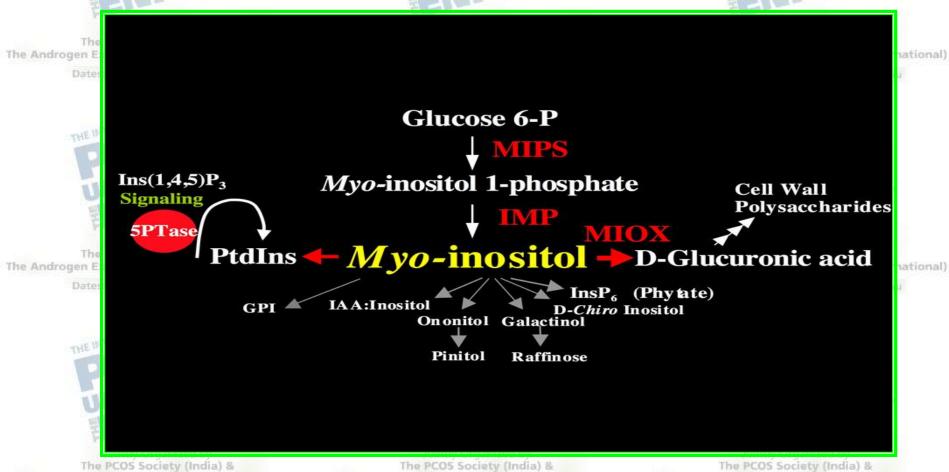
THE INTERNATIONAL CONFERENCE THE INTERNATIONAL CONFEREN Myoinositol Pharmacology and Mode of action



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Dates: June 16 - 18, 2017 Bengaluru

Dr. Nalini Mahajan

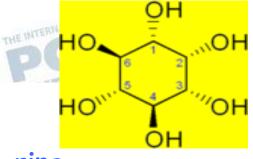
Director Mother & Child Hospital. Delhi

President FPSI



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- Inositol is a 6-carbon ring compound with a hydroxyl group attached to each carbon of the ring.
- Inositols & their derivatives are sugar alcohols- belong to
 Vitamin B family, chemically stable molecules
- There are 9 possible stereo-isomeric forms of inositol (constitutionally similar), related to epimerization of the six hydroxyl groups.
- Myo-inositol (MI) & D-chiro-inositol (DCI) are the 2 of 9 important existing stereoisomers.
- MI is abundant form in nature & mammalian cells, comprising up to 99% of inositol amount.
- DCI represents balance 1%

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Inositols



- Average daily intake of myo-inositol from diet varies between
 225 and 1500mg/day per 1800kcal diet
- Dietary products containing inositol include
 Fruits- mainly cantaloupe and oranges,
 High bran content cereals, nuts, and beans.
- Fresh fruits & vegetable contain more inositol compared to frozen, salted, or canned products.
- Inositols are not considered an essential nutrient since they can be formed endogenously from glucose



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MI- synthesis

Glucose



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Glucose 6 phosphate synthase

Glucose-6-phosphate

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Inside the cert in its a present both and as a present porm and free form trane (Biochimie, 2013) membrane

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inositol-3-phosphate synthase

Myo-inositol 1-phosphate

dephosphorylation by inositol monophosphatase

Free myo-inositol

NAD/NADH epimerase.

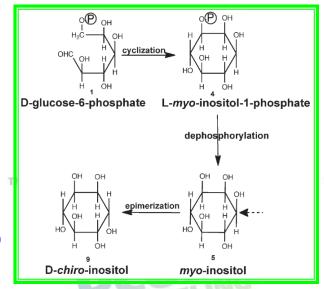
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The activity of this insulin-dependent enzyme strongly influences the intracellular ratio between these two molecules in adipose, hepatic, or muscle cells.



- Epimerase is an insulin-dependent enzyme that converts Myo-inositol to D-chiro-inositol through an oxidoreductive mechanism.
- Conversion rhythm is about 20-30% in normal insulin-sensitive tissues (liver, muscle and fat) and 5% only in diabetes (Mol. Cells, 1998).
- Ratio of MI; DCI 40:1



Jointly Organized by
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Myo inosital



- Precursors for the synthesis of phosphatidylinositol polyphosphates (PIPs). PIPs are key biomolecules belonging to the signal transduction system.
- Biological actions of Myo occur via PIPs or via inositol polyphosphates (InsPs)
- PIPs are crucial factors in regulating several cellular processes (membrane lipids)
- InsPs important role in calcium signaling through its receptors (InsP3Rs).



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Role of Myo-inositol



 Important role in cellular morphogenesis and cytogenesis

- synthesis of lipids
- creation of cell membranes &
- cell growth.
- Regulates, secretion of some exocrine glands such as pancreas & ovaries via signal transduction pathways.

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Involved in the release of cortical granules,

Inhibition of polyspermy,

cos society (India) & The PCOS Society (India) & Completion The of meiosis and conal)

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 Activation of the cell cycle - results in embryonic development (Papaleo 2009).

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Myo-inositol



Inositol tri phosphate IP3

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Intracellular

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Release Intracellular Ca+2

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Inositol - second messenger

MI & DCI are intracellularly incorporated into inositol phosphoglycans (IPGs), which are second messengers of Insulin, FSH & TSH

Some actions of insulin are mediated by these IPG's.

Two IPG's have been identified:

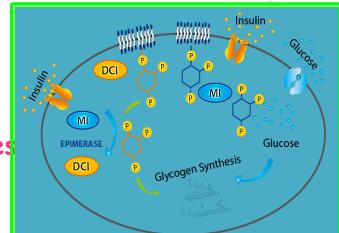
(ii) the MYO-IPG which inhibits cyclic AMP-dependent protein kinase -involved in Cellular Glucose uptake.

(i) the D-chiro-IPG mediator,
which activates pyruvate dehydrogenase

phosphatase, and involved in Glycogen synthes

iternational)

iternational)



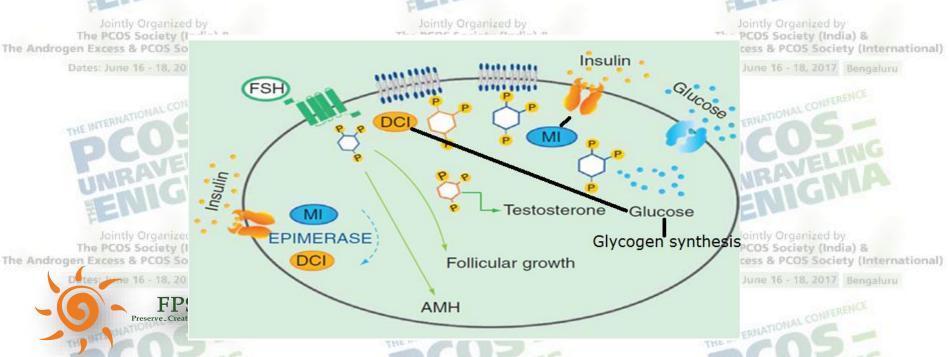
THE INTERNATIONAL CONFERENCE Actions in the ovary At ovarian level it has been shown that MI based

second messenger is involved in both glucose uptake

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and FSH signaling

DCI-based second messenger is devoted to the insulin-mediated androgen production.





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Derives from their activities as insulin mimetic (or "insulin sensitizing") agents and

their beneficial effects on metabolism.

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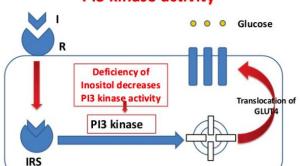
deficiency of IPGs in tissues

An altered metabolism of inositols to IPG

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mediators, could play a role in inducing

Deficiency of Inositol decreases PI3 kinase activity



(Baillergion et al 2010)

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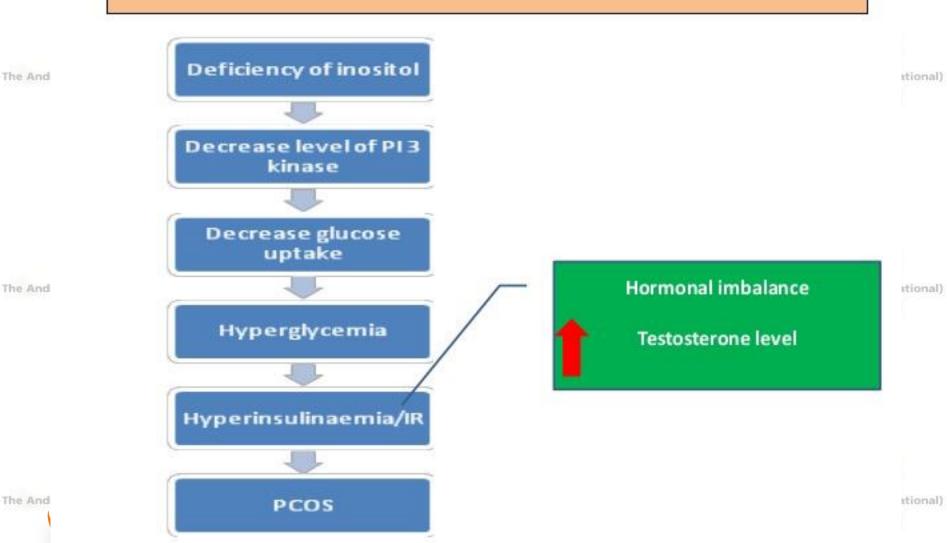
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Pathway of Inositol deficiency & PCOS











Inositol & PCOS



- The epimerase activity is increased in the theca cells of PCOS women, causing a deficit of MI. MI:DCI ratio altered.
 (Heimark et al 2014)
- Intraovarian MI may adversely affect glucose uptake and metabolism of both oocytes and follicular cells.
- Since oocytes are characterized by high glucose consumption this would compromise oocyte quality.
 - PCOS women have lower serum DCI levels & > urinary loss of DCI-IPG. (Baillergion et al 2008)

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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

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

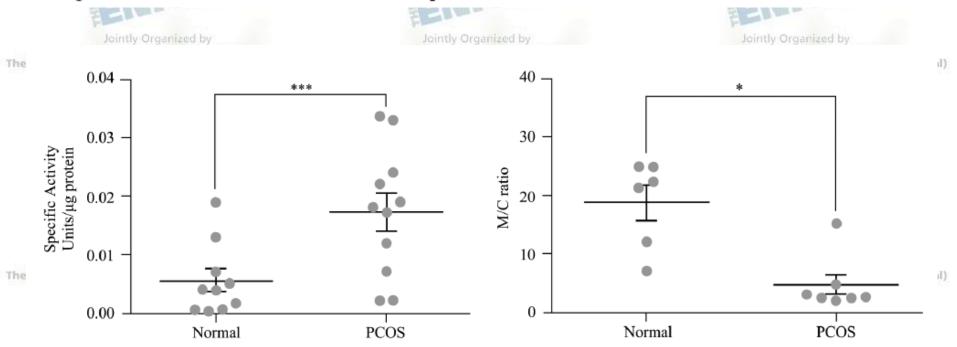


Fig. 1 Myo-inositol to chiro-inositol epimerase assay

Fig. 2 Myo-inositol to chiro-inositol ratios

How supplementation may help

MI reduces insulin levels, probably

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- by conversion to D-chiro-Ins (via the epimerase enzyme)
 restoring MI:DCI ratio.
- or by serving as substrate for formation of MI &DCI-IPGs,
- which would in turn amplify insulin signaling.
- DCI supplementation replenished stores of the mediator & improved insulin sensitivity in both lean and obese women with PCOS (Unfer et al 2017)
- MI deficiency responsible for oligo ovulation & poor oocyte quality in PCOS. Supplementation restores N ovarian function. (Carlomagno et al.)



Inositols and PCOS

The DCI "ovarian paradox"

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Normally, epimerase MYO/DCI conversion activity induces a specific MYO to DCI ratio that is different in each tissue, but in accordance to the metabolic balance.

However, in insulin-resistant and PCOS patients this ratio is altered, due to a decreased epimerase conversion activity (1% vs. 8% in sensitive tissues) and a consequent increase in MYO to DCI ratio.

On the contrary, in the ovary data show that epimerase activity is increased, therefore inducing an increase in DCI concentrations and a decrease in MYO

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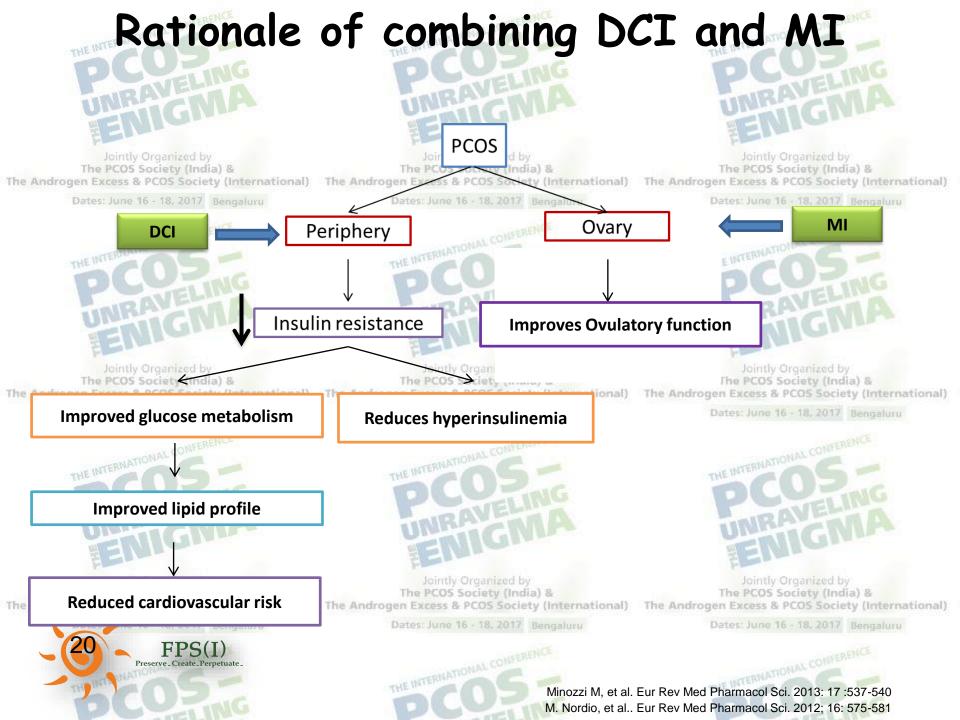
8, 2017 Bengaluru Dates: June 16 - 18, 2017 Bengaluru

Preserve_Create_Perpetuate_(Consensus Conference, Florence, 2013; Endocrine J., 2014)

The "DCI paradox" in the ovary

Unfer, Carlomagno and Roseff

- In PCOS HI stimulated epimerase activity in the ovary - an overproduction of DCI & a concomitant depletion of MI.
- DCI supplementation would be ineffective in such women as they already have > levels in ovary.
- > dose DCI negative effects.
- It was anticipated that the synergetic activity of the two stereoisomers would result in a
 - (1) DCI-mediated enhancement of insulin sensitivity in liver and muscle resulting in a decrease in circulating insulin, and
 - (2) repletion of MI in the ovary, resulting in restored FSH sensitivity & improved oocyte quality..



Myoinositol - Is there enough evidence?

Review Article

The Androger

Inositol Treatment and ART Outcomes in Women with PCOS

Deepika Garg¹ and Reshef Tal²

J.I Endocrinol 2016

- Admin. of inositol in PCOS improves metabolic & hormonal parameters ovarian function & ovarian response.
- E/o improved folliculogenesis, > M2 & embryo quality. Bizzarri et al 2014, Papelio et al 2007.
- Vascular permeability, VEGF and COX-2 expressions were < in animals treated with MI and/or metformin. Turan et al 2015







Analysis of studies

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UNRA				UNRAVE				\	
				TABLE	1				
Authors	Study design	Study size	Population characteristics	Type of treatment	Mean age (years)				
(Papaleo et al., 2009) [11]	Randomized controlled trial	60 women with PCOS Treatment: 30 Placebo: 30	Women with PCOS as defined by oligo/amenorrhea, hyperandro- genism/nemia, and PCO, undergoing ICSI	Treatment: 2 g myo-inosite twice a day plus 400 acid Place of FSH	P = 0.016 on $P = 0.016$	1, 0021, 0.0021, ± 0.9 ve	rsus 1.6 ± 1 group versu	o quality,	
(Ciotta et al., 2011) [41]	Randomized controlled trial	34 women	No. of day	ls of stin. level at hCG a level at hCG a level at hCG a	cy ^{tes} (1.0 cy ^{tes}) in the	reatment cleavage cleavage	arriage rate	agroup A service ocytes, greater respectively. Service of the service of the service of the service ocytes and the service ocytes occurs on the service ocytes occurs on the service occurs of the service occurs occurs on the service occurs occurs occurs on the service occurs occurs on the service occurs occu	A versus eater ificantly number total
	∠No. of .	of germ cancelle	inal vesicle d cycles (1) mature of mplantation	Treatment: 2g myo-inosito twice a day plus 400 acid Plan Of FSH dose of stimulating several at hCG and the several	pregnance 55.5 Proup B: 36.5	Group A: 24.6 Group B: 25.3	In group A, significant reduce 2360.5 IU, P < 0.01), number P < 0.01), and peak estradion P < 0.01); no cycle cancellati (P = 0.05); no difference between two group number of mature oocytes (8 grade 1 embryos (1.64 versus pregnancies (22 versus 10; P clinical pregnancies (15 versus abortions (4 versus 3; P = NS) respectively.	nancies between the two group tion in total rFSH units (1953.4 r of stimulation days (11.1 versu I levels (2261.2 versus 2740.0 p; on in group A versus 4 in group ween the total number of oocy s; in group A, significantly gree 1.21 versus 7.08, $P < 0.05$), num 0.76, $P < 0.01$), number of < 0.05); no significant differen is 5, $P = NS$) and spontaneous (5) in group A versus group B,	6 versus us 12.7, g/mL; up B ytes eater nber of nces in
(Isabella and Rah 2012) [54]	no ste	Placebo: 11 Group A: 10 Group B: 11 Group C: 10 Group D: 12	Women with PCOS (Rotterdam criteria) undergoing ICSI	Placebo group Group A: DCI 300 mg daily Group B: DCI 600 mg daily Group C: DCI 1200 mg daily Group D: DCI 2400 mg daily Treatment given for 8 weeks	Placebo: 36.9 ± 1.5 Group A: 36.8 ± 1.6 Group B: 36.9 ± 1.52 Group C: 36.7 ± 1.57 Group D: 37.0 ± 1.25	Placebo: 24.4 ± 2.8 Group A: 25.2 ± 3.5 Group B: 24.7 ± 3.5 Group C: 25.1 ± 3.1 Group D: 25.6 ± 2.9	group D 2983.0); number of in the 3 higher dose DCI gro versus group A 12.1 versus gr group D 13.8); estradiol level- increased in highest dose DC group 1429.69 versus group I in number of cycles canceller retrieved; significantly lower group D compared to placeb	stimulation days significantly j ups versus placebo (placebo 11 oup B 12.5 versus group C 12.9 s at hCG administration signif I group versus placebo (place D 1490.24); no significant differ	greater 1.4 9 versus ficantly 250 erences ytes in ntly





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Inositols are IS agents.

They act at an intra-cellular level via the second messenger system

They have an important role to play in oogenesis and embryogenesis (Ca metabolism).

• Deficiency can increase IR & its subsequent

effects.

Supplementation appears to improve IS & metabolic parameters.

Further studies required.

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