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中国优生科学协会
China Healthy Birth Science Association

How Polycystic Ovary Syndrome may affect outcomes with ART

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Center for Women's Reproductive Care

Consensus meetings on PCOS

- NIH 1991 (Diagnosis)
- Rotterdam 2004 (Diagnosis) – ESHRE/ASRM
- Thessaloniki 2007 (Infertility treatment) – ESHRE/ASRM
- Amsterdam 2010 (Medical management) - ESHRE/ASRM
- NIH 2012 – Diagnosis and research agenda

Various phenotypes possible in the diagnosis of PCOS

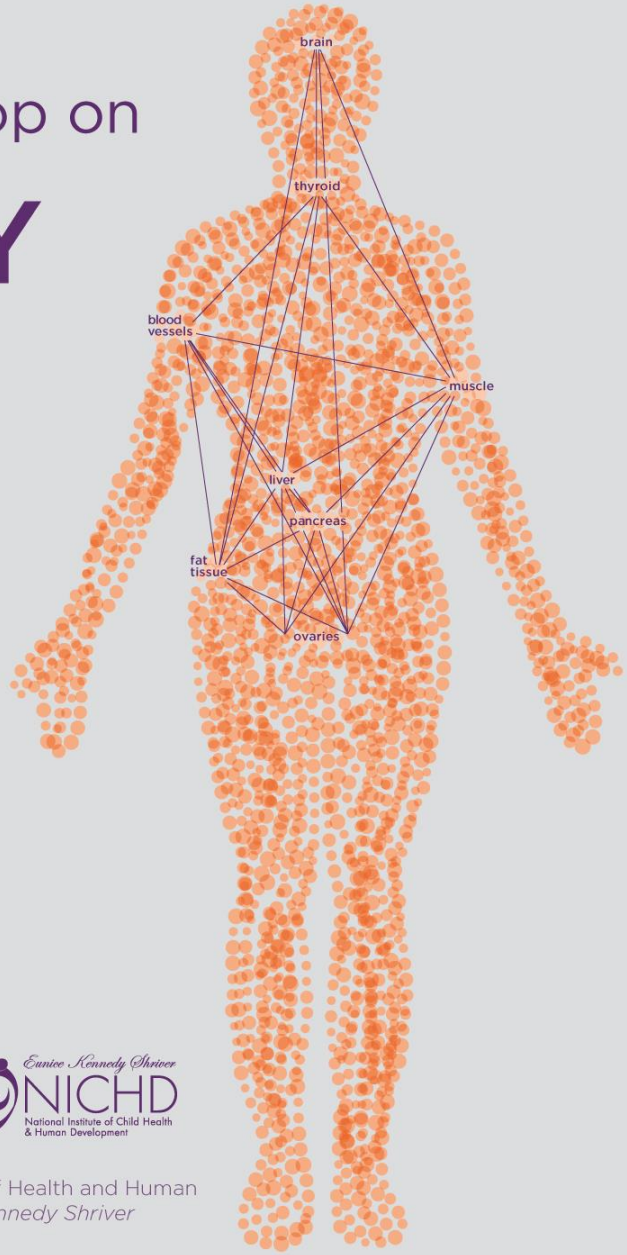
- "NIH" definition
- Rotterdam (ESHRE/ASRM)
- AEPCOS

NIH Office of Disease Prevention
Evidence-based Methodology Workshop on

POLYCYSTIC OVARY SYNDROME (PCOS)

DECEMBER 3-5, 2012

Natcher Conference Center
National Institutes of Health, Bethesda, Maryland



INFORMATION/REGISTRATION
prevention.nih.gov
prevention@mail.nih.gov
1-888-644-2667

Office of Disease Prevention
National Institutes of Health

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Presented by the National Institutes of Health, Department of Health and Human Services, NIH Office of Disease Prevention and the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development

NIH Workshop Panel Recommendations

- "The name "PCOS" is a distraction and an impediment to progress"
- "The right name will enhance recognition of this major public health issue for women…"
- No new name suggested

NIH Workshop Panel recommendations

Diagnosis

- Recommend "maintaining the broad inclusionary diagnostic criteria of Rotterdam"
- "Specific phenotypes should be reported explicitly in all research studies and clinical care"

"Rotterdam" definition of PCOS

- Polycystic Ovaries on Ultrasound
- Menstrual irregularity
- Hyperandrogenism (clinical or biochemical)
- No other competing diagnoses
- Only requires 2/3 criteria: many phenotypes possible (A-D)
  Fertil steril 2004; 81: 18
  Human Reprod 2004; 19: 41

Prevalence of PCOS in China (15942 in 10 provinces) by Rotterdam criteria ~ 6%

A = 29%

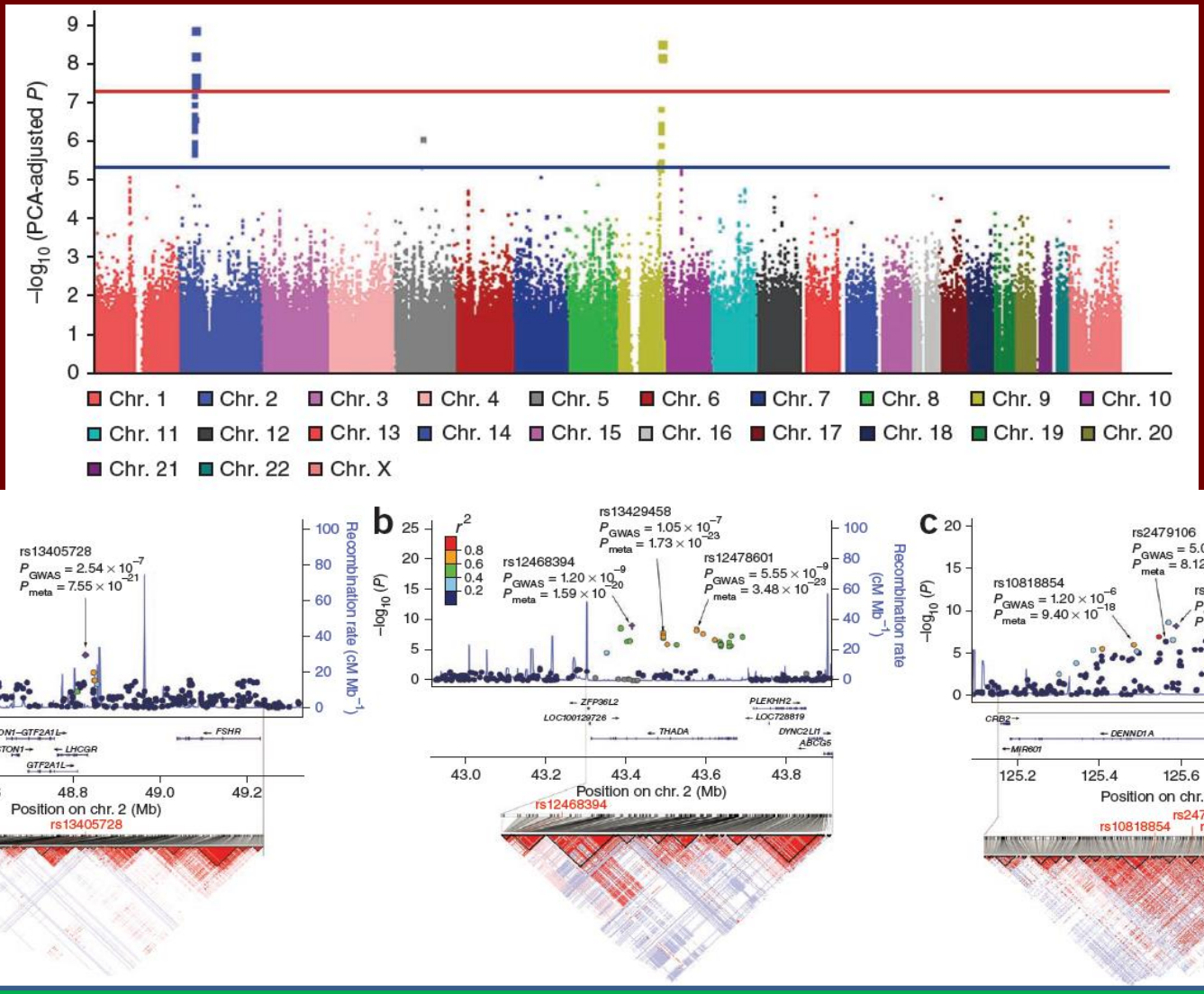
B = 19%

C = 37%

D = 15%

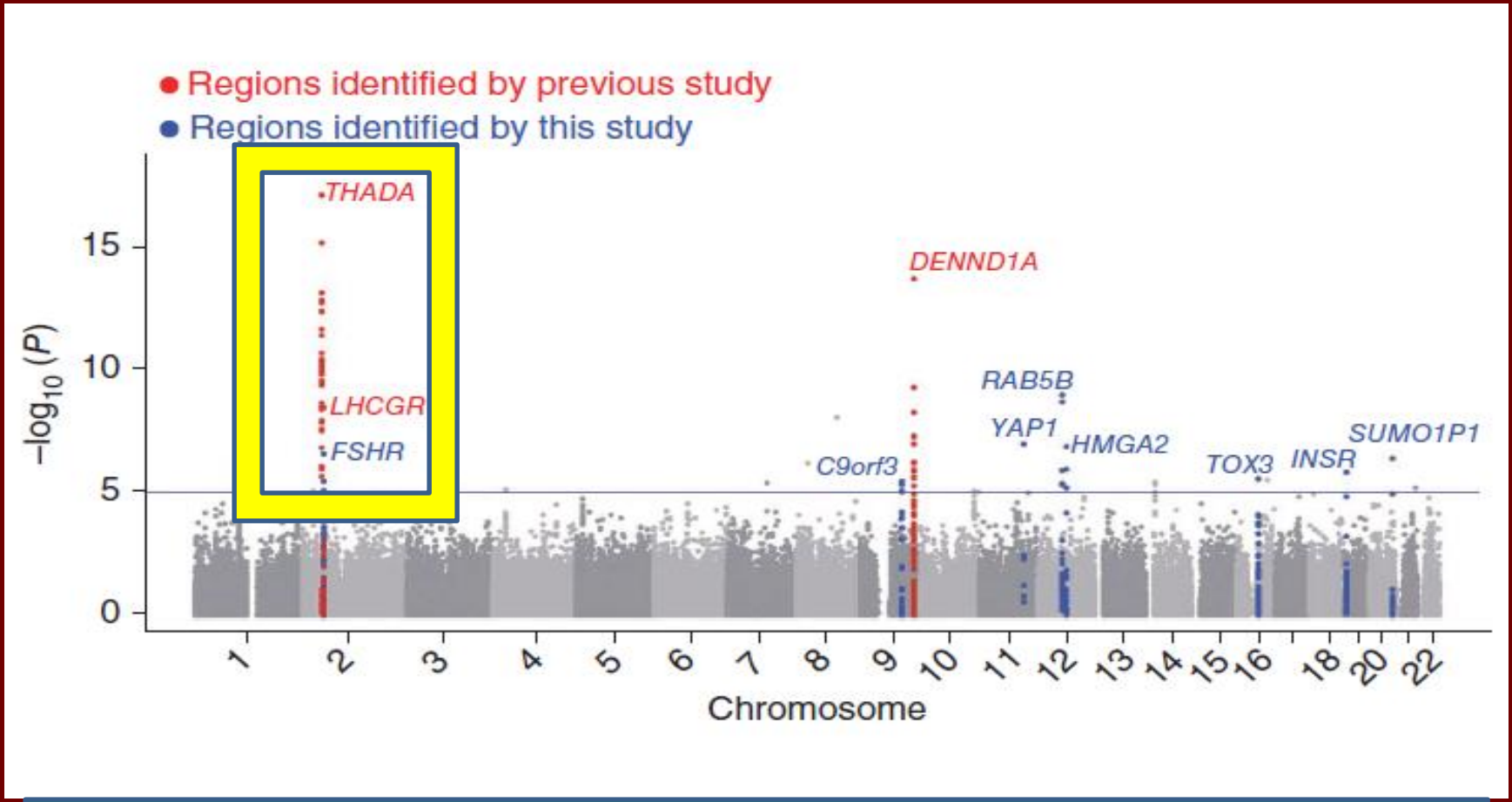
Li R and Qiao J. Human Reproduction 2013; 28: 2562-69

GWAS from Han Chinese showing susceptibility loci on 2p16.3, 2p21, 9q33.3



Chen Zi-Jiang. Nature Genetics 2010; doi: 10.1038/ng.732

GWAS 2 combination 1+2= 8226 cases; 7578 controls (not a very hyperandrogenic cohort): 8 risk loci



Shi Yongyong. Nature Genetics 2012; doi:10.1038/ng.2384

Family-based analysis of susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3

Han Zhao[1,2,3], Xinghua Xu[1,2,3], Xiuye Xing[1,2,3], Jianfeng Wang[1,2,3], Lin He[4,5,6], Yongyong Shi[6], Yuhua Shi[1,2,3], Yueran Zhao[1,2,3], and Zi-Jiang Chen[1,2,3,*]

METHODS: A total of 276 family trios (828 participants) having a proband with PCOS were included in the family-based study. The transmission disequilibrium test (TDT) was used to analyze the association between PCOS and five SNPs rs13429458, rs12478601, rs13405728, rs10818854 and rs2479106 in three susceptible loci 2p16.3, 2p21 and 9q33.3.

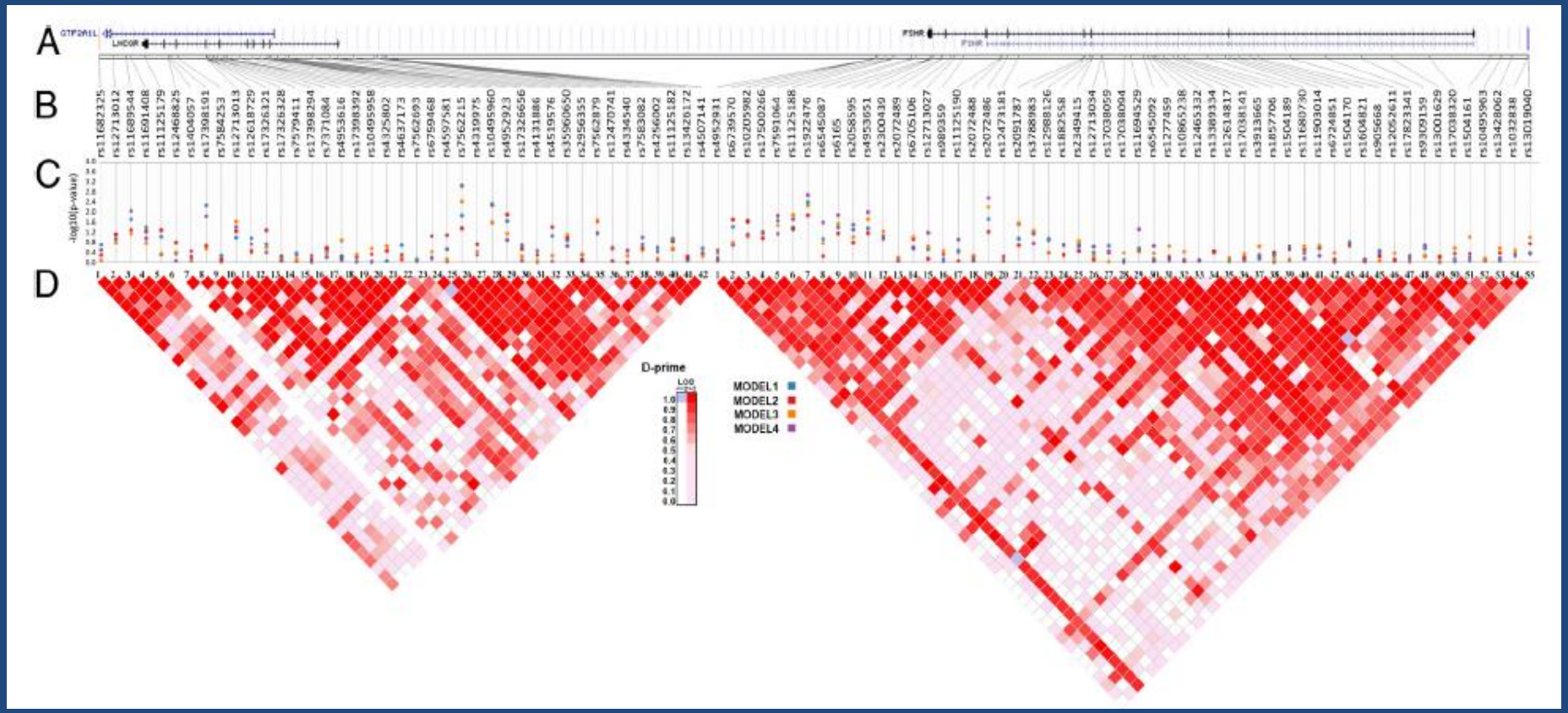
RESULTS: A positive association was observed for the SNP rs13429458 ($P = 3.74 \times 10^{-5}$).

CONCLUSIONS: TDT confirms that SNP rs13429458, in the *THADA* gene, is significantly associated with risk of PCOS. This family-based analysis enhances our previous case–control GWAS and provides further support for the role of susceptibility loci in PCOS.

Human Reproduction, Vol.27, No.1 pp. 294–298, 2012

Fine mapping of 2p16.3 (LHCGR, FSHR) PCOS (905)of European ancestry (956 con)

dark red: strong Linkage Disequilibrium



Muthgarasan P. J Clin Endocrinol Metab 2013; 98: E185-E190

AMH and ultrasound in various Phenotypes

	Number	BMI	Total T ng/mL	DHEAS µg/mL	AMH Ng/mL	FNPO	Ovarian Size c.c.
Classic - Anovulatory PCOS A/B	78	28.8 ± 7*^^	79 ± 19*^^	2.8 ± 1^^	10.8 ± 4.7**^^	33 ± 6**	10.1 ± 2.3**
Ovulatory PCOS C	20	25.5 ± 5	69 ± 18^^	3 ± 1.2^^	5.5 ± 1.8	29 ± 5	8.1 ± 2.5
Normoandrogenic PCOS D	15	25 ± 6	43 ± 17	1.8 ± 0.6	5.4 ± 2.5	30 ± 6	9.3 ± 3.4

Carmina and Lobo. Endocrine Practice, 2015

AMH is only helpful in "classic" patients while FNPO is helpful in all phenotypes

ROC analyses	Anovulatory PCOS	Ovulatory PCOS	Normoandrogenic PCOS	Specificity for diagnosis of PCOS
AMH > 4.7 ng/mL	91%	50%	53%	96%
FNPO >22	92.3%	95%	93%	85%
Ovarian volume >8cc	72%	50%	67%	91%

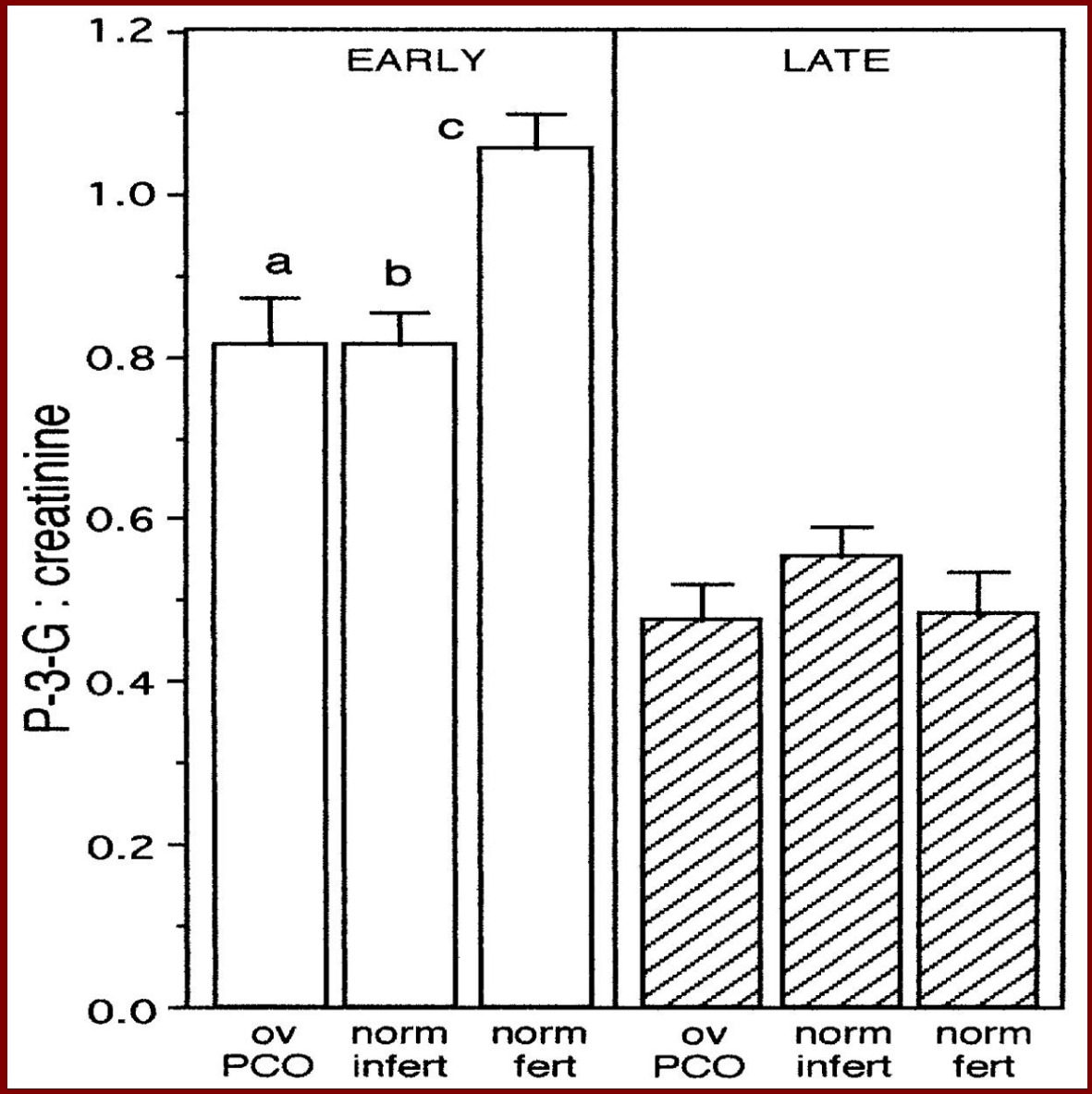
Carmina and Lobo. Endocrine Practice, 2015

Infertility in PCOS: nature of the problem

- "Classic" patients: anovulation is the norm, although spontaneous ovulations and pregnancies may occur sporadically. Represents majority of all PCOS
- "Ovulatory" PCOS – highly variable prevalence: 2.4% (Chae 2008) – 40% (Carmina 2007); 37% in China: Is fertility impacted?

Subfertility in Ovulatory PCOS

- Ovulatory PCOS – less fertile related to higher LH and FAI (Eden J. Clin Endocrinol 1989; 30: 77-82
- "PCO" over-represented among infertility patients including those with ovulatory function (Kousta E. Human Reproduction 1999; 14: 2720)
- Evidence for early luteal phase deficiency in progesterone in Ovulatory PCOS (Josph-Horne R. Human Reproduction 2002; 17: 1459-63)

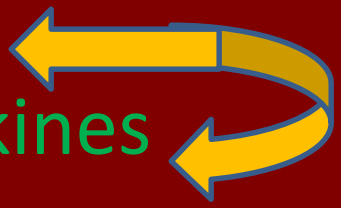


Joseph-Horne, R. et al. Hum. Reprod. 2002 17:1459-1463

Human Reproduction

What causes anovulation in PCOS? Candidates:

- Androgen
- Insulin resistance
- BMI – obesity/cytokines

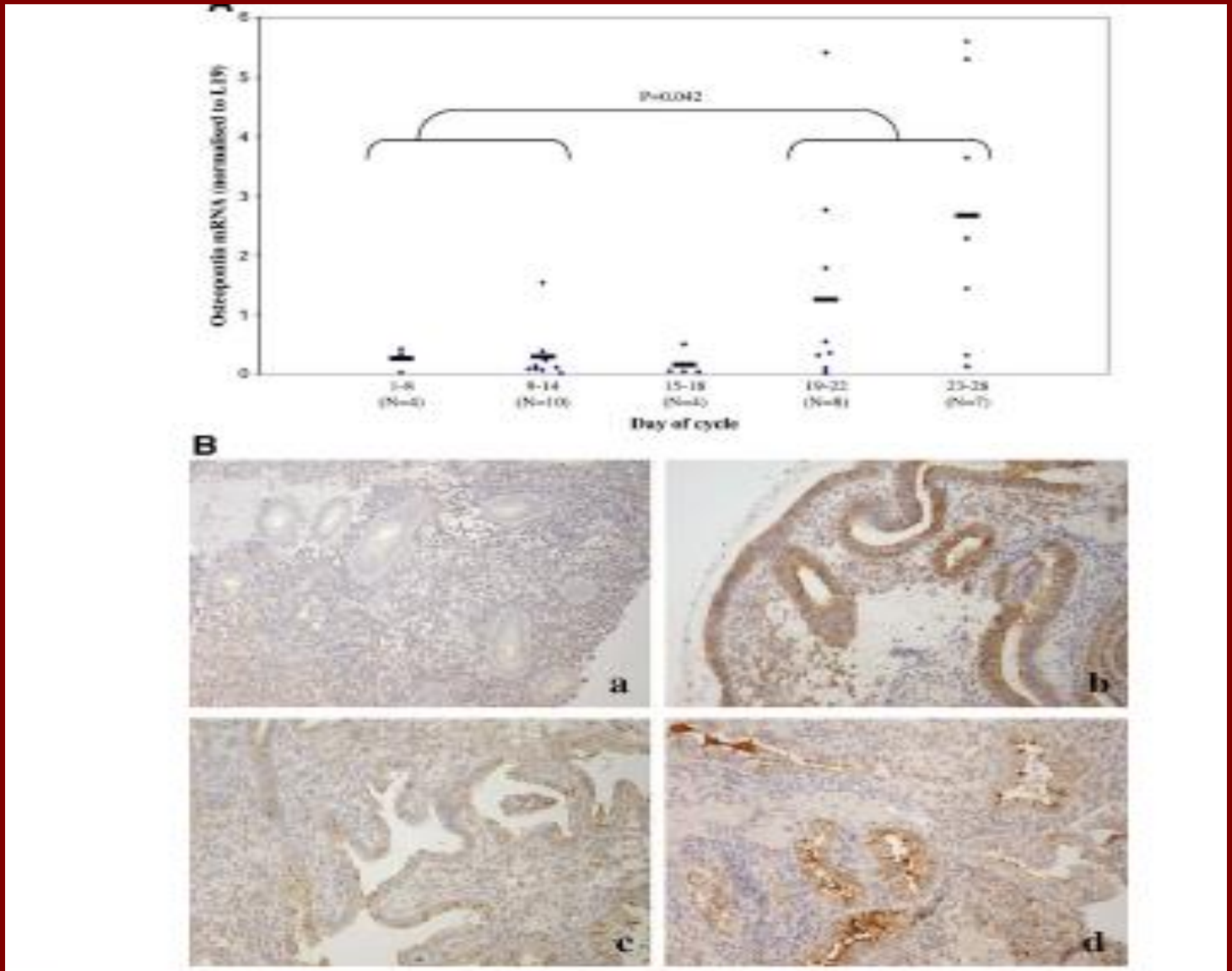


- Inherent ovarian characteristics (morphology/AMH)
- Inherent dysfunction of hypothalamic pituitary axis (GnRH/LH/FSH) ??? No definitive data except suggestion by GWAS

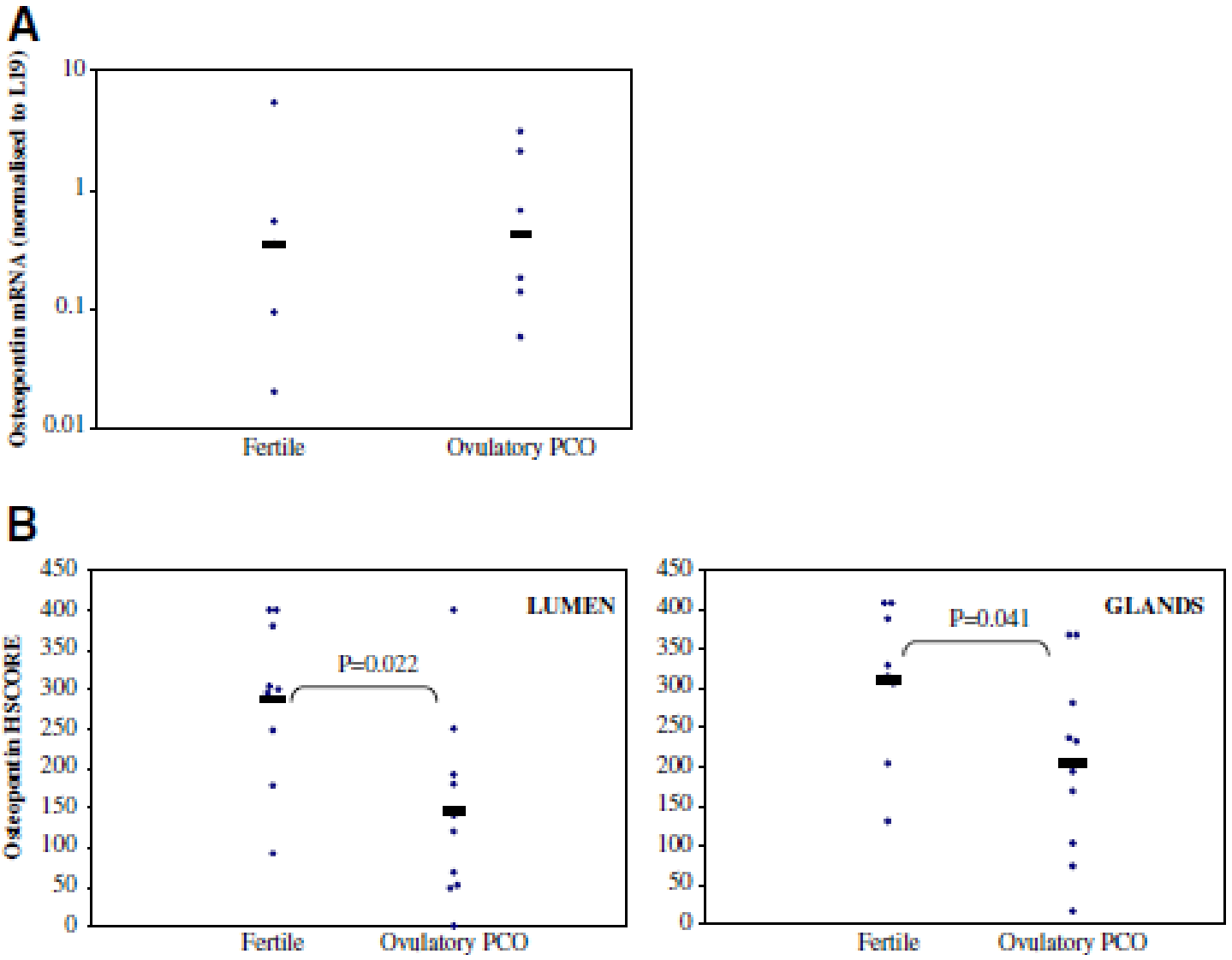
Suggestions of endometrial defects in women with PCOS

- Data a little confused based on inclusion of various phenotypes of PCOS
- Increased androgen receptor levels
  Apparao KB. Biol Reprod 2002;66:297-304
- Decreased HOXA-10 mRNA during implantation
  Cermik D. J Clin Endocrinol Metab 2003; 88:238-43
- Decreased expression of αvβ3 (?)
  Apparao 2002

Increased endometrial osteopontin expression during "Window of Implantation" (ligand for αvβ integrin 3)



Endometrial defects (decreased osteopontin) with isolated “PCO”: Potential abnormal cell-cell adhesion



DuQuesnay. Endometrial defects in isolated PCO. Fertil Steril 2009.

Consensus on Infertility treatment related to Polycystic Ovary Syndrome

- Thessaloniki ESHRE/ASRM meeting:
  Human Reproduction 23: 462-477 2008
  Fertility and Sterility 89: 505-522, 2008
- Sections:
  Lifestyle, Clomiphene, Gonadotropins,
  Laparoscopic ovarian surgery, IVF

Indication for IVF in PCOS

- Failure to conceive after several cycles of ovulation induction
- Difficult to manage cases of ovulation induction/hyperstimulation
- Other co-existing factors

Oocytes in PCOS

Are there really any abnormalities – if so, does this apply to all women with "PCOS"?

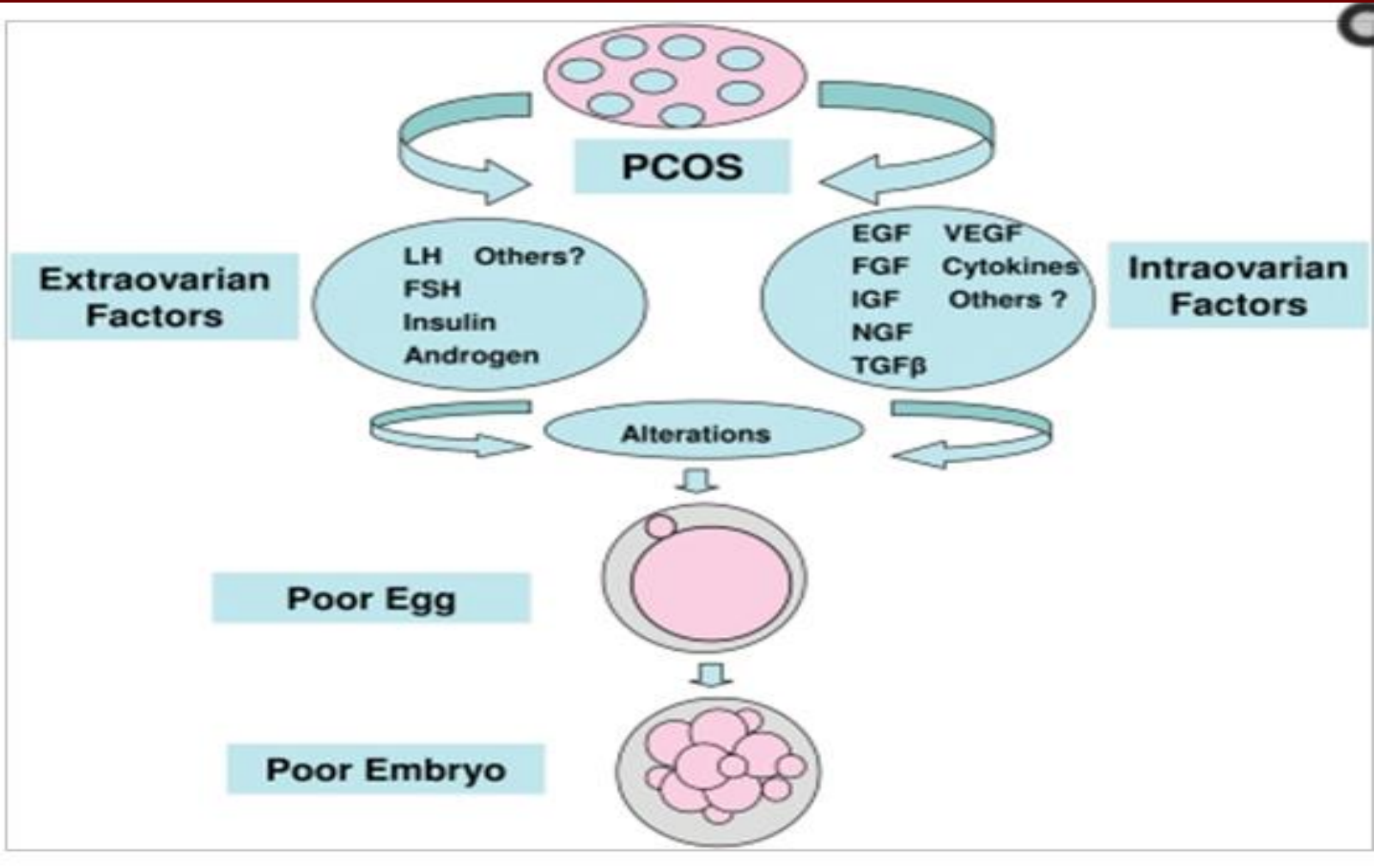
Steroid environment in small follicles 5-8 mm by LC-MS/MS

Follicular fluid steroid concentrations (in micrograms per liter) and steroid product-to-precursor concentration ratios in women with PCOS and in regularly menstruating women during the follicular phase of the menstrual cycle.

	PCOS (n = 27)	Controls[a] (n = 21)	*P* value[b]
Pregnenolone (5P)	56 (13.1–131)	52 (9.2–100)	.49
17OHpregnenolone (17-OH5P)	65 (14.3–124)	32 (4.4–82.1)	<.0001
17-OHprogesterone (17-OHP)	206 (45.1–696)	180 (59–313)	.17
DHEA	154 (36.2–263)	86 (26.8–197)	<.0001
Androstenedione (A)	769 (193–1,310)	424 (164–992)	.0003
T	27 (8.6–47)	18 (6.0–71)	.024
Androstandione	3.6 (0.4–11)	2.0 (0.5–7.2)	.024
Total androgens	991 (240–1,537)	534 (221–1,104)	<.0001[b]
Estrone (E_1)	11 (2.1–36)	34 (3.2–143)	.002
E_2	11 (0.3–145)	32 (1.2–588)	.032
Estriol	0.3 (0.07–2.8)	0.5 (0.08–10.9)	.028
Total estrogens	25 (3.6–183)	77 (5.6–670)	<.006[c]
Estrogens/androgens	0.028 (0.004–0.156)	0.11 (0.01–2.66)	.0004[c]
17-OH5P/5P (17-OHase) (CYP17)[e]	1.13 (0.80–1.88)	0.60 (0.15–1.13)	<.001
17-OHP4/17-OH5P (3βHSD)	3.45 (2.05–5.61)	6.21 (2.20–30.6)	.0011
DHEA/17-OH5P (17,20-lyase) (CYP17)	2.66 (1.67–4.31)	3.08 (2.21–7.81)	.032
Total androgens / 5P[d]	17.3 (7.9–44.2)	10.6 (2.5–68.2)	.0047
E_1/A (CYP19)[f]	0.014 (0.005–0.067)	0.067 (0.006–0.570)	<.001
E_2/T (CYP19)	0.455 (0.01–4.87)	1.54 (0.034–85.47)	.032
11-deoxycorticosterone	5.4 (1.8–16)	4.1 (1.6–6.6)	.007
Cortisol	23 (5.7–90)	17 (3.8–57)	.030
Cortisone	40 (24.8–58)	32 (18–49)	.004

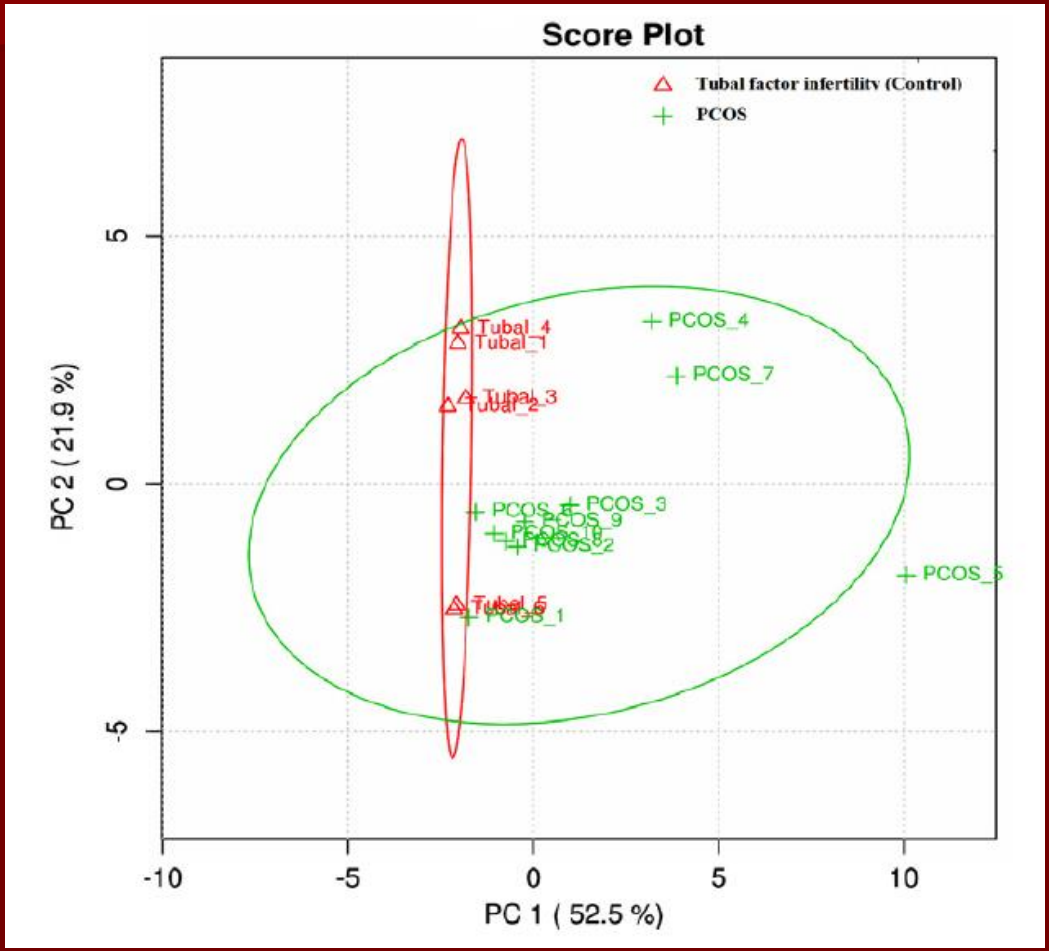
Naessen T. Fertil Steril 2010; Feb 18

Extra and Intra Ovarian Factors in PCOS affecting oocytes and embryos



Qiao J, Feng HL. Human Reprod Update 2011; 17: 17-33

NMR spectroscopy of FF: Oocyte quality affected by hypothesized decreased availability of glucose by defective transport

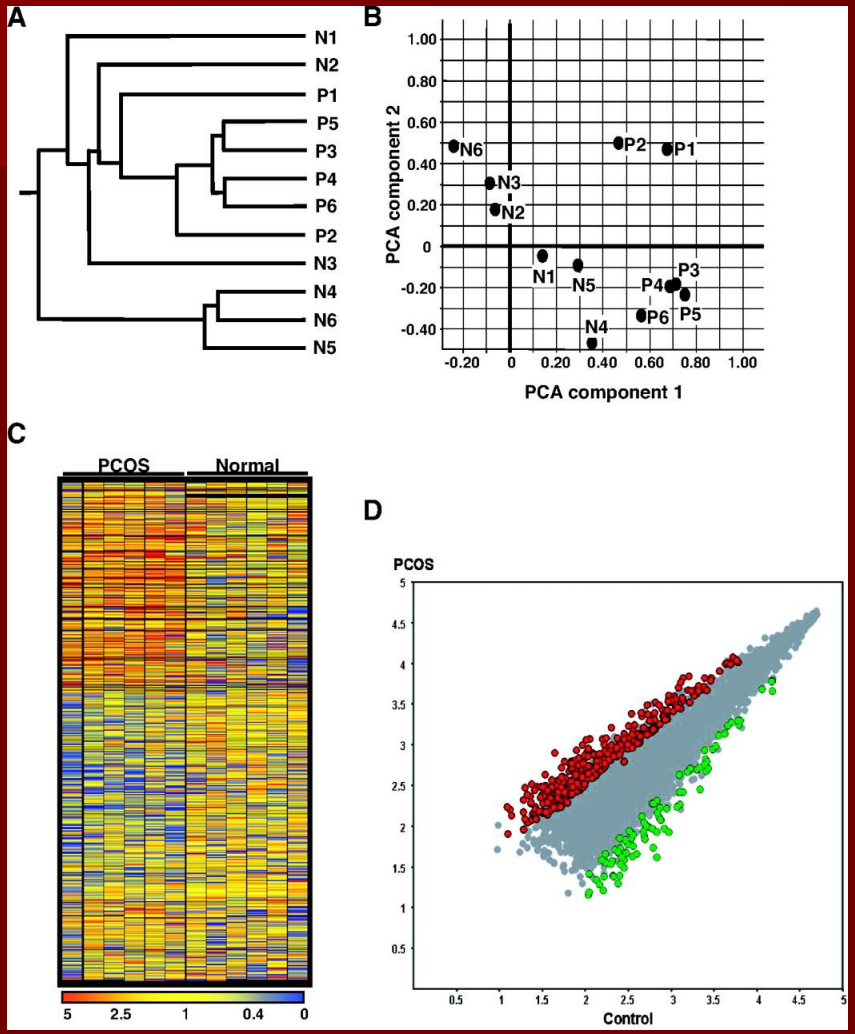


Arya BK. Medical Hypotheses 2012; 78: 475-8

Aberrant expression of growth expression factors in oocytes from women with PCOS

- Delayed or reduced GDF-9 mRNA in PCOS and PCO oocytes
  Teixeira Filho FL. J Clin Endocrinol Metab 2002; 87: 1337-44
- Decreased GDF-9 expression in cumulus granulosa cells
  Zhao SY. Fertil Steril 2009; April 17
- Decreased expression of GDF9 and BMP15 in mature oocytes in PCOS
  Wei LN. Zhonghua Fu Chan Ke Za Zhi. 2012

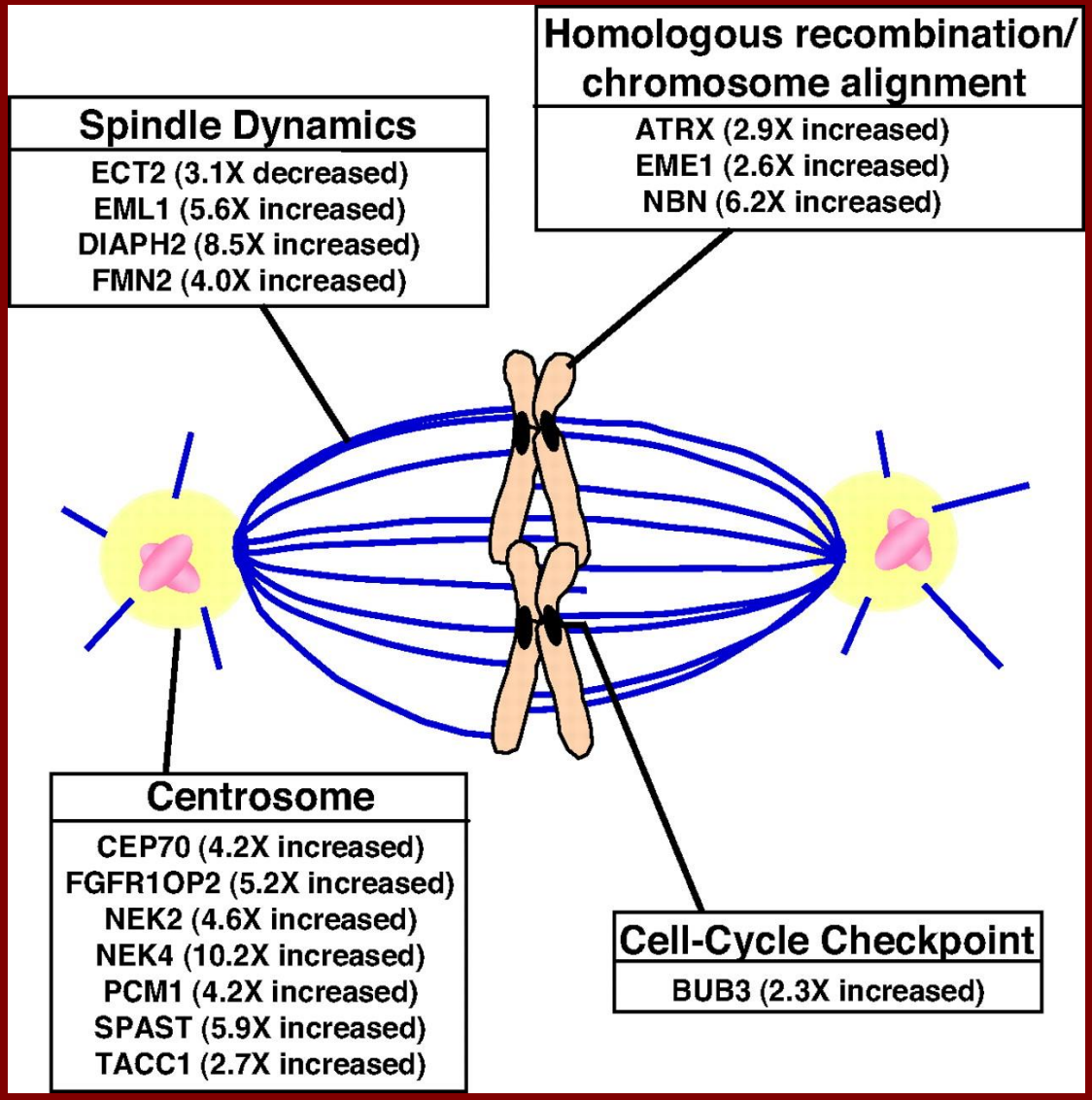
Distinct differences identified in the global gene expression profiles of NL and PCOS oocytes



Wood, J. R. et al. J Clin Endocrinol Metab 2007;92:705-713

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Fifteen genes involved in the meiotic/mitotic cell cycle pathway exhibited altered mRNA abundance in PCOS oocytes



Wood, J. R. et al. J Clin Endocrinol Metab 2007;92:705-713

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

No differences in oocyte quality in PCO or PCOS

Table 3 Number and quality of oocytes of the PCOS, PCO-only, and control groups

Variable	PCOS	PCO-only	Control	*P* value
No. of cumulus–oocyte complexes	14.1 ± 5.7	16.1 ± 5.0	12.4 ± 4.9	<0.05
No. of metaphase II oocytes	12.1 ± 5.2	14.3 ± 4.5	10.5 ± 4.4	<0.05
Metaphase II oocytes/total oocytes (%)	86.4	88.9	86.0	NS
Normal oocytes	45.9	42.8	42.8	NS
Central granular cytoplasm (%)	16.2	17.3	23.1	NS
Evenly granular cytoplasm (%)	15.6	16.1	15.2	NS
Refractile body (%)	2.2	4.0	2.9	NS
Aggregation sER (%)	9.2	8.1	6.2	NS
Vacuolization (%)	2.6	2.2	3.7	NS
Fragmented polar body (%)	39.2	34.8	40.3	NS
Abnormal zona pellucida (%)	22.6	21.1	28.9	NS

Values are expressed as mean ± SD

NS not significant, *sER* smooth endoplasmic reticulum

Sahu B. Arch Gyn Obstet 2008; 277: 239-44

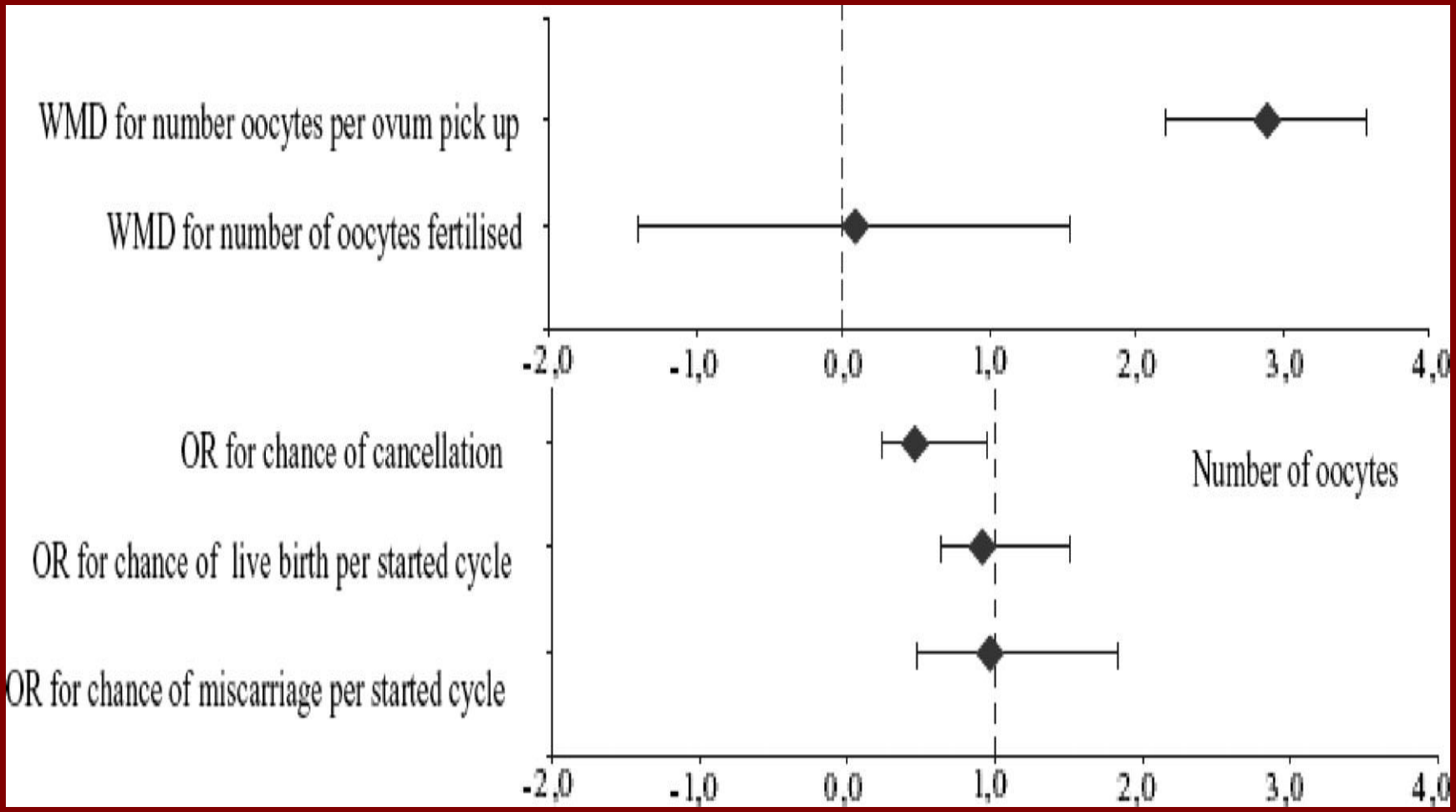
IVF outcomes in PCOS

- No evidence that overall outcomes are decreased (Thessaloniki, Human Reproduction 2008) – may be increased (Kalra, Fertil Steril 2013)
- Findings of oocyte and other abnormalities probably relate to specific phenotypes – major variable is BMI
- Clear evidence that obesity negatively affects outcomes

Thessaloniki 2007: Overall Conclusions

- IVF-ET: Third line treatment
- May reduce the risk of multiple pregnancies
- Overall outcomes not affected by PCOS status (implantation probably not a problem)
- More oocytes, but less fertilized
- Greater chance of cycle cancellation (poor response or OHSS)

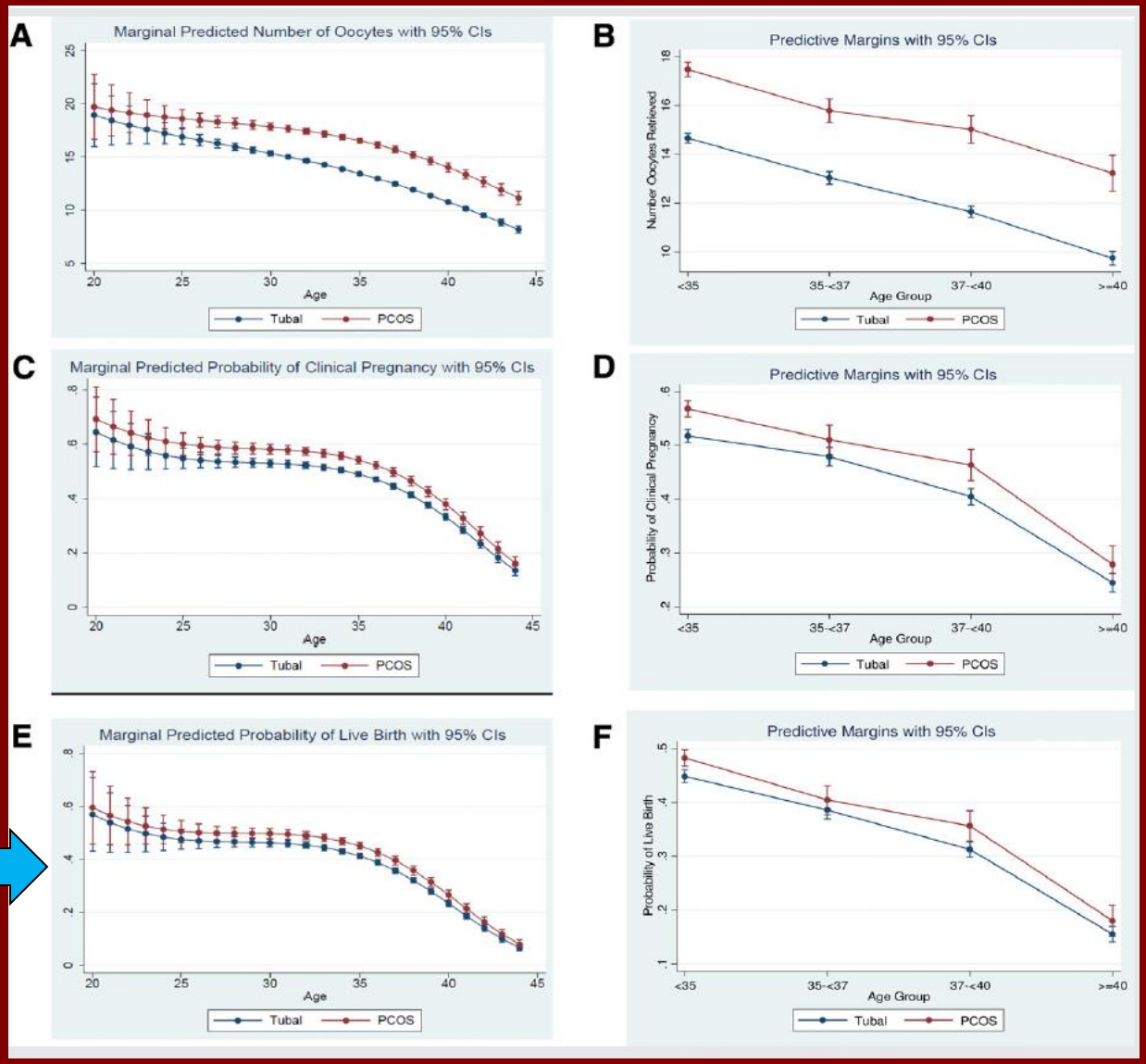
Main findings of clinical IVF outcomes in women with PCOS compared with matched controls (Heijnen et al., 2006, with permission)



The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, Hum. Reprod. 2008 23:462-477

Human Reproduction

IVF outcomes in PCOS vs Tubal – SART registry – higher in PCOS until >40 yrs



Kalra SK. Fertil Steril 2013, April 1

Effect of BMI on live birth rate from SART – fresh cycles

		Fresh			
Oocyte source	BMI	% Fetal death or stillborn	OR	AOR	95% CI
Autologous cycles, n			42,699		
	<18.5	15.3	0.91	0.98	0.83–1.15
	18.5–24.9	16.6	1.00	1.00	Reference
	25.0–29.9	18.5	1.14	1.10	1.03–1.17
	30.0–34.9	20.7	1.31	1.25	1.15–1.36
	35.0–39.9	21.4	1.37	1.34	1.18–1.51
	40.0–44.9	22.6	1.47	1.39	1.14–1.69
	45.0–49.9	26.0	1.76	1.67	1.21–2.31
	≥50.0	31.4	2.30	2.29	1.37–3.83

Lukes B. Fertil Steril 2011; 96: 820-5

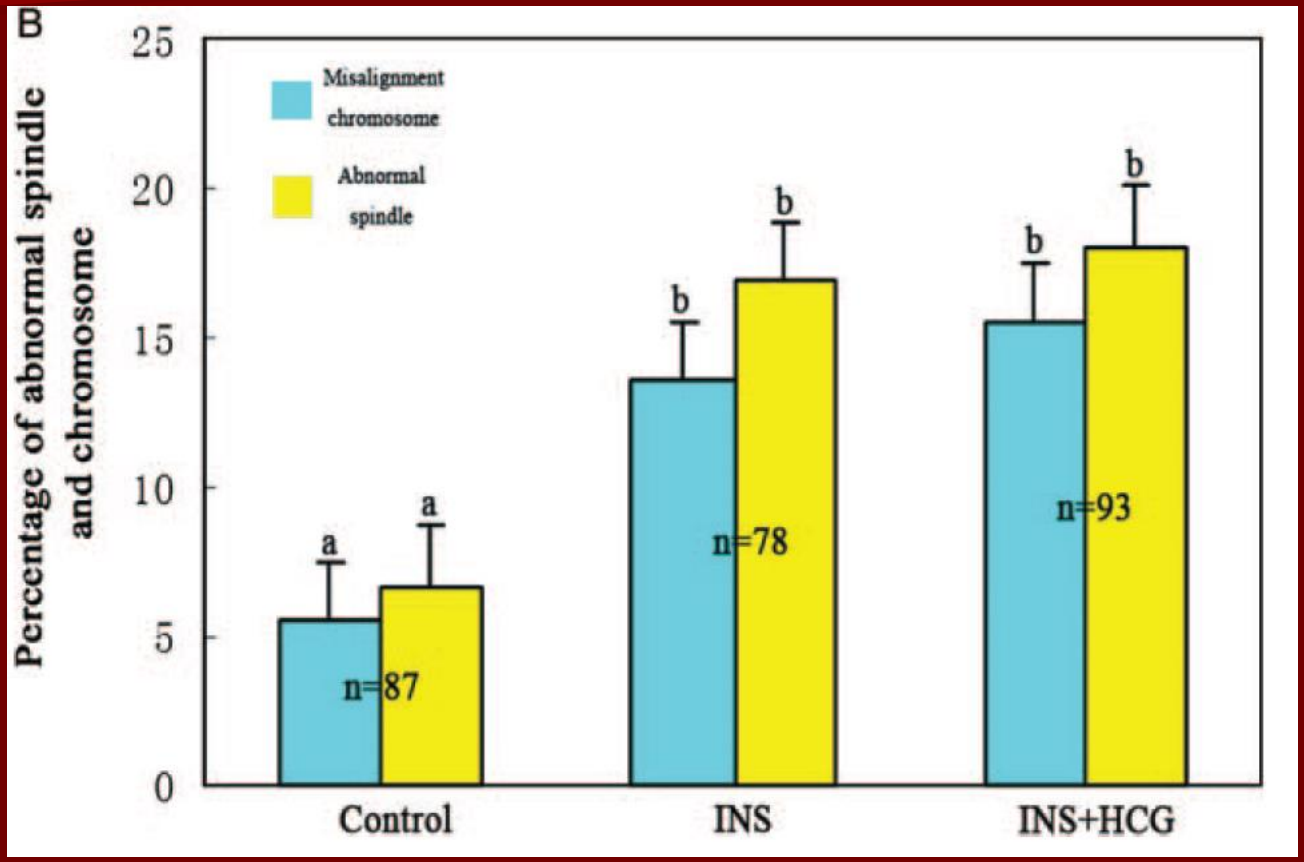
IVF outcomes in PCOS

- No evidence that overall outcomes are decreased (Thessaloniki, Human Reproduction 2008) – may be increased (Kalra, Fertil Steril 2013)
- Findings of oocyte and other abnormalities probably relate to specific phenotypes – major variable is BMI
- Clear evidence that obesity negatively affects outcomes (primarily mediated by adiponectin and other adipokines , insulin resistance)

Effects of Insulin Resistance

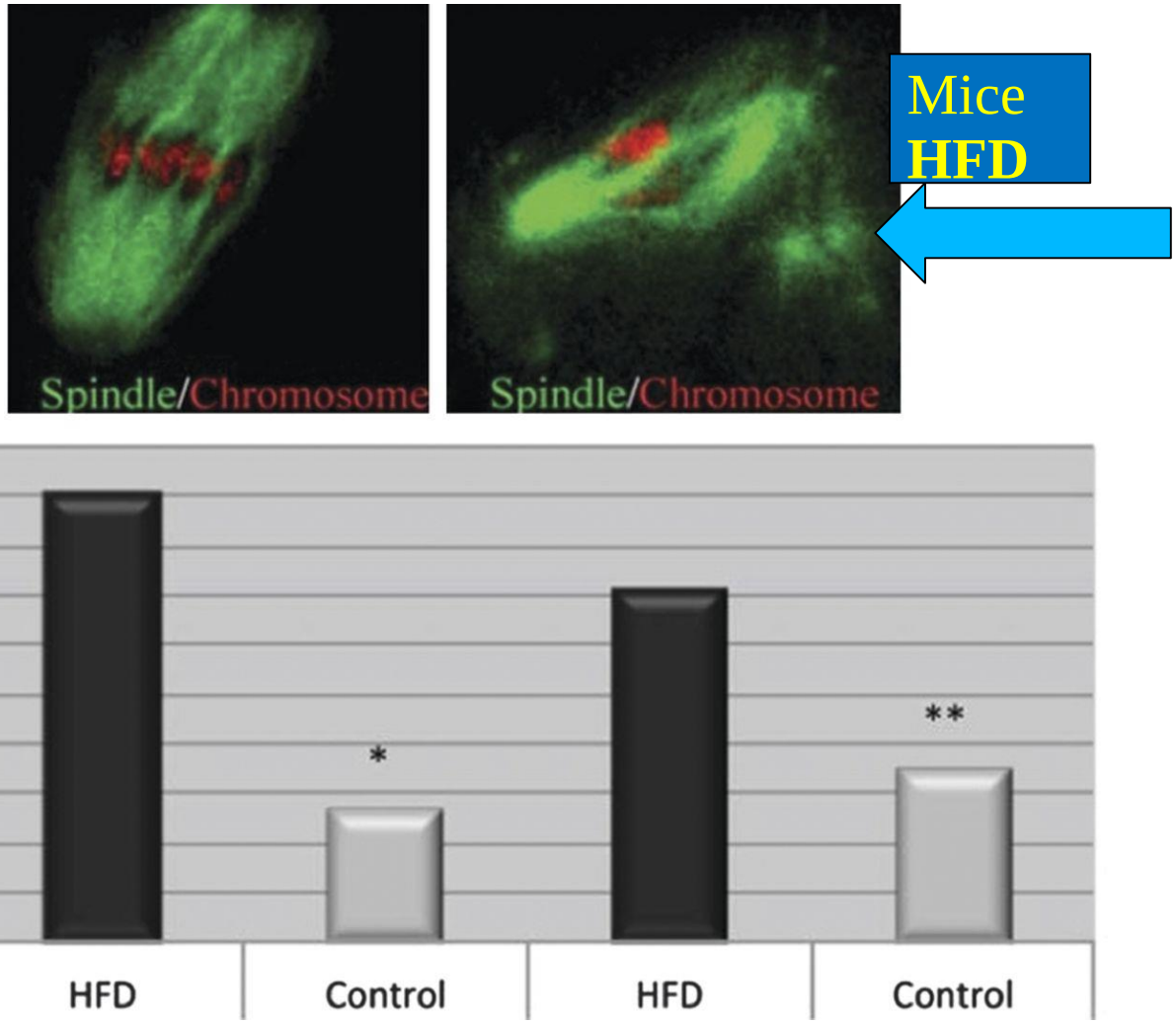
- Associations with anovulatory cycles
- Androgen metabolism
- Adipocytokine enhancement
- ? Direct effects on oocytes – oxidative stress and mitochrondrial dysfunction (the latter a factor in obesity – Molley) Ou XH. Hum Reprod 2012
- Endometrial effects?

Hyperinsulinemia /IR causing oxidative stress, mitochondrial dysfunction and abnormalities in spindle formation - mouse



Ou XH. Human Reproduction 2012; 27: 2130-45

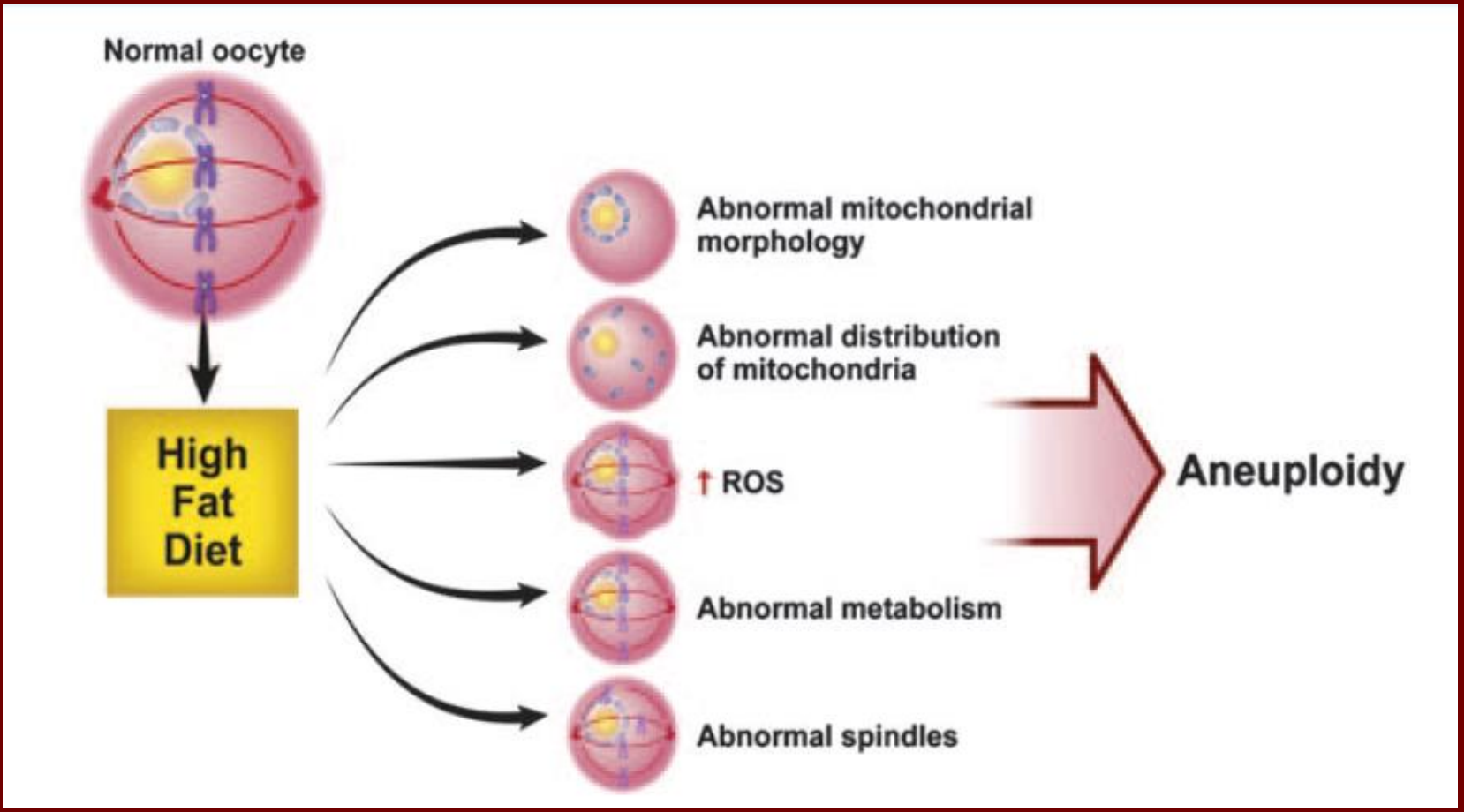
Oocyte aneuploidy and spindle formation/chromosome alignment.



Grindler N M , and Moley K H Mol. Hum. Reprod. 2013;molehr.gat026

MHR
Basic science of reproductive medicine

HFD contributing to abnormalities in oocytes – mouse model



Grindler and Moley. Mol Hum Reprod 2013; May17

Oocyte spindle abnormalities in Obese women using failed fertilization oocytes

Table II The association between spindle characteristics in oocytes that failed fertilization from women with normal BMI compared with severe obesity among 137 women undergoing assisted reproduction at a hospital-based infertility clinic.

	BMI 18.5–24.9 kg/m^2, 90 women, 171 oocytes	BMI ≥ 35 kg/m^2, 47 women, 105 oocytes	OR (95% CI)*	*P*-value*
Activated	24 (14.0%)	8 (7.6%)	0.46 (0.19–1.12)	0.09
Non-activated, no spindle	13 (8.8%)	7 (7.2%)	0.93 (0.33–2.57)	0.88
Non-activated with spindles	134 (91.2%)	90 (92.8%)	1.08 (0.39–3.00)	0.88
1 spindle	86 (64.1%)	34 (37.8%)	0.33 (0.17–0.63)	<0.001
>1 spindle	47 (35.1%)	53 (58.9%)	2.68 (1.39–5.15)	0.003
Accordion-shaped spindle	1 (0.8%)	3 (3.3%)	–	–

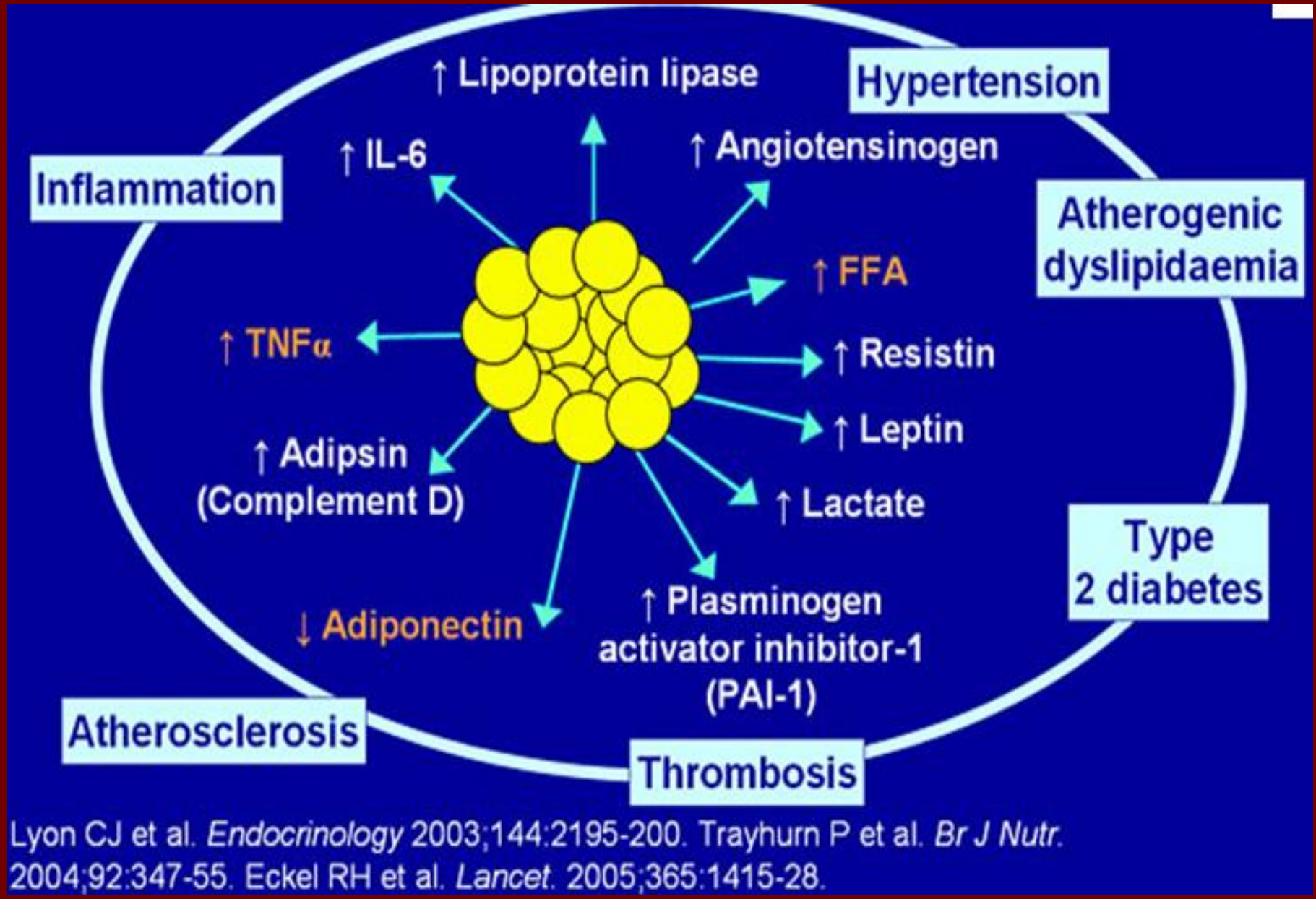
OR, odds ratio; CI, confidence interval.

Percentages in parentheses are the proportion of oocytes examined in each group.

*ORs, 95% CIs and two-sided Wald *P*-values are from generalized estimating equations to account for the correlation between oocytes from the same patient and are adjusted for continuous age at cycle start, cycle type (IVF or ICSI), and PCOS.

Machtinger R. Human Reproduction 2012; 27: 3198-207

Multiple factors affecting CV and Metabolic Health



Lyon CJ et al. *Endocrinology* 2003;144:2195-200. Trayhurn P et al. *Br J Nutr.* 2004;92:347-55. Eckel RH et al. *Lancet.* 2005;365:1415-28.

Higher Leptin in serum and FF in PCOS – related to increased BMI - linked to poor outcomes

Table I Factors in serum and follicular fluid of patients with PCOS: impact on quality of oocyte and embryo, fertilization and outcome of pregnancy.

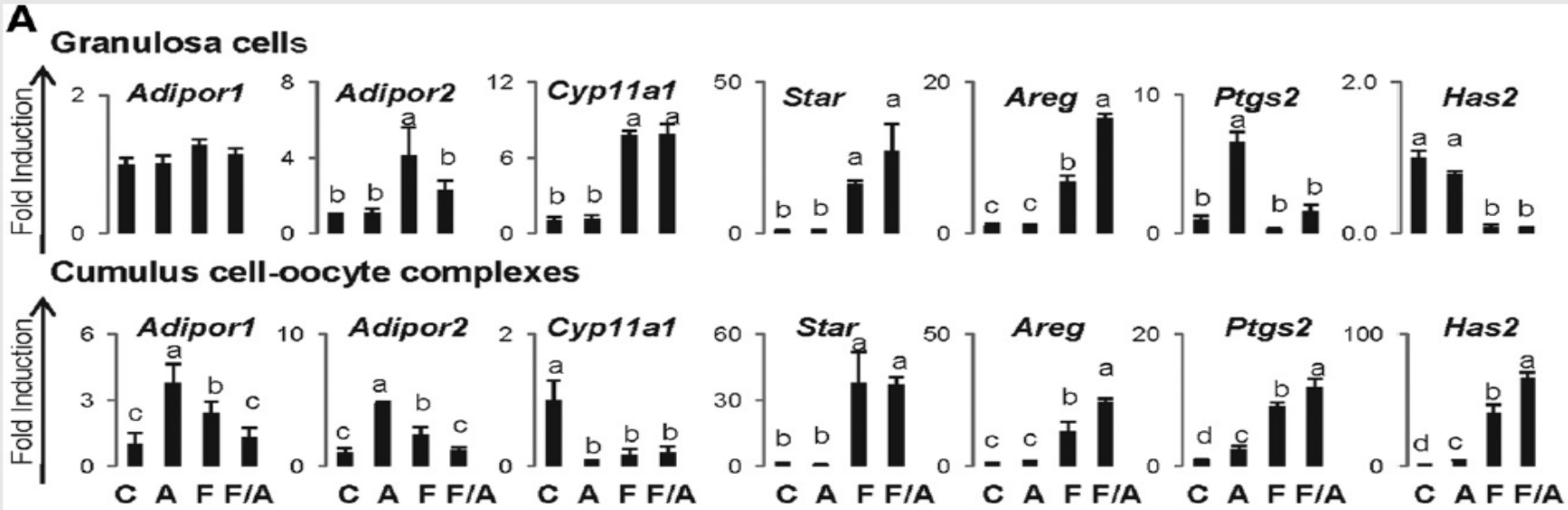
Factors	Serum level	FF level	Oocyte quality	Fertilization rate	Embryo quality	Pregnancy rate	References
Leptin	↑	↑	↓	↓	↓	↓	Mantzoros *et al.* (2000), Georgios *et al.* (2005), Li *et al.* (2007)
Tumor necrosis factor α	↑	↑	↓	↓	↓	↓	Amato *et al.* (2003), Wu *et al.* (2007a, b), Kim *et al.* (2009)
Reactive oxygen species		↑	↓	↓	↓	↓	Chattopadhayay *et al.* (2010), Samanta *et al.* (2008)

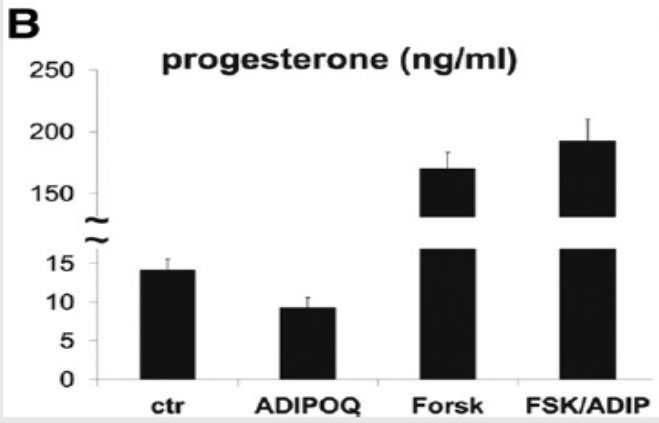
Qiao J. Human Reproduction Update 2011; 17: 17-33

Positive effects of adiponectin on oocytes and embryo development

- Decreased adiponectin in obesity; well documented in PCOS even after adjusting for BMI
- Abnormal L/A ratios in Obesity and PCOS
- Strong evidence that increasing adiponectin is beneficial for follicles and embryos
  Richards JS Fertil Steril 2012; 98: 471-9

Adiponectin modulates follicle growth and embryo development



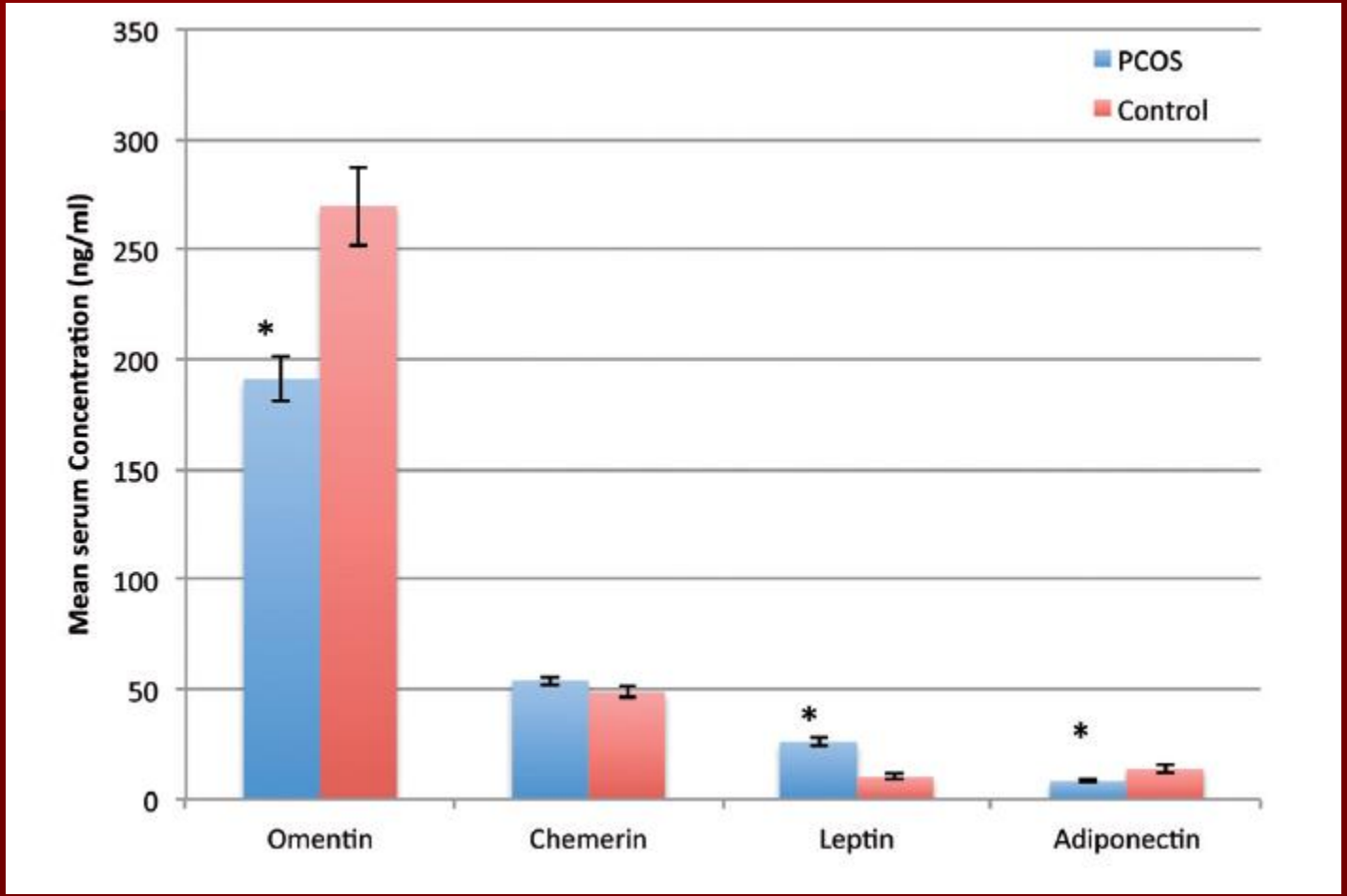


C

Treatment	FSH	FSH+ADIPOQ
#oocytes	62	70
MII	42 (67.7%)	55 (78.6%)
Fertilization (/MII)	25 (59,5%)	45 (81.8%)*
Cleavage (/Fertilized)	8 (32%)	27 (60%)*
Blastocyst (/Fertilized)	0	11 (24.4%)*

Richards JS. Fertil Steril 2012; 98: 471-9

Various adipocytokines in women with PCOS and age matched controls



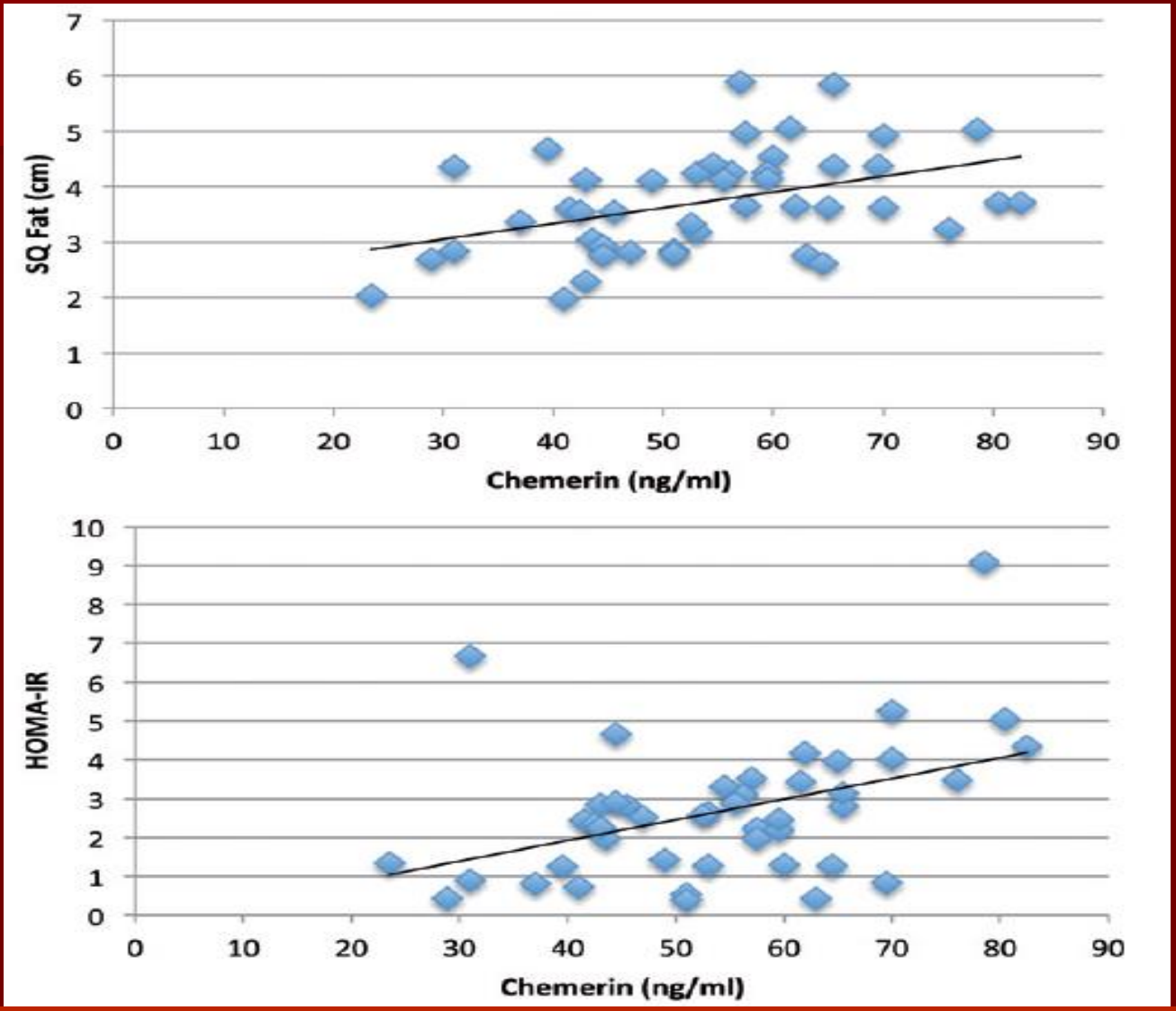
Kort and Lobo. Gynecol Endocrinol 31: 152-5, 2015

Best correlates of fat content and IR seen with Chemerin and L/A ratio

	Chemerin (*r*)	Omentin-1 (*r*)	Adiponectin (*r*)	Leptin (*r*)	L/A ratio (*r*)
BMI	0.317 ($p = 0.034$)	−0.014 (NS)	−0.2 (NS)	0.508 ($p = 0.004$)	0.468 ($p = 0.0012$)
SQ fat	0.451 ($p = 0.0019$)	−0.015 (NS)	−0.19 (NS)	0.355 ($p = 0.017$)	0.371 ($p = 0.012$)
HOMA-IR	0.428 ($p = 0.0034$)	−0.049 (NS)	−0.3301 ($p = 0.027$)	0.254 ($p = 0.092$)	0.376 ($p = 0.011$)

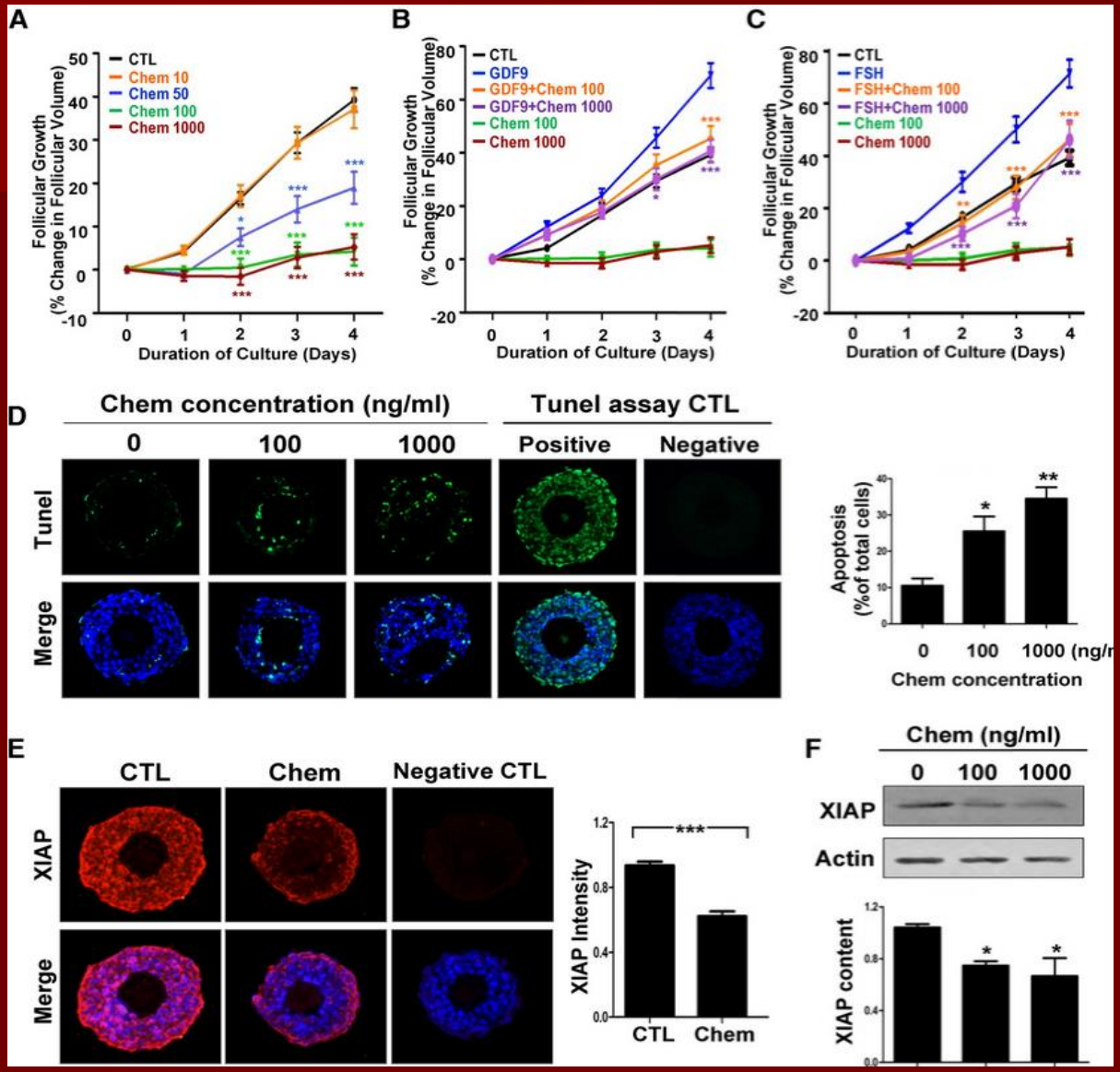
Kort and Lobo. Gynecol Endocrinol 31: 152-5, 2015

CHEMERIN correlates with FAT and HOMA-IR in PCOS



Kort and Lobo Gynecol Endocrinol 31: 152-5, 2015

Chemerin induces follicular arrest in a rat model



Kim JY. Endocrinology 2013; 154: 2912-23

Management of metabolic concerns – reproductive benefit?

- Life Style – diet and exercise
- Insulin sensitizers
  metformin
  inositols
  cinnamon
- "glitazones" unsafe? and can cause weight gain

Effects of Myo-Inositol in PCOS

- Suggestion that decreased tissue availability and/or altered metabolism of inositols in PCOS is related to insulin resistance
- Several studies showing improvement in oocyte quality with myo-inositol (>DCI)
  Unfer V. Gynecol Endocrinol 2012; 28:509-15
- Improvements in endocrine profiles, insulin resistance and menstrual cycles with myo-inositol
  Artini PG. Gynecol Endocrinol 2013; 29: 375-9

Oocyte quality in women with PCOS: is there a metabolic link?

- Myo-inositol with Folic acid (2 g bid) versus Folic acid alone (RCT) taken throughout stimulation and retrieval in PCOS resulted in lower gonadotropin doses, days of stimulation and lower E2 levels with Myo-inositol, and a trend for better quality oocytes
  Papaleo E. Fertil Steril 2009; 91: 1750-4

Improvement of oocytes in PCOS via alterations in metabolism?

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 E. Fertil Steril 2009; 91: 1750-4

Effects on the Endometrium (PCOS)

- Endometrial abnormalities even in ovulatory PCOS
  DuQuesnary. Fertil Steril 2009
  possibly androgen effects
- Obesity compounds defects in PCOS – altered gene expression in luteal phase - additional influence of insulin resistance/cytokines
  Beliver J. Fertil Steril 2011; 95: 2335-41

IR in PCOS may have a greater effect on endometrial receptivity

- IVM model: PCOS with IR (n=51); without IR (n= 64)
- No differences in oocyte maturity, fertilization, cleavage or embryo development
- Implantation: 11.6% vs 28.7 %; p=0.001
  Clinical and Ongoing Pregnancy: 23.5% vs 53.1%, p= 0.002; 21.6% vs 46.9%, p= 0.006
- OR of 4.9 after controlling for age, BMI and lipids
  Chang EM. Clin Endocrinol 2012;

Metformin may be beneficial for the endometrium in PCOS – direct vs via IR?

- Upregulation of GLUT4 expression which is decreased with IR – improvement in endometrial IR
  Zhai J. Biol Reprod 2012; 87: 29
- Improvement in various indices of endometrial vascular effects
  Mohsen IA. J Clin Ultrasound 2012

Additional concerns to improve outcomes in PCOS with IVF

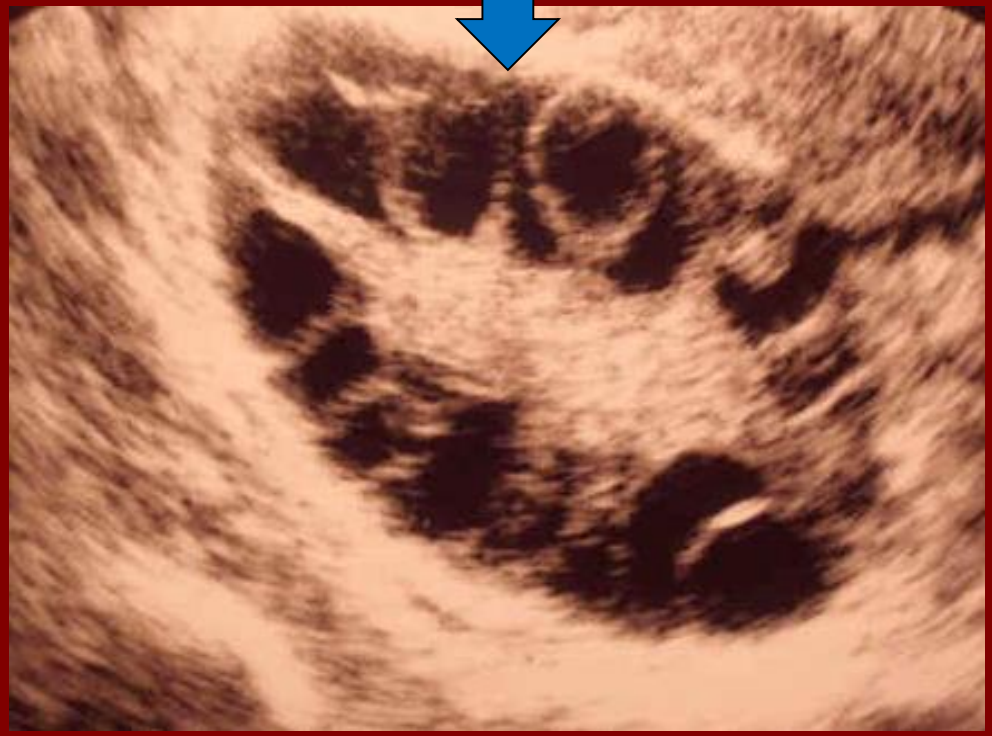
Narrowed FSH threshold

Elevated Androgens

Elevated Insulin

Elevated AMH

Other factors ?



Incidence of OHSS in PCOS

- Overall 10% (Delvigne E, Hum Repro Update 2002)
- Difference in rates with Induction of Ovulation: step-up: 2.25% versus step down: 11% per cycle (Christin-Maitre S, Human Repro 2003)
- Versus IVF : ~30%

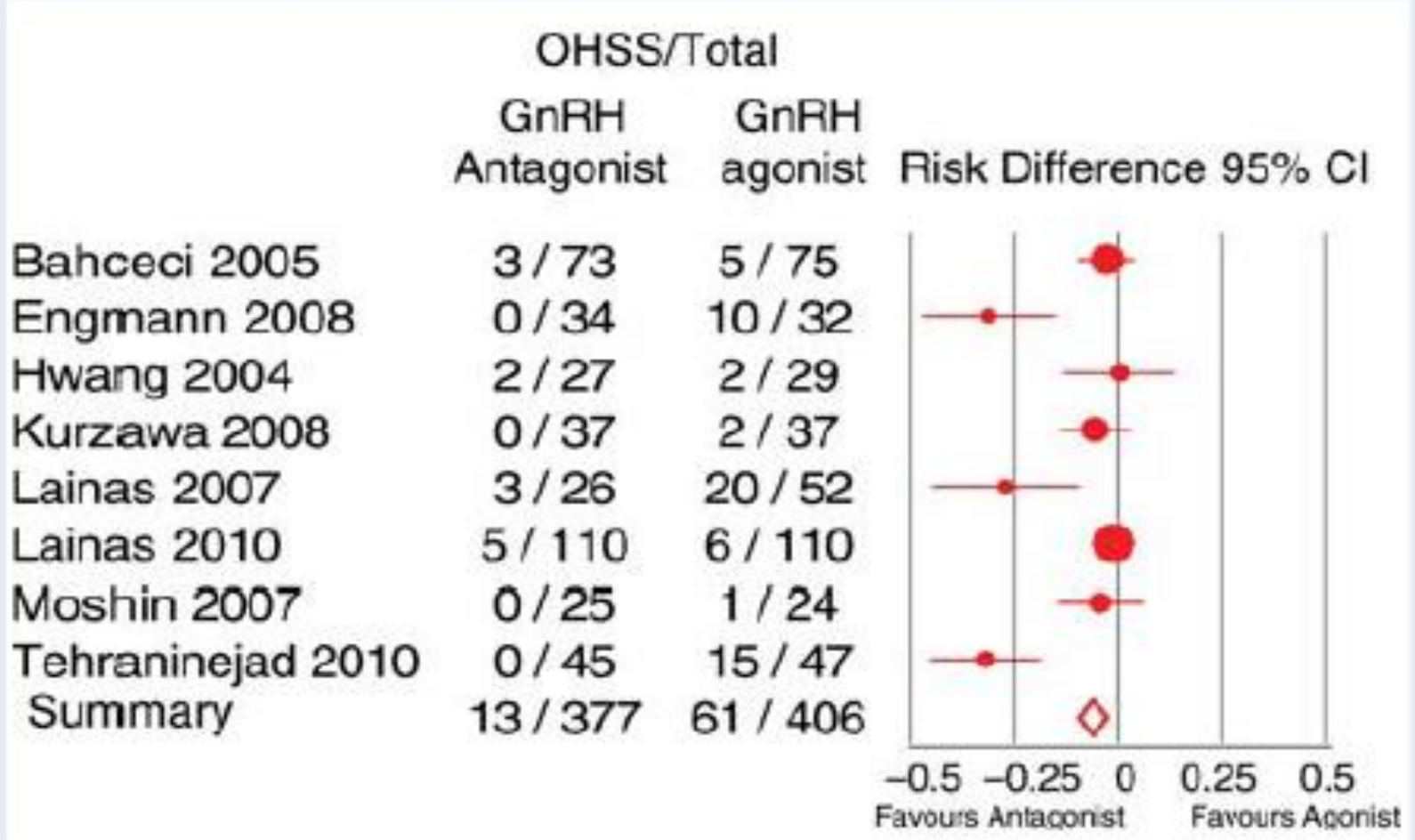
Predictability of OHSS in PCOS?

- PCOS is already a risk factor for OHSS
- Within the diagnosis:
  Higher androgen levels (Elder-Geva 2005)
  Higher AMH levels (Kaya 2010) – broad range – unclear if this is useful
  Higher insulin (Fulghesu 1997) – others suggesting greater gonadotropin dose requirement (Homburg 1996)
  Lower BMI?; Higher LH?
- No good way except prior history

Prevention of OHSS in PCOS

- Recognize the problem, make the diagnosis – what is important here is ovarian morphology (PCO/PAO and PCOS)
- Lower dose, step-up regimen
- Use of antagonists
- Use of metformin
- GnRH agonist trigger (routine or meeting preset criteria?)
- Dopamine agonists (experimental?) unnecessary with agonist trigger
- In vitro maturation (experimental consideration)

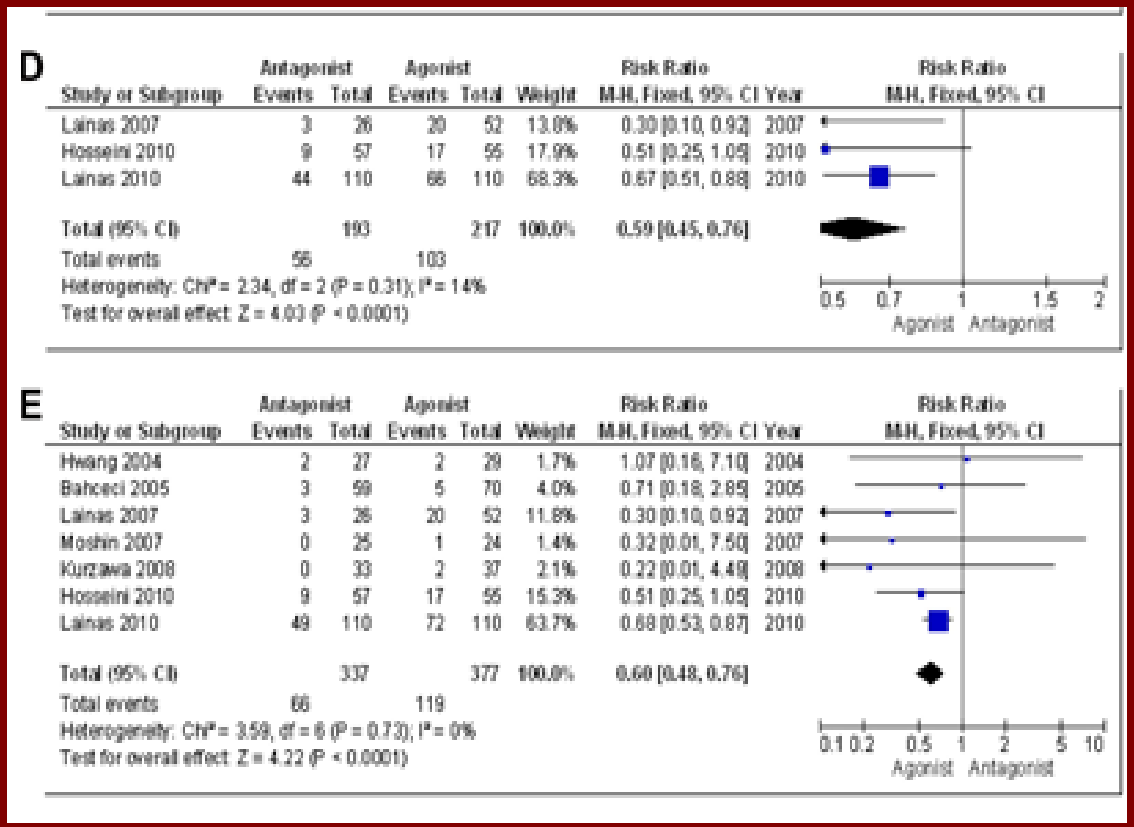
Updated Cochrane review: Lower rate of OHSS with antagonists versus agonists – all comers



Al-Inany HG. Human Reprod Update 2011; 17: 435

Meta-analysis of agonist versus antagonist cycles in PCOS

Significant reduction in moderate and severe OHSS with antagonist, but authors suggest data are not definitive



Pundir J. Reproductive BioMedicine Online 2012; 24: 6-22

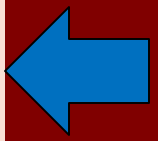
Does metformin improve outcomes of IVF in women with PCOS

- No improvement in Cochrane review
  Live birth rate OR: 0.77 (0.27-2.18)
  Clinical pregnancy rate: 0.71 (0.39-1.28)
  Risk of OHSS reduced: 0.27 (0.16-0.47)
  Tso LO Cochrane Library 2009, 2:CD006105
- Metformin versus placebo: No difference in pregnancy rate, but decrease in abortion rate and OHSS with metformin
  Qublan HS. J Obstet Gynaecol 2009;7:651-5

RCT of metformin versus placebo in women with PCOS undergoing IVF

Clinical data.

Variable	Metformin (n = 60)	Placebo (n = 60)	*P* value
Stimulation length (d)	13.0 (4; 9–15)	12.0 (3; 9–14)	.006
Gonadotropins dose (IU)	1,350.0 (450; 950–1,800)	1,275.0 (350; 900–1,750)	.018
Periovulatory follicles on day of ovulation triggering (n)	13.0 (7; 3–18)	13.9 (7; 5–20)	.066
Non-periovulatory follicles on day of ovulation triggering (n)	4.3 (2; 0–6)	5.5 (2.5; 2–9)	.034
Cancellation rate	3/60 (5.0)	11/60 (18.3)	.023
Peak E_2 levels on day of ovulation triggering (pg/mL)	1,950.5 (105; 342–4,021)	2,345.7 (130; 709–4,123)	.029
E_2 levels for periovulatory follicle (pg/mL)	315.0 (40; 203–510)	421.5 (34; 279–615)	.011
Retrieved oocytes	9.5 (5; 3–17)	10.0 (5; 5–20)	.097
Transferred embryos (no. per fertilized oocytes)	114/290 (39.3)	98/306 (32.0)	.063
Implantation rate (no. per transferred embryos)	41/114 (36.0)	31/98 (31.6)	.507
Clinical pregnancy rate (no. per started cycles)	26/60 (43.3)	24/60 (40.0)	.711
Ongoing pregnancy rate (no. per started cycles)	21/60 (35.0)	19/60 (31.7)	.699
Multiple pregnancies rate (no. per pregnancy)	5/26 (19.2)	5/24 (20.8)	.887
Live-birth rate (no. per started cycles)	29/60 (48.3)	27/60 (45.0)	.855
OHSS (no. per started cycles)	5/60 (8.3)	18/60 (30.0)	.003
Mild	3/60 (5.0)	11/60 (18.3)	.012
Moderate	2/60 (3.3)	6/60 (10.0)	
Severe	0/60 (0.0)	1/60 (1.7)	



Palomba S. Fertil Steril 2011; 96: 1384-90

GnRH agonist trigger in antagonist cycles in PCOS

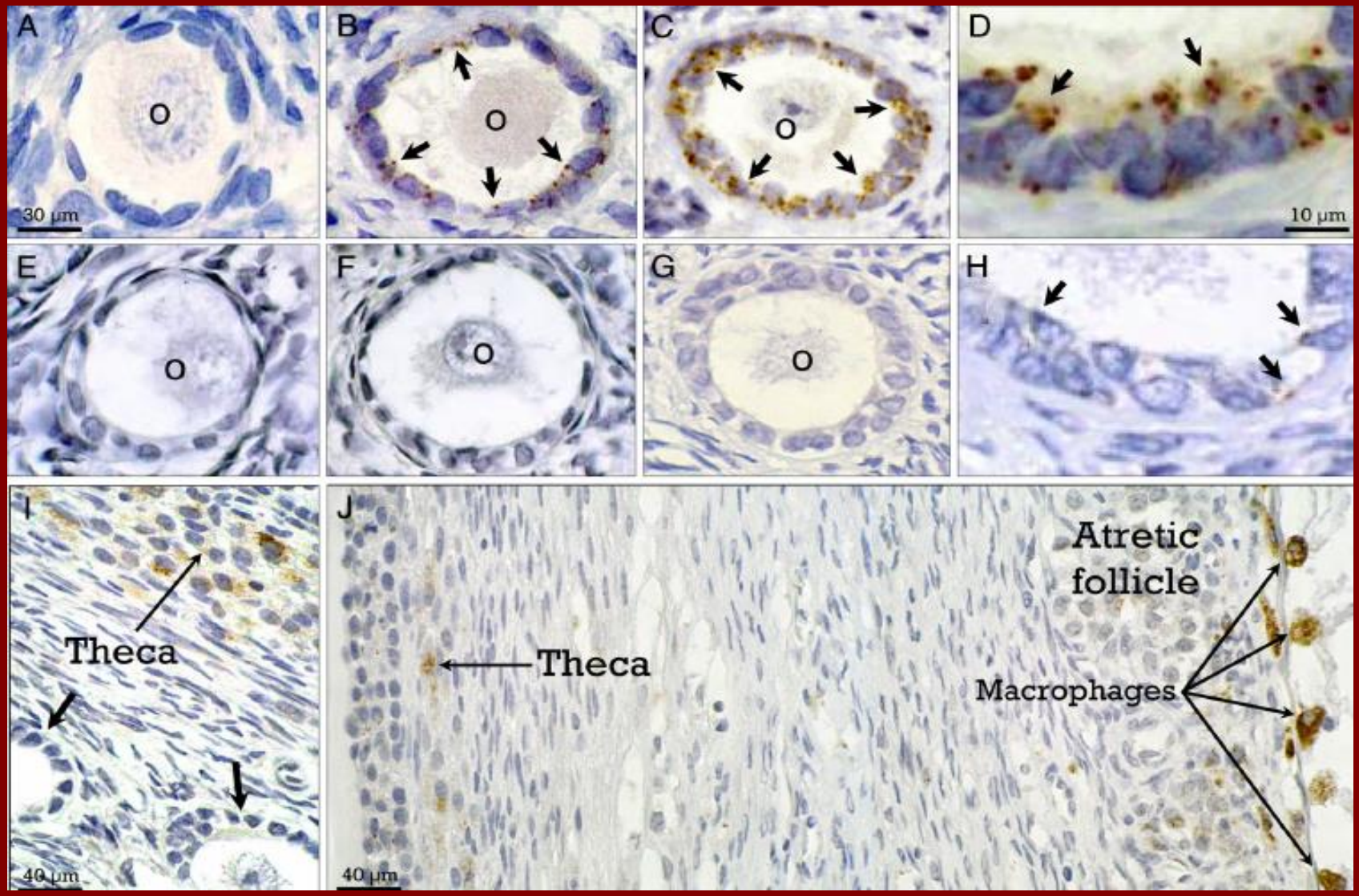
- Reduction/elimination of severe OHSS with use of agonist trigger
- No difference in pregnancy rates with intensive luteal support

  Babayof R. Hum Reprod 2006; 21: 1260-5

  Engmann L. Fertil Steril 2008; 89: 84-91

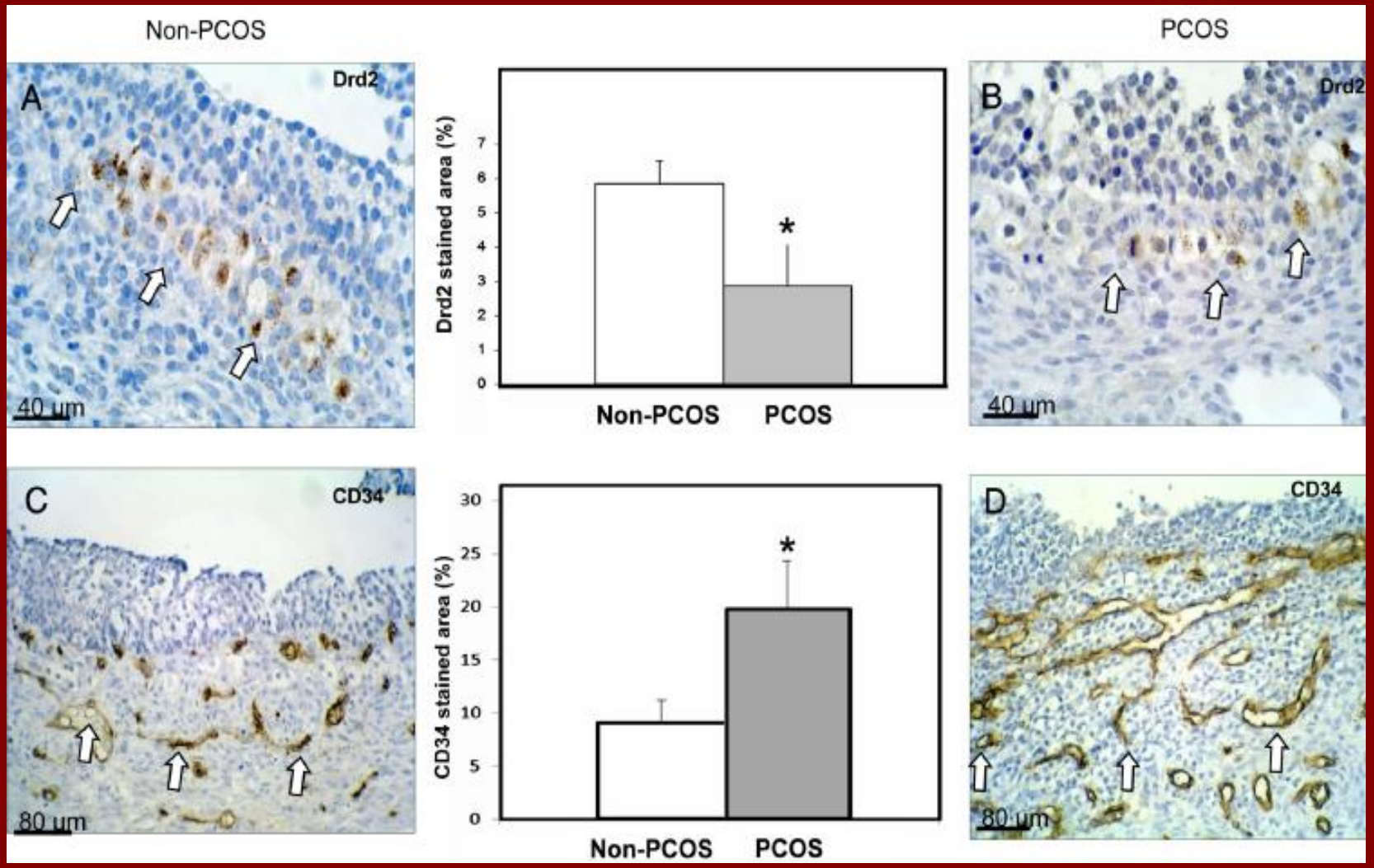
  Kolibiankis EM. Hum Reprod Update 2012; 18: 228-9

Decreased expression of Dopamine receptor 2 in PCOS ovaries versus normal women (A-D)



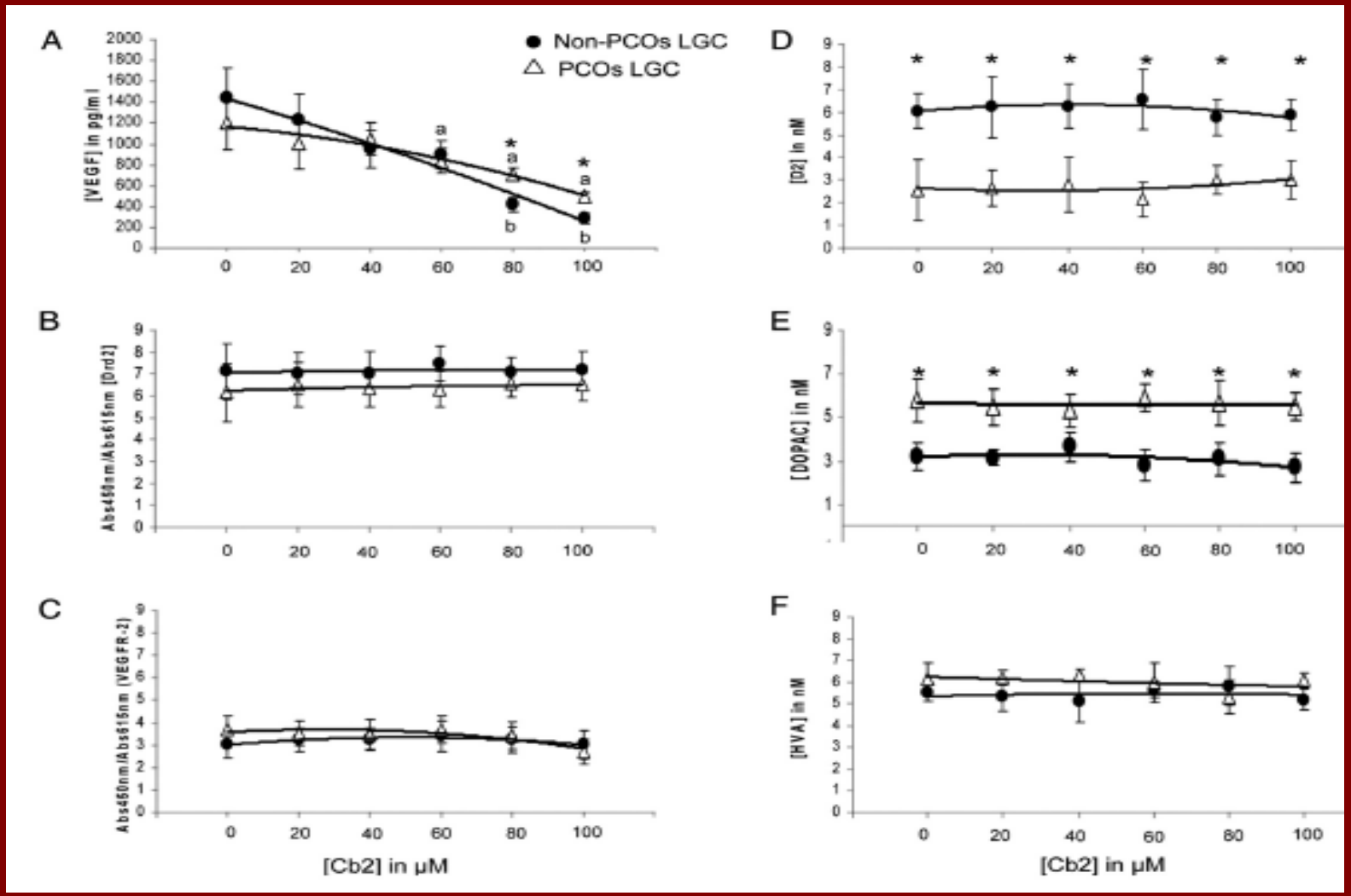
Gomez R. J Clin Endocrinol Metab 2011; 96: 2484-92

Decreased Dopamine receptor 2 and increased vascularizatrion in theca of luteinized cysts in PCOS



Gomez R. J Clin Endocrinol Metab 2012; 96: 2484-92

Inhibition of VEGF by cabergoline in cultured luteinized granulosa cells



Gomez R. J clin Endocrinol Metab 2012; 96: 2484-92

Cabergoline meta-analysis: evidence for benefit for moderate OHSS; no difference in pregnancies or miscarriage

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	control	cabergoline versus control			
Incidence of OHSS	312 per 1000	125 per 1000 (62 to 240)	OR 0.40 (0.20 to 0.77)	230 (2 studies)	⊕⊕◯◯ low
Incidence of severe OHSS	62 per 1000	48 per 1000 (15 to 152)	OR 0.77 (0.24 to 2.45)	230 (2 studies)	⊕⊕◯◯ low
Incidence of moderate OHSS	250 per 1000	95 per 1000 (48 to 195)	OR 0.38 (0.19 to 0.78)	230 (2 studies)	⊕⊕◯◯ low
Clinical pregnancy rate	429 per 1000	403 per 1000 (240 to 682)	OR 0.94 (0.56 to 1.59)	230 (2 studies)	⊕⊕◯◯ low
Miscarriage rate	38 per 1000	12 per 1000 (1 to 117)	RR 0.31 (0.03 to 3.07)	163 (1 study)	⊕⊕◯◯ low
Side effects	125 per 1000	259 per 1000 (70 to 963)	OR 2.07 (0.56 to 7.70)	67 (1 study)	⊕⊕◯◯ low

Tang H. Cochrane Database Syst Rev 2012; 2: CD008605

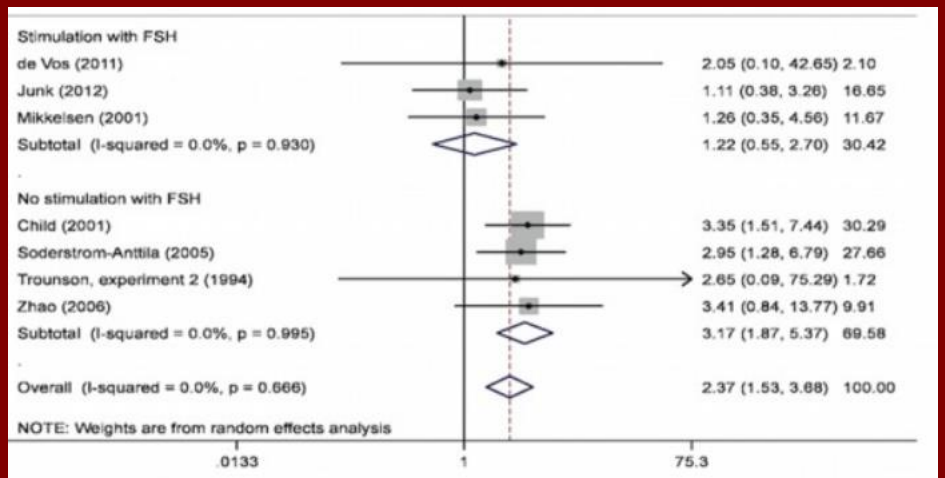
In Vitro maturation of oocytes for IVF in PCOS

- Theoretically a very attractive option:
  No stimulation
  No risk of OHSS
- Various protocols – none, or minimal stimulation with/without HCG; endometrial preparation; oocyte retreival; various cultures/ICSI/ET - no clear advantage of different techniques documented

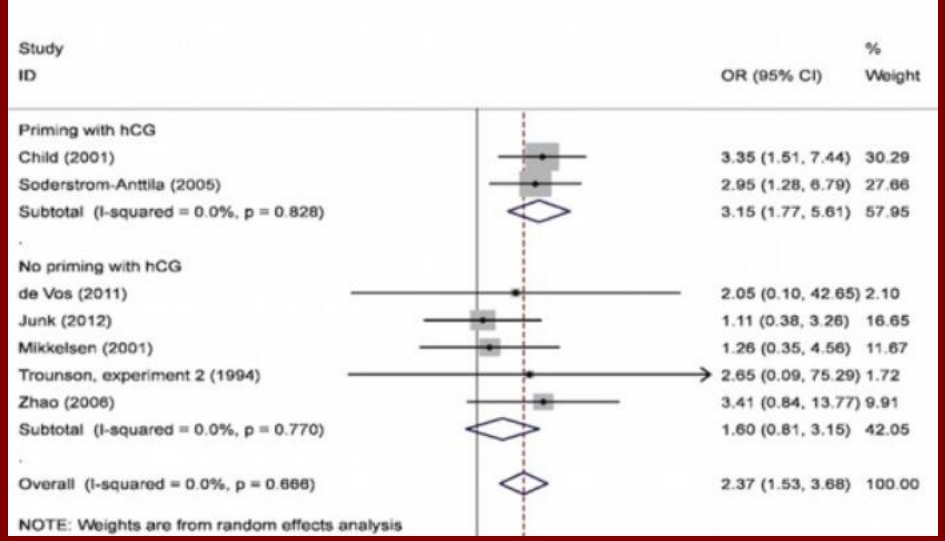
In Vitro maturation of oocytes for IVF in PCOS (continued)

- Clinical results: Cochrane: Modest benefit versus non PCOS Siristatidis CS, Cochrane PloS 2015; 10: e0134696
- Lower cummulative pregnancy rates versus traditional IVF for fresh cycles; similar in frozen cycles: Walls ML. Hum Reprod 2015; 30: 88-96

Cochrane: marginal benefit of IVM in PCOS versus non PCOS – not overall efficacy



Forest plot depicting the comparison PCOS vs. non-PCOS regarding clinical pregna
men-based analysis), stratified by priming with hCG



Siristatidis C
PloS One 2015; 10: e0134696

In Vitro maturation of oocytes for IVF in PCOS (continued)

- Montreal experience:
  Clinical pregnancy rate 30-35%; implantation rate 10-15%
  Chian RC. Reprod Biomed Online 2004; 8: 547-52
- French experience:
  Clinical pregnancy rates of 20% (per punture); 22.5% (per transfer)
  Le Du A. Hum Reprod 2005; 2: 420-4
- Korean Experience:
  Overall pregnancy rate ~21.9%
  Survey of pregnancy outcomes – not different from other women with PCOS
  Cha KY. Fertil Steril 2005; 83:1461-5

In Vitro maturation of oocytes for IVF in PCOS (continued)

- Chinese experience:
  Trial of pretreatment with OC and metformin
  Live Birth Rate: 37.7% versus 30.4% without (NS); beneficial effect of reduced miscarriage rate with OC+ metformin versus no pretreatment
  Zhao JZ. J Women's Health 2010; 2:261-5

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome

Z.-J. Chen, Y. Shi, Y. Sun, B. Zhang, X. Liang, Y. Cao, J. Yang, J. Liu, D. Wei, N. Weng, L. Tian, C. Hao, D. Yang, F. Zhou, J. Shi, Y. Xu, J. Li, J. Yan, Y. Qin, H. Zhao, H. Zhang, and R.S. Legro

Multicenter RCT: FET vs Fresh ET improves live birth rate in PCOS

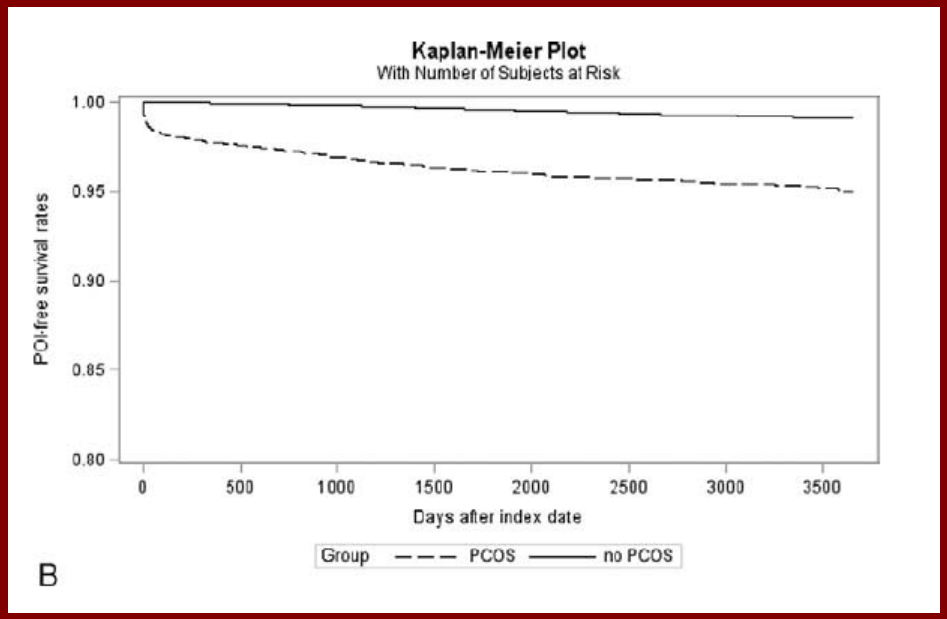
Outcome	Frozen-Embryo Transfer (N=746)	Fresh-Embryo Transfer (N=762)	Absolute Difference between Groups (95% CI)	Rate Ratio in Frozen-Embryo Group (95% CI)	P Value
Primary outcome: live birth — no. (%)†	368 (49.3)	320 (42.0)	7.3 (2.3 to 12.4)	1.17 (1.05 to 1.31)	0.004
Singleton	250 (33.5)	212 (27.8)	5.7 (1.0 to 10.3)	1.20 (1.03 to 1.40)	0.02
Twin	117 (15.7)	108 (14.2)	1.5 (–2.1 to 5.1)	1.11 (0.87 to 1.41)	0.41
Triplet‡	1 (0.1)	0			
Birth weight — g					
Singleton	3511.2±593.6	3349.4±553.2	161.8 (56.2 to 267.3)		0.005
Twin	2479.7±503.2§	2481.7±496.0	–2.0 (–94.9 to 90.8)		0.97
Secondary outcomes — no. (%)					
Biochemical pregnancy¶	492 (66.0)	492 (64.6)	1.4 (–3.4 to 6.2)	1.02 (0.95 to 1.10)	0.57
Clinical pregnancy‖	438 (58.7)	428 (56.2)	2.5 (–2.4 to 7.5)	1.05 (0.96 to 1.14)	0.32
Ongoing pregnancy**	393 (52.7)	372 (48.8)	3.9 (–1.1 to 8.9)	1.08 (0.98 to 1.19)	0.13
Pregnancy loss — no./total no. (%)					
Among biochemical pregnancies	108/492 (22.0)	161/492 (32.7)	–10.8 (–16.3 to –5.2)	0.67 (0.54 to 0.83)	<0.001
Among clinical pregnancies	64/438 (14.6)	107/428 (25.0)	–10.4 (–15.7 to –5.1)	0.58 (0.44 to 0.77)	<0.001

Chen ZJ. N Engl J Med 2016; 375: 523-33

Transition into menopause

- Age of menopause has been reported to be normal or slightly later
- Certain populations are destined for earlier menopause in all women (eg East Asian women)
- Premature ovarian insufficiency (POI) occurs in all populations of women; "paradoxically" it may occur more frequently in PCOS – thus a longer time of life after menopause

Increased risk of POI in PCOS: 3.73 vs 0.44 %;
in 10 year follow up: HR 8.64(7.33-10.18);
lower with metformin use

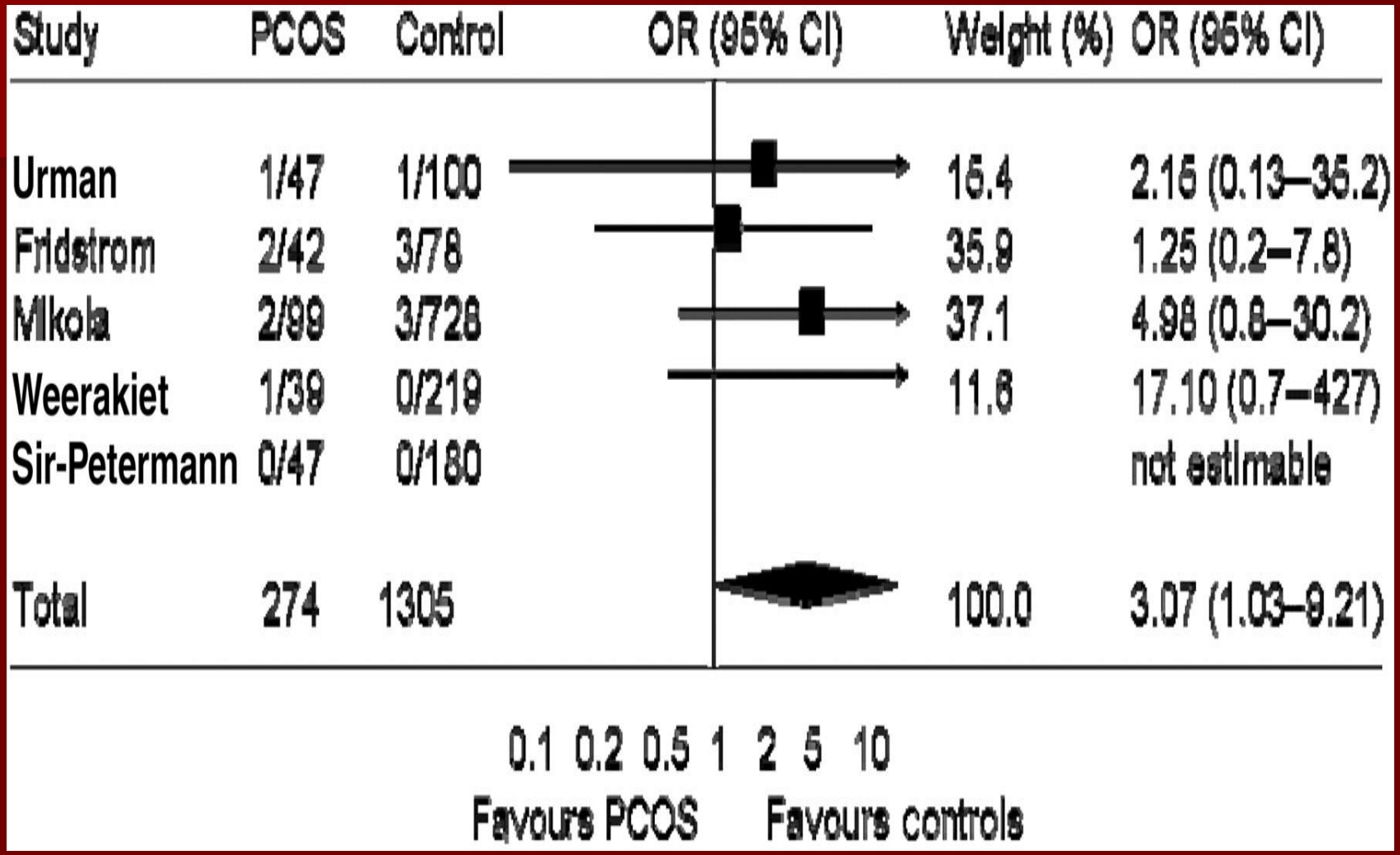


Pan M-L. Menopause 24: 2017

Adverse Pregnancy outcomes?

Highly dependent on the phenotype of PCOS – obesity is the dominant feature

OR for the incidence of perinatal mortality in babies from women with PCOS versus controls (Boomsma et al., 2006, with permission)



The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, Hum. Reprod. 2008 23:462-477

Human Reproduction

Adverse obstetric or neonatal outcomes in patients with PCOS categorized according to different ESHRE/ASRM phenotypes.

	Full-blown (n = 14)	Non-PCO (n = 7)	Nonhyperandrogenic (n = 5)	Ovulatory (n = 67)
Weight gain (kg)	13 (4 IQR; 8.5–16 range)	13 (3 IQR; 9–15.4 range)	12.5 (3 IQR; 9–14.0 range)	12.5 (3.5 IQR; 8–13.5 range)
Miscarriage (n,%)	9/14 (64.3)[a]	4/7 (57.1)[a]	3/5 (60.0)[a]	7/67 (10.4)
PIH (n,%)	5/14 (35.7)[a]	3/7 (42.9)[a]	2/5 (40.0)[a]	3/67 (4.5)
PE (n,%)	4/14 (28.6)[a]	2/7 (28.6)[a]	1/5 (20.0)	2/67 (3.0)
GDM (n,%)	5/14 (35.7)[a]	3/7 (42.9)[a]	2/5 (40.0)[a]	5/67 (7.5)
Antepartum hemorrhage (n,%)	9/14 (64.3)[a]	5/7 (71.4)[a]	3/5 (60.0)[a]	9/67 (13.4)
SGA (n,%)	6/14 (42.9)[a]	4/7 (57.1)[a]	1/5 (20.0)	7/67 (10.4)
LGA (n,%)	3/14 (21.4)	1/7 (14.3)	0/5 (0)	5/67 (7.5)
AGA (n,%)	6/14 (42.9)[a,b]	2/7 (28.6)[a,b]	4/5 (80.0)	58/67 (86.6)
Operative delivery (n,%)	12/14 (85.7)[a]	5/7 (71.4)[a]	4/5 (60.0)[a]	17/67 (25.4)
Gestational age at delivery (wk)	38 (4 IQR; 32–41 range)	39 (2 IQR; 33–40 range)	39 (2 IQR; 37–39 range)	39 (3 IQR; 36–40 range)
Preterm delivery (n,%)	2/14 (14.3)	1/7 (14.3)	0/5 (0)	3/67 (4.5)
FGR (n,%)	2/14 (14.3)	1/7 (14.3)	1/5 (20.0)	5/67 (7.5)
Apgar score	10 (1 IQR; 4–10 range)	10 (0.5 IQR; 5–10 range)	10 (1 IQR; 6–10 range)	10 (0.5 IQR; 5–10 range)
Fetal malformations (n,%)	0/14 (0)	0/7 (0)	0/5 (0)	2/67 (3.0)
Abruptio placentae (n,%)	0/14 (0)	0/7 (0)	0/5 (0)	0/67 (0)

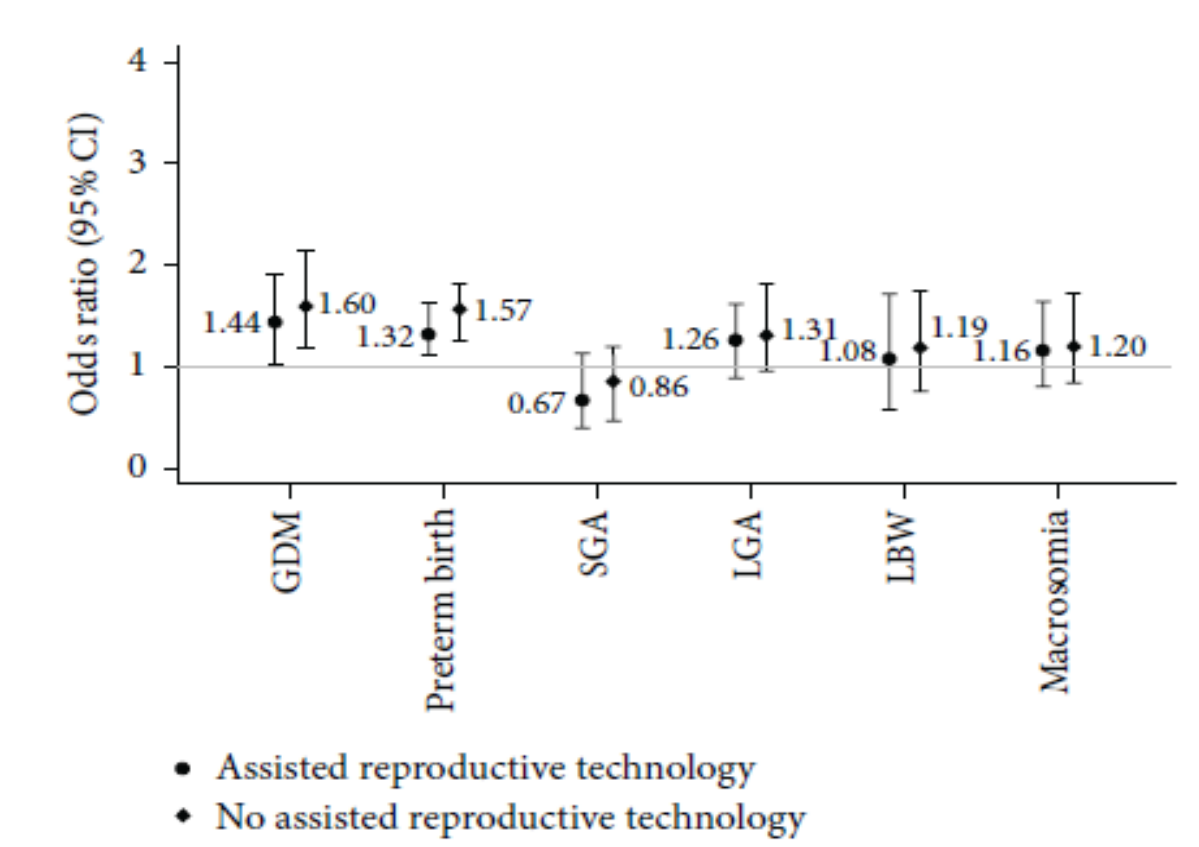
AGA = appropriate for gestational age; ASRM = American Society of Reproductive Medicine; ESHRE = European Society of Human Reproduction and Embryology; GDM = gestational diabetes mellitus; FGR = fetal growth restriction; LGA = large for gestational age; PCO = polycystic ovaries; PCOS = polycystic ovary syndrome; PE = preeclampsia; PIH = pregnancy-induced hypertension; SGA = small for gestational age.

[a] $P < .05$ vs. ovulatory phenotype.

[b] $P < .05$ vs. nonhyperandrogenic phenotype.

Palomba. Effects of PCOS phenotypes on pregnancy. Fertil Steril 2009.

Adverse pregnancy outcomes in Chinese women with PCOS: mainly risks of Gest DM and preterm birth



Xiao, Qing. International Journal of Endocrinology Feb, 2016

Conclusions: PCOS and ART

- PCOS is extremely prevalent among women presenting with infertility and can present with several phenotypes
- When IVF is indicated, in general, the prognosis is good (careful monitoring is imperative)
- There are important metabolic stressors that can lead to adverse outcomes; it is likely that these are related to increased body weight
- Pregnancy outcomes are worse in PCOS, in all phenotypes, but mainly in the more classic phenotypes; DM and neonatal prematurity are most prevalent