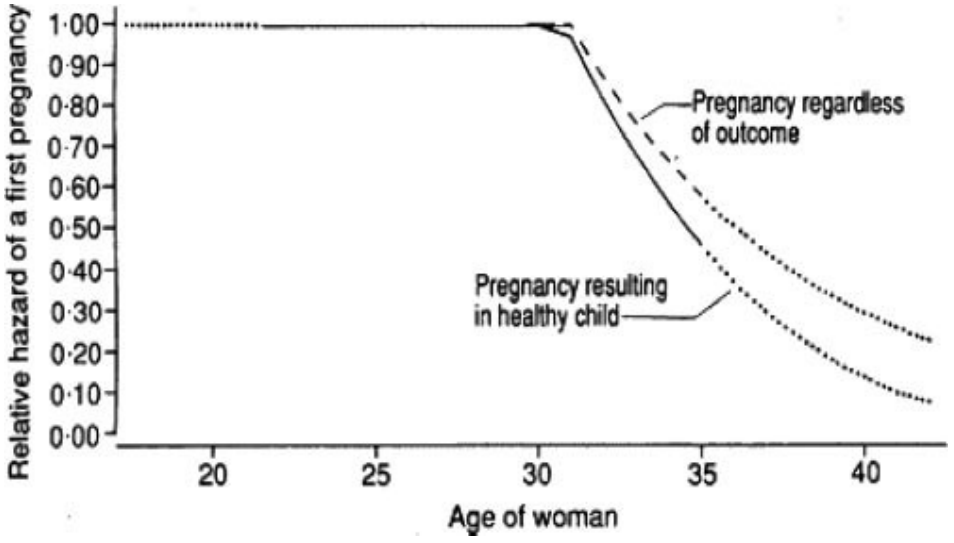
Inositol, Melatonin and oocyte quality

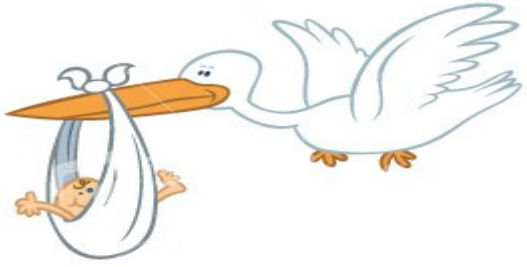
Gianfranco Carlomagno
Ferrara 11/03/11

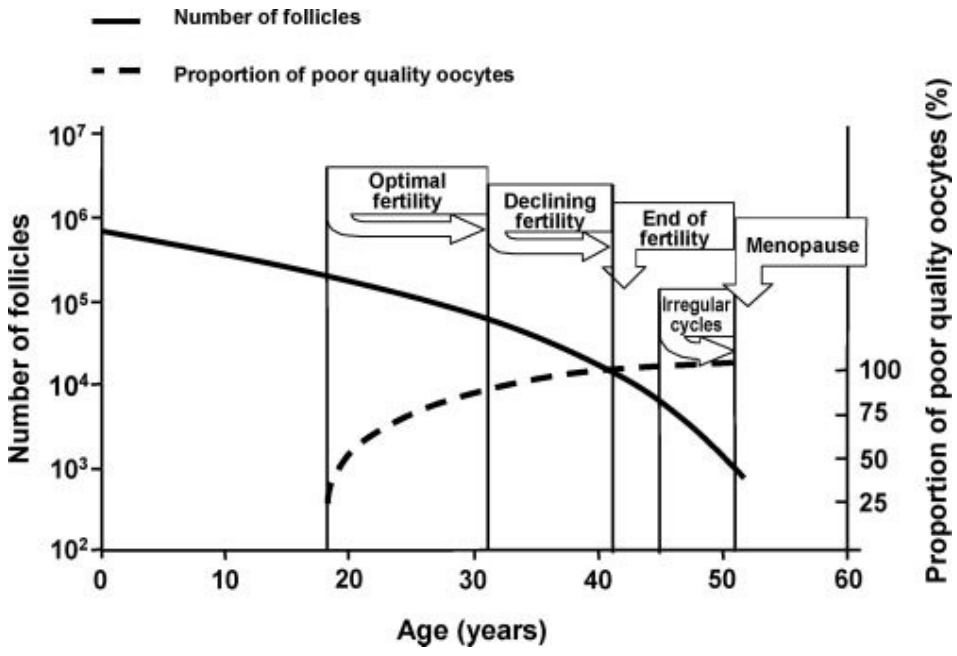
sifiog
Società Italiana di Fitoterapia
ed Integratori in Ostetricia e Ginecologia

Reproductive aging



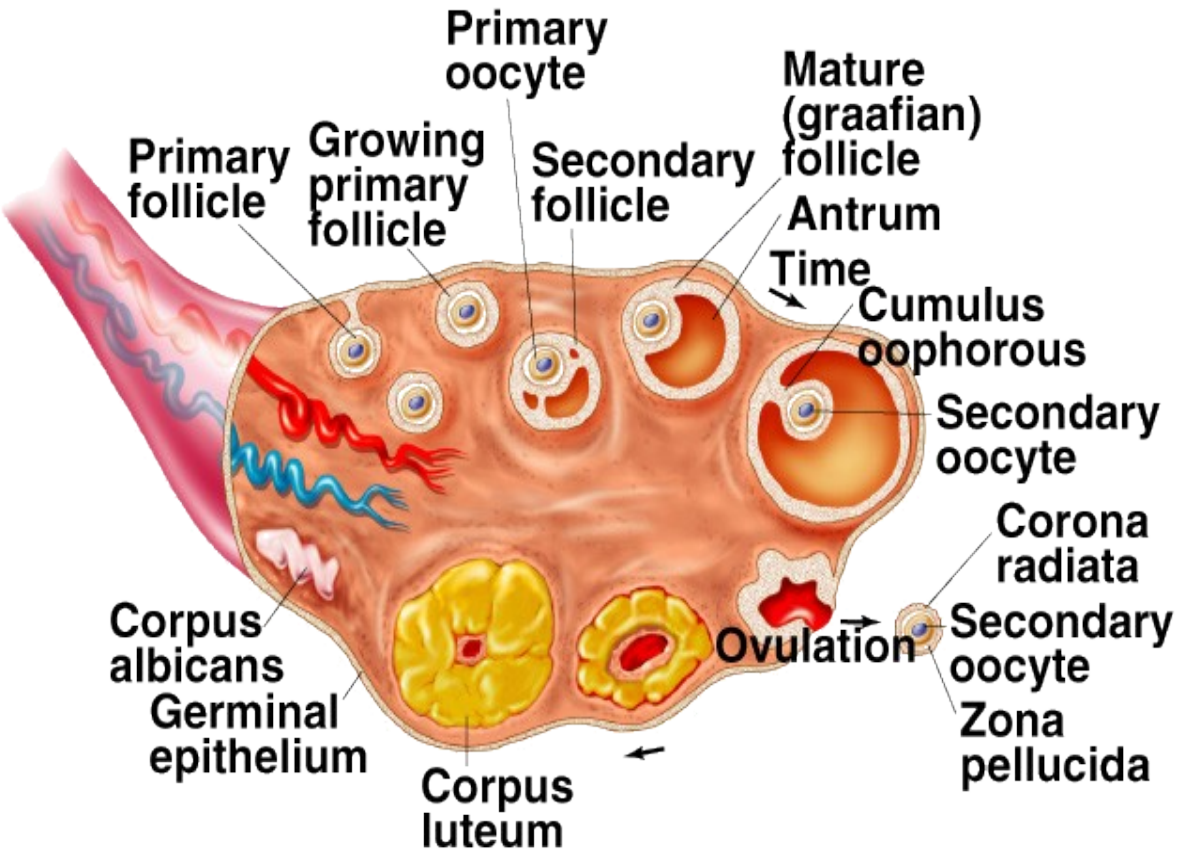
Influence of social environment





Ovary

The antral follicle is a small fluid-filled space, which culminates in the fully mature follicle. The FF that fills the antral cavity contains water, electrolytes, serum proteins,



Melatonin&Follicular Fluid

Melatonin and the ovary: physiological and pathophysiological implications

Hiroshi Tamura, M.D., Ph.D.,[a,b] *Yasuhiko Nakamura, M.D., Ph.D.,*[c] *Ahmet Korkmaz, M.D.,*[a] *Lucien C. Manchester, Ph.D.,*[a] *Dun-Xian Tan, M.D., Ph.D.,*[a] *Norihiro Sugino, M.D., Ph.D.,*[b] *and Russel J. Reiter, Ph.D.*[a]

[a] Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, Texas; [b] Department of Obstetrics and Gynecology, Yamaguchi University Graduate School of Medicine, Ube; and [c] Department of Obstetrics and Gynecology, Yamaguchi Grand Medical Center, Hofu, Japan

328 Fertility and Sterility® Vol. 92, No. 1, July 2009 0015-0282/09/$36.00

doi:10.1016/j.fertnstert.2008.05.016

TABLE 1

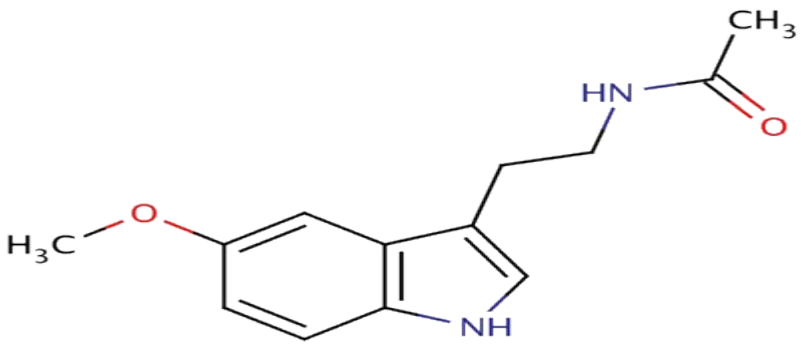
Melatonin, P, T, and E_2 concentrations in large and small follicles of humans.

Follicle size	Melatonin (pg/mL)	P (μg/mL)	T (ng/mL)	E_2 (ng/mL)
Large follicles (>18 mm)	123 ± 39	10.3 ± 0.7	5.2 ± 0.5	512 ± 39
Small follicles (<10 mm)	54 ± 11[a]	3.3 ± 0.7[b]	7.5 ± 0.8[c]	299 ± 30[b]

Note: Data are the mean ± SEM of 18 patients.
All significance values are as compared with large follicles.
From Nakamura et al. (22).
[a] $P<.05$.
[b] $P<.05$.
[c] $P<.05$.

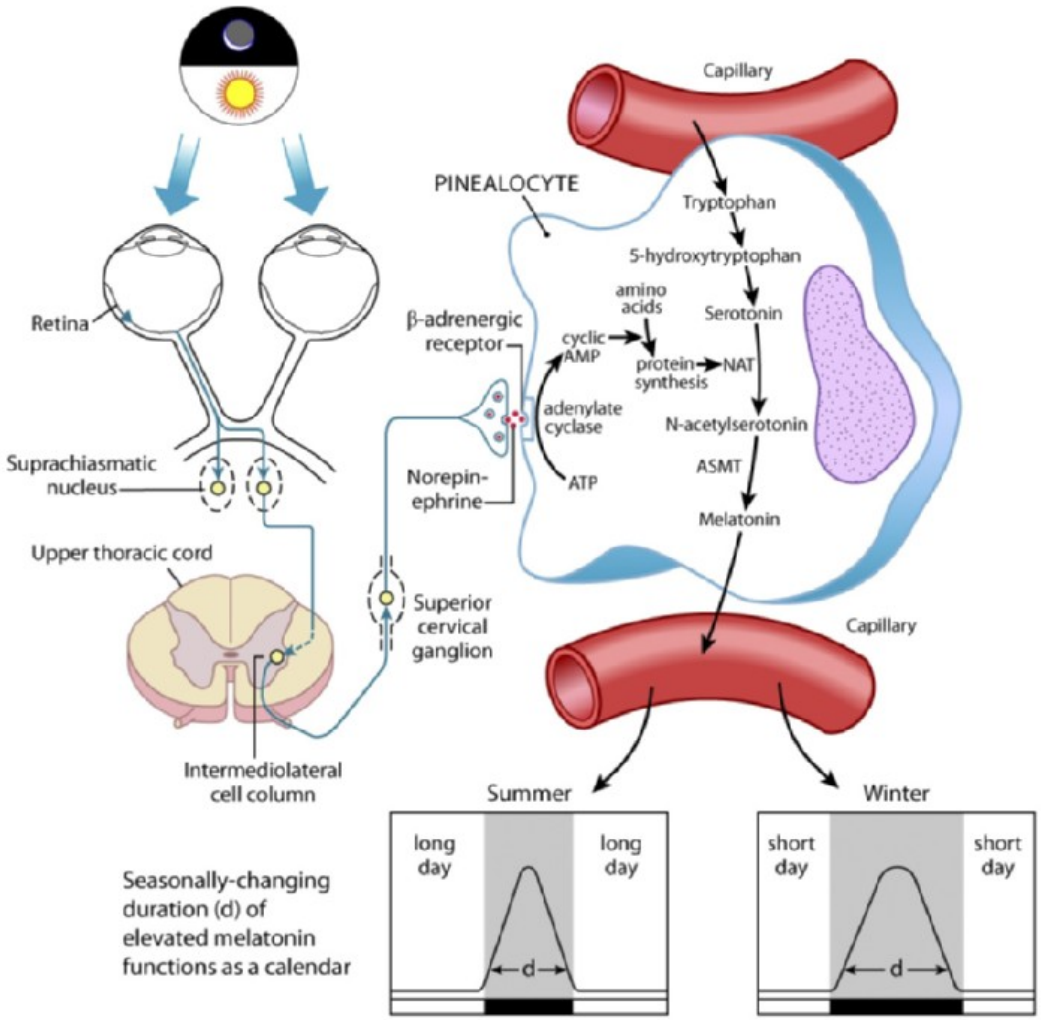
Tamura. Melatonin and the ovary. Fertil Steril 2008.

Melatonin



Melatonin is a hormone secreted by the pineal gland in the brain. It helps to regulate other hormones and maintains the body's circadian rhythm

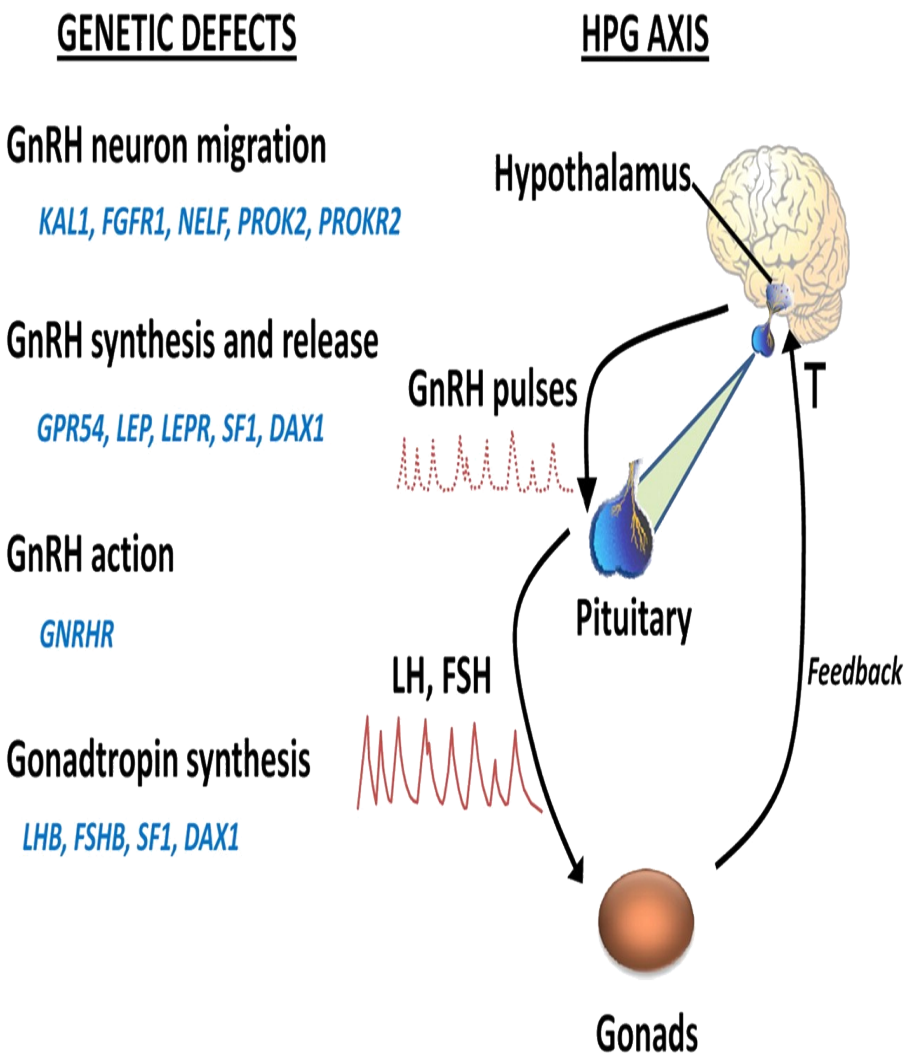
Melatonin Synthesis



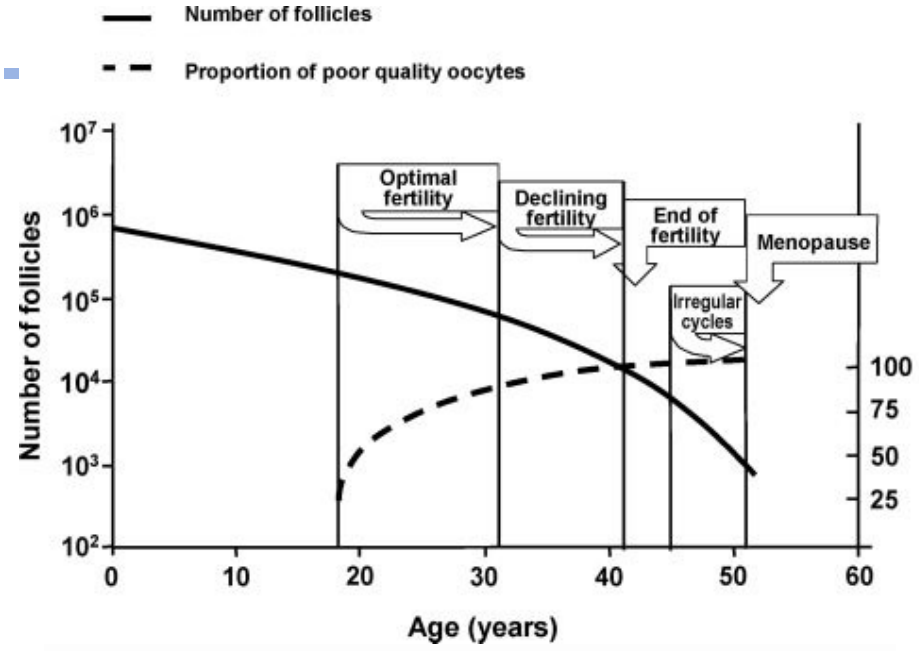
- It is mainly secreted during the night.
- M. synthesis occurs mainly in pineal gland, and in small extent in retina, gastrointestinal tract and lymphocytes and skin.

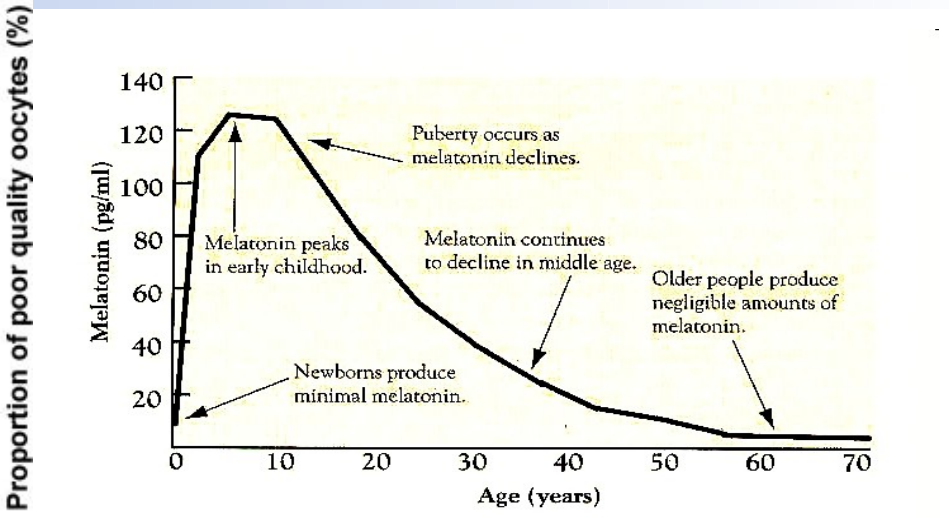
Melatonin and Puberty

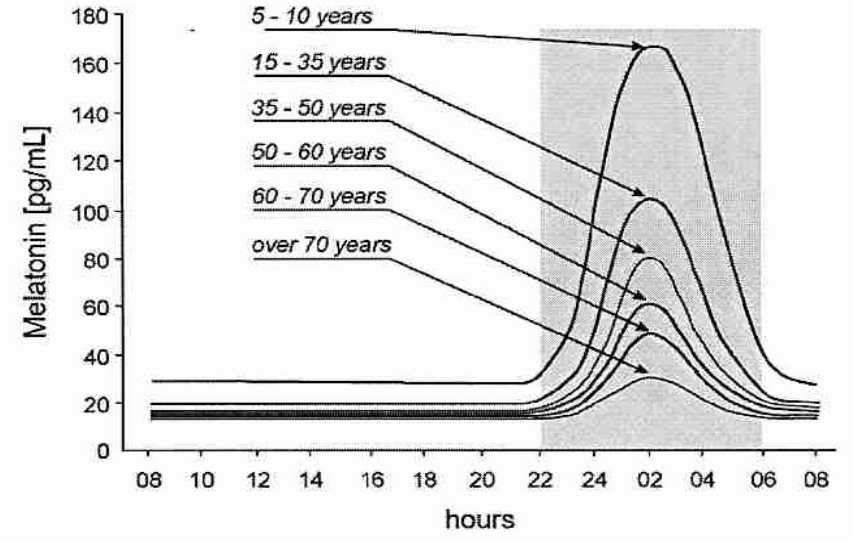
- Before the age of 10 nocturnal melatonin levels are too high and inhibit pitutary GnRH secretion.
- Children with delayed puberty have higher nocturnal melatonin levels.

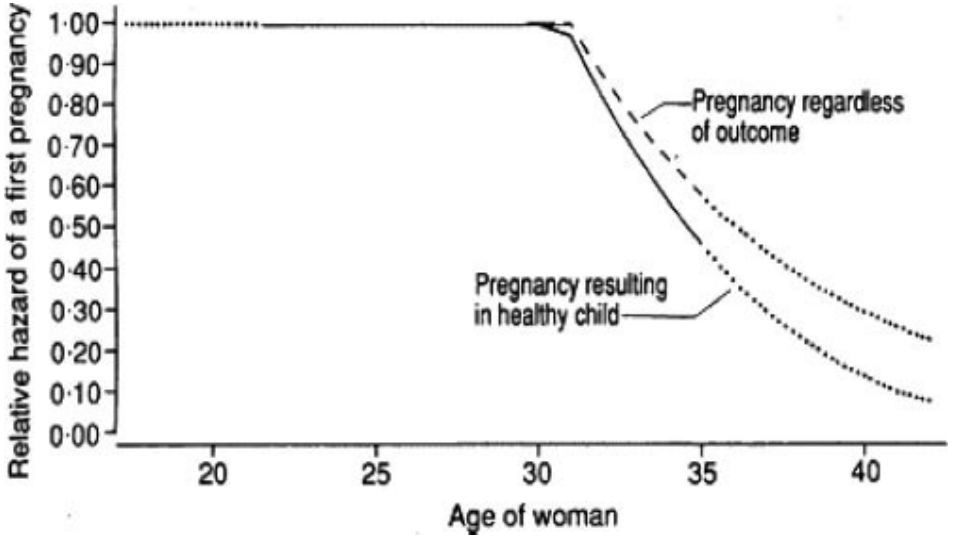


Melatonin


Number of follicles
Proportion of poor quality oocytes
Number of follicles
Optimal fertility
Declining fertility
End of fertility
Menopause
Irregular cycles
Proportion of poor quality oocytes (%)
Age (years)


Melatonin (pg/ml)
Puberty occurs as melatonin declines.
Melatonin peaks in early childhood.
Melatonin continues to decline in middle age.
Older people produce negligible amounts of melatonin.
Newborns produce minimal melatonin.
Age (years)


Melatonin [pg/mL]
5 - 10 years
15 - 35 years
35 - 50 years
50 - 60 years
60 - 70 years
over 70 years
hours

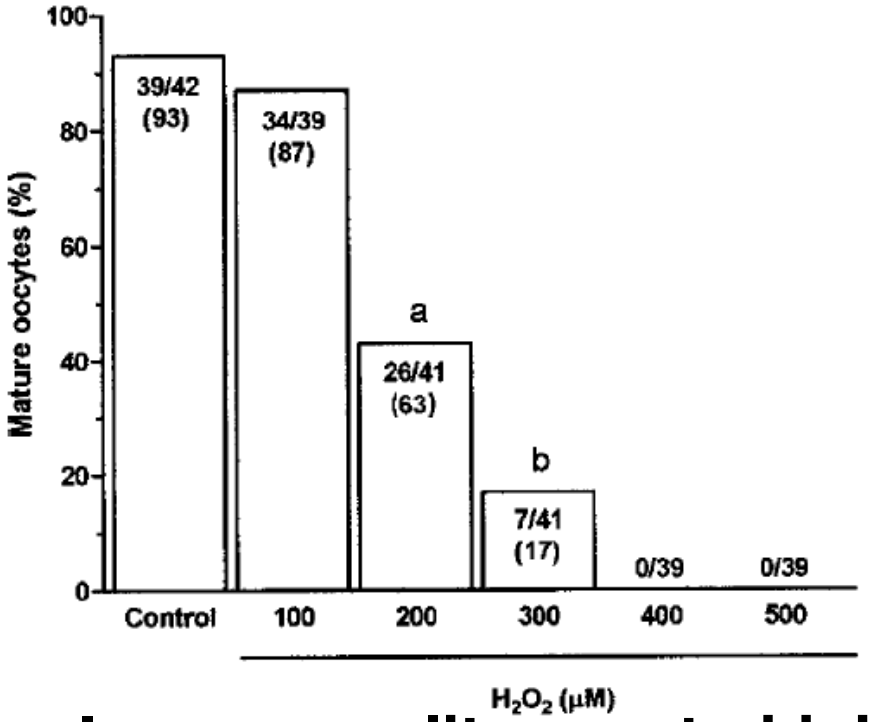

Relative hazard of a first pregnancy
Pregnancy regardless of outcome
Pregnancy resulting in healthy child
Age of woman

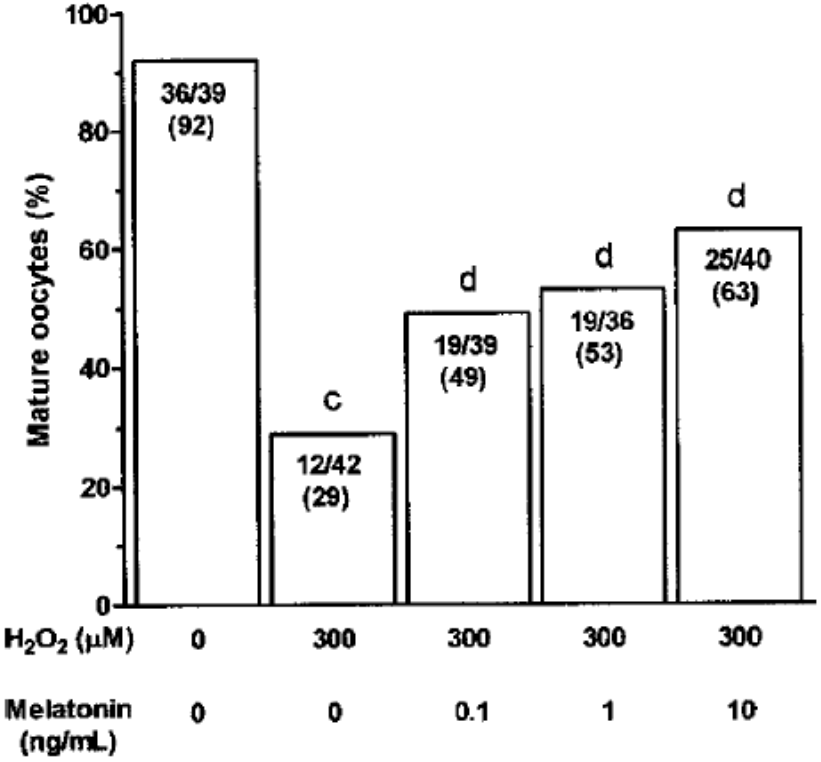
Oxidative stress and Oocyte quality

J. Pineal Res. 2008; 44:280–287
Doi:10.1111/j.1600-079X.2007.00524.x

Journal of Pineal Research

Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate





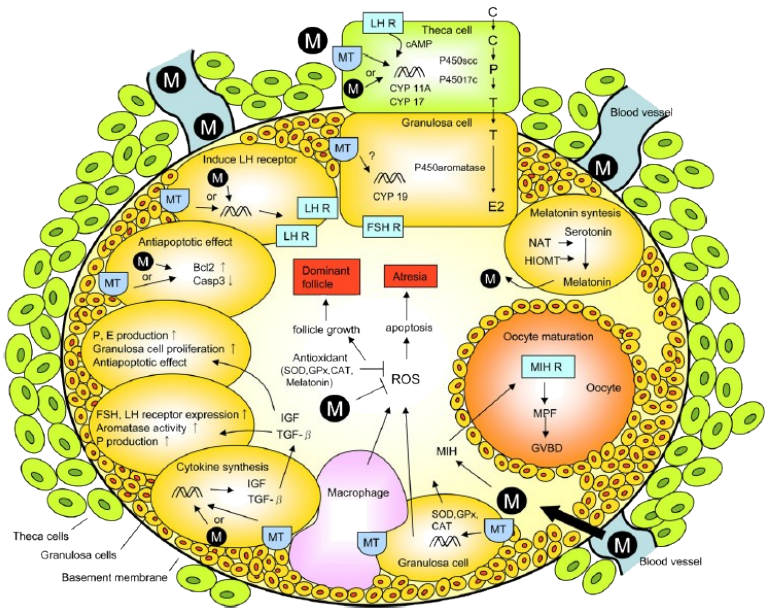
In poor quality oocyte high levels of lipids peroxidation are significantly reduce by melatonin administration

Melatonin and fertilization Rate

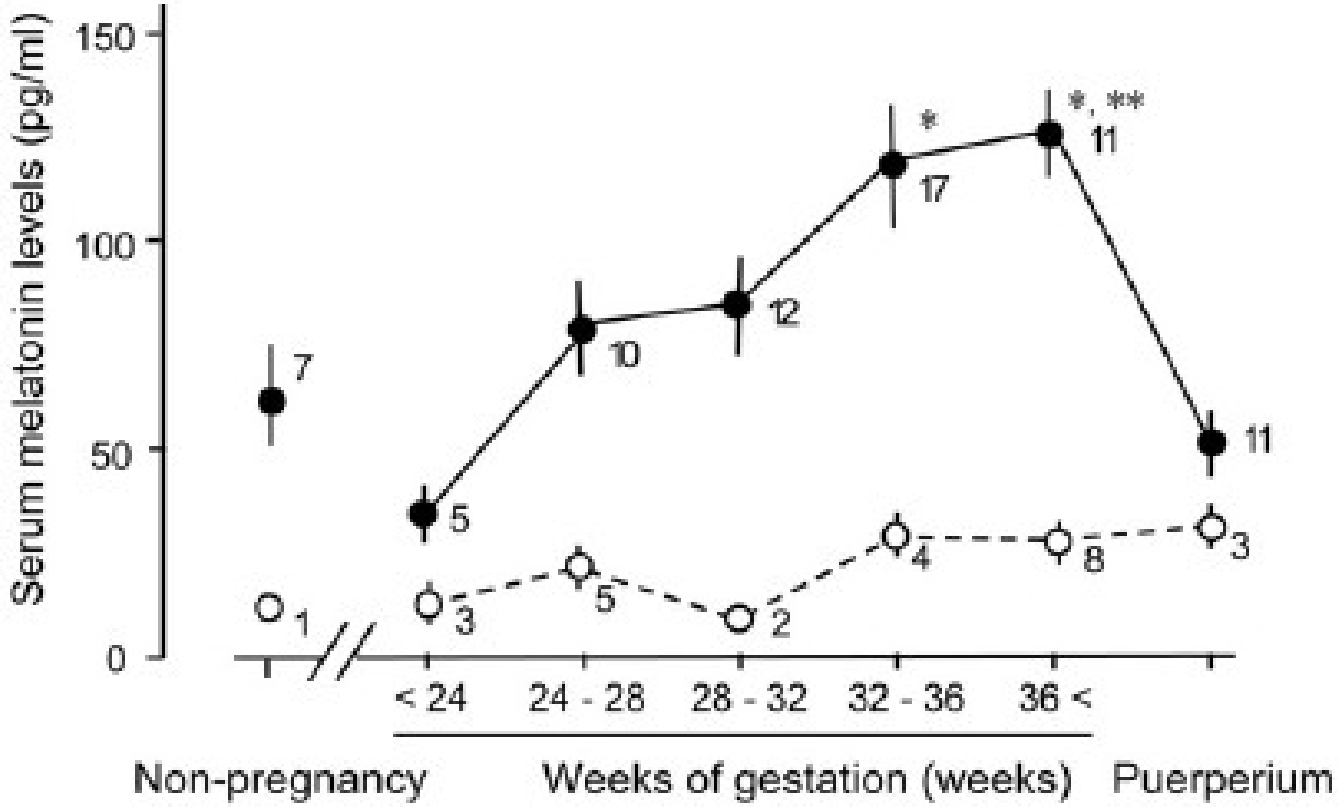
Table 1. Effects of melatonin treatment on clinical outcome of IVF-ET

	Melatonin treatment 56 cycles	No melatonin treatment 59 cycles
Fertilization rate in previous IVF-ET cycle	20.2 ± 19.0%	20.9 ± 16.5%
Fertilization rate	50.0 ± 38.0% *	22.8 ± 19.0%
Pregnancy rate	11/56 (19.6%)	6/59 (10.2%)

IVF-ET, in vitro fertilization and embryo transfer.
Values are mean ± S.E.M.
*$P < 0.01$ compared with the previous IVF-ET cycle (Mann–Whitney U-test).



MELATONIN AND THE PATHOPHYSIOLOGY OF PREGNANCY

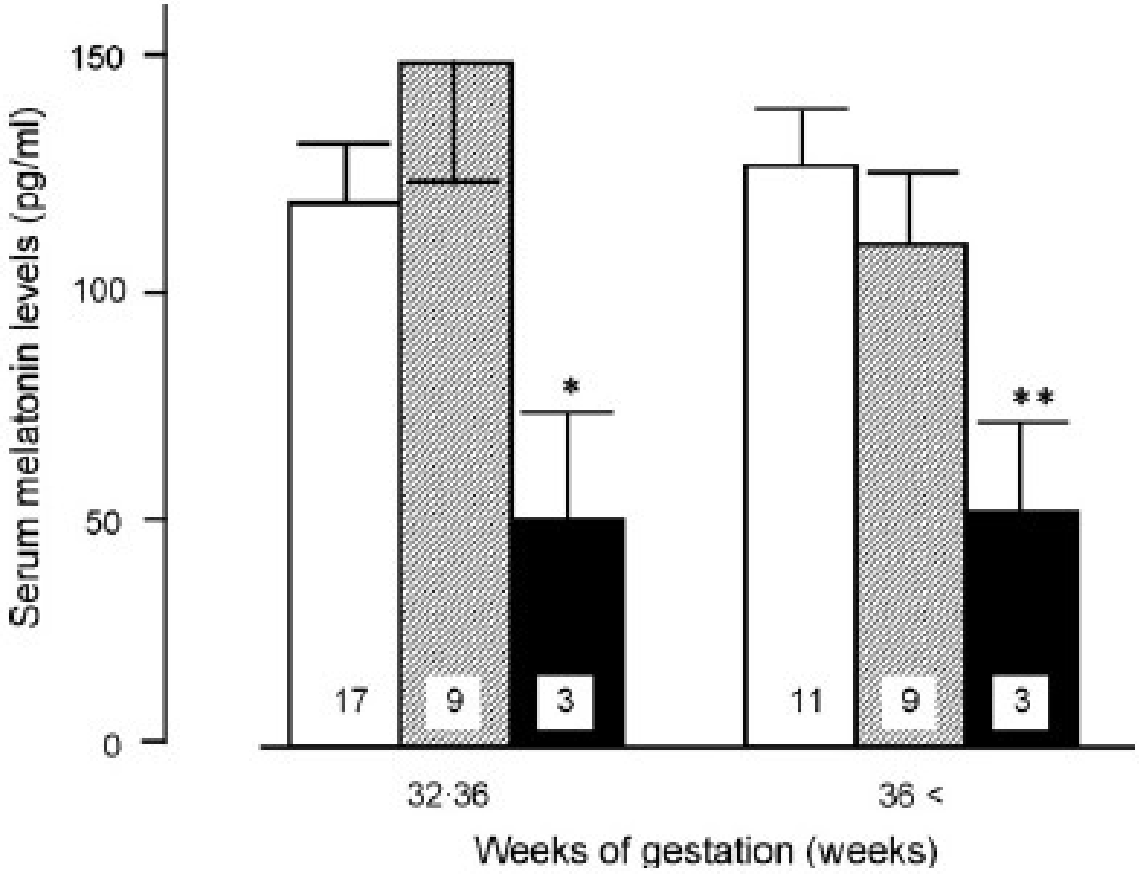


Pre-eclampsia

- Preeclampsia affects about 7% of all pregnancies.
- It is characterized by severe complications to both mother and fetus.
- Pre-eclampsia is a condition of elevated oxidative stress with high free radical generation and reduced antioxidants. The placenta is believed to be a major source of free radicals and lipid peroxidation products that are transported to distant sites, leading to systemic oxidative stress

Melatonin Pre-eclampisa

- At 33 wk of gestation, women with severe preeclampsia were found to have lower nighttime serum melatonin levels than those with mild or no preeclampsia



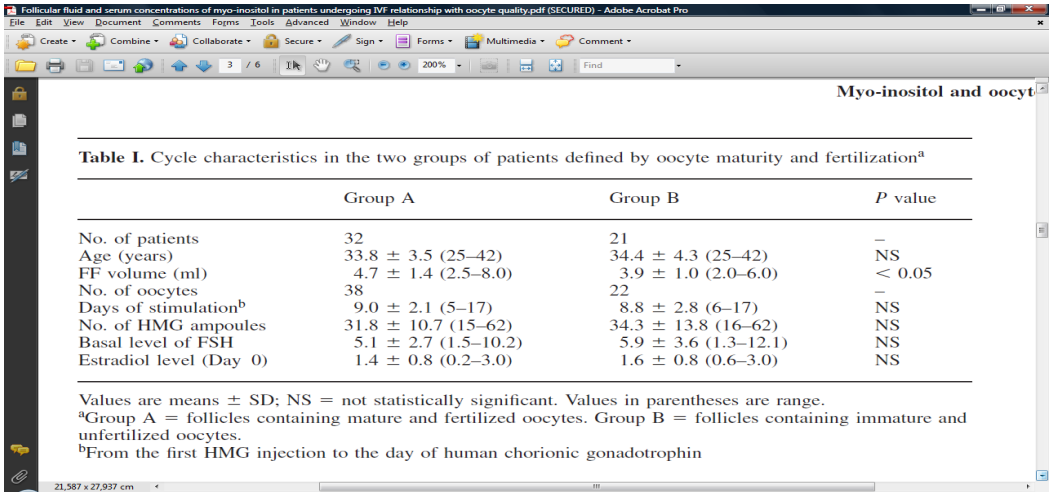
Myo-Inositol&Fc Fluid

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



Follicular fluid and serum concentrations of myo-inositol in patients undergoing IVF relationship with oocyte quality.pdf (SECURED) - Adobe Acrobat Pro

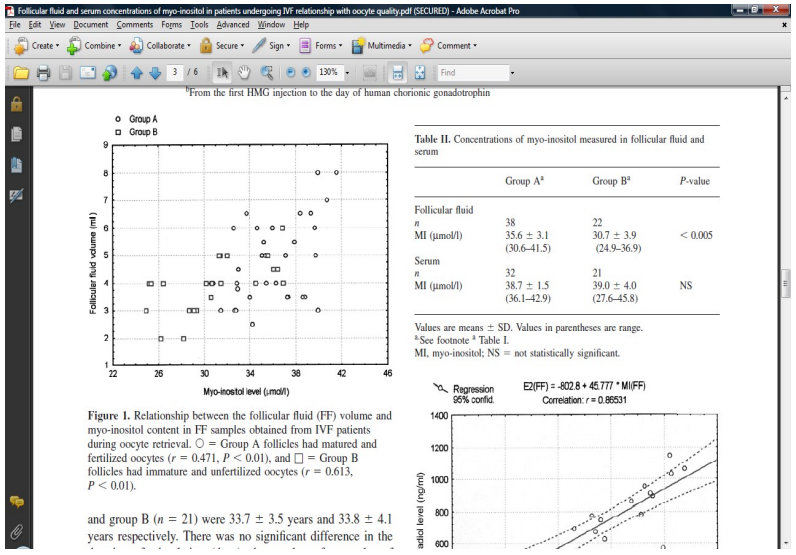
Myo-inositol and oocyt

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 range.
[a]Group A = follicles containing mature and fertilized oocytes. Group B = follicles containing immature and unfertilized oocytes.
[b]From the first HMG injection to the day of human chorionic gonadotrophin

The association between concentration of MI with FF volume, E2 and better development of the oocytes suggests that higher levels of MI in the FF may be related to the well being of the follicle and the quality of the oocyte



Follicular fluid and serum concentrations of myo-inositol in patients undergoing IVF relationship with oocyte quality.pdf (SECURED) - Adobe Acrobat Pro

[b]From the first HMG injection to the day of human chorionic gonadotrophin

Group A
Group B

Follicular fluid volume (ml)

Myo-inositol level (μmol/l)

Figure 1. Relationship between the follicular fluid (FF) volume and myo-inositol content in FF samples obtained from IVF patients during oocyte retrieval. ○ = Group A follicles had matured and fertilized oocytes ($r = 0.471$, $P < 0.01$), and □ = Group B follicles had immature and unfertilized oocytes ($r = 0.613$, $P < 0.01$).

and group B ($n = 21$) were 33.7 ± 3.5 years and 33.8 ± 4.1 years respectively. There was no significant difference in the

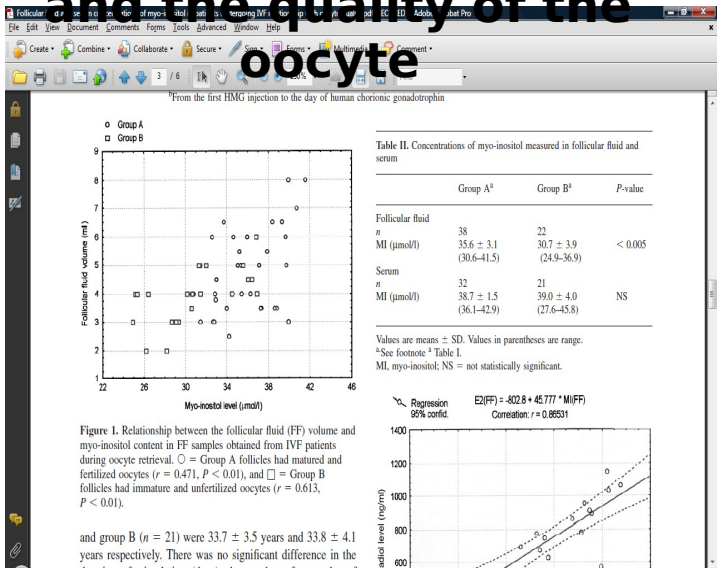
Table II. Concentrations of myo-inositol measured in follicular fluid and serum

	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.

Regression 95% confid.
E2(FF) = -802.8 + 45.777 * MI(FF)
Correlation: r = 0.86531

adiol level (ng/ml)



Follicular fluid and serum concentrations of myo-inositol in patients undergoing IVF relationship with oocyte quality.pdf (SECURED) - Adobe Acrobat Pro

[b]From the first HMG injection to the day of human chorionic gonadotrophin

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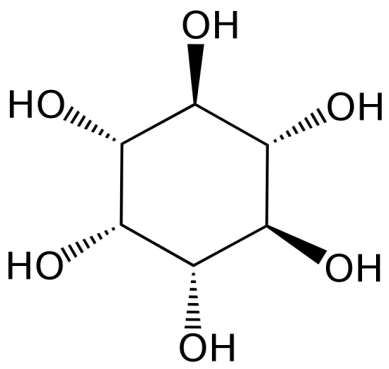
adiol level (ng/ml)

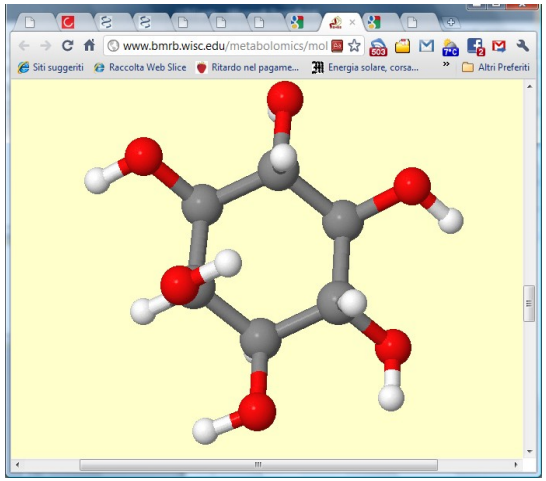
Inositol

- Inositol in PCOS was first described by Nestler (1999)

The New England Journal of Medicine



- Inositol is a 6-carbon, cyclic polyalcohol.
- It exists in nine different stereoisomers, Myo-inositol being the most abundant stereoisomer in nature.



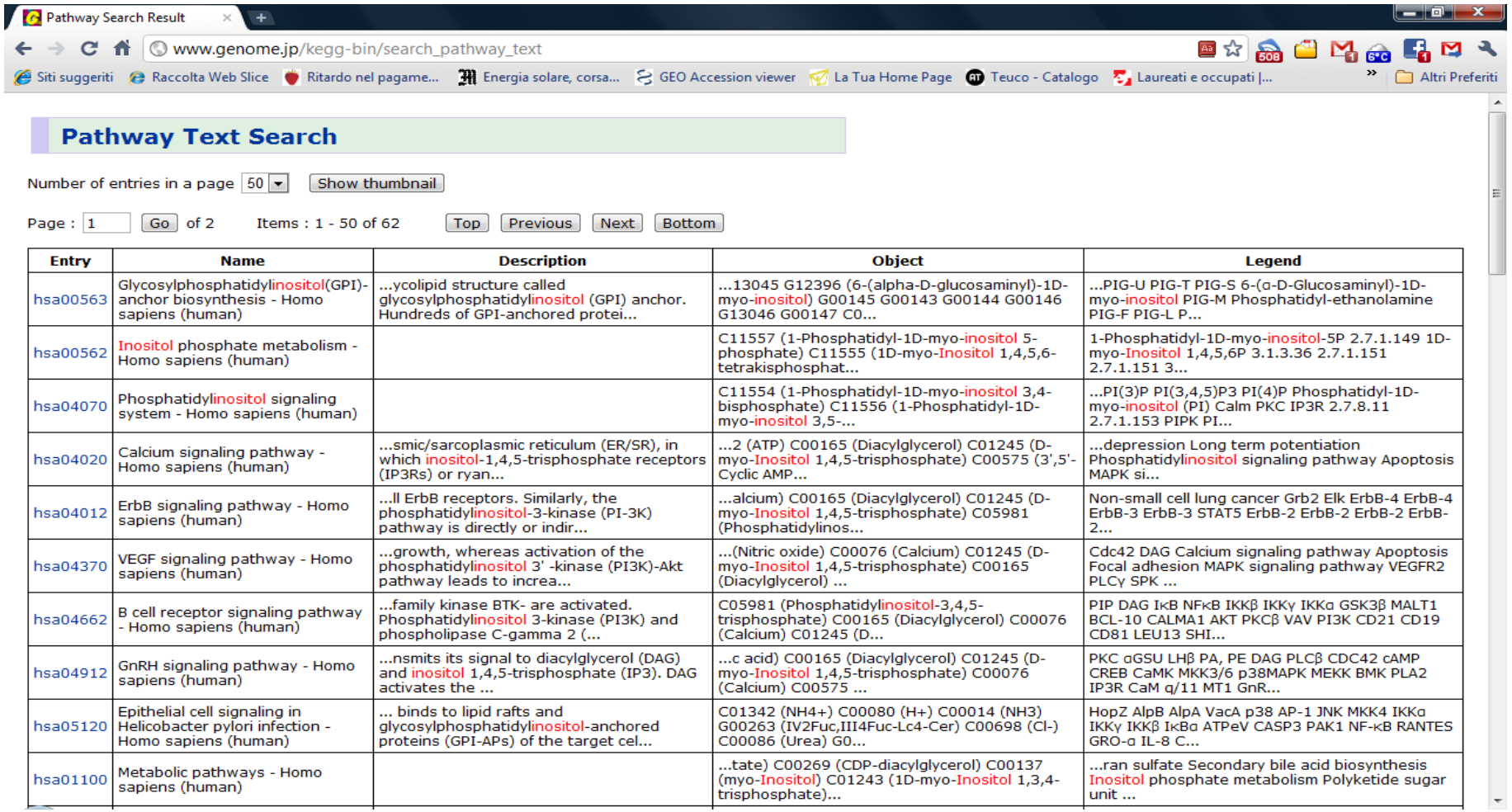
"Tratto dal Corriere della sera - Salute" - (11 Luglio 2008)

la sostanza favorisce l'ovulazione e la successiva fecondazione

Una vitamina per la fertilità

L'inositolo, che fa parte del gruppo B, sperimentato con successo nell'ovaio policistico

Why Inositol is important



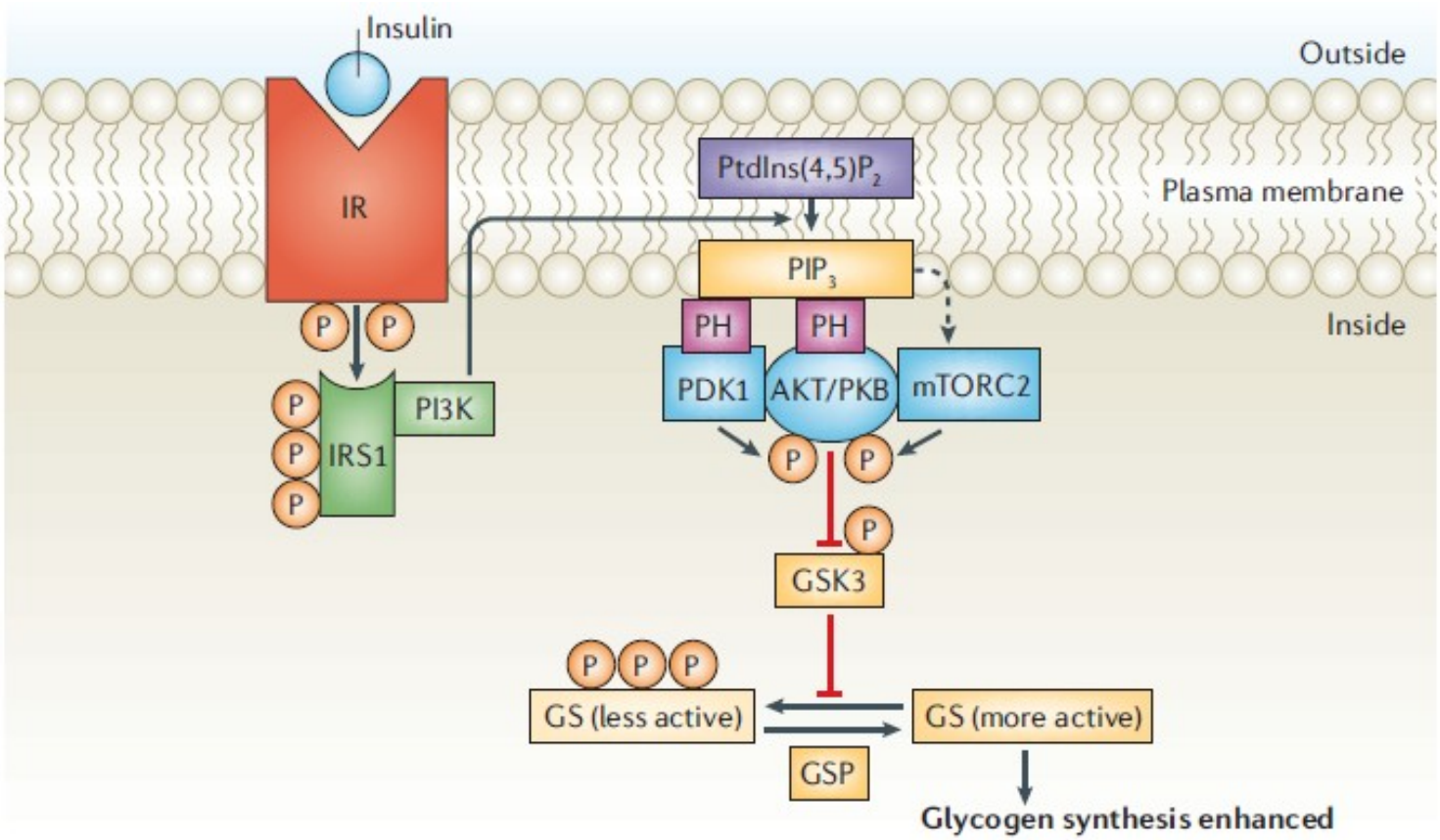
Pathway Text Search

Number of entries in a page 50 Show thumbnail

Page : 1 Go of 2 Items : 1 - 50 of 62 Top Previous Next Bottom

Entry	Name	Description	Object	Legend
hsa00563	Glycosylphosphatidylinositol(GPI)-anchor biosynthesis - Homo sapiens (human)	...ycolipid structure called glycosylphosphatidylinositol (GPI) anchor. Hundreds of GPI-anchored protei...	...13045 G12396 (6-(alpha-D-glucosaminyl)-1D-myo-inositol) G00145 G00143 G00144 G00146 G13046 G00147 C0...	...PIG-U PIG-T PIG-S 6-(α-D-Glucosaminyl)-1D-myo-inositol PIG-M Phosphatidyl-ethanolamine PIG-F PIG-L P...
hsa00562	Inositol phosphate metabolism - Homo sapiens (human)		C11557 (1-Phosphatidyl-1D-myo-inositol 5-phosphate) C11555 (1D-myo-Inositol 1,4,5,6-tetrakisphosphat...	1-Phosphatidyl-1D-myo-inositol-5P 2.7.1.149 1D-myo-Inositol 1,4,5,6P 3.1.3.36 2.7.1.151 2.7.1.151 3...
hsa04070	Phosphatidylinositol signaling system - Homo sapiens (human)		C11554 (1-Phosphatidyl-1D-myo-inositol 3,4-bisphosphate) C11556 (1-Phosphatidyl-1D-myo-inositol 3,5-...	...PI(3)P PI(3,4,5)P3 PI(4)P Phosphatidyl-1D-myo-inositol (PI) Calm PKC IP3R 2.7.8.11 2.7.1.153 PIPK PI...
hsa04020	Calcium signaling pathway - Homo sapiens (human)	...smic/sarcoplasmic reticulum (ER/SR), in which inositol-1,4,5-trisphosphate receptors (IP3Rs) or ryan...	...2 (ATP) C00165 (Diacylglycerol) C01245 (D-myo-Inositol 1,4,5-trisphosphate) C00575 (3',5'-Cyclic AMP...	...depression Long term potentiation Phosphatidylinositol signaling pathway Apoptosis MAPK si...
hsa04012	ErbB signaling pathway - Homo sapiens (human)	...ll ErbB receptors. Similarly, the phosphatidylinositol-3-kinase (PI-3K) pathway is directly or indir...	...alcium) C00165 (Diacylglycerol) C01245 (D-myo-Inositol 1,4,5-trisphosphate) C05981 (Phosphatidylinos...	Non-small cell lung cancer Grb2 Elk ErbB-4 ErbB-4 ErbB-3 ErbB-3 STAT5 ErbB-2 ErbB-2 ErbB-2 ErbB-2...
hsa04370	VEGF signaling pathway - Homo sapiens (human)	...growth, whereas activation of the phosphatidylinositol 3' -kinase (PI3K)-Akt pathway leads to increa...	...(Nitric oxide) C00076 (Calcium) C01245 (D-myo-Inositol 1,4,5-trisphosphate) C00165 (Diacylglycerol) ...	Cdc42 DAG Calcium signaling pathway Apoptosis Focal adhesion MAPK signaling pathway VEGFR2 PLCγ SPK ...
hsa04662	B cell receptor signaling pathway - Homo sapiens (human)	...family kinase BTK- are activated. Phosphatidylinositol 3-kinase (PI3K) and phospholipase C-gamma 2 (...	C05981 (Phosphatidylinositol-3,4,5-trisphosphate) C00165 (Diacylglycerol) C00076 (Calcium) C01245 (D...	PIP DAG IκB NFκB IKKβ IKKγ IKKα GSK3β MALT1 BCL-10 CALMA1 AKT PKCβ VAV PI3K CD21 CD19 CD81 LEU13 SHI...
hsa04912	GnRH signaling pathway - Homo sapiens (human)	...nsmits its signal to diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG activates the ...	...c acid) C00165 (Diacylglycerol) C01245 (D-myo-Inositol 1,4,5-trisphosphate) C00076 (Calcium) C00575 ...	PKC αGSU LHβ PA, PE DAG PLCβ CDC42 cAMP CREB CaMK MKK3/6 p38MAPK MEKK BMK PLA2 IP3R CaM q/11 MT1 GnR...
hsa05120	Epithelial cell signaling in Helicobacter pylori infection - Homo sapiens (human)	... binds to lipid rafts and glycosylphosphatidylinositol-anchored proteins (GPI-APs) of the target cel...	C01342 (NH4+) C00080 (H+) C00014 (NH3) G00263 (IV2Fuc,III4Fuc-Lc4-Cer) C00698 (Cl-) C00086 (Urea) G0...	HopZ AlpB AlpA VacA p38 AP-1 JNK MKK4 IKKα IKKγ IKKβ IκBα ATPeV CASP3 PAK1 NF-κB RANTES GRO-α IL-8 C...
hsa01100	Metabolic pathways - Homo sapiens (human)		...tate) C00269 (CDP-diacylglycerol) C00137 (myo-Inositol) C01243 (1D-myo-Inositol 1,3,4-trisphosphate)...	...ran sulfate Secondary bile acid biosynthesis Inositol phosphate metabolism Polyketide sugar unit ...

Insulin sensitizing agents



NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 7 | NOVEMBER 2006

Inositol and PCO

OVULATORY AND METABOLIC EFFECTS OF D-*CHIRO*-INOSITOL IN THE POLYCYSTIC OVARY SYNDROME

JOHN E. NESTLER, M.D., DANIELA J. JAKUBOWICZ, M.D., PAULA REAMER, M.A., RONALD D. GUNN, M.S., AND GEOFFREY ALLAN, PH.D.

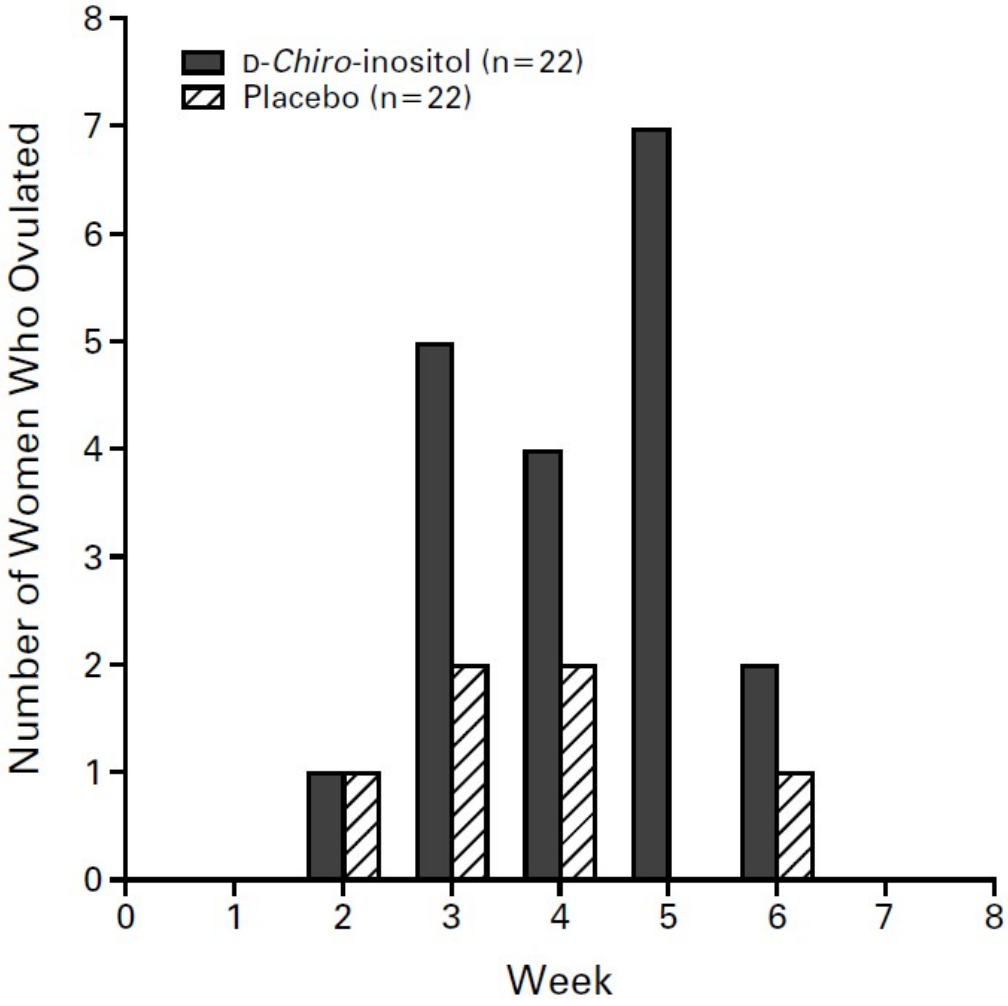
The New England Journal of Medicine

- Inositol as PCOS treatment was first described by Ne

CHARACTERISTIC	D-*CHIRO*-INOSITOL GROUP (N=22)		PLACEBO GROUP (N=22)	
	BASE LINE	AFTER D-*CHIRO*-INOSITOL	BASE LINE	AFTER PLACEBO
Age (yr)	29±6	—	26±5	—
Body-mass index	31.3±2.4	31.5±2.4	31.0±2.2	31.0±2.2
Waist-to-hip ratio	0.86±0.05	0.84±0.06†	0.84±0.08	0.85±0.08
Blood pressure (mm Hg)				
Systolic	130±7	126±7‡	131±13	128±6
Diastolic	89±5	85±6†	87±6	89±5
Plasma cholesterol (mg/dl)				
Total	209±45	192±58§	200±36	201±39
High-density lipoprotein	36±11	38±8	36±9	38±8
Low-density lipoprotein	124±36	124±7	127±35	126±27
Plasma triglycerides (mg/dl)	184±88	110±61¶	136±71	130±63
Plasma insulin during fasting (μU/ml)	35±40	22±21	38±51	42±52
Area under the plasma insulin curve (μU/ml/min)	13,417±11,572	5158±6714‖	11,371±8027	9210±7840
Plasma glucose during fasting (mg/dl)	86±12	90±19	95±21	95±24
Area under the plasma glucose curve (mg/dl/min)	13,796±2591	12,656±4316	14,115±2462	14,014±3089
Serum progesterone (ng/ml)	0.7±0.4	0.6±0.2	0.8±0.4	0.7±0.2
Serum testosterone (ng/dl)	90±47	61±33**	80±43	79±39
Serum free testosterone (ng/dl)	1.1±0.8	0.5±0.5††	0.8±0.4	0.8±0.4
Serum androstenedione (ng/dl)	201±69	173±50	180±51	186±53
Serum 17β-estradiol (ng/dl)	8.8±4.0	8.9±4.4	9.6±4.1	10.8±9.4
Serum dehydroepiandrosterone sulfate (μg/dl)	519±229	274±91‡‡	459±177	421±179
Serum sex hormone–binding globulin (μg/dl)	2.5±1.0	4.8±2.2**	2.6±0.9	2.8±0.9

Ovulation Induction

- 30% of the patients showed restored ovulation in 3 weeks
- 50% in 4weeks



Myo-inositol and oocyte quality

Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial

Enrico Papaleo, M.D.,[a] *Vittorio Unfer, M.D.,*[b] *Jean-Patrice Baillargeon, M.D.,*[c] *Francesco Fusi, M.D.,*[a] *Francesca Occhi, M.D.,*[a] *and Lucia De Santis, B.Sc.*[a]

[a] IVF unit, Gynecologic-Obstetric Department, Istituto di Ricovera e Cura a Carattere Scientifico, San Raffaele Hospital, Vita-Salute University, Milan, Italy; [b] Gynecology Association Unfer Costabile (A.G.UN.CO.), Obstetrics and Gynecology Center, Rome, Italy; and [c] Department of Medicine, Université de Sherbrooke, Sherbrooke, Canada.

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TABLE 2

Oocyte maturity and embryo score in patients who received *myo*-inositol plus folic acid (group A; n = 30) or folic acid alone (group B; n = 30).

Characteristic	Group A	Group B	*P* value
No. of retrieved oocytes	8.76 ± 4.12	9.37 ± 3.31	NS
No. of MII oocytes	7.14 ± 3.49	7.07 ± 3.04	NS
MII/total oocytes retrieved (%)	0.82 ± 0.11	0.75 ± 0.15	NS (.06)
No. of mmature oocytes (GV-DEG)	1.03 ± 0.87	1.63 ± 1.01	.02
Fertilization rate	0.79 ± 0,19	0.74 ± 0,18	NS
Cleavage rate	0.88 ± 0.07	0.87 ± 0.1	NS
No. of embryos transfered	2.07 ± 0.75	1.86 ± 0.85	NS
Embryo score grade 1 (%)	0.86 ± 0.83	0.81 ± 0.83	NS
Embryo score grade 2 (%)	0.93 ± 0.80	0.74 ± 0.66	NS
Embryo score grade 3 (%)	0.31 ± 0.54	0.30 ± 0.47	NS

Note: Values are mean ± SD. The embryos were scored according to the criteria established by Veeck (26). DEG = degenerated occytes; MII = metaphase II; NS = not significant; GV = germinal vesicle.

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

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

Myo-inositol&ovarian stimulation protocols

- PCOS patients have an increased risk of going trough 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
TSH (mIU/L)	1.56 ± 0.95	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

Note: Values are mean ± SD. NS = not significant.

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

Myo-inositol

PCOS

Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction

Gynecological Endocrinology, December 2007; 23(12): 700–703

ENRICO PAPALEO[1], VITTORIO UNFER[2], JEAN-PATRICE BAILLARGEON[3], LUCIA DE SANTIS[1], FRANCESCO FUSI[1], CLAUDIO BRIGANTE[1], GUIDO MARELLI[1], ILARIA CINO[1], ANNA REDAELLI[1], & AUGUSTO FERRARI[1]

[1]*IVF Unit, Gynaecological-Obstetric Department, IRCCS San Raffaele Hospital, Vita-Salute University, Milan, Italy,* [2]*AGUNCO Obstetrics and Gynecology Centre, Rome, Italy, and* [3]*Department of Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada*

Table I. Clinical and biochemical features of the patients.

	Baseline	After myo-inositol
Age (years)	32 ± 4	
Body mass index (kg/m^2)	28.5 ± 2.4	
Follicle-stimulating hormone (mUI/ml)	4.5 ± 2.8	
Luteinizing hormone TSH (mUI/ml)	6.3 ± 3.1	
Prolactin (ng/ml)	19.1 ± 2.7	
Thyroid-stimulating hormone	1.78 ± 0.85	
Serum progesterone (ng/ml)	1.8 ± 0.7	10.5 ± 1.8
Serum total testosterone (ng/dl)	95.6 ± 8.5	45.2 ± 6.7*
Serum free testosterone (ng/dl)	1.0 ± 0.8	0.38 ± 0.1†
Serum androstenedione (ng/dl)	230 ± 35	205 ± 28

Significant difference compared with baseline: *$p = 0.003$; †$p = 0.005$.

Table II. Outcome of treatment with myo-inositol.

No. of patients treated	25
No. of patients with menstrual cycle after treatment (% of patients)	22 (88)
No. of patients with restored monthly ovulation (% of patients)	18 (72)
No. of pregnancies	10
No. of pregnancies/no. of treated patients (%)	40
No. of pregnancies/no. patients with restored monthly ovulation (%)	55
No. of abortions (% of pregnancies)	2 (20)
Multiple pregnancy	0

Myo-inositol plus Melatonin

European Review for Medical and Pharmacological Sciences 2010; 14: 555-561

Effect of the treatment with myo-inositol plus folic acid plus melatonin in comparison with a treatment with myo-inositol plus folic acid on oocyte quality and pregnancy outcome in IVF cycles. A prospective, clinical trial

P. RIZZO, E. RAFFONE, V. BENEDETTO

Table II. Oocyte maturity and embryo score in patients who received Inofolic plus (group A; n=32) or Inofolic (group B; n=33).

Variable	Group A (Inofolic plus) (n = 32)	Group B (Inofolic) (n = 33)	*p*
No. of oocytes retrieved	7.88 ± 1.76	7.67 ± 1.88	NS
No. of mature oocytes (MII)	6.56 ± 1.64	5.76 ± 1.56	0.047
No. of immature oocytes (GV, degenerated oocytes)	1.31 ± 0.74	1.90 ± 0.68	0.001
Fertilization rate	0.82 ± 0.19	0.79 ± 0,23	NS
Cleavage rate	0.89 ± 0.18	0.87 ± 0,23	NS
No. of embryos transferred	2.03 ± 0.69	1.91 ± 0.58	NS
No. of top-quality embryos transferred (score 1 and 2)	1.69 ± 0.64	1.24 ± 0.75	0.01
Embryo score grade 1	0.72 ± 0.46	0.63 ± 0.50	NS
Embryo score grade 2	1.13 ± 0.49	0.94 ± 0.61	NS
Embryo score grade 3	0.50 ± 0.51	0.58 ± 0.61	NS
Embryo score grade 4	0.03 ± 0.18	0.27 ± 0.52	0.01

Thanks!