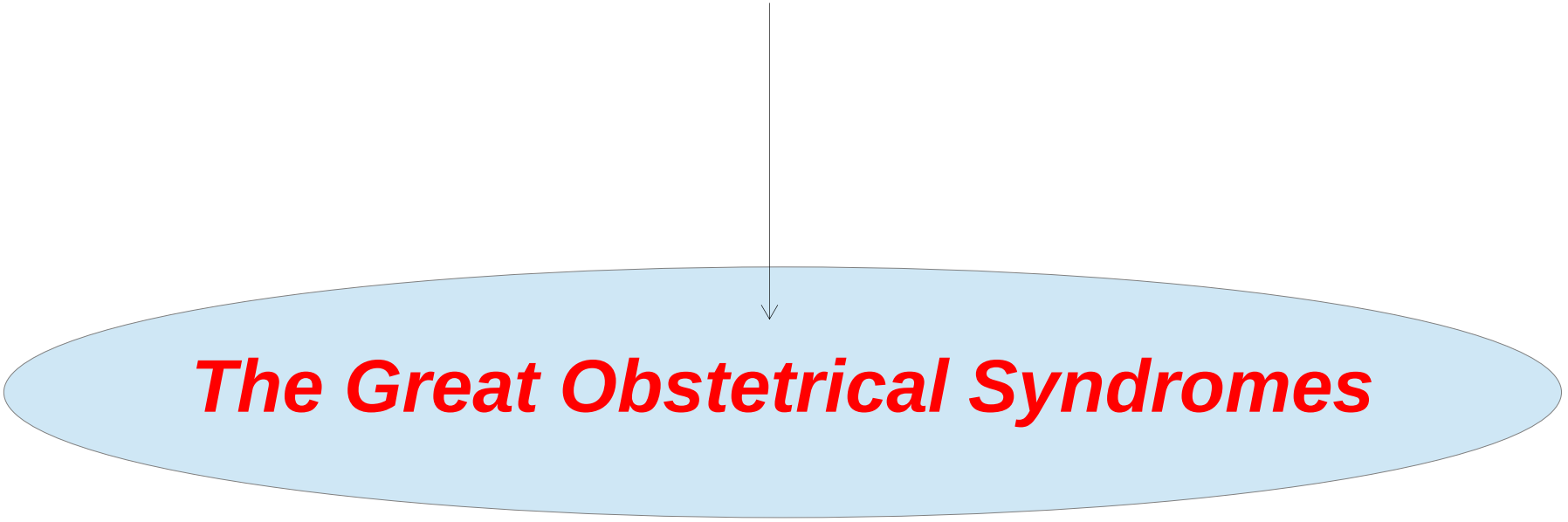
Perinatology Research Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Wayne State University/Hutzel Women's Hospital, Detroit, MI and Bethesda, MD, USA


SECOND EDITION
Mothers, Babies and Health in Later Life
D. J. P. Barker
CHURCHILL LIVINGSTONE

The current taxonomy of disease in obstetrics is based on the *clinical presentation* of the mother and/or fetus, and not on the mechanism of the disease responsible for the clinical manifestations

Therefore, the diagnosis simply describes the clinical manifestations without consideration of the specific etiology

Obstetrical disorders responsible for high degree of maternal and perinatal morbidity and mortality



Key features of the obstetrical syndromes

1. **multiples etiologies**

2. **long preclinical stage**

3. **frequent fetal/neonatal involvement**

4. **predisposition to a particular syndrome influenced by gene-environment interaction and/or complex gene-gene interactions involving maternal and/or fetal genotypes**

5. **clinical manifestations often adaptive in nature**

Romero, 1996, Di Renzo 2009, JMFNM

- "**Perinatal medicine is at a stage when we can only recognize clinical syndromes rather than distinct disease entities caused by specific pathological mechanisms"**

- **"Many obstetric syndromes result from adaptive responses of the maternal fetal unit to pathological insults"**

- **"Most obstetric syndromes are often the late clinical manifestations of chronic pathophysiological processes that have a long subclinical phase"**

Romero 2009, J Matern Fetal Neonatal Med

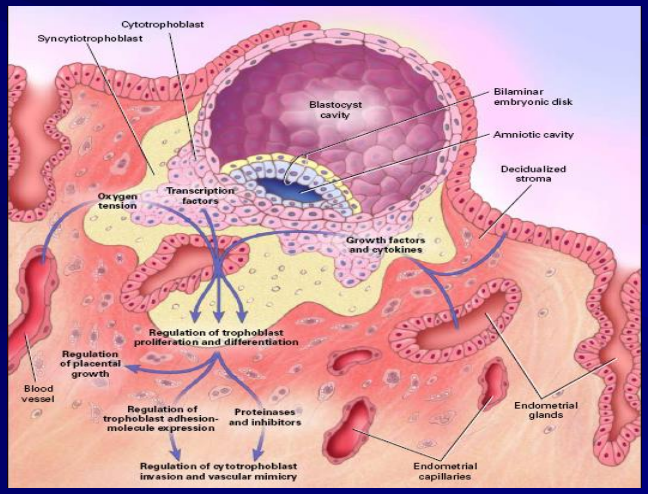
"Accumulating observations now indicate that preterm labor, preterm premature rupture of membranes, preeclampsia, small for gestational age (SGA), large for gestational age (LGA), stillbirth and many other conditions that we deal with in clinical practice are not discrete entities, but are syndromes with more than one cause."

Di Renzo 2009, J Matern Fetal Neonatal Med

PREGNANCY IS A CONTINUUM

IMPLANTATION

Immune tolerance



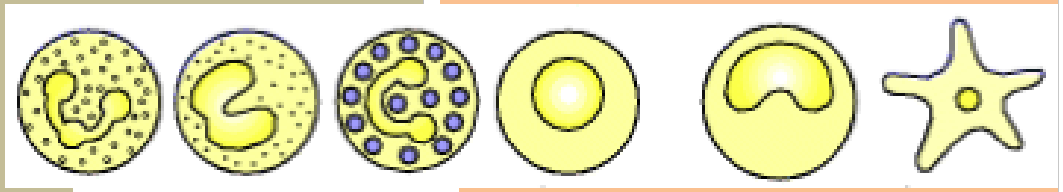
Successful mammalian pregnancy depends upon tolerance of a genetically incompatible fetus by the maternal immune system.

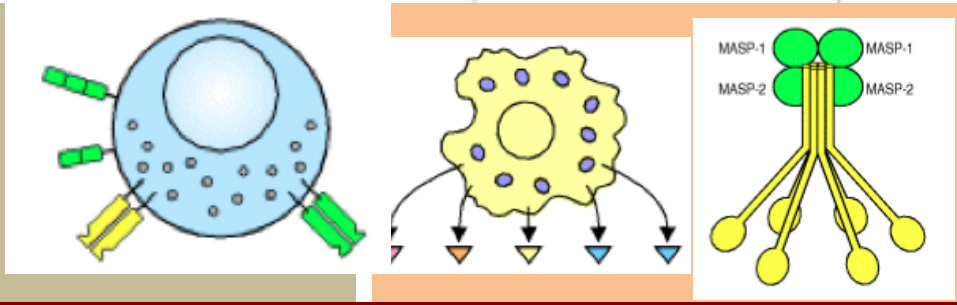
I AM **A SEMIALLOGRAFT**

Maternal-fetal interface

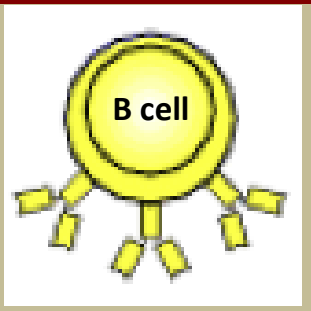
Maternal immune system

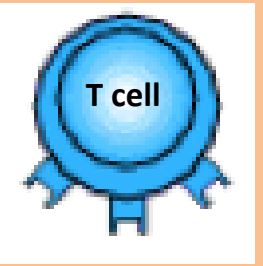
Innate immunity

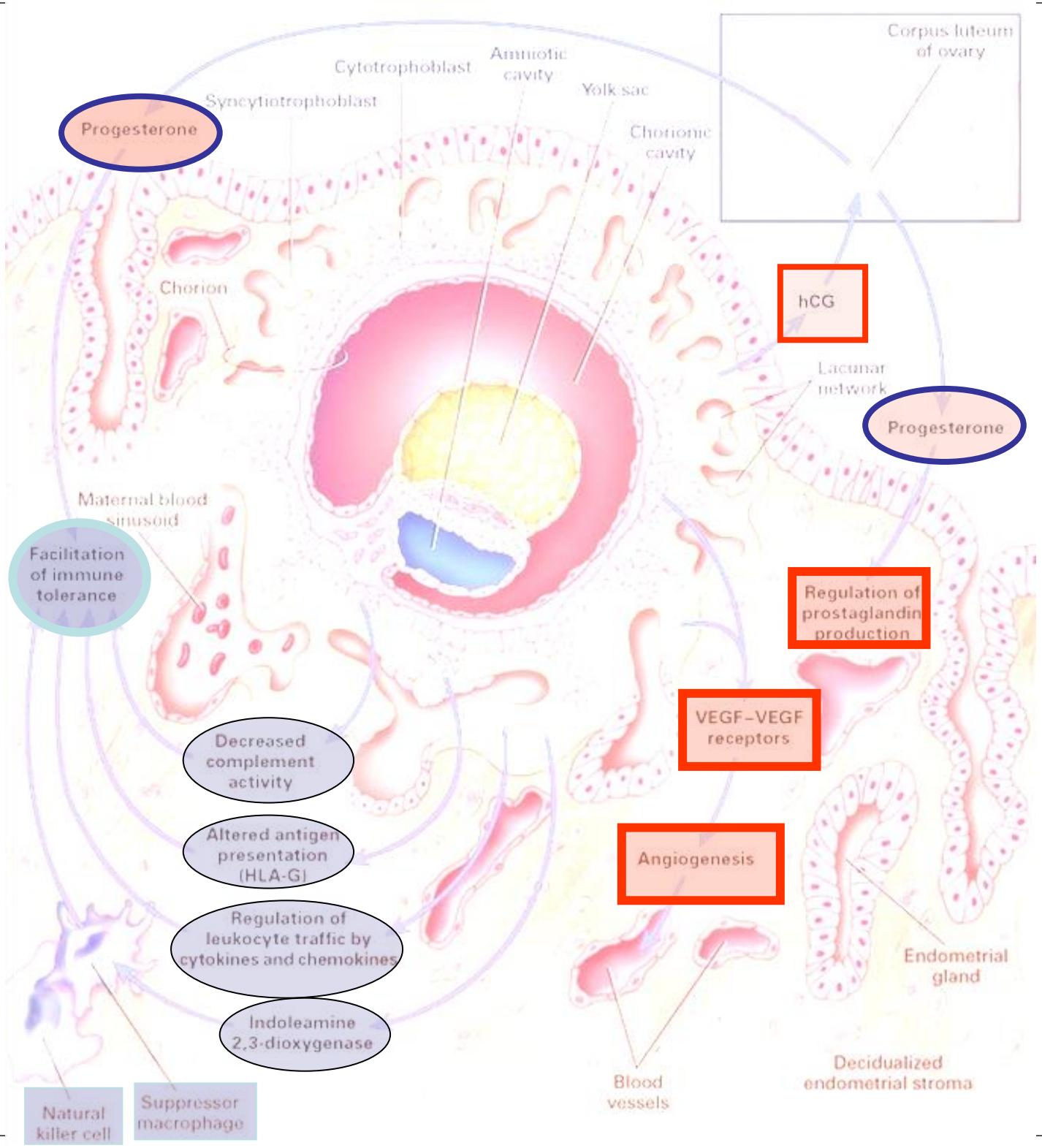




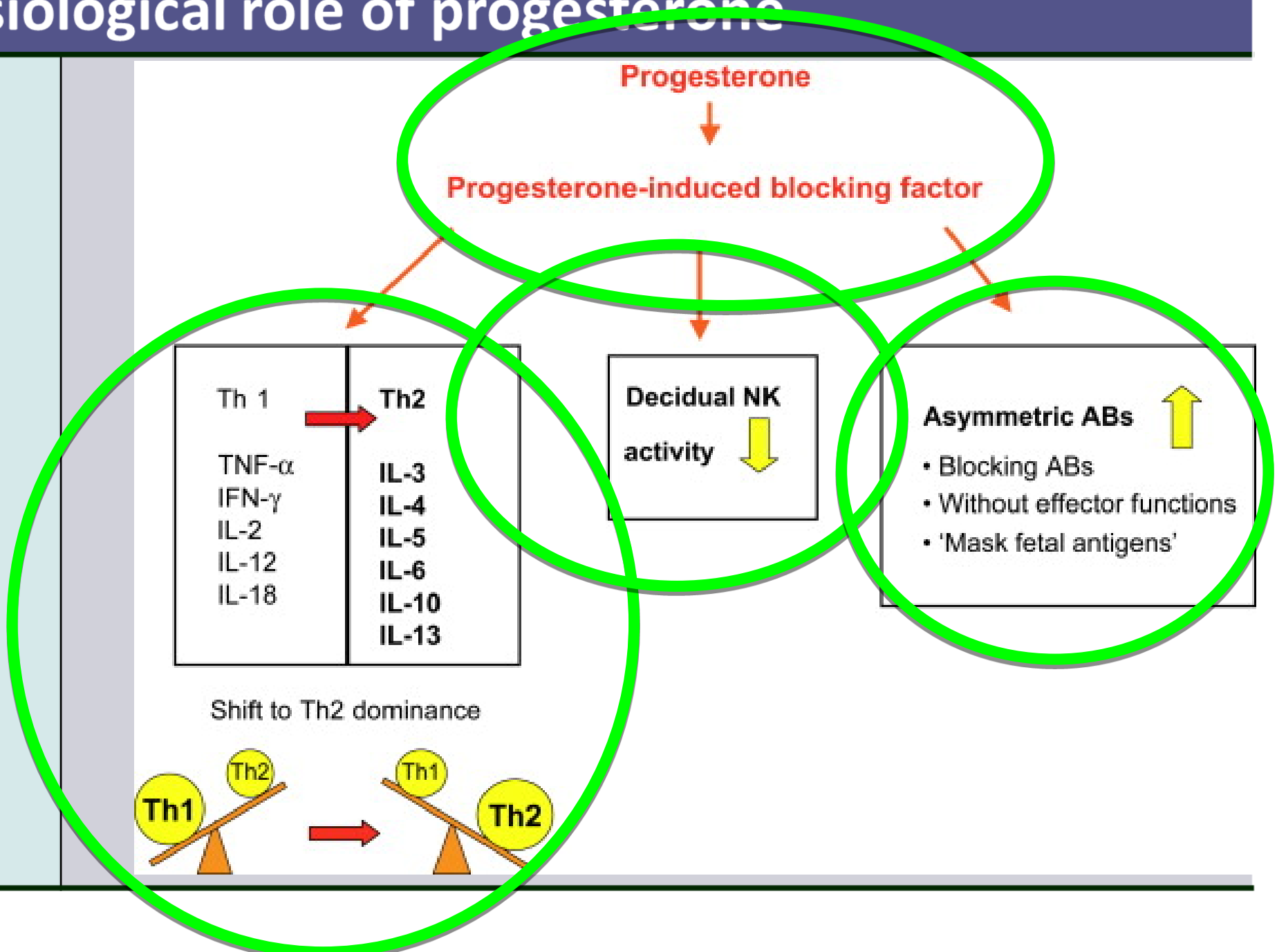
Adaptive immunity



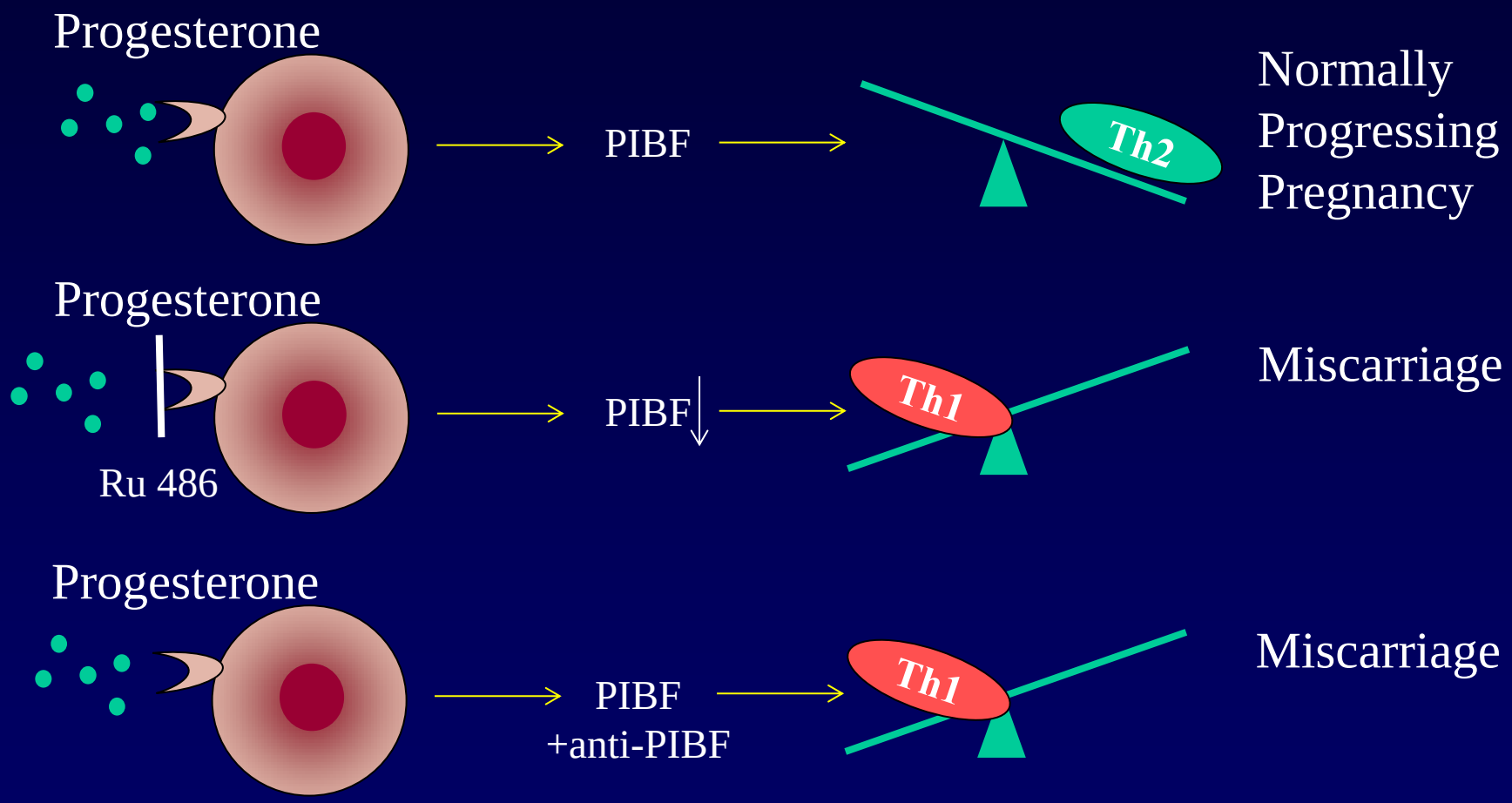



Corpus luteum of ovary
Progesterone
Cytotrophoblast
Amniotic cavity
Syncytiotrophoblast
Yolk sac
Chorionic cavity
Chorion
hCG
Lacunar network
Progesterone
Maternal blood sinusoid
Facilitation of immune tolerance
Regulation of prostaglandin production
VEGF–VEGF receptors
Decreased complement activity
Altered antigen presentation (HLA-G)
Angiogenesis
Regulation of leukocyte traffic by cytokines and chemokines
Endometrial gland
Indoleamine 2,3-dioxygenase
Blood vessels
Decidualized endometrial stroma
Natural killer cell
Suppressor macrophage

Physiological role of progesterone



Progesterone-induced Blocking Factor (PIBF) Link between the Endocrine and Immune System



PREGNANCY OUTCOME

FETUS/TROPHOBLAST
50%PATERNAL/50%MATERNAL

↓

ALLOGENIC IMMUNE REACTION

↓

Progesterone induced blocking factor (PIBF) at the decidual (CD56+) and PBMC level

↓	↓
Progesterone level sufficient to form PIBF	Progesterone level insufficient to form PIBF
↓	↓
Asymmetric antibodies Th2 bias'NK cells	Symmetric antibodies Th1 bias LAK cells
↓	↓
Fetus protection	Cytotoxic, inflammatory Abortogenic reaction
↓	↓
Delivery	Abortion

The pivotal role of progesterone receptor-mediated immunomodulation in successful pregnancy (PBMC= Peripheral blood mononuclear cells; NK= Natural killer cells; LAK cells= Lymphokine activated killer cell)

DI RENZO GYN ENDOCR 2012

Immunological effects of progesterone

1	Maintains decidualization[1]	
2	Maintains trophoblast invasion	Reduces signs of endometrial apoptosis from cycle day 26[2]
		Inhibits apoptosis of extravillous trophoblasts[3]
3	Promotes maternal immune tolerance to fetal semi-allograft	Activates progesterone-induced blocking factor (PIBF) → PIBF inhibits NK activity and induces TH2 cytokine production[4-6]
		Blocks TH1 cell immunity[4-6]

[1]Arck PC, et al. Reprod Biomed Online. 2008 Jul;17(1):101-13. [2]Lovely LP, et al. J Clin Endocrinol Metab. 2005 Apr;90(4):2351-6. [3]Liu J, et al. Mol Hum Reprod. 2007 Dec;13(12):869-74. [4]Choi BC, et al. Hum Reprod. 2000 Jun;15 Suppl 1:46-59. [5]Arck P, et al. J. Am J Reprod Immunol. 2007 Sep;58(3):268-79. [6]Piccinni MP. Reprod Biomed Online. 2006 Dec;13(6):840-4.

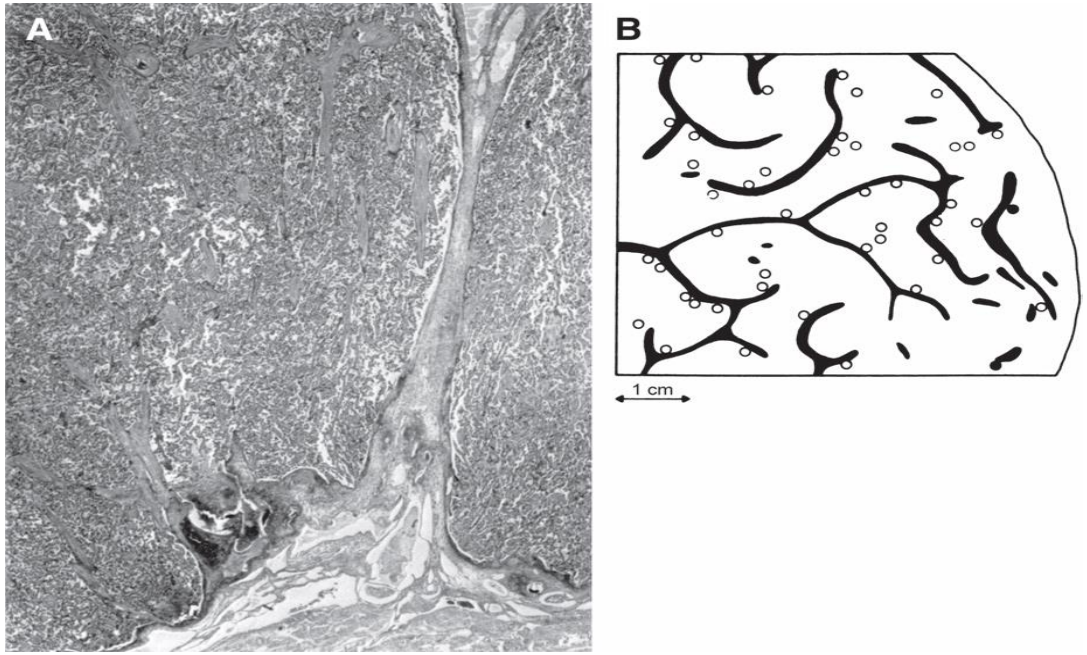
PLACENTAL BED FORMATION

The placental bed

- It is a distinct anatomical site important for the physiology and the pathology of pregnancy

- Strategically placed (anatomically and functionally) to be a site for the development of pathological processes

- It is not the decidua basalis attached to the floor of the placenta, but the uterine tissues (endometrium and myometrium) under the placenta



A, Opening of spiral artery at base of septum (*left side*).

B, Distribution of spiral artery openings with physiologic changes (*open circles*) in the central area and without physiologic changes (*closed circle*)

Brosens. Am J Obstet Gynecol 2011.

The Journal of Maternal-Fetal and Neonatal Medicine, January 2008; 21(1): 3–7

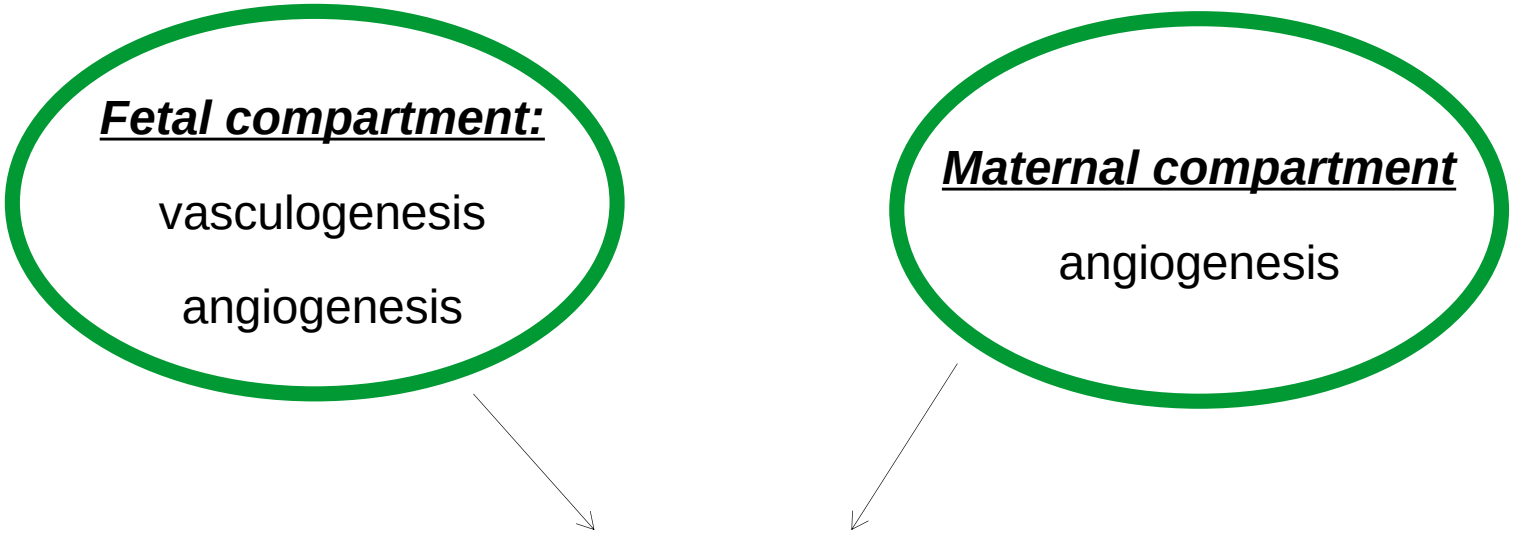
EDITORIAL

The role of an 'anti-angiogenic state' in complications of pregnancy

"The development of new blood vessels is essential for mother and fetus. The fetus must develop a circulation if it is to develop and survive. The mother must increase the blood supply to support the placenta and fetus"

"A deficiency in placental growth factor (an angiogenic factor) may be observed in patients with preeclampsia and in those with growth-restricted neonates..an imbalance between angiogenic and anti-angiogenic factors may be associated with disease during pregnancy"

Di Renzo, JMFNM 2008



Remodelling and transformation of the spiral arteries is necessary to ensure adequate delivery of nutrients and oxygen to maintain pregnancy

Inadequate angiogenesis, thrombosis and/or inadequate physiologic transformation of the spiral arteries can lead to **hypoxia-*ischemia of the placenta and the uterus***

The specific clinical **phenotype** in response to ischemia is probably a function of the **severity, timing and duration of the ischemic insult**

Reprinted from: OBSTETRICS AND GYNECOLOGY ANNUAL

Edited by Ralph M. Wynn, M. D.

Published by Appleton-Century-Crofts, New York
Educational Division, Meredith Corporation

4 steps have been distinguished in the spiral artery remodeling:

(1) the initial stage of decidua-associated remodeling,

(2) intraarterial trophoblast migration,

(3) intramural invasion and trophoblast-associated remodeling

(4) re-endothelialization and other maternal- induced changes.

Spiral artery remodelling steps

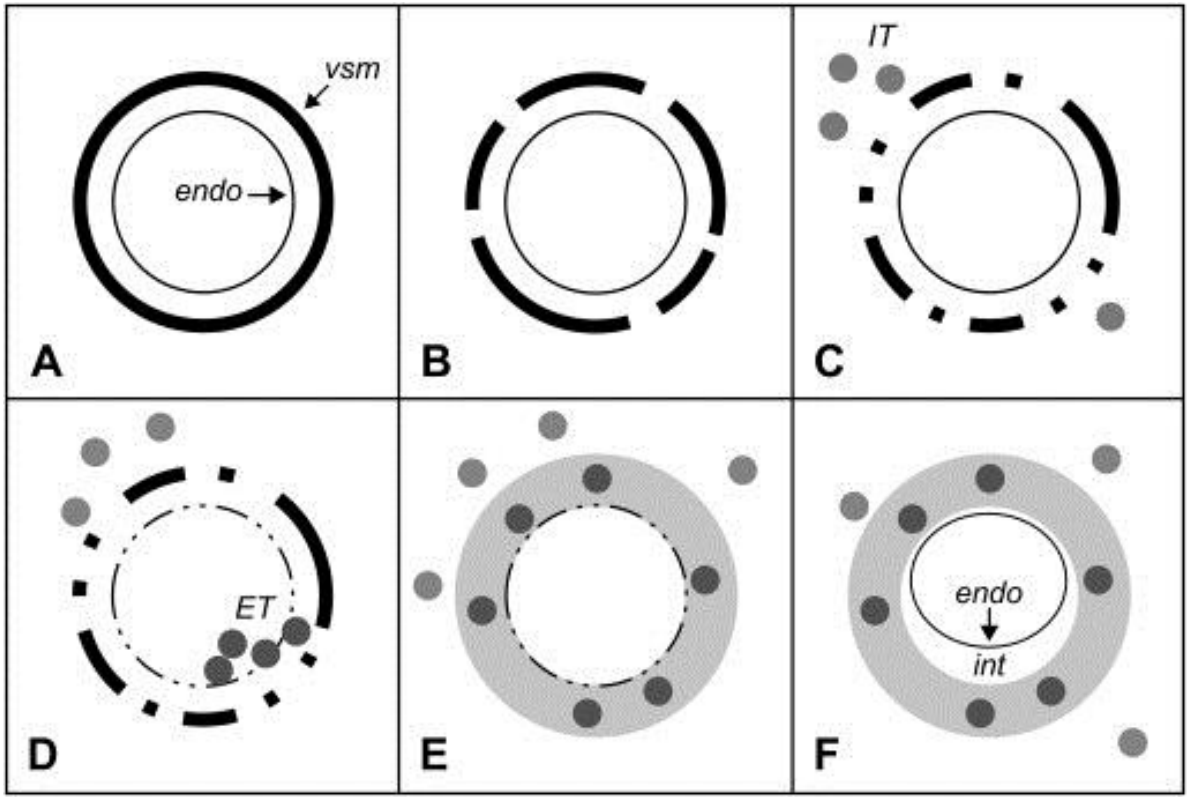
Pijnenborg et al. BPROG 2012

A. Unmodified

B. Disorganization of SM cells

C. Interstitial trophoblast enhances changes

D. Endotrophoblast replaces endothelium



Spiral artery in junctional zone

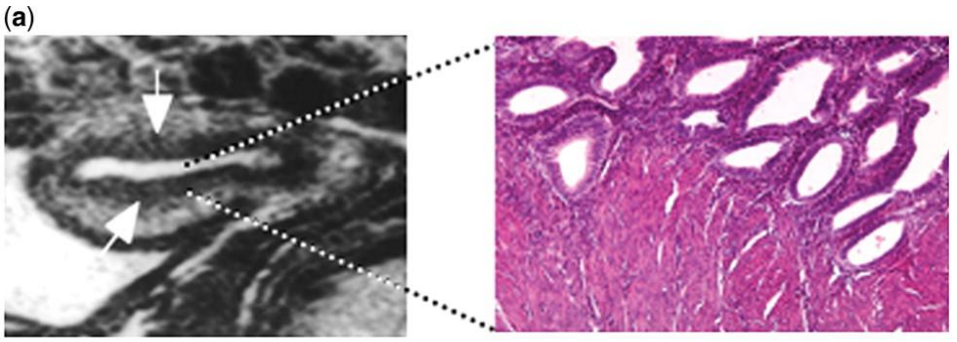
Normal Pregnancy

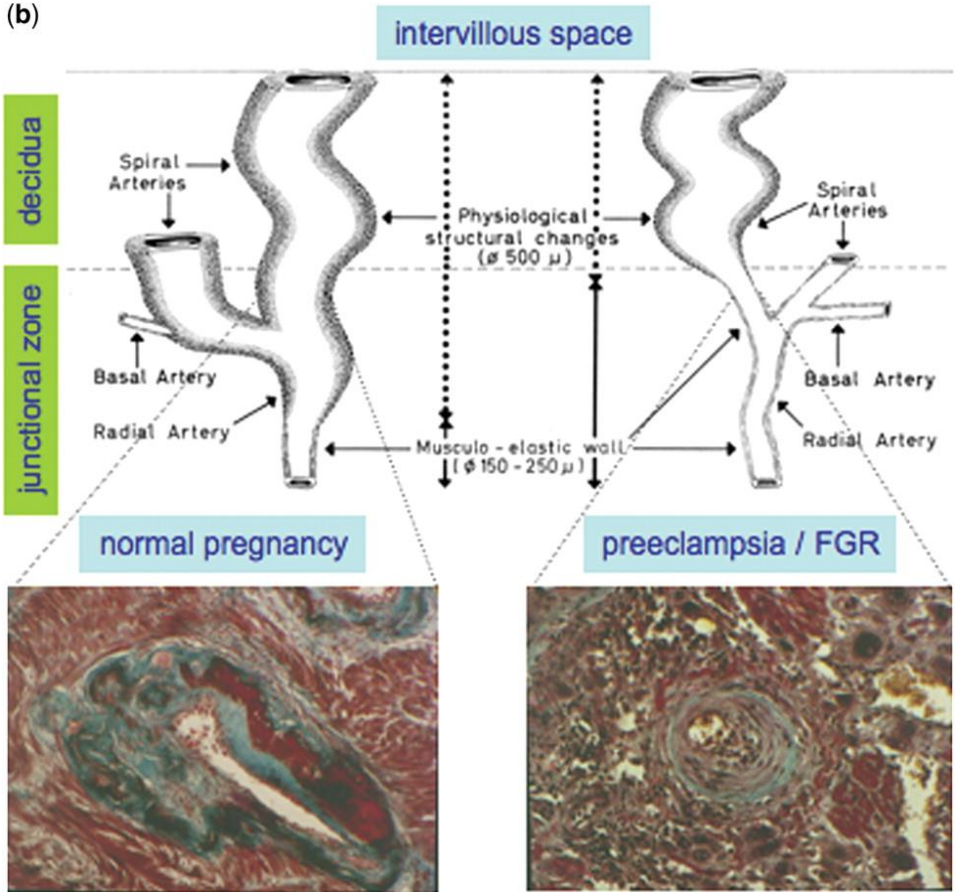
Full remodelling of wall:

-Loss of musculo-elastica

-Fibrofibrinoid wall

-Trophoblast



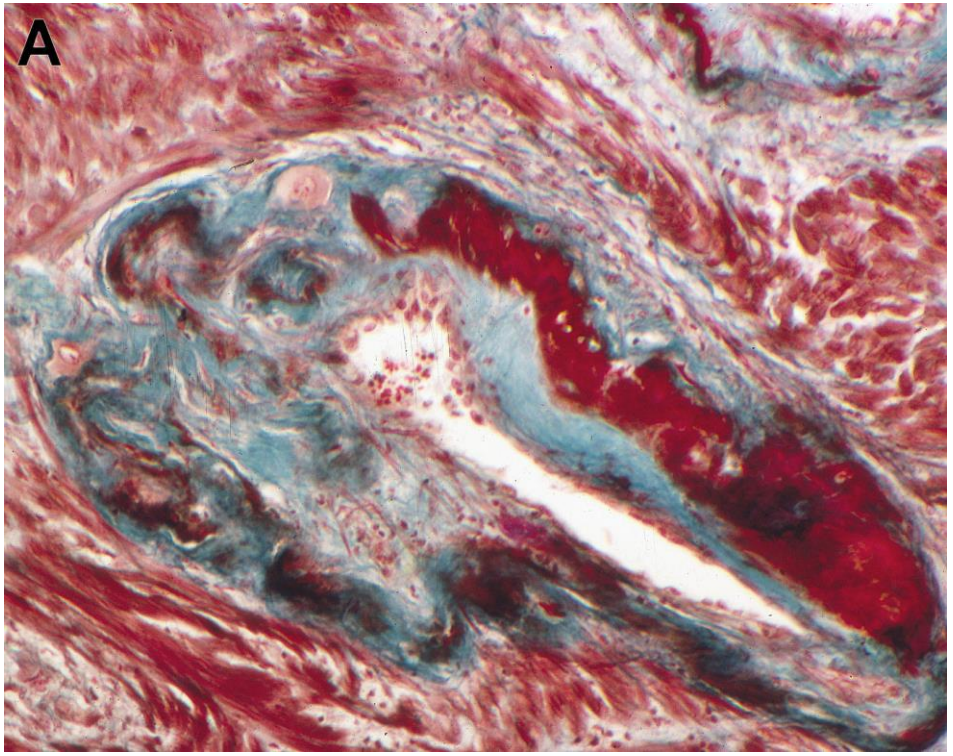


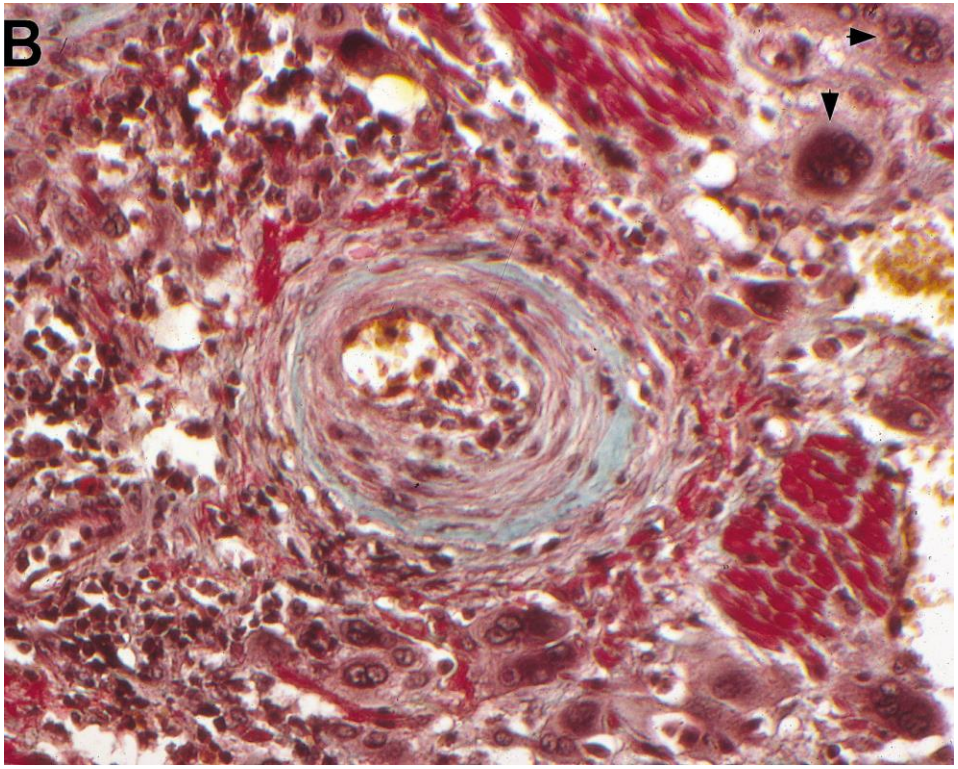
Obstetric Syndromes

Uteroplacental artery in JZ myometrium

Normal

Preeclampsia

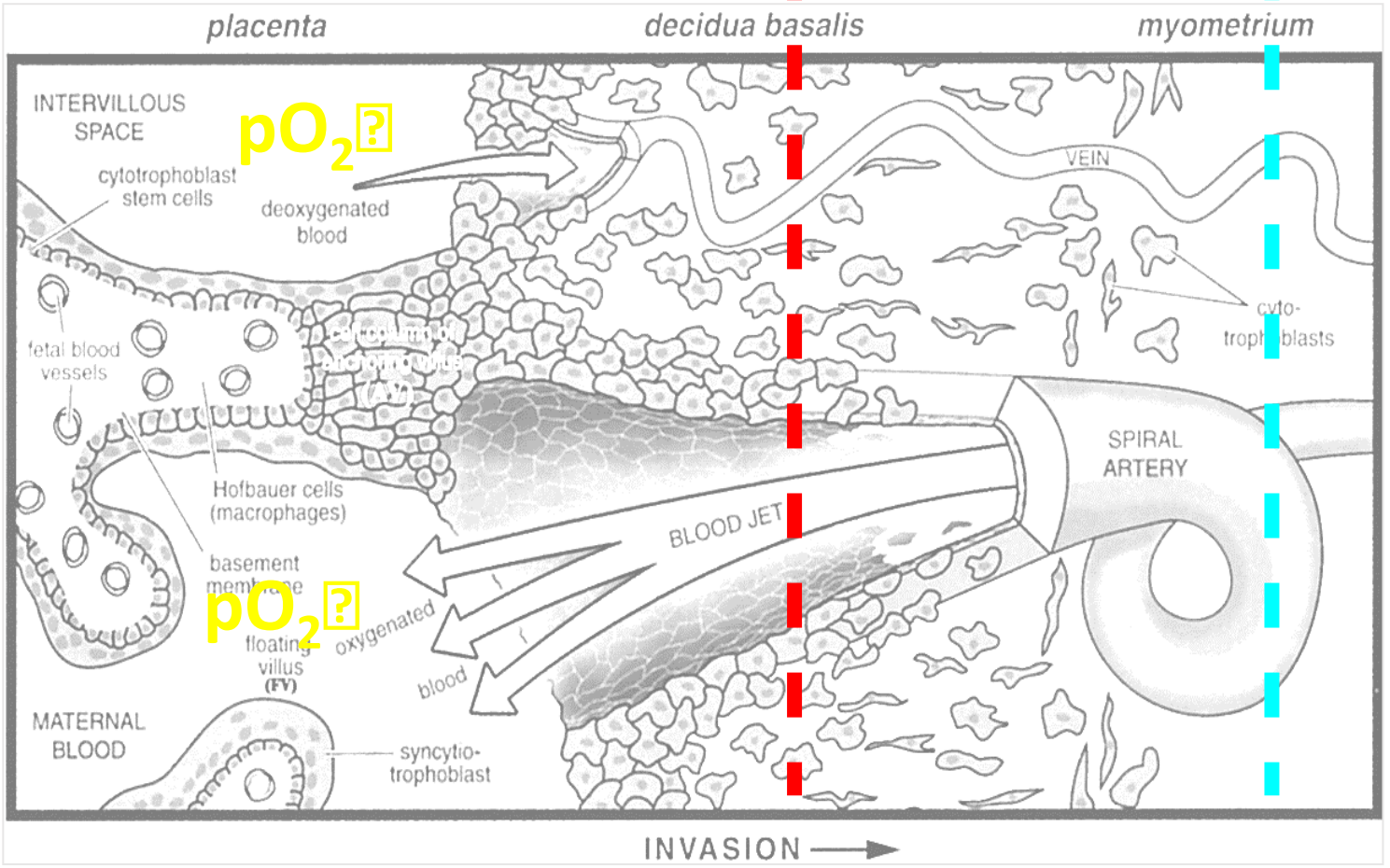




Consequences of reduced trophoblast invasion

Preeclampsia/ IUGR/PTL

Normal pregnancy



Modified from *Biochemistry* 2001;40:4077-4086 and *Kobe J Med Sci* 2002;48:13-23

Hypothesis

Reduced invasion

Incomplete conversion of arteries

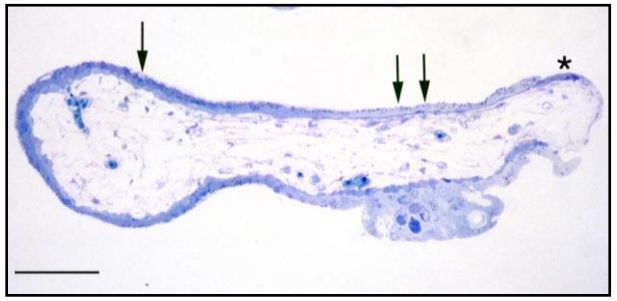
Retention of vasoreactivity

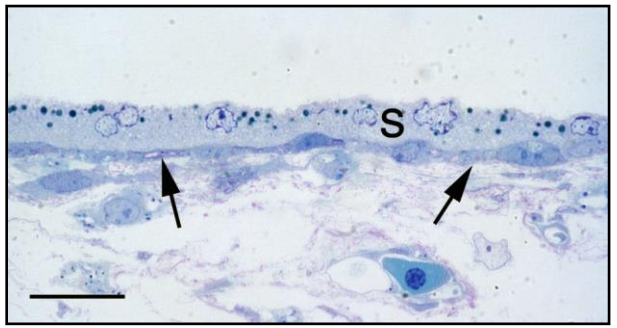
Intermittent perfusion of IVS

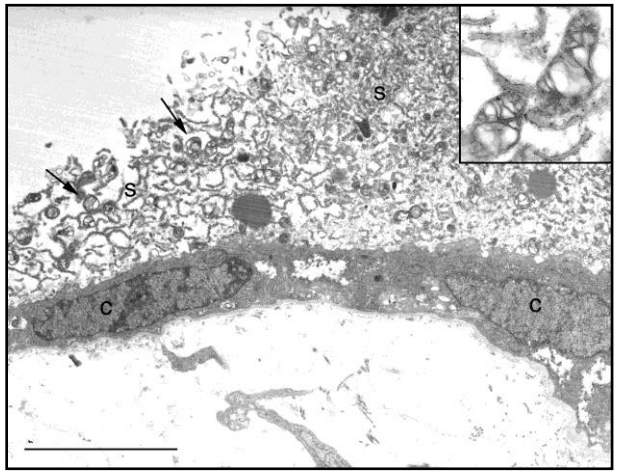
Fluctuating pO_2

Ischaemia-reperfusion type injury

PLACENTAL OXIDATIVE STRESS IN EARLY PREGNANCY FAILURE





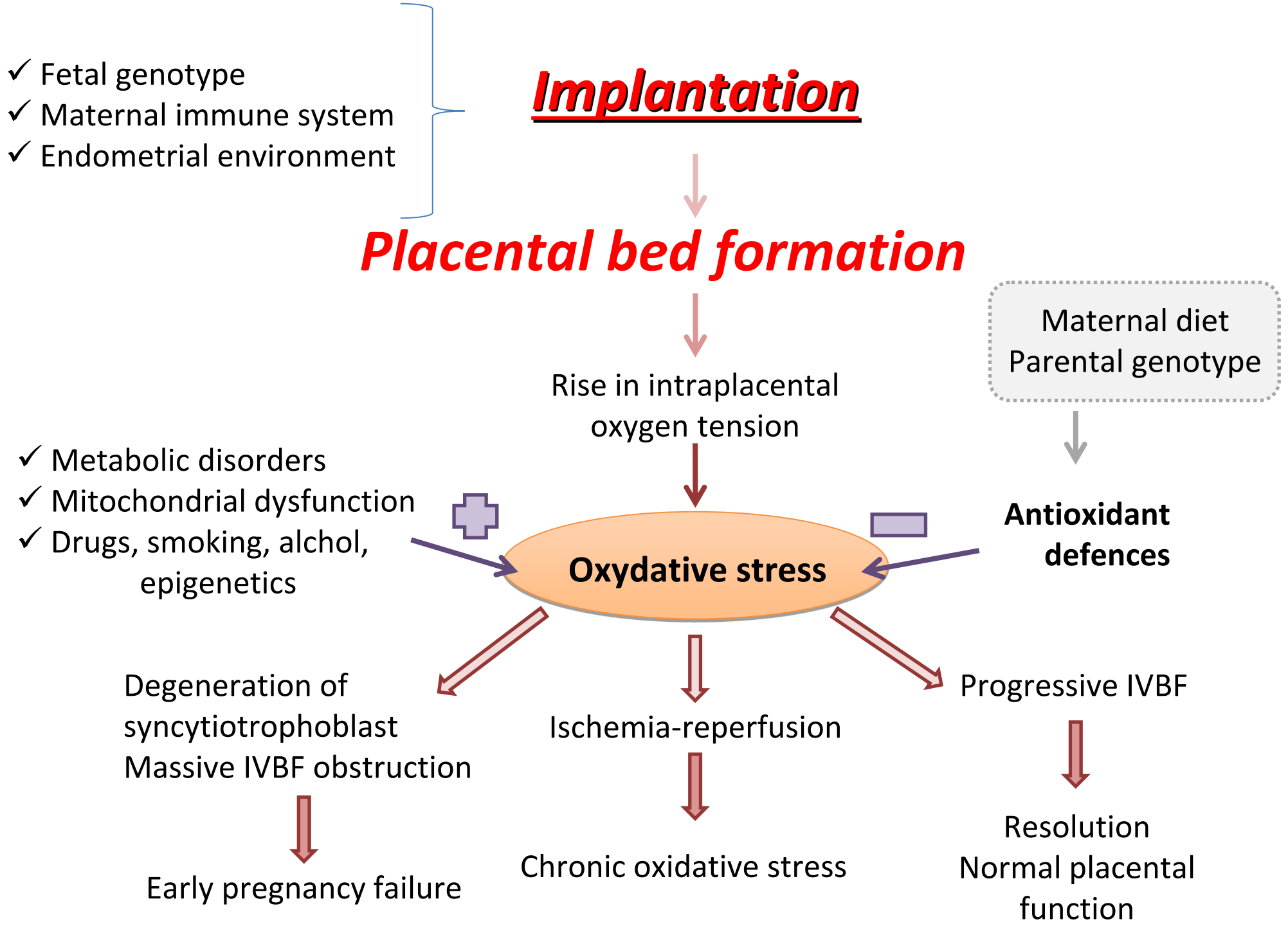


Villi from missed miscarriage show morphology & IHC markers of cellular stress and damage (increased apoptosis and decreased proliferation)

Consistent with the hypothesis that overwhelming oxidative stress mediates spontaneous miscarriage

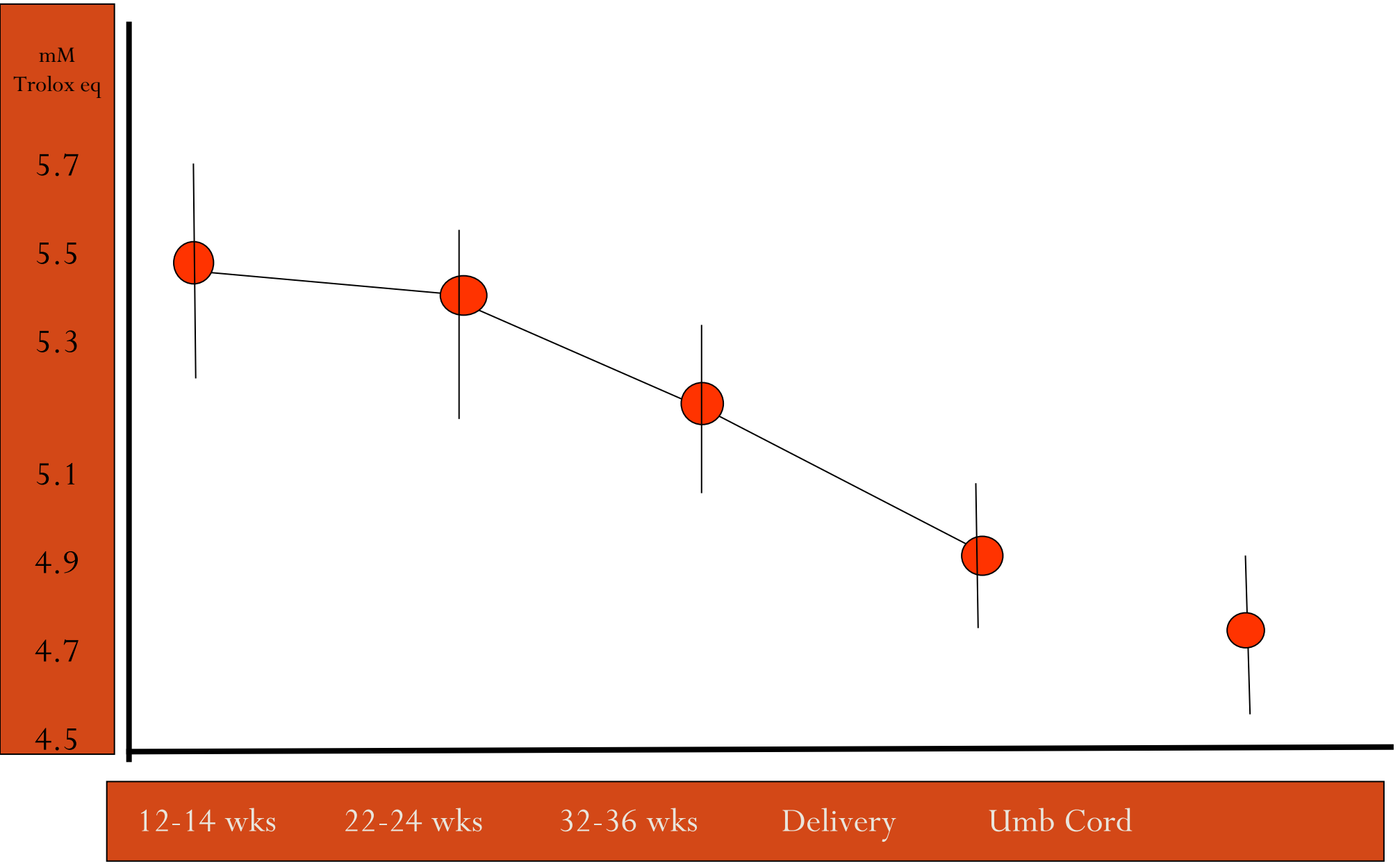
UNRELATED TO CONCEPTUS KARYOTYPE

Hempstock et al. *Hum Pathol 2003*
Greenwold et al. *Fertil Steril 2003*

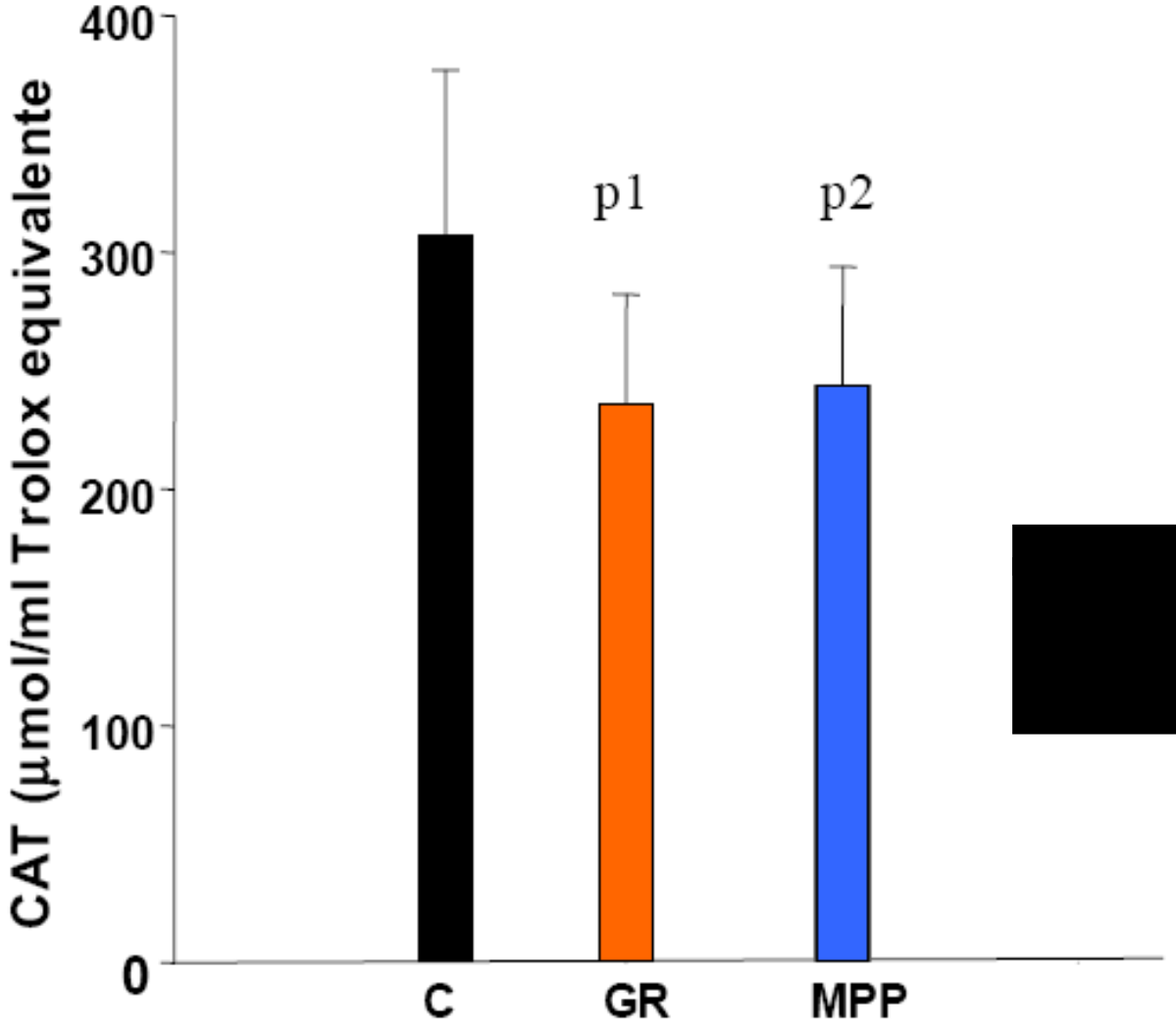

✓ Fetal genotype
✓ Maternal immune system
✓ Endometrial environment
Implantation
Placental bed formation
Maternal diet
Parental genotype
Rise in intraplacental oxygen tension
✓ Metabolic disorders
✓ Mitochondrial dysfunction
✓ Drugs, smoking, alchol, epigenetics
Oxydative stress
Antioxidant defences
Degeneration of syncytiotrophoblast
Massive IVBF obstruction
Ischemia-reperfusion
Progressive IVBF
Early pregnancy failure
Chronic oxidative stress
Resolution
Normal placental function

TOTAL ANTIOXIDANT CAPACITY IN PREGNANCY AND IN CORD BLOOD

(Alberti & Di Renzo, JMFNM 2002)



TOTAL ANTIOXIDANT CAPACITY (CAT)

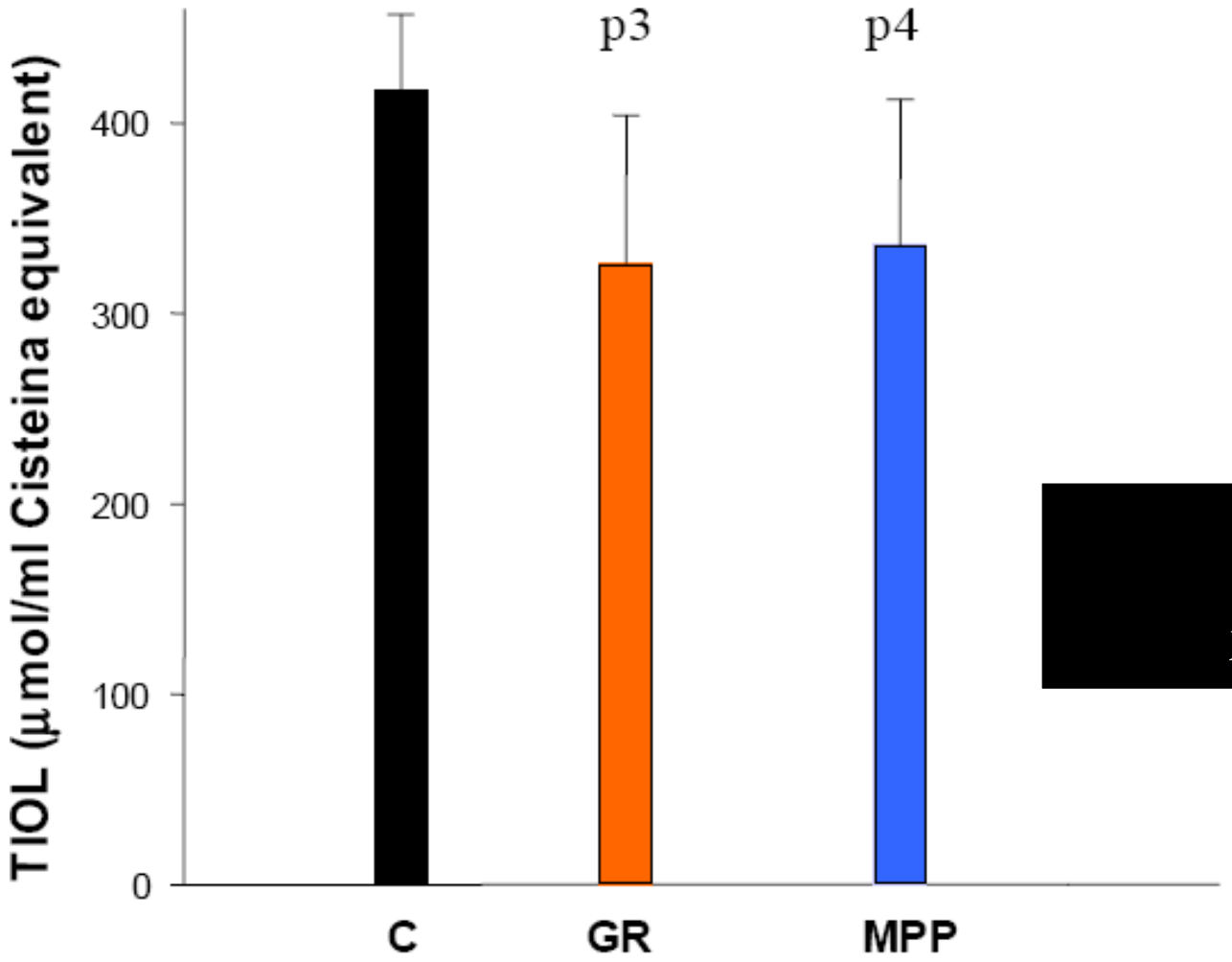


C: Controls
GR: Gest Diabetes
MPP: Preterm labour

p1=0.0086 (p1<0.05) GR vs Controls
p2=0.0479 (p2<0.05) MPP vs Controls

Di Renzo et al, JOG 2011

TIOLIC CAPACITY

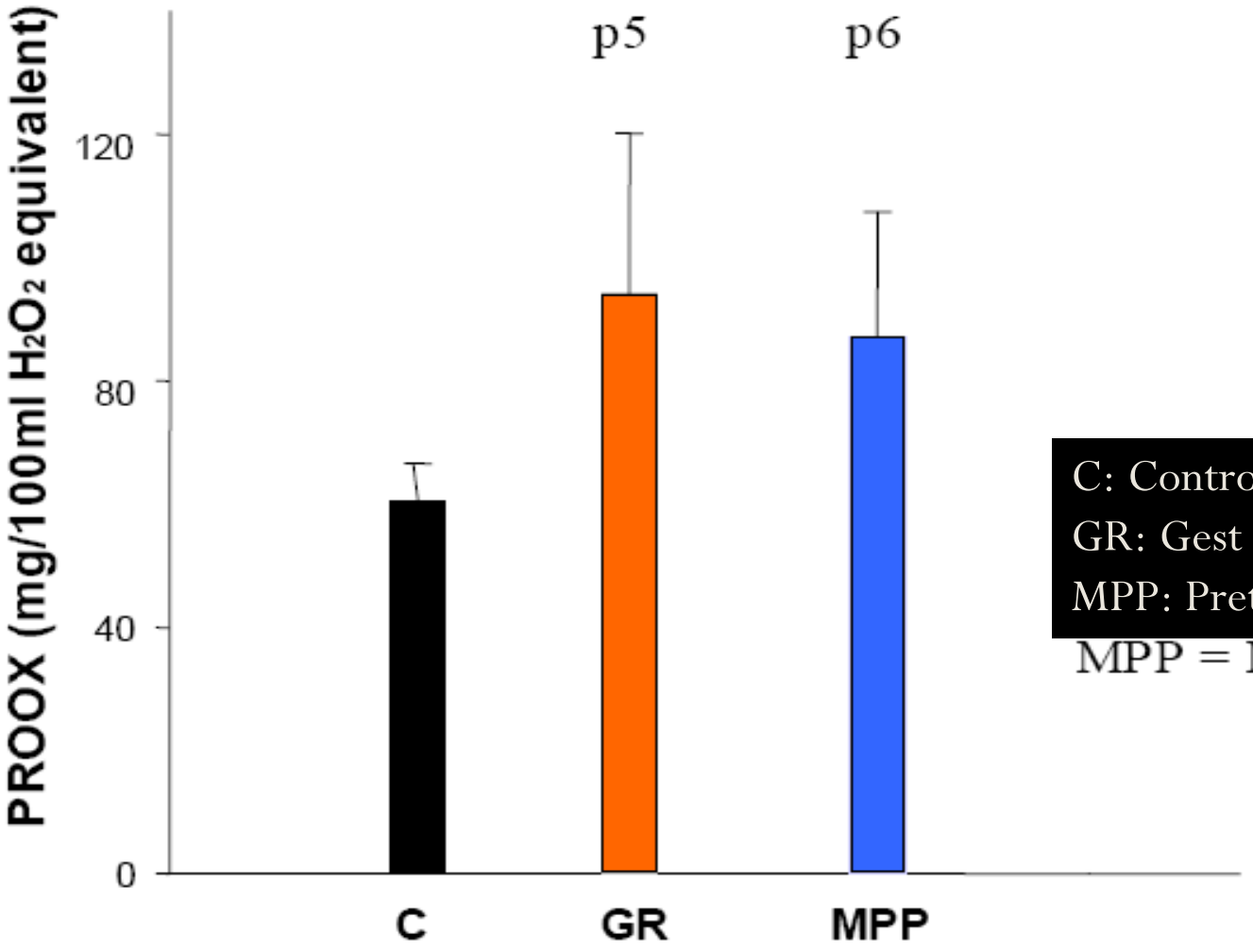


C: Controls
GR: Gest Diabetes
MPP: Preterm labour

p3=0.0029 (p3<0.05) GR vs Controls
p4=0.0084 (p4<0.05) MPP vs Controls

Di Renzo et al, JOG 2011

PROOXIDANT CAPACITY



C: Controls
GR: Gest Diabetes
MPP: Preterm labour

MPP = Minaccia parto pretermine

p5=0.00034 (p5<0.05) GR vs Controls
p6=0.00044 (p6<0.05) MPP vs Controls

Di Renzo et al, JOG 2011

The ***pathology of the placental bed***, primarly through ischemia, but pheraps through other mechanisms (immune-related), may give rise to:

- preeclampsia

- small-for-gestational-age fetuses

- preterm labour with intact or ruptured membranes

- abruptio placentae

- fetal death

- **The manifestation with different clinical phenotipes is dependent upon genetic and environmental factors, as well as the time of onset, duration and extent of the ischemic insult**

- **The potential conflictual relationship between the fetus and the mother plays a role in determining the phenotypic expression of disorders of the placental bed**

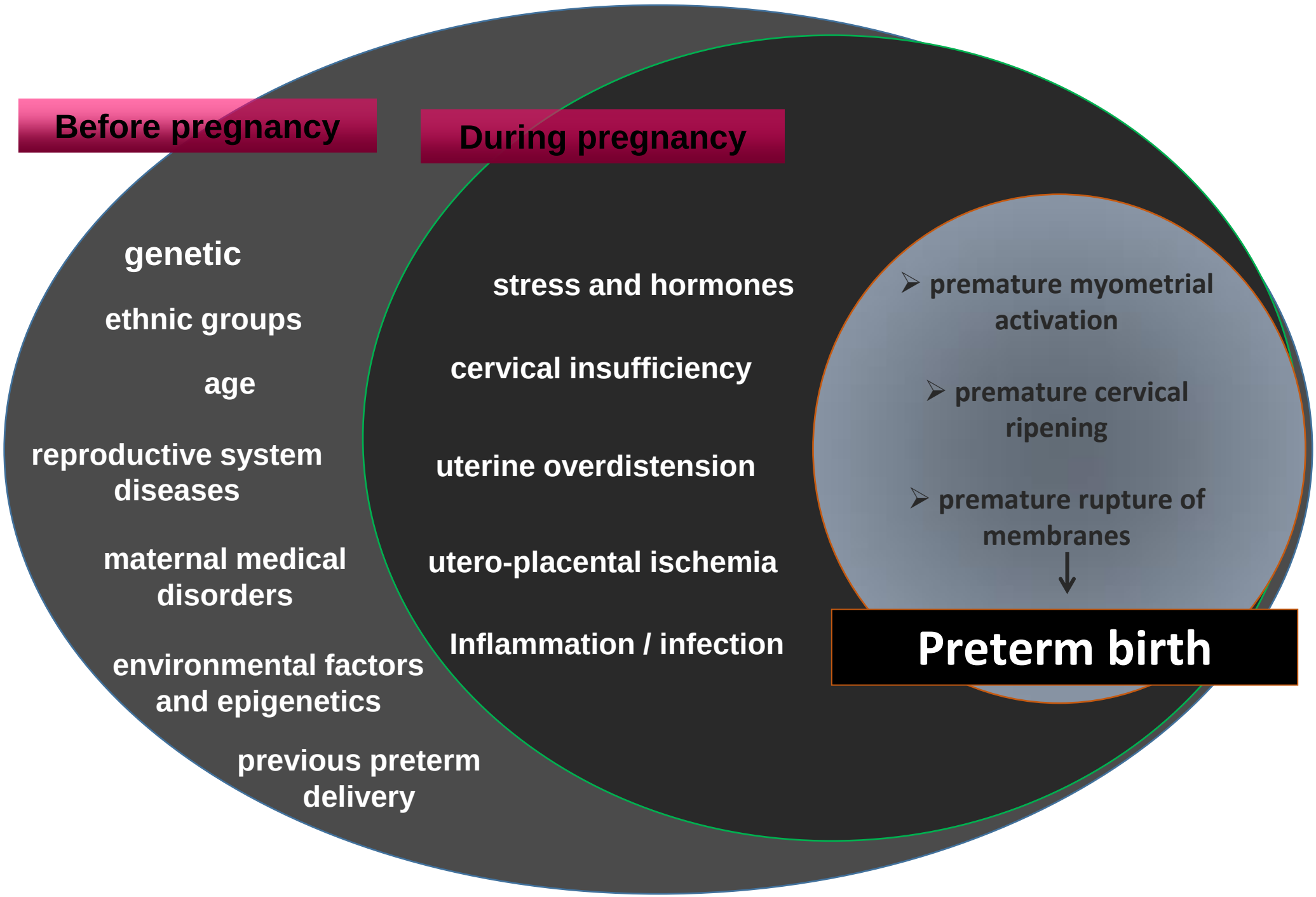
Spontaneous abortion

- Inadequate development of most spiral arteries in the decidual bed with preservation of the musculo-elastic tissue; no evidence of invasion by extravillous trophoblasts of the decidual segment of the spiral artery

- Further investigation is required to elucidate the role of trophoblast plugging of the spiral arteries and physiologic transformation of the decidual and myometrial segments in ***early spontaneous abortions***. Since myometrial invasion of the spiral arteries does not occur until after 14 weeks of gestation, one may not expect that failure of transformation of this particular segment may be associated with spontaneous abortion

- When compared with normal pregnancies, myometrial spiral arteries of patients with a ***second-trimester abortion*** (late fetal death) showed reduced endovascular and intramural trophoblasts and less extensive fibrinoid deposits in the wall of the spiral artery.

Preterm birth: pathogenesis



Preterm birth: reproductive system diseases

Polycystic ovary syndrome

Endometriosis

PCOS is associated with a higher risk of developing gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and

preterm birth

Boomsma et al, Hum Reprod Update 2006

Increased risk of preterm delivery among women with endometriosis

Stephansson O et al., Hum Reprod 2010

Gravid women with adenomyosis were associated with increased risk of both spontaneous preterm delivery and PPROM

Juang CM, BJOG 2007

ENDOMETRIOSIS
AND
THE "GREAT OBSTETRICAL SYNDROMES"

1. Endometriosis is associated with myometrial JZ hyperplasia.
2. **The role of myometrial JZ in pregnancy**
3. JZ changes and major obstetrical disorders

Preterm parturition syndrome

(following the key features of these syndromes)

1. ***multiple etiologies*** are implicated in the pathophysiology such as intrauterine infection/inflammation, uterine ischemia, uterine over-distension, cervical disease, endocrine disorders, abnormal allogenic recognition, allergy-like reaction

2. the pathologic condition of short cervix leading to this disorder is **"chronic"** in nature

3. ***fetal involvement*** has been demonstrated in patients with microbial invasion of the amniotic cavity

4. the inclination to use a mechanism of host defense may be determined by *"**gene-environmental interaction**"*

5. the *"**adaptive nature**"* of the clinical manifestation has been proposed in case of microbial invasion of the amniotic cavity, in which the onset of preterm labour and delivery can be considered as a mechanism of defense against intrauterine infection

Placental abruption

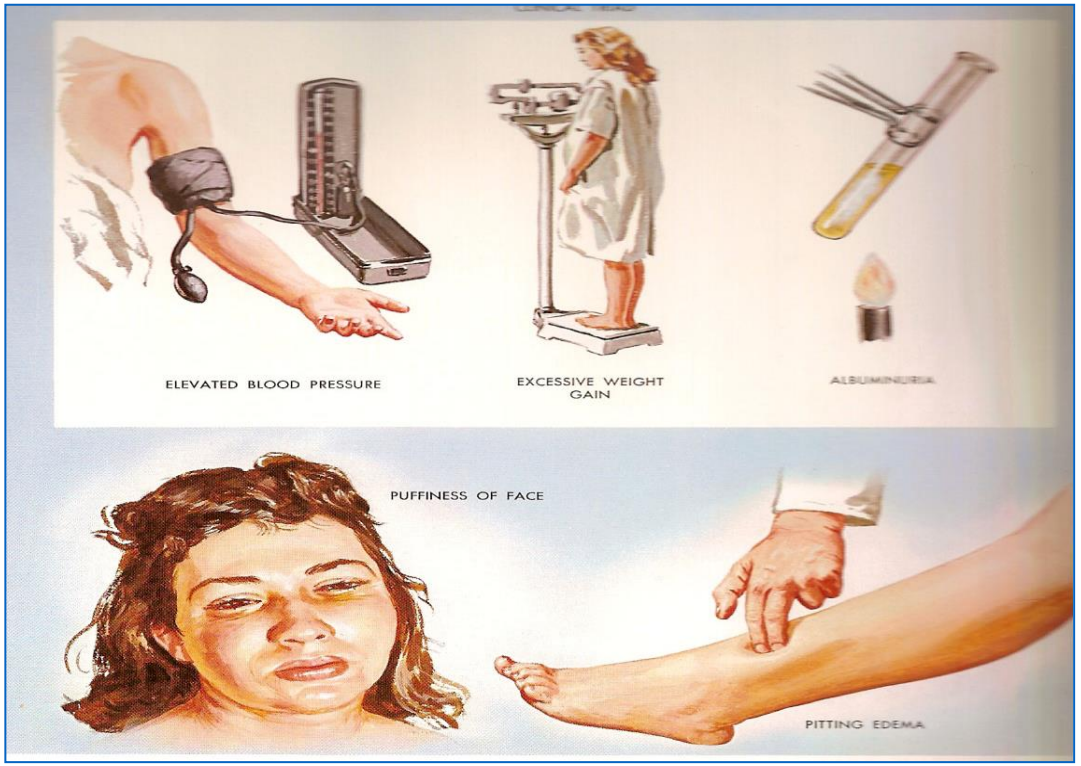
Ischemic lesion of the decidua, leading to decidual necrosis, vascular disruption and bleeding

↓

as hemorrhage occurs, laceration and dissection along a decidual plane and placental separation takes place

↓

more vascular rhexis, arterial hemorrhage, and retroplacental accumulation of blood and furthers placental separation.



PREECLAMPSIA

Preclampsia- Eclampsia

The placental bed of patients with preeclampsia is characterized by a decreased number of spiral arteries with transformation of the myometrial segment

- ***hypertrophic muscular structure***

In preeclampsia associated with IUGR, defective deep placentation is frequently observed with the presence of obstructive lesions in the nontransformed myometrial spiral arteries

Antiangiogenic and angiogenic factors in preeclamptic and controls (mean±SD)

Parameters	Controls (n:80)	Preclampsia (n:86)
sEng(ng/ml)	9.8±1.20	46.4±5.30*
sFLt-1 (pg/ml)	1654.47±150.8	4462.34±230.40*
Free VEGF	254.61±47.39	170.53±36.65*
Free PlGF(pg/ml)	712.44±132.55	136.77±33.50*
Log (sFlt-1/PlGF) score	0.36±0.01	1.51±0.04*

*P<0.05 vs controls

*P<0.05 vs controls.

FRs and AOs in PIH

Increased activity of free radicals promote maternal uterine vascular malformations

- FRs are promoters of maternal vasoconstriction
  - O2 , H2 O2 and NO2 in combinations
    - Inactivate the NO (a vasorelaxant)
    - Causes > PG synthetase activity.
    - Produce peroxynitrate, a potent oxidant

leading to the subsequent development of PIH

Evidence

- Lipid peroxide in pre-eclamptic placenta is about 1.8 times higher in comparison to normal placenta
- Vit. E conc. is decreased in serum of PIH patients
- Severity of hypertension has been found to be inversely proportional to concentration of Vit. E

Preclampsia syndrome

(following the key features of these syndromes)

1. ***multiple etiologies*** are implicated in the pathophysiology such as hydatiform mole, “mirror syndrome” or in the context of the first pregnancy of women at risk(e.g. Metabolic syndrome)

2. ***a long preclinical phase*** has been known to occur (abnormal angiotensin II response, bilateral uterine atery notch, change in the concentrations of anti-angiogenic factors and angiogenic factors)

3. ***fetal involvement*** is represented by fetal growth restriction

4. ***adaptive nature*** of maternal hypertension (hypertension is the consequence of ischemia and not the cause)

5. ***genetic and environmental factors*** play a role in determining the risk of preeclampsia

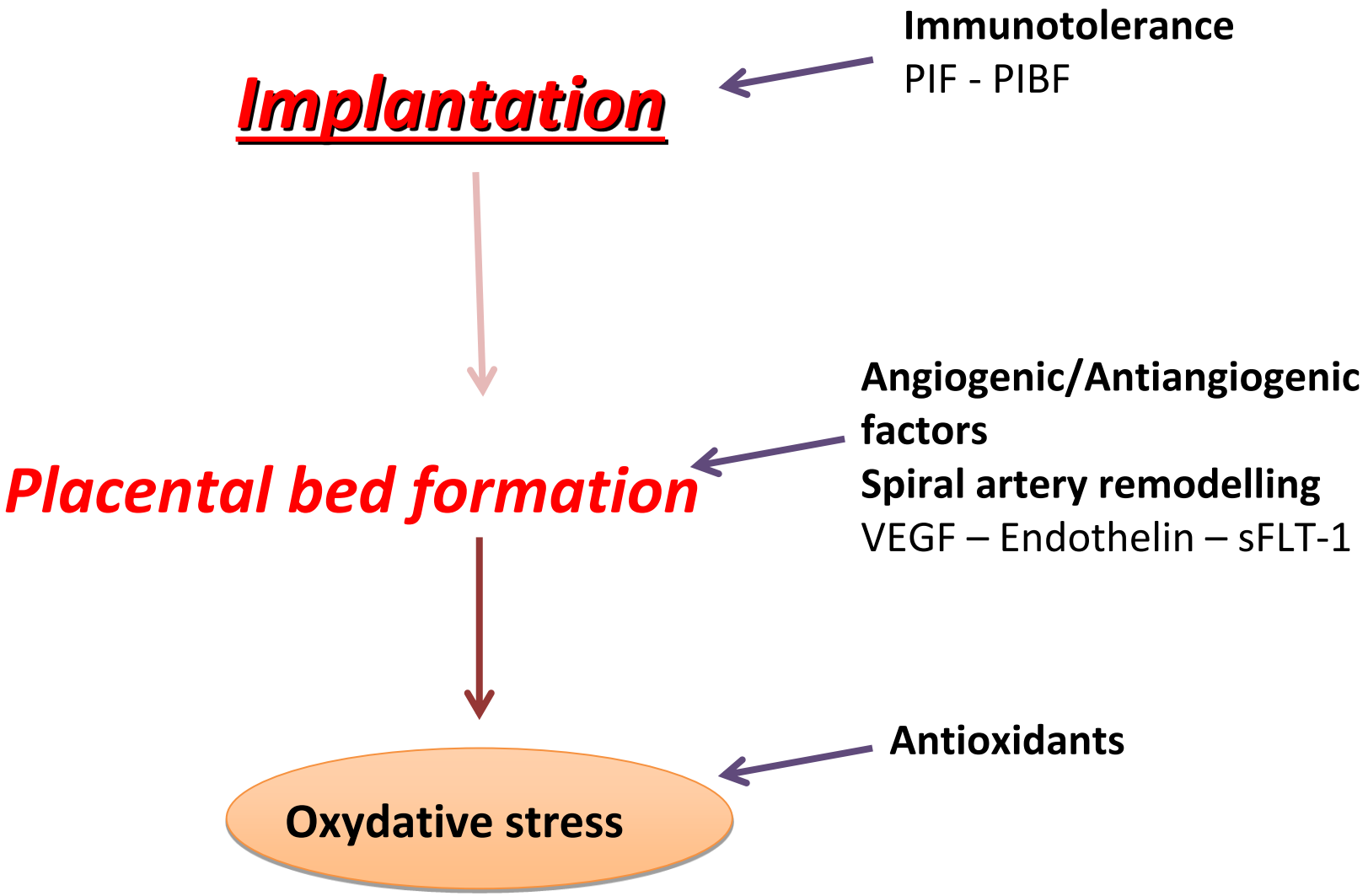
Preeclampsia and gestational diabetes share similar pathopysiologic abnormalities

Insulin resistance
Hypertension
Central obesity/dyslipidemia
Oxidative stress/endothelial dysfunction
Exuberant systemic inflammatory process **o Abnormal cytochines** **o Neutrophils activation**
Increased leptin/reduced adinopectin

CONCLUSIONS

The association of obstetrical syndromes with different vascular diseases in the junctional zone myometrium suggests that the preconditioning of this zone at the time of conception may be a critical factor for successful implantation and the development of normal placentation.

The characterization of angiogenesis and the development of biomarkers in early placental development are likely to provide diagnostic and hopefully noninvasive predictive markers to identify mothers at risk for defective deep placentation syndromes such as preeclampsia, IUGR, preterm birth, and other adverse pregnancy outcomes


Immunotolerance
PIF - PIBF
Implantation
Angiogenic/Antiangiogenic factors
Spiral artery remodelling
VEGF – Endothelin – sFLT-1
Placental bed formation
Antioxidants
Oxydative stress

Types of defective placentation associated with adverse pregnancy outcome

Placental bed formation / Spiral artery remodelling	***Phenotype***
PARTIAL	✓Preterm labor ✓Preterm premature rupture of membranes ✓Intrauterine growth restriction (without hypertension)
ABSENT	✓Preeclampsia ✓Eclampsia ✓HELLP syndrome
ABSENT WITH OBSTRUCTIVE LESIONS	✓Recurent miscarriage ✓Preeclampsia with intrauterine growth restriction ✓Abruptio placentae ✓Stillbirth

Critical determinants

1. PIF-Progesterone-PIBF roles
2. Angiogenic-antiangiogenic factors balance – endothelial damage
3. Oxidative stress
4. Hypoxia – Ischemia – Reperfusion
5. Infection – Inflammation
6. Sex of the fetus-placenta

Reproductive Medicine

MATERNAL-FETAL MEDICINE

Neona-tology

Perinatal medicine

P

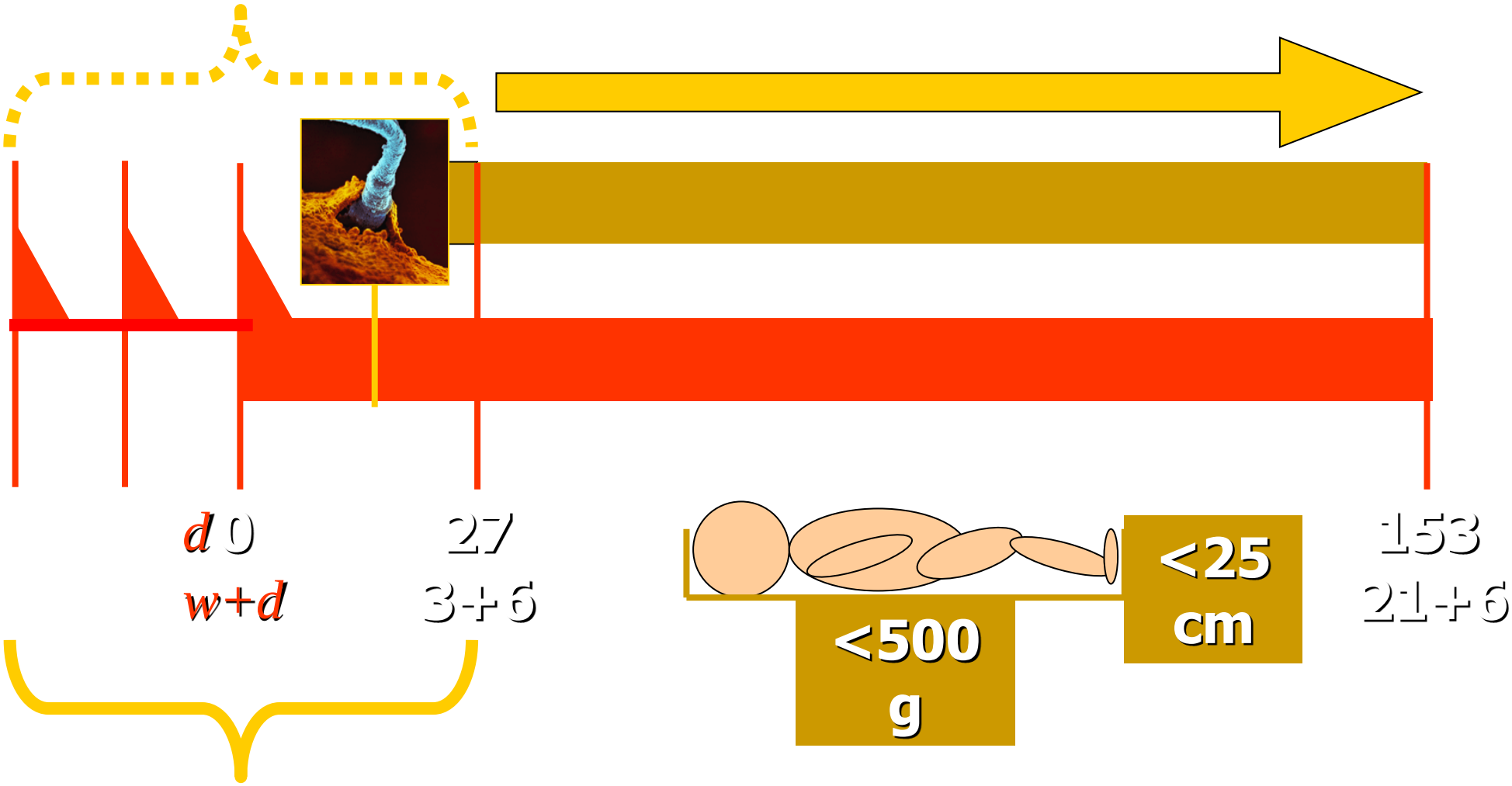
Conception

22 wks

Birth

1 wk

PERICONCEPTIONAL MEDICINE



Counseling to plan pregnancy

REFRAME

Reproductive history

Enviromental toxic chemicals and climate

Folic acid- inositol supplementation

Review genetic history

Antioxidants and oxidative stress

Medical preexisting conditions

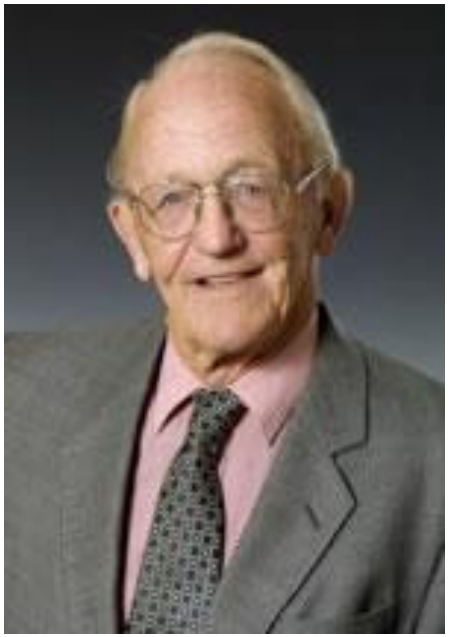
Evaluate immunizations and infections

If ones has seen further than others
it is by standing on the shoulders of giants

Isaac Newton (1642–1727)

Arpad Csapo

Leon C Chesley



Graham Mont Liggins

Ivo Brosens

Roberto Romero


THANK YOU
GRAZIE