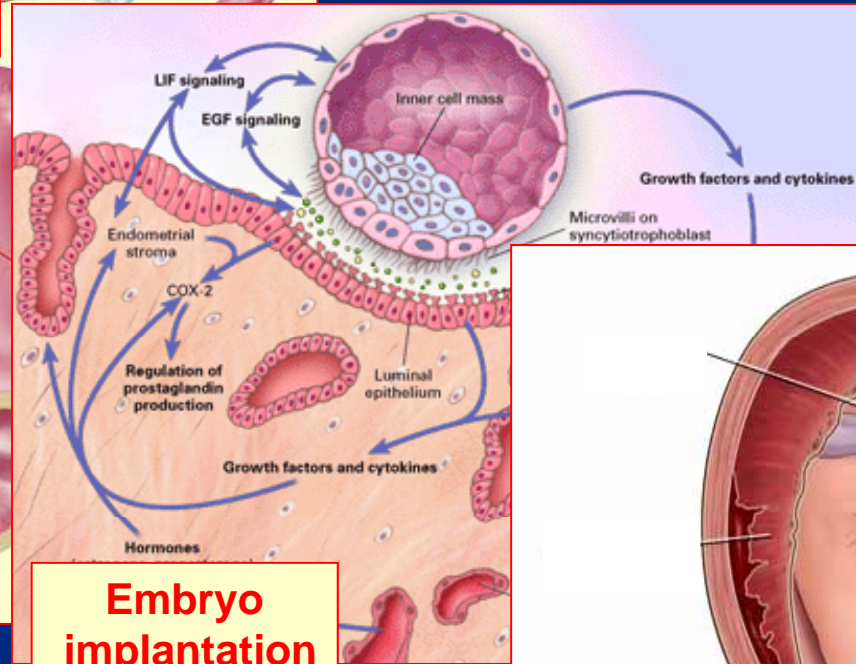
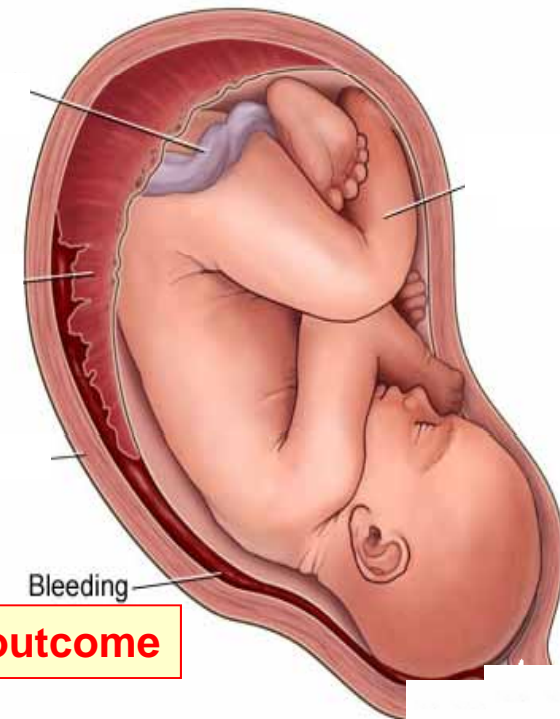


# PCOS and reproductive outcome

**Periconceptional influences**



**Embryo implantation**



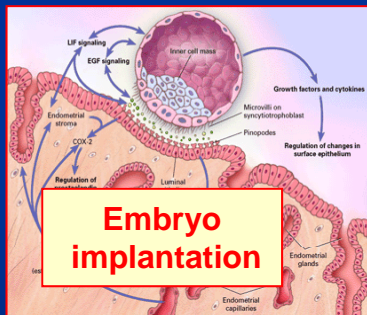
**Pregnancy outcome**

# Impact of PCOS on reproductive outcome



## ✓ Incidence of periconceptional damage

*Sahu B, Arch Gynecol Obstet 2008  
Qiao Human Reprod, 2010*



## ✓ Incidence of miscarriage 30-50%

*Giudice LC, Best Pract Res Clin Endocrinol Metab 2006  
Homburg R, Best Practice Research, 2006*



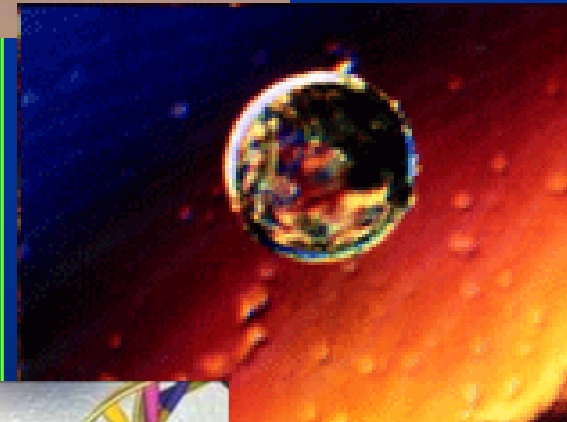
## ✓ Incidence of negative pregnancy outcome

- Gestational Diabetes Mellitus: 20-30%
- PIH: 13.3 %
- Fetal Growth Restriction: 10 -15 %

*Boomsma, Hum Reprod Update 2006  
Eshre Consensus Thessalaniki 2008*

# Periconceptional damage and PCOS

1. Poor oocyte quality
2. Poor embryo quality
3. Epigenetic influences



PCOS patients have a poor oocyte quality

**hyperinsulinism**

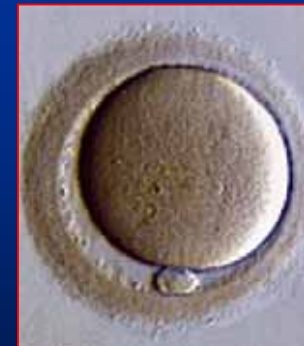
**hyperandrogenemia**

**aberrant ovarian growth factors**

abnormal follicle development

poor oocyte quality

**low fertilization rate**



# Ovarian growth factors and oocytes maturation in PCOS

**GDF-9 deficit  
(growth differentiation  
factor)**

**increased TNF alfa**

**increased expression  
EGF receptors**

**GDF-9 reduces  
LH receptors on  
granulosa cells**

**increased  
AMH**

**increased  
inhibin**

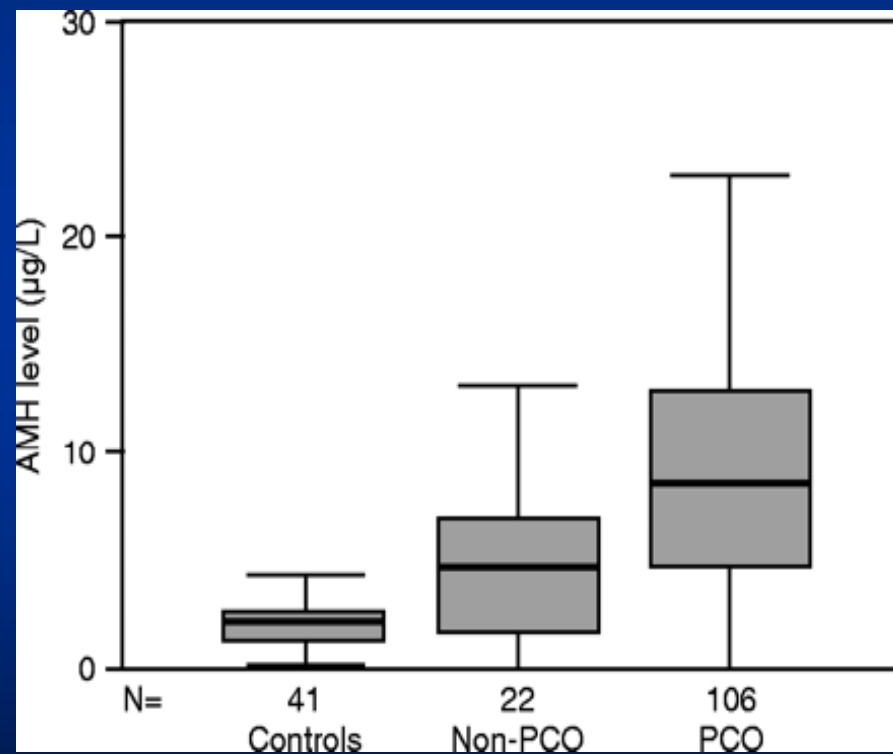
**abnormal  
chromosomal  
allignment of  
oocytes**



**POOR OOCYTE QUALITY**

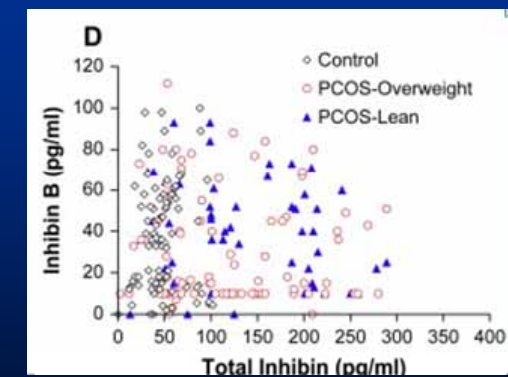
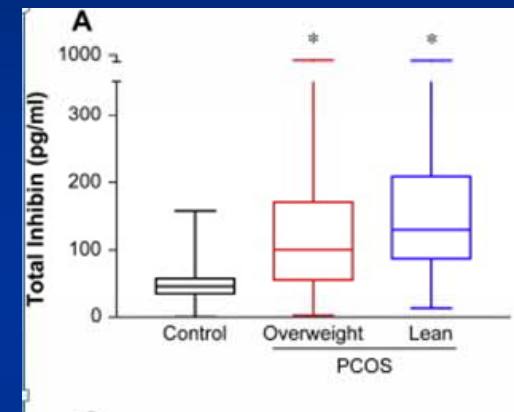
# Ovarian growth factors and oocyte maturation in PCOS

## AMH



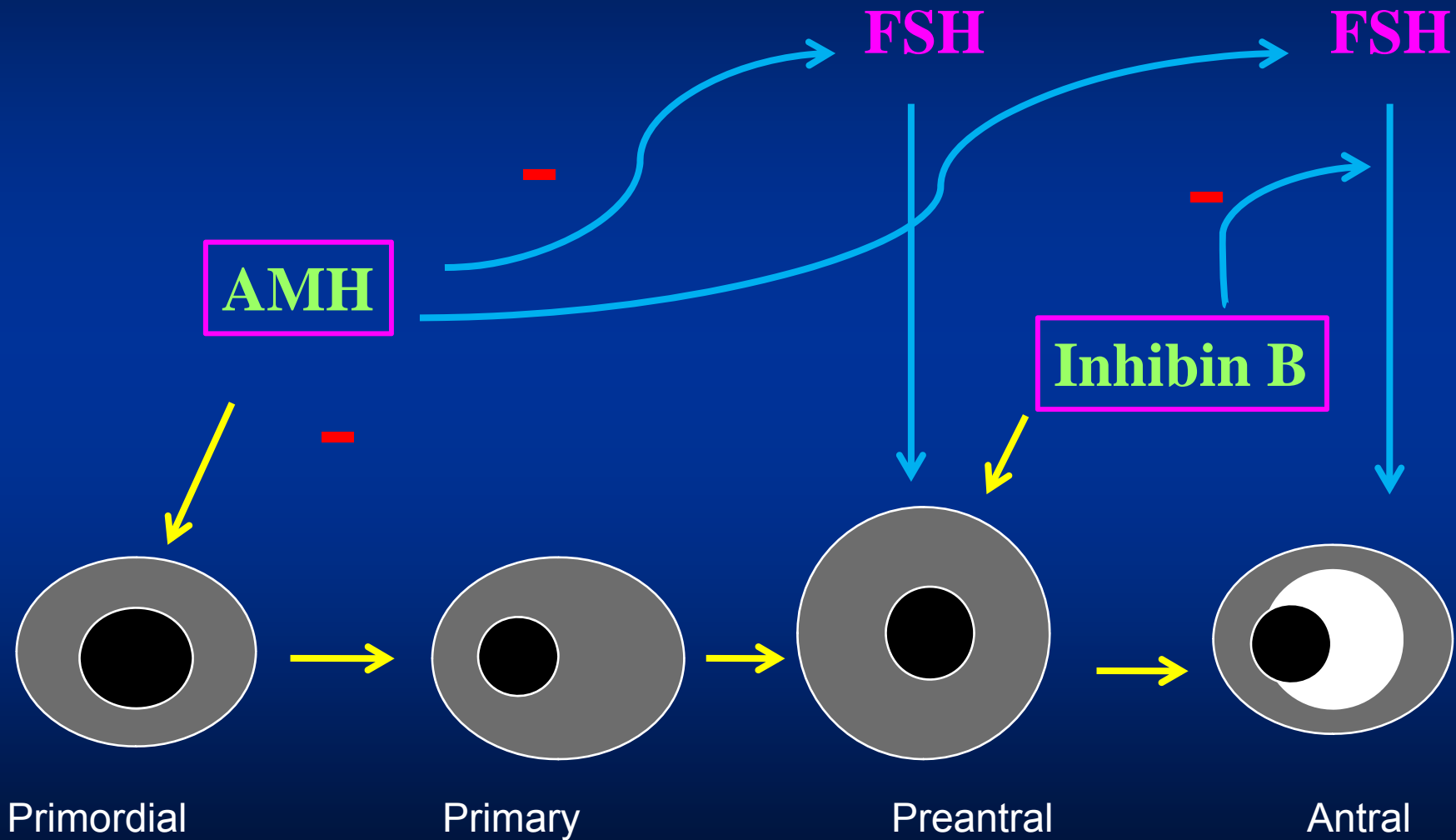
Visser et al, *Reproduction* 2006

## Inhibins



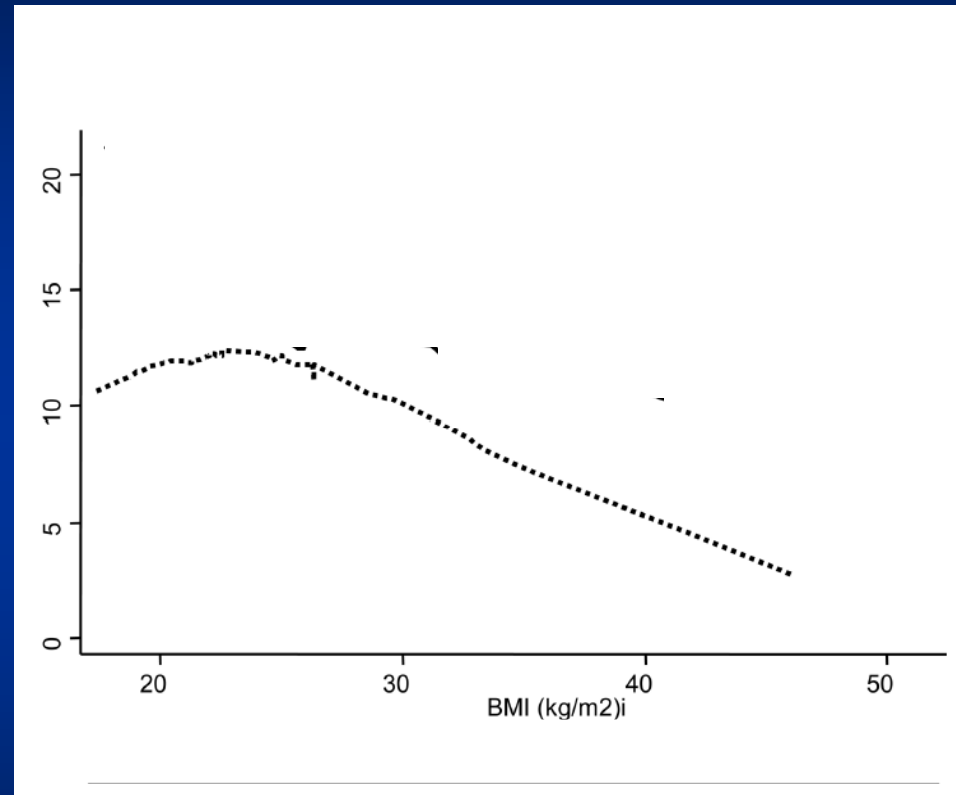
Tsigkou et al, *Fertil Steril* 2008

# Ovarian growth factors and oocyte maturation in PCOS



## Poor Oocyte quantity in PCOS/obesity?

Oocytes



PCOS

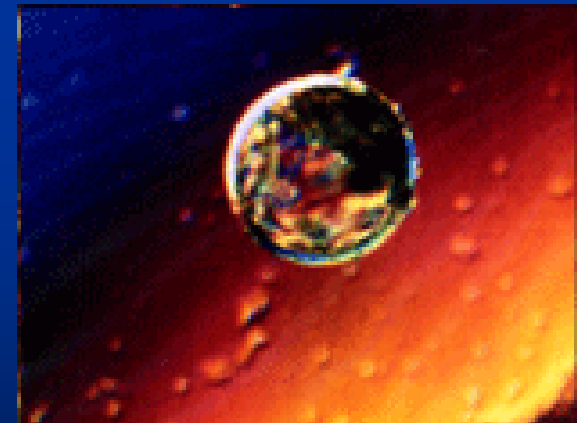
Non-PCOS

In PCOS women the BMI is inversely correlation with oocyte retrieved



# Periconceptional events and PCOS

1. Poor oocyte quality
2. Poor embryo quality
3. Epigenetic influences



# Poor Embryo quality in PCOS?

**NO**

**“There are few indications that embryo quality are significantly compromised in women with PCOS, at least as far as in vitro maturation and IVF are concerned”**

*Weghofer et al Fertil Steril 2007*

**YES**

**Poor oocyte quality**



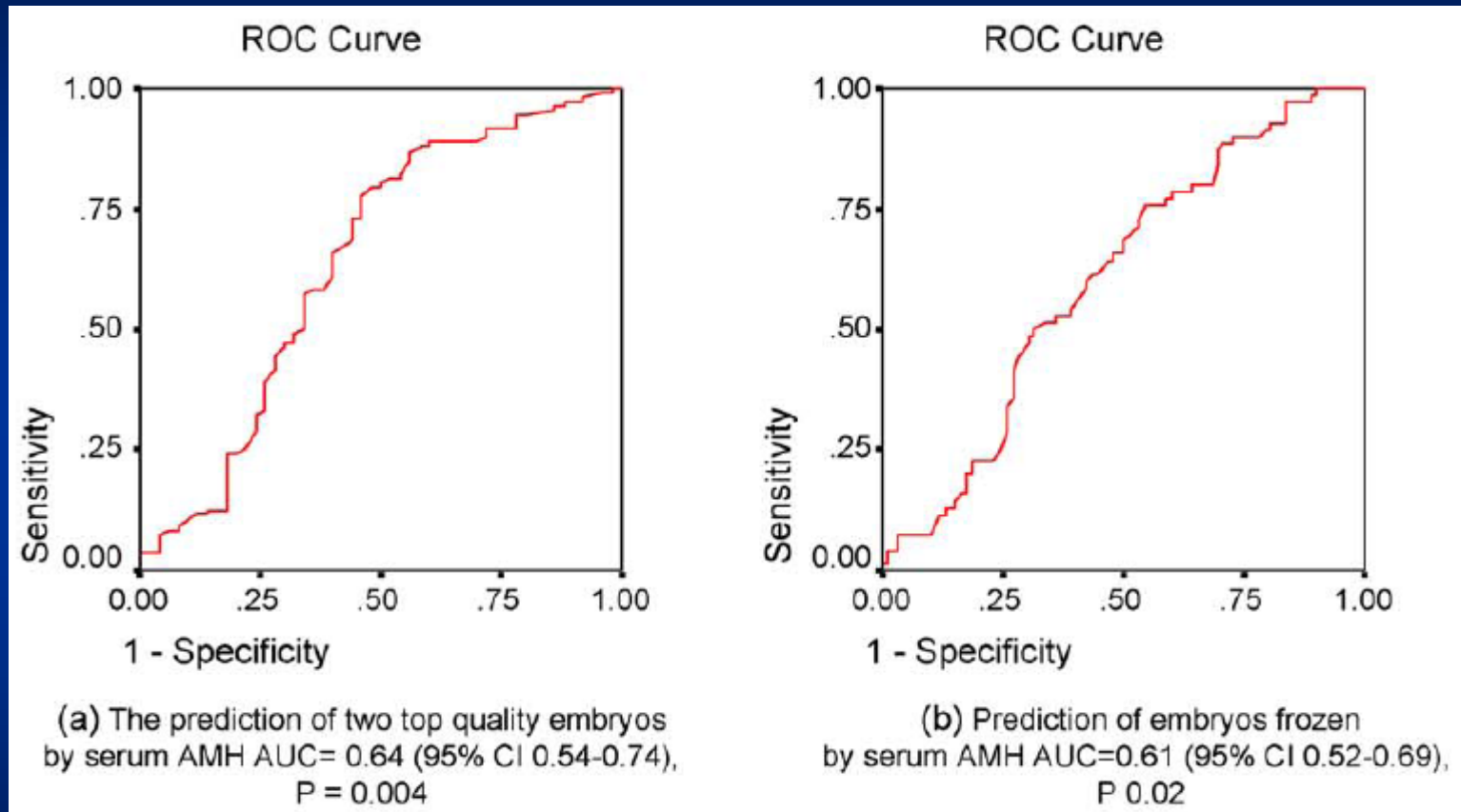
**Increased markers of oxidative stress**

**Increased follicular fluids  
homocysteine levels PCOS**

**Poor embryo quality**

*Qiao et al Human Reprod 2010*

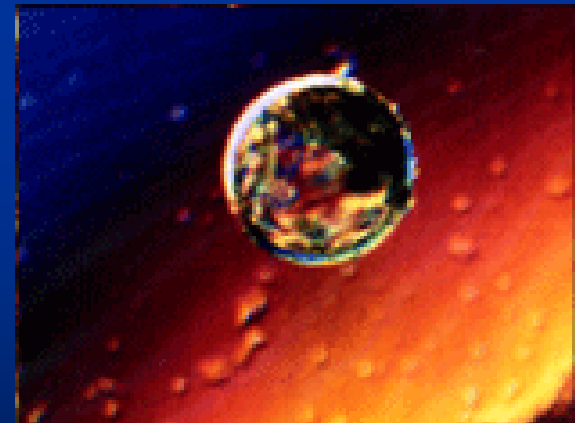
## AMH, oocyte and embryo quality



**AMH is a predictor of oocytes retrieved and of the number of good quality embryos available for transfer and freezing.**

# Periconceptional events and PCOS

1. Poor oocyte quality
2. Poor embryo quality
3. Epigenetic influences



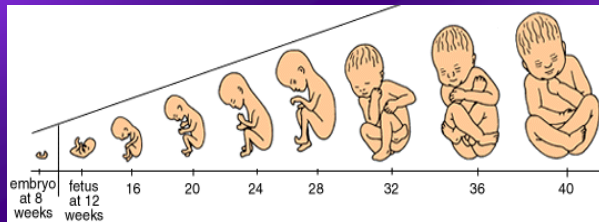
# Fetal origins of adult disease

Undernutrition – Hypoxia -  
Infection – Stress hormones

*Barker DJ Lancet 1989*

↓

**Altered Developmental  
Physiology**



**Neonatal  
Responses**

→

**Predisposition  
Permanent Effects  
CHD, Type II Diabetes**

The associations are thought to be consequences of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development.

## PCOS and epigenetic influences

“...in utero hyperandrogenemia exposure may lead to abnormal epigenetic reprogramming during fetal development, thus resulting in PCOS phenotype in the adult...”

### 1. Increased incidence of :

- AR (CAG repeats)
- chromosome X inactivation

### 2. Altered fetal LH secretion

### 3. Reproductive consequences on the fetus

### 4. Metabolic consequences on the fetus



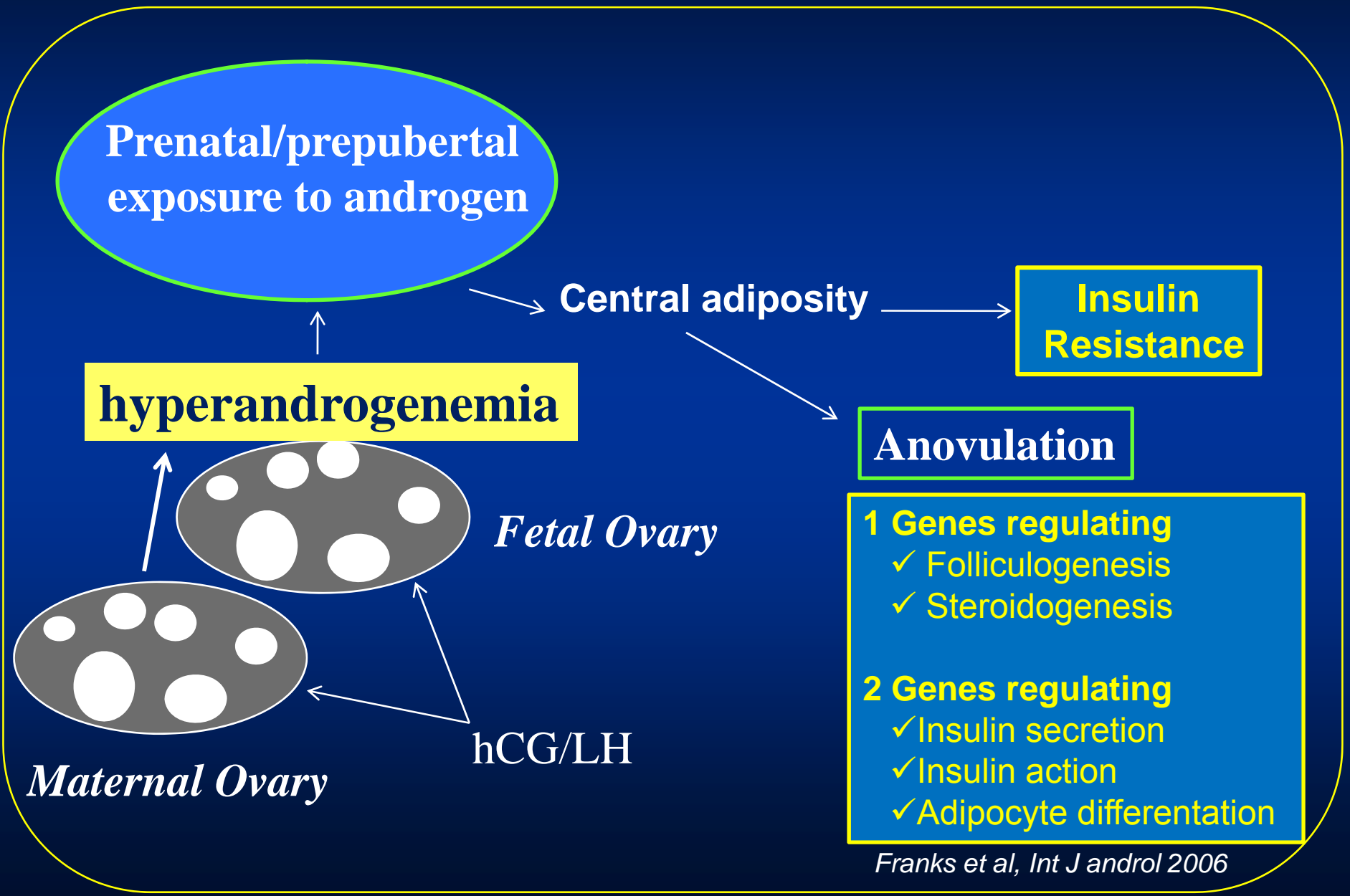
# PCOS and its developmental origin

**Table 1** Reproductive and metabolic PCOS-like abnormalities in prenatally androgenized female rhesus monkeys and sheep

PCOS trait <sup>a</sup>	Rhesus monkeys		Sheep
	Early treated	Late treated	
<b>Reproductive</b>			
Ovarian hyperandrogenism	Yes	Yes	Ovarian androgen receptor upregulation
Anovulation	Yes	Yes	Yes
Enlarged polyfollicular ovaries	Yes	Yes	Yes
LH hypersecretion	Yes	No	Yes
Reduced steroid negative feedback on LH	Yes	Yes	Yes
Impaired embryonic development	Yes	Yes	Impaired fertility
<b>Metabolic</b>			
Insulin resistance	Yes	No	Yes
Beta cell impairment	Yes	No	?
Hyperglycemia	Yes	Yes	No
Increased type 2 diabetes	Yes	No	Unknown
Increased abdominal fat	Yes	With increasing BMI	Unknown
Hypertension	Unknown	Unknown	Yes
Hyperlipidemia	Yes	Unknown	Yes

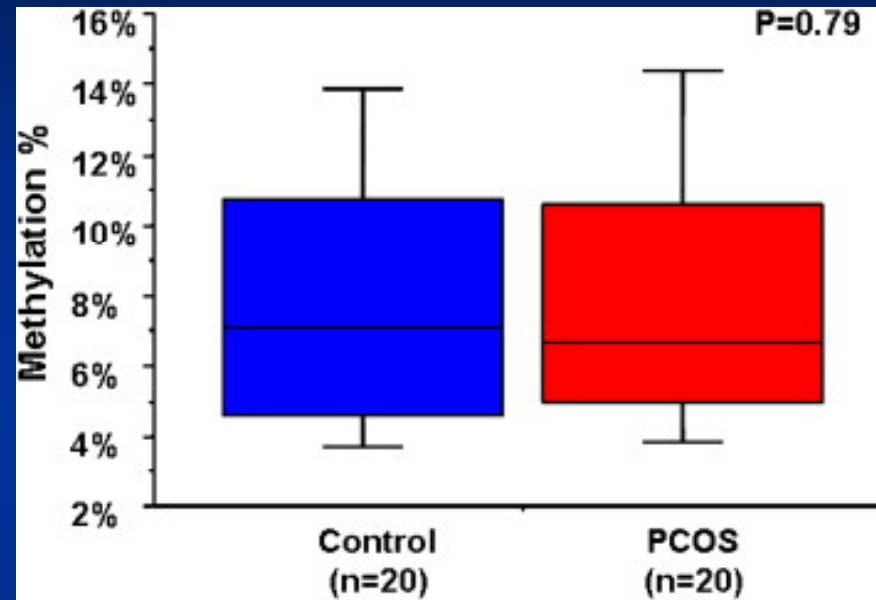
**Critical times exist during fetal development when the steroidal status of the mother permanently may alter the physiology of the fetus and its susceptibility to disease after birth.**

# PCOS and its developmental origin





## Epigenetics in polycystic ovary syndrome: A pilot study of global DNA methylation



“... no significant difference in the global methylation of peripheral leukocyte DNA between patients with PCOS and matched controls.

*Xu Fertil and Steril 2009*

It's necessary to investigate methylation in key tissues other than peripheral leukocytes, such as human ovaries, adipose tissue or adrenals, and specific target genes or regions.

## Periconceptional damage and PCOS:



**hyperandrogenemia**

**obesity**

**hyperinsulinism**

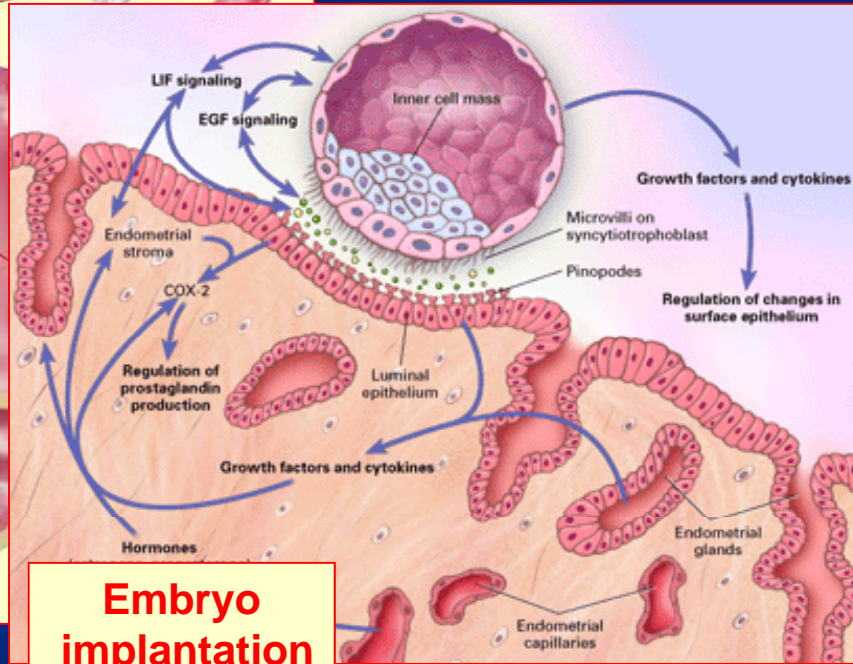
**aberrant ovarian growth factors**



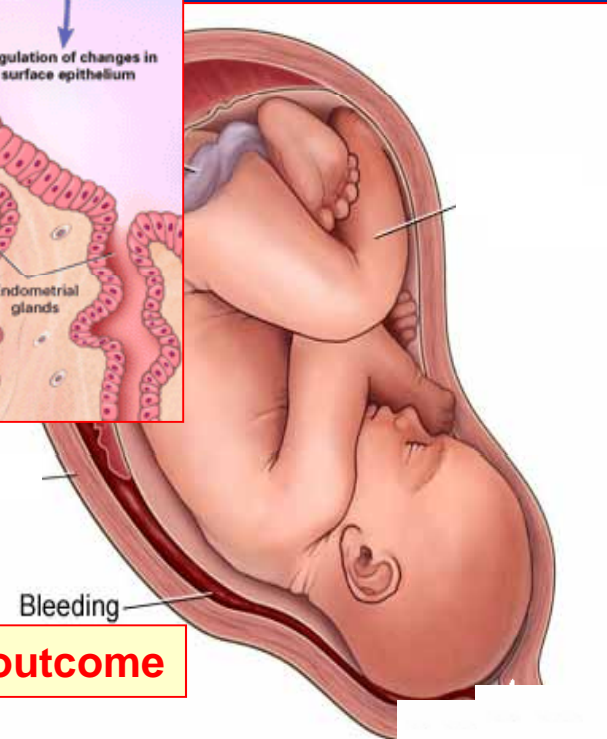
- ✓ Poor oocyte and embryo quality
- ✓ Susceptibility to adult disease

# PCOS and reproductive outcome

**Periconceptional influences**

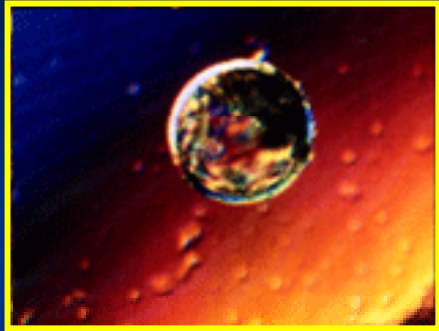


**Embryo implantation**



**Pregnancy outcome**

# PCOS and miscarriage: epidemiology



Miscarriage rate in  
healthy women



10-15%

Miscarriage rate in women  
with PCOS



30-50%

PCOS in women with  
recurrent miscarriage



30%

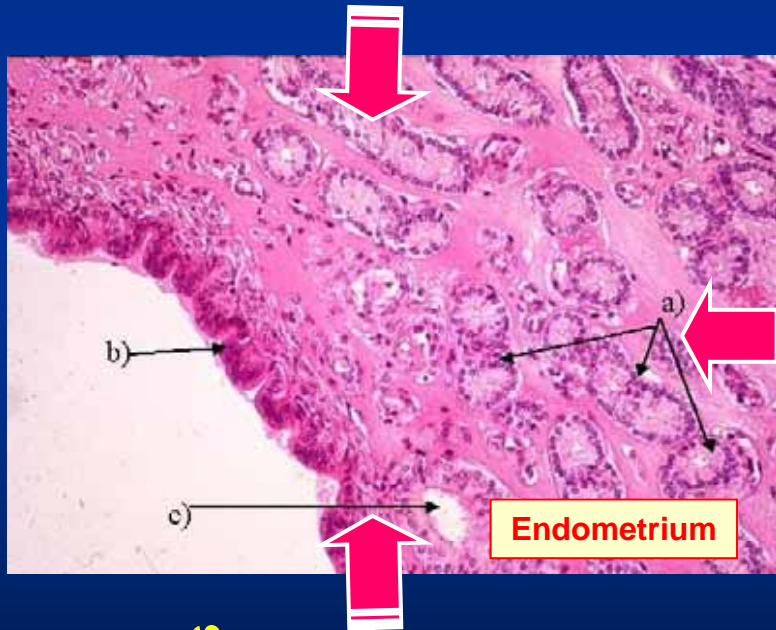
*Giudice LC, Best Pract Res Clin Endocrinol Metab 2006*

*Homburg R, Best Practice Research, 2006*

# Endometrium and PCOS

## endocrine

- elevate serum LH
- persistent estrogen action
- hyperandrogenemia
- hyperinsulinism



## paracrine

- altered expression of:
- growth factors (IGFBP-I; activin A)
  - cytokines and inflammatory factors (IL-1; LIF; CRH)
  - cell adhesion molecules (integrins; glycodeclin)

## others

- decreased endometrial vascularity
- increased plasminogen activator inhibitor (PAI)

Van Der Spuy ZM, Best Pract Res Clin Obstet Gynecol 2004

Giudice LC, Best Pract Res Clin Endocrinol Metab 2006

# PCOS and miscarriage: : endocrine factors

**hyperinsulinism**

**hyperandrogenemia**

**anovulation**

**IGFR**

**++AR**

**persistent estrogen action**



**endometrial dysfunction**

**++ER $\alpha$**

**Impaired  
decidualization**

**decreased expression of  
glycodelin and  $\beta 3$   
integrin**

**Early pregnancy loss**

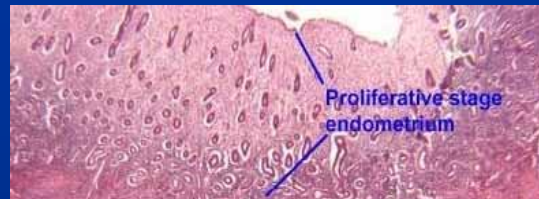
# PCOS and miscarriage paracrine and metabolic factors

Growth factors

+ IGFBP  
- IGF-1

Cytokines

- LIF  
- IL-1



Endometrial dysfunction



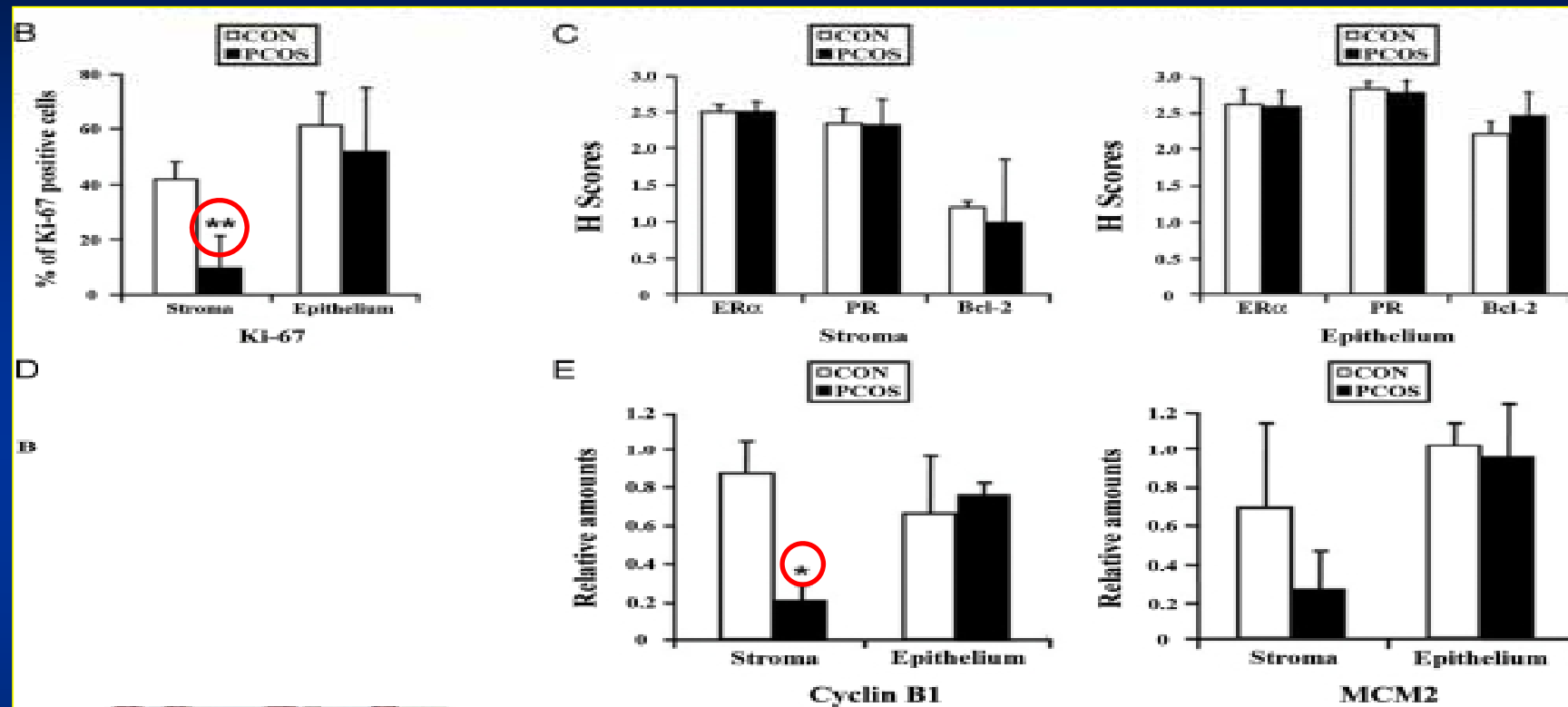
Early pregnancy loss

Metabolic factors

+ PAI  
+ homocystein

Altered  
fibrinolysis-  
antifibrinolysis  
balance

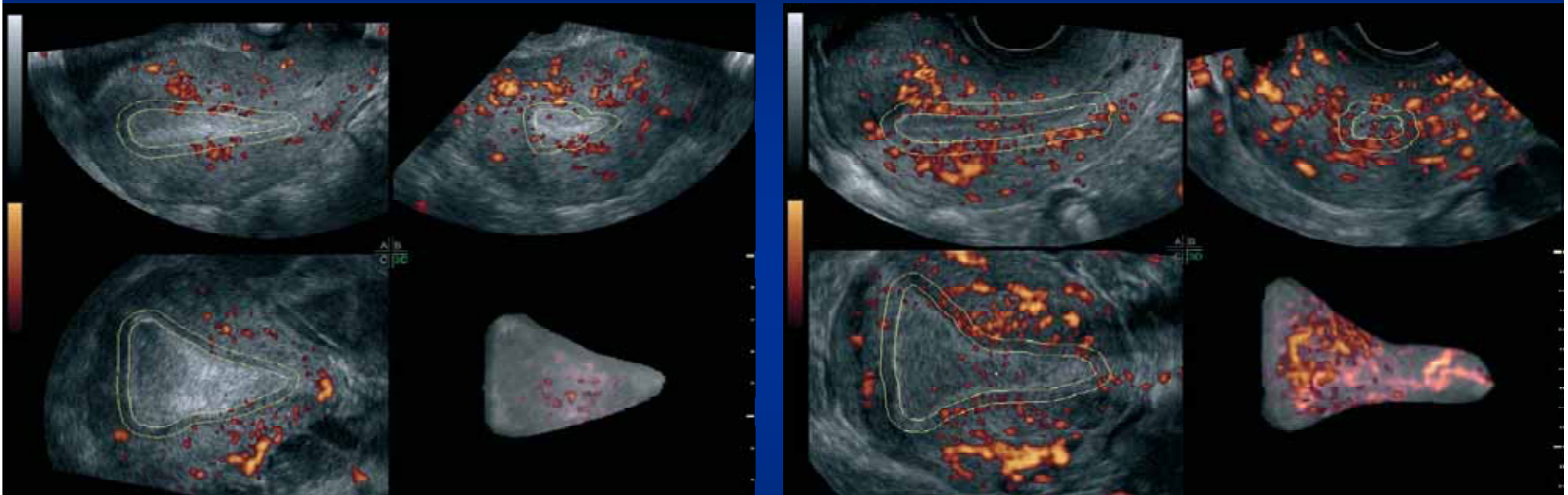
# PCOS and miscarriage: endometrial expression profile.



Impaired endometrial mRNA of cell cycle regulators, enzyme glycoysis and integrines in PCOS are distinctly different from those of regularly cycling women.

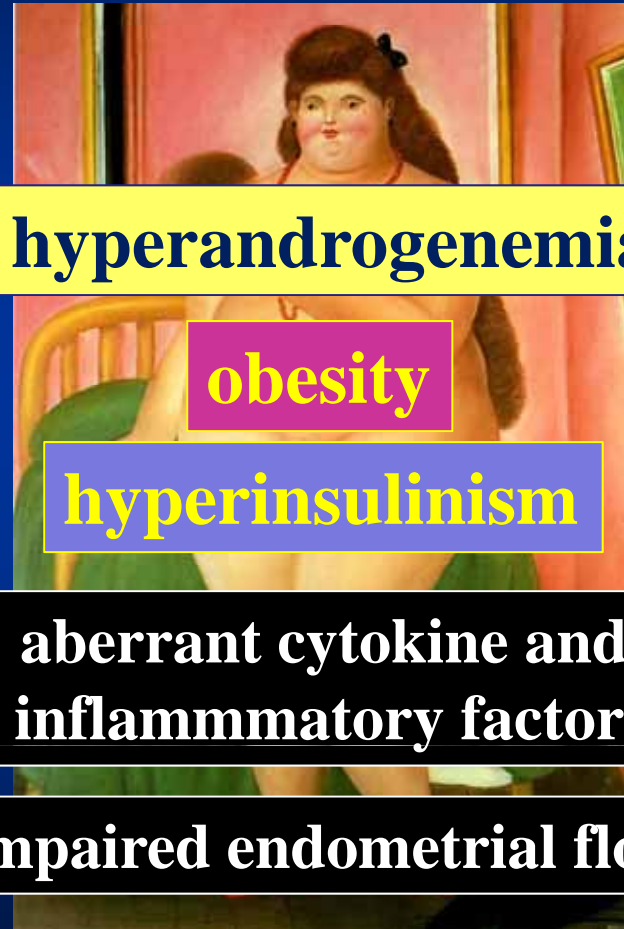


## PCOS and miscarriage: impaired endometrial blood flow



**Subendometrial and endometrial blood flow is significantly impaired in women with PCOS who have clinical signs of hyperandrogenism, but not in women without hyperandrogenism.**

# Miscarriage and PCOS



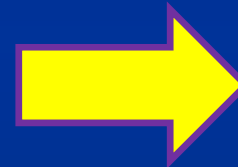
**hyperandrogenemia**

**obesity**

**hyperinsulinism**

**aberrant cytokine and  
inflammatory factors**

**impaired endometrial flow**



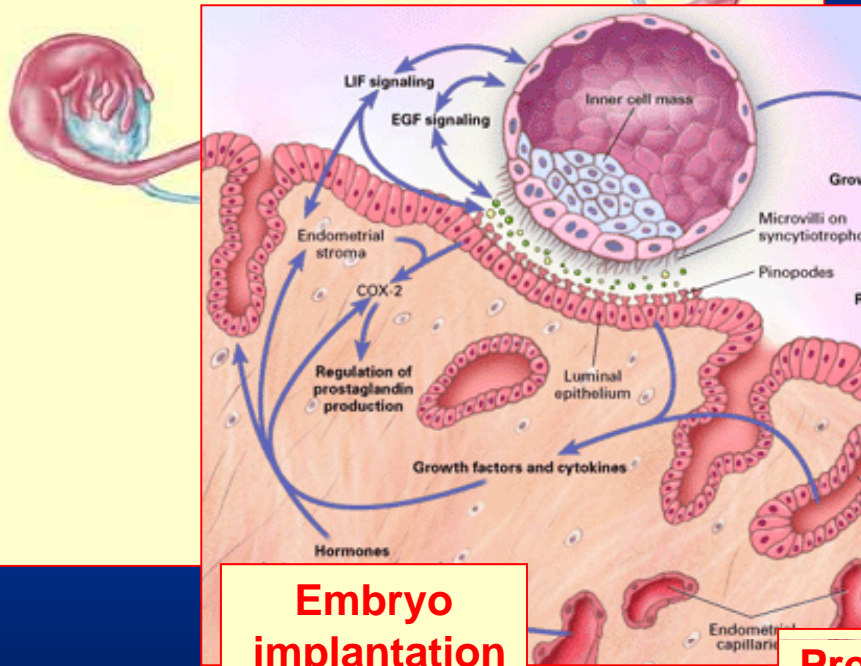
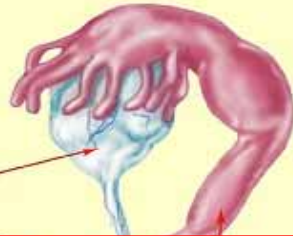
**Endometrial dysfunction**



**Miscarriage**

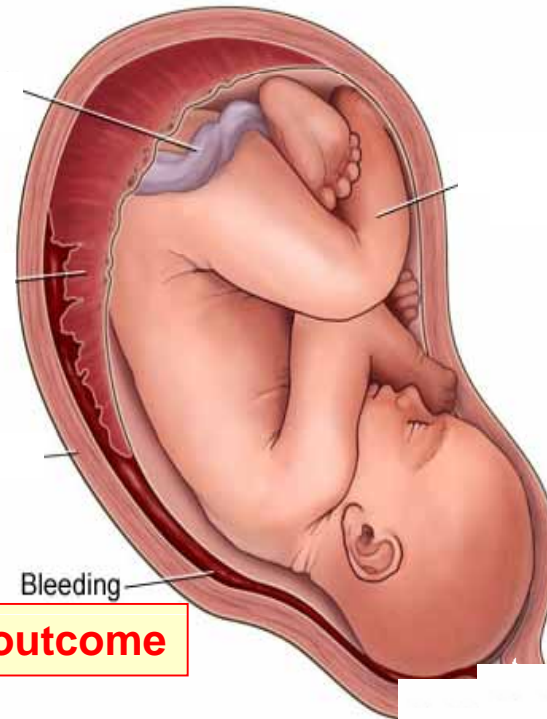
# PCOS and reproductive outcome

**Periconceptional influences**



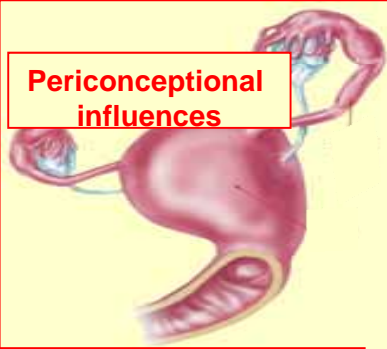
**Embryo implantation**

**Pregnancy outcome**



# Impact of PCOS on reproductive outcome

## Periconceptional influences



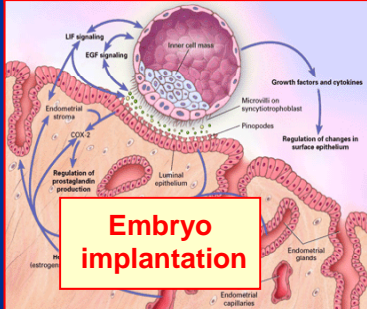
## ✓ Incidence of periconceptional damage

*Sahu B, Arch Gynecol Obstet 2008  
Qiao Human Reprod, 2010*

## ✓ Incidence of miscarriage 30-50%

*Giudice LC, Best Pract Res Clin Endocrinol Metab 2006  
Homburg R, Best Practice Research, 2006*

## Embryo implantation



## Pregnancy outcome



## ✓ Incidence of negative pregnancy outcome

- Gestational Diabetes Mellitus: 20-30%
- PIH: 13.3 %
- Fetal Growth Restriction: 10 -15 %

*Boomsma, Hum Reprod Update 2006  
Eshre Consensus Thessalaniki 2008*

# PCOS and pregnancy outcome: pathogenesis

**obesity**

**hyperandrogenemia**

**hyperinsulinism**



- ✓ Gestational diabetes mellitus
- ✓ Pregnancy-induced hypertension
- ✓ Preeclampsia
- ✓ Fetal growth restriction

- ✓ Preterm birth
- ✓ Increase caesarean section
- ✓ Increased operative delivery
- ✓ Neonatal intensive care unit

# PCOS and pregnancy outcome: the role of hyperglycemia



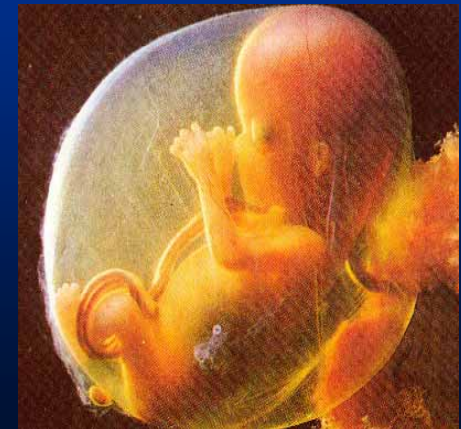
## Counterregulatory Hormones and cytokines

hPL  
Placental GH  
CRH  
Progesterone  
Adipokines (TNF- $\alpha$ )



insulin  
resistance

Glucose, AA



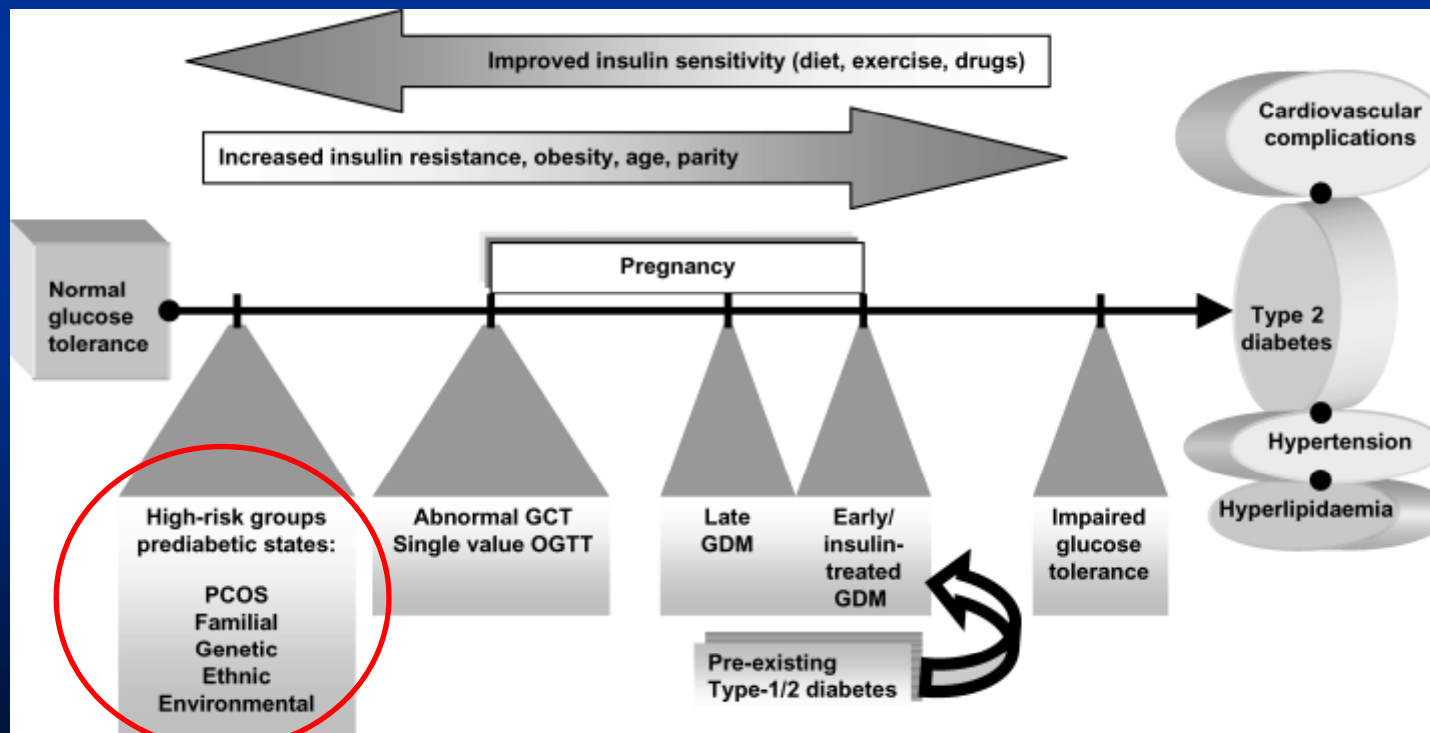
# PCOS and pregnancy outcome: the role of hyperglycemia

GDM in  
healthy women

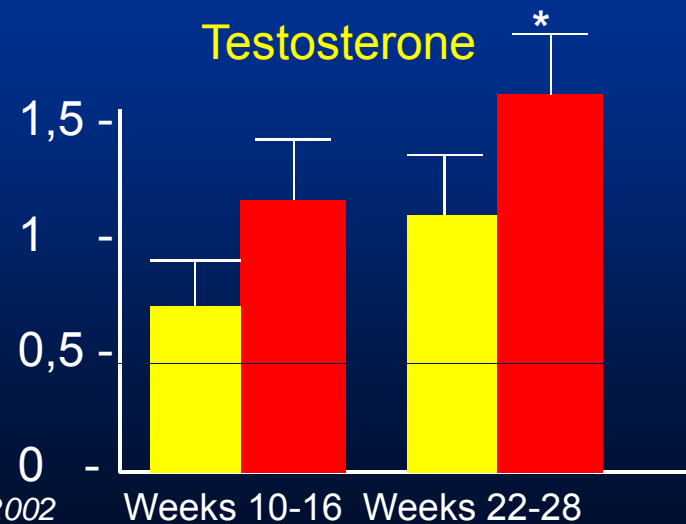
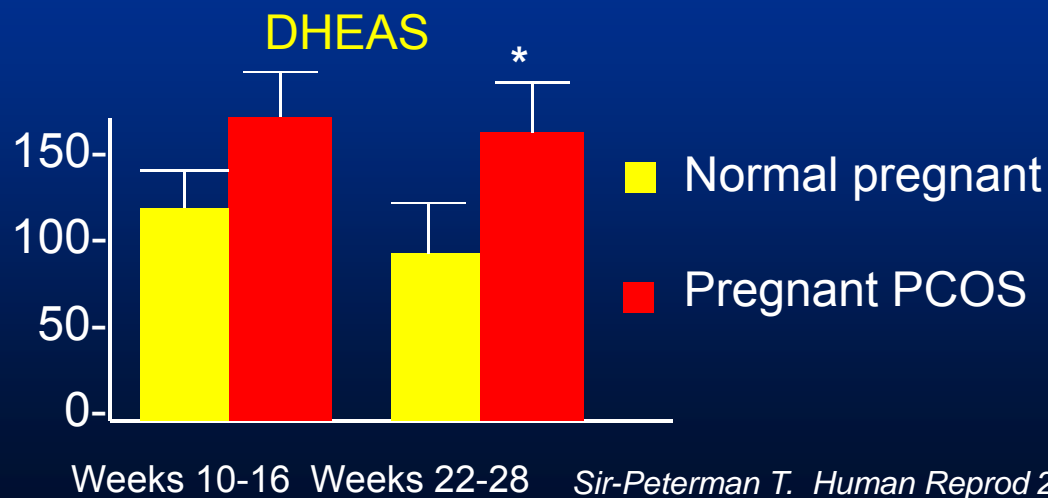
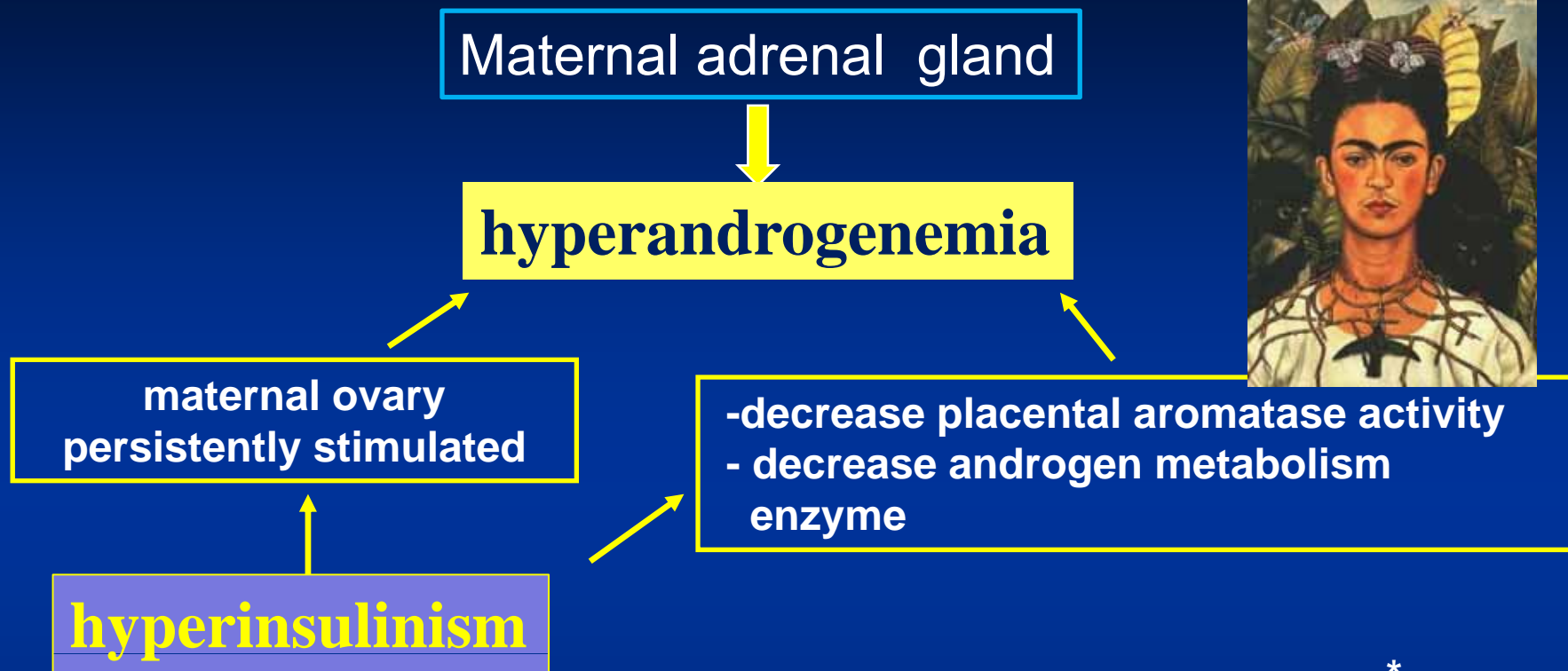
1-14%

GDM in women with PCOS

20-30%



# PCOS pregnancy outcome: the role of hyperandrogenemia





# PCOS and pregnancy outcome: the role of hyperandrogenemia

Placenta of women with PE express more androgen receptors mRNA

	Preeclamptic women (n=40)	Normal pregnant women (n=40)	p
Gestational age (yr)	29.6±5.0	28.7±4.4	NS
Gestational week (wk)	35.9±1.33	37.0±0.89	NS
Body weight (g)	1,822.0±726.1	3,268.2±368.8	<0.01
Systolic blood pressure (mmHg)	179.4±18.7	123.0±8.5	<0.01
Diastolic blood pressure (mmHg)	110.5±11.5	77.6±8.0	<0.01
Serum testosterone (ng/mL)	0.52±0.13	0.34±0.11	<0.01

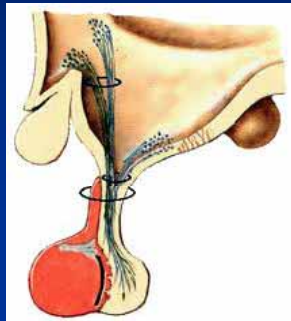


## Increased Androgen Receptor (AR) expression

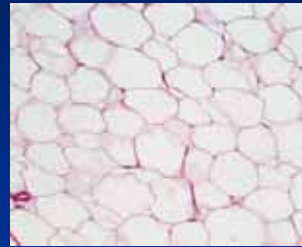
	Normal	Preeclampsia	p*
AR:β	3,7 ± 1,8	36,8 ± 19,0	< 0,001

# PCOS and pregnancy outcome: the role of obesity

Hypothalamus



adipose tissue



dysregulation adipokine secretion

Adiponectin -  
Leptin +  
Resistin +  
RBP4 +  
TNF-alfa +  
IL-6 +  
Free fatty acids +

Leptin  
CRH  
Urocortin 3  
IL-6

muscle



liver



# PCOS and pregnancy outcome: the role of obesity



↑ TNF

↑ IL-6

↓ MCP-1

↑ Leptin

CRH ?  
Urocortin 3 ?



## PCOS, obesity and pregnancy outcome

	OBESITY	PCOS
GESTATIONAL DIABETES	5-6%	20-30%
PRE-ECLAMPSIA	11,4%	5-15%
FETAL GROWTH RESTRICTION	7,5%	10-15%

# PCOS and gestational hypertension

Insulin-resistance  
Obesity  
Hyperandrogenemia  
Aberrant cytokines (TNF- $\alpha$ )  
Growth Factors

Endothelial dysfunction

**PRE-ECLAMPSIA**

# PCOS and pregnancy outcome



**aberrant placental  
cytokines and  
growth factors**



## What to do



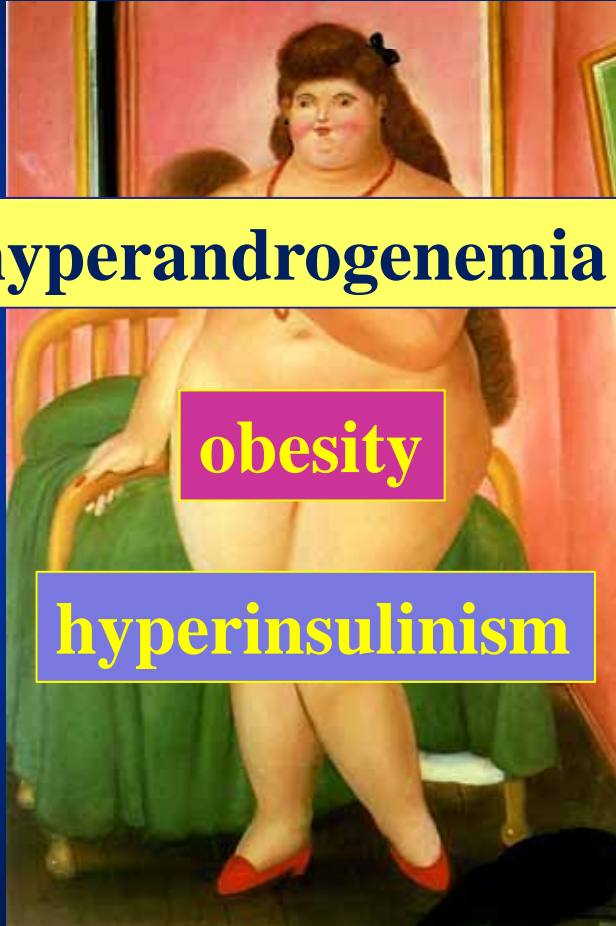
- to lose weight
- reduce androgen levels
- to correct of hyperinsulinemia
- to attenuation of pro-inflammatory signals

## When to do



- before conception
- during pregnancy

## Reproductive outcome and PCOS



**hyperandrogenemia**

**obesity**

**hyperinsulinism**

**Gestational diabetes mellitus**

**(GDM)**

**Pregnancy-induced hypertension**

**Pre-eclampsia**

**Increased operative delivery**

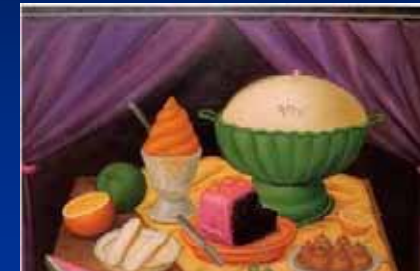
# Impact of PCOS on reproductive outcome



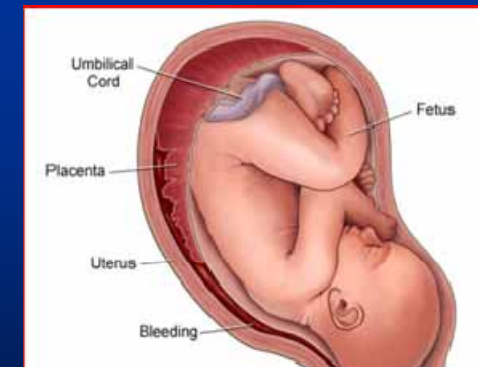
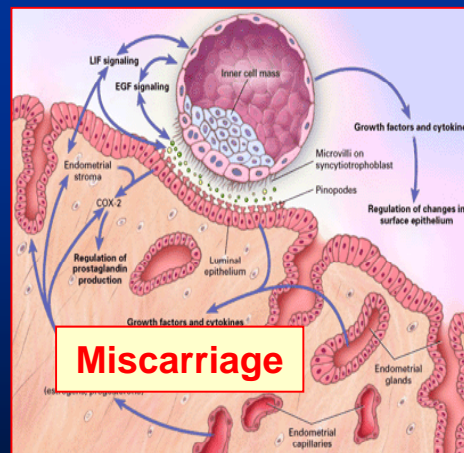
**hyperandrogenemia**



**obesity**



**hyperinsulinism**





## Recommendations

✓ The value of periconceptional diet or insulin lowering agents in treating women with PCOS

✓ The clinical management of PCOS women during the course of gestation

✓ The follow-up of neonate born by PCOS women