INOSITOLO
DUBBI E CERTEZZE

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MOTHER-INFANT DEPT.

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NAPOLI 21 giu, 2017

UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Trasparenza

Lo.Li. Pharma ha sostenuto le spese di viaggio per questo convegno

Nessuna relazione con i produttori di Metformina

OUTLINES

- **Inositoli e Insulino Resistenza**
- **Inositoli/Metformina per la PCOS**
- **Inositoli e gravide a rischio per GDM**
- **Effetti transgenerazionali degli inositoli**
- **Inositoli e RDS dei prematuri**

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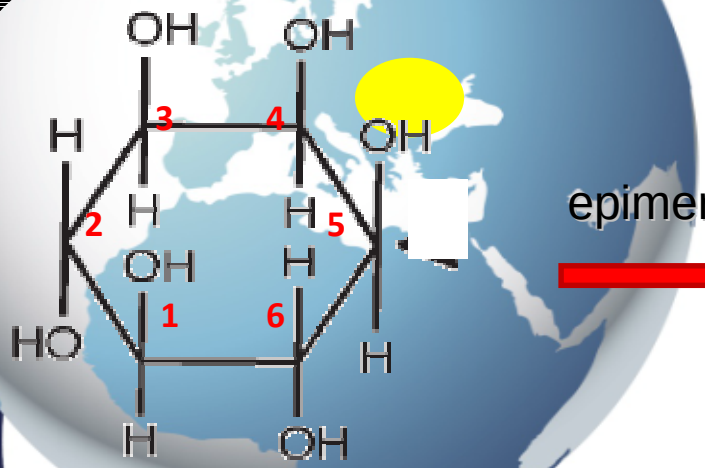
Inositols

A 6-carbon, cyclic polyalcohol family composed by **9 different stereoisomers,** Myo-inositol being the most abundant stereoisomer in nature.

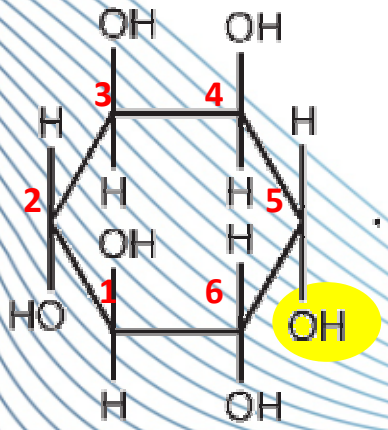
Inositol-dependent hormonal signalling:

INSULIN, FSH, TSH, 5-HT



Myo-inositol

epimerase



D-chiro-inositol

Conversion is unidirectional and insulin-dependent

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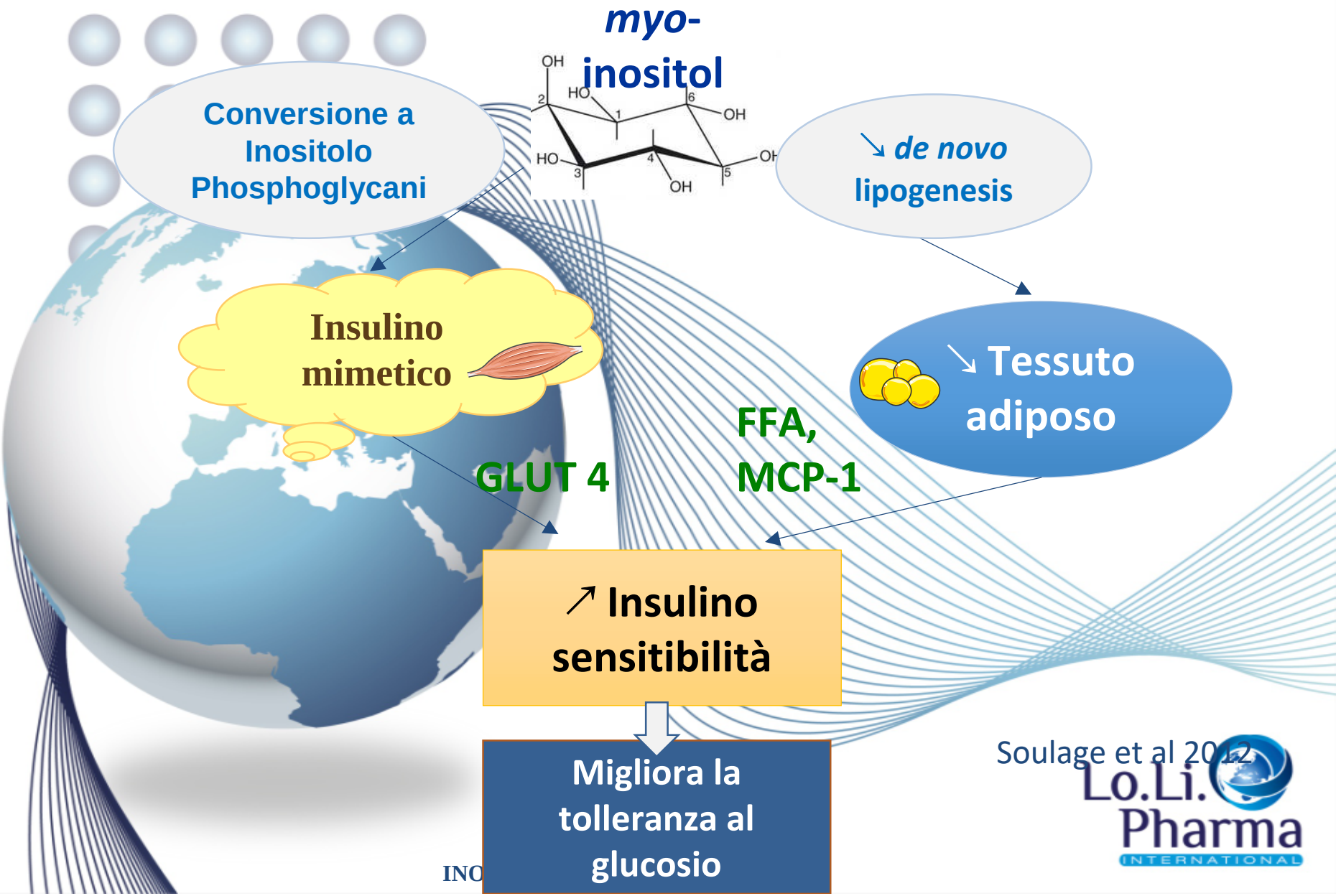
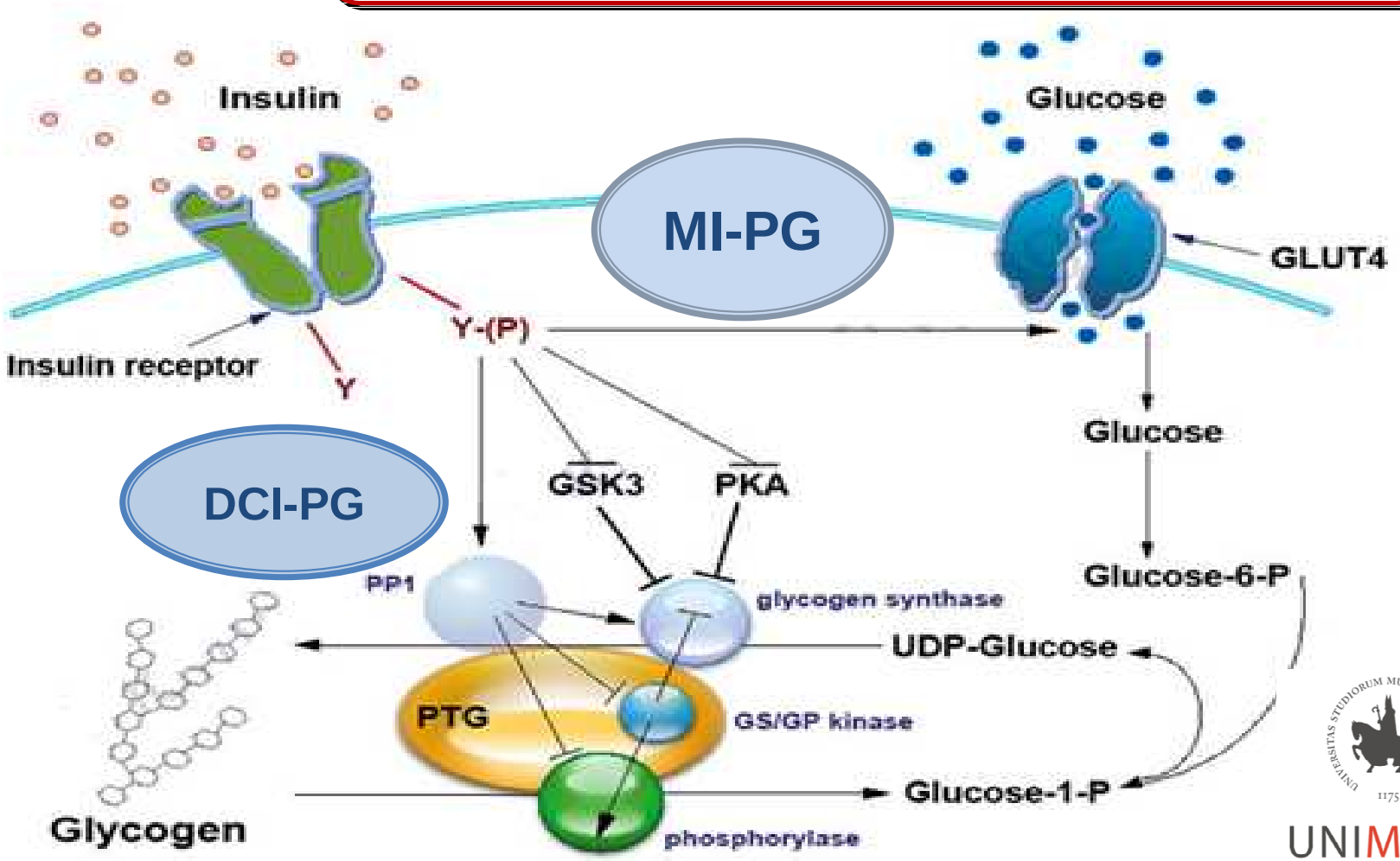
Myo-inositol effect in mice



Soulage et al 2012

HEPATIC CELL

The binding between insulin and its receptor mediates the production of low molecular weight inositol-phosphoglycans that act as second messengers



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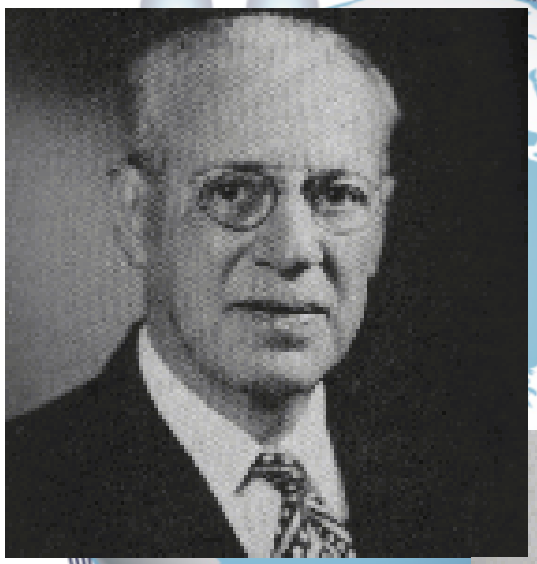
The PCO discovery

Ste...
Amenor...
polyc...
Am J Obstet Gynecol 1935



Surgical cone excision
Laparoscopic drilling
Ovarian suppression

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'90ies

Increased LH (>10 IU/ml)

Increased LH/FSH ratio (>2.5)

Reduced SHBG & IGF-BPs

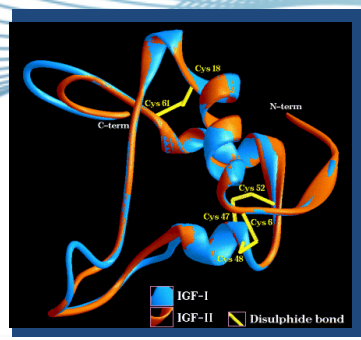
Increased free Testosterone and Androstenedione

Reduced Progesterone (Chronic anovulation)

Increased LDL-cholesterol, triglycerides, visceral fat

Increased Insulin & Insulin-resistance

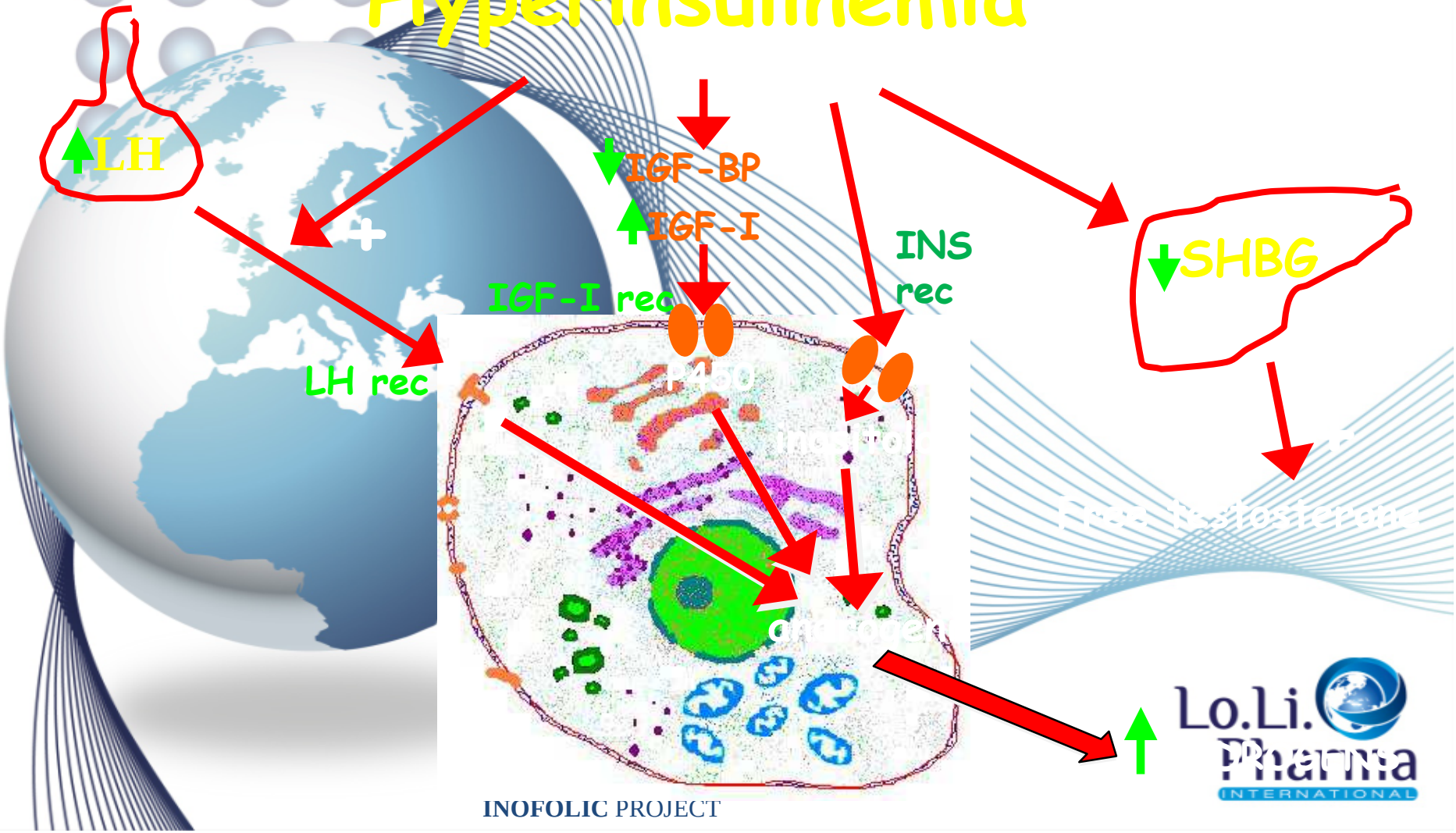
Insulin sensitizers



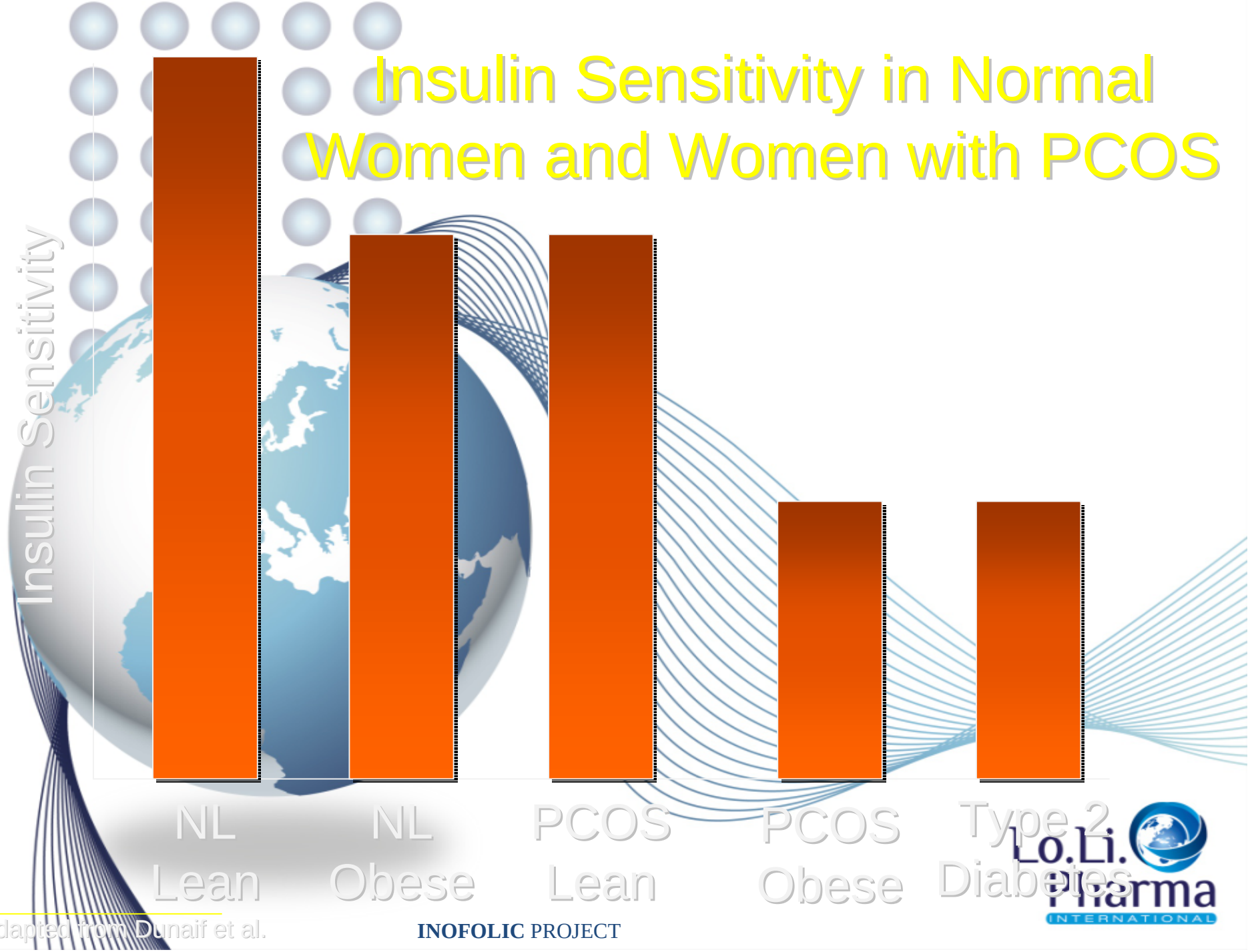
IGF-I

Insulin and androgens

Hyperinsulinemia



Insulin Sensitivity in Normal Women and Women with PCOS

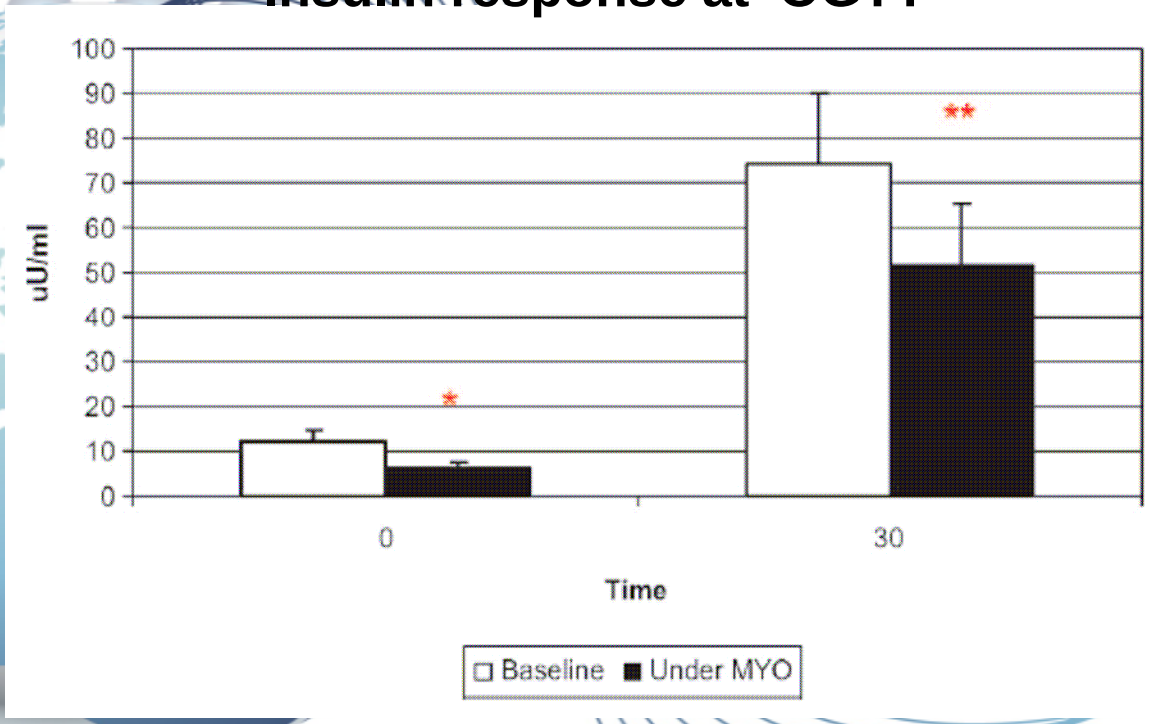


Adapted from Dunaif et al.

Inositol and insulin resistance

Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome

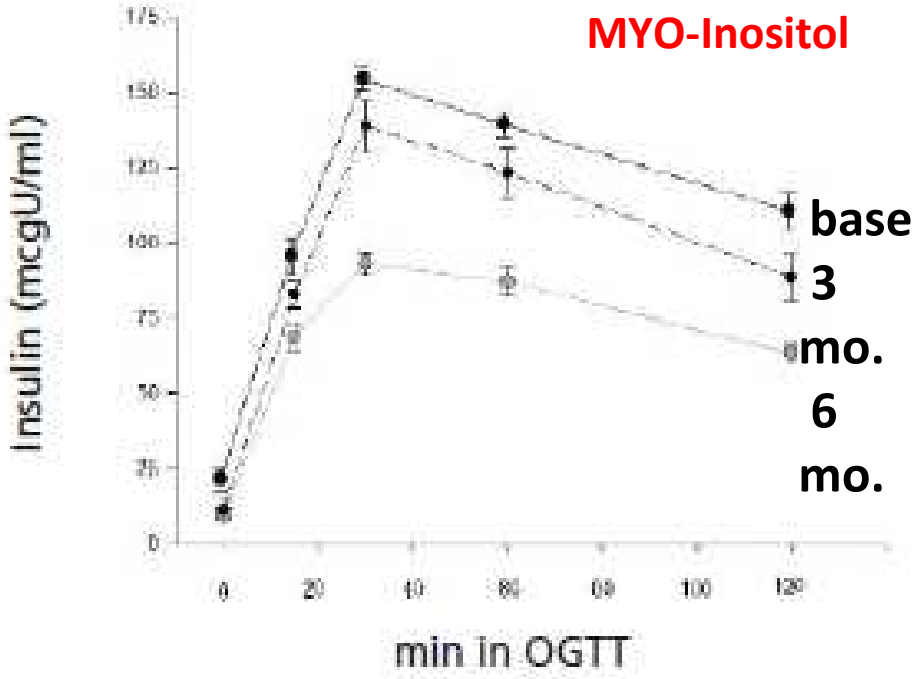
Insulin response at OGTT

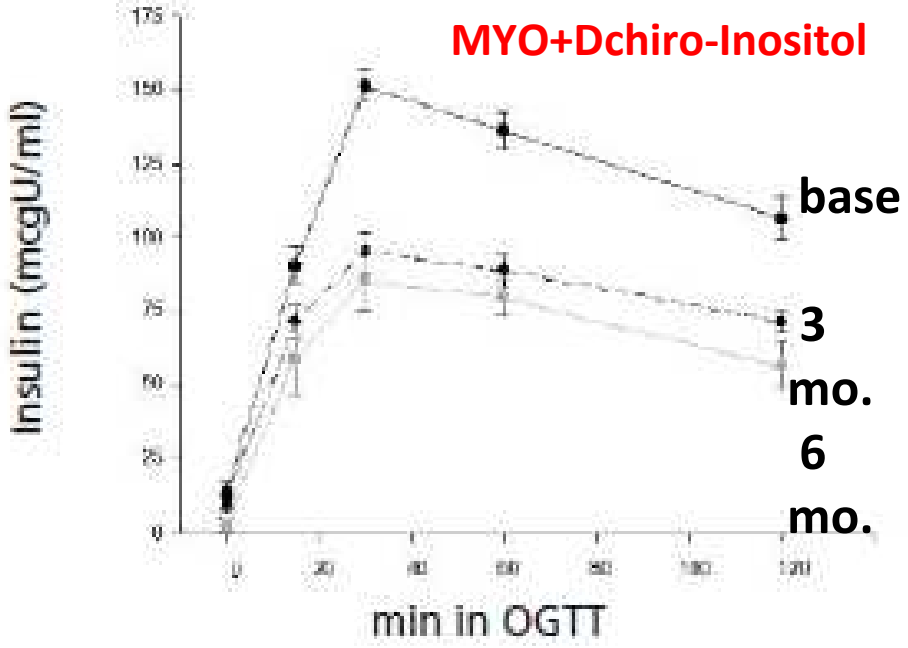


Patients under MYO administration showed a reduction of both insulin plasma levels before and 30 minutes after oral glucose load.

***p<0.05, **p<0.01**

Gynecol Endocrinol 2008





The mixture MYO+DCI 40:1, according to physiological ratio, induces a prompter normalization of the Insulin response than MYO alone

Nordio et al 2014

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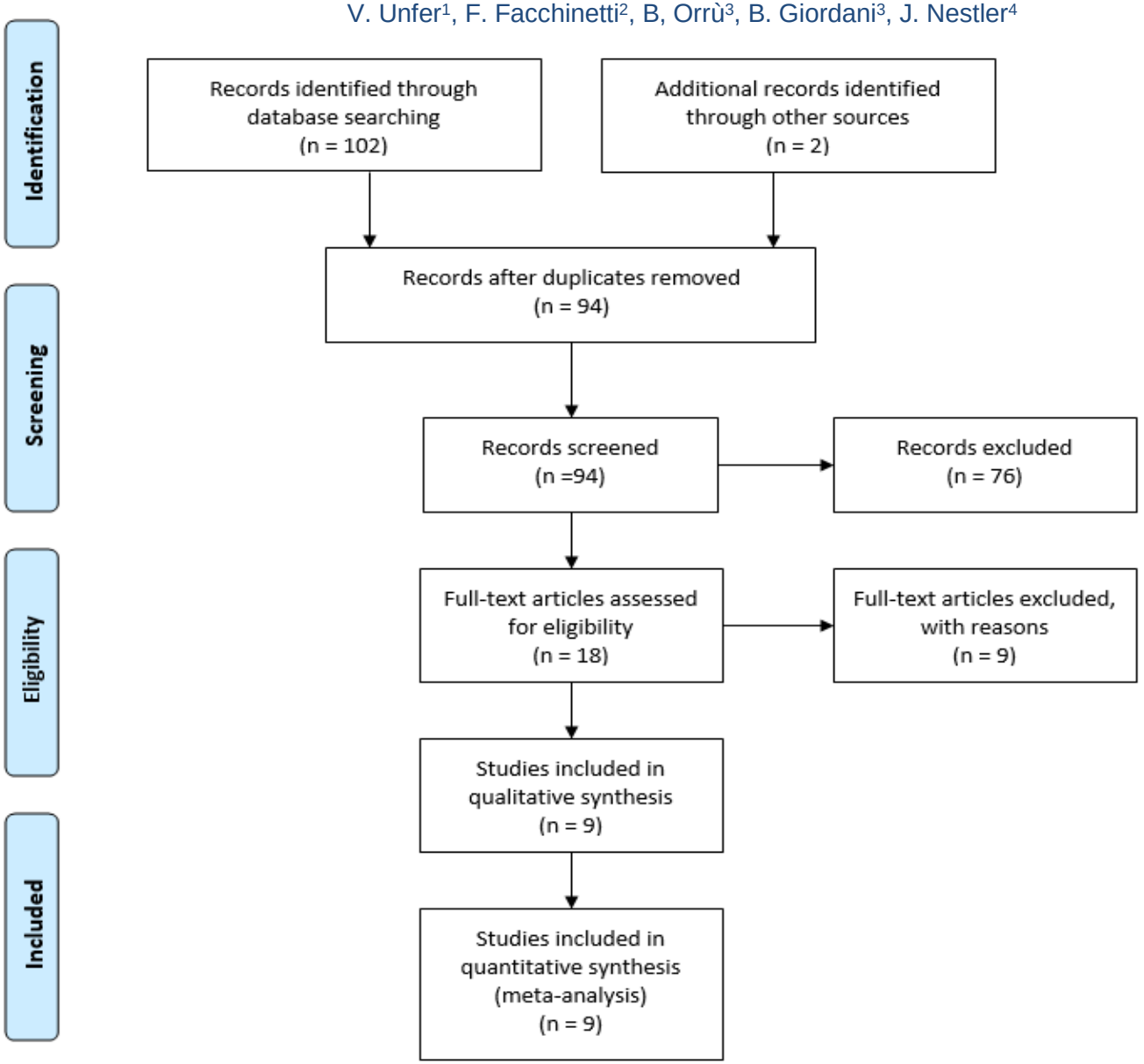
Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials

V. Unfer[1], F. Facchinetti[2], B, Orrù[3], B. Giordani[3], J. Nestler[4]



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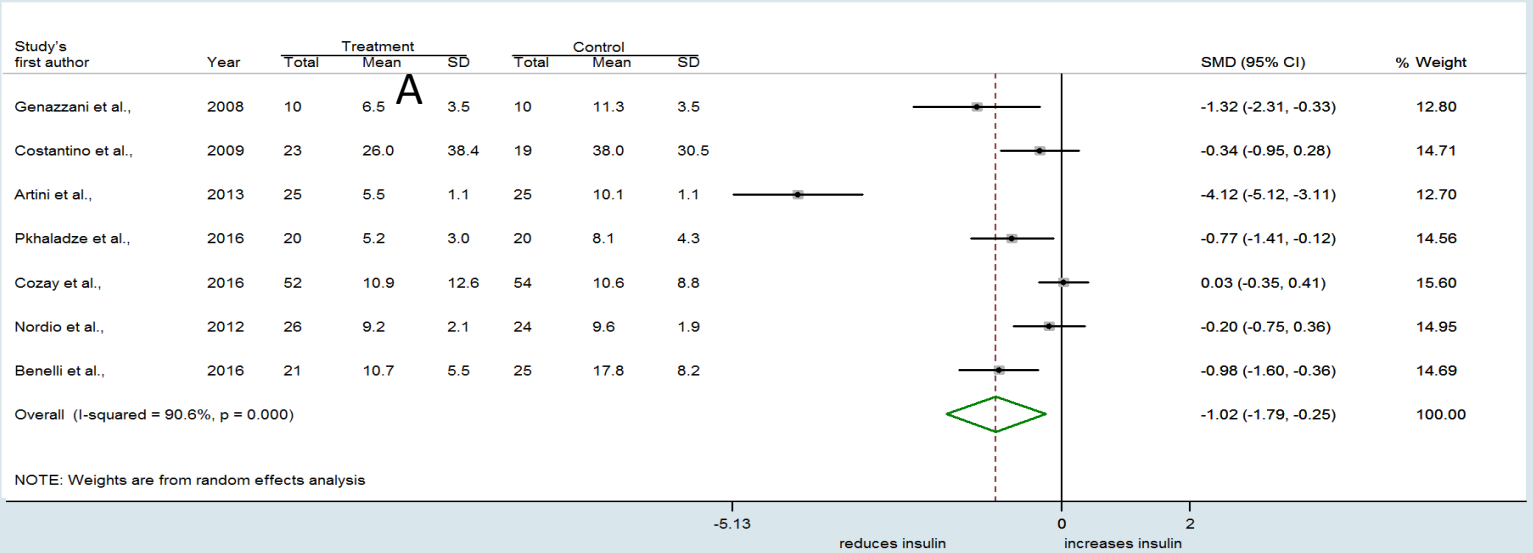
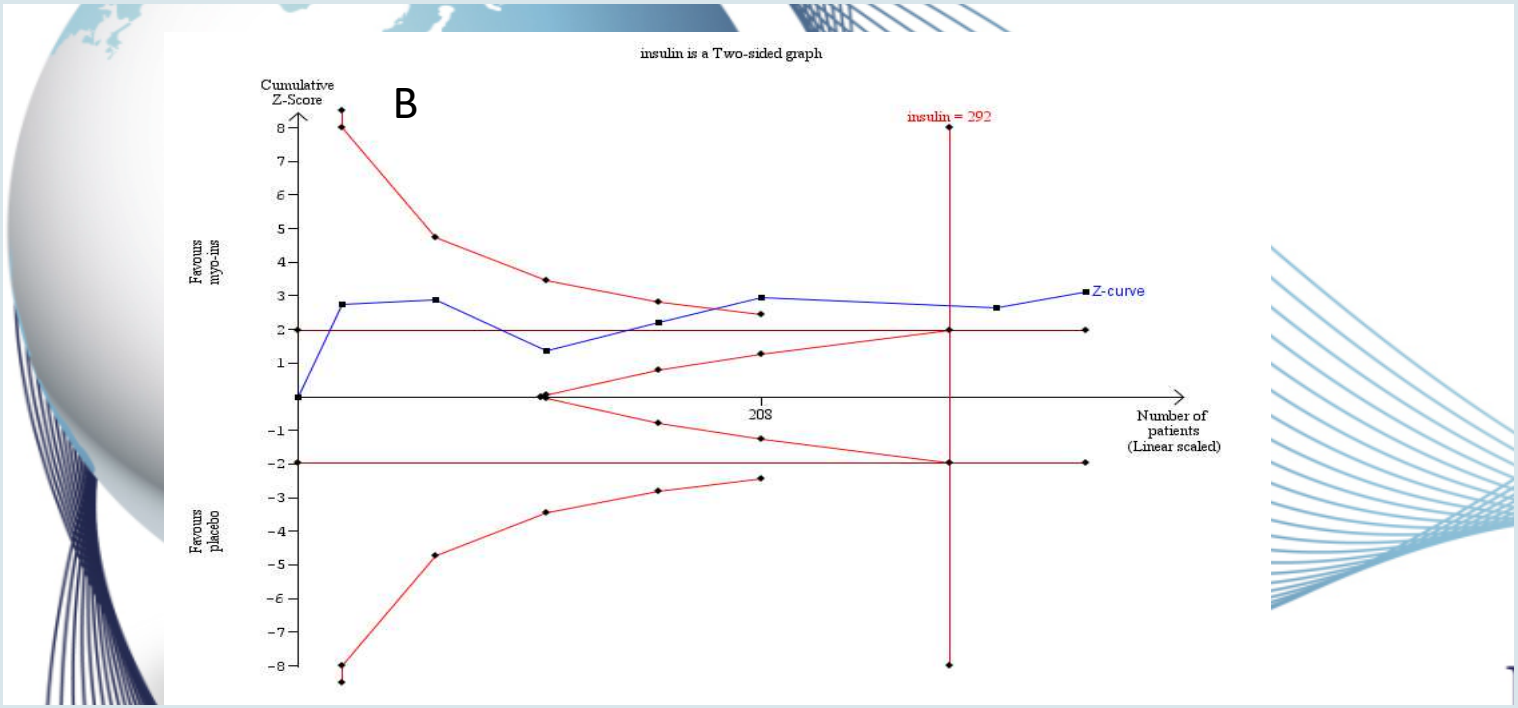


FASTING INSULIN



Trial sequential analysis

Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials

V. Unfer[1], F. Facchinetti[2], B, Orrù[3], B. Giordani[3], J. Nestler[4]

Inositols vs Placebo

Glycaemic factors

Study or Subgroup	Inositol Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Insulin(fasting) µU/ml								
Artini 2013	5.5	1.1	25	10.1	1.1	25	4.7%	-4.12 [-5.12, -3.11]
Costantino 2009	26	8	23	38	7	19	5.0%	-1.56 [-2.26, -0.86]
Dona 2012	5.16	2.61	18	7.75	0.76	8	4.8%	-1.12 [-2.02, -0.23]
Genazzani* 2008	6.5	1.1	10	11.3	1.1	10	4.0%	-4.18 [-5.87, -2.49]
Iuorno 2002	24	8	10	36	7	10	4.7%	-1.53 [-2.55, -0.51]
Nestler 1999	22	21	22	42	52	22	5.1%	-0.50 [-1.10, 0.11]
Subtotal (95% CI)			**108**			**94**	**28.3%**	**-2.06 [-3.18, -0.94]**
Heterogeneity: Tau² = 1.68; Chi² = 46.96, df = 5 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.62 (P = 0.0003)								
Glucose(fasting) mg/dl								
Costantino 2009	81.6	4	23	88	4	19	5.0%	-1.57 [-2.27, -0.87]
Dona 2012	83.7	5.6	18	86.2	2.3	8	4.9%	-0.50 [-1.34, 0.35]
Iuorno 2002	80	4	10	87	4	10	4.7%	-1.68 [-2.73, -0.63]
Nestler 1999	90	19	22	95	24	22	5.1%	-0.23 [-0.82, 0.37]
Subtotal (95% CI)			**73**			**59**	**19.6%**	**-0.95 [-1.70, -0.20]**
Heterogeneity: Tau² = 0.43; Chi² = 11.32, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 2.47 (P = 0.01)								
Glucose/Insulin ratio								
Artini 2013	16.5	2.9	25	8.4	2.6	25	4.9%	2.89 [2.08, 3.71]
Genazzani* 2008	17.4	2.9	10	8.6	2.6	10	4.3%	3.06 [1.69, 4.43]
Subtotal (95% CI)			**35**			**35**	**9.2%**	**2.94 [2.24, 3.64]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%								
Test for overall effect: Z = 8.25 (P < 0.00001)								
HOMA-IR Index (Insulin Resistance))								
Artini 2013	1.1	0.3	25	2.4	0.7	25	5.0%	-2.38 [-3.11, -1.64]
Dona 2012	1.06	0.62	18	1.66	0.16	8	4.8%	-1.10 [-1.99, -0.20]
Genazzani* 2008	1.4	0.3	10	2.5	0.7	10	4.6%	-1.96 [-3.06, -0.85]
Subtotal (95% CI)			**53**			**43**	**14.4%**	**-1.83 [-2.63, -1.03]**
Heterogeneity: Tau² = 0.28; Chi² = 4.70, df = 2 (P = 0.10); I² = 57%								
Test for overall effect: Z = 4.50 (P < 0.00001)								
Glucose Area Under Curve (AUC)								
Costantino 2009	10,452	414	23	12,992	793	19	4.6%	-4.06 [-5.15, -2.96]
Iuorno 2002	10,052	414	10	12,592	793	10	4.1%	-3.85 [-5.44, -2.25]
Nestler 1999	12,656	4,316	22	14,014	3,089	22	5.1%	-0.36 [-0.95, 0.24]
Subtotal (95% CI)			**55**			**51**	**13.8%**	**-2.70 [-5.50, 0.09]**
Heterogeneity: Tau² = 5.76; Chi² = 43.41, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 1.89 (P = 0.06)								
Insulin Area Under Curve (AUC)								
Costantino 2009	5,535	1,792	23	9,100	1,162	19	4.9%	-2.27 [-3.06, -1.48]
Iuorno 2002	5,335	1,792	10	8,600	1,161	10	4.6%	-2.07 [-3.20, -0.94]
Nestler 1999	5,158	6,714	22	9,210	7,840	22	5.1%	-0.55 [-1.15, 0.06]
Subtotal (95% CI)			**55**			**51**	**14.6%**	**-1.59 [-2.82, -0.36]**
Heterogeneity: Tau² = 0.99; Chi² = 13.55, df = 2 (P = 0.001); I² = 85%								
Test for overall effect: Z = 2.53 (P = 0.01)								

INSULIN

GLUCOSE

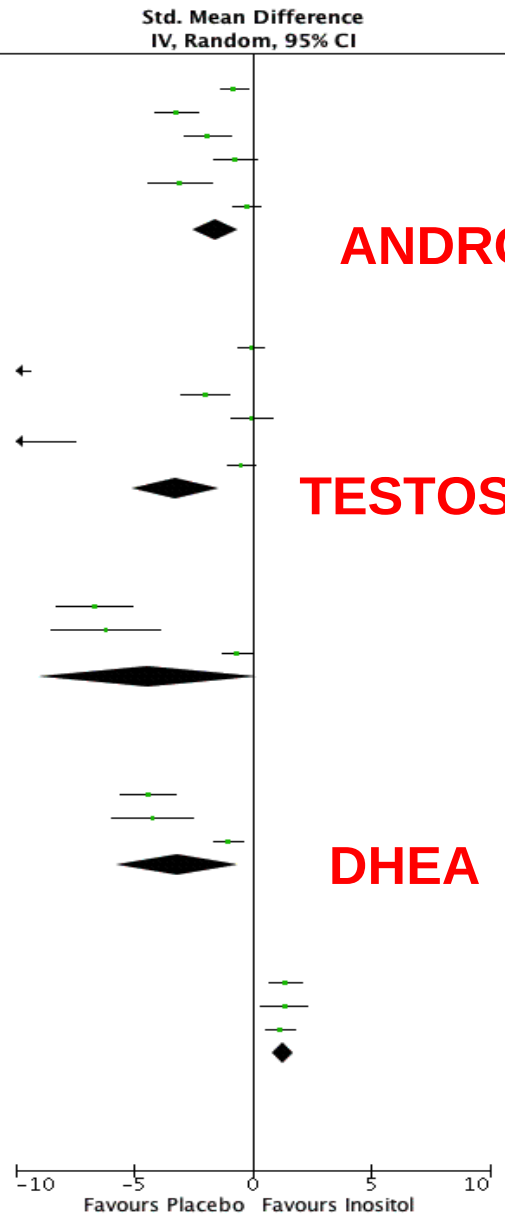
HOMA IR

Pundir et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2017

Inositols vs Placebo

Hormone Changes

Study or Subgroup	Inositol Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Total Androgens ng/dl								
Artini 2013	167.5	29	25	189	24	25	5.3%	-0.80 [-1.37, -0.22]
Costantino 2009	196	26	23	306	41	19	5.0%	-3.21 [-4.16, -2.27]
Dona 2012	316.05	61.89	18	418.91	11.17	8	5.0%	-1.90 [-2.90, -0.90]
Genazzani* 2008	170.5	29	10	191	24	10	5.1%	-0.74 [-1.65, 0.18]
Iuorno 2002	193	26	10	303	41	10	4.7%	-3.07 [-4.45, -1.69]
Nestler 1999	173	50	22	186	53	22	5.3%	-0.25 [-0.84, 0.35]
Subtotal (95% CI)			**108**			**94**	**30.3%**	**-1.58 [-2.53, -0.63]**
Heterogeneity: Tau² = 1.18; Chi² = 39.09, df = 5 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.27 (P = 0.001)								
Total Testosterone ng/dl								
Artini 2013	53.8	6.2	25	54.2	9.1	25	5.3%	-0.05 [-0.61, 0.50]
Costantino 2009	34.8	4.3	23	109	7.5	19	3.3%	-12.22 [-15.03, -9.41]
Dona 2012	41	7	18	56	8	8	5.0%	-1.99 [-3.01, -0.97]
Genazzani* 2008	54.8	6.2	10	55.2	9.1	10	5.1%	-0.05 [-0.93, 0.83]
Iuorno 2002	34	4.3	10	108	7.5	10	2.3%	-11.59 [-15.70, -7.49]
Nestler 1999	61	33	22	79	39	22	5.3%	-0.49 [-1.09, 0.11]
Subtotal (95% CI)			**108**			**94**	**26.2%**	**-3.28 [-5.10, -1.46]**
Heterogeneity: Tau² = 4.36; Chi² = 105.54, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
Free Testosterone ng/dl								
Costantino 2009	0.24	0.03	23	0.85	0.13	19	4.5%	-6.65 [-8.26, -5.04]
Iuorno 2002	0.22	0.03	10	0.83	0.13	10	3.8%	-6.19 [-8.51, -3.88]
Nestler 1999	0.5	0.5	22	0.8	0.4	22	5.3%	-0.65 [-1.26, -0.04]
Subtotal (95% CI)			**55**			**51**	**13.5%**	**-4.43 [-9.03, 0.18]**
Heterogeneity: Tau² = 15.85; Chi² = 62.10, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Dehydroepiandrosterone (DHEA) mcg/dl								
Costantino 2009	188	24	23	320	35	19	4.9%	-4.40 [-5.56, -3.24]
Iuorno 2002	187	24	10	319	35	10	4.4%	-4.21 [-5.91, -2.51]
Nestler 1999	274	91	22	421	179	22	5.2%	-1.02 [-1.65, -0.39]
Subtotal (95% CI)			**55**			**51**	**14.5%**	**-3.15 [-5.71, -0.59]**
Heterogeneity: Tau² = 4.73; Chi² = 32.21, df = 2 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 2.41 (P = 0.02)								
Sex Hormone-Binding Globulin (SHBG) nmol/l								
Costantino 2009	198	24	23	163	26	19	5.2%	1.38 [0.70, 2.06]
Iuorno 2002	196	24	10	161	26	10	5.0%	1.34 [0.35, 2.33]
Nestler 1999	132.4	60.7	22	77.3	24.8	22	5.2%	1.17 [0.52, 1.81]
Subtotal (95% CI)			**55**			**51**	**15.5%**	**1.28 [0.86, 1.70]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%								
Test for overall effect: Z = 5.93 (P < 0.00001)								



ANDROGENS

TESTOSTERONE

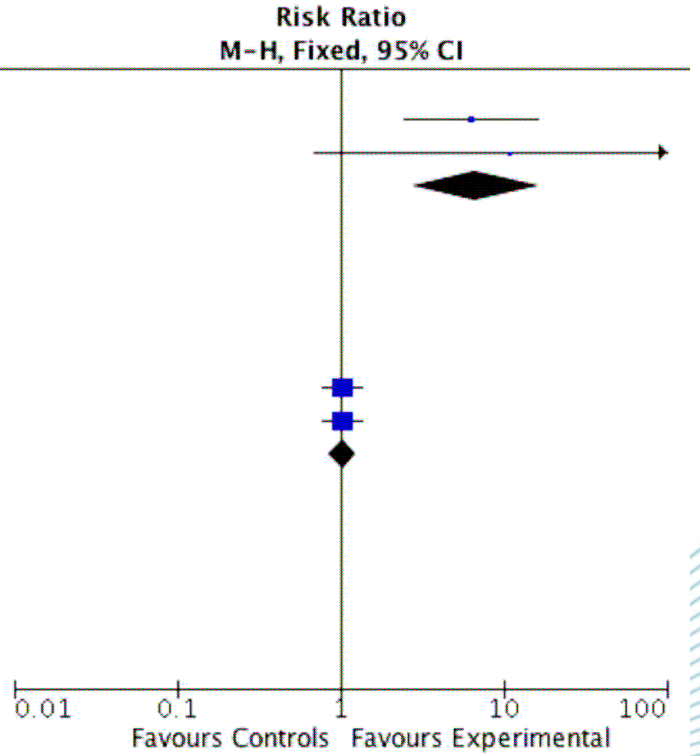
DHEA

Pundir et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2017

Myo-Inositol vs Placebo
Myo-Inositol vs D-Chiro-Inositol

Menstrual cycle regularization

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Myo-Inositol versus Placebo						
Formuso 2015	34	51	4	38	6.6%	6.33 [2.46, 16.33]
Genazzani 2008	5	10	0	10	0.7%	11.00 [0.69, 175.86]
Subtotal (95% CI)		**61**		**48**	**7.4%**	**6.79 [2.78, 16.62]**
Total events	39		4			
Heterogeneity: $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$						
Test for overall effect: Z = 4.20 (P < 0.0001)						
Myo-inositol versus D-chiro-inositol						
Formuso 2015	34	51	31	48	46.3%	1.03 [0.78, 1.37]
Pizzo 2014	34	51	31	48	46.3%	1.03 [0.78, 1.37]
Subtotal (95% CI)		**102**		**96**	**92.6%**	**1.03 [0.84, 1.26]**
Total events	68		62			
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 0.31 (P = 0.76)						



Pundir et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2017

Inositolo in ginecologia e ostetricia

Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome

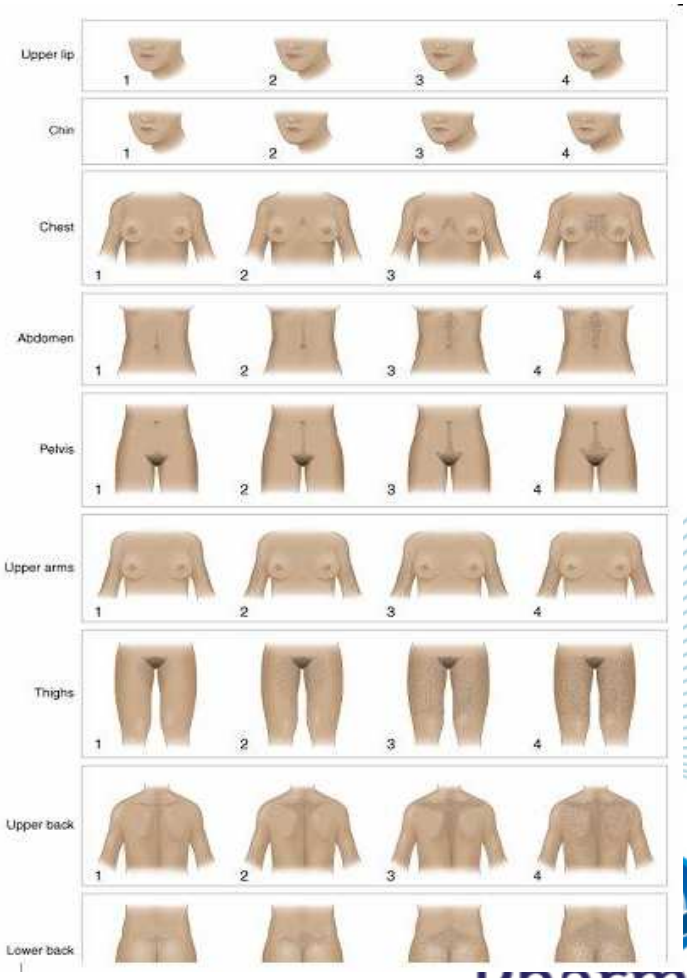
Irsutismo valutato con lo score di Ferriman - Gallwey

	Baseline	T1	T2
Mild	20 (40%)	17 (34%)	16 (32%)
Moderate	21 (42%)	18 (36%)	15 (30%)
Severe	9 (18%)	7 (14%)	4 (8%)
Disappearance	–	8 (16%)	15 (30%)
Mean mFG score	11.4 ± 3.2	9.9 ± 2.8	8.1 ± 2.6*

T1= 3 mesi

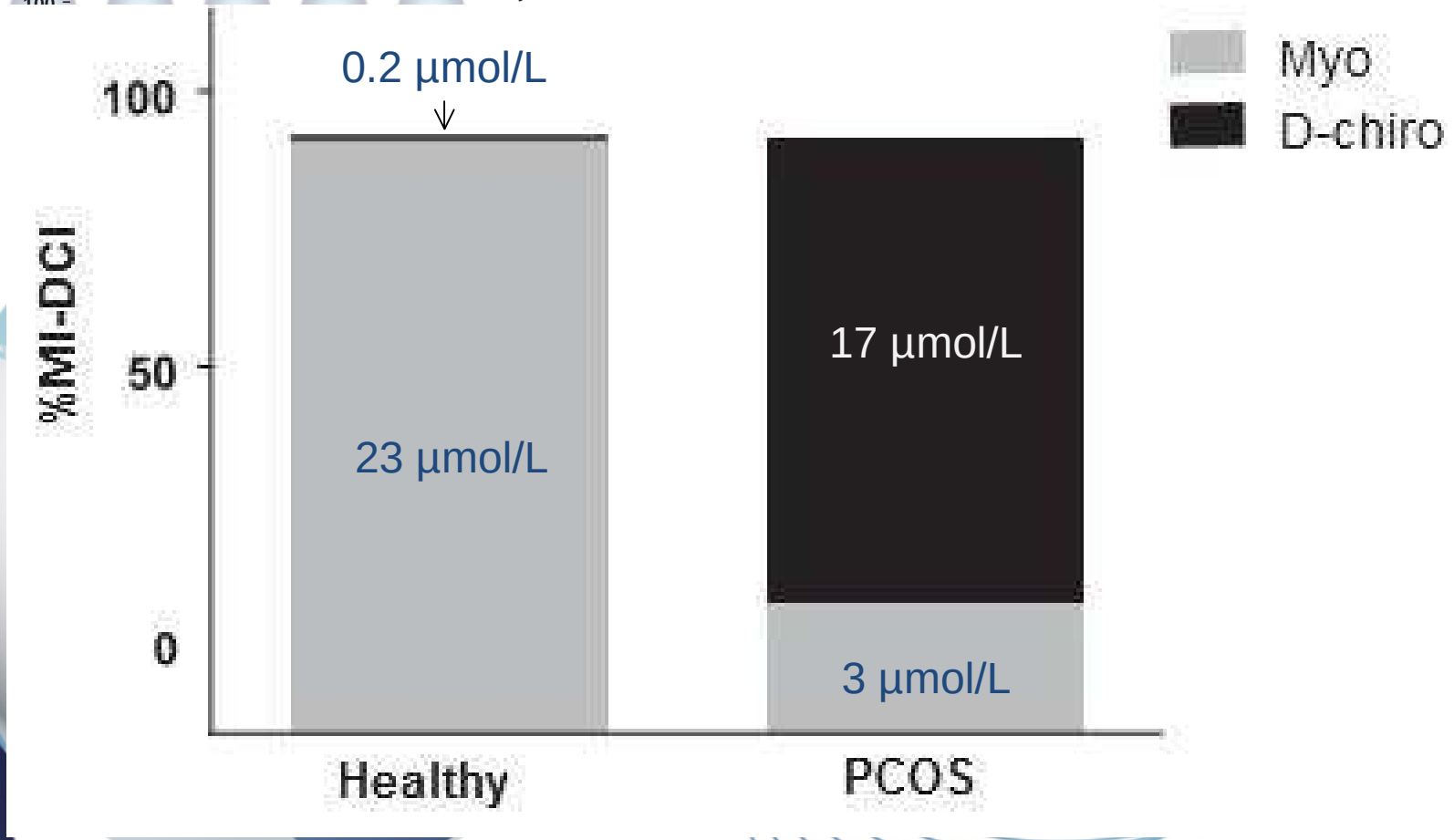
T2= 6 mesi

*$p = 0.03$.



Zacchè et al, Gynecol Endocrinol 2009

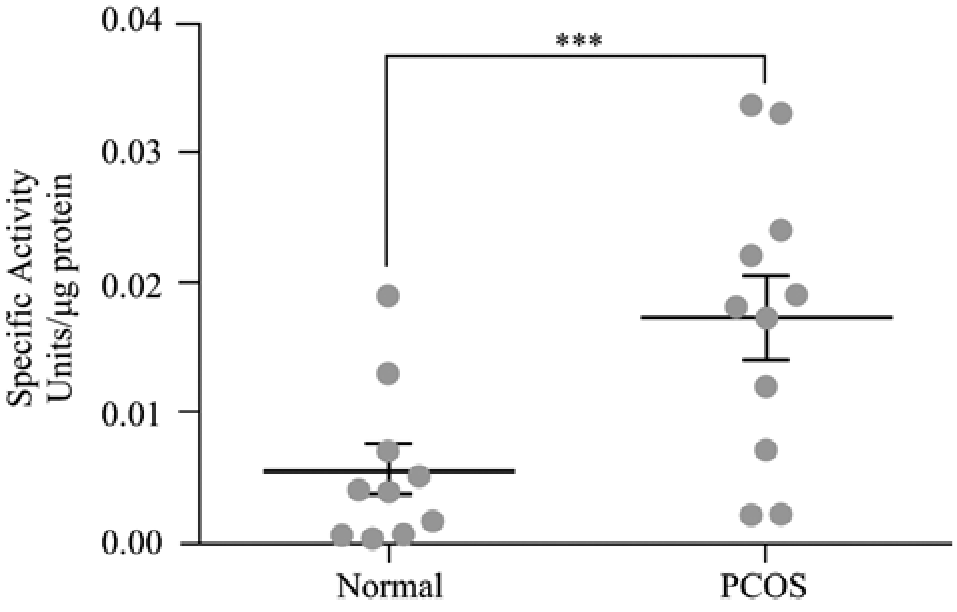
MYO and DCI Contents in FF of Normal and PCOS Women



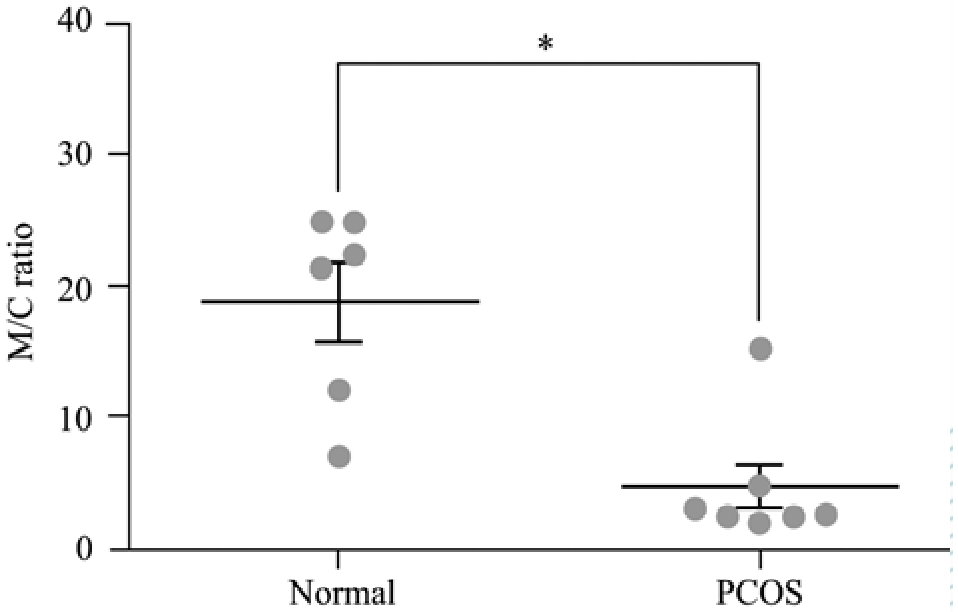
Content of MYO and DCI in follicular fluid of 20 normal women and 20 women with PCOS. The ratio of MYO to DCI was 100:1 in normal women but only 0.2:1 in women with PCOS.

Reprod Sci 2014;21:854-858

Epimerase Activity in Theca Cells from Normal and PCOS Women



MYO to DCI epimerase activity assay
Data points for PCOS and normals shown in scatter plot with mean shown as horizontal bar. ***p<0.001



MYO to DCI ratios
Data points for PCOS and normals shown in scatter plot with mean shown as horizontal bar. ***p<0.002

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Heimark D, McAllister J, Larner J. *Endocrine J* 2014;61:111-117

ART on PCOS patients

PCOS patients have an increased risk of hyperstimulation syndrome

TABLE 1

Characteristics and outcome of patients who received *myo*-inositol plus folic acid (group A; n = 30) or folic acid alone (group B; n = 30).

Variable	Group A	Group B	*P* value
No. of patients	30	30	—
Age (yrs)	36.2 ± 2.4	35.4 ± 2.5	NS
Duration of infertility (months)	46.1 ± 18.5	37.7 ± 9.6	NS
Body mass index (kg/m^2)	26.7 ± 7.5	26.3 ± 6.8	NS
PRL (ng/mL)	17.8 ± 1.9	19.1 ± 2.1	NS
FSH (mIU/L)	1.56 ± 0.05	1.66 ± 1.01	NS
Duration of stimulation (days)	11.3 ± 0.9	12.3 ± 1.4	.002
No. of 75-IU ampules or vials of FSH	26 ± 7.7	31,7 ± 9.2	.016
17β-E_2 level on day of hCG administration (pg/mL)	2,232.1 ± 510	2,713.3 ± 595	.002
No. of canceled cycles (E_2 level >4,000 pg/mL)	1	3	.003

Papaleo. MI, PCO, and oocyte quality in ICSI cycles. Fertil Steril 2009.

- The number of immature oocytes was significantly
- lower in the MYO treated group.

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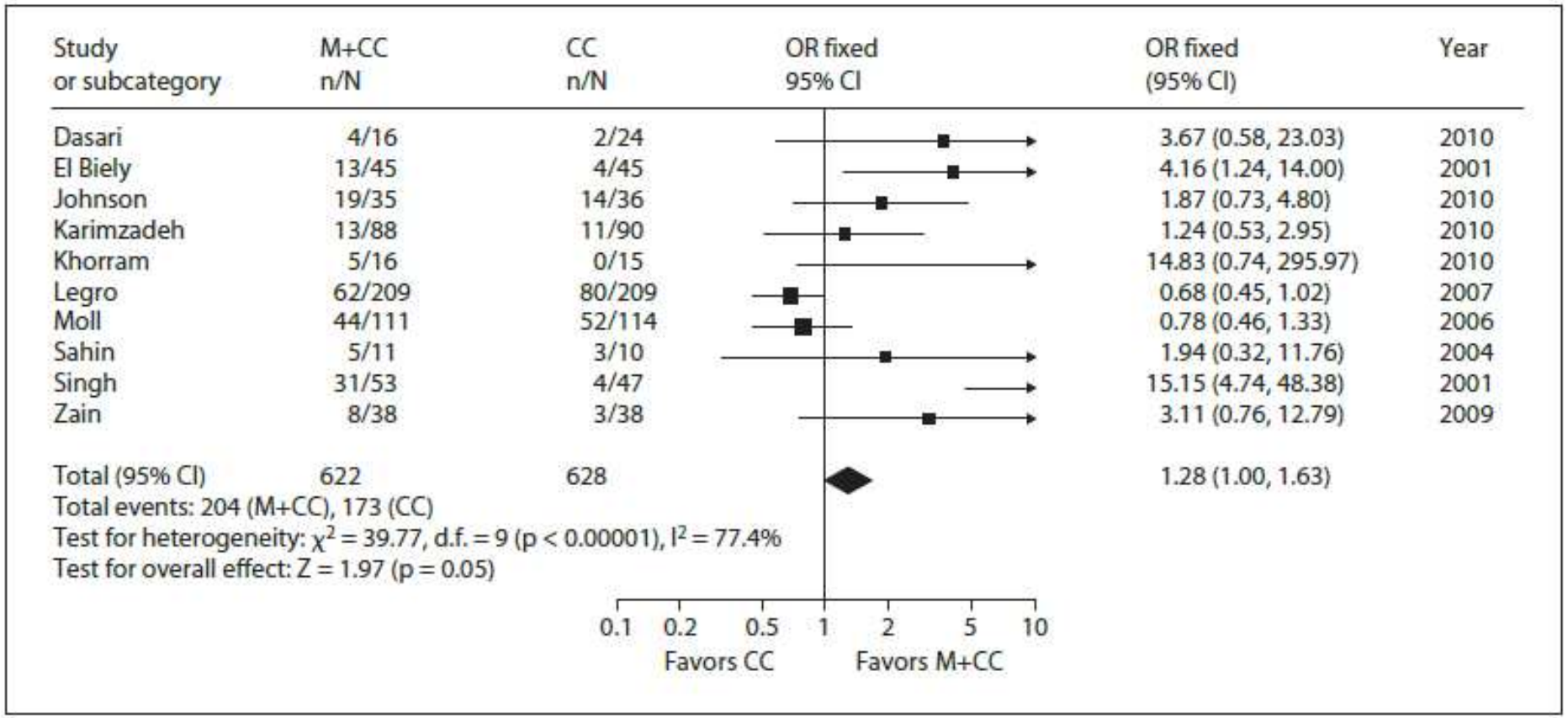
Metformin in PCOS -Pregnancy Rate-



M+CC vs CC

Pregnancy rate was slightly better with the combination (CC+M) compared to CC alone

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Met vs. CC in ovulation and pregnancy rate
30<BMI<33

	INCLUSION	DURATION	METFORMIN		CLOMIPHENE		COMBINATION	
			OVULATION RATE	PREGNANCY RATE	OVULATION RATE	PREGNANCY RATE	OVULATION RATE	PREGNANCY RATE
Legro (135)	Oligo	6M	44%	16%	54%	19%	60%	21%
Zain (115)	Oligo/ amenorr	6M	24%	8%	59%	15%	68%	21%
Ashrafi (35)	Oligo	2M met - 3M met. + CC	59%	11%	//	//	69%	8%
Jhonson (171)	Oligo/ amenorr	6M	66%	40%	70%	39%	80%	54%
	Average %		48%		60%		63%	

Either for ovulation rate or pregnancy rate:

MET perform lower than CC
MET add few to CC, if combo (8%)

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~~Myo-inositol & Clomiphene~~

GYNECOLOGICAL ENDOCRINOLOGY
ISSN: 0951-3590 (print), 1473-0766 (electronic)
Gynecol Endocrinol, Early Online: 1–5

DOI: 10.3109/09513590.2014.964640
informa healthcare

ORIGINAL ARTICLE

Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance

Zdravko Kamenov[1], Georgi Kolarov[2], Antoaneta Gateva[1], Gianfranco Carlomagno[3], and Alessandro D. Genazzani[4]

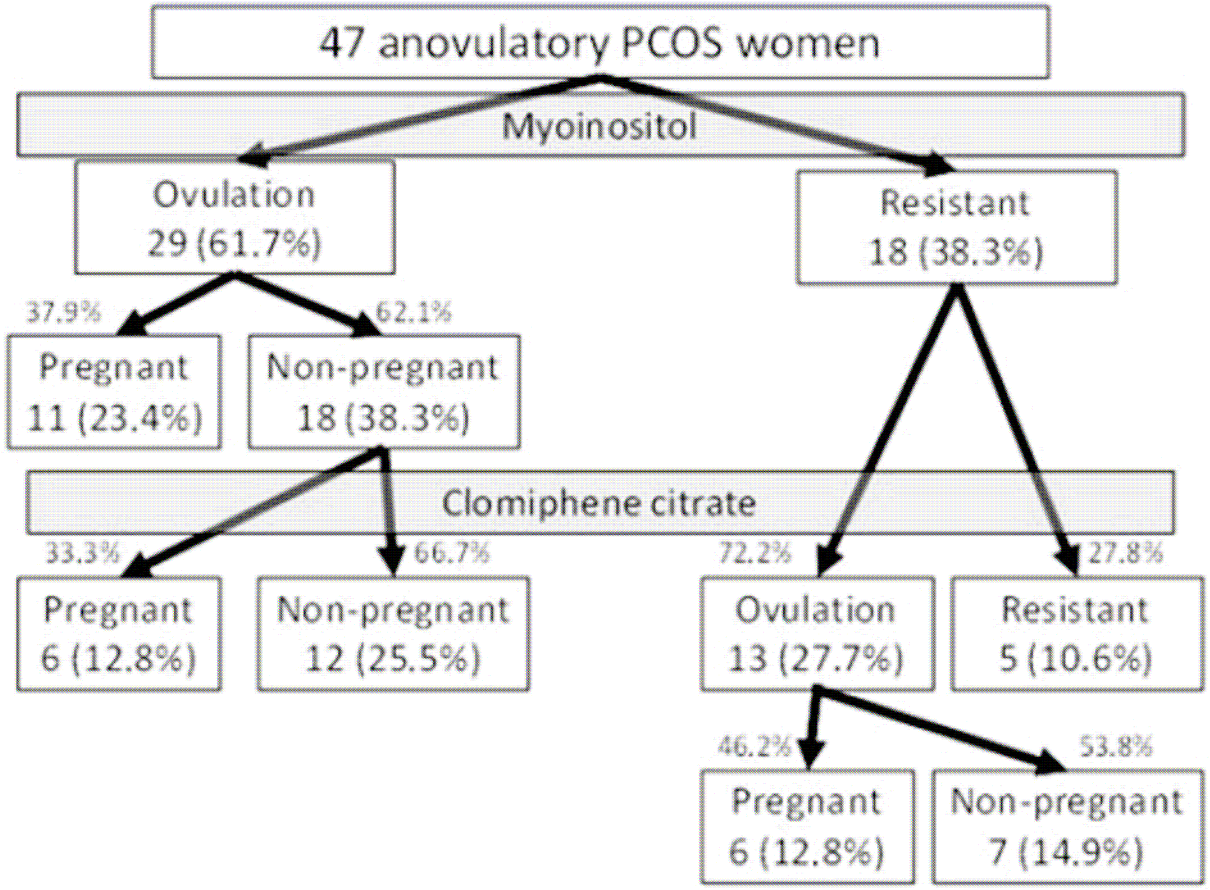

Figure 1. Study design. The numbers given in the rectangles represent *N* (%) from the total number of women. The numbers out of the rectangles represent the *N* (%) distribution in the previous group of patients.

European Review for Medical and Pharmacological Sciences

2011; 15: 931-936

Inositol safety: clinical evidences

Study	Pathology	Patients (inositol group)	Placebo-controlled trials			Adverse events
			Dose	Duration	Dropouts	
Papaleo et al, 2008	PCOS	30	4 g/day	12 months	None	
Gerli et al, 2007	PCOs	45	4 g/day	14 weeks		None
Agostini et al, 2006	Erectile dysfunction in type II diabetes men	88	4 g/day	1 month	None	Two patients complained of mild insomnia and one of flatus
Barak Y et al, 1996	Alzheimer's disease	12	6 g/day	1 month		
Allan SJ et al, 2004	Psoriasis, bipolar disorders	15 inositol + lithium 8 inositol	6 g/day	1 month		None
Levine J et al, 1997	Depression	13	12 g/day	1 month	11 4 placebo 7 inositol	1 nausea and 1 flatus 2 mild increases in glycemia after 4 week 1 transient, although the patient continued (at her request) to receive inositol. The other patient showed the same mild increase several weeks after discontinuation of inositol.
Benjamin J et al, 1995	Panic disorder with or without agoraphobia	21	12 g/day	1 month		Two patients complained of sleepiness while taking Inositol
Palatnik A et al, 2001	Depression panic	25	18 g/day	1 month	4 had no panic attacks	3 subjects nausea, tiredness, headache, and dizziness
Gelber D et al, 2001	Bulimia nervosa and binge eating	24	18 g/day	6 weeks		_
Fux M et al, 1996	Obsessive-compulsive disorder	13	18 g/day	6 weeks		_
Levine J et al, 1996.	Antidepressant	18+36	18 g/day	1 month		_
Stephen Lam et al, 2006	Safety tolerability	16	From 12 to 30 g/day	1 month		The most frequently reported symptoms were flatulence, loose stool, or diarrhea
	MTD	10	18 g/day	3 months		Mild gastrointestinal symptoms were experienced for the first month only

The main outcome was that only at the highest dose myo-inositol (12g/day) induced mild gastrointestinal side effects such as nausea, flatus and diarrhea.

Metformin in PCOS

TABLE 4. Effects of metformin on glucose metabolism and side effects

Glucose utilization
Peripheral glucose utilization[a]
Oxidative glucose metabolism[a]
Nonoxidative glucose metabolism[a]
Glucose transporter expression[a]
Intracellular glucose transport[a]
Glucose production
Hepatic glucose production[b]
Insulinemia and insulin receptor
Insulinemia[b]
Insulin receptor binding[a]
Insulin receptor tyrosine kinase activity[a]
Side effects and toxicity
Diarrhea
Nausea
Abdominal discomfort
Lactic acidosis

[a] Increase in.
[b] Reduction in.

De Leo et al 2003

Cochrane Library
Cochrane Database of Systematic Reviews

Inositol in preterm infants at risk for or having respiratory distress syndrome (Review)

Howlett A, Ohlsson A, Plakkal N

Main results

Four published RCTs and one ongoing RCT were identified. Study quality varied and interim analyses had occurred in all trials of repeat doses of inositol that provided data for the outcomes of interest in this review. In these trials neonatal death was found to be significantly reduced (3 trials, 355 neonates; typical RR 0.53, 95% CI 0.31 to 0.91; typical RD -0.09, 95% CI -0.17 to -0.03; NNTB 11, 95% CI 6 to 33). Infant deaths were reduced (3 trials, 355 infants; typical RR 0.55, 95% CI 0.40 to 0.77; typical RD -0.18, 95% CI -0.27 to -0.08; NNTB 6, 95% CI 4 to 13). ROP stage ≥ 3 was significantly reduced (2 trials, 262 infants; typical RR 0.09, 95% CI 0.01 to 0.67; typical RD -0.08, 95% CI -0.13 to -0.03; NNTB 13, 95% CI 8 to 33) and IVH grade > II was significantly decreased (3 trials, 355 infants; typical RR 0.53, 95% CI 0.31 to 0.90; typical RD -0.09, 95% CI -0.16 to -0.02; NNTB 11, 95% CI 6 to 50). Neither sepsis nor NEC differed significantly between groups. One study (74 infants) that administered a single dose of inositol (60 or 120 mg/kg) found no significant differences in adverse outcomes using RR, but an increased RD for BPD at 36 weeks postmenstrual age (RD 0.23, 95% CI 0.03 to 0.43; NNTH 4, 95% CI 2 to 33). This result should be interpreted with caution as only one dose of inositol was given and only the RD, but not the RR, was significant. One ongoing large study of repeat doses of inositol in preterm infants was identified.

Authors' conclusions

Inositol supplementation results in statistically significant and clinically important reductions in important short-term adverse neonatal outcomes. A large size multi-centre randomised controlled trial is currently ongoing and the trial will likely confirm or refute the findings from this systematic review.

MS NO: ONG-15-359

Original Research

Myo-inositol Supplementation for Prevention of Gestational Diabetes in Obese Pregnant Women

A Randomized Controlled Trial

Rosario D'Anna, MD, Antonino Di Benedetto, Angela Scilipoti, Angelo Santamaria, Maria Lieta Interdonato, Elisabetta Petrella, Isabella Neri, Basilio Pintaudi, Francesco Corrado, AU1 *and Fabio Facchinetti*

MIO 15.5%

FA 34.6%

Obstet Gynecol, 2015

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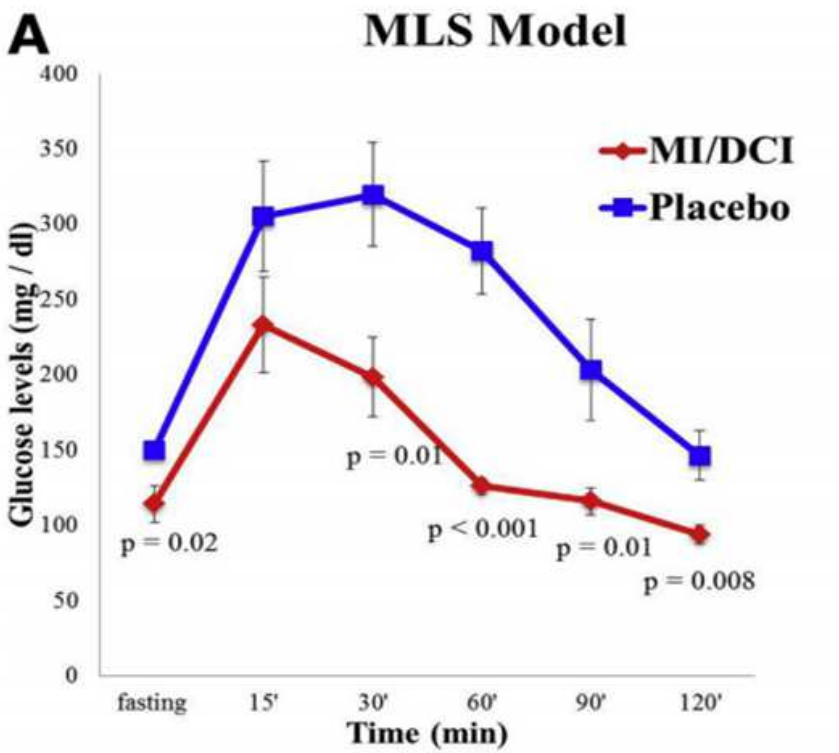
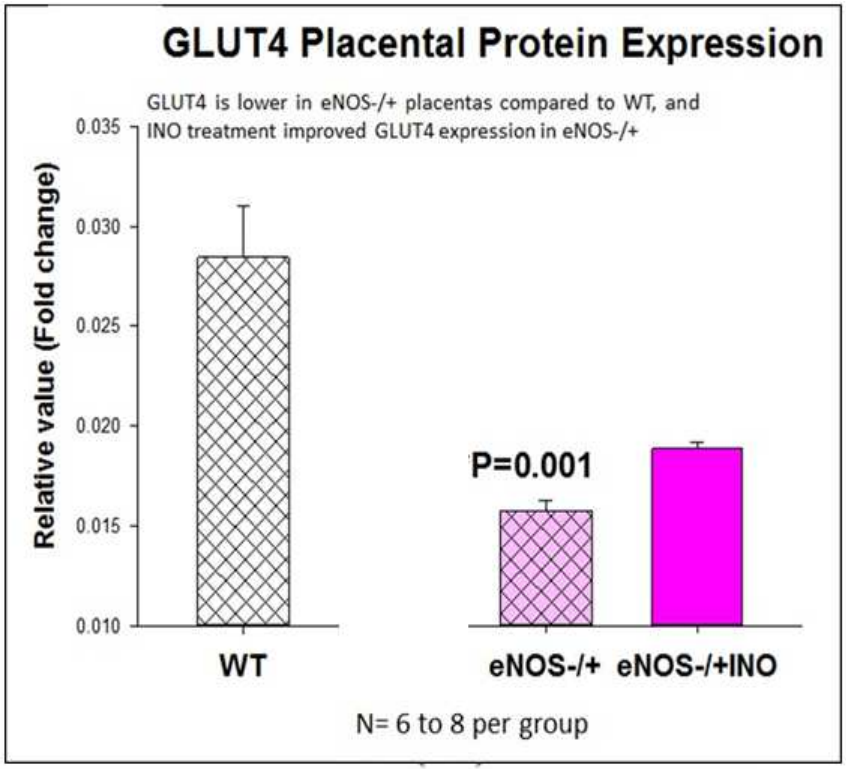
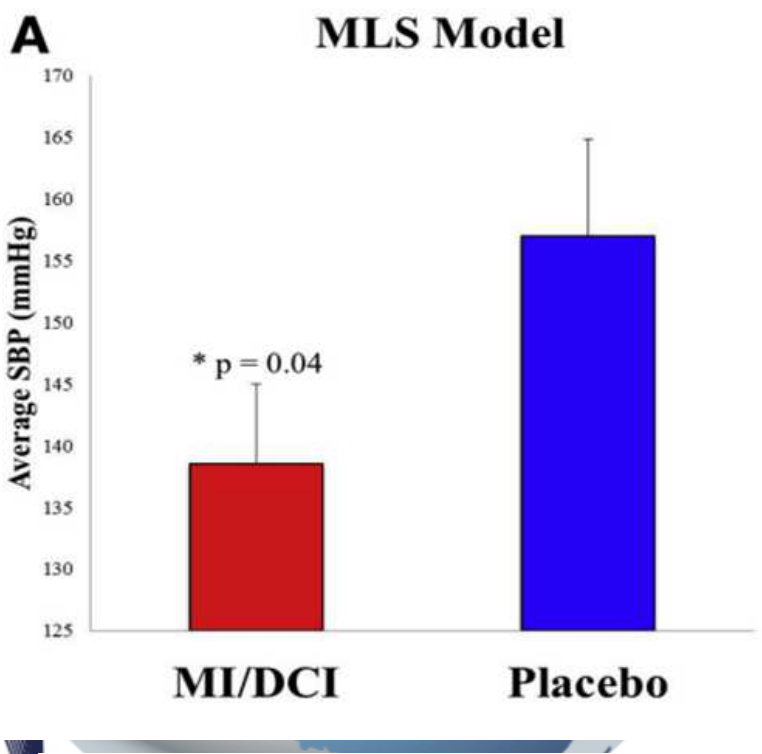
Glucose Tolerance Test (mg/dL) in MLS and obese pregnant mice

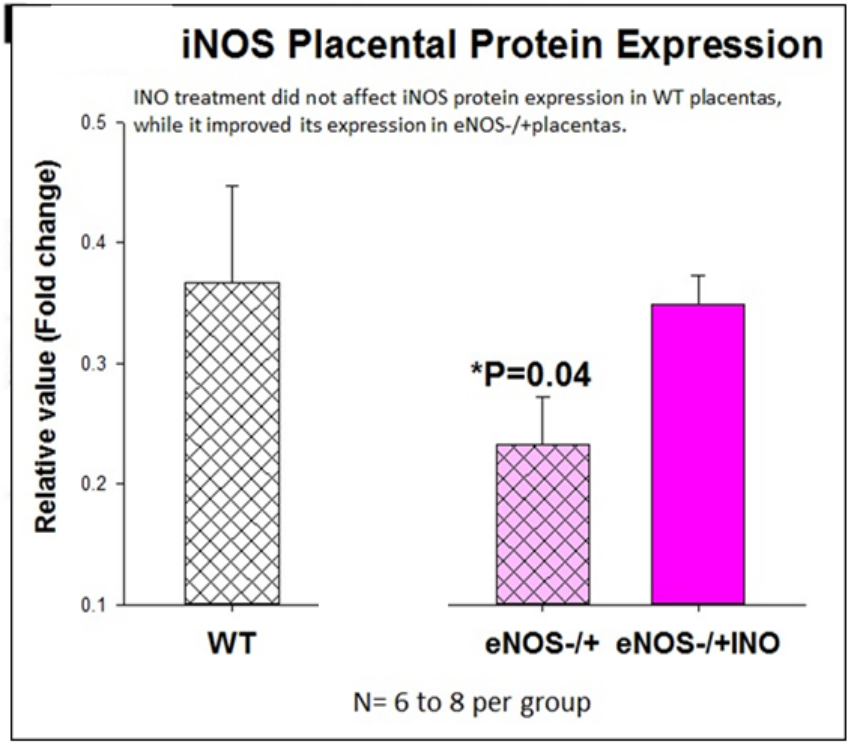




Ferrari F, Facchinetti F, Ontiveros AE, Roberts RP, Saade MM, Blackwell. SC, Sibai BM, Refuerzo JS, Longo M, The effect of combined Inositols supplementation on maternal metabolic profile in pregnancies complicated by metabolic syndrome and obesity, *American Journal of Obstetrics and Gynecology* (2016), doi: 10.1016/j.ajog.2016.05.038.

Average systolic blood pressure (mm Hg) in MLS and obese pregnant mice





Ferrari F, Facchinetti F, Ontiveros AE, Roberts RP, Saade MM, Blackwell. SC, Sibai BM, ReTuerzo JS, Longo M, The effect of combined inositols supplementation on maternal metabolic profile in pregnancies complicated by metabolic syndrome and obesity, *American Journal of Obstetrics and Gynecology* (2016), doi: 10.1016/j.ajog.2016.05.038.

Take Home Points

Gli inositoli (MYO e DCI) esercitano importanti effetti insulino-mimetici, anche nella PCOS

La PCOS è caratterizata da insulino resistenza (soprattutto nelle obese) oltre che da un eccessiva conversione da MYO a DCI, in particolare nell'ovaio

La supplementazione di MYO, e MYO/DCI, migliora iperandrogenismo e iperinsulinemia nelle PCOS, e regolarizza il ciclo mestruale.

In gravidanza il MYO previene lo sviluppo di GDM

Take Home Points

Il profilo di tollerabilità degli inositoli è superiore a quello della MET

In termine di ovulazione, l'inositolo è superiore alla MET, sia da solo che in associazione alle gonadotropine.

Aspettiamo la Cohrane, ma soprattutto altri studi, per poter trarre conclusioni!

INOFOLIC PROJECT

Take Home Points

MYO supplementation counteract clinical and biochemical hyperandrogenic state, restoring menstrual cyclicity and ovulation in PCOS

Evidence indicates that MYO+DCI promote ovulation and reduce serum testosterone, working faster than MYO alone

Inositols supplementation seems at least equally effective than Metformin, being better tolerated

GDM Prevention through Myo-Inositol

STUDY	INCLUSION CRITERIA	EXCLUSION CRITERIA	TREATED	CONTROLS
	BMI > 27	- Twin pregnancy - Previous GDM		

GDM prevention through myo-inositol

Treated	Controls
22/211	86/233
10.4%	36.9%

OR= 0.20 (0.11-0.34)

MYO vs Metformin in PCOS

(Raffone E et al. *Gynecol Endocrinol* 2010;26:275-280)

	MYO (n=60)	Metformin (n=60)	P value
Women with restored monthly ovulation	39	30	0.09
Median length of follicular phase (days)	14.8 ± 1.8	16.7 ± 2.5	0.003
Number of pregnancies (%)	18/60 (30%)	11/60 (18.3%)	0.13
Number of pregnancies in women with restored ovulation (%)	18/39 (46.1%)	11/30 (36.6%)	0.42

Metformin in PCOS

Does metformin affect the ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve? A randomized controlled trial

Stefano Palomba, M.D.,[a] Angela Falbo, M.D.,[a] Annalisa Di Cello, M.D.,[a] Fulvio Cappiello, M.D.,[b] Achille Tolino, M.D.,[c] and Fulvio Zullo, M.D.[a]

TABLE 2

Effect of metformin on ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve: reproductive results.

Groups	Metformin (n = 44)	Placebo (n = 44)	*P* value
Stimulation length (d)	13 (4; 9–15)	11 (4; 9–14)	.071
Gonadotropins dose (IU)	3,900 (1,462.5; 1,835–4,200)	2,400 (1,656; 2,100–4,125)	<.001
Dominant follicles on day of ovulation triggering (no.)	4 (4; 1–10)	6 (4; 2–12)	.002
Cancellation rate (no., %)	13/44 (29.5)	6/44 (13.6)	.089
Peak E_2 levels on day of ovulation triggering (pg/mL)	480.0 (503.8; 124.3–1,200)	733.5 (342.5; 230–1,400)	.001
Retrieved oocytes (no.)	3 (3.5; 0–8)	5 (4; 1–10)	.009
MII oocytes (no.)	2.3 (1.5; 0–6)	4 (2.5; 1–7)	.017
Fertilization rate (no., %)	157/205 (76.6)	248/328 (75.6)	.798
Zygote quality (no., %)			.659
Z1	72/157 (45.9)	99/248 (39.9)	
Z2	40/157 (25.5)	57/248 (23.0)	
Z3	29/157 (18.5)	53/248 (21.4)	
Z4	16/157 (10.2)	39/248 (15.7)	
Cleaved embryo quality (no., %)			.766
Grade 1	65/157 (41.4)	85/248 (34.3)	
Grade 2	33/157 (21.0)	64/248 (25.8)	
Grade 3	32/157 (20.4)	49/248 (19.8)	
Grade 4	14/157 (8.9)	30/248 (12.1)	
Grade 6	13/157 (8.3)	20/248 (8.1)	
Transferred embryos (no. per fertilized oocytes, %)	61/157 (38.9)	92/248 (37.1)	.722
Implantation rate (no. per transferred embryos, %)	26/61 (42.6)	34/92 (37.0)	.482
Clinical pregnancy rate (no. per started cycles, %)	13/44 (29.5)	16/44 (36.4)	.496
Ongoing pregnancy rate (no. per started cycles, %)	11/44 (25.0)	14/44 (31.8)	.637
Multiple pregnancies rate (no. per pregnancies, %)	1/12 (8.3)	2/15 (13.3)	.742
Live-birth rate (no. per started cycles, %)	12/44 (27.3)	13/44 (29.5)	.816

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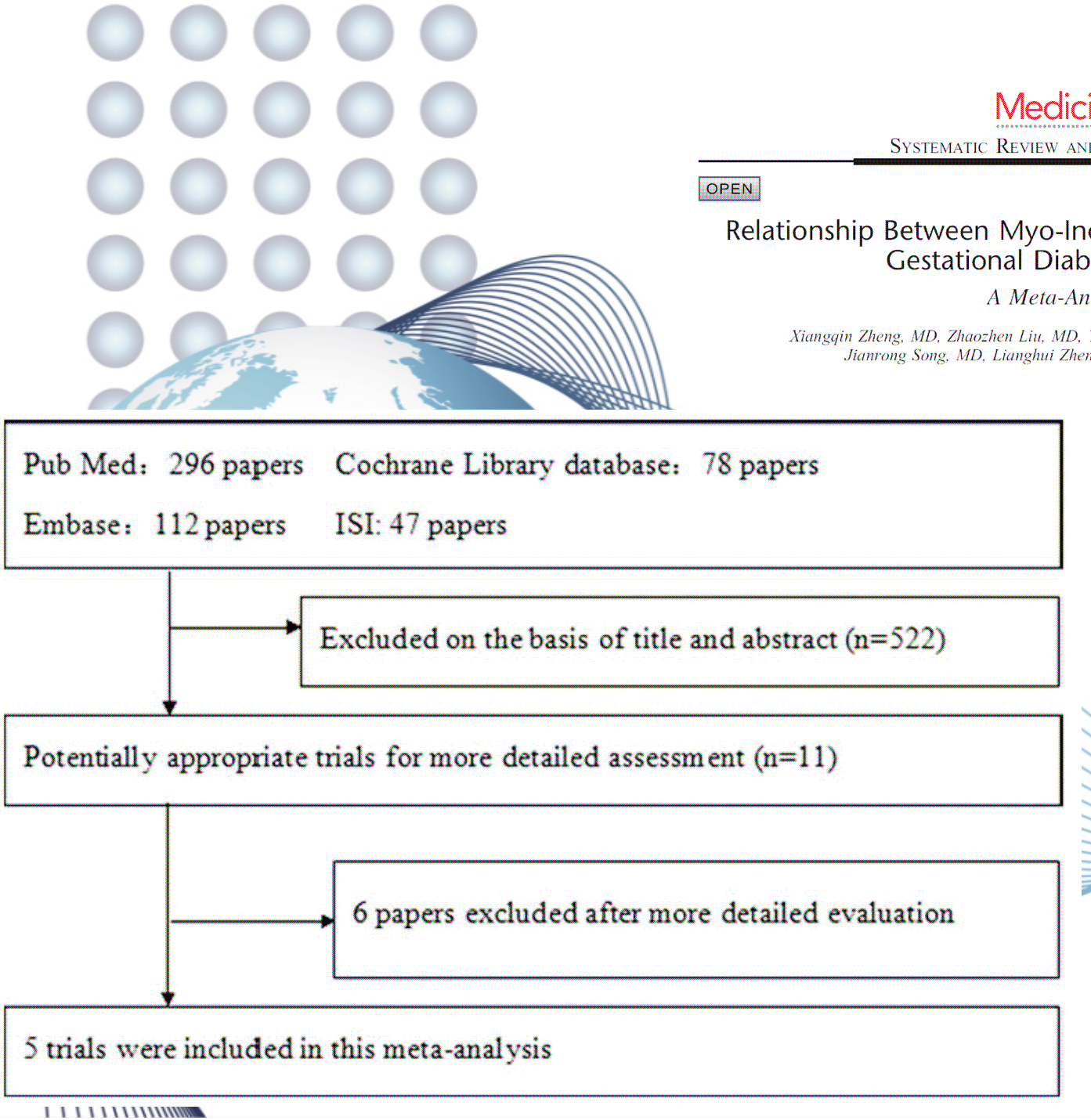
Relationship Between Myo-Inositol Supplementary and Gestational Diabetes Mellitus

A Meta-Analysis

Xiangqin Zheng, MD, Zhaozhen Liu, MD, Yulong Zhang, MD, Yuan Lin, MD, Jianrong Song, MD, Lianghui Zheng, MD, and Sheng Lin, MD



- **5 trials**
- **513 women**

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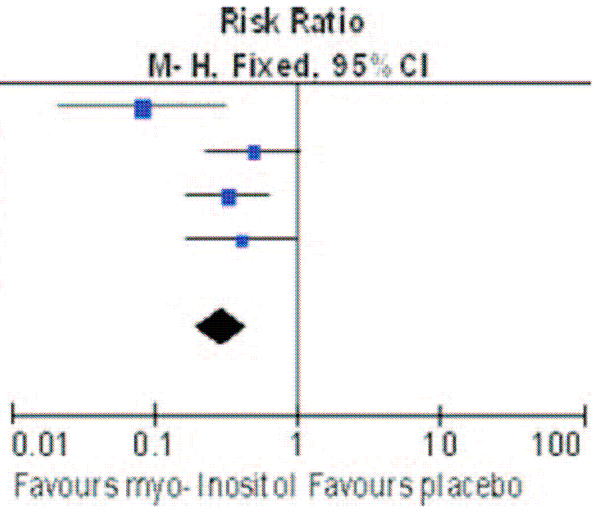
Study or Subgroup	myo-Inositol Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barbara Matarrelli 2013	2	35	27	38	32.6%	0.08 [0.02, 0.31]
Fabio Facchinetti 2013	6	31	24	60	20.6%	0.48 [0.22, 1.06]
R. D' Anna 2012	8	46	20	37	27.9%	0.32 [0.16, 0.65]
ROSARIO D' ANNA 2013	6	99	15	98	19.0%	0.40 [0.16, 0.98]
Total (95% CI)		**211**		**233**	**100.0%**	**0.29 [0.19, 0.44]**
Total events	22		86			

Heterogeneity: Chi² = 5.59, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 5.72 (P < 0.00001)



Significant reduction of GDM rate (-71%)
in the Myo-inositol group

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Relationship Between Myo-Inositol Supplementary and Gestational Diabetes Mellitus

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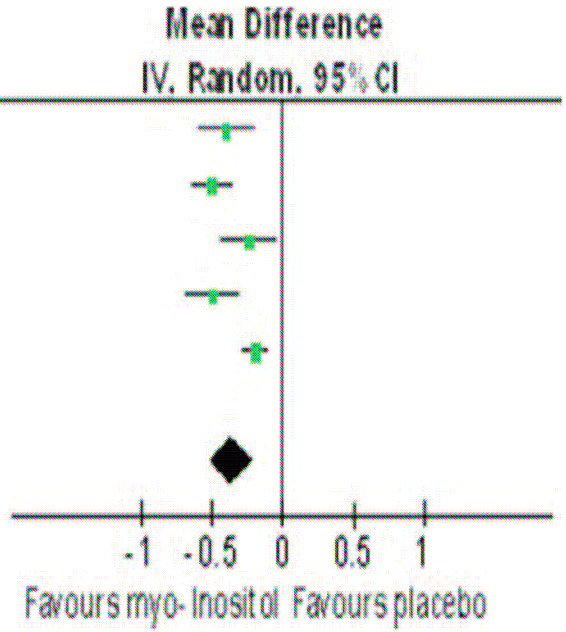
Study or Subgroup	myo-Inositol Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barbara Matarrelli 2013	4.7	0.4	35	5.1	0.5	38	17.7%	-0.40 [-0.61, -0.19]
F. Corrado 2011	4.6	0.3	24	5.1	0.3	45	21.3%	-0.50 [-0.65, -0.35]
Fabio Facchinetti 2013	4.48	0.38	31	4.72	0.62	60	17.8%	-0.24 [-0.45, -0.03]
R. D' Anna 2012	4.83	0.43	46	5.32	0.45	37	18.7%	-0.49 [-0.68, -0.30]
ROSARIO D' ANNA 2013	4.278	0.15	99	4.47	0.45	98	24.5%	-0.19 [-0.29, -0.10]
Total (95% CI)			235			278	100.0%	-0.36 [-0.51, -0.21]

Heterogeneity: Tau² = 0.02; Chi² = 16.93, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 4.76 (P < 0.00001)



MI significantly improves glucose tolerance

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SGA or LGA and PCOS

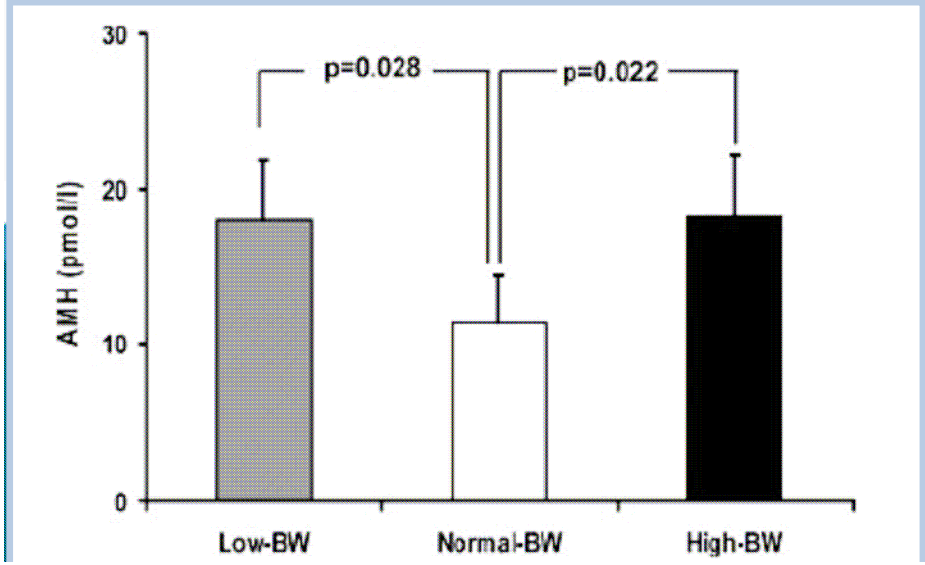
Retrospectives studies demonstrated that SGA newborns have higher AMH and subsequent early puberty and menarche and finally PCOS.

Ibanez L et al. Hum Reprod 2007;22:395-400
Ibanez L et al. Pedriatics 2006;117:117-21

human reproduction

On the other hand also the high birth weight newborns have higher levels of AMH at 2-3 months of life and lower levels of adiponectin (more insulin-resistance).

Sir-Petermann T et al. JCEM 2010;95:903-10



JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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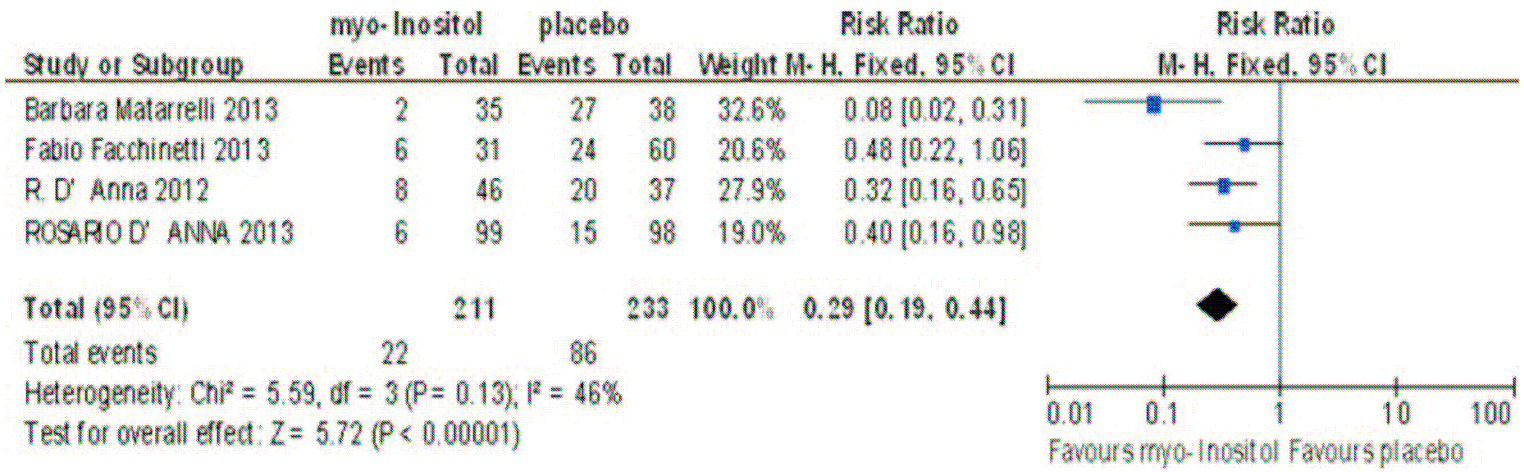


FIGURE 2. Meta-analysis result of the incidence of gestational diabetes between the groups.

Birth weight

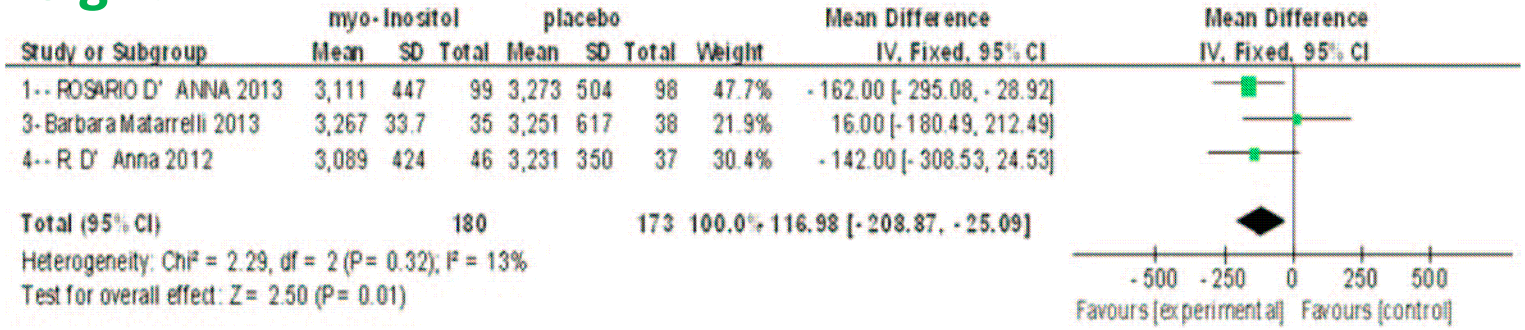
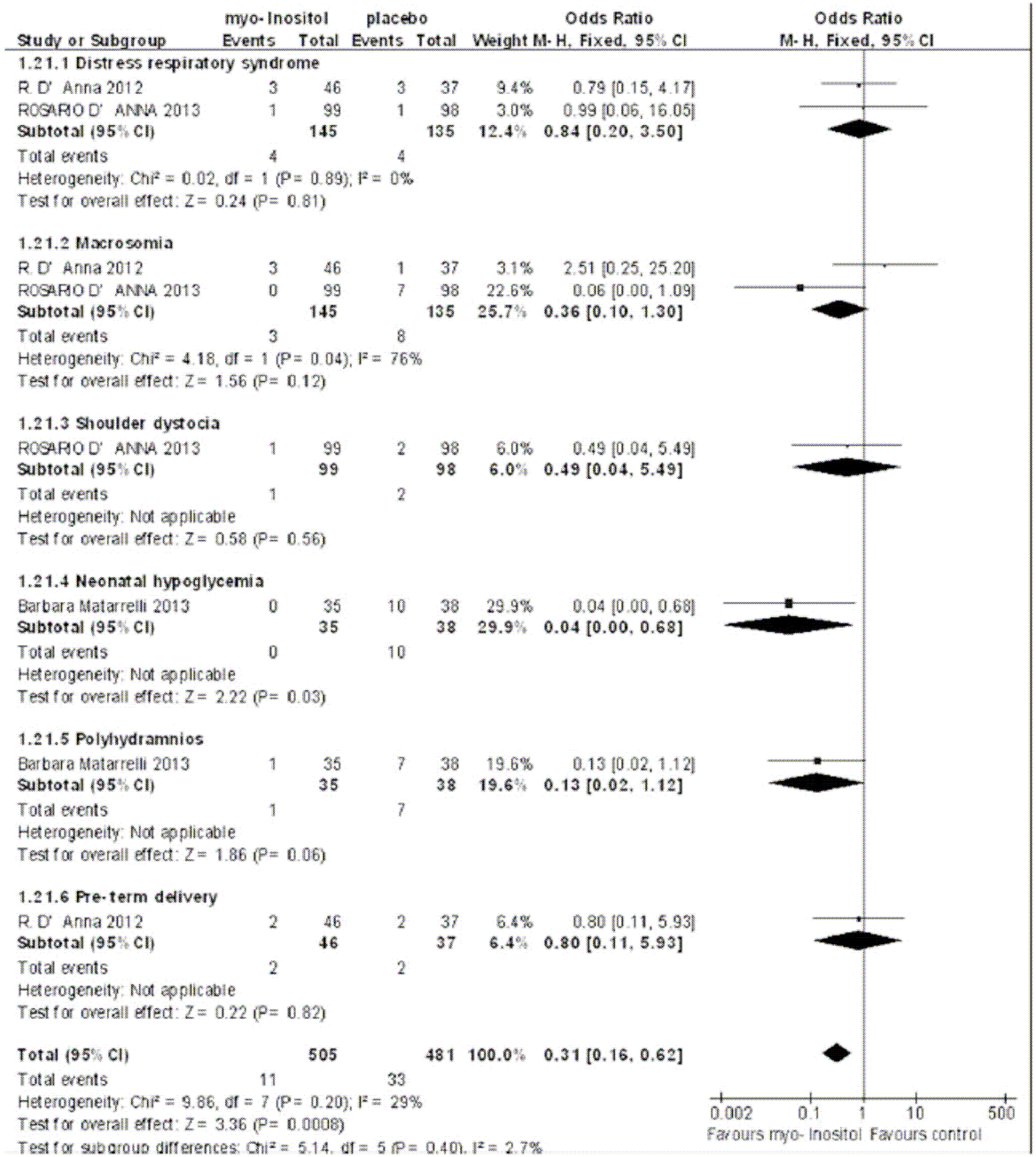


FIGURE 3. Meta-analysis result of birth weight between the groups.



MI reduce the incidence of some GDM-related complications

Neonatal hypoglicemia

Q & A

J. Physiol. (1954) 126, 71–80

THE INOSITOL CONTENT OF FOETAL BLOOD AND FOETAL FLUIDS

BY J. D. CAMPLING AND D. A. NIXON

From the Physiology Department, St Mary's Hospital Medical School, London

(*Received 4 March* 1954)

TABLE 9. Placental permeability in the sheep towards inositol

	Ewe to foetus		Foetus to ewe	
Time (min)	Maternal blood (mg/100 ml.)	Foetal blood (mg/100 ml.)	Maternal blood (mg/100 ml.)	Foetal blood (mg/100 ml.)
0	2·0	21·4	1·4	10·8
	10·5 g inositol to ewe		6·0 g inositol to foetus	
+ 30	91·8	20·1	1·5	474·0
+ 90	47·6	20·3	1·7	328·0
+150	26·0	20·4	2·6	270·0
+210	17·3	19·8	3·0	210·0
+270	—	—	2·9	182·0

ORIGIN OF THE FETAL BLOOD INOSITOL:

-**Maternal** transfer via the placenta

-**Placental** synthesis

-Synthesis within the **fetus itself**

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Summary of comparison

Inositol	Metformin
Improves insulin sensitivity and reduces hyperinsulinemia	Improves insulin-sensitivity and reduces hyperinsulinemia
Restores menses regularity and ovulation	Restores menses regularity and ovulation
Insulin and FSH sensitizer	Insulin sensitizer through Inositols
Promotes follicular growth and improves oocyte quality	Controversial effects on ART outcomes
Reduces hyperandrogenism, hirsutism and acne	Controversial effects on acne
Well tolerated and extremely safe	Side effects even at low doses

Metformin Therapy Increases Insulin-Stimulated Release of D-*Chiro*-Inositol-Containing Inositolphosphoglycan Mediator in Women with Polycystic Ovary Syndrome

JEAN-PATRICE BAILLARGEON, MARIA J. IUORNO, DANIELA J. JAKUBOWICZ, TEIMURAZ APRIDONIDZE, NA HE, AND JOHN E. NESTLER

Department of Medicine (J.-P.B.), Université de Sherbrooke, Sherbrooke, J1H 5N4 Canada; Departments of Medicine (M.J.I., T.A., N.H., J.E.N.) and Obstetrics and Gynecology (J.E.N.), Virginia Commonwealth University, Richmond, Virginia 23298-0111; and Hospital de Clinicas Caracas (D.J.J.), 1040 Caracas, Venezuela

In obese women with PCOS, metformin therapy significantly decreased serum insulin concentrations without changing the release of DCI-IPG during OGTT.

Therefore, the release of bioactive DCI-IPG per unit of insulin was much higher after metformin than after placebo, and the correlation between the release of DCI-IPG and insulin also seemed to improve after metformin.

These findings suggest that metformin may enhance the action of insulin in PCOS in part by improving insulin-mediated release of the Inositols Phosphoglycan mediator.

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Intriguing Possibilities

Expert Opinion:

Metformin remains first-line agent

MYO or MYO+DCI combination in women who cannot tolerate metformin or who fail to respond to metformin

Another possibility:

Metformin *plus* MYO

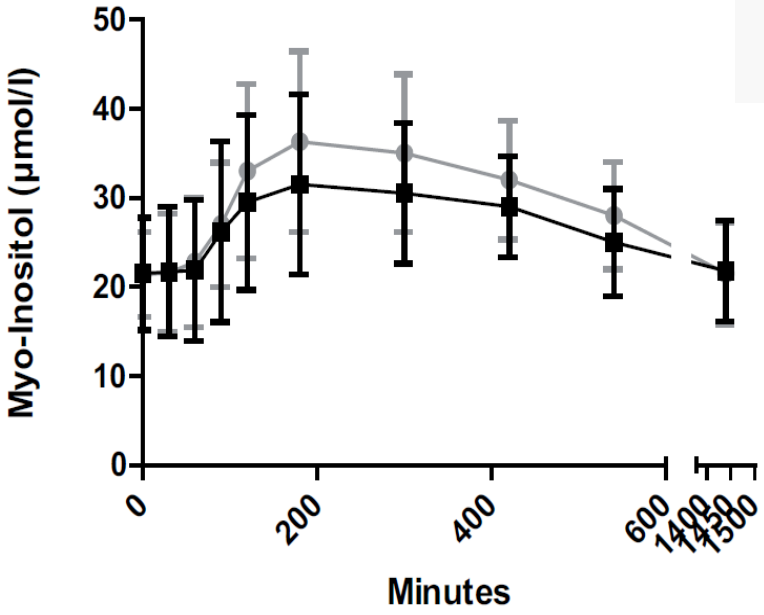
or

metformin *plus* MYO+DCI?

Kinetics in non-pregnant volunteers

MI tablets (0.55 g)

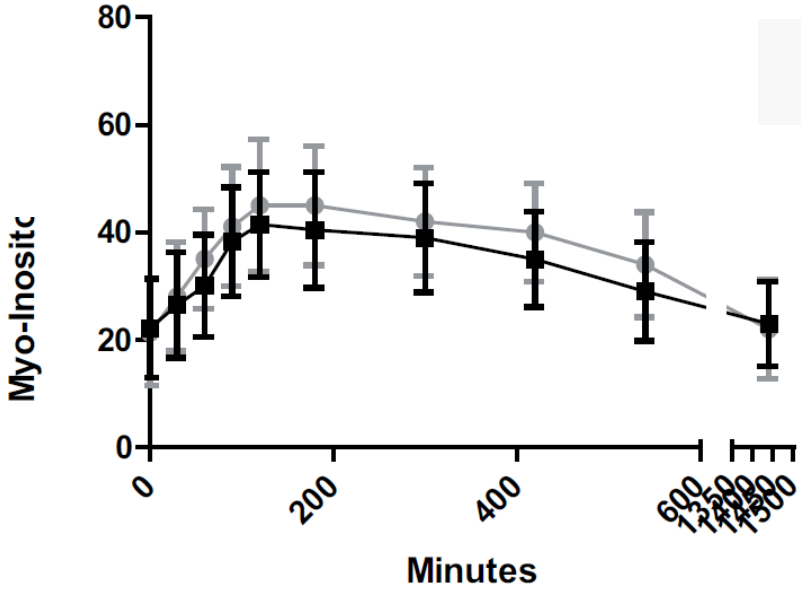
MI powder (2 g)



Carlomagno et al. *Expert Opinion on Drug Delivery*, 2012, 9 (3), 267-271

MI tablets (1.1 g)

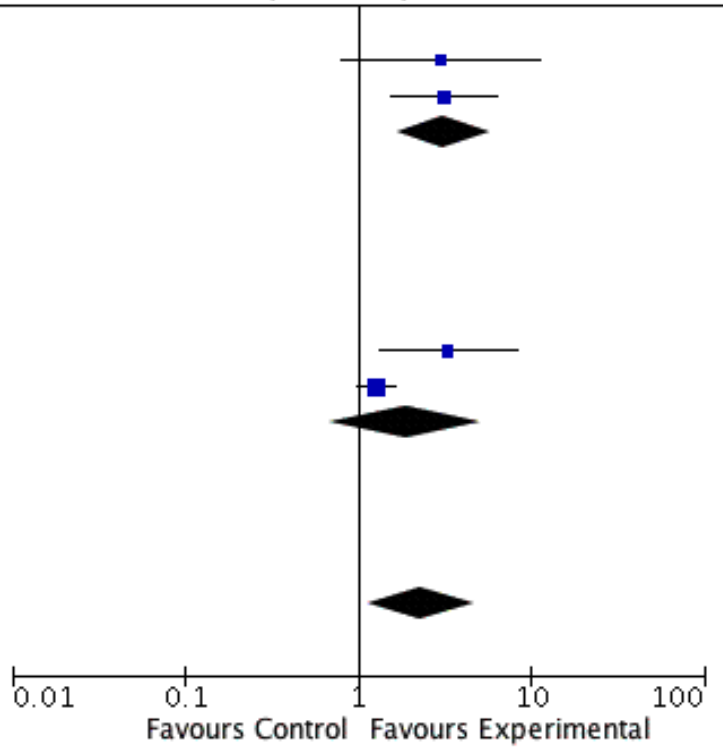
MI powder (4 g)



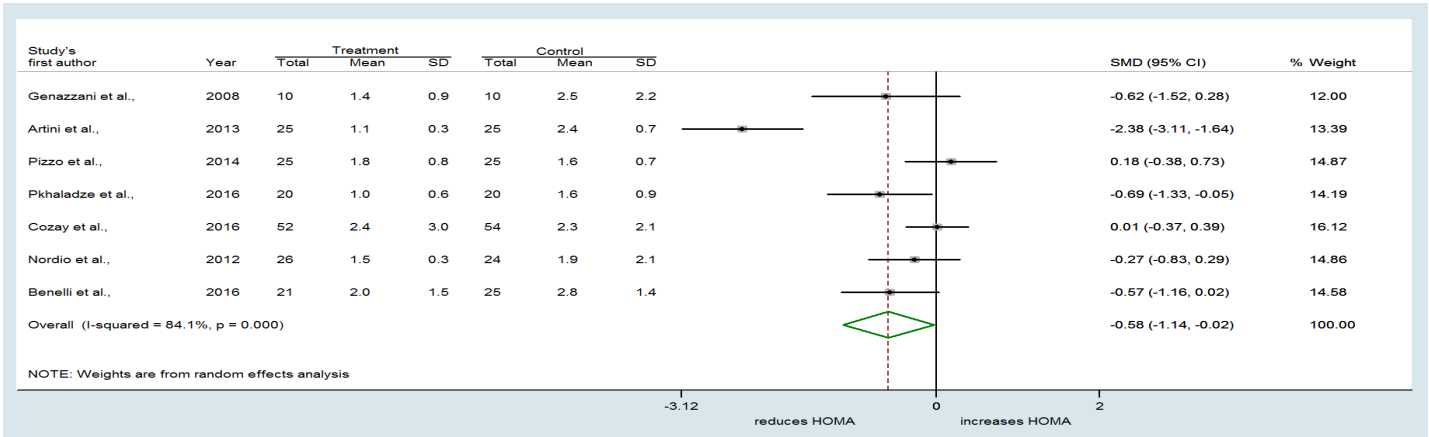
Inositol vs Placebo

Ovulation

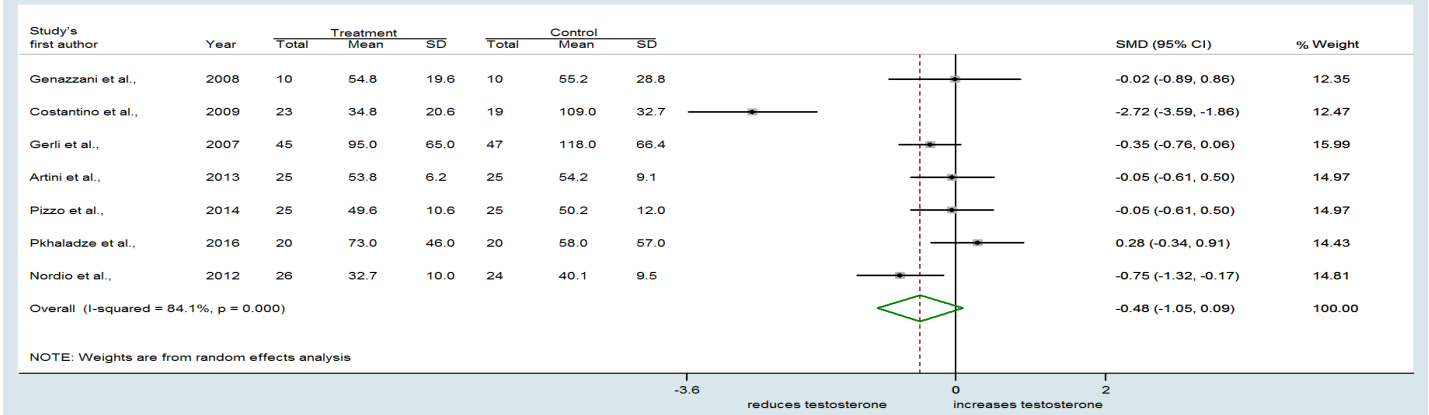
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Di-Chorio-inositol						
Iuorno 2002	6	10	2	10	15.9%	3.00 [0.79, 11.44]
Nestler 1999	19	22	6	22	26.8%	3.17 [1.57, 6.39]
Subtotal (95% CI)		**32**		**32**	**42.6%**	**3.13 [1.68, 5.83]**
Total events	25		8			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.94); $I^2 = 0\%$						
Test for overall effect: Z = 3.60 (P = 0.0003)						
1.1.2 Myo-inositol						
Costantino 2009	16	23	4	19	22.7%	3.30 [1.33, 8.22]
Gerli 2007	37	45	30	47	34.6%	1.29 [1.00, 1.66]
Subtotal (95% CI)		**68**		**66**	**57.4%**	**1.89 [0.69, 5.18]**
Total events	53		34			
Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 4.68$, df = 1 (P = 0.03); $I^2 = 79\%$						
Test for overall effect: Z = 1.24 (P = 0.21)						
Total (95% CI)		**100**		**98**	**100.0%**	**2.32 [1.14, 4.73]**
Total events	78		42			
Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 12.11$, df = 3 (P = 0.007); $I^2 = 75\%$						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 0.69$, df = 1 (P = 0.40), $I^2 = 0\%$						



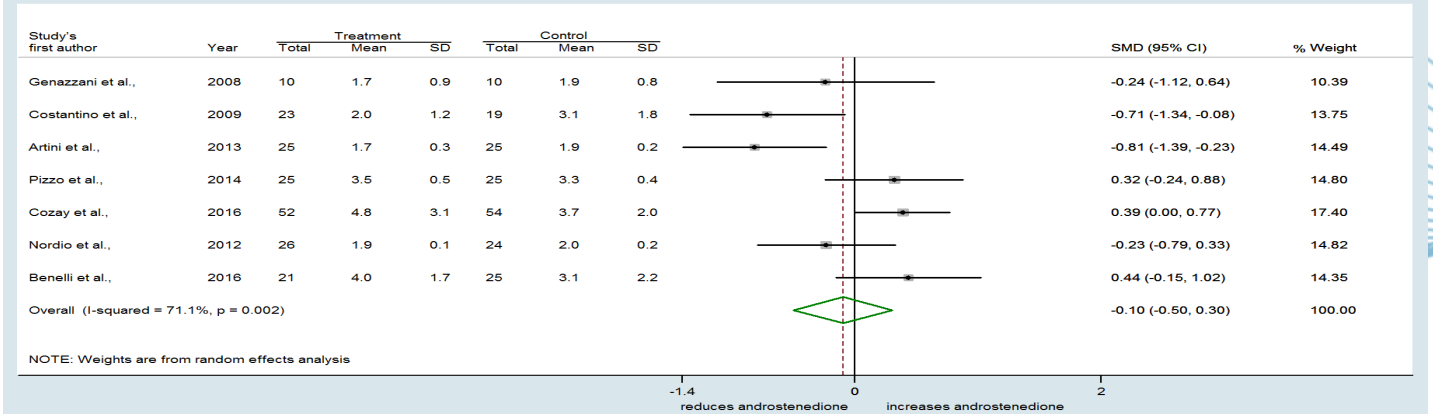
Pundir et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2017



HOMA IR



TESTOSTERONE



ANDROSTENEDIONE

Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials

V. Unfer[1], F. Facchinetti[2], B, Orrù[3], B. Giordani[3], J. Nestler[4]

INOFOLIC PROJECT

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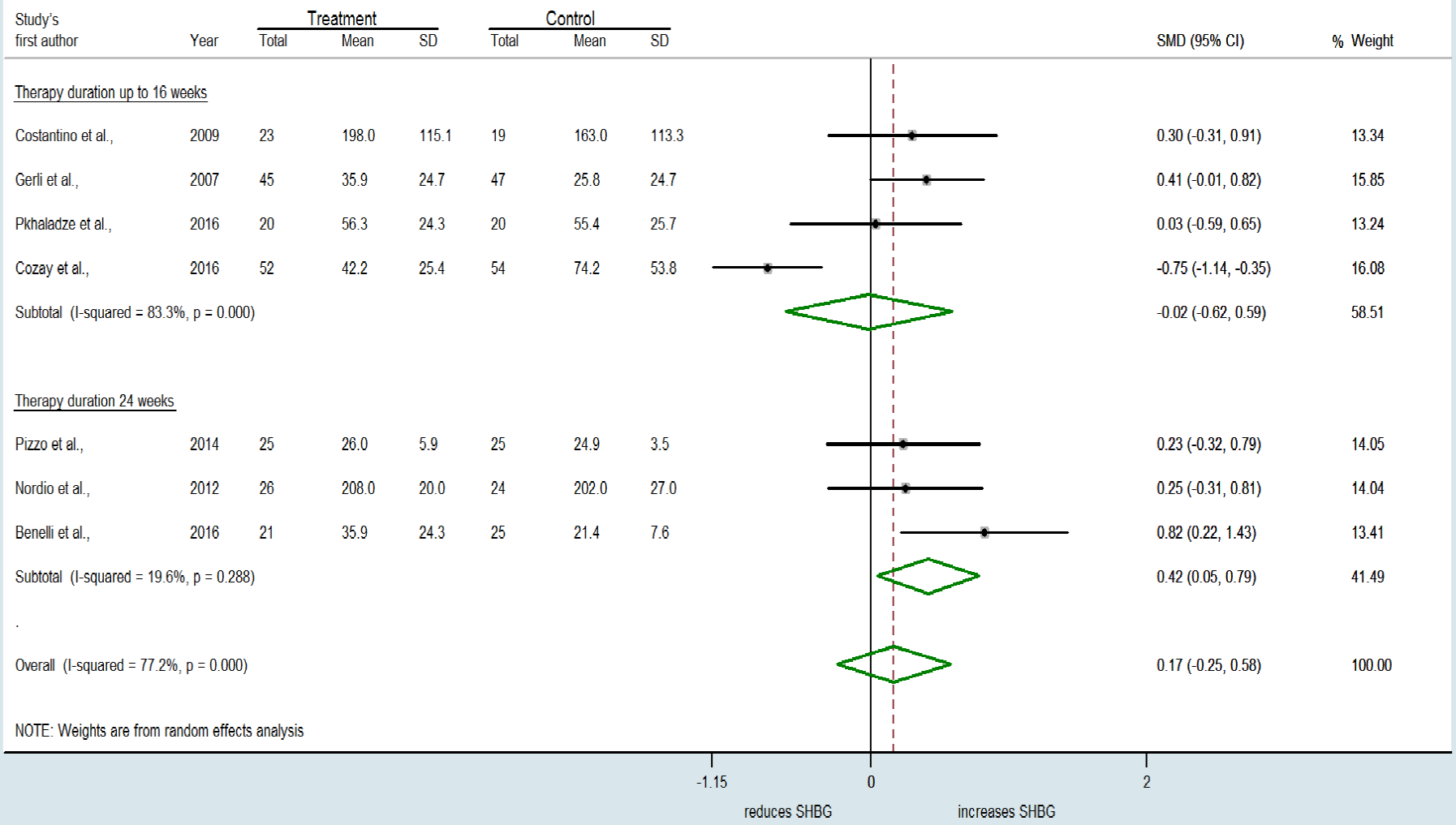
Subgroup meta-analysis for SHBG stratifying the studies by treatment duration (MI up to 16 weeks or 24 weeks).



Combined treatment Myo and D-chiro-inositol

40:1

30 overweight PCOS women (BMI>25)

Randomization

MYO
twice day
POWDER

MYO + D-Chiro
Twice day
SOFT GEL

Treatment : 6 months

Outcomes: Ovarian function and hormone profile

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Facchinetti F. et al, in preparation

Hormones

30 overweight PCOS women (BMI>27)

	MI group n = 15			MI+DCI group n = 15		
	Baseline	3mo.	6mo.	Baseline	3mo.	6mo.
Free testost. (ng/dl)	0.98±0.11	0.75±0.09	0.24±0.03**	1.1±0.14	0.34±0.11*	0.23±0.02**
Mean 2-h LH (mIU/ml)	14.1±1.4	8.4±2.5*	6.4±1.9*	15.2±2.0	7.5±2.8*	5.2±2.0*
Progesterone (ng/ml)	3±2.0	11±3.1*	18±3.8**	2.8±2.1	15±3.2*	20±4.6**

Facchinetti F. et al, in preparation

*, p < 0.05, respect baseline **, p< 0.01 respect baseline.

Restored ovulation
(Progesterone > 12ng/ml)

	MI	MI+DCI
6° Week	6 out of 15	9 out of 15
%	40%	60%

Facchinetti F. et al, in preparation

Lo.Li. Pharma INTERNATIONAL

Targeting PCOS Metabolism with Inositol

REDUCES insulin resistance

REDUCES hyperandrogenism

RESTORES hormonal balance

REDUCES hirsutism and acne

RESTORES metabolic profile

Eur J Obstet Gynecol RB 2015

Gynecological Endocrinology, August 2009; 25(8): 508–513

ORIGINAL PAPER

Efficacy of myo-inositol in the treatment young women with polycystic ovary syndr

MARTINO M. ZACCHÈ[1], LUIGI CAPUTO[1], SUSANNA FILIPPIS[1], GABRIO ZACCHÈ[1], MORENO DINDELLI[1], & AUGUSTO FERRARI[1]

PCOS

Domenico Giordano, MD,[1] Francesco Corrado, MD,[2] Angelo Santamaria, MD,[2] Simona Quattrone, MD,[1] Basilio Pintaudi, MD,[3] Antonino Di Benedetto, MD,[3] and Rosario D'Anna, MD[2]

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Metformin in PCOS

Does metformin affect the ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve? A randomized controlled trial

Stefano Palomba, M.D.,[a] Angela Falbo, M.D.,[a] Annalisa Di Cello, M.D.,[a] Fulvio Cappiello, M.D.,[b] Achille Tolino, M.D.,[c] and Fulvio Zullo, M.D.[a]

TABLE 2

Effect of metformin on ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve: reproductive results.

Groups	Metformin (n = 44)	Placebo (n = 44)	*P* value
Stimulation length (d)	13 (4; 9–15)	11 (4; 9–14)	.071
Gonadotropins dose (IU)	3,900 (1,462.5; 1,835–4,200)	2,400 (1,656; 2,100–4,125)	<.001
Dominant follicles on day of ovulation triggering (no.)	4 (4; 1–10)	6 (4; 2–12)	.002
Cancellation rate (no., %)	13/44 (29.5)	6/44 (13.6)	.089
Peak E_2 levels on day of ovulation triggering (pg/mL)	480.0 (503.8; 124.3–1,200)	733.5 (342.5; 230–1,400)	.001
Retrieved oocytes (no.)	3 (3.5; 0–8)	5 (4; 1–10)	.009
MII oocytes (no.)	2.3 (1.5; 0–6)	4 (2.5; 1–7)	.017
Fertilization rate (no., %)	157/205 (76.6)	248/328 (75.6)	.798
Zygote quality (no., %)			.659
Z1	72/157 (45.9)	99/248 (39.9)	
Z2	40/157 (25.5)	57/248 (23.0)	
Z3	29/157 (18.5)	53/248 (21.4)	
Z4	16/157 (10.2)	39/248 (15.7)	
Cleaved embryo quality (no., %)			.766
Grade 1	65/157 (41.4)	85/248 (34.3)	
Grade 2	33/157 (21.0)	64/248 (25.8)	
Grade 3	32/157 (20.4)	49/248 (19.8)	
Grade 4	14/157 (8.9)	30/248 (12.1)	
Grade 6	13/157 (8.3)	20/248 (8.1)	
Transferred embryos (no. per fertilized oocytes, %)	61/157 (38.9)	92/248 (37.1)	.722
Implantation rate (no. per transferred embryos, %)	26/61 (42.6)	34/92 (37.0)	.482
Clinical pregnancy rate (no. per started cycles, %)	13/44 (29.5)	16/44 (36.4)	.496
Ongoing pregnancy rate (no. per started cycles, %)	11/44 (25.0)	14/44 (31.8)	.637
Multiple pregnancies rate (no. per pregnancies, %)	1/12 (8.3)	2/15 (13.3)	.742
Live-birth rate (no. per started cycles, %)	12/44 (27.3)	13/44 (29.5)	.816

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R	Time	testosterone ng/dl		Androstenedione ng/ml		SHBG nmol/L	
		treated	control	treated	control	treated	control
1	baseline	53.4±5.6	61.3±7.2	1.71±0.19	1.80±0.23	NA	NA
	post-treatm.	54.8±6.2	55.2±9.1	1.7±0.29	1.91±0.24	NA	NA
2	baseline	99.5±7	116.8±15	2.67±0.19	2.71±0.21	144.4±2	147±4
	post-treatm.	34.8±4.3	109±7.5	1.96±0.26	3.06±0.41	198±24	163±26
3	baseline	87	110	NA	NA	29.2	28.1
	post-treatm.	72	101	NA	NA	36.5	26.3
4	baseline	81	115	NA	NA	29.3	27.8
	post-treatm.	66	98	NA	NA	35.9	25.8
5	baseline	52.4±5.6	60.3±7.2	1.68±0.19	1.80±0.23	NA	NA
	post-treatm.	53.8±6.2	54.2±9.1	1.67 ±0.29	1.89±0.24	NA	NA
6	baseline	77.7±14.2	75.3±13.6	3.71±0.58	3.45±0.49	21.5±5.5	21.2±3.9
	post-treatm.	49.6±10.6	50.2±12.0	3.50±0.54	3.34±0.44	26.0±5.9	24.87±3.5
7	baseline	73±25	72±25	NA	NA	53.7±27.4	45.0±24.4
	post-treatm.	73±46	58±57	NA	NA	56.3±24.3	55.4±25.7
8	baseline	NA	NA	4.82±3.79	4.25±2.97	39.1±29.5	59.4±47.7
	post-treatm.	NA	NA	4.75±3.10	3.74±1.95	42.2±25.4	74.2±53.8
9	baseline	95.4±10.7	97.2±19.2	2.63±0.15	2.71±0.14	145±16	149±20
	post-treatm.	32.7±10.0	40.1±9.5	1.94 ±0.15	1.98±0.19	208±20	202 ± 27
	baseline	NA	NA	4.25±1.48	3.48±1.21	24.1±10.3	20.4±8.8

Human Reproduction Vol.17, No.6 pp. 1591–1596, 2002

Follicular fluid and serum concentrations of myo-inositol in patients undergoing IVF: relationship with oocyte quality

Tony T.Y.Chiu[1,3], Michael S.Rogers[1], Eric L.K.Law[2], Christine M.Briton-Jones[1], L.P.Cheung[1] and Christopher J.Haines[1]

[1]Department of Obstetrics and Gynaecology and [2]Department of Chemical Pathology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China

The association between MI conc., FF volume, E_2 and better development of the oocytes suggests that higher levels of MI in the FF are related to mature follicle high quality oocyte

Table I. Cycle characteristics in the two groups of patients defined by oocyte maturity and fertilization[a]

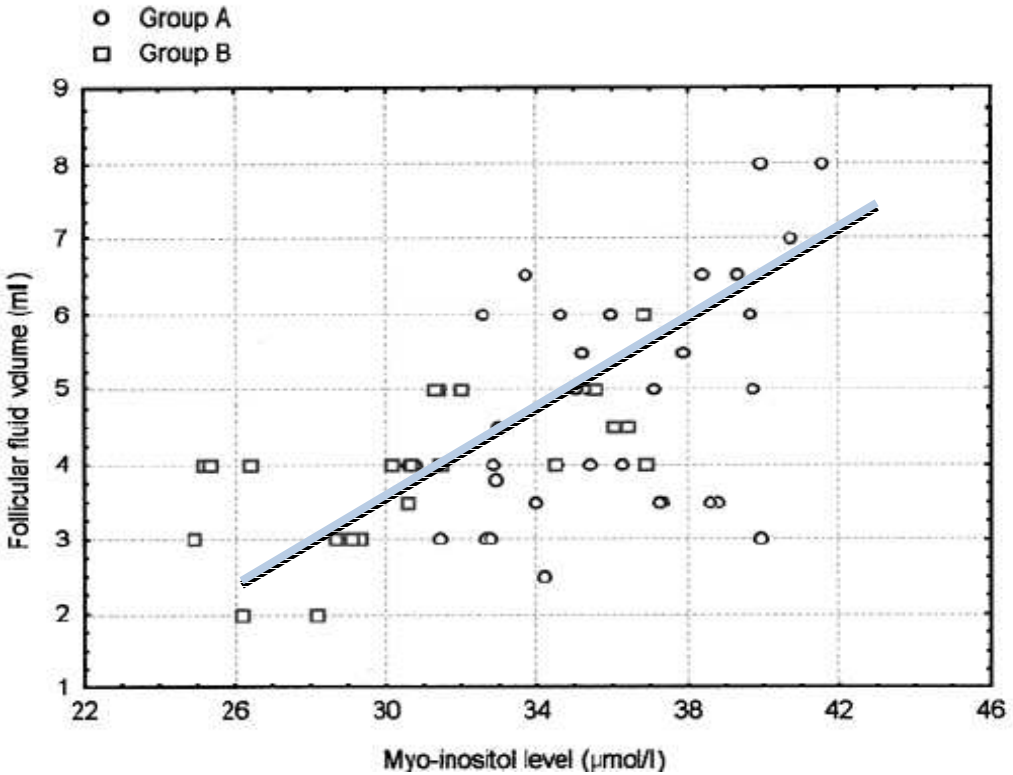
	Group A	Group B	*P* value
No. of patients	32	21	–
Age (years)	33.8 ± 3.5 (25–42)	34.4 ± 4.3 (25–42)	NS
FF volume (ml)	4.7 ± 1.4 (2.5–8.0)	3.9 ± 1.0 (2.0–6.0)	< 0.05
No. of oocytes	38	22	–
Days of stimulation[b]	9.0 ± 2.1 (5–17)	8.8 ± 2.8 (6–17)	NS
No. of HMG ampoules	31.8 ± 10.7 (15–62)	34.3 ± 13.8 (16–62)	NS
Basal level of FSH	5.1 ± 2.7 (1.5–10.2)	5.9 ± 3.6 (1.3–12.1)	NS
Estradiol level (Day 0)	1.4 ± 0.8 (0.2–3.0)	1.6 ± 0.8 (0.6–3.0)	NS

Values are means ± SD; NS = not statistically significant. Values in parentheses are r
[a]Group A = follicles containing mature and fertilized oocytes. Group B = follicles co
unfertilized oocytes.
[b]From the first HMG injection to the day of human chorionic gonadotrophin

Table II. Concentrations of myo-inositol measured in follicular fluid and serum

	Group A[a]	Group B[a]	*P*-value
Follicular fluid			
n	38	22	
MI (μmol/l)	35.6 ± 3.1 (30.6–41.5)	30.7 ± 3.9 (24.9–36.9)	< 0.005
Serum			
n	32	21	
MI (μmol/l)	38.7 ± 1.5 (36.1–42.9)	39.0 ± 4.0 (27.6–45.8)	NS

Values are means ± SD. Values in parentheses are range.
[a]See footnote [a] Table I.
MI, myo-inositol; NS = not statistically significant.



OUTLINES

- **Issues of Polycystyc Ovary Syndrome**
- **Inositols and Insulin Resistance**
- **Inositols/Metformin for PCOS**
- **Pregnancy in women with PCOS**
- **Fetal programming**

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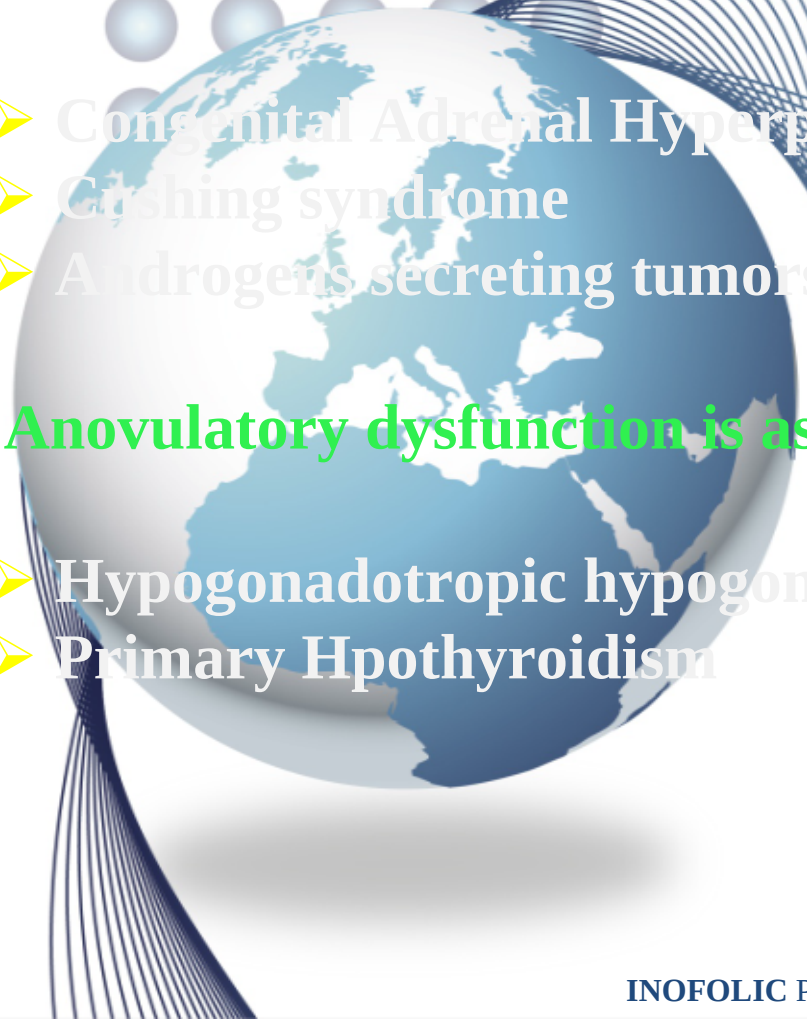
PCOS EXCLUSION CRITERIA

Hirsutism and Menstrual Disorders are typical of

- Congenital Adrenal Hyperplasia — 21 OH deficiency — **(17P)**
- Cushing syndrome — **(urinary F)**
- Androgens secreting tumors — Thecoma — **(Hystory, US)**

Anovulatory dysfunction is associated with

- Hypogonadotropic hypogonadism — Kalmann S. — **(LH)**
- Primary Hpothyroidism — **(TSH, PRL)**



PCOS Definition

	Clinical or biochemical hyperandrogenism	Oligo/anovulation	US finding of polycystic ovaries*
NIH, 1990 Both of the following:	+	+	
ESHRE/ASRM, 2003 Only 2 of the following:	+	+	+
AES, 2006 All 3 of the following:	+	+	+

NIH: National Institute of Health of the United States; ESHRE: European Society of Human Reproduction and Embryology; ASRM: American Society of Reproductive Medicine; AES: Androgen Excess and PCOS Society.

All sets of criteria require the exclusion of other etiologies such as congenital adrenal hyperplasia, androgen-secreting neoplasms, and Cushing's síndrome.

*Ultrasound polycystic ovaries can be defined as the presence of ≥12 follicles of 2–9 mm width or an increase in ovarian volume (>10 mL) in at least one ovary, in women not consuming oral contraceptives.

eshre
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AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Sam Yen's Central Hypothesis ('70ies)

Increased LH (>10 IU/ml)

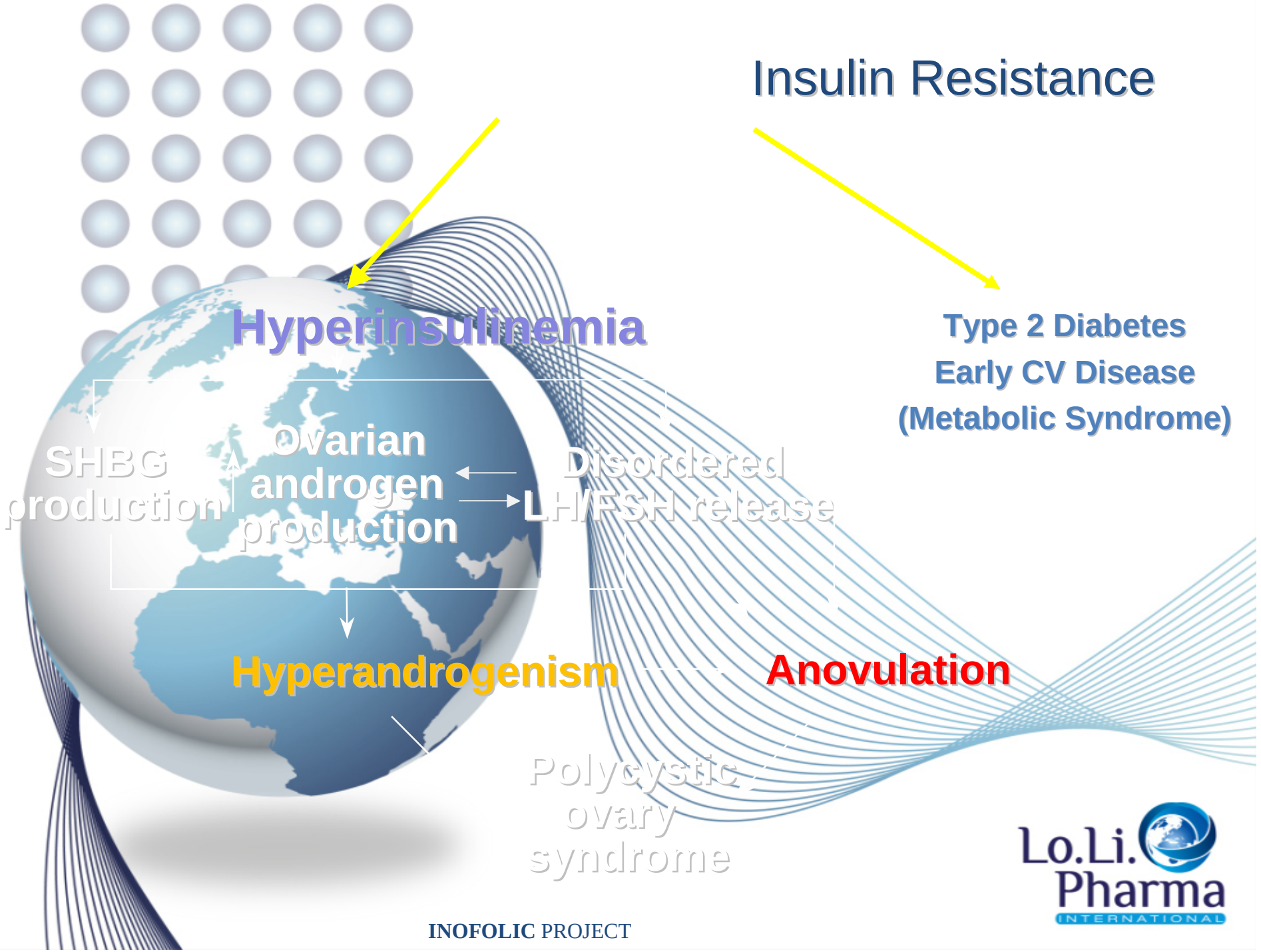
Increased LH/FSH ratio (>2.5)

Reduced SHBG

Increased free Testosterone and Androstenedione

Reduced Progesterone (Chronic anovulation)

LH-RH agonists, then waiting for rescue cycles


Insulin Resistance
Hyperinsulinemia
Type 2 Diabetes
Early CV Disease
(Metabolic Syndrome)
SHBG production
Ovarian androgen production
Disordered LH/FSH release
Hyperandrogenism
Anovulation
Polycystic ovary syndrome

Being a PCOS women: a big Burden!

Participants: A total of 2566 women with PCOS hospitalized from 1997–2011 and 25 660 randomly selected age-matched women without a PCOS diagnosis derived from the electoral roll.

Table 1. Associations Between PCOS Diagnosis and Hospitalizations and Procedures for Gynecological Indications

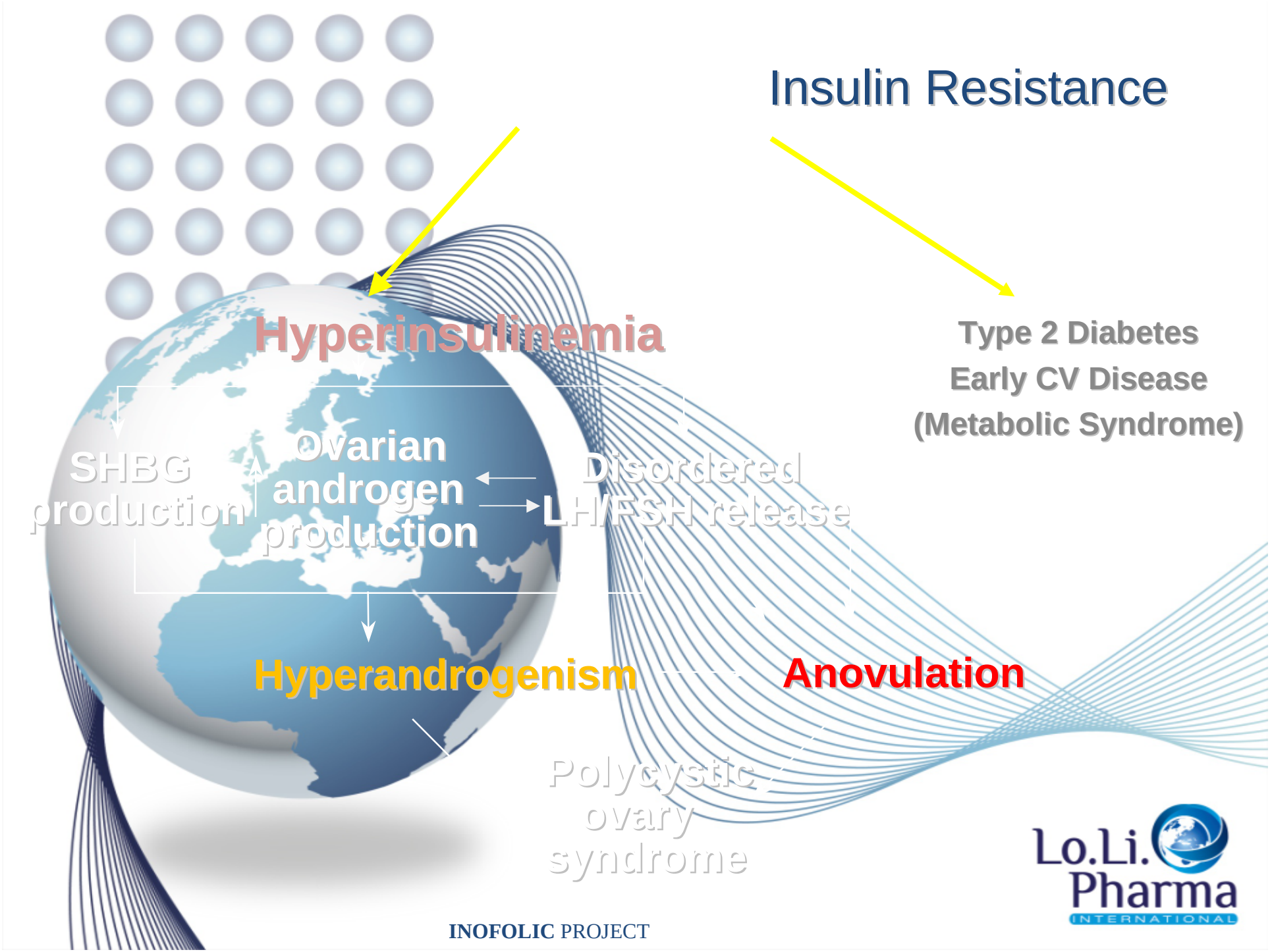
Gynecological Diagnoses/Procedures	Non-PCOS	PCOS	*P* Value	HR	95% CI
n	25 660	2560			
Endometriosis	1121 (4.4)	677 (26.4)	<.001	6.87	6.25–7.56
Endometrial glandular hyperplasia[a]	24 (0.1)	46 (1.8)	<.001	19.45	11.9–31.9
Menstrual problems	1269 (4.9)	520 (20.3)	<.001	4.65	4.20–5.15
Hysteroscopy	1965 (7.7)	1107 (43.1)	<.001	7.37	6.84–7.93
Dilatation and curettage	5695 (22.2)	1641 (64.0)	<.001	3.83	3.62–4.05
Endometrial ablation	244 (1.0)	94 (3.7)	<.001	3.94	3.11–5.00
Hysterectomy	649 (2.5)	204 (8.0)	<.001	3.36	2.87–3.93
Infertility	1188 (4.6)	1050 (40.9)	<.001	11.44	10.5–12.4
Spontaneous miscarriage	1572 (6.1)	286 (11.1)	<.001	1.86	1.64–2.11
Ectopic pregnancy	386 (1.5)	97 (3.8)	<.001	2.54	2.03–3.17
Procreative management	668 (2.6)	527 (20.5)	<.001	8.74	7.78–9.78
Investigation/testing	91 (0.4)	93 (3.6)	<.001	10.34	7.74–13.80
IVF	518 (2.0)	445 (17.2)	<.001	9.38	8.26–10.65
Pregnancy ≥ 20 wk	16 132 (62.9)	1786 (69.6)	<.001	1.10	1.05–1.15

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

The Potential Implications of a PCOS Diagnosis on a Woman's Long-Term Health Using Data Linkage

Roger Hart and Dorota A. Doherty

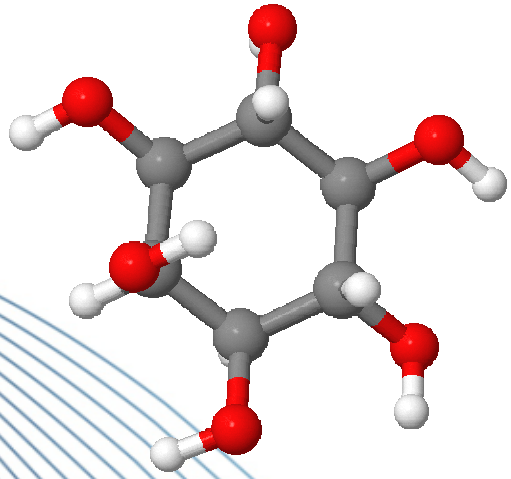
2015;100:911-919

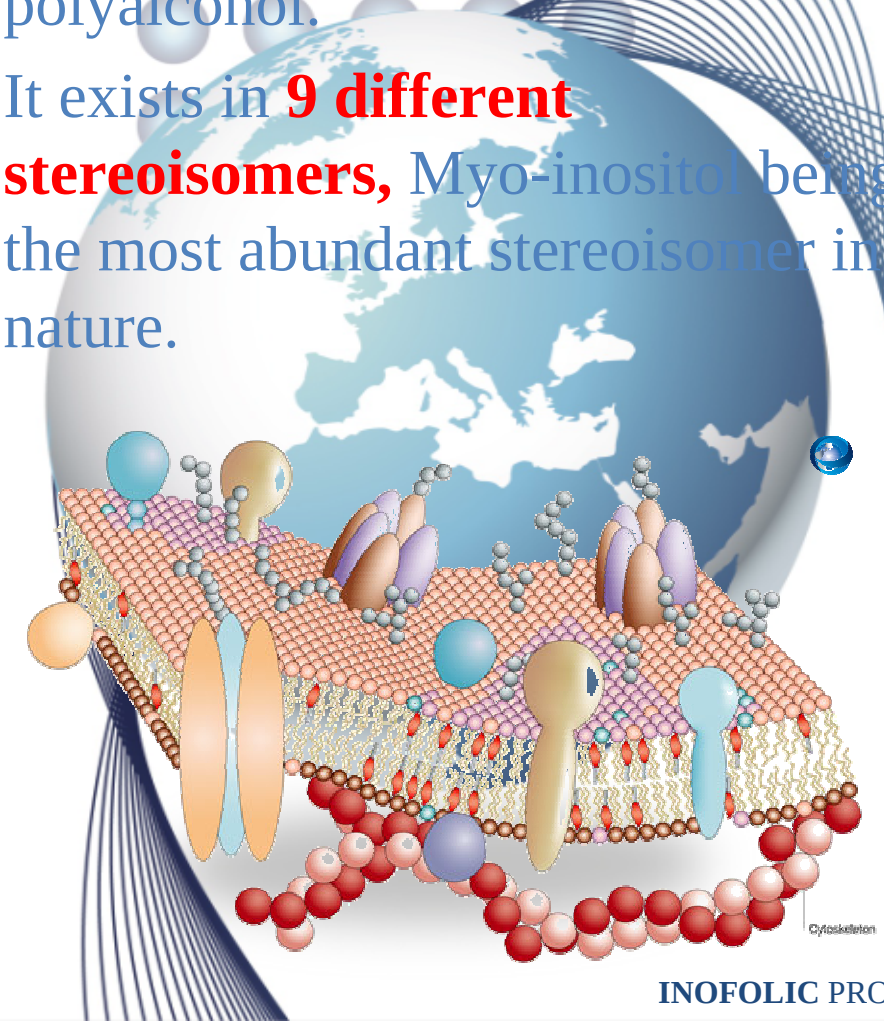

Insulin Resistance
Hyperinsulinemia
Type 2 Diabetes
Early CV Disease
(Metabolic Syndrome)
SHBG production
Ovarian androgen production
Disordered LH/FSH release
Hyperandrogenism
Anovulation
Polycystic ovary syndrome

Inositol

Inositol is a 6-carbon, cyclic polyalcohol.

It exists in **9 different stereoisomers,** Myo-inositol being the most abundant stereoisomer in nature.





The **phosphatidylinositol polyphoshate** lipids the functional biological compounds, based on the myo-inositol motif

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Summary of Endocrine effects of MYO in RCTs

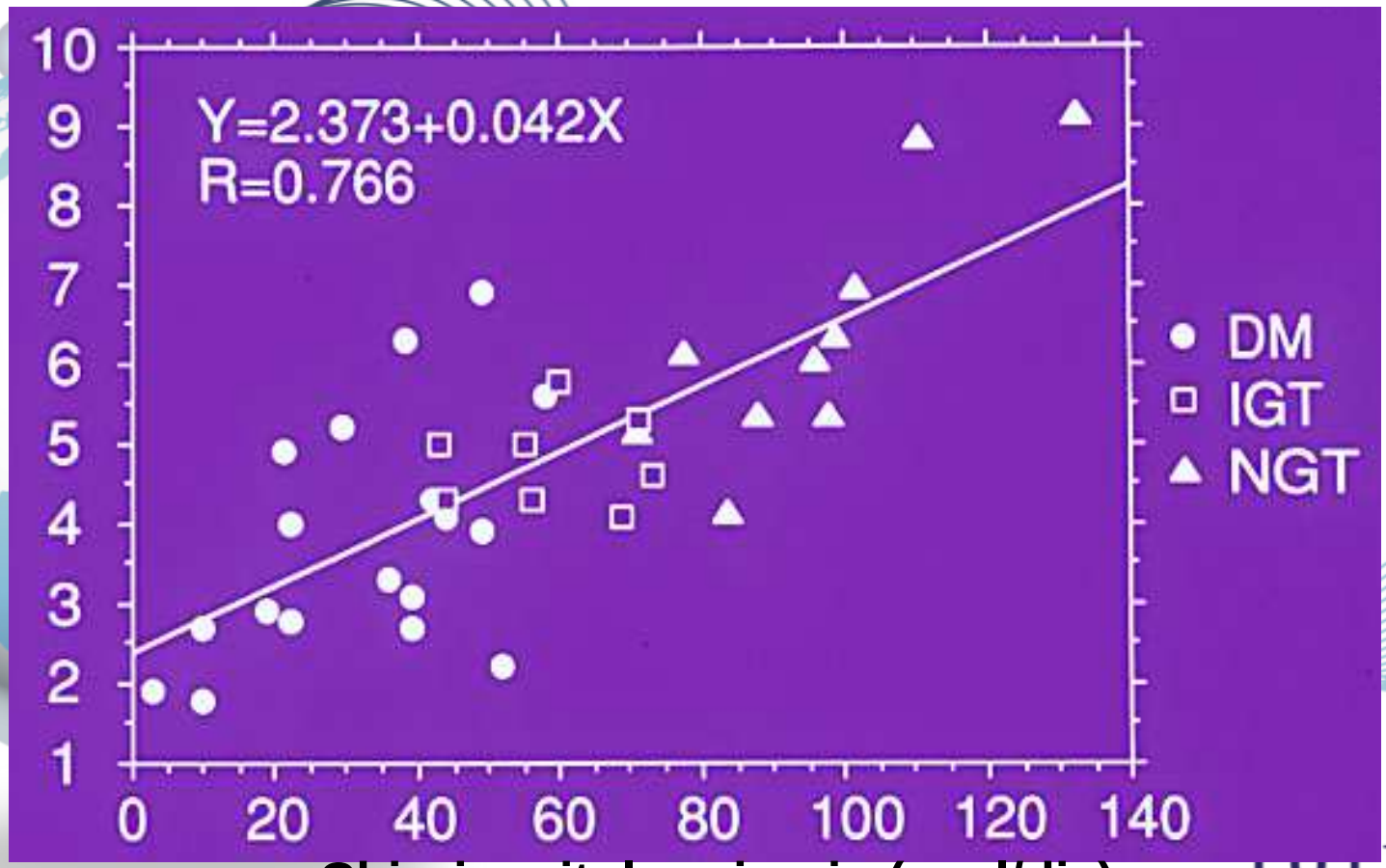
AUTHORS/ YEAR	SUBJECTS	DOSE/ DURATION	ANDROST	TOTAL TEST	FG score	SHGB
Gerli et al 2007	45	MYO 2gr+FA200mg 12-16weeks	NE	↓	NE	↓
Genazzani et al 2008	10	MYO 2gr+FA200mg 12 weeks	NE	↓	↓	NE
Minozzi et al 2008	46	MYO 4gr+FA400mg 6 months	↓	↓	↓	↓
Costantino et al 2009	23	MYO 4gr+FA400mg 12-16weeks	↓	↓	NE	↑
Zacchè et al 2009	50	MYO 4gr+FA400mg 3 months	↓	↓	↓	NE
Minozzi et al 2011	80	MYO 4gr+FA400mg+ EE30mg/ Gestodene 75mg 12 months	↓	↓	↓	↑
Nordio et al 2012	24	MYO 2gr+FA200mg 6 months	↓	↓	NE	↑

Effect of Inositols and Metformin on the insulin-sensitivity in PCOS patients

INOFOLIC PROJECT

Ruolo del D – Chiro inositolo nell'insulino – resistenza

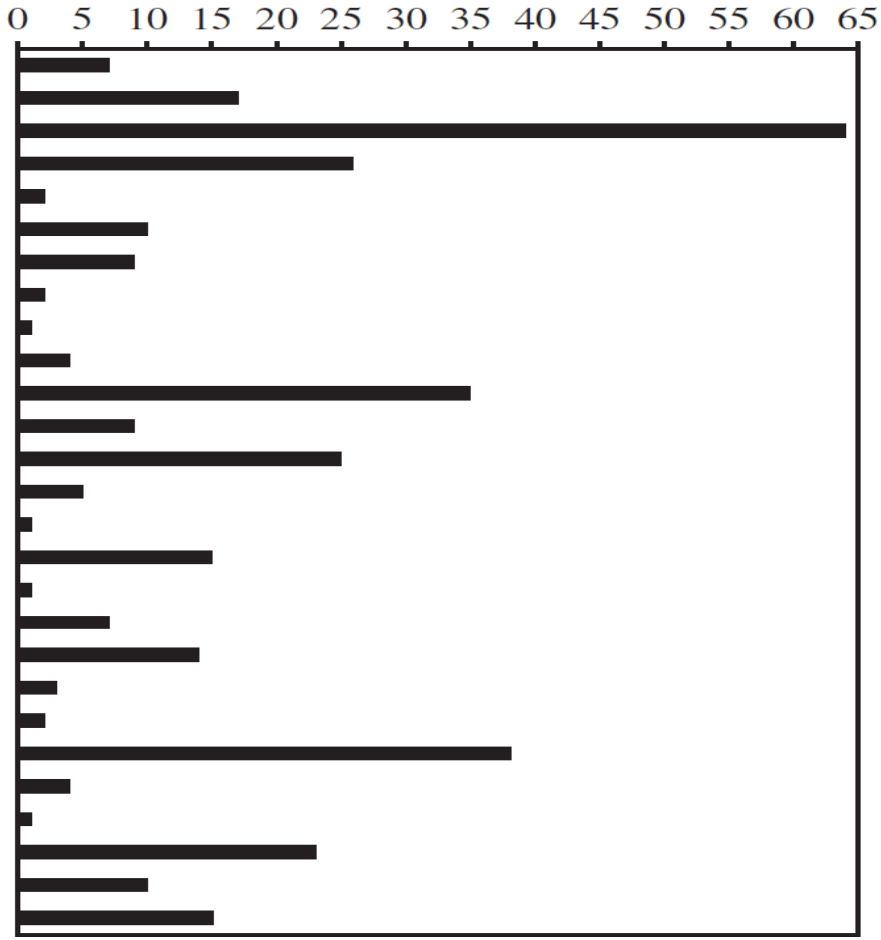
Correlazione tra la riduzione del D – Chiro inositolo urinario e l'aumento dell' insulino - resistenza



Suzuki S. et al, Diabetes Care 1994

European survey of diagnosis and management of the polycystic ovary syndrome: results of the ESE PCOS Special Interest Group's Questionnaire

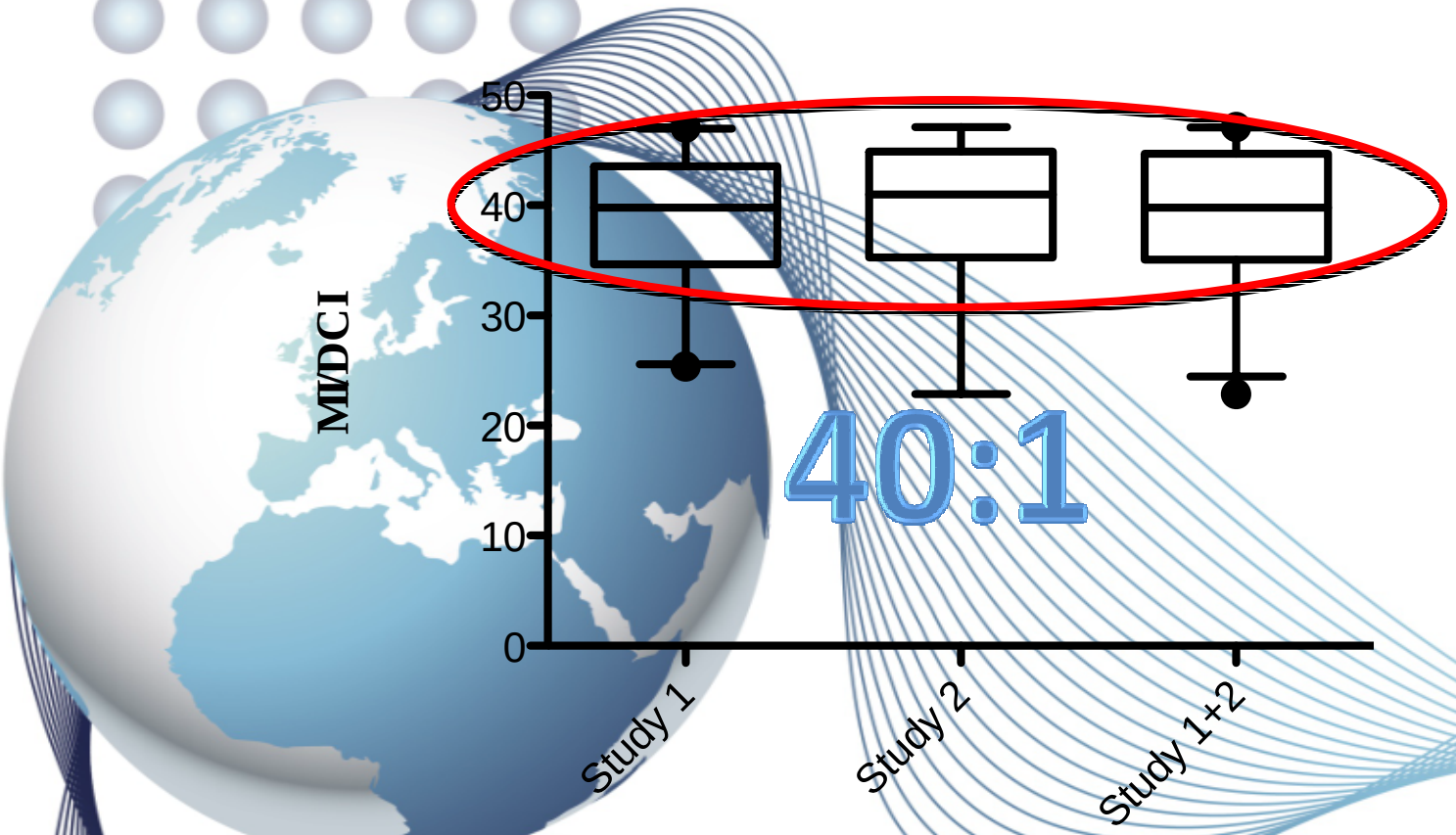
Conway et al, Eur J Endocrinol 2014;171:489-98



%	Treatments
2.0	Antiandrogens
4.9	Lifestyle
18.3	Metformin
7.4	Oral contraceptives
0.6	Antiandrogens+lifestyle
2.9	Antiandrogens+metformin
2.6	Antiandrogens+oral contraceptives
0.6	Laser depilation+lifestyle
0.3	Laser depilation+metformin
1.1	Laser depilation+oral contraceptives
10.3	Lifestyle+metformin
2.6	Lifestyle+oral contraceptives
7.1	Metformin+oral contraceptives
1.4	Antiandrogens+laser depilation+lifestyle
0.3	Antiandrogens+laser depilation+oral contraceptives
4.3	Antiandrogens+lifestyle+metformin
0.3	Antiandrogens+lifestyle+oral contraceptives
2.0	Antiandrogens+metformin+oral contraceptives
4.0	Laser depilation+lifestyle+metformin
0.9	Laser depilation+lifestyle+oral contraceptives
0.6	Laser depilation+metformin+oral contraceptives
10.9	Lifestyle+metformin+oral contraceptives
1.1	Antiandrogens+laser depilation+lifestyle+oral contraceptives
0.3	Antiandrogens+laser depilation+lifestyle+metformin
6.6	Antiandrogens+lifestyle+metformin+oral contraceptives
2.9	Laser depilation+lifestyle+metformin+oral contraceptives
4.3	Antiandrogens+laser depilation+lifestyle+metformin+oral contraceptives

Off label

MI/DCI physiological ratio



Summary of Metabolic effects of MYO in RCTs

AUTHORS/ YEAR	SUBJECTS	DOSE/ DURATION	TG	TOTAL CHOL	LDL	HDL	BASAL INSULIN	HOMA INDEX
Gerli et al 2007	45	MYO 2gr + FA200mg 12-16 wks	=	↓	↓	↑	=	NE
Genazzani et al 2008	10	MYO 2gr + FA200mg 12 wks	NE	NE	NE	NE	↓	↓
Minozzi et al 2008	46	MYO 4gr + FA400mg 6 mo.	=	↓	↓	↑	↓	↓
Costantino et al 2009	23	MYO 4gr + FA400mg 12-16wks	↓	↓	NE	NE	↓	NE
Zacchè et al 2009	50	MYO 4gr + FA400mg 3 mo	NE	NE	NE	NE	↓	↓
Minozzi et al 2011	80	MYO 4gr + FA 400mg+ EE30mg/GDN 75mg 12 mo	↑	↑	↓	↑	↓	↓
Nordio et al 2012	24	MYO 2gr + FA200mg 6 mo	NE	NE	NE	NE	↓	↓
Kamenov et al. 2014	50	MYO 4gr + FA400mg 3 mo	NE	NE	NE	NE	↓	↓

R	Time	Insulin (µU/ml)		HOMA	
		treated	control	treated	control
1	Baseline OW Post-	12.4±2.2	12.8±1.3	2.8±0.6	2.6±0.4
		6.5±1.1 (-47,6%)	11.3±1.1 (-11,7%)	1.4±0.3 (-50%)	2.5±0.7 (-3,8%)
2	Baseline N post-	32±4	30.8±7	NA	NA
		26±8 (-18,7%)	38.0±7.0 (+23,4%)	NA	NA
3	Baseline O Post-	16.8	18.4	NA	NA
		16.4 (-2,4%)	17.5 (-4,9%)	NA	NA
4	Baseline O Post-	16.6	18.1	NA	NA
		16.8 (+1,2%)	17.3 (-4,4%)	NA	NA
5	Baseline OW Post-	11.4±2.2	11.4±1.3	2.5±0.6	2.5±0.4
		5.5±1.1 (-51,7%)	10.1±1.1 (-11,4%)	1.1±0.3 (-56%)	2.4±0.7 (-4%)
6	Baseline OW post (vs DCI)	NA	NA	3.51±1.65	3.14±1.08
		NA	NA	1.75±0.84 (-50%)	1.61±0.70 (-48,7%)
7	Baseline N Post- (+COC)	8.5±6.7	8.1±5.2	1.81±1.38	1.59±1.07
		5.2±3.0 (-38,8%)	8.1±4.3	1.03±0.64 (-43%)	1.57±0.87 (-1,2%)
8	Baseline OW post– (+COC)	12.1±10.4	11.1±8.9	2.62±2.30	2.42±2.08
		10.9±12.6 (-9,0%)	10.6±8.8 (-4,5%)	2.36±2.97 (-9,9%)	2.33±2.09 (-3,7%)
9	Baseline OW Post- (COMBI)	12.8±4.1	12.3±3.7	2.7±1.1	2.4±1.2
		9.2 ± 2.1 (-28,1%)	9.6±1.9 (-21,9%)	1.5 ± 0.28 (-44,4%)	1.9 ± 2.1 (-20%)
10	Baseline O Post- (COMBI)	20.2±8.1	18.0±8.0	3.38±1.97	3.48±2.02
		10.7±5.5 (-46,8%)	17.8±8.2 (-1,1%)	1.97±1.48 (-41,7%)	2.8±1.4 (-19,5%)

Metformin in PCOS

Is Metformin Indicated as Primary Ovulation Induction Agent in Women with PCOS? A Systematic Review and Meta-Analysis

T.I. Siebert M.I. Viola D.W. Steyn T.F. Kruger

Department of Obstetrics and Gynaecology, Faculty of Health Sciences, Stellenbosch University and Tygerberg Academic Hospital, Tygerberg, South Africa

- 14 prospective RCT included in the review
- Aim: Determine metformin effect given alone or in combination with clomiphene citrate (CC+M) when compared with CC alone in ovulation induction protocols
- Target population: women with PCOS and anovulation
- Primary outcome: Live birth rate
- Secondary outcomes: Ovulation, pregnancy rate

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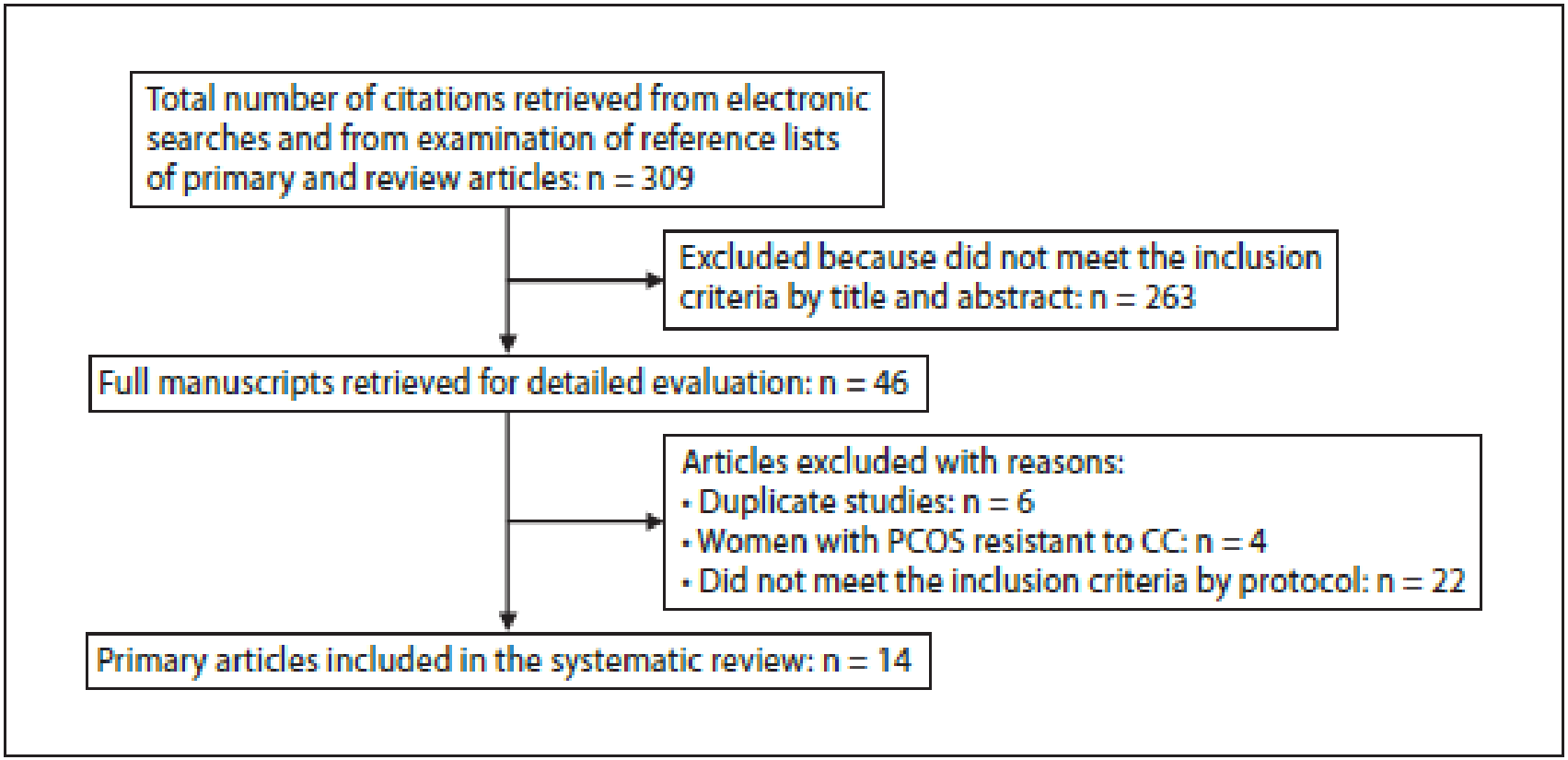

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Metformin in PCOS -Ovulation Rate -

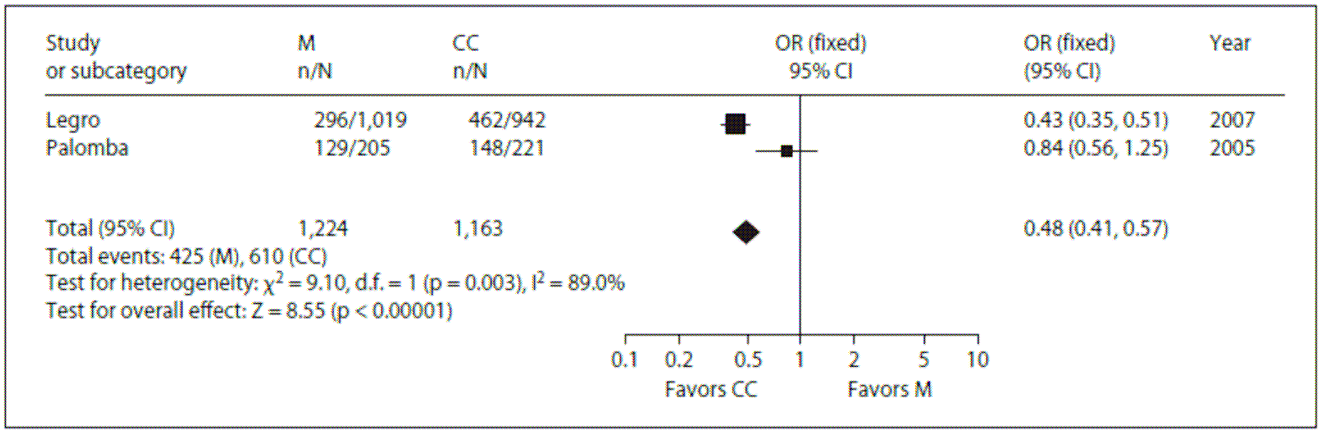

Fig. 4. CC vs. M: ovulation. When ovulation is the primary endpoint, CC alone performed significantly better than M alone. $p < 0.00001$.

CC alone performed significantly better than M alone

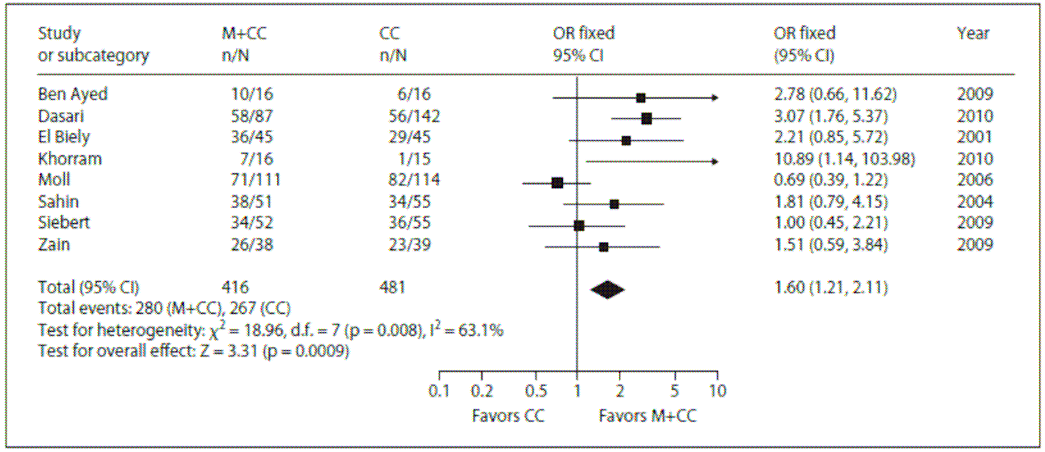

Fig. 5. M+CC vs. CC: ovulation. Ovulation was significantly better with the combination (CC+M) compared with CC alone. $p < 0.00001$.

Ovulation was better with the combination CC + M compared with CC alone

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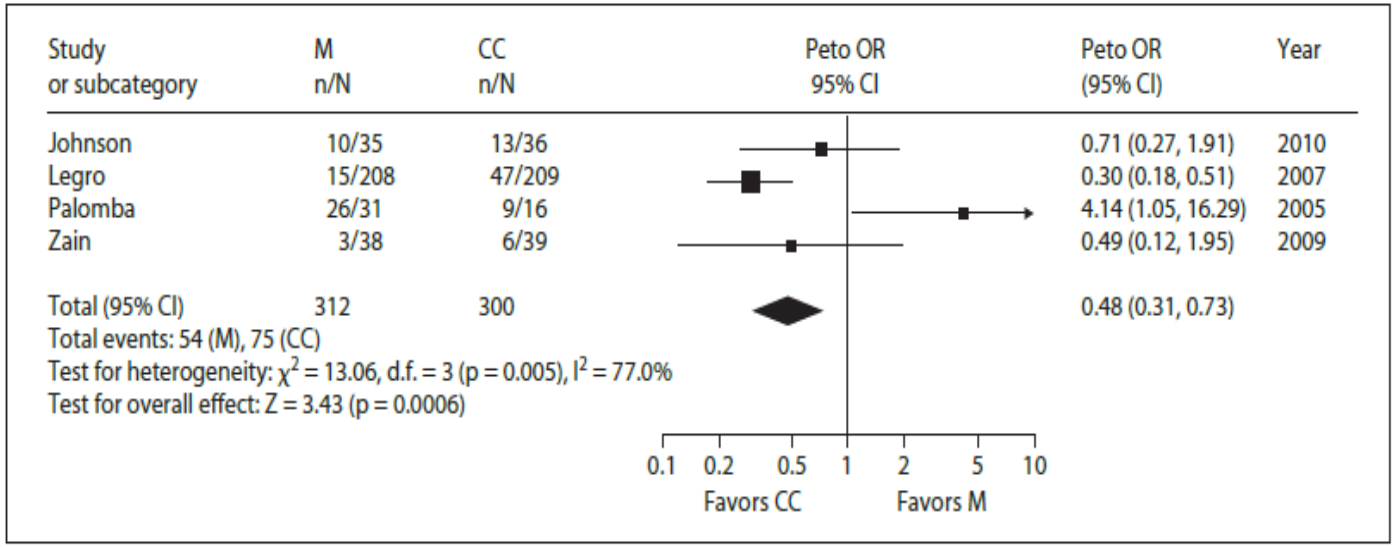
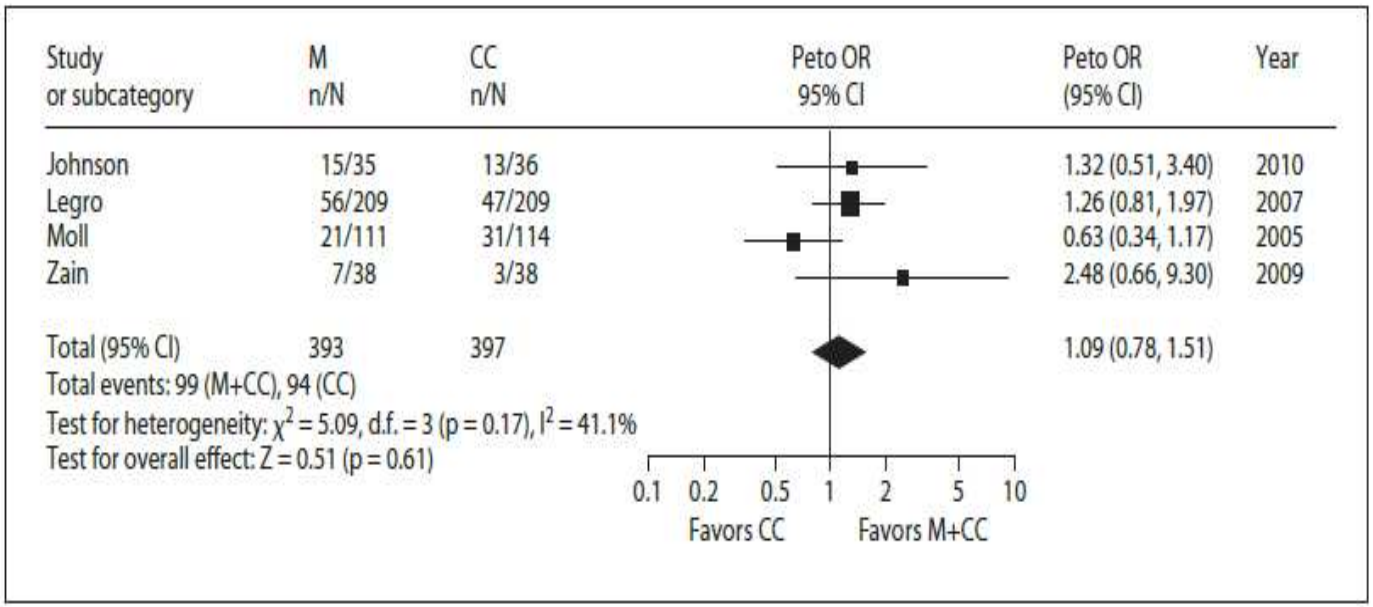
Metformin in PCOS -Live birth Rate -

CC vs M

Lower live birth rate with M alone compared to CC





M+CC vs CC

No difference between groups

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Metformin vs Myo-inositol

PCOS

Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women

EMANUELA RAFFONE, PIETRO RIZZO, & VINCENZO BENEDETTO

Obstetrics and Gynecology Department, G. Martino Hospital, Messina, Italy

120 PCOS women, < 35 years old

- Group I: **60 women treated with metformin 1500 mg/day for 6 months**
- Group II: **60 women treated with 4 gr myo-inositol+ 400 µg folic acid for 6 months**

Ovulation induction with recombinant FSH for a maximum of 3 attempts if no pregnancy occurred

Primary endpoint:
restoration of a spontaneous ovarian activity

Secondary endpoints:
-myo- or metformin- resistance
-pregnancy rate
-abortion rate

Lo.Li. Pharma INTERNATIONAL

Metformin and insulin/HOMA index in overweight/obese PCOS

	PATIENTS BMI	N.	DURATION	HOMA		% change	P value	Fasting Insulin		% change	P value
				Pre-treatment	After-treatment			pre	after		
Hanh 2004	25-30	48	6M	5,4±4,2	2,5±2,0	-53.7	0,001				
Tan 2007	I 25-30	42	6M	3.0±1.7	2.0±1.2	-33.3	<0.001	14.2±7.6	9.8±5.2	-31	<0.001
Otta 2010	32,4±6,7	30	4M	3,2±1,1	2,4±1,4	-25	0,35	14.2+4.03	9.4+5.1	-33.8	0,003
Laure 1998	27 - 36	20	6M	//	//	//		17,3±7,1	15,2±8,3	-12.1	0,04
Behradmanesh 2011	25 - 30	19	3M	1,8±0,9	2,5±1,2	+37	0,07	11.8±9.6	11.6±8.3	-1.7	0,9
Berker 2004	22 - 29	58	4M	6,0±2,8	5,1±2,0	-15	0,003	31,7±12,1	21,8±8,4	-31.2	0,000
Gadekal Rajagopal 2012	24 – 32	25	3M	3,9±1,8	4,0±2,0	+2.6	NS	18.4 – 8.7	19.9 – 9.4		NS
Minyan 2014	20 - 30	54	6M	5,09	6,7	+32.4	0,01				
Esfahanian 2013	28 - 34	17	3M	3±1.5	2,4±1,4	-20	0,001	13.4 ± 7	11.5 ± 6.2	-14,2	0,01

------ *non significant results*

Around 50% of the published studies didn't confirm the efficacy of metformin as strong insulin-sensitizer active in overweight/obese PCOS women

HOMA/Insulin MI or MI/DCI= -50.2% -29.7% MET= -8.8% -24.9%