CLINICAL AND BIOCHEMICAL PRESENTATIONS OF POLYCYSTIC OVARY SYNDROME AMONG OBESE AND NON-OBESE WOMEN

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BACKGROUND

- Objective: To study the differences in clinical and biochemical characteristics between obese and nonobese women with polycystic ovary syndrome (PCOS)
- Design: Retrospective study
- Setting: University teaching hospital
- Patient(s): Taiwan Chinese women
- Main Outcome Measure(s): Body mass index, average menstrual interval, modified Ferriman-Gallwey score, acne, total T (testosterone), and waist-to-hip ratio

POLYCYSTIC OVARY SYNDROME (PCOS)

- The most common endocrinopathy, affecting approximately 5%–8% of reproductive-age women
- Characterized by
  - Hyperandrogenism
  - Chronic anovulation
- Morbidity may include
  - Hyperinsulinemia
  - Insulin Resistance
  - Early onset of type 2 DM
  - Dyslipidemia

PCOS

- A Reproductive endocrinopathy
- A Metabolic disorder
- Obesity is a prominent feature (occurring in 40%–50% of PCOS)

- The effect of obesity on the Diagnosis and clinical presentations of PCOS-related syndromes is an important issue

OBESITY

- Additive, synergistic impact on the manifestations of PCOS
- Plays an important role in the development and maintenance of PCOS (Much evidence)
- Independently & negatively affecting Insulin sensitivity/Risk of diabetes/Cardiovascular profile
- ↓The influence of excess adiposity on ovarian and metabolic function is fundamental to the Mx of PCOS
- The nature of the complex interrelation of obesity, insulin resistance, and endocrine abnormalities in PCOS remains unresolved

- Adiposity <-> symptom severity in women with PCOS, modest reductions in weight usually → significant improvements in menstrual regularity, fertility, HA features
- Before the onset of oligomenorrhea & hyperandrogenism → frequently a history of weight gain → A patho-genetic role of obesity in the subsequent development of the syndrome
- Obese women (compare to non-obese)
  - with/without PCOS => significantly higher total T
  - with PCOS => significantly lower LH-to-FSH ratios

- PCOS & obesity: common and complex disorders —affected by genetic & environmental factors
- Understanding the link between obesity <-> PCOS might provide significant information for the Dx & Tx of PCOS
- Most publications concentrate on:
  - Obesity's effect on insulin resistance and the metabolic consequences in women with PCOS
- This study was conducted to determine:
  - The impact of obesity on the clinical and biochemical presentations of PCOS

MATERIALS AND METHODS

STUDY SUBJECTS

- Patients:
  - Visited the Reproductive Endocrinology Clinic at Taipei Medical University-Wan Fang Medical Center
  - April 1, 2004 ~ December 31, 2007
- 464 consecutive patients,
- Average age: 27.6 ± 5.5 years (14-40 years)

EXCLUSIONS

[1] Had been diagnosed with other etiologies that should be excluded in PCOS diagnosis:

Androgen-secreting tumor, Congenital adrenal hyperplasia, Hypogonadotropic hypogonadism, Hyperprolactinemia, Cushing's syndrome, Premature ovarian failure, Uterine disorders (Asherman's syndrome, Müllerian agenesis) Chromosomal anomalies (e.g., Turner syndrome)

[2] > 40 or began menarche < 3 years earlier

[3] Inadequate clinical/biochemical records

[4] Echo: ovarian cysts or ovarian tumor

COLLECT INFORMATION

- Menstrual Hx, BW, BH, hirsutism, clinical acne
  - Average interval= 365 Days divided by number of menstrual cycle in the previous 12 months
  - Body mass index (BMI)= BW/BH^2 (kg/m^2)
  - Hirsutism: A modification of the Ferriman-Gallwey (mF-G) method: was defined as an mF-G score $\geq$ 6
- FSH, LH, PRL, total T, fasting insulin, fasting glucose
  - FSH, LH, PRL: An enzyme immunoassay

    (AxSym System, Abbott, IL)
  - [Total T]: Radioimmunoassay

    (Diagnostic Systems Laboratories, Inc., Webster, TX)

COLLECT INFORMATION

- Obesity = BMI ≧ 25 kg/m 2, (Asia-Pacific definition)
- Waist-to-hip ratio (WHR):
  - WC = Iliac crest — lateral costal margin (Smallest)
  - HC = Largest measurement over the buttocks
- Clinical androgen excess = Hirsutism and/or acne
- Biochemical Hyperandrogenemia = Total serum T ≧ 2.98 mmol/L (0.86 ng/mL, 1 ng/mL ___ 3.47 mmol/L)
- Ultrasound scan of the pelvis, preferably transvagina
  - To detect PCO

PCOM

- An ultrasound criterion in the definition of PCOS:
  - ≧ 12 follicles (2–9 mm)in either ovary
  - And/or increased ovarian volume >7 Ml
- Prevalence: > 20% in both Western and Asian women
- The most frequently used criterion in PCOS diagnosis

PCOS

Definition (The European Society for Human Reproduction / American Society of Reproductive Medicine case)

- Requires presentation of signs and/or symptoms of a minimum of 2 of the following 3 criteria:
  - Polycystic ovary morphology (PCOM)
  - Oligomenorrhea or amenorrhea (Oligo-An)
    - Amenorrhea: Absence of menstruation for ≧ 180 days.
  - Androgen excess (HA)

CLASIFICATION

- Two groups: PCOS and non-PCOS

1. Non-PCOS control group (169 x women)
   - To avoid selection bias, women who had one and only one of the above diagnostic criteria should not be excluded from the non-PCOS control group
2. PCOS group (295 women)

- None of the subjects had been on hormone therapy for at least 2 months before the retrospective study

STATISTICAL ANALYSIS

- Statistical Package for the Social Sciences, version 13.0, for Windows (SPSS, Inc., Chicago).
- Data presentation: Mean SD.
- Compare the categorical variables: c2 test
- Compare the continuous variables: Analysis of variance
- Correlations between BMI and total T, mFG score, average menstruation interval, LH, and LH/FSH ratio: Pearson correlation coefficients with the two-tailed method
- Adjusted odds ratios (ORs) & 95% confidence intervals (95% CIs): Multiple logistic regression analyses
- Statistically significant: P<.05

RESULTS

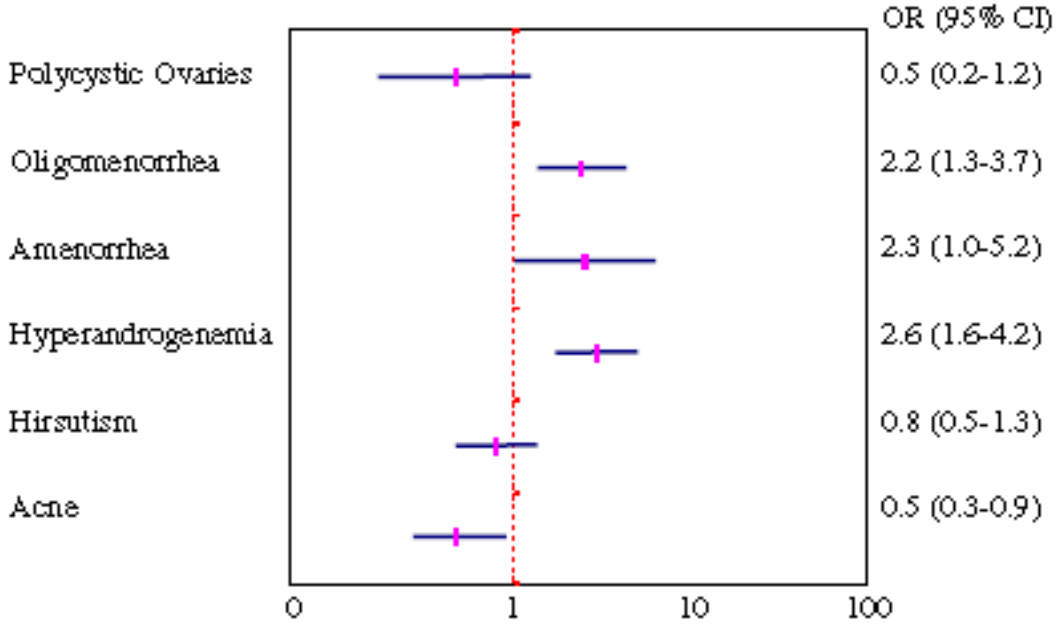
TABLE 1

Clinical and biochemical presentation of obesity and nonobesity in the PCOS and non-PCOS groups.

	PCOS				Non-PCOS			
	Total	Obesity	Nonobesity	*P*	Total	Obesity	Nonobesity	*P*
No. of cases (%)	295	115 (39)	180 (61)		169	38 (23)	131 (77)	
Age, years	26.7 ± 5.4	27.6 ± 5.5	26.2 ± 5.2	.027	29.8 ± 5.9	29.2 ± 6.6	30.0 ± 5.7	NS
Polycystic ovaries, %	93	90	95	NS	33	29	34	NS
Oligomenorrhea, %	64	75	57	.002	7	18	3	.001
Amenorrhea, %	9	13	6	.041	2	3	2	NS
Hyperandrogenemia, %	46	61	37	<.001	12	18	11	NS
Hirsutism and/or acne, %	57	49	63	.017	20	21	19	NS
Hirsutism, %	28	25	30	NS	6	16	3	.003
Acne, %	48	36	54	.009	18	16	18	NS
LH/FSH > 1, %	71	67	74	NS	25	35	23	NS
mF-G score	3.1 ± 3.5	3.1 ± 3.6	3.1 ± 3.3	NS	1.0 ± 2.2	1.7 ± 2.7	0.8 ± 1.0	.020
Total T, mmol/L	3.0 ± 1.4	3.5 ± 1.5	2.7 ± 1.2	<.001	1.9 ± 0.8	2.3 ± 0.8	1.8 ± 0.8	.003
Interval[a]	80.7 ± 62.3	95.2 ± 65.9	71.3 ± 59.2	.001	37.7 ± 33.2	46.5 ± 33.3	35.9 ± 33.0	NS
PRL, mIU/mL	13.7 ± 5.0	13.3 ± 4.9	13.9 ± 5.1	NS	14.3 ± 5.4	14.1 ± 5.8	14.3 ± 5.3	NS
FSH, mIU/mL	5.9 ± 1.9	6.0 ± 2.0	5.9 ± 1.9	NS	6.9 ± 2.6	6.4 ± 2.4	7.1 ± 2.6	NS
LH, mIU/mL	10.2 ± 7.0	8.6 ± 5.8	11.3 ± 7.5	.005	6.01 ± 6.17	5.58 ± 3.62	6.12 ± 6.68	NS
LH to FSH ratio	1.8 ± 1.2	1.5 ± 1.1	2.0 ± 1.3	.003	1.0 ± 1.0	1.0 ± 0.7	0.9 ± 1.0	NS
BMI, kg/m^2	24.5 ± 6.2	31.2 ± 4.4	20.3 ± 2.1	<.001	22.5 ± 5.0	30.4 ± 3.8	20.2 ± 2.2	<.001
Waist, cm	73.8 ± 15.2	89.9 ± 14.1	63.9 ± 6.6	<.001	68.0 ± 11.6	85.3 ± 10.2	63.2 ± 6.0	<.001
WHR	0.80 ± 0.10	0.86 ± 0.10	0.76 ± 0.07	<.001	0.77 ± 0.07	0.83 ± 0.06	0.75 ± 0.05	<.001

FIGURE 1

OR for the incidence of some clinical manifestations in obese versus nonobese women with PCOS.



Liou. Obesity and PCOS. Fertil Steril 2009.

OBESITY AND PCOM

Total 464 women

- 71% (331/464) had PCOM
  - 83% (275/331) were diagnosed with PCOS
  - 35% (115/331) were obese
  - 65% (216/331) were non-obese
- 49% (229/464) had Oligo-An
- 58% (271/464) had HA

WOMEN WITH PCOM (OBESE VS. NON-OBESE)

- **Incidence of PCOS**
  (90% vs.79%; OR 2.5; 95% CI 1.5–10.4)
- **Risk of developing biochemical hyperandrogenemia**
  (52% vs. 30%; OR, 2.5; 95% CI, 1.6–4.0)
- **Oligomenorrhea** (67% vs. 44%; OR, 2.6; 95% CI, 1.6–4.1)
- **Amenorrhea** (11% vs. 5%; OR, 2.6; 95% CI, 1.1–6.2)
- **Serum total T levels** (3.3±1.5 vs. 2.5±1.2; P<.001)
- **Menstrual intervals** (89.3±66.7 vs. 61.9±54.5; P<.001)
- **Serum LH levels** (8.1±5.7 vs. 10.2±7.4; P=.032)

OBESITY IN WOMEN WITH PCOS

- PCOS group: 39% obese & 61% nonobese women

Obese subjects with PCOS (compare to nonobese women with PCOS)

- Higher risk of developing Oligo-An, oligomenorrhea, amenorrhea, and biochemical hyperandrogenemia
- Significantly higher serum total T levels
- Prolonged menstrual intervals
- Lower serum LH levels
- Lower LH-to-FSH ratio
- Presented a lower incidence of acne

BMI

In women with PCOM

- Significantly positive correlation
  - Serum total T (γ: 0.34, P<0.001)
  - Average menstrual interval (γ: 0.22, P=0.002).

in women with PCOS

- Significantly positive correlation
  - Serum total T (γ: 0.33, P<0.001)
  - Average menstrual interval (γ: 0.18, P=0.002)
- Significantly negative correlation
  - Serum LH (γ: 0.19, P=0.005)

Pearson correlation between BMI and clinical and biochemical presentation in patients with and without PCOS

	Total (N = 464)		PCOS (n = 295)		Non-PCOS (n = 169)	
	Correlation	P	Correlation	P	Correlation	P
Age, years	0.053	NS	0.104	NS	0.094	NS
mF-G score	0.079	NS	0.013	NS	0.091	NS
Total T, ng/dL	0.345*	<0.001	0.330*	<0.001	0.243*	.001
Interval[a]	0.221*	<0.001	0.180*	.002	0.144	NS
PRL, mIU/mL	−0.088	NS	−0.091	NS	−0.060	NS
FSH, mIU/mL	−0.047	NS	0.027	NS	−0.053	NS
LH, mIU/mL	−0.099	NS	−0.189*	.005	−0.118	NS
LH/FSH	−0.063	NS	−0.173*	.010	−0.057	NS
Average ovaries volume, mL	0.098*	.041	0.085	NS	−0.105	NS
Waist	0.923*	<0.001	0.918*	<0.001	0.935*	<0.001
Waist/hip	0.606*	<0.001	0.598*	<0.001	0.598*	<0.001

DISCUSSION

I. Obesity in Women with PCOM
II. Obesity's Effect on Menstrual Disturbances and Serum Total T Levels
III. Obesity and Hirsutism and/or Acne

I. OBESITY IN WOMEN WITH PCOM

PCOM

- Prevalence >20% in both Western and Asian women
- The most frequently used criterion in PCOS diagnosis
  - 93% of patients diagnosed with the Rotterdam criteria had PCOM this study
- Women with PCOM should be carefully evaluated for the risk of ovulatory dysfunction and/or HA

OBESE WOMEN WITH PCOM

Kiddy et al., 263x (women with PCOM)

« ↑Prevalence of menstrual disorders & free T levels

This study, 331x (women with PCOM)

« ↑Risk of developing PCOS (OR, 2.5; 95% CI, 1.5–10.4)

« Higher incidences of oligomenorrhea, amenorrhea, and biochemical hyperandrogenemia

¢ BMI was correlated positively with total T level and average menstrual interval

« Significantly higher serum total T levels, longer menstrual intervals, and lower serum LH levels

II. OBESITY'S EFFECT ON MENSTRUAL DISTURBANCES & SERUM TOTAL T LEVELS

1. Obese Women with PCOS
   - « Had a greater frequency of Oligo–An (OR, 4.2; 95% CI, 2.2–7.9), oligomenorrhea, and amenorrhea
   - « Had a greater incidence of amenorrhea

   Singh et al., (56x Women with PCOS)

1. Obese women with/without PCOS
   - « Higher percentage of Oligo–An than nonobese
2. Obesity
   - « ↑Prevalence of biochemical hyperandrogenemia in PCOS (OR, 2.6; 95% CI, 1.6–4.2).

BMI

- Had a significantly positive correlation with average menstruation interval
- Was correlated positively with total T level and average menstrual interval
- This study and previous reports found a significant positive correlation between total T and **BMI** regardless of whether women have PCOS or not

III. OBESITY AND HIRSUTISM AND/OR ACNE

- The percentage of hirsutism and/or acne in obese women with PCOS was significantly less than in nonobese women (OR, 0.6; 95% CI, 0.4–0.9)
- Obese women with PCOS show no significant difference in prevalence of hirsutism compared with lean subjects, despite having higher total T levels
- In the group of 295 women with PCOS, obese women had significantly less acne than nonobese women (38% vs. 54%, P = 0.009)

SERUM LEVELS OF SEX HORMONE–BINDING GLOBULIN

- Serum levels of sex hormone–binding globulin
  - Are much lower in obese women
- Obese women with PCOS:
  - Having greater total T and lower SHBG

    → High free androgen indexes

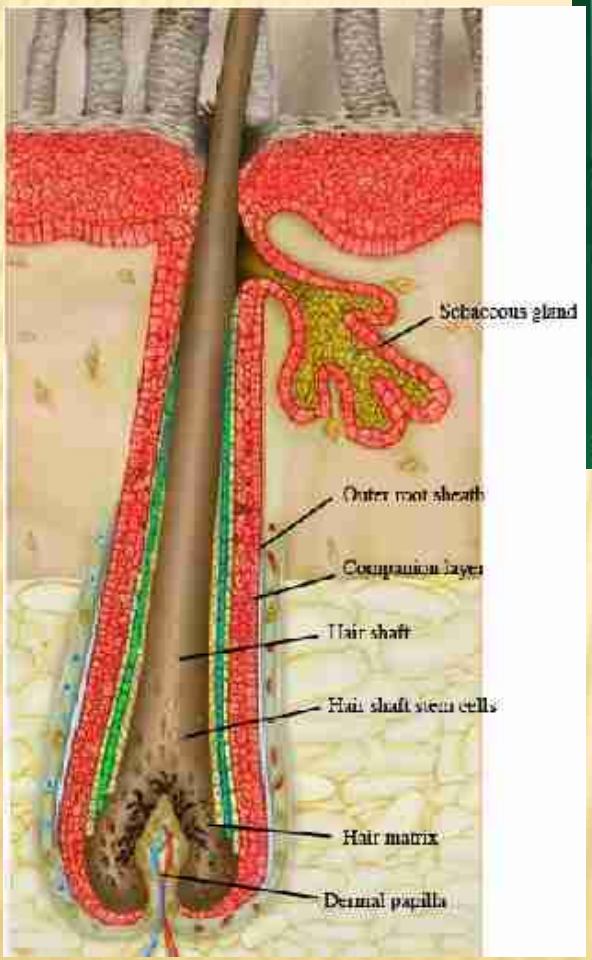
    → Would expect obese women with PCOS to show more severe functional hyperandrogenism

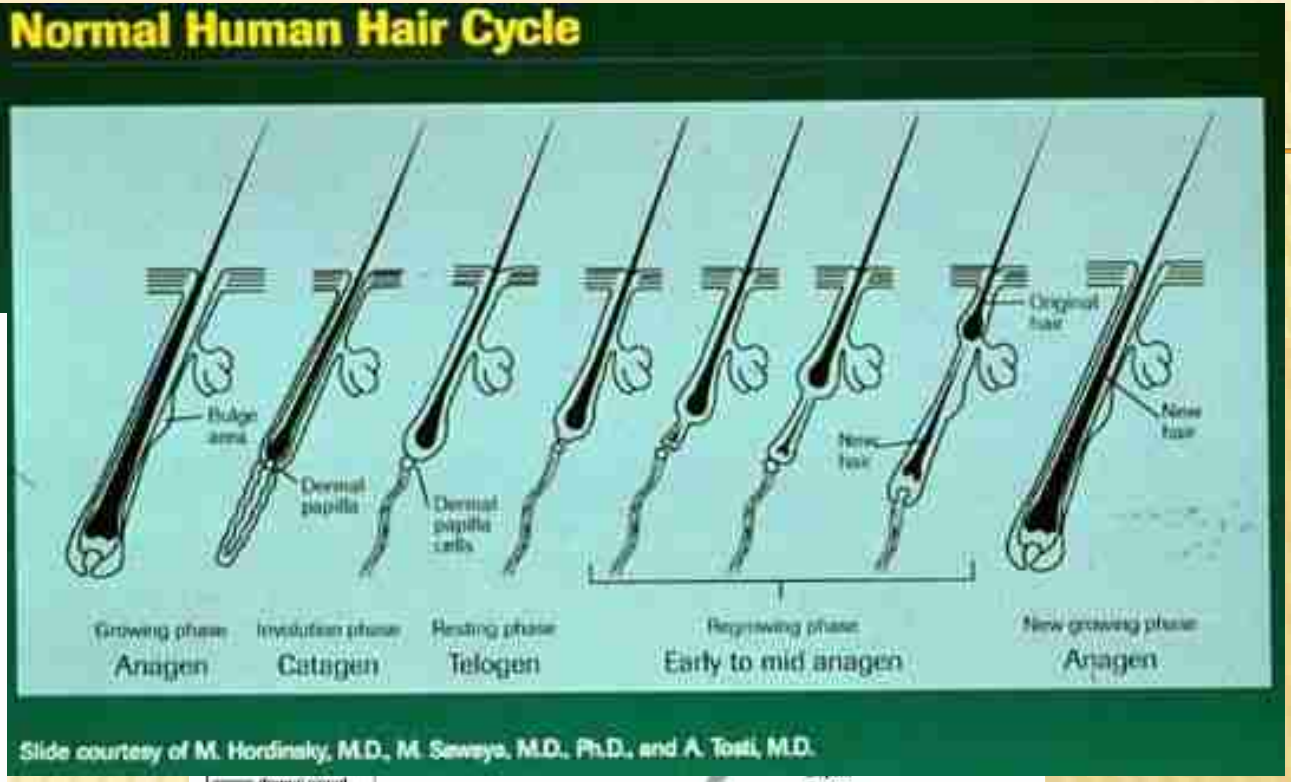
- Few studies have provided clinical evidence comparing the prevalence of hirsutism and/or acne in obese and nonobese women with PCOS and with inconsistent results
- (Lin et al.)192 Chinese cases:
  - No significant difference in the prevalence of hirsutism between obese and nonobese women with PCOS
- (Gambineri et al.)80 obese & 19 normal-weight PCOS subjects:
  - Acne was present in 25% of the obese PCOS women and 58% of the nonobese PCOS women

- something hinders the clinical presentation of hyperandrogenism in obese women with PCOS, especially in regards to acne
- Although the sebaceous gland and the hair follicle are derived from the pilosebaceous unit, acne and hirsutism do not always appear concomitantly

  → these two structures may have different degrees of sensitivity to androgenic stimulation

- The raised androgen production rates in obesity might be associated with a similar increase in androgen clearance rates
- A delicate balance probably exists between production and clearance of these biologically active hormones
- Obesity might be a state of increased androgen production with simultaneous accelerated clearance in the hirsute women, presenting as apparently ineffective androgen


Sebaceous gland
Outer root sheath
Companion layer
Hair shaft
Hair shaft stem cells
Hair matrix
Dermal papilla


Normal Human Hair Cycle
Bulge area
Dermal papilla
Dermal papilla cells
Original hair
New hair
New hair
Growing phase
Anagen
Involution phase
Catagen
Resting phase
Telogen
Regrowing phase
Early to mid anagen
New growing phase
Anagen
Slide courtesy of M. Hordinsky, M.D., M. Sawaya, M.D., Ph.D., and A. Tosti, M.D.


dermal signal
epidermal signal
Anagen
Catagen
Telogen
BCC
Adult
Hair Cycle
ORS
IRS
dermal papilla
basaloid tumor nest
bulge

AROMATASE

- (Cohen): Adipose tissue ↑← → enzyme aromatase ↑
- Converts T to E2
- Localized to sebaceous glands, both inner and outer root sheath cells of anagen terminal hair follicles
- May play a "detoxifying" role by removing excess androgens
- Idiopathic obesity has also been associated with an increase in the measured level of SC mRNAs for enzymes of aromatase

HIRSUTISM AND/OR ACNE

- Hirsutism and/or acne
  - Are considered to be the 1° clinical indicators of HA
  - Among hyperandrogenism symptoms, hirsutism is most closely linked with androgen dependence
    - Several studies => positive correlation:

      hirsutism and/or acne severity ——

      circulating serum free androgen levels

HIRSUTISM

- Function of circulating androgen levels and can be determined by genetic factors
- Androgen receptors in the pilosebaceous unit are specific for androgen dihydrotestosterone (DHT)
- Activation of 5α-reductase is required to convert T to DHT in hair follicles
- The effect of ethnicity on the ↓incidence of hirsutism in Chinese women with PCOS may be explained by the low level of 5α-reductase activity in the skin of Asian women

OBESITY

- Worsens both biochemical hyperandrogenemia and chronic anovulation, which are the two most important diagnostic criteria of PCOS
- Prevalence of obesity: In PCOS > In general female population
- Prevalence of PCOS: In overweight and obese women > lean women

- Obese women with PCOS do not display a greater prevalence of hirsutism and/or acne than nonobese women with PCOS
  - The lower prevalence of acne among obese women with PCOS could be further investigated
  - Suspect racial difference (Asian population)
  - Repeat this analysis in other parts of the world would help to exclude racial differences in the diagnosis of PCOS

CONCLUSIONS

1. Obese women with PCOM have a higher prevalence of PCOS than nonobese subjects

2. Obese women with PCOS have a greater frequency of ovulatory dysfunction and biochemical hyperandrogenemia than nonobese PCOS women.

3. Although obese women with PCOS had a higher total T level, they do not present with a higher prevalence of hirsutism and in fact have a lower incidence of acne than nonobese subjects.

THE END

THANK YOU FOR YOUR ATTENTION