



# İnsulin Direnci ve PCOS

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## POLYCYSTIC OVARY SYNDROME: AN ANCIENT DISORDER?

Ricardo Azziz, M.D., M.P.H., M.B.A.<sup>a,d,e,\*</sup>, Daniel A. Dumesic, M.D.<sup>f,g</sup>, and Mark O. Goodarzi, M.D., Ph.D.<sup>a,b,c,d</sup>



Is Polycystic Ovary Syndrome (PCOS) an ancient disorder? Or is it a disorder of recent development, the consequence of rising metabolic stress in an increasingly obese society? And if it is ancient, why has it persisted despite its reproductive disadvantage? And can the

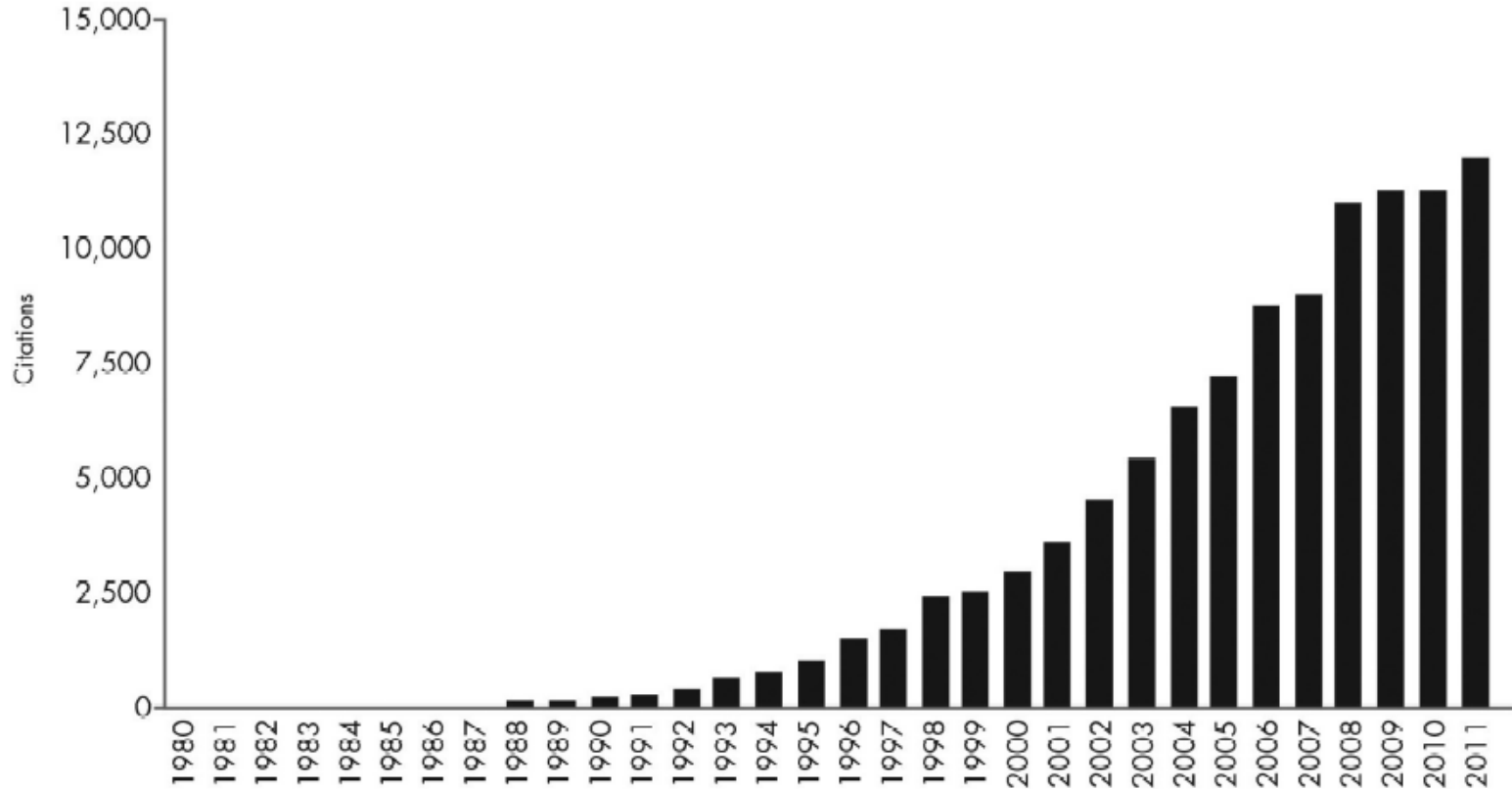


# TANISAL KRITERLER

**TABLE 2.** Percentage of participants agreeing on various criteria at 1990 NICHD PCOS conference (54)

<b>Definite or probable</b>	<b>Possible</b>
Hyperandrogenemia, 64%	Insulin resistance, 69%
Exclusion of other etiologies, 60%	Perimenarchal onset, 62%
Exclusion of CAH, 59%	Elevated LH/FSH, 55%
Menstrual dysfunction, 52%	PCO by ultrasound, 52%
Clinical hyperandrogenism, 48%	Clinical hyperandrogenism, 52%
	Menstrual dysfunction, 45%

# İnsülin Direnci ve PCOS





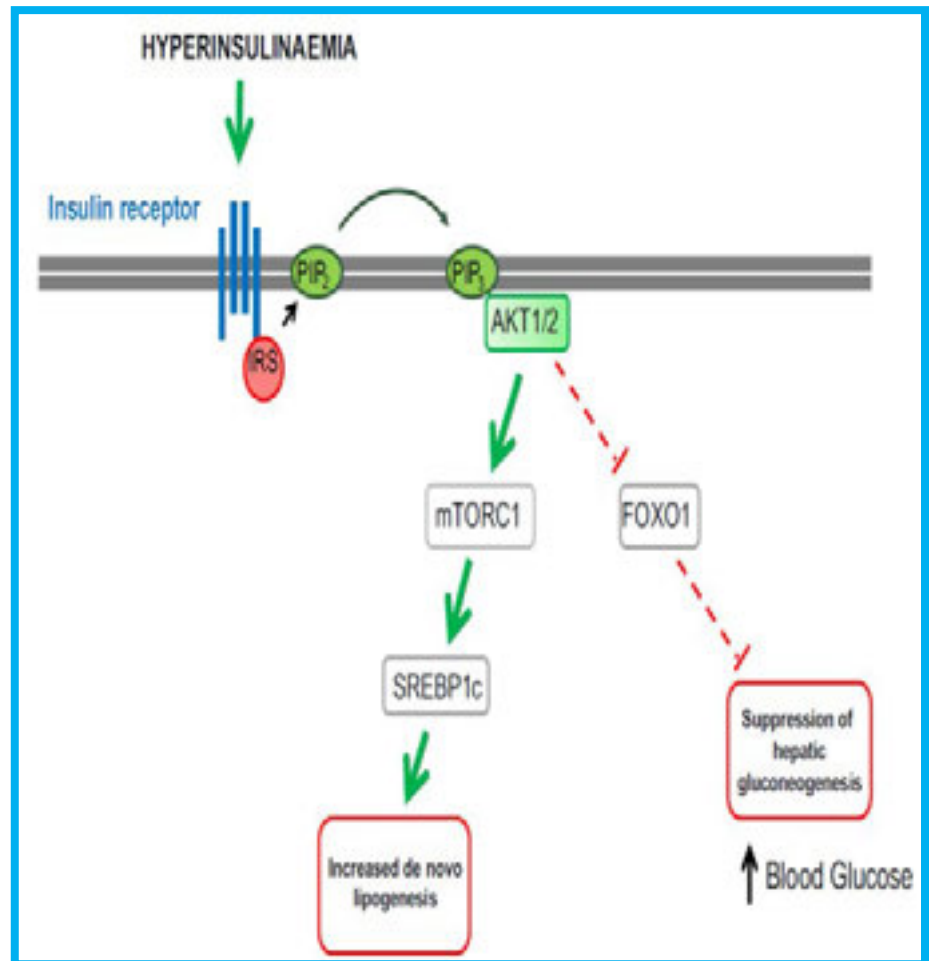
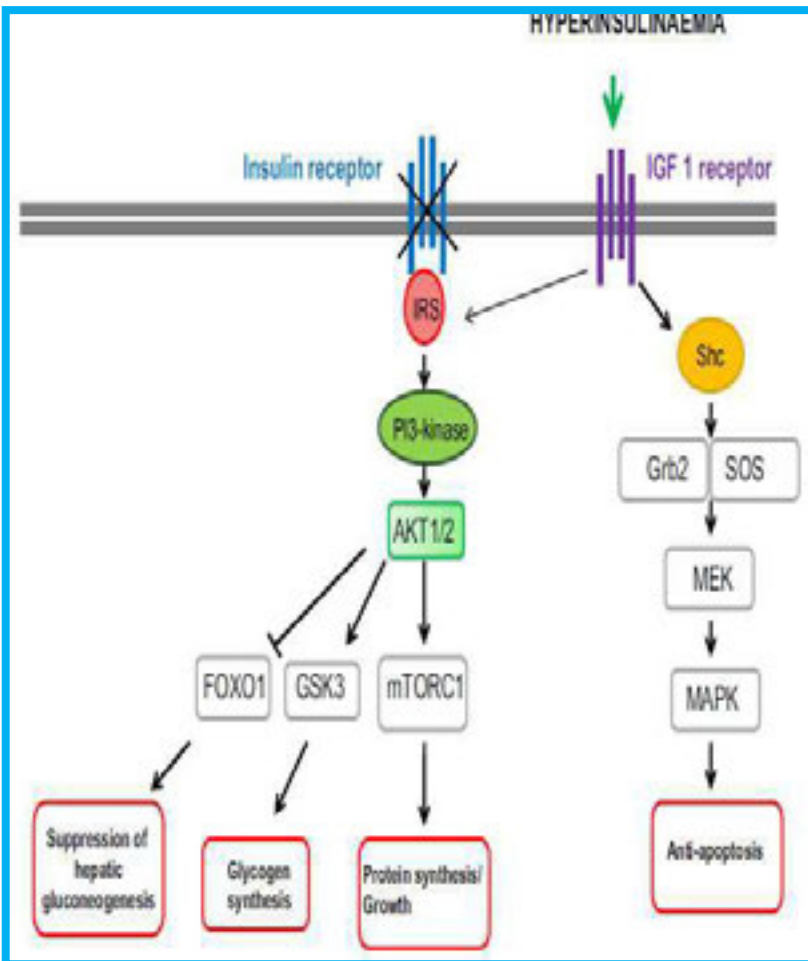
### 3 Metabolic insights from extreme human insulin resistance phenotypes

# İnsülin Direnci-Tanım

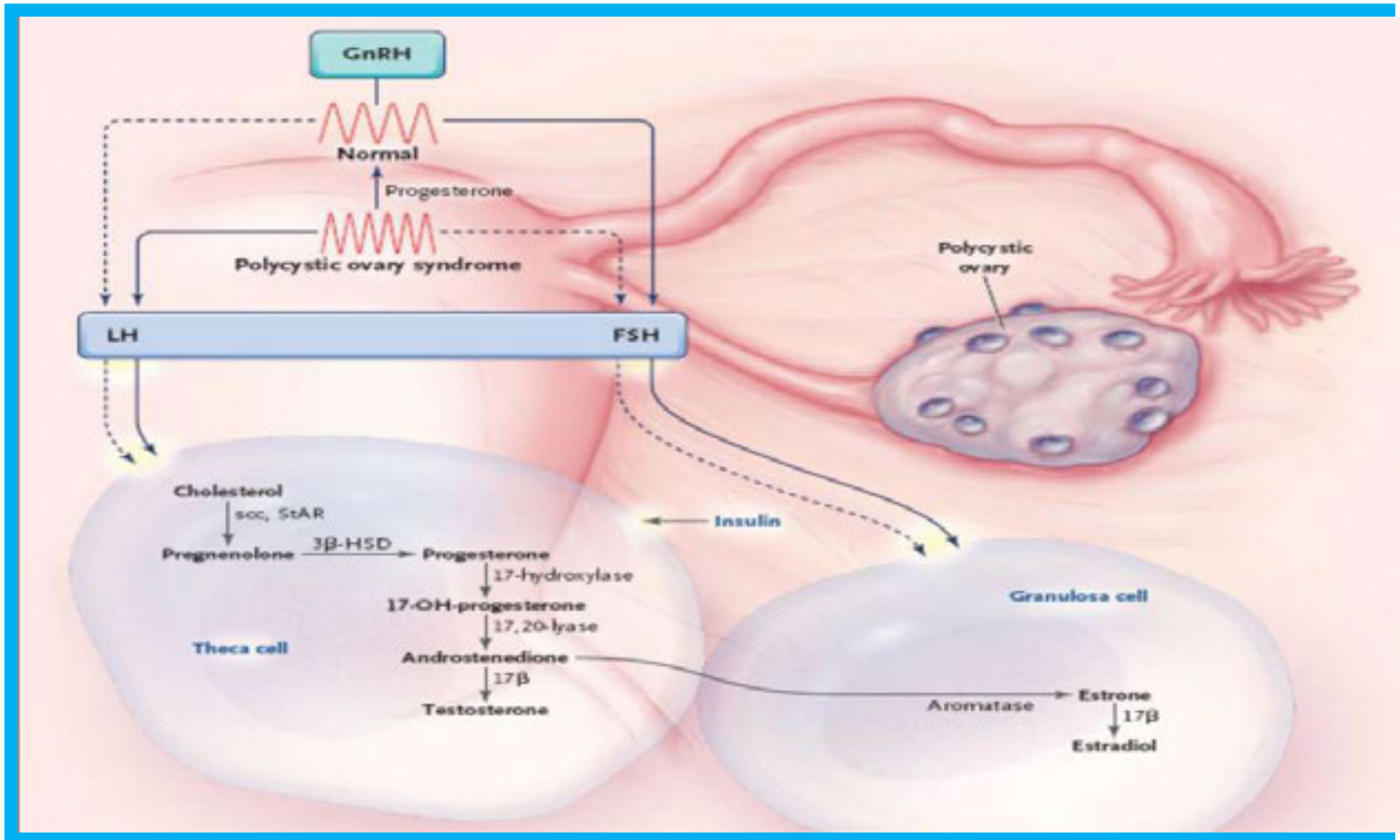
Comparison of key features of syndromes of insulin resistance.

	'Common' IR	INSR defect	Lipodystrophy
Insulin resistance	+	+++	++
T2DM	+	++	++
Dyslipidaemia	+	0	++
Fatty liver	+	0	++
PCOS	+	+++	++
Hypertension	++	0	+
Acanthosis nigricans	+	+++	++
Adiponectin	↓	↑↑	↓↓
SHBG	↓	↑↑	↓
IGFBP1	↓	↑↑	↓

# Hiperinsulinemi

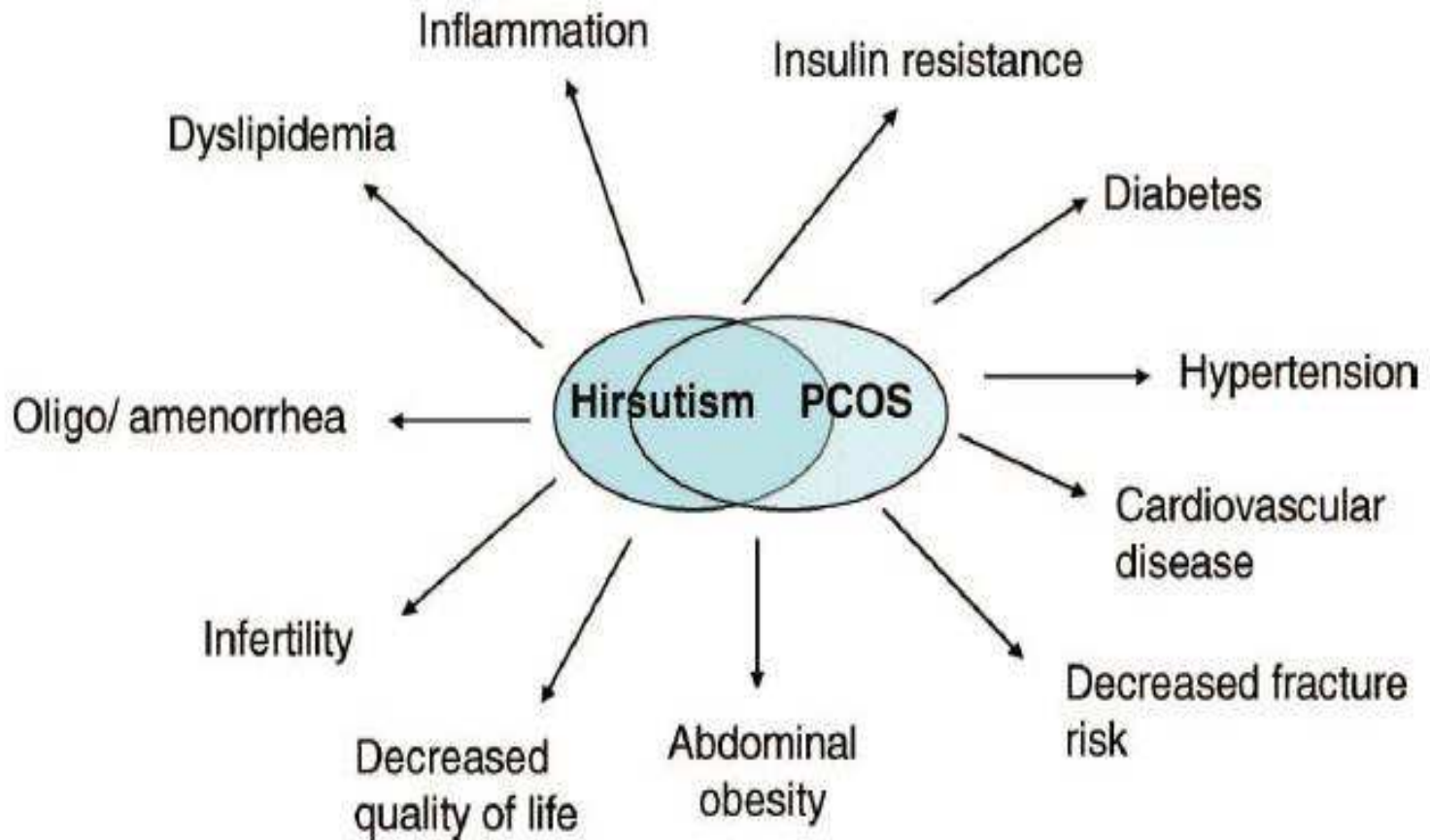


# Patofizyoloji





# İnsülin direnci



# Klinik fenotip

## Clinical manifestations of insulin resistance

### Glucose homeostasis

Variable, including overt diabetes, impaired glucose tolerance, normal, and hypoglycemia

### Cutaneous

Acanthosis nigricans

Skin tags

Alopecia

### Reproductive

Amenorrhea

Hirsutism

Virilization

Infertility (in women)

### Linear growth

Variable, including normal, impaired, increased

### Adipose tissue

Variable, including normal, lipoatrophy, lipohypertrophy, obesity

### Musculoskeletal

Variable, including normal, cramps, muscle hypertrophy, pseudoacromegaly

### Lipid metabolism

Normal or hypertriglyceridemia

### Autoimmunity

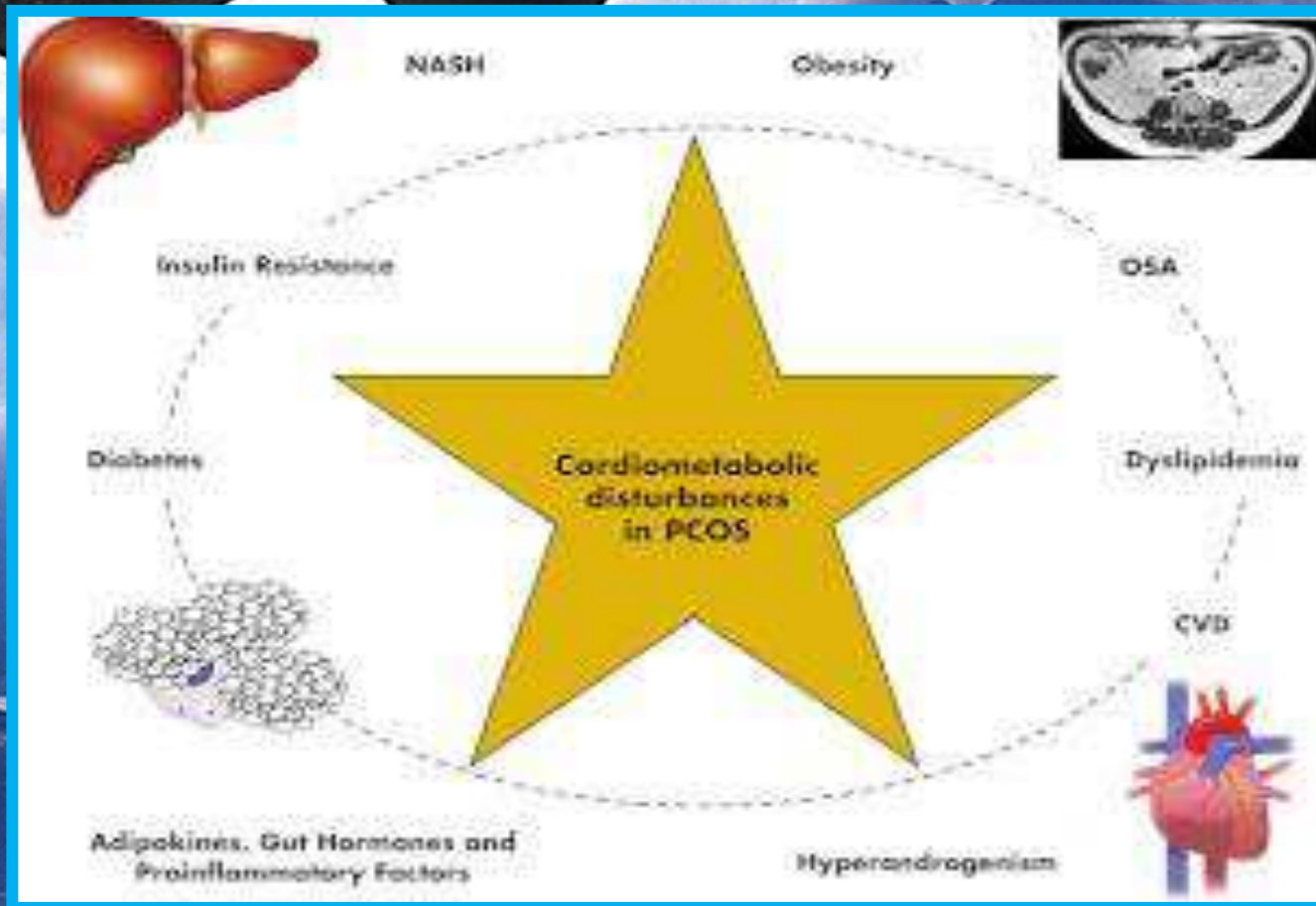
Type B syndrome with variety of immune phenotypes



# Hiperinsülinemi- hiperandrojenizm



# Kardiyometabolik Etkiler



# Not all women diagnosed with PCOS share the same cardiovascular risk profiles

Vuk P. Jovanovic, M.D.,<sup>a</sup> Enrico Carmina, M.D.,<sup>b</sup> and Rogerio A. Lobo, M.D.<sup>a</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, New York; and <sup>b</sup> Department of Clinical Medicine and Emerging Diseases, University of Palermo, Palermo, Italy

Fertil Steril 2010;94:826-32

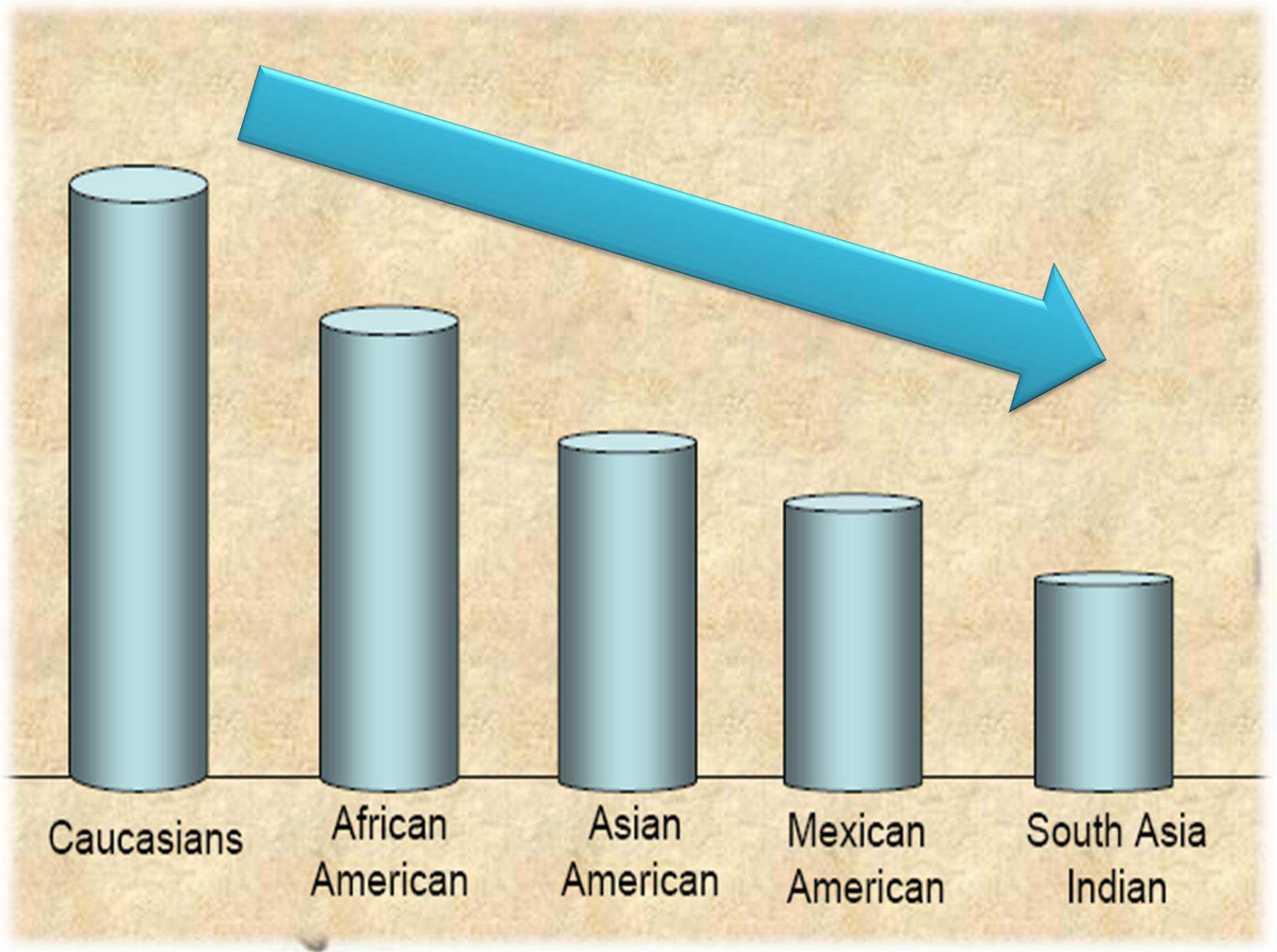
**TABLE 2**

Evolving cardiometabolic risks with various phenotype relating to PCOS.

	PCOS criteria not met		Euandrogenic PCOS	Ovulatory PCOS	Classic PCOS	
	ISOLATED PAO	IH	Phenotype D	Phenotype C	Phenotype B	Phenotype A
Androgens	Normal	Elevated	Normal	Elevated	Elevated	Elevated
Cycles	Normal	Normal	Irreg (ANOV)	Normal (OVULAT)	Irreg (ANOV)	Irreg (ANOV)
Ovaries	Polycystic	Normal	Polycystic	Polycystic	Normal or unknown status	Polycystic
CV/Metabolic risk	Normal	Normal – small increase	Small increase (?)	Some increase	Increase	Increase

Note: Spectrum of risk modified by weight and familial/genetic profile. IH = idiopathic hyperandrogenism; IRREG = irregular; ANOV = anovulatory; OVULAT = ovulatory; PAO = polycystic appearing ovaries; ? = questionable.

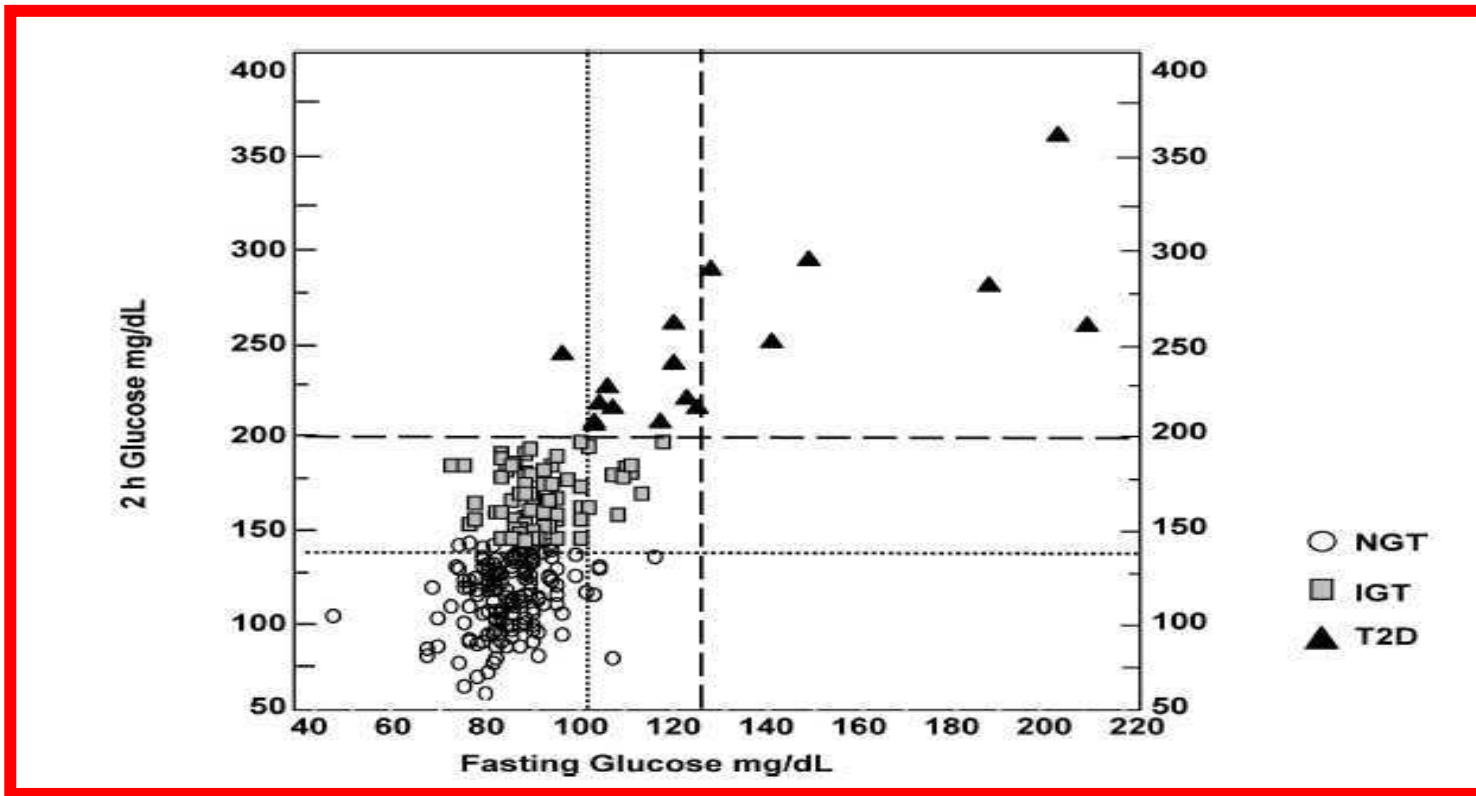
*Jovanovic. PCOS associated risk by phenotypes. Fertil Steril 2010.*



# İnsülin Direnci-Tanı

Test	Formül	Tanı
Euglisemik insülin klemp tekniği		
75 gr OGTT IGT Tip 2 DM	AKŞ:100-125 mg/dl, 2.saat 140-199 mg/dl AKŞ:≥126 mg/dl, 2.saat ≥ 200 mg/dl	
Bazal İnsülin	$\mu\text{U/ml}$	>20
Glukoz/İnsülin indeksi	$\text{Glukoz(mg/dl)}/\text{İnsülin } (\mu\text{U/ml})$	<4.5
HOMA-IR (Homeostasis model assessment)	$\text{Glukoz (mg/dl)} \times \text{İnsülin } (\mu\text{U/ml}) / 405$	>2.7
QUICKI (Quantitative insulin sensitivity check index)	$1/\log \text{ insülin } (\mu\text{U/ml}) + \log \text{ glukoz (mg/dl)}$	<0.33

# Disglisemi ve PCOS



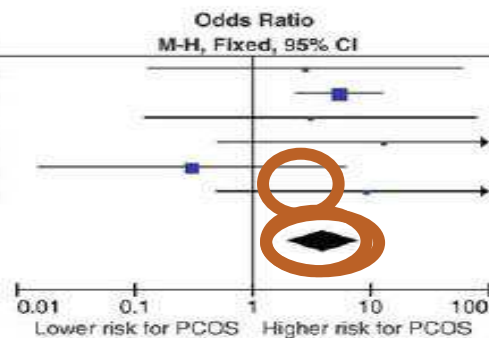
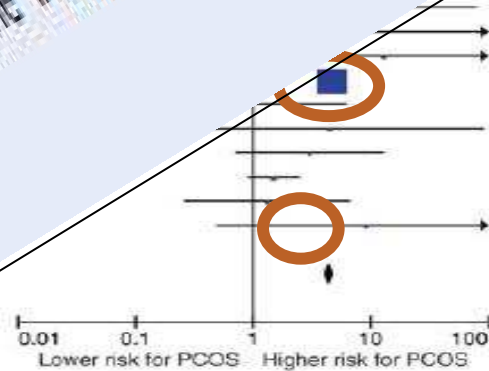
Legro et al. J Clin Endocrinol Metab 1999

# Impaired glucose tolerance, diabetes and metabolic syndrome in women with polycystic ovary syndrome: a systematic review and meta-analysis

Lisa J. Moran<sup>1,\*</sup>, Marie L. Misso<sup>2</sup>, Robyn M. Teede<sup>1,3</sup> and Robert J. Norman<sup>4,†</sup>

A

Study or Subgroup	PCOS		Control		Weight	M-H, Random, 95% CI
	Events	Total	Events	Total		
Dos Reis 1995	3	29	0	19	0.1%	
Rajkhowa 1996	2	72	0	39	0.1%	
Cibula 2000	9	28	60	752	100.0%	
Yarali 2001	1	30	0	30	0.1%	
Sir-Petermann 2004	4	146	0	146	0.1%	
Sawathipamich 2005	3	6	0	6	0.1%	
Lo 2006	988	11035	0	11035	100.0%	
Alvarez-Blasco 2006	0	2	0	2	0.0%	
Leibel 2006	3	3	0	3	0.1%	
Marquez 2008	0	1	0	1	0.0%	
Shaw 2008	0	1	0	1	0.0%	
Bhattacharya 2009	0	1	0	1	0.0%	
Moini 2009	0	1	0	1	0.0%	
Total (95% CI)	1000	11175	60	11175	100.0%	4.00 [1.97, 8.10]
Total events	1000		60			
Heterogeneity: $\tau^2 = 0.00$ ; $I^2 = 0.0%$						



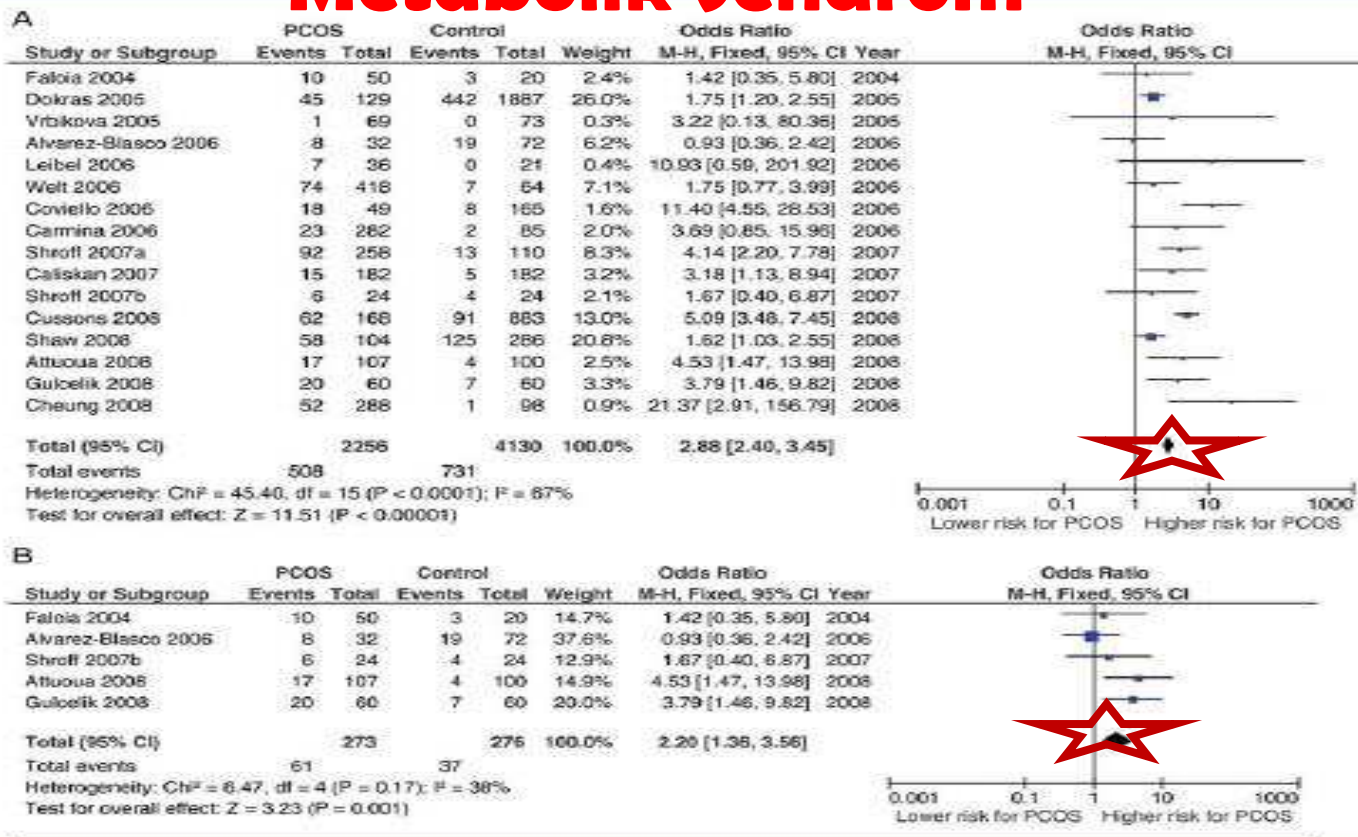
**CONCLUSIONS:** Women with PCOS had an elevated prevalence of IGT, DM2 and metabolic syndrome in both BMI and non-BMI matched studies. Few studies have determined IGT/DM2 or metabolic syndrome incidence in women with and without PCOS and further research is required.

Study or Subgroup	Events	Total	Weight	Odds Ratio		Year
				M-H, Fixed, 95% CI	Year	
Dos Reis 1995	3	29	0.1%	2.80 [0.13, 59.82]	1996	
Rajkhowa 1996	2	72	0.1%	5.46 [2.37, 12.60]	2000	
Cibula 2000	9	28	100.0%	3.10 [0.12, 79.23]	2001	
Yarali 2001	1	30	0.1%	13.00 [0.51, 330.48]	2005	
Sir-Petermann 2004	4	146	0.1%	0.31 [0.02, 6.09]	2006	
Sawathipamich 2005	3	6	0.1%	9.23 [0.49, 172.33]	2009	
Lo 2006	988	11035	100.0%	4.00 [1.97, 8.10]		
Alvarez-Blasco 2006	0	2	0.0%			
Leibel 2006	3	3	0.1%			
Marquez 2008	0	1	0.0%			
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# Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis

Lisa J. Moran<sup>1,\*</sup>, Marie L. Misso<sup>2</sup>, Robert A. Wild<sup>3,†</sup>,  
 and Robert J. Norman<sup>4,†</sup>

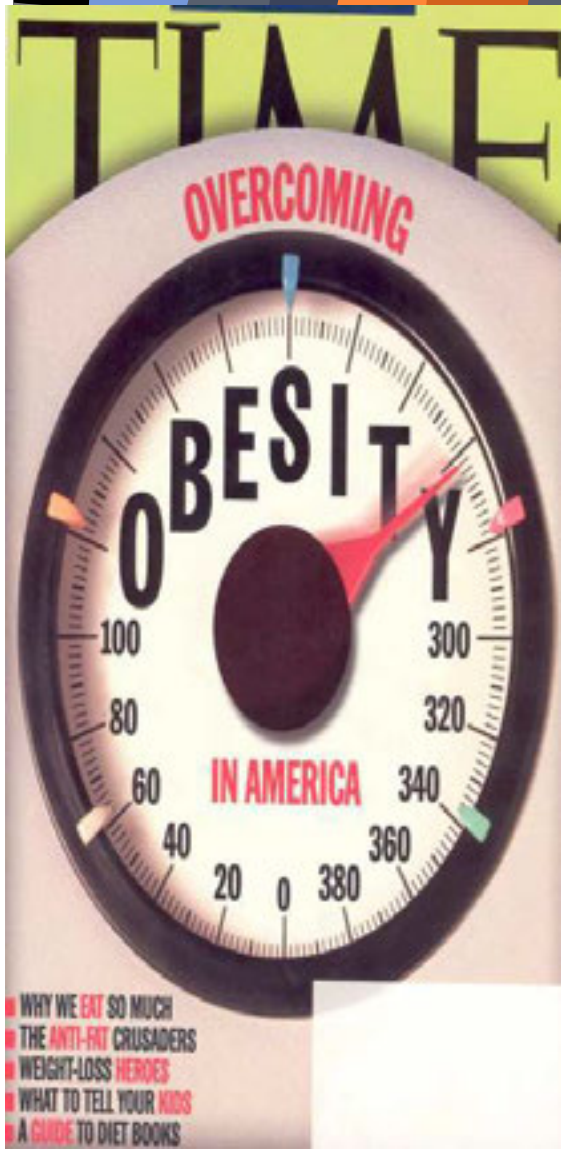
## Metabolik Sendrom



# Metabolik Sendrom

Parameters	NCEP ATP3 2005*	IDF 2006	EGIR 1999	WHO 1999	AACE 2003
Required		Waist $\geq 94$ cm (men) or $\geq 80$ cm (women)*	Insulin resistance or fasting hyperinsulinemia in top 25 percent	Insulin resistance in top 25 percent <sup>A</sup> ; glucose $\geq 6.1$ mmol/L (110 mg/dL); 2-hour glucose $\geq 7.8$ mmol/L (140 mg/dL)	High risk of insulin resistance <sup>o</sup> or BMI $\geq 25$ kg/m <sup>2</sup> or waist $\geq 102$ cm (men) or $\geq 88$ cm (women)
Number of abnormalities	$\geq 3$ of:	And $\geq 2$ of:	And $\geq 2$ of:	And $\geq 2$ of:	And $\geq 2$ of:
Glucose	$\geq 5.6$ mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	$\geq 5.6$ mmol/L (100 mg/dL) or diagnosed diabetes	6.1-6.9 mmol/ (110-125 mg/dL)		$\geq 6.1$ mmol/L (110 mg/dL); $\geq 2$ -hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	$< 1.0$ mmol/L (40 mg/dL) (men); $< 1.3$ mmol/L ( $\leq 0$ mg/dL) (women) or drug treatment for low HDL-C <sup>S</sup>	$< 1.0$ mmol/L (40 mg/dL) (men); $< 1.3$ mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C	$< 1.0$ mmol/L (40 mg/dL)	$< 0.9$ mmol/L (35 mg/dL) (men); $< 1.0$ mmol/L (40 mg/dL) (women)	$< 1.0$ mmol/L (40 mg/dL) (men); $< 1.3$ mmol/L (50 mg/dL) (women)
Triglycerides	$\geq 1.7$ mmol/L (150 mg/dL) or drug treatment for elevated triglycerides <sup>S</sup>	$\geq 1.7$ mmol/L (150 mg/dL) or drug treatment for high triglycerides	or $\geq 2.0$ mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or $\geq 1.7$ mmol/L (150 mg/dL)	$\geq 1.7$ mmol/L (150 mg/dL)
Obesity	Waist $\geq 102$ cm (men) or $\geq 88$ cm (women) <sup>z</sup>		Waist $\geq 94$ cm (men) or $\geq 80$ cm (women)	Waist/hip ratio $> 0.9$ (men) or $> 0.85$ (women) or BMI $\geq 30$ kg/m <sup>2</sup>	
Hypertension	$\geq 130/85$ mmHg or drug treatment for hypertension	$\geq 130/85$ mmHg or drug treatment for hypertension	$\geq 140/90$ mmHg or drug treatment for hypertension	$\geq 140/90$ mmHg	$\geq 130/85$ mmHg

# IGT-Metabolik Sendrom-Obezite



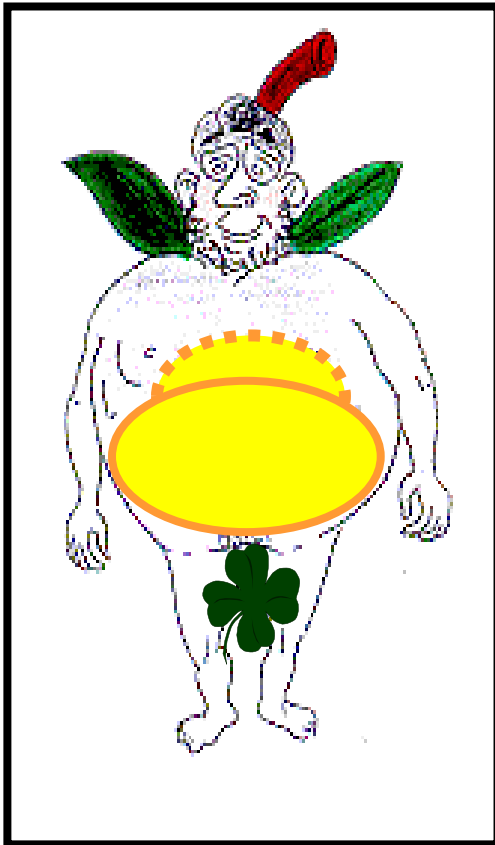
- ❖ IR : %60-80 PCOS  
%95 obez PCOS
- ❖ IGT, Tip 2 DM: %40
- ❖ MS: %33-47
- ❖ Obez PCOS IGT ve Tip 2 DM daha fazla



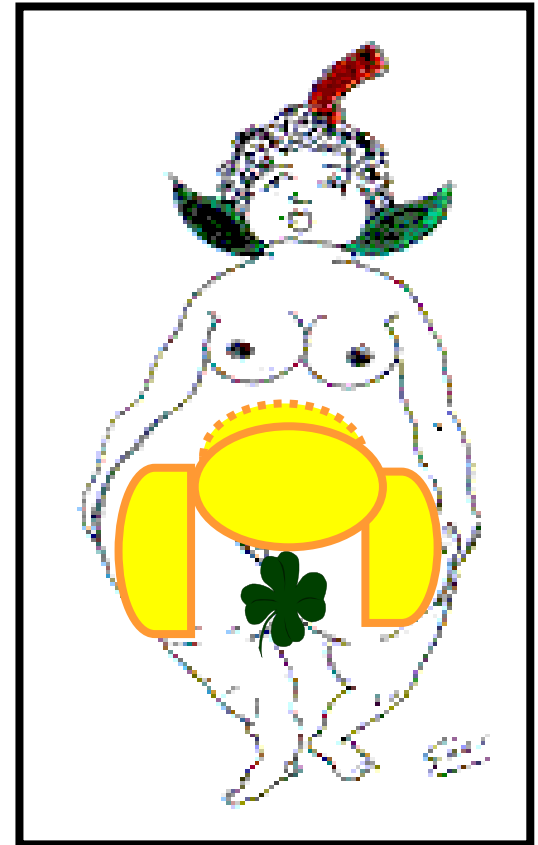
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## Polycystic ovaries and obesity

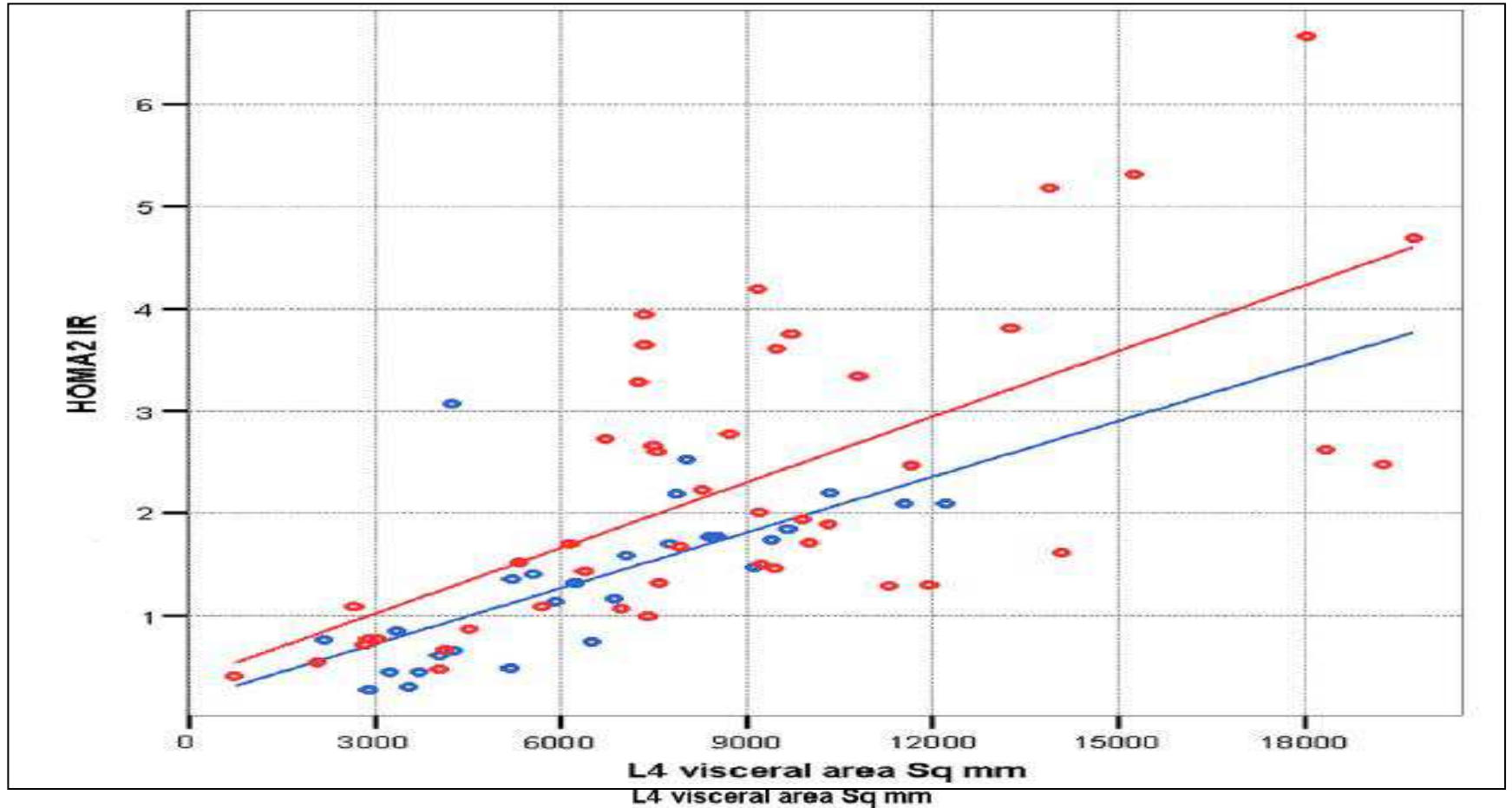
Ioannis E. Messinis, MD, PhD, FRCOG, Professor <sup>a, \*</sup>,



- ❖ Hiperinsülinemi
- ❖ Hiperandrojenizm (total testosteron ↑, FAI ↑, SHBG ↓)
- ❖ Adipokinler
  - Leptin
  - Adiponektin
  - Resistin
  - Visfatin
- ❖ Abdominal obezite hiperinsülinemi
- ❖ Kötü metabolik ve reproduktif sonuçlar



# Viseral yağ - İnsülin direnci



# Adiponektin

**THE trouble WITH FAT**

To get an inside look at how fat affects our health, we asked two women—one morbidly obese, the other a healthy weight—to spend the hours under a state-of-the-art scanner to get a high-resolution, low-dose CT scan (HRCT).

After scanning, we reported to the more common—and MRI helps us determine—adiposity got her.

**ADIPONEKTIN**  
Adipoz dokudan salinan (244 aa protein) adipokin Kilo alımı ile ters orantılı

**INSÜLİN DUYARLAŞTIRICI**  
anti-aterojenik, anti-inflamatuar

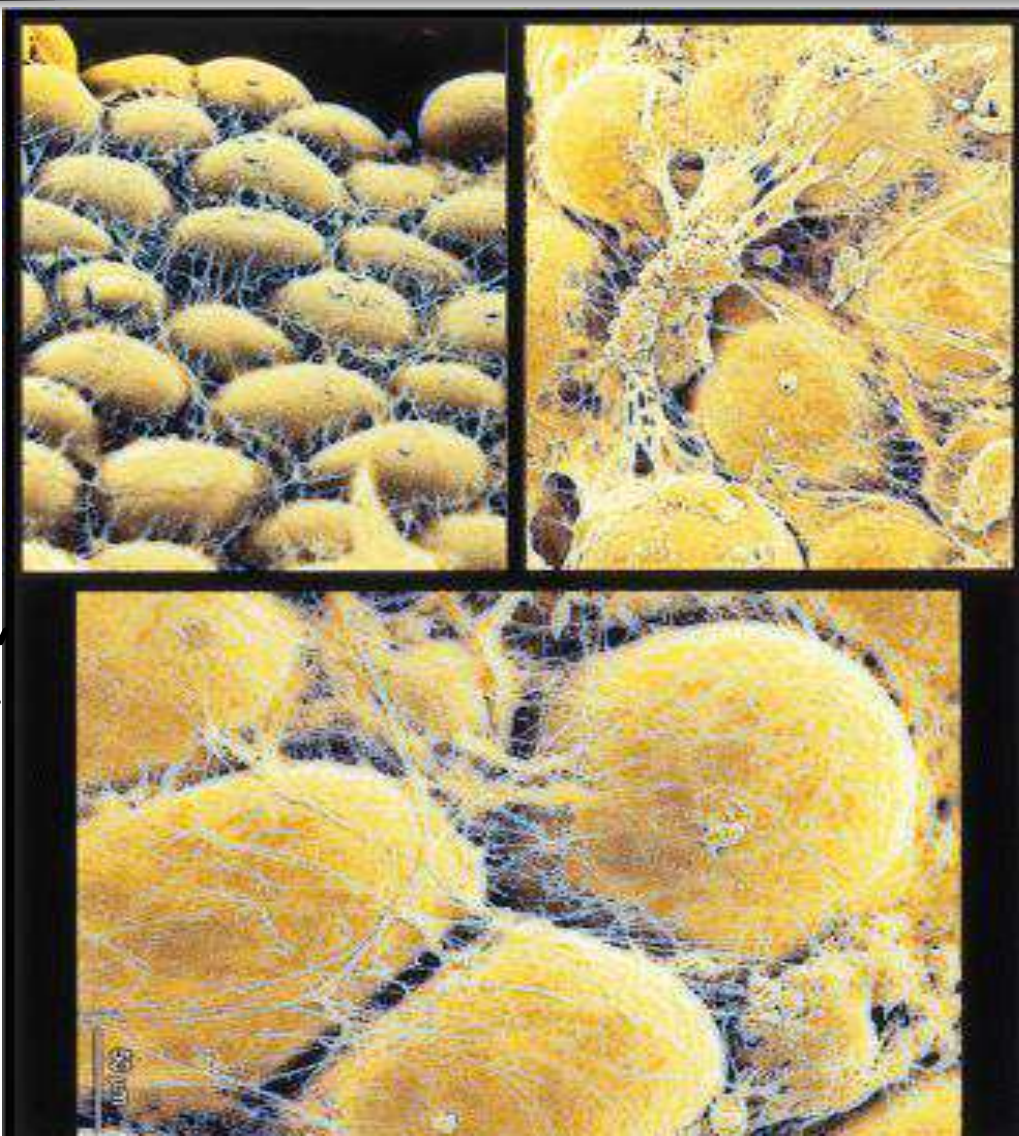
**PCOS** adiponektin ↓↓

**LIVER DISEASE**  
More obese people develop deposits of fat inside the liver, a condition that can progress to cirrhosis in about 10 years, and eventually die from failure.

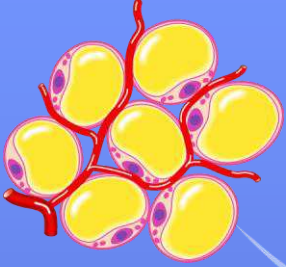
**COLON CANCER**  
Obese people have a greater risk of colon cancer. Research has found that fat appears to increase risk more than fat alone, which may explain why men who tend to store fat in their abdomens have a higher risk.

**STROKE**  
The risk of having a stroke is five to four times higher in people with type 2 diabetes. 40 percent of those are at night. Stroke occurs either when a blood vessel ruptures or a blood clot blocks an artery in the brain, causing damage to nerve cells.

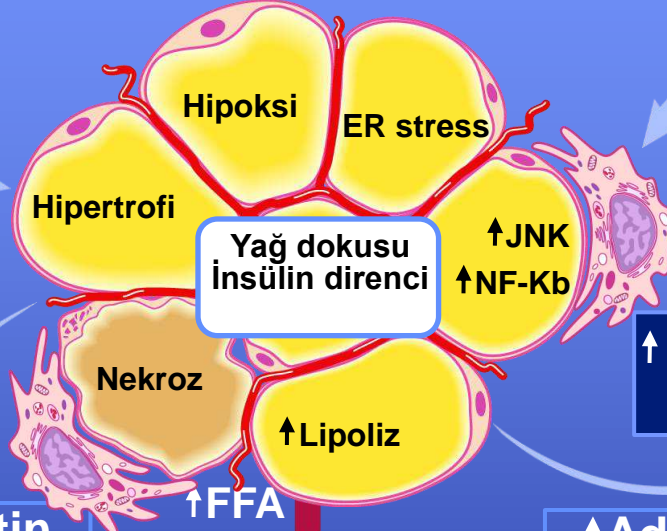
**TYPE 2 DIABETES**  
Obese people tend to have elevated cholesterol, which can lead to plaque building up in the arteries. They are twice as likely to have hypertension.



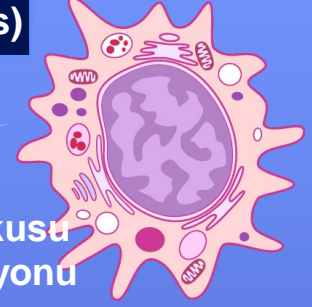
## Sağlıklı yağ dokusu



## Hipertrofik disfonksiyonel yağ dokusu



## Makrofaj aktivasyonu



↑ Makrofaj sitokinleri  
(TNF $\alpha$ , IL-6, CRP, others)

Yağ dokusu infiltrasyonu

↑ Adiposit-makrofaj ilişkisi

- Genetik
- Erken yaşam nutrisyon
- Kronik fazla beslenme

?

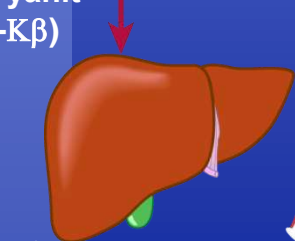
↓ Adiponektin

Sistemik etkiler

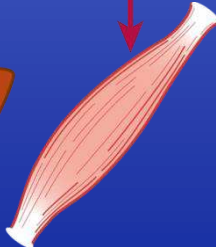
↑ Adipokin

Sistemik etkiler

Lipotoksiste



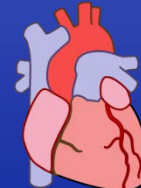
↑ HGP  
- NAFLD  
- NASH



↓ insuline bağlı  
glukoz alımı



↑ β-hücrel apoptosis  
↓ insülin salınımı  
- T2DM



- Endotelyal disfonksiyon  
- Pro-aterojenik hasar

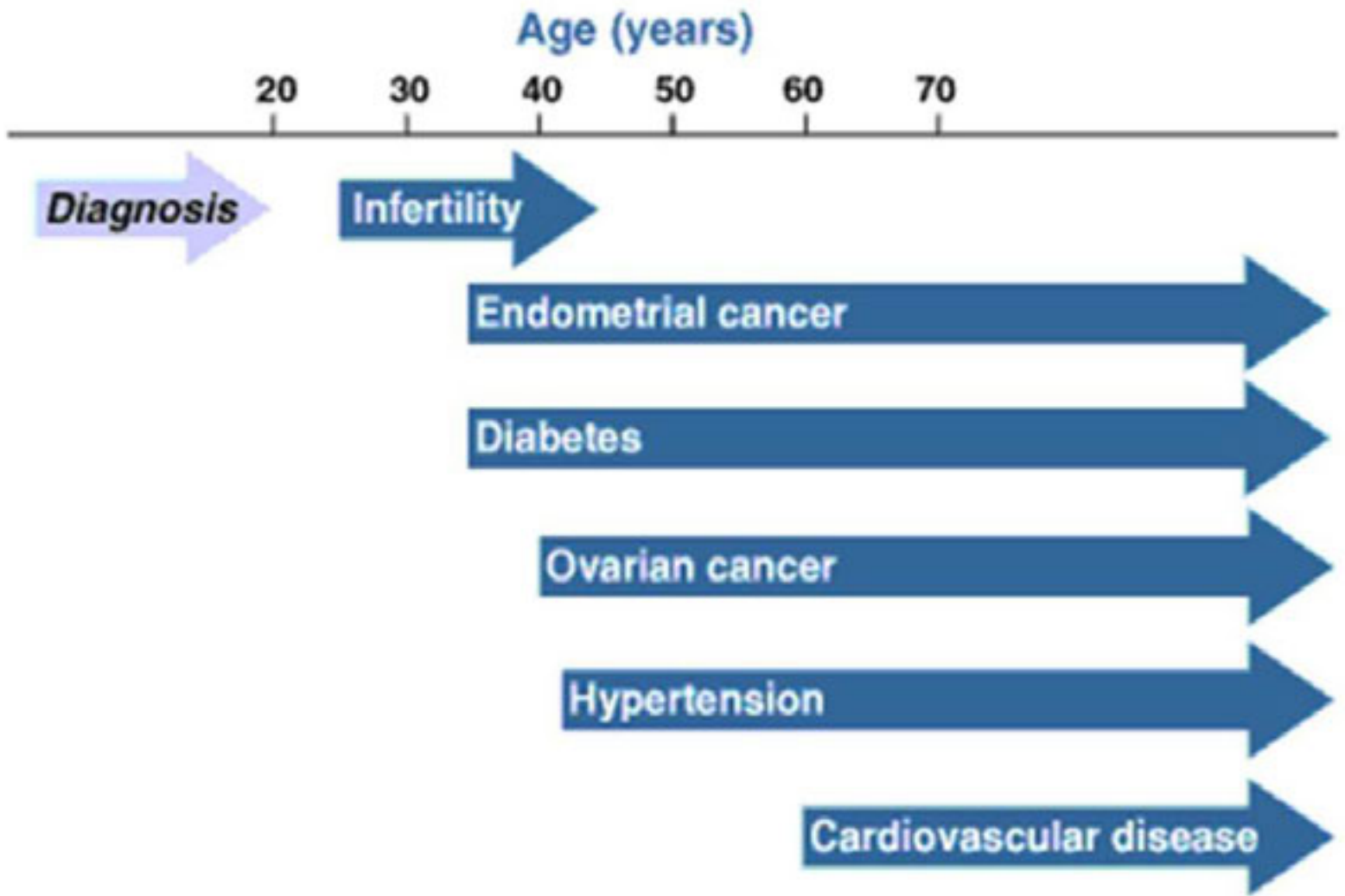


ateroskleroz

Lipotoksistenin Moleküler mekanizmaları

- ER stress
- İnflamatuar yanıt ( JNK, NF- $\kappa$ B)
- ↑ insülin direnci

**Risk or consequences of polycystic ovary syndrome from the time of early diagnosis at less than 20 years of age throughout life.**



## Age of Onset of Polycystic Ovarian Syndrome in Girls May Be Earlier Than Previously Thought

Jason Bronstein MD<sup>1</sup>, Sonali Tawdekar MD, MPH<sup>1</sup>, Yinghua Liu MD, MPA<sup>1</sup>, Melissa Pawelczak MD<sup>2</sup>, Raphael David MD<sup>2</sup>, Bina Shah MD<sup>2,\*</sup>

### Risk faktörleri

1. Makrozomik bebek
2. Konjenital virilizasyon
3. Düşük doğum ağırlığı
4. Prematür pubarş
5. Santral prekoks puberte
6. Obezite sendromları
7. Akantozis nigricans
8. Metabolik sendrom
9. Akne
10. Hirşutismus
11. Anovulasyon
12. Polikistik overler

Biochemical risk factors associated with PCOS, by age group: preadolescent < 13 years, adolescent ≥ 13 years (N = 58)

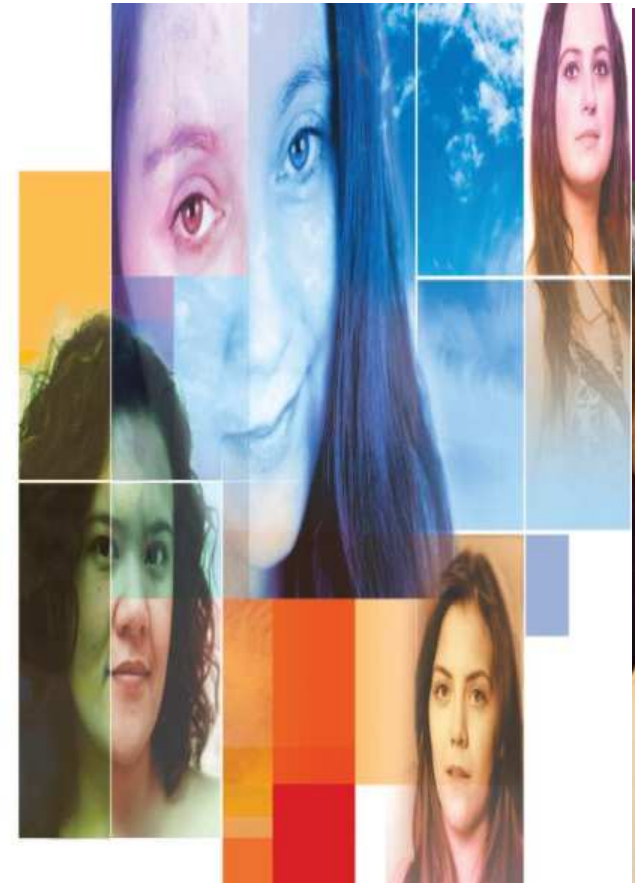
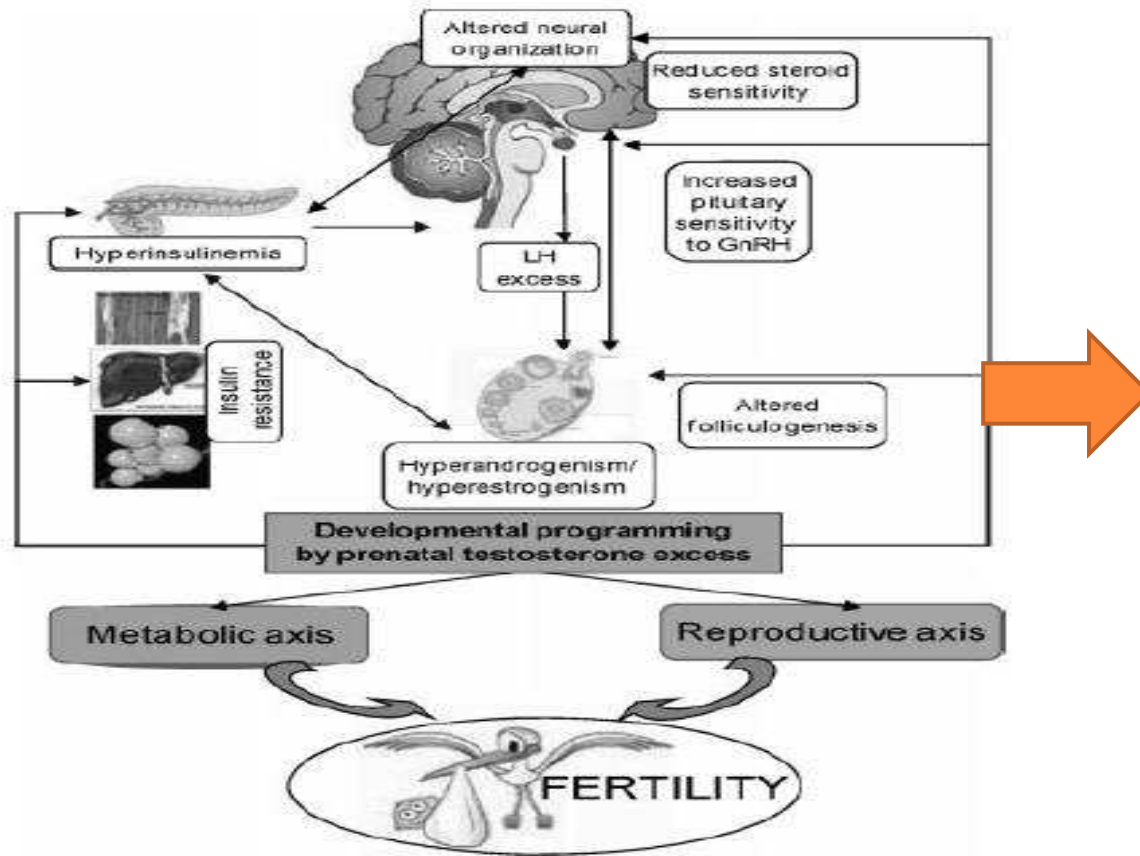
	N (Total)	Preadolescent (< 13 yrs)	Adolescent (≥ 13 yrs)	P value
Number of Patients	58	15	43	
High Total Testosterone				0.66
Yes	44	14	30	
No	14	1	13	
★ <u>High Free Testosterone</u>				0.077
Yes	56	19	37	
No	2	0	2	
Abnormal LH/FSH				<b>0.014</b>
Yes	36	5	31	
No	21	9	12	
Not suggestive*				0.839
Yes	17	2	15	
No	41	12	29	
★ <u>Any insulin resistance*</u>				0.533
No	48	12	36	
Yes	10	3	7	
Low HDL cholesterol				0.51
HDL < 40	20	6	14	
HDL ≥ 40	37	9	28	
High Triglycerides				1
Low or normal triglycerides	28	7	21	
High Triglycerides	24	8	16	
Elevated Fasting glucose				0.965
Fasting glucose ≥ 100 mg/dl	4	1	3	
Fasting glucose < 100	54	14	40	

**SONUÇ:** Hiperinsülinemi metabolik bozuklukları öngörebilir. Erken tanı ve tedavi erişkin dönem morbiditeyi azaltabilir.

# Developmental Origin of Reproductive and Metabolic Dysfunctions: Androgenic Versus Estrogenic Reprogramming

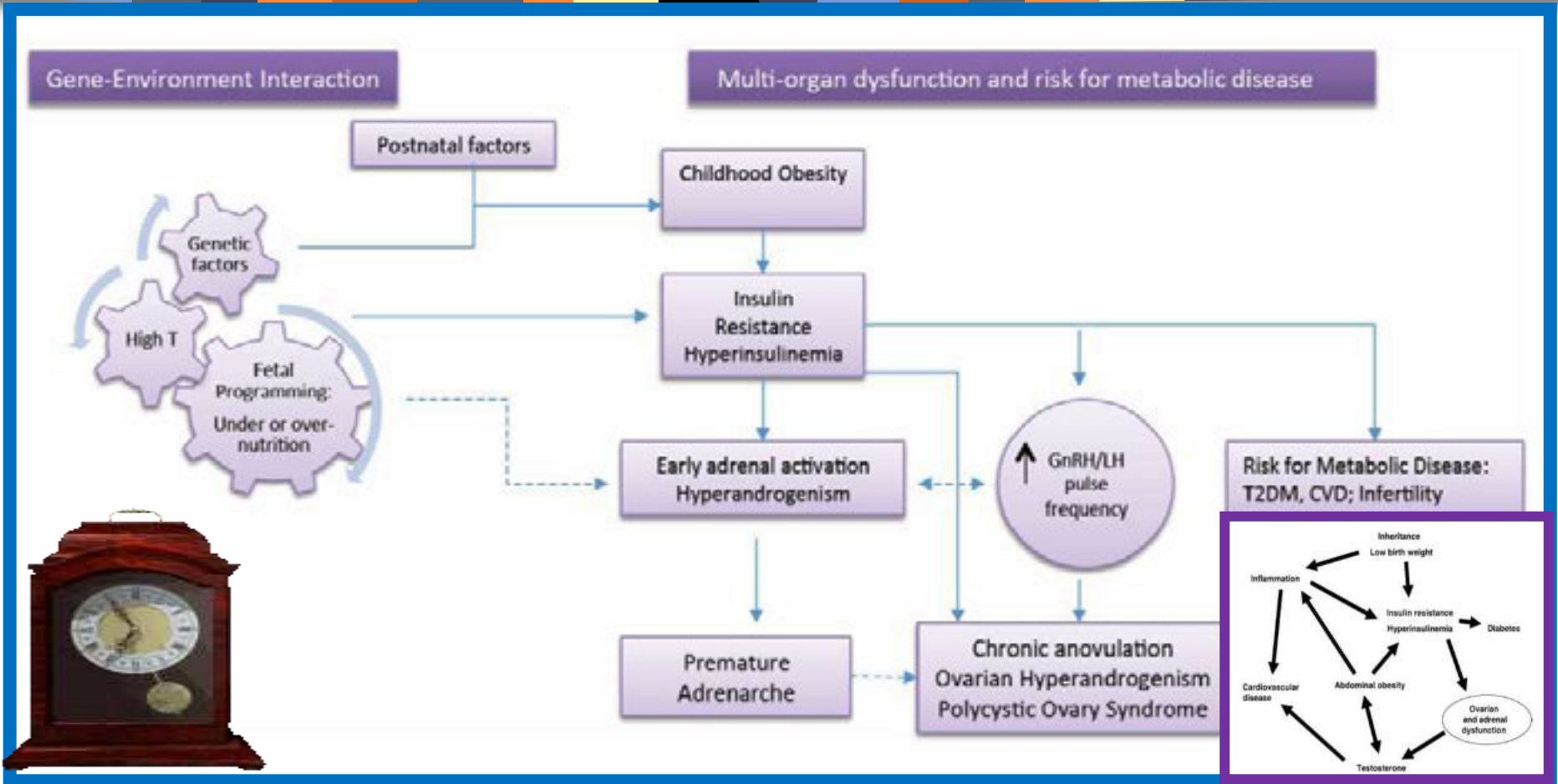
Vasanth Padmanabhan, Ph.D.,<sup>1</sup> and Almudena Veiga-Lopez, D.V.M., Ph.D.<sup>2</sup>

Semin Reprod Med 2011;29:173–186



# Ontogeny of Polycystic Ovary Syndrome and Insulin Resistance In Utero and Early Childhood

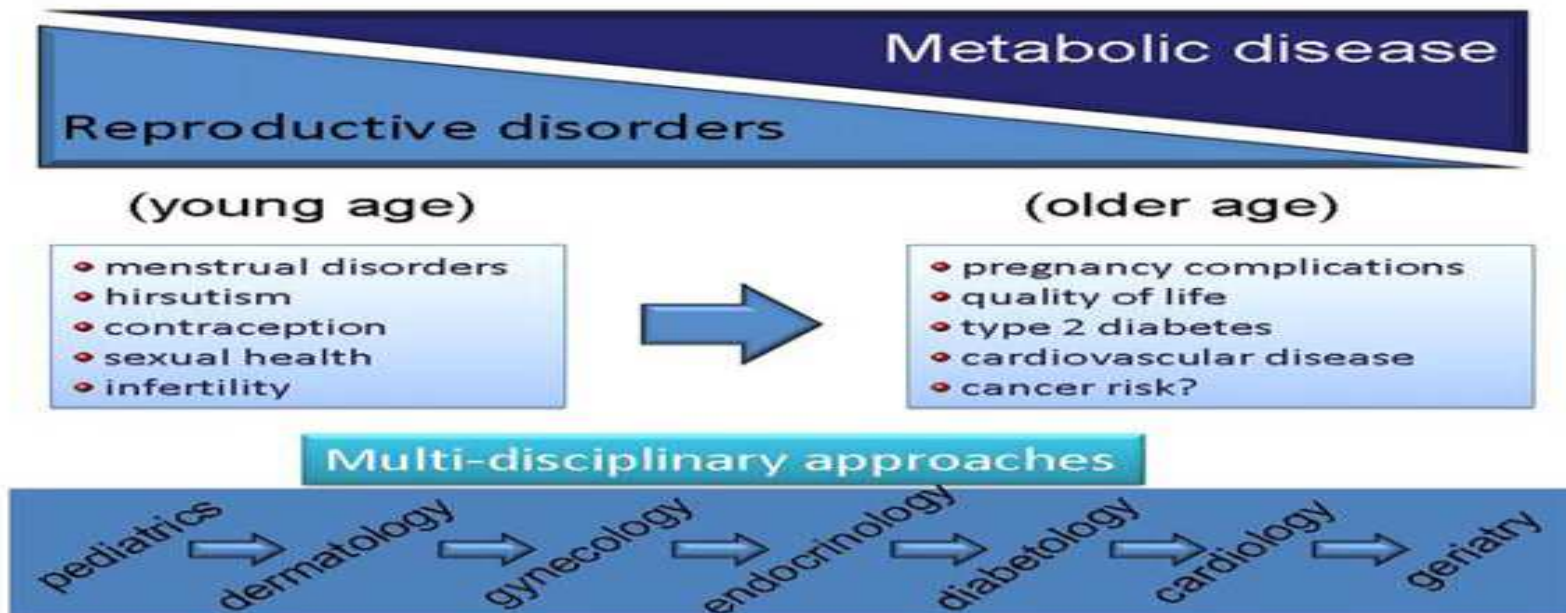
David H Abbott, PhD<sup>a</sup> and Fida Bacha, MD<sup>b</sup>



# Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group

Bart C. J. M. Fauser, M.D.,<sup>a</sup> Basil C. Tarlatzis, M.D.,<sup>b</sup> Robert W. Rebar, M.D.,<sup>c</sup> Richard S. Legro, M.D.,<sup>d</sup> Adam H. Balen, M.D.,<sup>e</sup> Roger Lobo, M.D.,<sup>f</sup> Enrico Carmina, M.D.,<sup>g</sup> Jeffrey Chang, M.D.,<sup>h</sup> Bulent O. Yildiz, M.D.,<sup>i</sup> Joop S. E. Laven, M.D.,<sup>j</sup> Jacky Boivin, M.D.,<sup>k</sup> Felice Petraglia, M.D.,<sup>l</sup> C. N. Wijeyeratne, M.D.,<sup>m</sup> Robert J. Norman, M.D.,<sup>n</sup> Andrea Dunaif, M.D.,<sup>o</sup> Stephen Franks, M.D.,<sup>p</sup> Robert A. Wild, M.D.,<sup>q</sup> Daniel Dumesic, M.D.,<sup>r</sup> and Kurt Bamhart, M.D.<sup>s</sup>

## PCOS: changing women's health paradigm



# Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group

- ❖ **İnsulin direnci-Metabolik Sendrom-Obezite-Tip 2 DM**
  - # PCOS- IGT ve T2DM için major risk faktörü (Kanıt A)
  - # Obezite (IR etkisi) IGT ve T2DM arttıran faktör(Kanıt A)
  - # Obezite prevalansının artmasıyla PCOS da DM artması bekleniyor (Kanıt B)
  - # IGT ve T2DM taraması OGTT (75 gr) yapılmalı. İnsülin ölçümünün faydası yok (Kanıt C)
  - # Tarama: HA+OA, AN, obezite (BMI >30 kg/m<sup>2</sup>), aile DM öyküsü, GDM (Kanıt C)
  - # Diyet ve yaşam tarzı değişiklikleri fertilitiyi arttırmak ve DM önlemede ilk seçenek (Kanıt B)
  - # Metformin IGT ve T2DM kullanılabilir. Diğer insülin duyarlaştırıcı ajanların kullanımından kaçın (GPP)

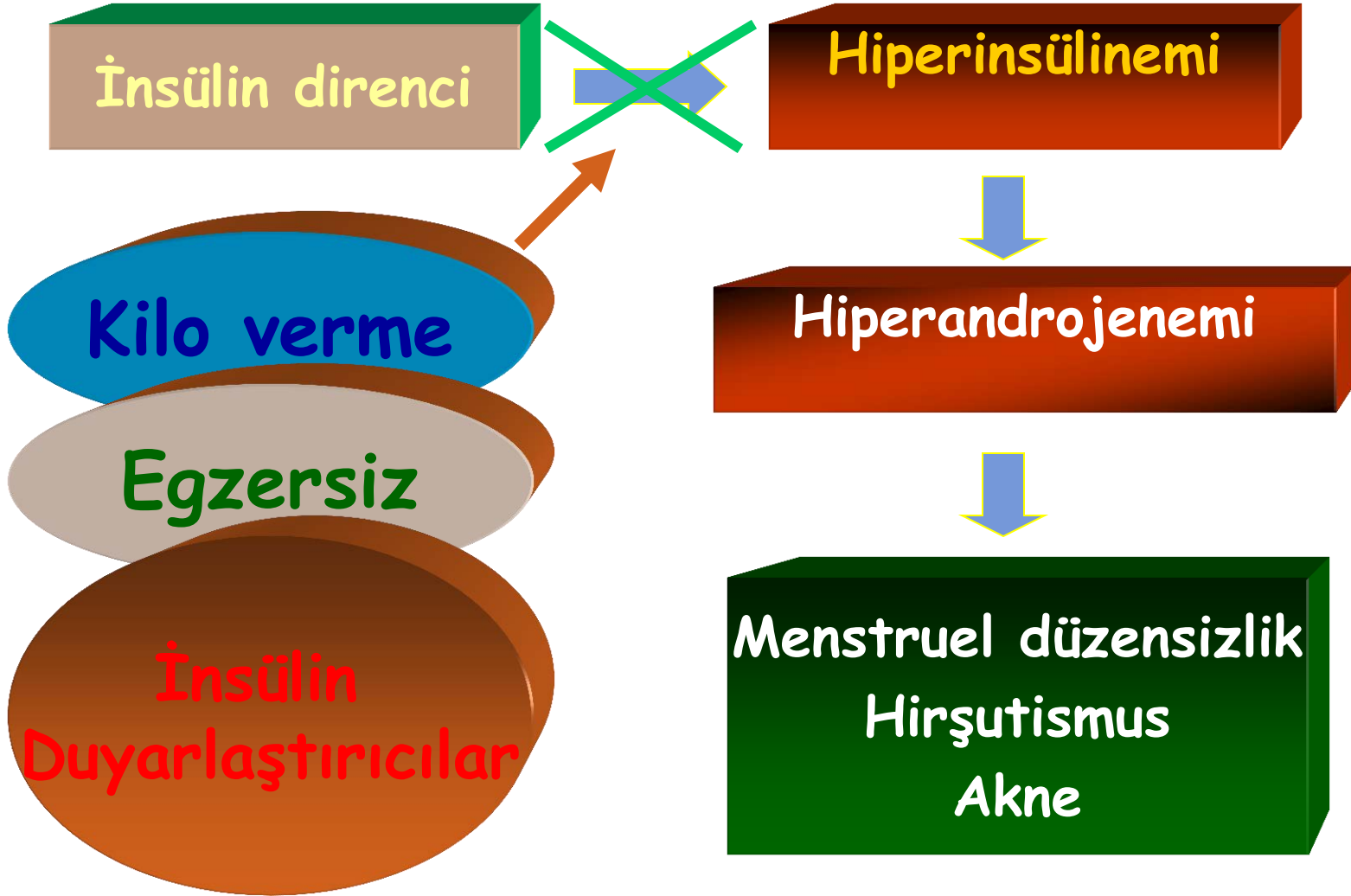


## Assessment of Cardiovascular Risk and Prevention of Cardiovascular Disease in Women with the Polycystic Ovary Syndrome: A Consensus Statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society

**Table 1. Current cardiovascular disease risk screening recommendations for women with polycystic ovary syndrome according to the Androgen Excess-Polycystic Ovarian Syndrome Society Consensus Statement**

Metabolic and CVD risk factors	Testing	Target population	Frequency
Hypercholesterolemia and dyslipidemia	<ul style="list-style-type: none"> <li>Fasting lipid profile (TC, non-HDLc, HDLc, TGs, LDLc)</li> </ul>	<ul style="list-style-type: none"> <li>All women with PCOS</li> <li>No additional CVD risk, LDLc goal &lt;130mg/dl</li> <li>With metabolic syndrome, LDLc goal 70–100mg/dl</li> <li>With T2DM/vascular/renal disease, LDLc goal &lt;70 mg/dl</li> </ul>	<ul style="list-style-type: none"> <li>Biannually or sooner if weight gain occurs</li> </ul>
Impaired glucose tolerance	<ul style="list-style-type: none"> <li>75-g OGTT – 2-h glucose concentration</li> </ul>	<ul style="list-style-type: none"> <li>BMI &gt;30 kg/m<sup>2</sup></li> <li>Lean PCOS with age &gt;40 years or hx GDM, FHx: T2DM</li> </ul>	<ul style="list-style-type: none"> <li>Normal baseline 75-g OGTT, biannually or sooner depending on CVD risk factors</li> <li>Baseline IGT, 75-g OGTT annually</li> </ul>
Type 2 diabetes	<ul style="list-style-type: none"> <li>75-g OGTT – 2-h glucose concentration</li> <li>Hemoglobin A1c<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>BMI &gt;30 kg/m<sup>2</sup></li> <li>Lean PCOS with age &gt;40 years or hx GDM, FHx: T2DM</li> </ul>	<ul style="list-style-type: none"> <li>Normal baseline 75-g OGTT, biannually or sooner depending on CVD risk factors</li> <li>Baseline IGT, 75-g OGTT annually</li> </ul>
Obesity/central adiposity	<ul style="list-style-type: none"> <li>BMI, waist circumference</li> </ul>	<ul style="list-style-type: none"> <li>All women with PCOS</li> </ul>	<ul style="list-style-type: none"> <li>Every visit</li> </ul>
Hypertension	<ul style="list-style-type: none"> <li>Blood pressure</li> </ul>	<ul style="list-style-type: none"> <li>All women with PCOS</li> </ul>	<ul style="list-style-type: none"> <li>Every visit</li> </ul>
<sup>b</sup> Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> <li>ALT, AST, <math>\gamma</math>GT<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Particularly in PCOS women with metabolic syndrome<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Annually<sup>b</sup> (Frequency of testing not clearly established)</li> </ul>

# Yaklaşım



# Lifestyle changes in women with polycystic ovary syndrome (Review)

Moran LJ, Hutchison SK, Norman RJ, Teede HJ



This is a review of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2011, Issue 2

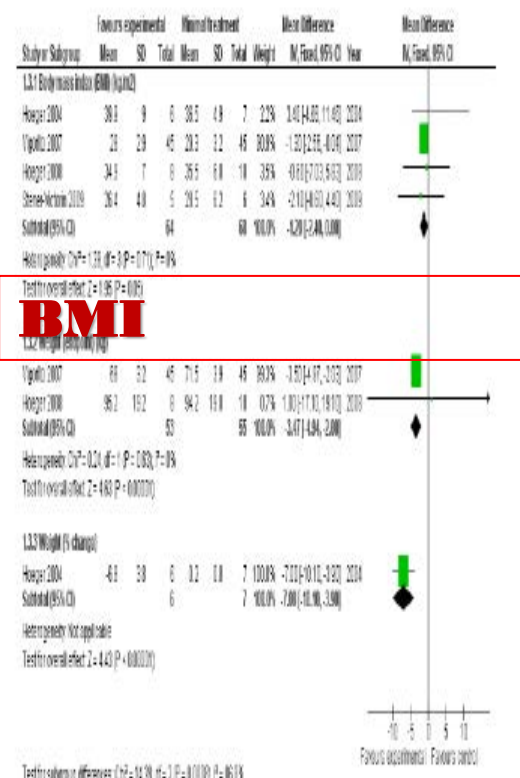
<http://www.cochrane.org>

Figure 3. Forest plot of comparison: I Lifestyle intervention versus minimal treatment: Combined data, outcome: I.2 Secondary reproductive outcomes.



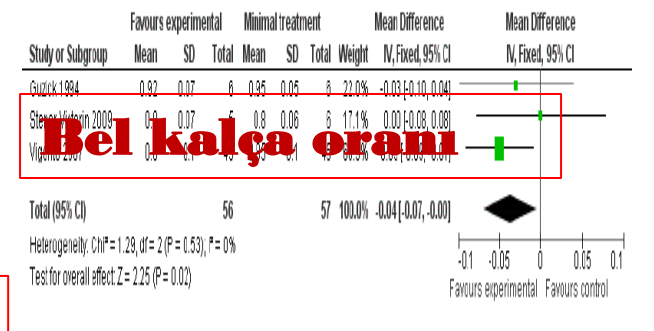
**Klinik hiperandrojenizm**

Figure 4. Forest plot of comparison: I Lifestyle intervention versus minimal treatment: Combined data, outcome: I.6 Secondary anthropometric outcomes (adiposity).



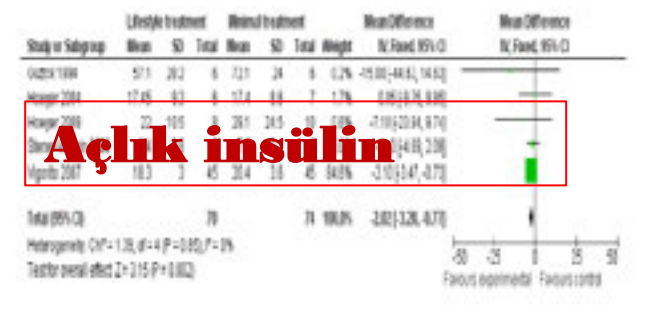
**BMI**

Figure 5. Forest plot of comparison: I Lifestyle intervention versus minimal treatment: Combined data, outcome: I.9 Adiposity distribution (waist-to-hip ratio (WHR)).



**Bel kalça oranı**

Figure 6. Forest plot of comparison: I Lifestyle intervention versus minimal treatment: Combined data, outcome: I.11 Fasting insulin (µU/mL).

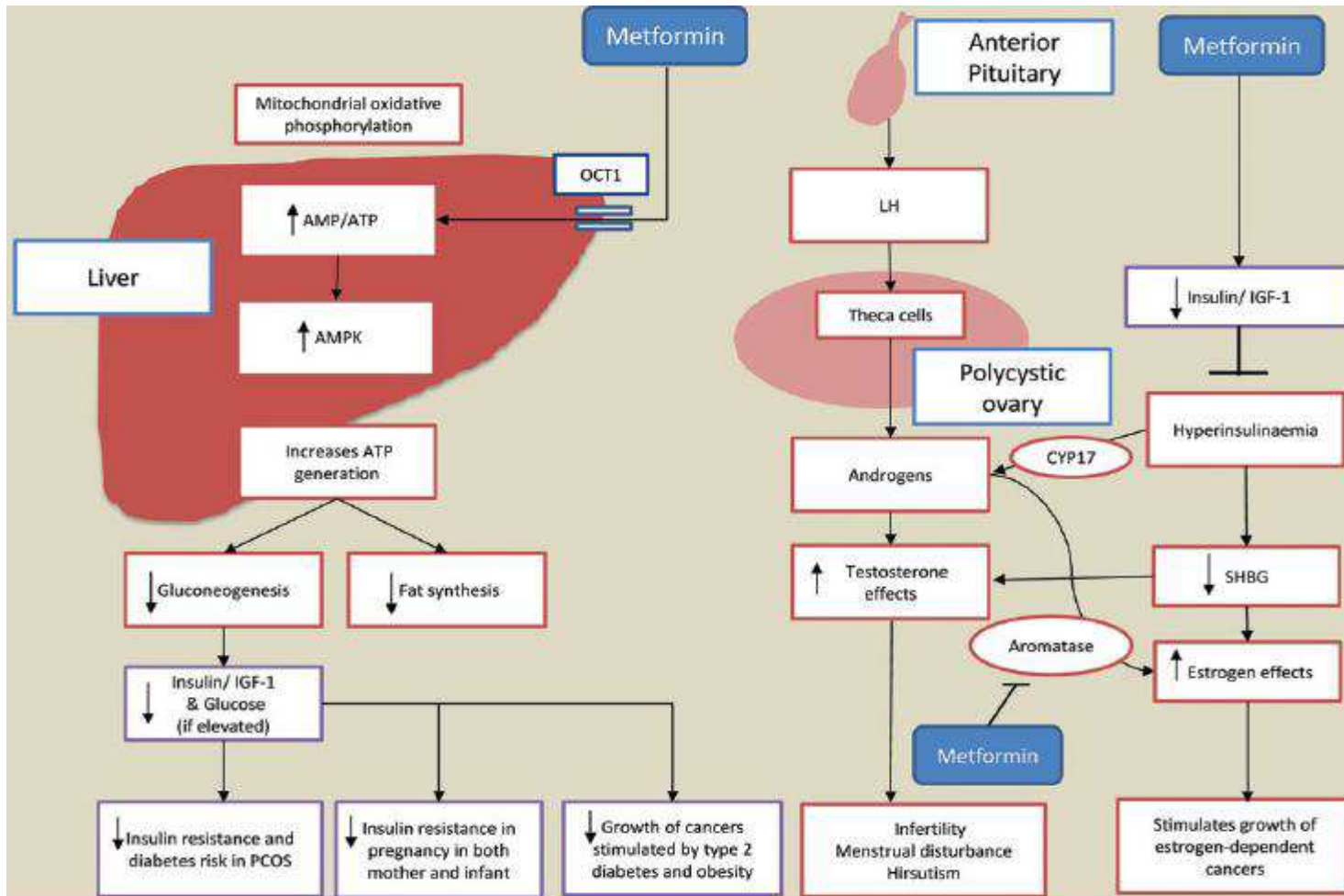


**Açlık insülin**

# İnsülin duyarlaştırıcılar

- ❖ Biguanidler
  - Metformin (Glukophage®, Glukofen®, Glifor®)
- ❖ Tiazolidinedionlar (TZD)
  - Troglitazon- Hepatotoksik
  - Rosiglitazon-MI
  - Pioglitazon-Mesane ca

# Metformin etki mekanizması

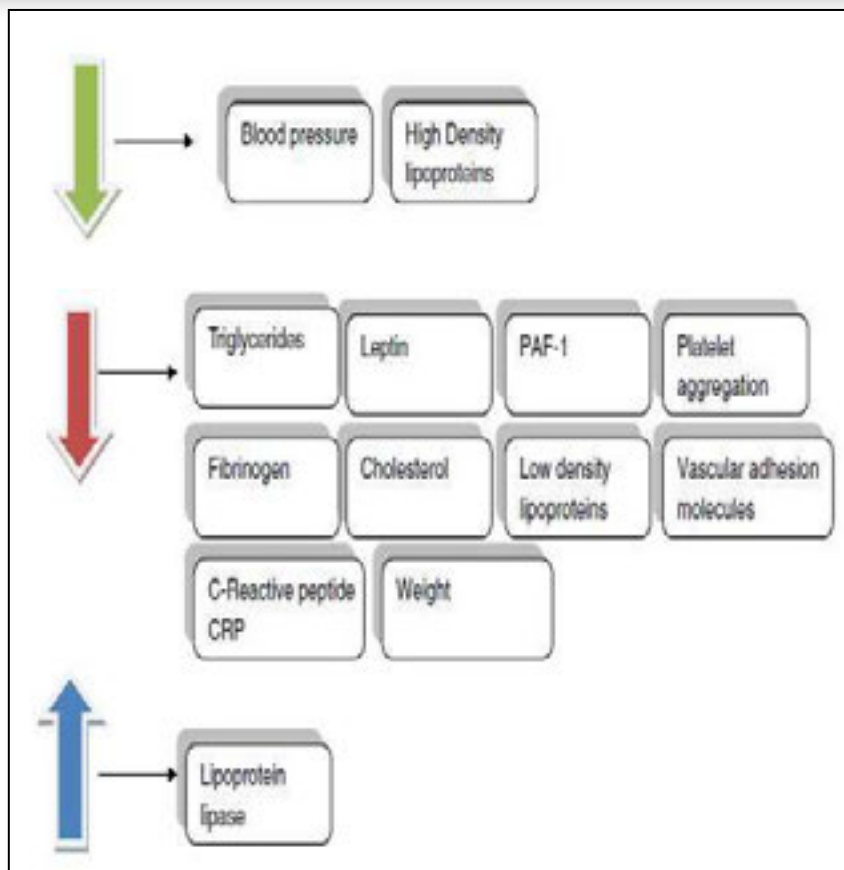




Review article

# Metformin: The hidden chronicles of a magic drug <sup>☆</sup>

Khalid Mahmood <sup>a</sup>, Muhammad Naeem <sup>b,\*</sup>, Nasir Ali Rahimnajad <sup>b</sup>



NAFLD  
Inflamasyon  
Anti-aging  
Kanser

# Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review)

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH

2012, Issue 5

- ❖ Metformin klinik gebelik hızını özellikle non-obez grupta arttırıyor
- ❖ Ovulasyon hızında düzelme? (subgrup analizleri heterojen)
- ❖ Menstruel frekansta düzelme
- ❖ BMI, Bel-kalça oranı üzerine etki yok
- ❖ Sistolik kan basıncında azalma
- ❖ Endokrin
  - Serum total testosteron azalma
  - SHBG etki yok
  - AKŞ üzerine etki minimal
  - Açlık insülin seviyesinde azalma
  - Kolesterol ve TG üzerine etkisi yok

# Metformin monotherapy for type 2 diabetes mellitus (Review)

Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roqué i Figuls M, Moher D



1- Metformin monoterapisi 5 ay (medyan) kullanımında HbA1c, AKŞ, BMI, kolesterol, LDL, TG, insülin, DBP anlamlı azalma, HDL artma

2- Sulfonilüre, alfa-glukosidaz inhibitör, tiazolidinedion, insülin ve diyetin glisemik kontrol, kilo veya lipidler üzerine metforminden daha üstünlüğü görülmemiştir

3- Metformin kilolu veya obez Tip 2 DM tedavisinde ilk seçenek olabilir

# Metformin-PCOS

Kullanım alanı	SONUÇ
Tip 2 DM Bozulmuş glikoz toleransı	Ana endikasyon alanı
Klinik hiperandrojenizm	-
Anovulasyon-Menstruel düzensizlik	İyileşme, KOK kullanamayanlarda alternatif
Gebelik komplikasyonlarının önlenmesi	-
Obezite	Egzersiz+diyete alternatif
İnfertilite	OHSS önlenmesinde adjuvan tedavi

## Effects of Thiazolidinediones on Polycystic Ovary Syndrome: a Meta-analysis of Randomized Placebo-Controlled Trials

Qiang Du · Sheng Yang · Yan-Jun Wang · Bo Wu · Yue-Yang Zhao · Bin Fan

- ❖ Selektif peroxisom proliferator-activated reseptor  $\gamma$  (PPAR  $\gamma$ ) agonisti
- ❖ Hedef dokuda (iskelet kası, KC, yağ dokusu) insülin duyarlılığını arttıırırlar
- ❖ Kategori C
- ❖ Roziglitazon MI riski nedeniyle kaldırıldı
- ❖ Metformin direnci-şiddetli insülin rezistansı (ailesel lipodistrofi..) tercih

- 1- İnsülin ve AKŞ azalma
- 2- Klinik hiperandrojenemi veya androjen seviyelerinde azalma yok
- 3- Kilo artışı

# Inositol: history of an effective therapy for Polycystic Ovary Syndrome

M. BIZZARRI<sup>1</sup>, G. CARLOMAGNO<sup>2</sup>

- ❖ Myo-inositol (MI) D-chiro-inositol (DCI)
- ❖ İnsülin mimetik etki, hücresel olaylarda ikincil haberci yapısında (IP<sub>3</sub>)
- ❖ 6 RCT (Unfer et.al Gynecol Endocrinol 2012)
  - 2-4 g/gün, 12-16 hafta, yan etki yok
  - PCOS'da basit, güvenli ve etkili destek

## REPRODUCTION

Restores normal ovulatory activity (Unfer et al, 2012)

↑ Oocyte and egg quality (Giotta et al, 2011 – Unfer et al, 2011)

↑ Fertilization rate

↑ sperm motility and mitochondrial membrane potential in vitro

(Condorelli et al, 2012 et 2011)

## METABOLISM

↑ Insulin Sensitivity

(↓HOMA-IR, ↓Glycemia, ↓insulinemia)

↓ Total and LDL-cholesterol

↑ HDL-cholesterol

↓ Serum Triglycerides

(Unfer et al, 2012 – Santamaria et al, 2012 – Croze et al, 2012 - Maeba et al, 2008 – Ortmeyer et al, 1996)

# What Is New in Polycystic Ovary Syndrome?

Best Articles From the Past Year

Keith A. Hansen, MD

## Box 1. Abstracts Discussed in This Commentary

1. Salameh WA, Redor-Goldman MM, Clarke NS, Mathur R, Azziz R, Reitz RE. Specificity and predictive value of circulating testosterone assessed by tandem mass spectrometry for the diagnosis of polycystic ovary syndrome by the National Institutes of Health 1990 criteria. *Fertil Steril* 2014;101:1135–41. Available at: <http://dx.doi.org/10.1016/j.fertnstert.2013.12.056>.
2. Franik S, Kremer JAM, Nelen WJDM, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD010287. Available at: <http://dx.doi.org/10.1002/14651858.CD010287.pub2>.
3. Iliodromiti S, Kelsey TW, Anderson RA, Nelson SM. Can anti-Müllerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data. *J Clin Endocrinol Metab* 2013;98:3332–40. Available at <http://dx.doi.org/10.1210/jc.2013-1393>.
4. Puurunen J, Piltonen T, Puukka K, Ruokonen A, Savolainen MJ, Bloigu R, et al. Statin Therapy worsens insulin sensitivity in women with polycystic ovary syndrome (PCOS): a prospective, randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2013;98:4798–807. Available at: <http://dx.doi.org/10.1210/jc.2013-2674>.
5. Agapova SE, Cameo T, Sopher AB, Oberfield SE. Diagnosis and Challenges of Polycystic Ovary Syndrome in Adolescence. *Semin Reprod Med* 2014;32:194-201. Available at: <http://dx.doi.org/10.1055/s-0034-1371091>.
6. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM,

## Diagnosis and Challenges of Polycystic Ovary Syndrome in Adolescence

The physiologic changes of puberty can mimic PCOS and provide unique challenges to making the diagnosis of PCOS in the adolescent. The diagnosis is also challenging because of the lack of accepted diagnostic criteria for PCOS at the extremes of age, including adolescence. In this article, the authors discuss the importance of achieving a satisfactory diagnostic balance so that adolescents with PCOS can be identified early and started on appropriate treatment while avoiding over-diagnosis and inappropriate treatment. Questions have been raised about the use of adult criteria for diagnosing PCOS in adolescents. One proposal to rectify this situation is to require adolescents to meet all three of the Rotterdam criteria—hyperandrogenism, chronic anovulation, and polycystic ovaries—before making the diagnosis of PCOS.



## Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

Richard S. Legro, Silva A. Arslanian, David A. Ehrmann, Kathleen M. Hoeger, M. Hassan Murad, Renato Pasquall, and Corrine K. Welt

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### Table 5. Cardiovascular Risk Stratification in Women with PCOS

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At risk—PCOS women with any of the following risk factors:

- Obesity (especially increased abdominal adiposity)
- Cigarette smoking
- Hypertension
- Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol)
- Subclinical vascular disease
- Impaired glucose tolerance

Family history of premature cardiovascular disease (<55 y of age in male relative; <65 y of age in female relative)

At high risk—PCOS women with:

- Metabolic syndrome
  - T2DM
  - Overt vascular or renal disease, cardiovascular diseases
  - OSA
- 

The Androgen Excess and Polycystic Ovary Syndrome Society relied

## Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

Richard S. Legro, Silva A. Arslanian, David A. Ehrmann, Kathleen M. Hoeger, M. Hassan Murad, Renato Pasquall, and Corrine K. Welt

### ❖ Yaşam tarzı değişiklikleri:

- Egzersiz: Fazla kilolu ve obezlerde sadece veya diyetle birlikte kilo kaybı KV risk faktörlerini ve DM riskini azaltır
- Kilo verilmesi: Fazla kilolu veya obez adolesan ve erişkinlerde kalori kısıtlayıcı diyet reproduktif ve metabolik disfonksiyonda olumlu etki, normal kilolu kadınlarda tedavi edici etkisi yetersiz

### ❖ Metformin:

- Cilt bulguları, gebelik komplikasyonlarının önlenmesi veya obezite tedavisinde önerilmez
- Tip 2 DM PCOS veya başarısız yaşam tarzı değişikliği IGT
- Menstruel düzensizlikte HC kullanılmıyorsa, 2. basamak tedavi
- IVF'de OHSS önlenmesinde adjuvan tedavi olarak önerilir

### ❖ Diğer insülin sensitize edici ajanlar önerilmez

- İnositol: Faydası gösterilememiş
- Thiazolidinediones: Güvenli değil



Invited critical review

## Metabolomics in polycystic ovary syndrome ☆

Mora Murri <sup>a,b,c</sup>, María Insenser <sup>a,b,c</sup>, Héctor F. Escobar-Morreale <sup>a,b,c,\*</sup>**Table 2**

Summary of metabolites associated with polycystic ovary syndrome and their changes compared with controls.

Carbohydrate related markers		
Glucose	↓	Zhao et al., 2012
Undentified sugar	↑	Zhao et al., 2012
Lactate	↑	Zhao et al., 2012; Sun et al., 2012
Lipid related markers		
α-Tocopherol	↓	Escobar-Morreale et al., 2012
Acetone	↓	Atiomo et al., 2012
Cholesterol	↓	Zhao et al., 2012; Escobar-Morreale et al., 2012
HDL	↓	Zhao et al., 2012
Phosphatidylcholine	↓	Zhao et al., 2012; Sun et al., 2012
Fatty acid	↑	Zhao et al., 2012
Linoleic acid	↑	Zhao et al., 2012
Lipoprotein	↑	Zhao et al., 2012
Palmitic acid	↑	Zhao et al., 2012
Stearic acid	↑	Zhao et al., 2012
Unsaturated fatty acid	↑	Zhao et al., 2012
VLDL/LDL	↑	Zhao et al., 2012
Lipid-CH <sub>2</sub> CH <sub>2</sub> CO	↓	Atiomo et al., 2012
	↑	Zhao et al., 2012
Protein related markers		
Creatinine	↓	Sun et al., 2012
Lysyl-albumin	↓	Zhao et al., 2012
Trimethylamine N-oxide	↓	Sun et al., 2012
2-Ketoisocaproic acid	↓	Escobar-Morreale et al., 2012
Creatine	↑	Sun et al., 2012
Dimethylamine	↑	Sun et al., 2012

Amino acids		
Arginine	↓	Atiomo et al., 2012; Sun et al., 2012
Choline	↓	Sun et al., 2012
Citrulline	↓	Atiomo et al., 2012
Glutamate	↓	Atiomo et al., 2012
Glutamine	↓	Sun et al., 2012
Glycerophosphocholine/phosphocholine	↓	Sun et al., 2012
Glycine	↓	Zhao et al., 2012
Histidine	↓	Atiomo et al., 2012
Isoleucine	↓	Zhao et al., 2012
Methionine	↓	Sun et al., 2012
Proline	↓	Zhao et al., 2012; Atiomo et al., 2012
AAA	↑	Zhao et al., 2012
BCAA	↑	Zhao et al., 2012
BCAA/AAA	↓	Zhao et al., 2012
Aspartate	↑	Zhao et al., 2012
Endogenous AAs	↑	Zhao et al., 2012
Gluconeogenic AAs	↑	Zhao et al., 2012
Phenylalanine	↑	Zhao et al., 2012
Serine	↑	Zhao et al., 2012
Threonine	↑	Zhao et al., 2012
Tryptophan	↑	Zhao et al., 2012
Tyrosine	↑	Zhao et al., 2012
Valine	↑	Zhao et al., 2012
Alanine	↓	Escobar-Morreale et al., 2012
	↑	Zhao et al., 2012
Leucine	↓	Sun et al., 2012
	↑	Zhao et al., 2012
Lysine	↓	Atiomo et al., 2012
	↑	Zhao et al., 2012
Ornithine	↓	Atiomo et al., 2012
	↑	Zhao et al., 2012

# SONUÇ



- ❖ PCOS kısa etkisini reproduktif bozukluklar, uzun etkisini metabolik ve kardiovasküler sistem üzerine gösteren multisistemik bir hastalıktır
- ❖ PCOS patofizyolojisinde insülin direnci-hiperandrojenizm anahtar
- ❖ PCOS'da IGT, Tip2DM ve metabolik sendrom prevalansı yüksek
- ❖ Hiperinsülinemi disgliseminin başlangıcı olduğundan erken tanısı metabolik bozuklukları önleyecektir.
- ❖ Adolesan ve çocukluk döneminde PCOS düşündürülecek bulgular açısından dikkatli olunmalıdır (prematur adrenarş, hiperinsülinemi..)
- ❖ PCOS hastaları reproduktif sistem dışındaki bozukluklar açısından değerlendirilmeli (OSA, NAFLD, KVS...), multidisipliner yaklaşılmalı
- ❖ Yaşam tarzı değişiklikleri 1. basamak yaklaşım
- ❖ Metformin ana endikasyonu IGT ve Tip 2 DM, OHSS önlenmesinde etkili
- ❖ TZD kullanımı önerilmemekte, myoinositol için daha fazla kanıt ihtiyacı var

# TEŞEKKÜR EDERİM...



Power and Control Over any Situation

Living life with PCOS

The good times, the bad times

MILLIONS OF WOMEN WITH  
**POLYCYSTIC OVARIAN SYNDROME**  
ARE GOING  
**UNDIAGNOSED**  
**UNTREATED**  
**UNSUPPORTED**  
THIS MUST CHANGE

The most common endocrine disorder

PCOS AFFECTS 5 TO 10 PERCENT OF THE FEMALE POPULATION.

Let's understand it more about the HEART IN MIND

PCOS AFFECTS FRIENDS, LOVERS AND SPOUSES TOO.

EXPERIENCING ERRATIC PERIODS? IT COULD BE PCOS

Symptoms may include:  
Chronically irregular menstrual cycles and/or absent periods.

September  
is  
**PCOS**  
awareness  
month

**FEEL LIKE A GIRL**  
Support PCOS Awareness