XXIII CONGRESSO NAZIONALE A.GI.CO.

FERRARA
17 - 18 MAGGIO 2019
SALA IMBARCADERO
CASTELLO ESTENSE

"È attraverso la salute della donna
che passa la salute della famiglia e di una società"

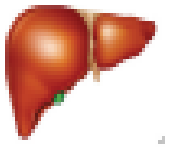
Centro Salute Donna
AUSL FERRARA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

Ovaio policistico e sindrome metabolica: il ruolo terapeutico degli inositoli

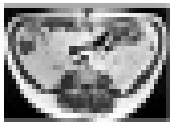
Giuseppe Morgante
Università degli Studi di Siena

Old and New Vision of PCOS



NAFLD

Obesity



Insulin Resistance

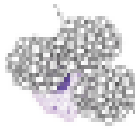
OSA

PCOS

2018

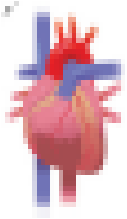
Diabetes

Dyslipidemia



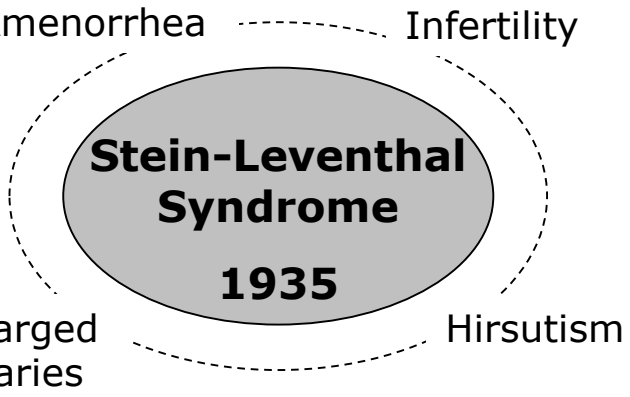
Inflammation

CVD



Hyperandrogenism

Infertility



Manifestazioni della PCOS

1

Cliniche

- alterazioni mestruali (66-75%)
- iperandrogenismo (50-70%)
- obesità (40-60%)
- infertilità (33-50%)

2

Endocrine

- aumento androgeni
- aumento LH
- aumento insulina
- aumento AMH
- riduzione SHBG

3

Metaboliche

- sindrome metabolica (dislipidemia, iperglicemia, etc)
- aumento colesterolo LDL
- insulino-resistenza (50-60%)

4

Possibili sequele

- menopausa tardiva
- patologia cardiovascolare
- carcinoma endometriale

Sindrome metabolica

Per Sindrome Metabolica si intende la contemporanea presenza, in uno stesso paziente, di un gruppo di disordini metabolici, caratterizzato da una risposta biologicamente "subnormale" dell'insulina associato ad obesità viscerale. Comporta una elevata probabilità di sviluppare diabete di tipo 2 (DM2) e malattia cardiovascolare (CVD). I disturbi metabolici influenzano la funzione riproduttiva controllata dall'ipotalamo e dall'ipofisi.

Criteri diagnostici

NCEP-ATPIII

3 o più dei seguenti criteri:

- ✓ **Obesità viscerale → Circonferenza vita (CV)**
  - **≥ 88 cm ♀**
  - **≥ 102 cm ♂**
- ✓ **Trigliceridi (TG)**
  - **≥ 150 mg/dl o terapia mirata**
- ✓ **Colesterolo HDL**
  - **< 50 mg/dl ♀**
  - **< 40 mg/dl ♂**
  - **o terapia mirata**
- ✓ **Pressione arteriosa**
  - **≥ 130/85 mmHg**
  - **o terapia mirata**
- ✓ **Glicemia a digiuno**
  - **≥ 100 mg/dl o terapia mirata**

IDF

- **Obesita viscerale →**
- **Circonferenza vita (CV)**
  - ≥ 80 cm ♀
  - ≥ 94 cm ♂
- ***+ almeno 2 dei seguenti criteri:***

- **Trigliceridi (TG)**
  - ≥ 150 mg/dl *o terapia mirata*
- **Colesterolo HDL**
  - < 50 mg/dl ♀
  - < 40 mg/dl ♂
  - *o terapia mirata*
- **Pressione arteriosa**
  - ≥ 130/85 mmHg
  - *o terapia mirata*
- **Glicemia a digiuno**
  - ≥ 100 mg/dl *o terapia mirata*

Criteri per la SM nelle donne con PCOS

La presenza di 3 criteri identifica la sindrome metabolica

1. **Obesità addominale > 88 cm**
2. **Trigliceridi > 150 mg/dl**
3. **HDL <50 mg/dl**
4. **Pressione arteriosa > 130/85**
5. **Glicemia a digiuno 110-126 mg/dl e dopo 2 h (OGTT) 140-199 mg/dl**

1. **Non sono necessari test di insulino-resistenza per effettuare diagnosi di PCOS**
2. **Le donne obese e quelle che hanno familiarità per diabete dovrebbero essere screenate per la sindrome metabolica**

The incidence of metabolic syndrome in adolescents with different phenotypes of PCOS

Kubra Zengin Altintas, Berna Dilbaz, Derya Akdag Cirik, Runa Ozelci, Tuba Zengin, Osman Nuri Erginay, Serdar Dilbaz

Department of Reproductive Endocrinology and Infertility,

	Phenotype A	Phenotype B	Phenotype C	Phenotype D	p value
Overweight	27 (71.1%)	17 (43.6%)	17 (50.0%)	18 (54.5%)	0.10
Abdominal obesity	31 (81.6%)	30 (76.9%)	27 (79.4%)	28 (24.1%)	0.85
Hypertension	8 (21.1%)	4 (10.3%)	5 (14.7%)	2 (6.1%)	0.27
TG ≥ 150 [mg/dL]	17 (44.7%)	8 (20.5%)	8 (23.5%)	5 (15.2%)	0.023
HDL < 50 [mg/dL]	33 (86.9%)	31 (79.5%)	28 (82.4%)	30 (90.9%)	0.56
Glu ≥ 100 [mg/dL]	7 (18.4%)	2 (5.1%)	4 (11.8%)	1 (3.0%)	0.11
Systolic BP [mm Hg]	115.0 (10.0)	110.0 (10.0)	110 (10.0)	110 (10.0)	p = 0.26
Diastolic BP [mm Hg]	73.7 (10.0)	71.3 (5.0)	72.6 (10.0)	69.7 (5.0)	p = 0.19
Mets (IDF)	15 (39.5%)	8 (20.5%)	9 (26.5%)	5 (15.2%)	0.10

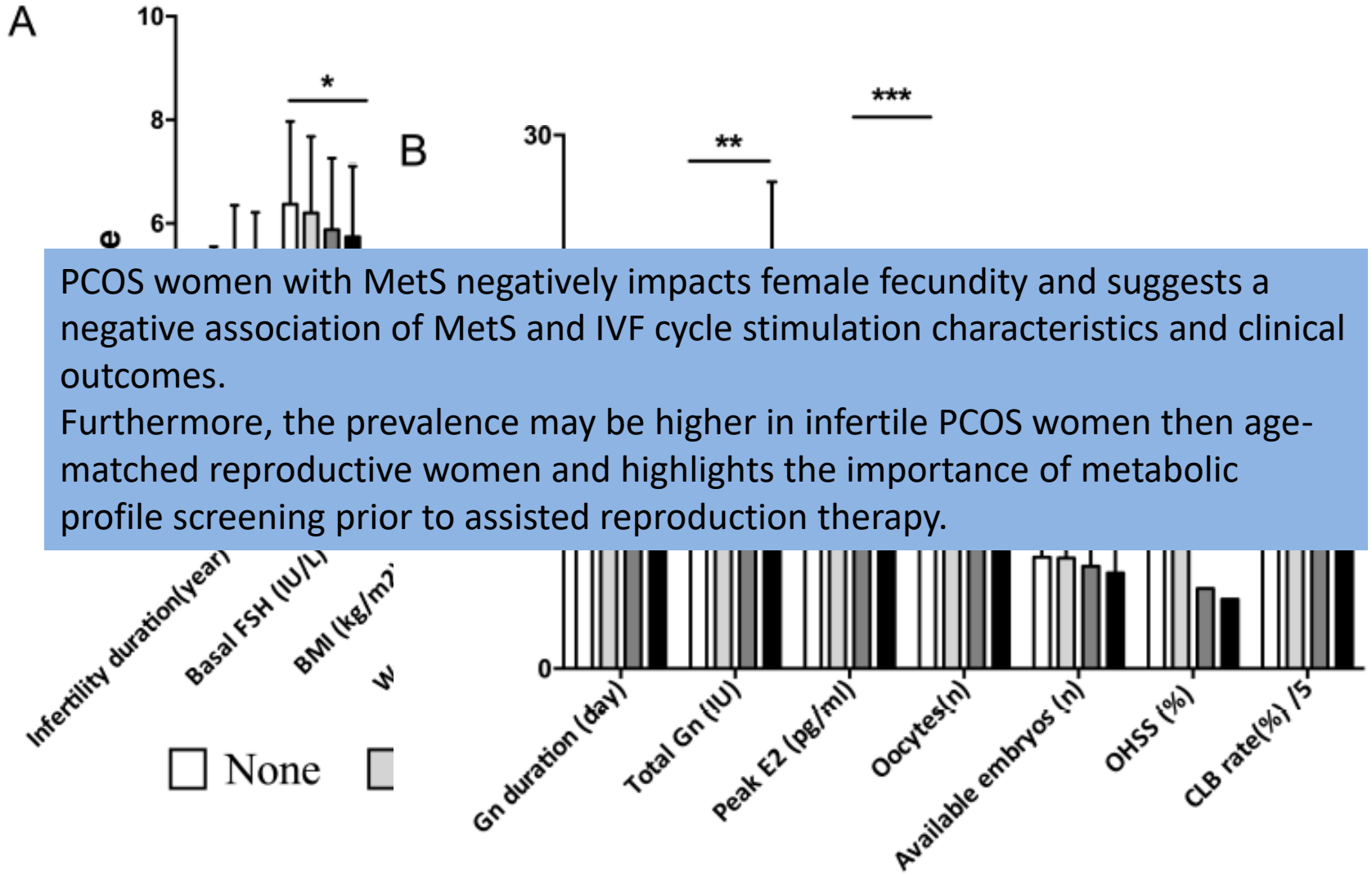
Abbreviations: TG —triglyceride; HDL — high-density lipoprotein; Glu — fasting plasma glucose; Mets (IDF) — metabolic syndrome diagnosed with International Diabetes Federation; BP — blood pressure

Conclusions: Although low HDL-C levels and insulin resistance are common PCOS findings in adolescents, the metabolic profile seems to be worse in Phenotype A than the other phenotypes. Therefore, screening programs should evaluate patients based on the known risk factors and phenotypes for adolescents with PCOS.

KZ Altintas et al, Gin Pol 2017

Influence of metabolic syndrome on female fertility and in vitro fertilization outcomes in PCOS women.

Yaqiong HE et al, Am J Obstet Gynecol 2018



PCOS women with MetS negatively impacts female fecundity and suggests a negative association of MetS and IVF cycle stimulation characteristics and clinical outcomes.

Furthermore, the prevalence may be higher in infertile PCOS women then age-matched reproductive women and highlights the importance of metabolic profile screening prior to assisted reproduction therapy.

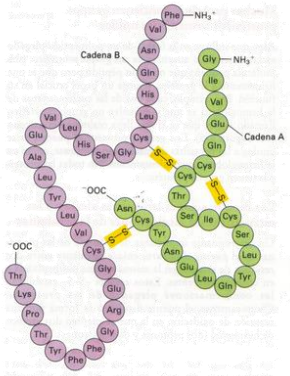
PCOS e Sindrome Metabolica

La PCOS ha implicazioni sistemiche, oltre che sulla sfera riproduttiva.

- La prevalenza di PCOS tra le donne con DM2 è 5 volte quella di controlli.
- Il DM2 ha una forte componente genetica, riscontrata anche nelle pazienti con PCOS.

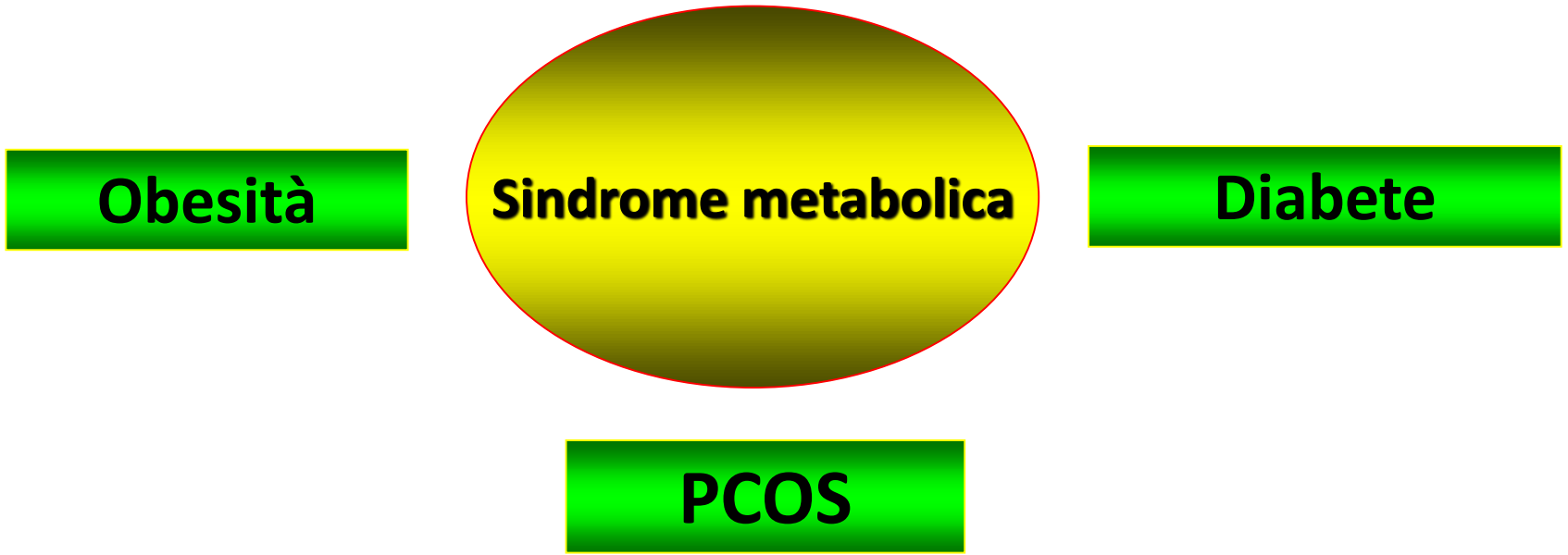
Quale il link tra Sindrome Metabolica e PCOS?

L'insulina!



Per Insulino-resistenza si intende una ridotta sensibilità dei tessuti all'azione dell'insulina. Questa alterazione viene inizialmente e solitamente compensata da una super produzione dell'ormone insulina (iperinsulinismo compensatorio). In taluni frangenti della giornata e in particolare dopo il pasto, quando vi è un ulteriore stimolo alla produzione di insulina determinato dall'ingestione di cibo, l' iperinsulinemia può determinare una caduta dei livelli di glucosio nel sangue (ipoglicemia reattiva).

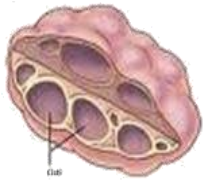
Essa rappresenta la base fisiopatologica della sindrome metabolica.



Patogenesi: 'Insulin school'

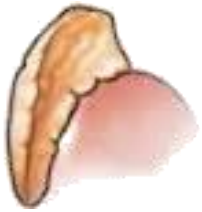
L'iperinsulinemia è una condizione predisponente all'iperandrogenismo attraverso molteplici meccanismi.

Ipofisi → Aumenta l'ampiezza dell'increzione di LH

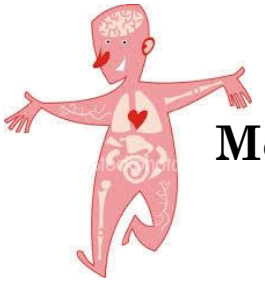


Ovaio

- **Diretta:** aumenta l'increzione di androgeni per stimolo dell'attività del citocromo p450
- **Indiretta:** aumenta la risposta secretoria allo stimolo dell'LH



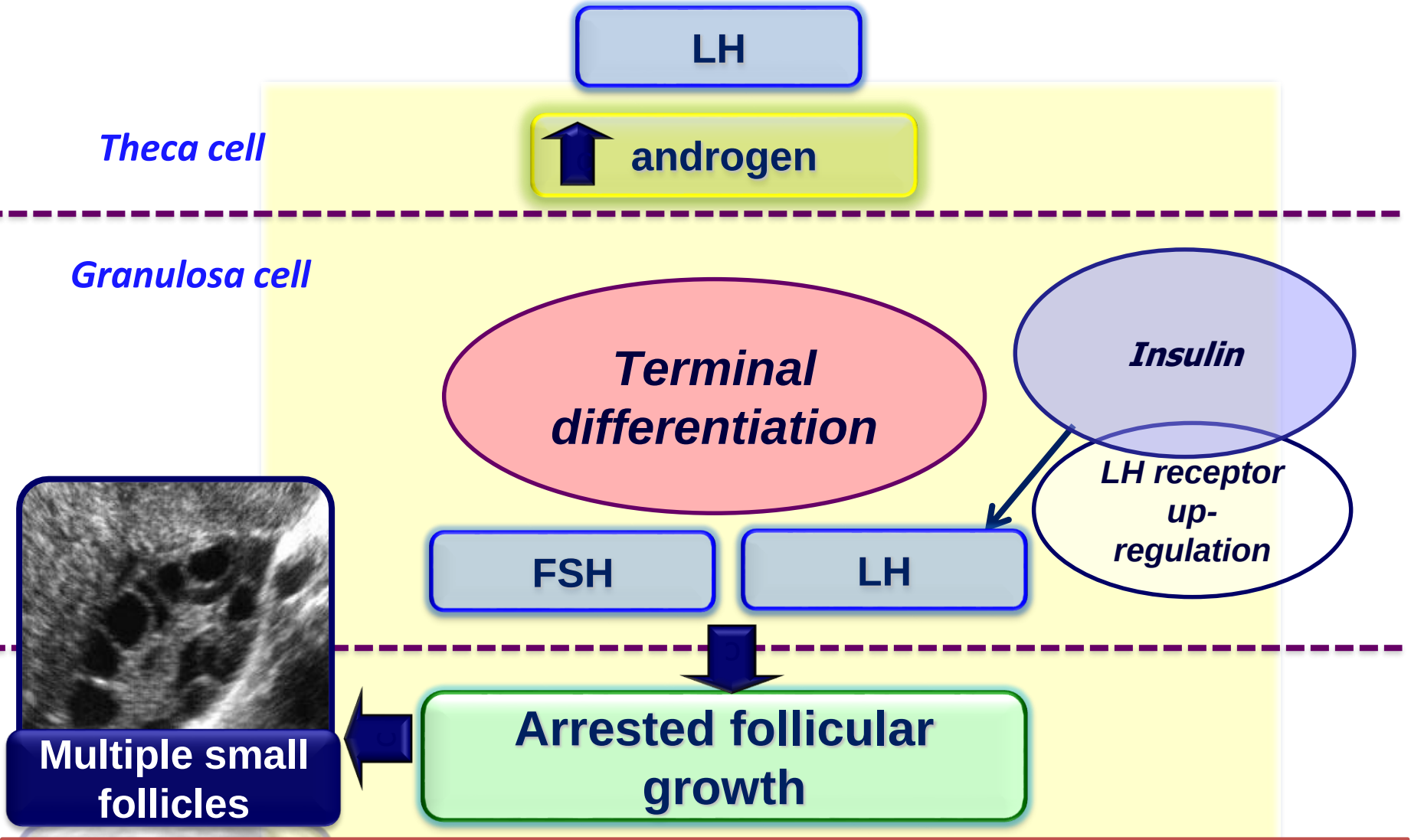
Surrene → Aumenta la risposta androgenica surrenalica allo stimolo indotto dall'ACTH



Metabolico

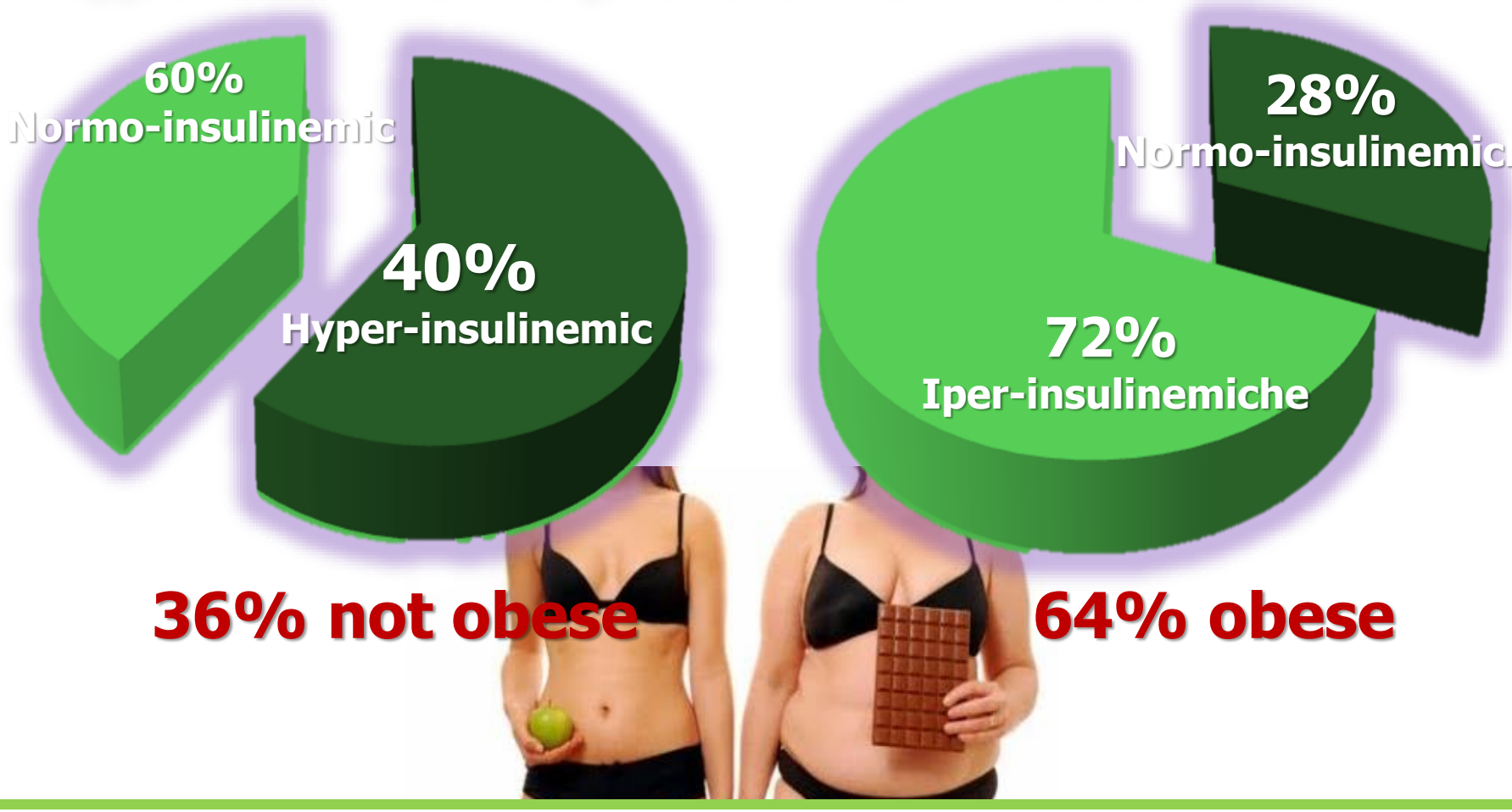
- Riduce i livelli sierici delle SHBG e IGFBP-1 ed aumenta la quota libera degli androgeni circolanti e IGF-1
- Riduce la clearance degli androgeni e l'attività delle aromatasi mentre aumenta l'attività della 5α-reduttasi

Insulin action on the ovary



Hyperinsulinemia accelerates development of granulosa cell LH responsiveness by amplifying the induction of LH receptors and induces before a block of follicular growth and after multiple small follicles formation

Hyperinsulinemia prevalence in PCOS women



Insulin resistance and the compensatory hyperinsulinemia affect some 65–70% of women with PCOS, with 70–80% of obese (BMI > 30) and 20–25% of lean (BMI < 25)

Marshall JC et al., Fertil Steril 2012

Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society.

Controllo peso e PA

Livelli sierici lipidi e glicemia

Cambiamento stile di vita

Obesità, età avanzata, storia di diabete gestazionale o storia familiare di diabete di tipo II

OGTT

Dislipidemia e altri fattori di rischio

Insulino-sensibilizzanti

J Endocrinol metab 2010

Positive effects induced by weight loss in obese women

Insulin-resistance

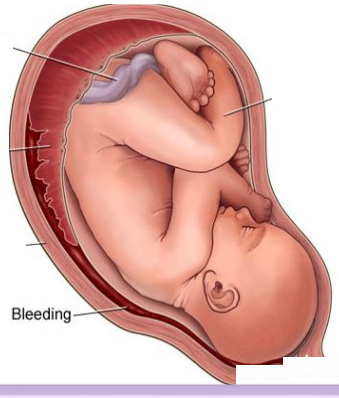
Androgens

Menstrual cyclicity

Ovulation

Fertility

Effetti collaterali feto-neonatali



Non sono state riportate malformazioni

Non sono state riportati casi di ipoglicemia neonatale

FDA:

FARMACO DI CLASSE B

Metformina

Troglitazone

Rosiglitazone/Pioglitazone

Somatostatina

Diazossido

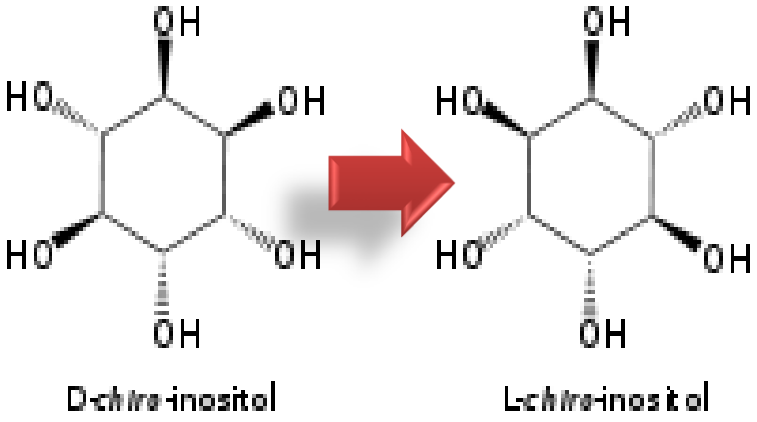
Acarbosio

Inositolo

Diarrea
Nausea
Disturbi addominali
Acidosi lattica

Aumento di peso
Edema
Diarrea
Nausea
Cefalea
Tossicità epatica

Inositols



- ✓ At intracellular level, myo-inositol is converted into D-chiro-inositol
- ✓ Morphogenesis and cellular cytogenesis
- ✓ Synthesis of lipids
- ✓ Important for cell membrane structure and cell growth
- ✓ Precursor of phosphoinositide synthesis (signal translation mechanism)
- ✓ Is an insulin-sensitizing substance that interferes with the intracellular insulin signal transduction
- ✓ Administered to women with PCOS causes a reduction of insulin resistance and testosterone levels

Un adulto consuma circa **1 gr** di inositolo al giorno

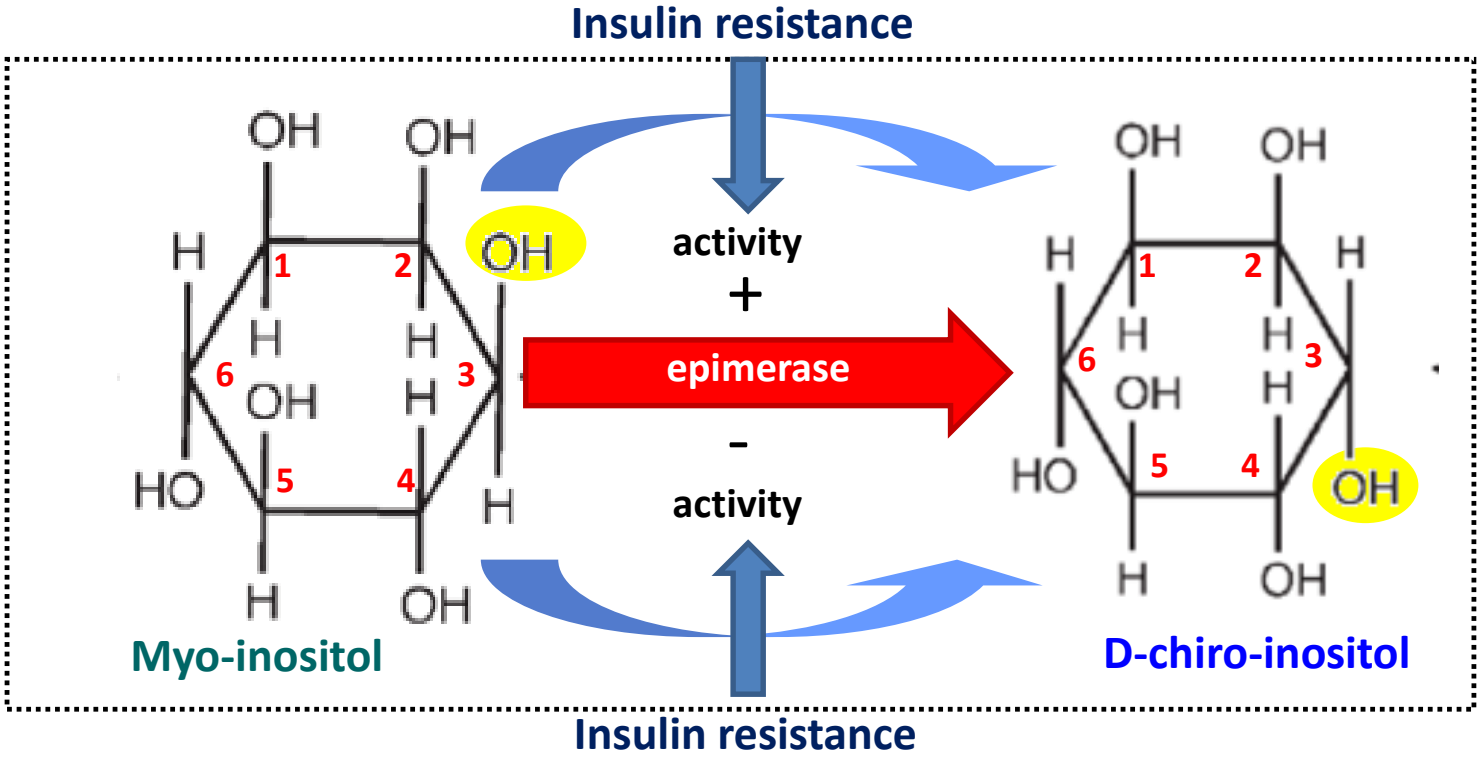
L'inositolo è contenuto:

- ✓ negli agrumi,
- ✓ nel lievito di birra,
- ✓ nel latte,
- ✓ nella verdura

No side effects have been reported

De Leo, Morgante et al, Endocrine Review, 2003

Myo/D-Chiro-Inositol ratio



✓At tissue level, the relationship between myo and d-chiro is regulated by the activity of the epimerase enzyme[1]

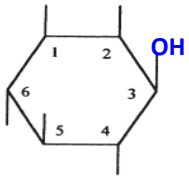
✓Insulin resistance modifies the action of the epimerase differently in different tissues

[1]Carlomagno G. et al.: " The D-chiro-inositol paradox in the ovary"- Fertil Steril 2011; 95: 2515-2516

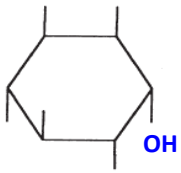
[2]Nor dio M. e Proietti E.: "The combined therapy with myo-inositol and D-Chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone"-Eur Rev Med Pharmacol Sci 2012; 16:575-581

Scopo della supplementazione mirata nelle donne con PCOS e in sovrappeso

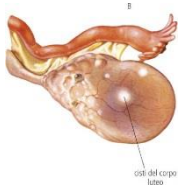
MYO



DCI

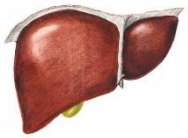


OVAIO



- Ripristina l'uptake del glucosio cellulare
- Migliora la qualità e la maturità ovocitaria
- Riduce le unità di r-FSH somministrate durante i cicli IVF

FEGATO E TESSUTI RESPONSABILI DELLO STOCCAGGIO DEL GLICOGENO



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Consente lo stoccaggio in glicogeno del glucosio

- Migliora la sensibilità dei tessuti all'insulina in donne con PCOS insulino-resistenti e obese, evitando il peggioramento del quadro iper-insulinemico

Decreased myo-inositol to chiro-inositol (m/c) ratios and increased m/c epimerase activity in pcos theca cells demonstrate increased insulin sensitivity compared to controls

Douglas Heimark [1)], Jan McAllister [2)] and Joseph Larner [1)]

Insulin resistance is associated with an inositol imbalance of excess myo-inositol and deficient chiro-inositol together with a deficiency of myo-inositol to chiro-inositol epimerase

In insulin sensitive PCOS theca cells the inositol imbalance goes in the opposite direction to that observed in insulin resistant cells, and there is a decreased M/C ratio and an increased myo-inositol to chiro-inositol epimerase activity

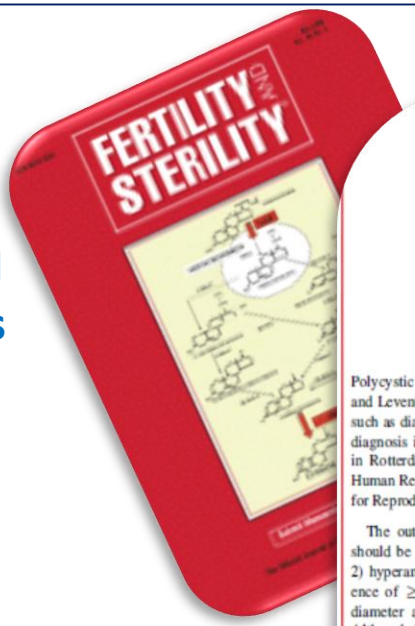
Endocrine Journal 2013

Il paradosso ovarico

- […] Therefore, we could speculate that PCOS patients with hyperinsulinemia likely present an enhanced MI to DCI epimerization in the ovary; this would result in an increased DCI/MI ratio (i.e., overproduction of DCI), which in turn would lead to an **MI deficiency in the ovary.**

[…]

- […] Furthermore, because MI supplementation reduces the rFSH IU administrated during IVF cycles, it is likely that the putative **MI deficiency in the ovary would also impair the FSH signaling,** resulting in an increased risk of ovarian hyperstimulation syndrome for PCOS patients.[…]



The D-*chiro*-inositol paradox in the ovary

The D-*chiro*-inositol–to-*myo*-inositol ratio is regulated by an insulin-dependent epimerase. Enzyme activity varies among tissue, likely owing to the specific needs of the two different molecules. We hypothesize that in the ovaries of polycystic ovary syndrome patients, epimerase activity is enhanced, leading to a local *myo*-inositol deficiency which in turn is responsible for the poor oocyte quality. (Fertil Steril® 2011;■:■–■. ©2011 by American Society for Reproductive Medicine.)

Key Words: ■, ■■■;

Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935 (1), and several aspects of this syndrome, such as diagnosis and treatments, are still debated. Currently, the diagnosis is based on the outcome of a consensus meeting held in Rotterdam in 2003 sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine.

The outcome of the meeting defined that PCOS diagnosis should be based on three different factors: 1) oligoanovulation; 2) hyperandrogenism (clinical or biochemical); and 3) the presence of ≥12 follicles in each ovary measuring 2 ± 9 mm in diameter and/or increased ovarian volume (>10 mL) (2, 3). Although 16% to 80% of PCOS patients show insulin resistance (IR), the consensus meeting decided to exclude IR from the diagnostic criteria (4).

Among the treatments routinely used in clinical practice, the most promising ones are insulin-sensitizing agents (5), including inositol. Inositol is a polyalchol existing as nine different stereoisomers, two of which have been shown to be insulin mediators: *myo*-inositol (MI) and D-*chiro*-inositol (DCI) (6).

In vivo, DCI is synthetized by an epimerase that converts MI into DCI and, depending on the specific needs of the two different molecules, each tissue has a typical conversion rate (6, 7). In particular, it was shown that the ratio of these two insulin mediators was itself insulin dependent. Indeed, in subjects with type 2 diabetes, the DCI/MI ratio was reduced and less DCI was synthetized, owing to a reduction in the epimerase activity (7–10).

In 1999 Nestler et al. used DCI in the treatment of PCOS (11). In their study, 19 out of 22 obese hyperinsulinemic PCOS patients treated with 1.2 g/d DCI showed restored ovulation compared with the placebo group. Furthermore, an improvement of the hormonal profile was observed in the DCI group. Recent studies showed that 4 g/d MI, besides improving hormonal profile and restoring ovulation, is able to induce regular menses in both lean and obese PCOS patients (12–15).

Furthermore, a direct correlation of MI concentration in the follicular fluid and high oocyte quality has been found (16). Additional studies also showed that MI supplementation is able to improve oocyte quality (17), and in a recent study we showed that MI rather than DCI is able to improve both oocyte and embryo quality (18). Interestingly, in both studies reductions of the amount of recombinant FSH (rFSH) administered and the number of canceled cycles were observed (17, 18).

Unlike tissues such as muscle and liver, ovaries never become insulin resistant (19–21). Therefore, we could speculate that PCOS patients with hyperinsulinemia likely present an enhanced MI to DCI epimerization in the ovary; this would result in an increased DCI/MI ratio (i.e., overproduction of DCI), which in turn would lead to an MI deficiency in the ovary. This MI depletion could eventually be responsible for the poor oocyte quality observed in these patients (22).

Furthermore, because MI supplementation reduces the rFSH IU administrated during IVF cycles (17, 18), it is likely that the putative MI deficiency in the ovary would also impair the FSH signaling, resulting in an increased risk of ovarian hyperstimulation syndrome for PCOS patients.

Therefore, we could speak of a "DCI paradox": indeed, although DCI is useful in the treatment of PCOS patients to reduce IR, it has no effect at ovarian level.

We hope that the present letter will be used as a starting point for further research to unravel the precise role played by MI and DCI at the ovarian level.

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G.C. has nothing to disclose; S.R. has nothing to disclose; V.U. has served as consultant to Lo.Li. Pharma.
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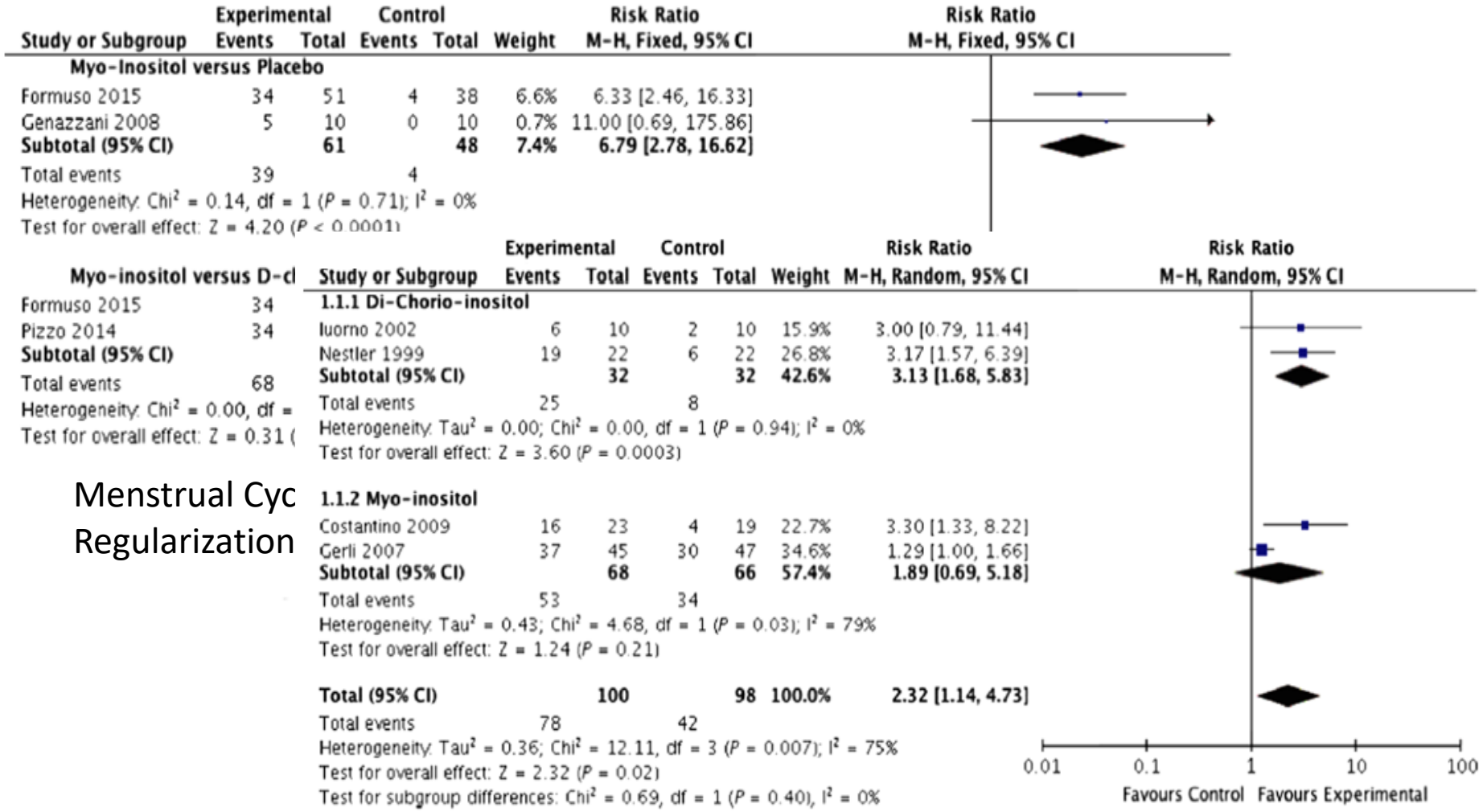
Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials

J Pundir, BJOG 2017

BJOG An International Journal of Obstetrics and Gynaecology



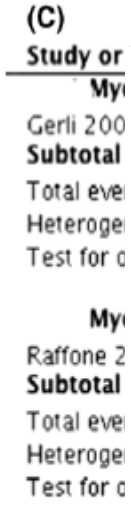
Menstrual Cyc
Regularization

Ovulation

Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials

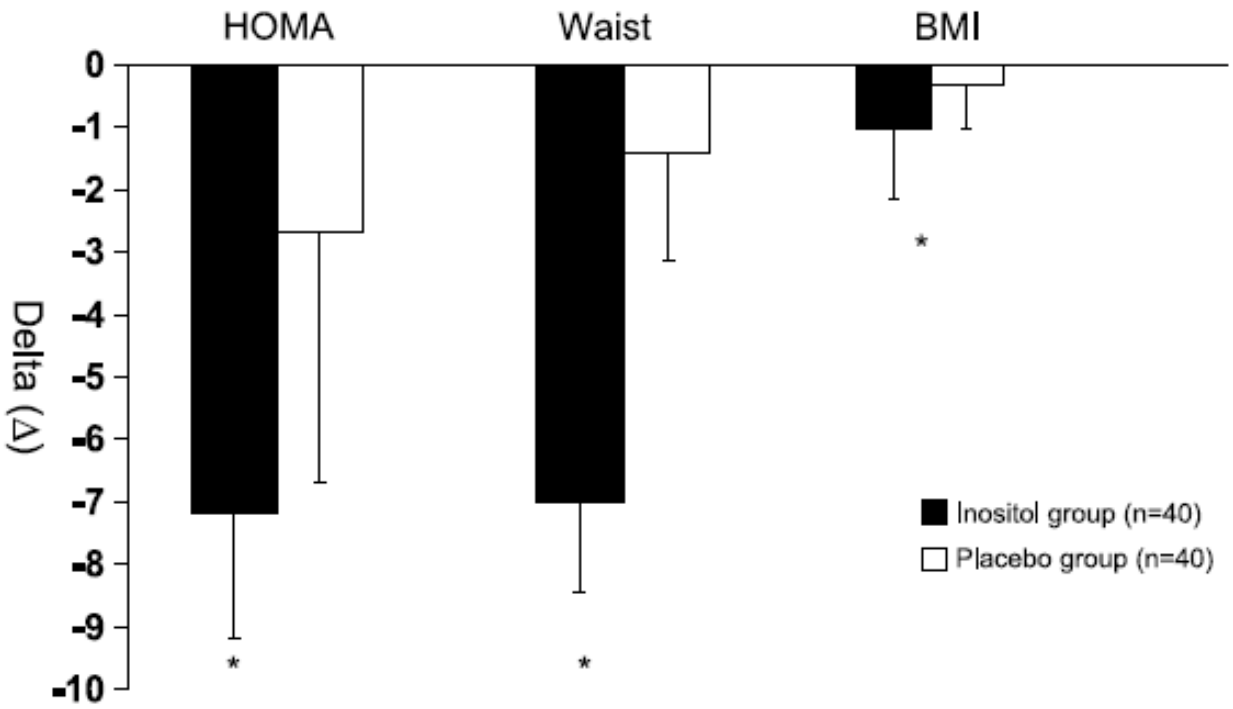
J Pundir, BJOG 2017

BJOG An International Journal of Obstetrics and Gynaecology



Inositol appears to significantly improve the ovulation rate, and metabolic and hormonal profiles in women with PCOS compared with placebo. There is a need to assess its effect on pregnancy and live birth rates and on longer term metabolic health outcomes. This review shows promising but preliminary favourable results with myo-inositol in women with PCOS. A well-designed and well-conducted multicentre trial to address this issue to provide robust evidence of benefit is warranted before the widespread use of inositol can be recommended.

Effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome: a perspective, randomized, placebo-controlled study



Myo-inositol (2 grx2/die vs placebo) supplementation for 6 months in postmenopausal women affected by metabolic syndrome demonstrated that it may improve some of the metabolic features of the syndrome such as carbohydrate metabolism, lipid profile, and blood pressure.

Giordano D et al, Menopause 2011

OBSTETRICS

Clinical and metabolic outcomes in pregnant women at risk for gestational diabetes mellitus supplemented with myo-inositol: a secondary analysis from 3 RCTs

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Am J Obst Gynecol 9-2018

TABLE 4
Clinical outcomes in bc

Outcome
Gestational age at delivery, v
Fetal weight, g[a]
Preterm birth, n (%)
Macrosomia (≥4 kg), n (%)
Large for gestational age (≥90th percentile), n (%)
Gestational hypertension, n (

TABLE 6
Univariate logistic regression analysis on myo-inositol treatment

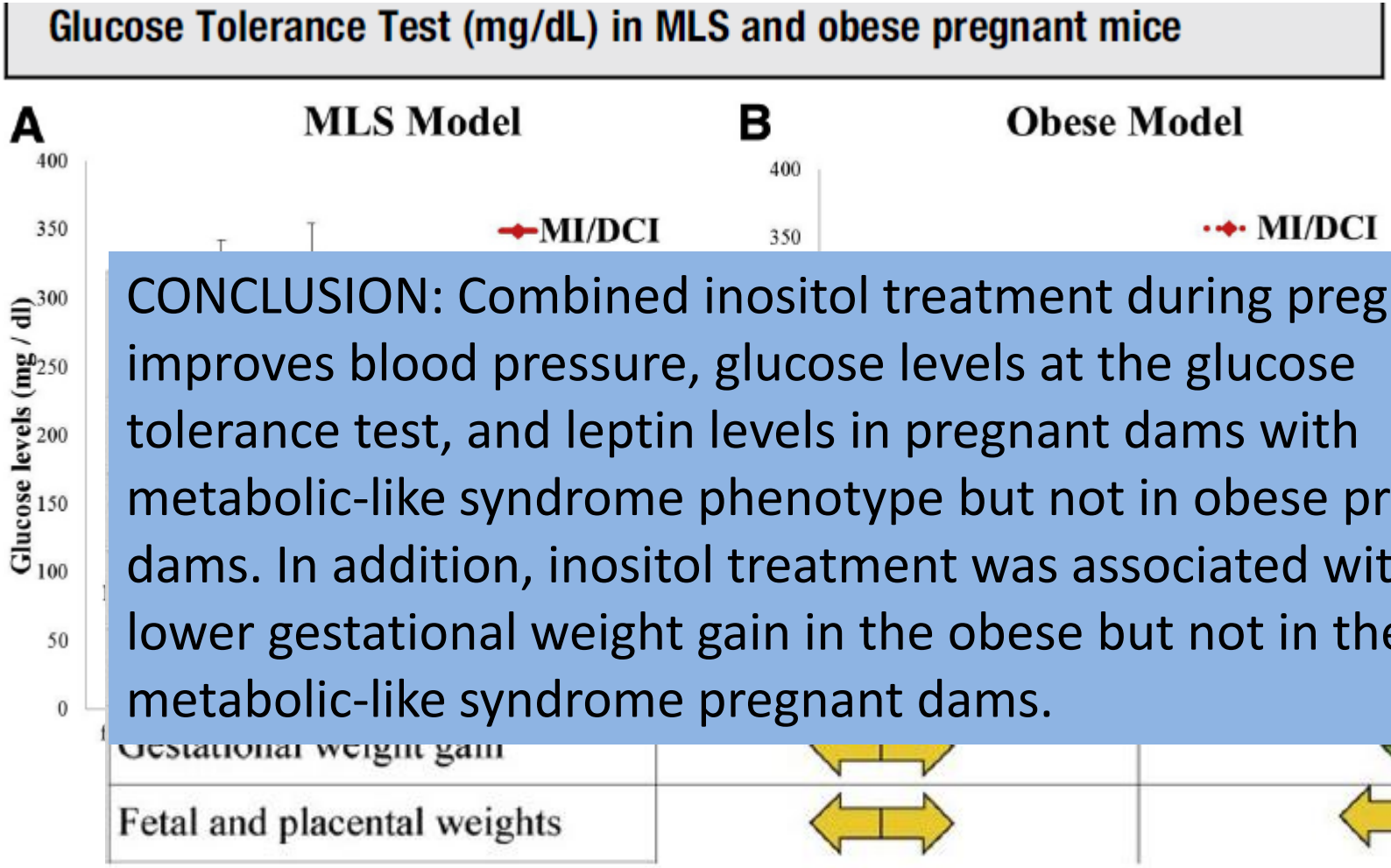
Outcome	P value	Odds ratio	95% Confidence interval
Gestational diabetes mellitus	<.001	0.36	0.23–0.57
Gestational hypertension	.06	.34	0.11–1.06
Preterm birth	.03	.44	0.20–0.93
Macrosomia	.04	.38	0.14–0.98
Large for gestational age	.05	.52	0.27–1.01
Fetal growth restriction	.66	1.39	0.31–6.30
Glucose value			

Although confirming a significant reduction of GDM rate in women who received MI in comparison with placebo, we also demonstrated a reduction of preterm birth rate and in the rates of macrosomia and LGA babies. Indeed, MI supplementation reduced the risk for macrosomia and preterm birth by 60% and 50%, respectively, as shown by univariate and multivariate analysis.

Starting early in pregnancy, MI supplementation reduced preterm birth and large infants, in addition to preventing GDM development in approximately twothirds of the population.

The effect of combined inositol supplementation on maternal metabolic profile in pregnancies complicated by metabolic syndrome and obesity

Ferrari F et al, Am J Obstet Gynecol, 2016



CONCLUSION: Combined inositol treatment during pregnancy improves blood pressure, glucose levels at the glucose tolerance test, and leptin levels in pregnant dams with metabolic-like syndrome phenotype but not in obese pregnant dams. In addition, inositol treatment was associated with lower gestational weight gain in the obese but not in the metabolic-like syndrome pregnant dams.

International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

Chapter Four

Whilst the evidence at this time on the benefit of inositol (in all forms) was inadequate to make an evidence-based recommendation, there is some emerging data suggesting metabolic, hormonal and ovulatory benefits. As this agent is freely available as a nutritional supplement, at low to moderate cost and appears to have a limited side effect profile, it may warrant consideration for use despite limited and low quality evidence. As with other supplements or complementary therapies, women taking this agent are encouraged to advise their health care team.

PCOS Terapeutic Options

Inositolo e PCOS
- proposte terapeutiche -

- **BMI**
  - **< 24,9 ⟹ 2/2.4 gr myo-inositolo**
  - **< 24,9 ⟹ 250/600 mg chiro-inositolo**
  - **> 24,9 ⟹ 3/4 gr myo-inositolo**
  - **> 24,9 ⟹ 1/1.2 gr chiro-inositolo**

½ h prima dei pasti (a digiuno)

- **Associazione di inositolo a metformina a basse dosi (850-1000 mg) per ridurne gli effetti collaterali**
- **Inositolo e CO (dosaggio in base al BMI)**
- **Inositolo e clomifene citrato/gonadotropine per induzione ovulazione (dosaggio in base al BMI)**

Inositol

- MYO is effective in improving *reproductive profile*
- DCI more *metabolic effect* (hyperandrogenism and IR)
- They seem to play different but synergistic roles in glucose metabolism and insulin regulation, in counteracting reproductive / endocrine-metabolic defects
- Both treatments are proposable
- The *combination of MYO: DCI* could be more effective but ....

- Precise relationship are not still clear
- Pharmacokinetic studies are ongoing
  - Importance of the dosage