



24° CONGRESSO NAZIONALE

A.Gi.Co.

Sindrome dell'ovaio policistico
e disturbi metabolici della menopausa:
due facce della stessa medaglia?

19-21
Ottobre
2022

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PCOS e gravidanza

R. D'Anna

Università di Messina

1935

PCOS: The State of the Art



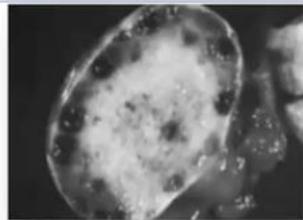
Stein IF, Leventhal ML.

Amenorrhea associated with bilateral polycystic ovaries.

Am J Obstet Gynecol 1935; 29: 181-910

**Irving Stein and
Michael Leventhal
Northwestern University
Chicago (USA)**

*Inferility in women with a triad of signs:
polycystic ovaries, hirsutism, and
oligo/amenorrhea*



2012

PCO

short- and longterm metabolic implications



15 yrs

60 yrs

Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group

FS 2012

San, C.L., & Cohen, M.S. (2012). "Reproductive Health Aspects of Polycystic Ovary Syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group." *Journal of Clinical Endocrinology and Metabolism*, 104(1), 1-10.

Infertility

Future health women

Consensus on women's health aspects of polycystic ovary syndrome (PCOS)[†]

The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group[†]

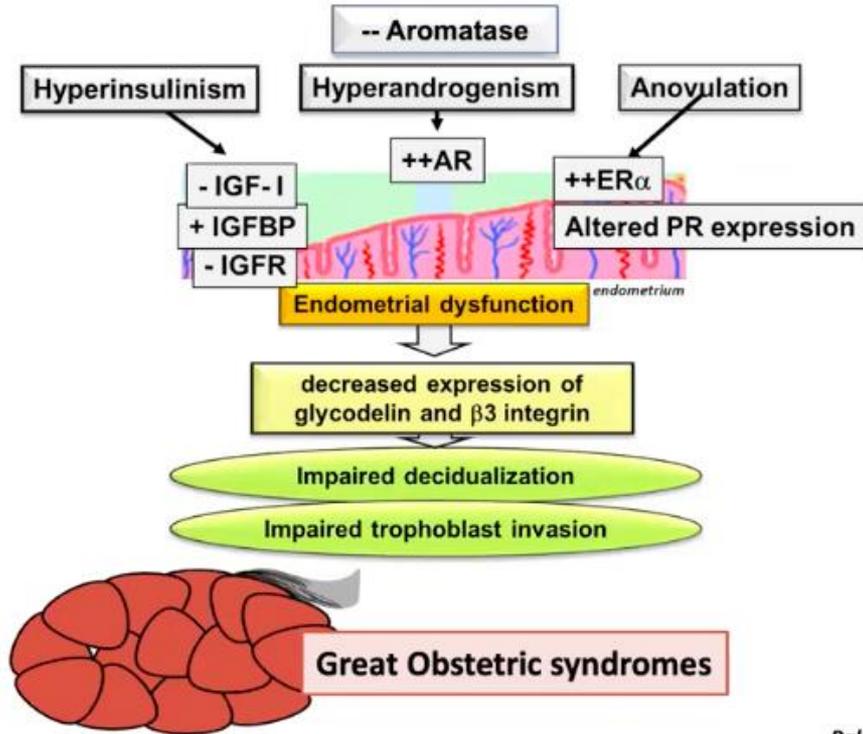
HR 2012

Pregnancy complic.

Future health child

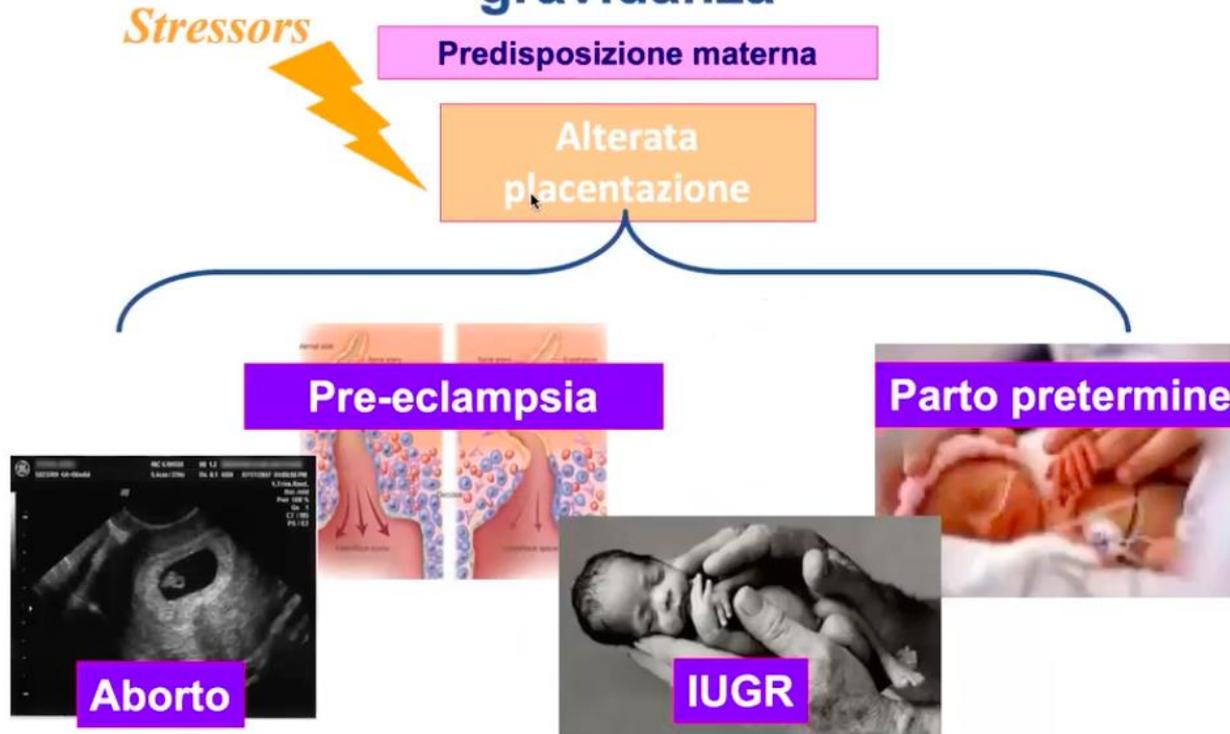


PCOS: endometrial, decidual and trophoblast changes



Palomba S, Hum Reprod, 2013
Makieva S, Hum Reprod Update, 2014
Piltonen TT, Hum Reprod, 2015

Alterata placentazione e le patologie della gravidanza



PCOS and pregnancy outcome

A woman with PCOS is at increased risk of adverse pregnancy and birth outcomes

- *Miscarriage*
- *Gestational diabetes*
- *Preeclampsia*
- *Low birth weight*
- *Preterm birth*
- *Pre-Prom*
- *Placental abruption*
- *Cesarean section*



Roos et al. 2011, Palomba et al. 2015
Mills et al 2020



Mills G et al, Hum Reprod, 2020

Maternal characteristics	PCOS n 14.882	non-PCOS n 9.081.906	p value
Obesity (BMI \geq 30)	22.3%	3.5%	< 0.001
Chronic Hypertension	8.4%	1.8%	< 0.001
Pre-gestational diabetes	4.1%	0.9%	< 0.001
Thyroid Disease	12,6%	2.4%	< 0.001
In vitro fertilization	2.4%	0.1%	< 0.001
Multiple gestation	5.9%	1.5%	< 0.001



Mills G et al, Hum Reprod, 2020

Maternal characteristics	PCOS n 14.882	non-PCOS n 9.081.906	p value
All hypertensive disorders	16.1%	7.4%	< 0.001
Gestational hypertension	6.6%	3.3%	< 0.001
Pre-eclampsia	7.1%	3.6%	< 0.001
Gestational diabetes	18.7%	5.7%	< 0.001

2003



CONSENSUS STATEMENT

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group

October 2003
Rotterdam, The Netherlands

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)

The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group

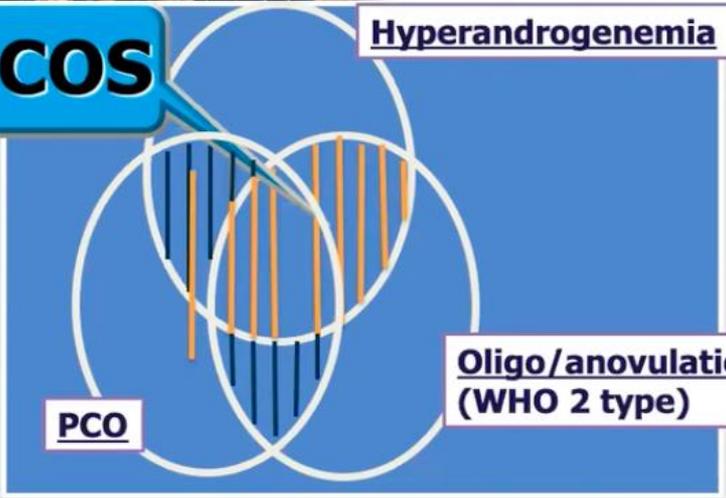
Correspondence to: Bart C.J.M. Fauser, Center of Reproductive Medicine, Erasmus Medical Center, 3015 GD Rotterdam, The Netherlands. E-mail: b.c.j.m.fauser@erasmusmc.nl

PCOS

Hyperandrogenemia

PCO

Oligo/anovulation (WHO 2 type)





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PCOS features

- Iperandrogenismo
- Iperinsulinemia
- Obesità
- PMA



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PCOS features

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RUOLO DEGLI ANDROGENI

unconjugated steroids

3b-hydroxysteroid dehydrogenase type 1 (3b-HSD-1)

Androstenedione

17b-hydroxysteroid dehydrogenase

Testosterone

P450 aromatase

Estrone

Estradiolo



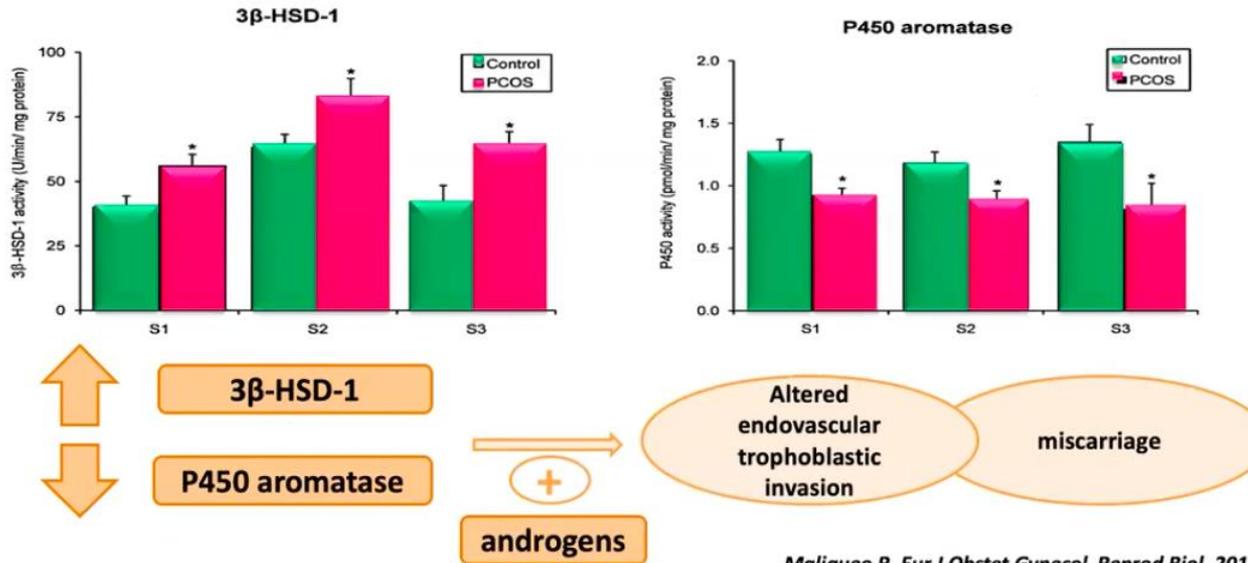
RUOLO DEGLI ANDROGENI

- The unconjugated steroids are converted by the activity of 3 β -hydroxysteroid dehydrogenase type 1 (**3 β -HSD-1**) into **androstenedione**, which is subsequently transformed into **testosterone** by 17 β -hydroxysteroid dehydrogenase.
- These C19 androgens are then aromatized to estrone and estradiol, respectively, by **P450 aromatase**.
- Therefore, modifications in the STS, 3 β -HSD-1 and/or P450 aromatase activities in the placenta of women with PCOS could lead to an **increase of androgen concentrations in maternal or fetal circulation**

Pasqualini JR, 2005

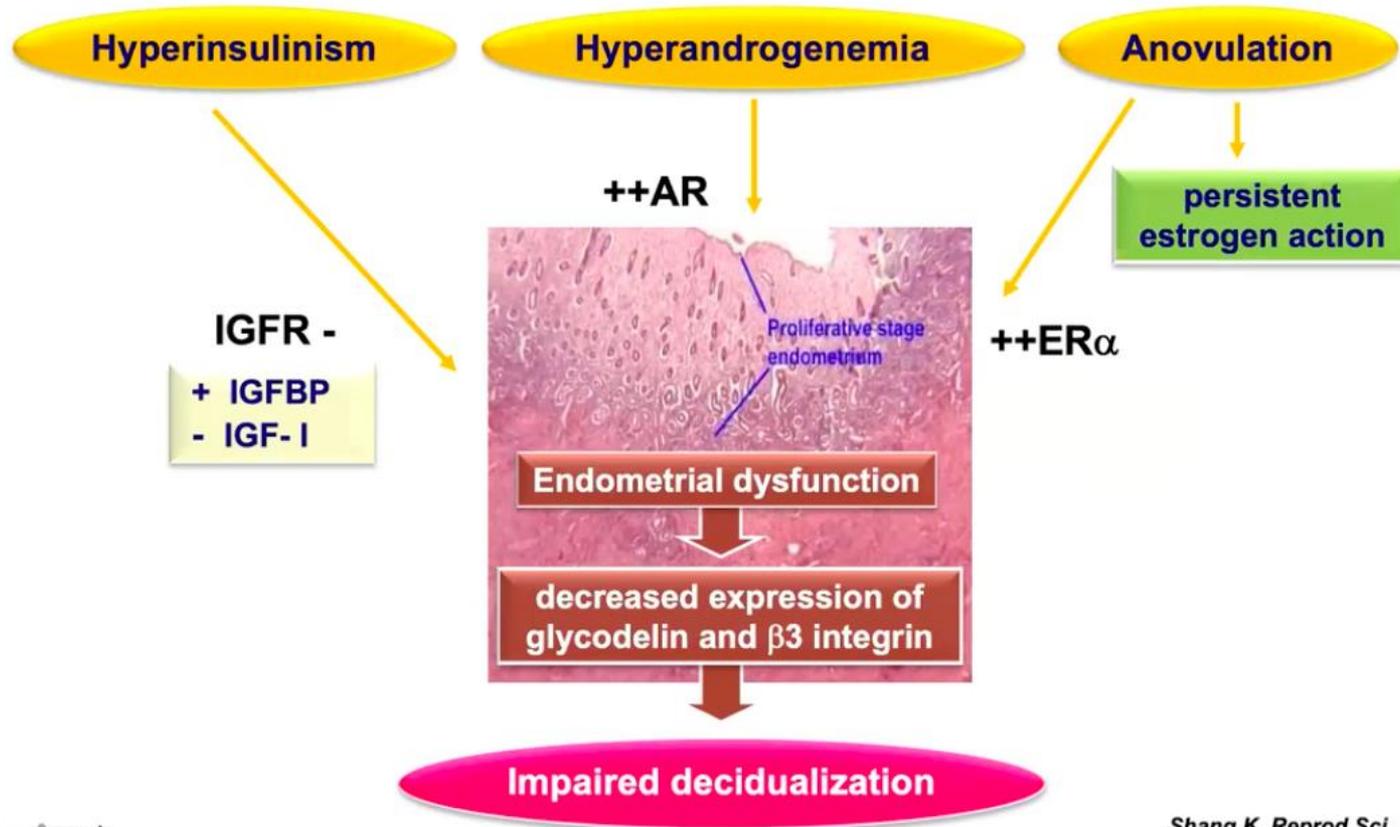
PCOS: androgens and pregnancy complications

The steroidogenic function of placenta in PCOS women is altered



Maliqeo R, Eur J Obstet Gynecol Reprod Biol, 2013
Patel B, Hum Reprod Update, 2015

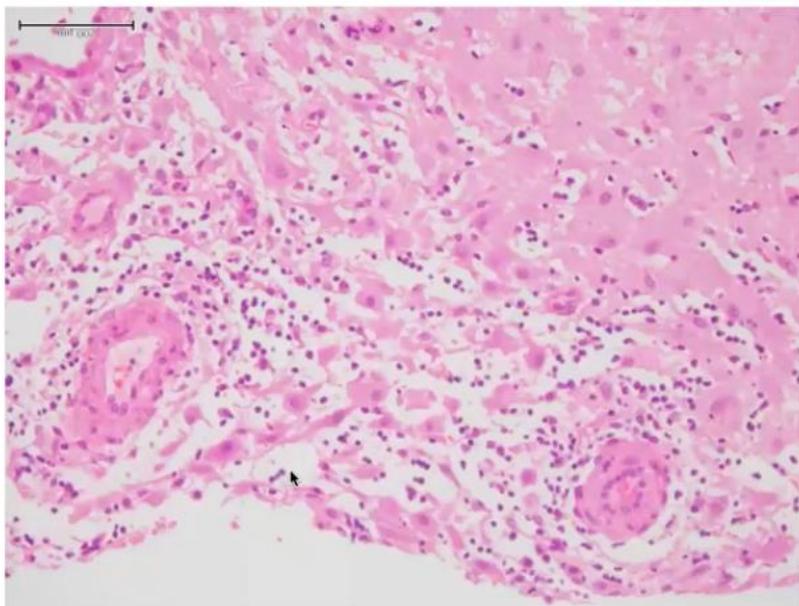
PCOS and miscarriage





La blastocisti si impianta ma il trofoblasto lavora male

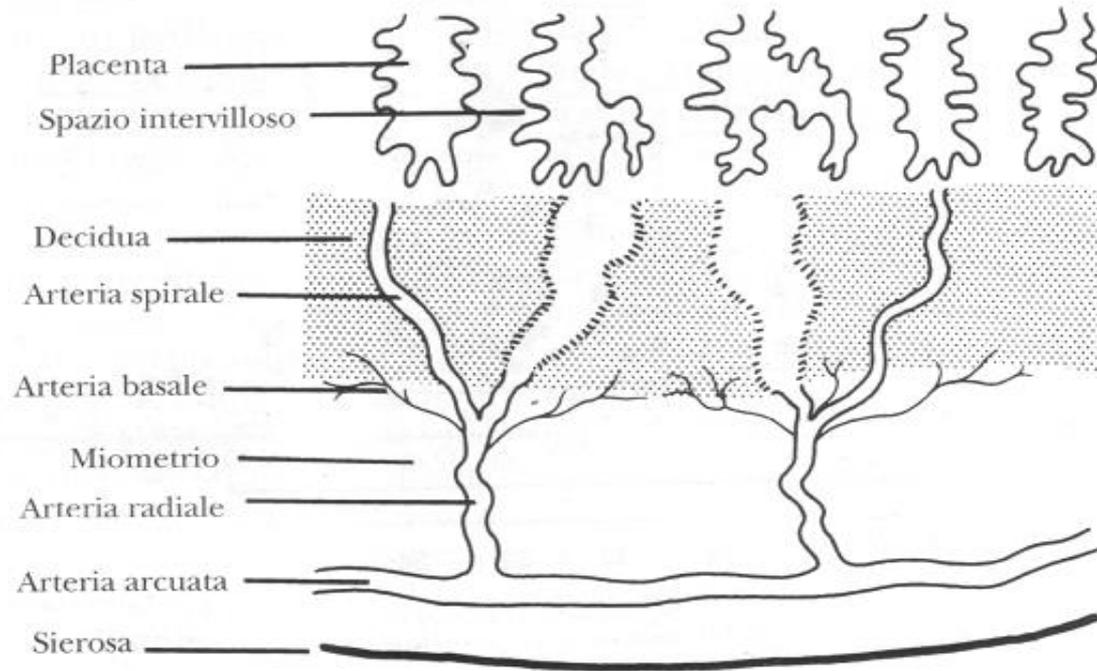
**LE CAUSE DEL DIFETTIVO ADATTAMENTO ALLA GRAVIDANZA
DELLE ARTERIE SPIRALIFORMI
NELLA SEDE DI IMPIANTO PLACENTARE**



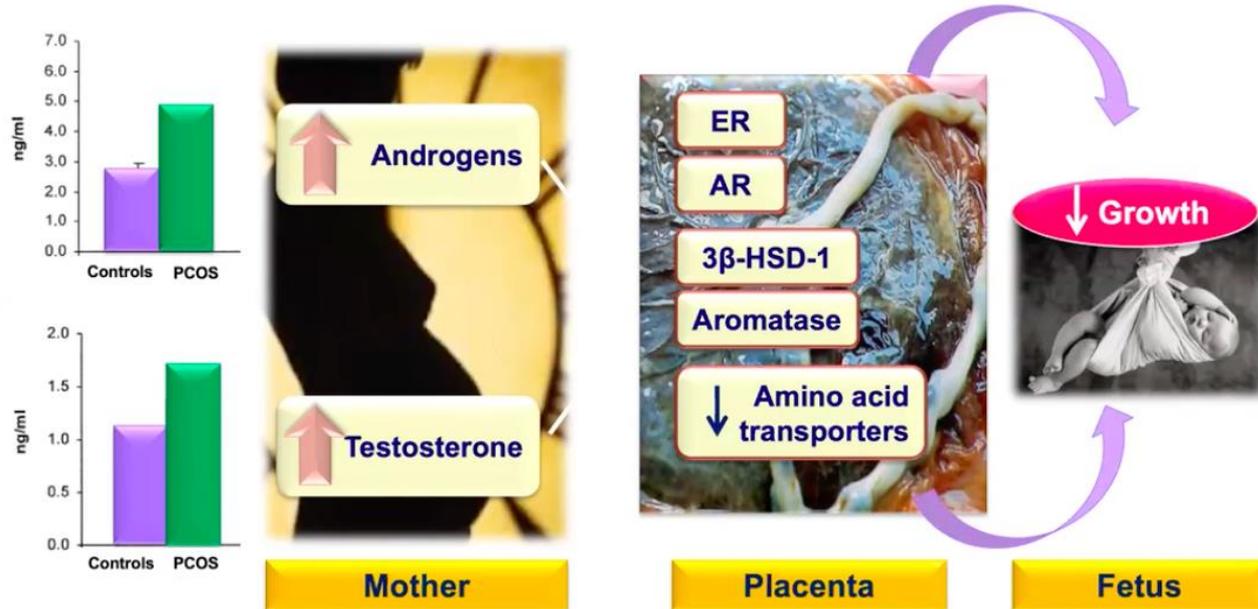
1. L'AMBIENTE UTERINO

**2. LA CAPACITA' DELLE CELLULE
TROFOBASTICHE DI INVADERE
L'ENDOMETRIO E MODIFICARE LE ARTERIE
MATERNE.**

3. LE PATOLOGIE AUTOIMMUNI MATERNE



PCOS: 1. hyperandrogenemia and pregnancy

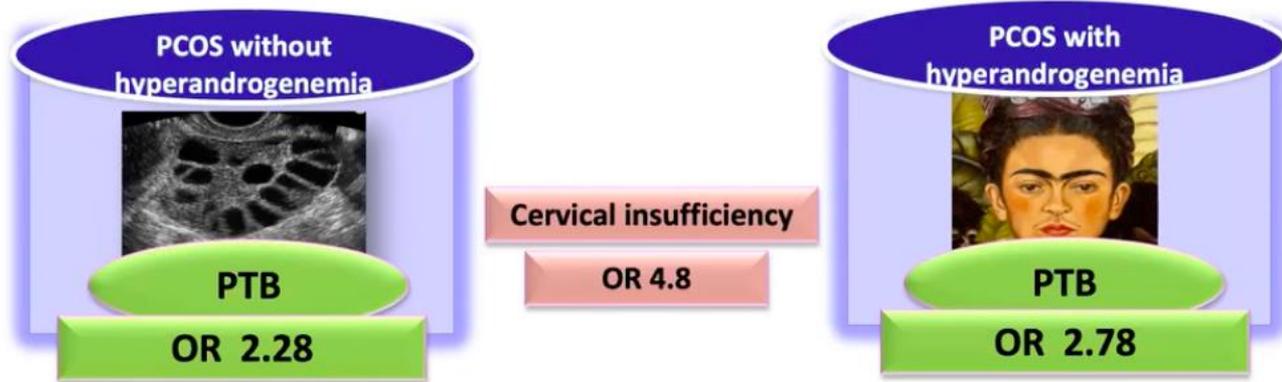


Sir-Peterrmann T, Hum Reprod, 2002

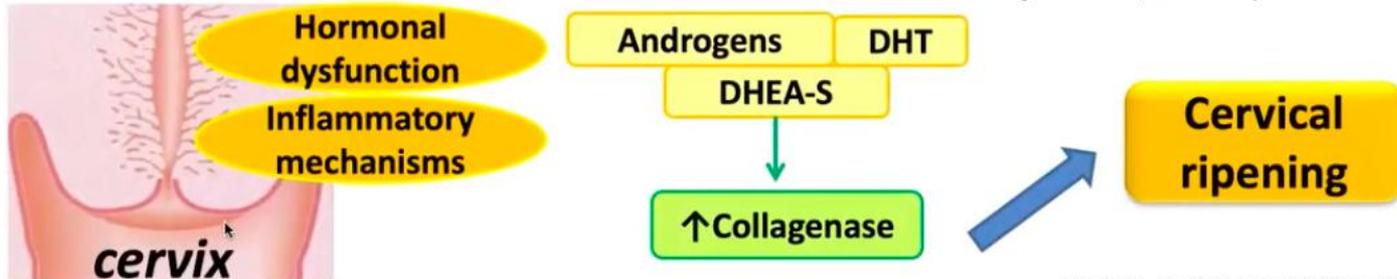
Satishumar K, Reprod Biol Endocrinol. 2011

Miao S, Am J Physiol Endocrinol Metab. 2012

PCOS, androgens and pregnancy complications



Naver KV, BJOG, 2014
Feigenbaum S, Human Reproduction 2012



Makieva, Hum Reprod Update, 2014

PCOS, androgens and pregnancy complications

normoandrogenic PCOS
(Free androgens index <4.5)

24%

Maternal
complications

hyperandrogenic PCOS
(Free androgens index >4.5)

45%

	Normoandrogenic PCOS	Hyperandrogenic PCOS
Any maternal complications	2.24 (1.37–3.65)	5.55 (3.47–8.87)
Pregnancy-induced hypertension	0.94 (0.41–2.18)	1.68 (0.80–3.55)
Preeclampsia/HELLP	1.27 (0.31–5.32)	3.36 (1.18–9.57)
Gestational diabetes	3.91 (2.20–6.98)	11.1 (6.71–18.5)
sPTB	1.82 (0.72–4.58)	2.35 (0.93–5.98)
LGA babies	0.57 (0.26–1.24)	0.73 (0.34–1.61)
SGA babies	1.35 (0.64–2.83)	2.00 (0.98–4.07)
Any neonatal complications	0.97 (0.59–1.59)	1.60 (0.98–2.61)

De Wilde et al, Fert Ster, 2017



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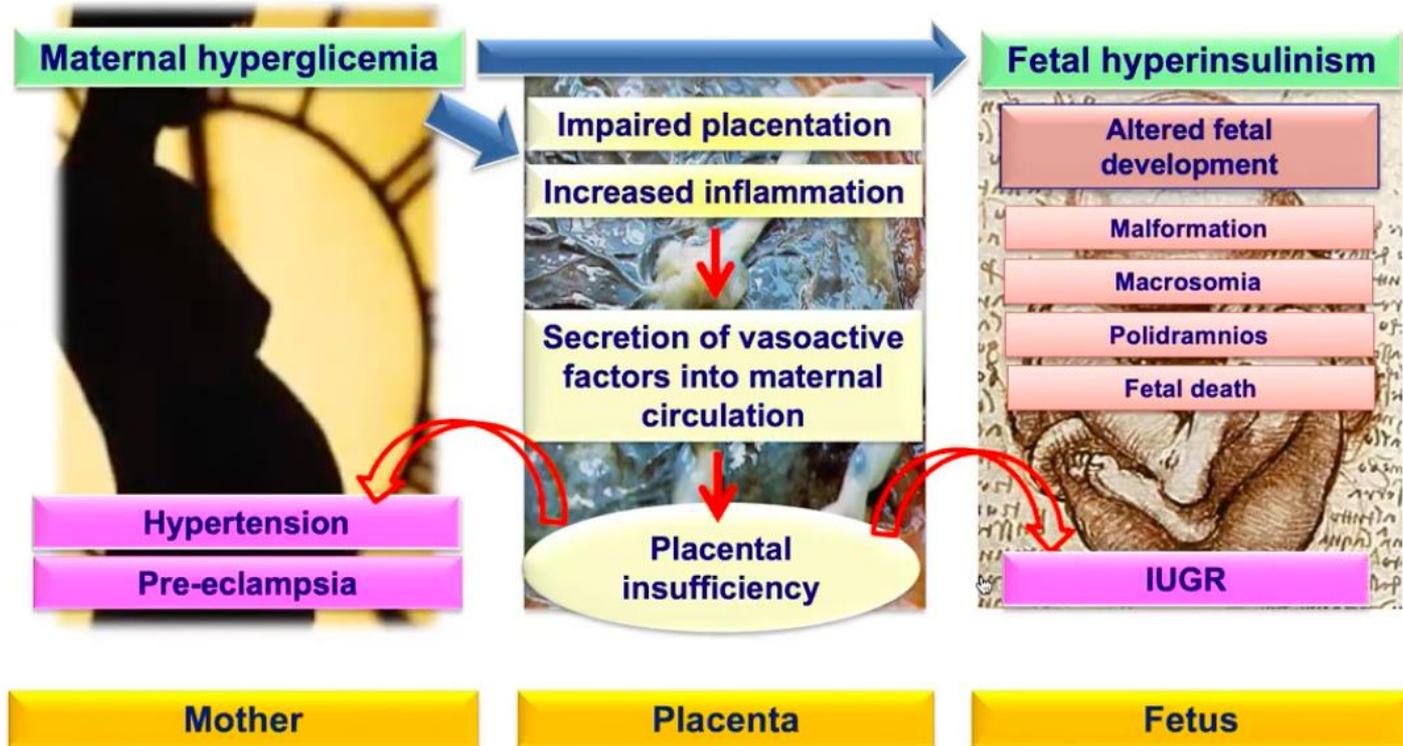
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PCOS features

- Iperandrogenismo
- Iperinsulinemia
- Obesità
- PMA

PCOS: 2.hyperinsulinism and pregnancy





IPERGLICEMIA ED ENDOTELIO

- **Alterati livelli di glucosio materno con persistente iperglicemia riducono la vasodilatazione endotelio-dipendente, con minore produzione di ossido nitrico**

Williams SB et al, Circulation, 1998

- Moderate, Short-Term, Local Hyperglycemia Attenuates Forearm Endothelium-Dependent Vasodilation After Transient Ischemia-Reperfusion in Human Volunteers

Ebert TJ et al, J Cardiothorac Vasc Anest, 2017



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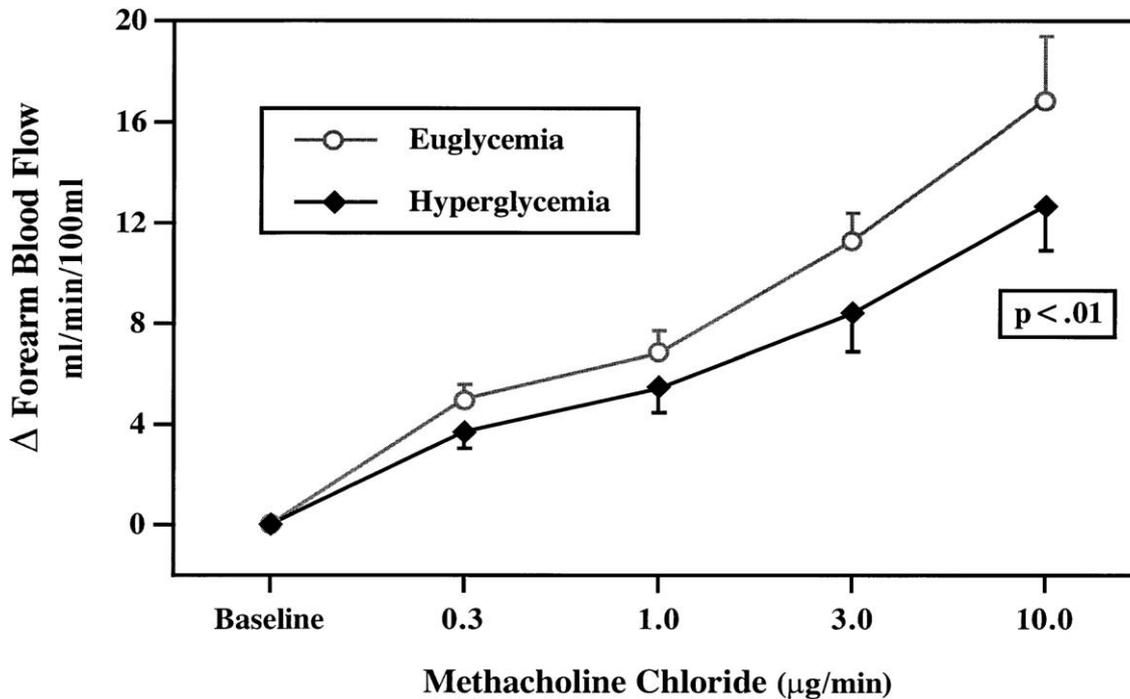
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Williams SB et al, Circulation, 1998





IPERGLICEMIA E PRESSIONE ARTERIOSA

In giovani volontari sani, l'**iperinsulinemia** in risposta all'iperglicemia indotta **aumenta significativamente**:

- la frequenza cardiaca,
- la pressione arteriosa media
- la pressione diastolica

Horton WB et al, Diab Vasc Dis Res, 2021



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Caratteristiche emodinamiche materne nel GDM

GDM (n. 69) vs controlli (n. 128)

- **Ridotta gittata cardiaca**
- **Ridotto «stroke volume»**
- **Aumento delle resistenze vascolari periferiche**

Mecacci F et al, Arch Gynecol Obstet, 2021

Effect of maternal diabetes on fetal heart function on echocardiography: systematic review and meta-analysis

Depla AL et al, Ultrasound Obstet Gynecol, 2021

Parameter	All diabetes	PDM	GDM
Myocardial thickness	Increased	Increased	Increased
Diastolic function	Decreased	Decreased	Decreased
Systolic function	Inconclusive	No difference	Inconclusive
Overall cardiac function	Decreased	Decreased	Decreased



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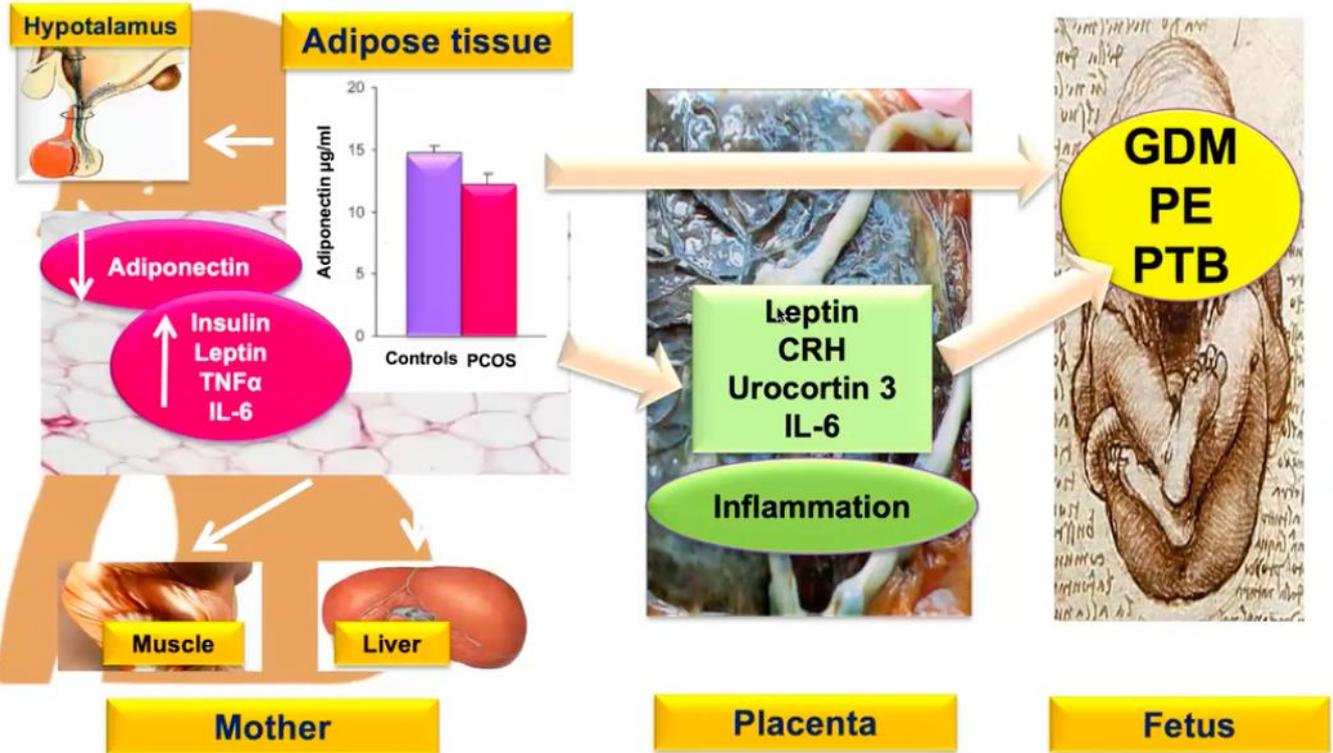
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PCOS features

- Iperandrogenismo
- Iperinsulinemia
- **Obesità**
- PMA

PCOS: 3. obesity and pregnancy



Hotamisligil GS, Nature, 2006
 Denison FC, Reproduction, 2010
 Crujeiras and Casanueva, Hum Reprod Update, 2015



Peeva N, Reprod Biomed online, 2022

Maternal complications	obese PCOS n. 3.286	non obese PCOS n. 11.569	OR
Gestational diabetes	25.0%	16.9%	1.74
Gestational Hypertension	9.0%	5.9%	1.55
Preeclampsia	10.2%	6.2%	2.17
Chorioamnionitis	3.7%	2.9%	1.55
Caesarean delivery	62.5%	50.0%	1.41



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PCOS features

- Iperandrogenismo
- Iperinsulinemia
- Obesità
- PMA

ART, PCOS and pregnancy outcome

Patients with PCOS represent the 80% of anovulatory infertility and undergoing to ART have a further increased rate of:



Miscarriage



PTB

PIH



ART, PCOS, obesity and pregnancy outcome

Patients with PCOS and obesity undergoing to ART have a further increased incidence of:

- PIH
- PE
- GDM
- Chorioamnionites
- Cesarean section



ART, PCOS and multiple gestation

Patients with PCOS and multiple gestation have a further increased incidence of:

- PIH and PE
- GDM
- PTB and pPROM
- Cesarean section and wound complications
- PPH





CONCLUSIONI

Le gravide PCOS hanno un outcome ostetrico peggiore rispetto ai controlli

Tale condizione è ulteriormente peggiorata da:

- Iperandrogenismo
- Iperinsulinemia
- Obesità
- PMA

GRAZIE PER L'ATTENZIONE



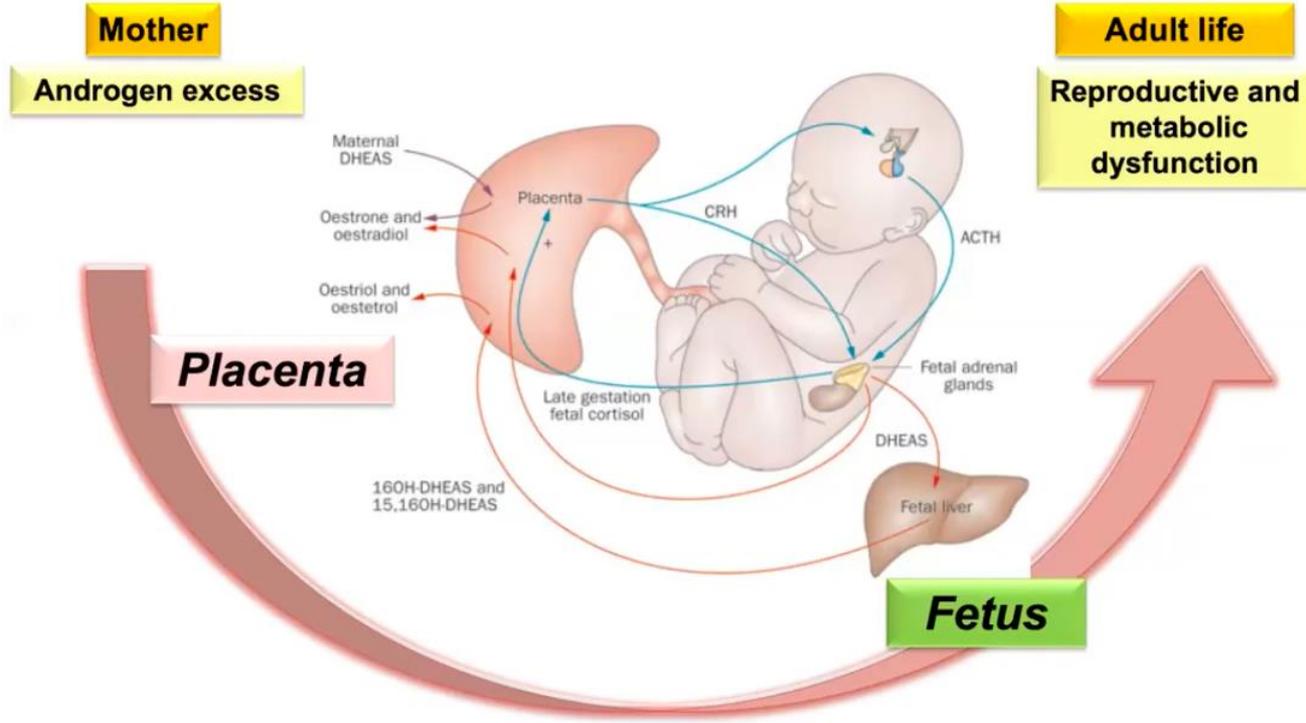
2014



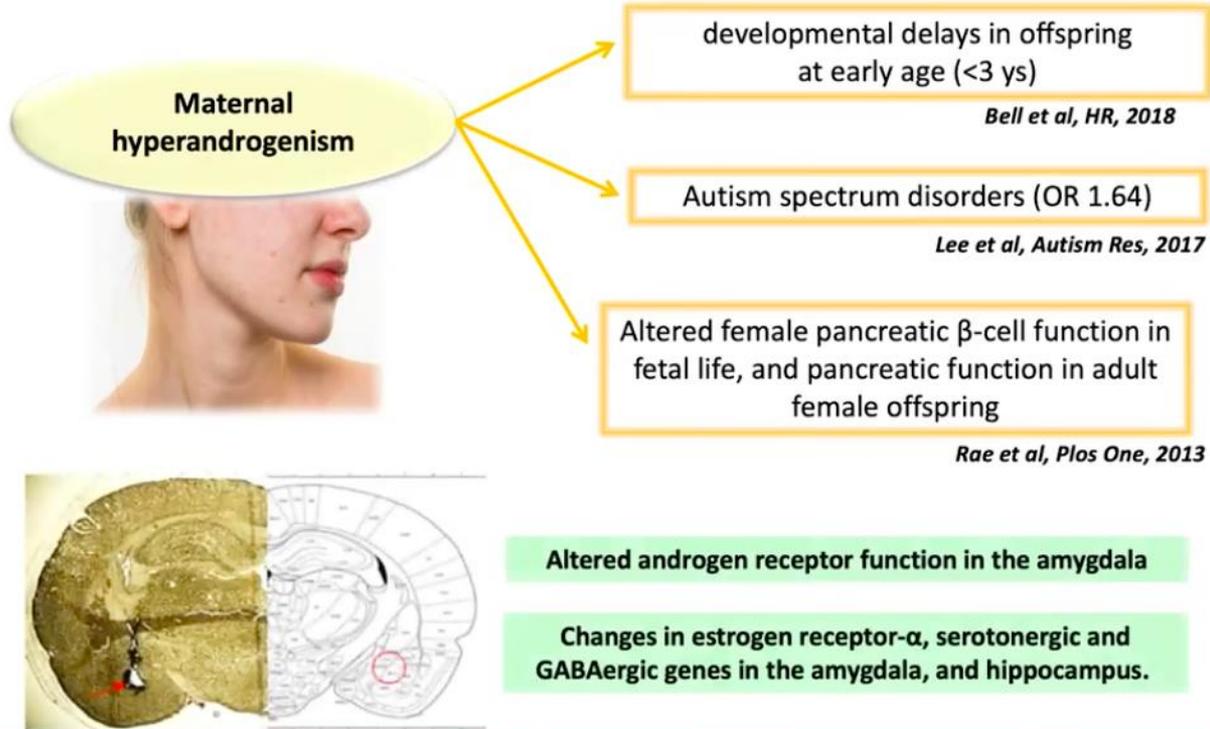
Perinatal programming

L' uomo si adatta all'ambiente: in risposta a un fenomeno transitorio intrauterino mette in atto modifiche della fisiologia e del metabolismo che divengono permanenti o "programmate" poiché si verificano in un periodo critico dello sviluppo e della differenziazione cellulare

Pregnant, PCOS and adult life pathologies



Maternal PCOS and offspring health



maternal androgen excess increases the risk of developing anxiety disorders in the offspring



Maternal PCOS and offspring health

Pubertal PCOS daughters have ↑levels of testosterone,
↑triglycerides, ↑ insulin after stimulation and ↓levels of SHBG
↓levels of adiponectin



Sir-Petermann et al, JCEM, 2007



Daughters of women with PCOS have an **increased risk of cardiovascular diseases**, due to a significantly increased blood pressure, arterial stiffness, and glucose and insulin levels

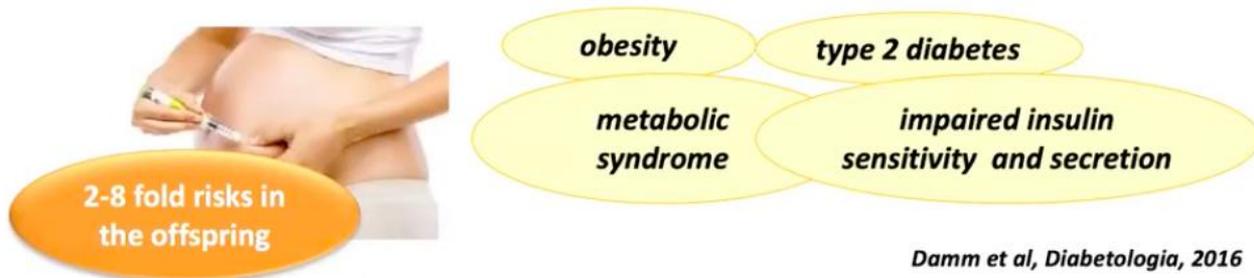
Battaglia et al, Fert Ster, 2009

PCOS neonates have a similar metabolic, hormonal and oxidative stress status as neonates of mother with GDM.



Boutzios et al, Fert Ster, 2013

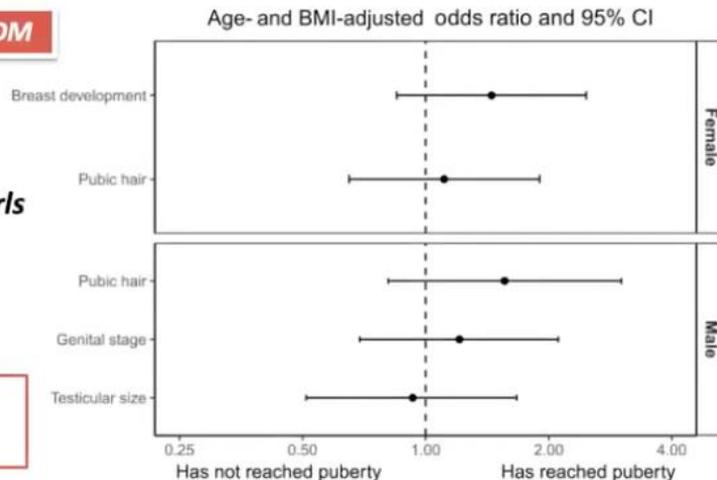
Gestational diabetes and offspring health



adolescent offspring of women with GDM

- **increased adiposity**
- **adverse cardiometabolic profile**
- **earlier onset of puberty among girls**
- **increased fasting glucose**
- **PCOS**

Programming effects of hyperglycemia in pregnancy



Grunnet et al, Diabetes Care, 2017



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Fetal programming and childhood complications

- **Programming** is the process where a stimulation at a critical window of development has long-term effects.
- Barker DJ et al explained very clearly how intrauterine environment is associated with epigenetic malprogramming of the fetal metabolism as in GDM occurs, predisposing to chronic metabolic disorders and obesity



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Fetal programming and childhood complications

- **Epigenetics is the study of heritable changes in gene expression that occur without changes in the DNA sequence.**
- DNA methylation and histone modifications are two major epigenetic regulators in mammalian cells, and may provide a mechanism for the stable propagation of gene activity from one generation of cells to the next.



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Fetal programming and childhood complications

Follow-up study performed on children from 10 to 14 years old whose mothers participated in the “Hyperglycemia and Adverse Pregnancy Outcome” (HAPO) study ([published in 2008](#))

589 with maternal GDM and 3571 without, children whose mother performed an Oral Glucose Tolerance Test (OGTT) according to IADPSG/WHO criteria.

Lowe Jr. WL et al, Diabetes Care, 2019



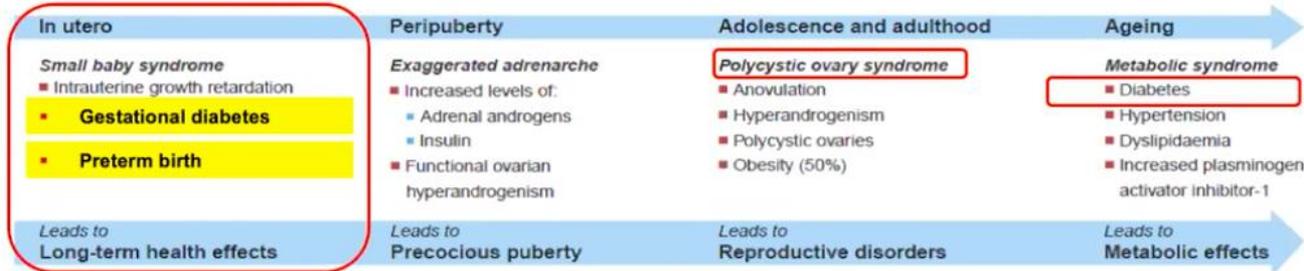
Fetal programming and childhood complications

- The most important result of this study was that **10.6%** offspring of mothers with GDM had Impaired Glucose Tolerance (IGT) compared with **5.0%** offspring of mothers without GDM
- the difference was statistically significant even after adjusting for child BMI or adiposity and it was independent of the child's family history of diabetes type 2.
- **fetal programming remains the only explanation to the observed significant association.**

Lowe Jr. WL et al, Diabetes Care, 2019

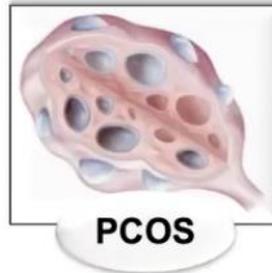
PCOS, pregnancy and women's health

Long term effects of PCOS



Norman RJ, MJA, 2013

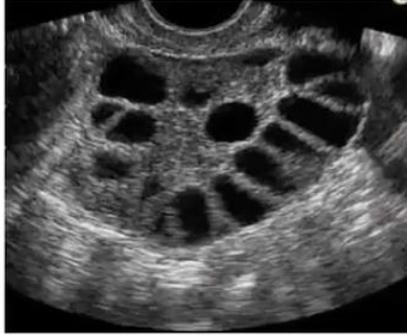
Long term effects of PTB



Women with a history of both medically indicated and spontaneous preterm births have increased prevalence of PCOS and DM later in life

Eilertsen, BJOG, 2012

PCOS and management of pregnancy



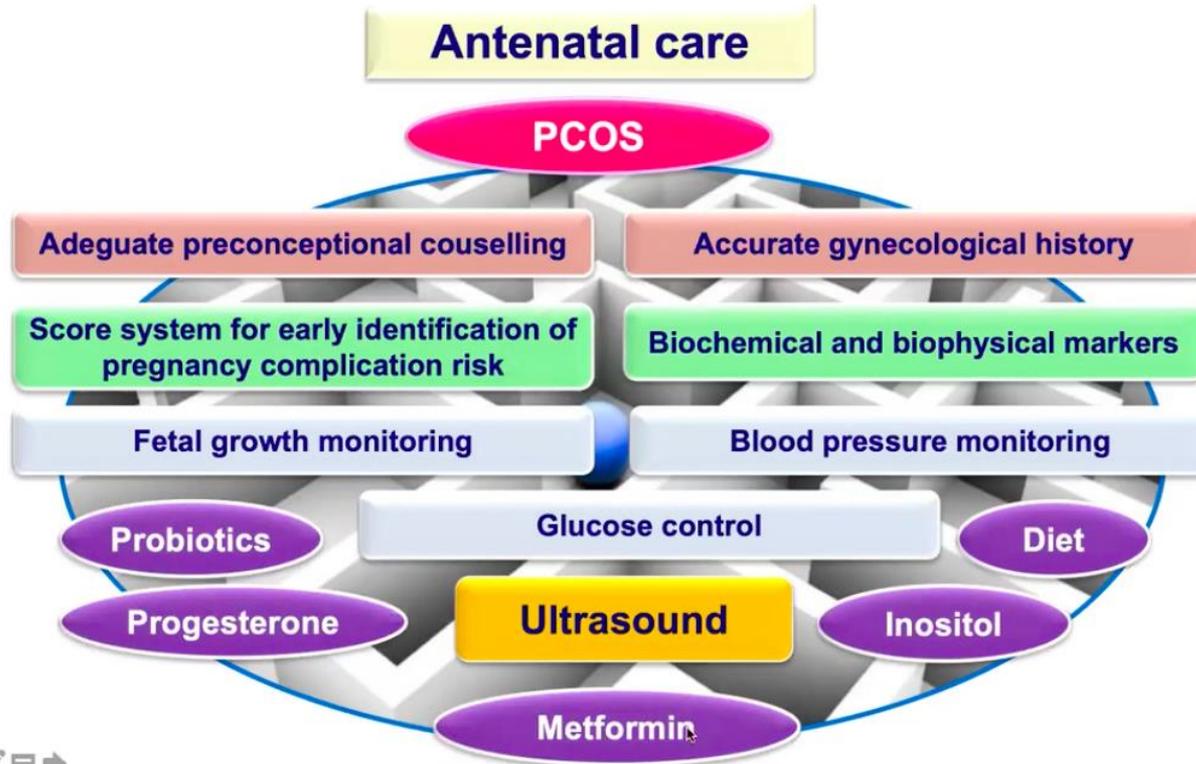
**Increased risk of adverse pregnancy
and birth outcome**



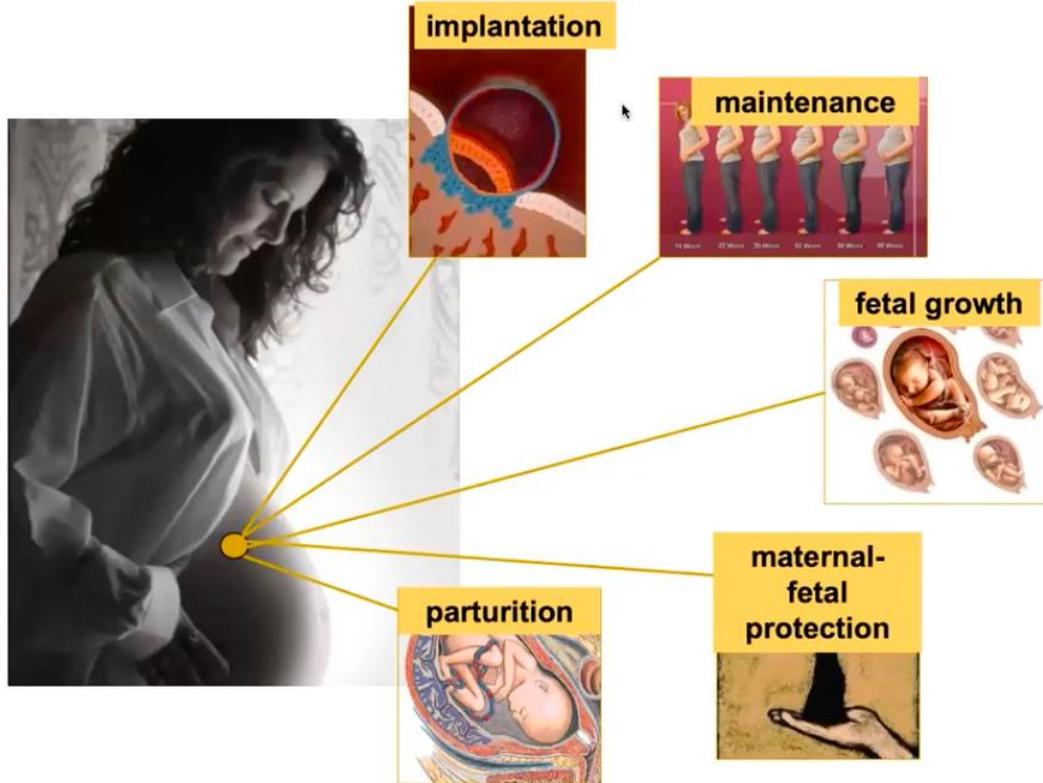
**Increased surveillance during
pregnancy and parturition**



Identification and management of PCOS patients



Adaptive mechanisms and placenta



High risk pregnancy: do reproductive disorders matter?



Genetic and medical disorders	Age	Infertility	Uterine disorders
<ul style="list-style-type: none">• Diabetes, obesity and metabolic diseases• Lupus and autoimmune diseases• Hypertension and cardiovascular diseases• Thyroid and endocrine diseases	Advanced Maternal age	PCOS ART	Uterine fibroids Endometriosis Adenomyosis

Reproductive disorders may affect gestational development

