多囊性卵巢症候群
Polycystic Ovarian Syndrome

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- Introduction
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- Conclusion

Introduction

- Chereau, 1844: morphology of PCO
- Stein and Levental 1935: PCO linked to the clinical symptoms
- McArthur, *1958:* LH ↑
- Raj *et al,*1978: hyperandrogenemia
- Burghen *et al*, 1980: Hyperinsulinaemia
- Adams *et al,* 1985: Ovarian morphology by ultrasound.

什麼是多囊性卵巢症候群？

1. 多囊性卵巢症候群最早是在西元1935年Stein 及 Leventhal 兩位學者首度發表七例這種症候群，包括「無月經」(amenorrhea)，多毛症(hirsutism)，肥胖(obesity)，以及合併卵巢呈現多發性的囊狀腫大(enlarged polycystic ovaries)等症狀，將臨床症狀與多囊性卵巢做一個結合。
2. 長久以來，關於所謂的多囊性卵巢症候群的診斷標準始終莫衷一是，因為這類病患的臨床症狀變化多端、表現也是相當的異質性。

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多囊性卵巢形成的原因？

- 多囊性卵巢形成的原因目前尚未有明確的結論，但是可以由一個簡單的觀念加以詮釋，每個月經週期，卵巢在月經初期開始會有濾泡逐漸長大，待其成熟之後，會將卵子釋放出來，這個過程便為「排卵」。
- 若在濾泡生長的過程中，發生男性賀爾蒙上昇，就會影響濾泡的生長速度，並使其無法排卵，這個沒有釋放卵子的濾泡就會逐漸堆積於卵巢之中，同時也會逐漸影響日後的排卵，並形成超音波影像下所謂的「多囊性卵巢」。

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多囊性卵巢症候群的發生率？

- 依據Adam於1985年在Lancet所表之文章的定義，在超音波檢查時，可以發現這些囊腫大小約2-8mm (數目經常大於20顆)，通常排列於卵巢回音部分較強之基質周圍，圍繞成如珍珠項鍊般的特徵(“black pearl necklace” sign)，形成所謂的多囊性卵巢。
- 臨床上，大約有百分之二十的婦女可以在超音波檢查時發現這種超音波表徵，其中約有三分之一至一半合併有臨床症狀，是屬於所謂的「多囊性卵巢症候群」，所以多囊性卵巢症候群的發生率大約百分之六至十之間。

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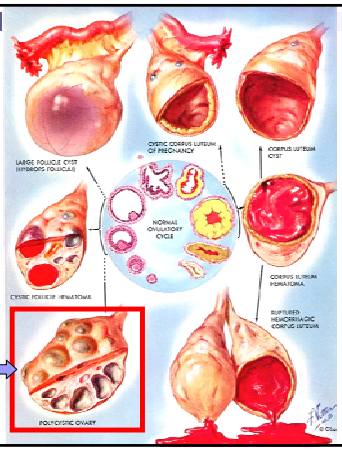

多囊性卵巢

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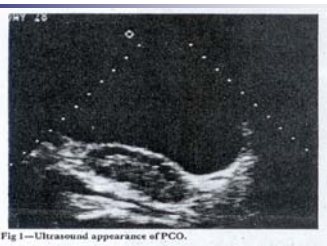

Fig 1—Ultrasound appearance of PCO.

The ovary is enlarged and contains many cysts distributed peripherally around a dense core of stroma.

TABLE 1—OVARIAN AND UTERINE DIMENSIONS

	Ovarian volume (cm^3)	Uterine area (cm^2)
Normal (follicular phase, n = 17)	6·4±0·8	22·4±1·0
MFO (n = 17)	8·0±0·8	13·1±0·9
PCO (n = 25)	14·8±1·1	26·0±1·4

Values shown are mean±SEM. Ovarian volume for each patient was the average value for both ovaries.
a vs b, not significant; a vs c, p<0·001; b vs c, p<0·001; d vs e, p<0·001; d vs f, p<0·02, e vs f, p<0·001.

多囊性卵巢
卵巢體積增加

(Lancet, 1985)

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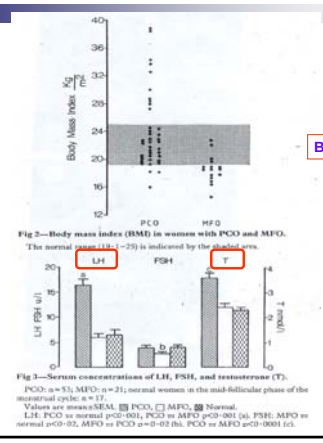

Fig 2—Body mass index (BMI) in women with PCO and MFO.
The normal range (19·1–25) is indicated by the shaded area.

BMI ↑

Fig 3—Serum concentrations of LH, FSH, and testosterone (T).
PCO: n = 53; MFO: n = 21; normal women in the mid-follicular phase of the menstrual cycle: n = 17.
Values are mean±SEM. ▨ PCO, □ MFO, ▩ Normal.
LH: PCO vs normal p<0·001, PCO vs MFO p<0·001 (a). FSH: MFO vs normal p<0·02, MFO vs PCO p = 0·02 (b). PCO vs MFO p<0·0001 (c).

LH ↑, T ↑

(Lancet, 1985)

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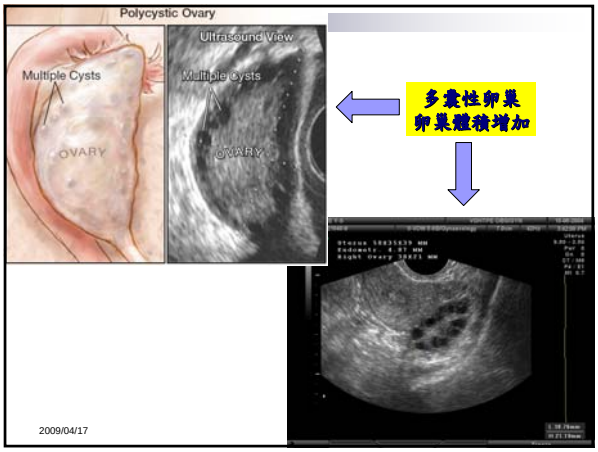

多囊性卵巢
卵巢體積增加

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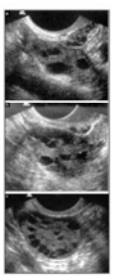
Assessment of Capacity for Response



Representative transvaginal ultrasound images

- normal ovary (total volume, 4.89 cm^3)
- multifollicular ovary (total volume, 7.8 cm^3)
- polycystic ovary (total volume, 19.93 cm^3)

多囊性卵巢
卵巢體積增加

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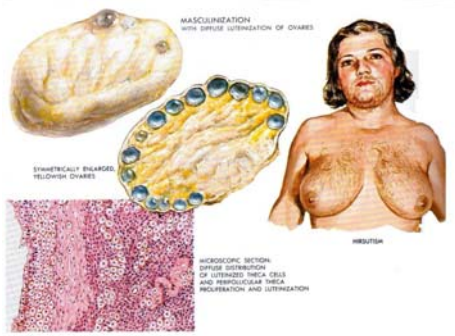

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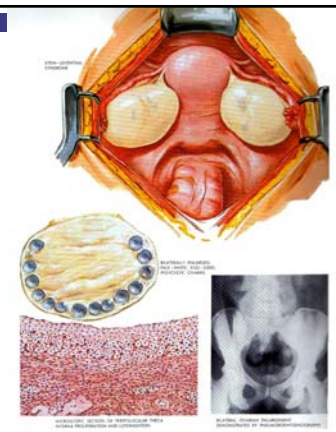


多囊性卵巢
卵巢體積增加

多囊性卵巢症候群的臨床表現

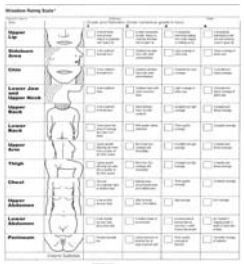
- 一、 慢性不排卵與不孕症(Anovulation and Infertility)：

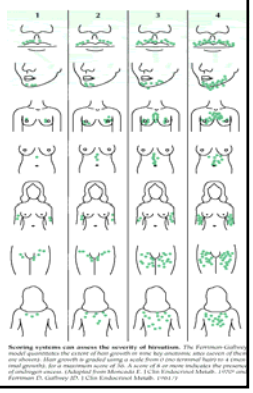
1. 多囊性卵巢症候群**最常見的症狀**還是**「慢性不排卵」**與「不孕症」。慢性不排卵的症狀包括：月經不規則，月經過少或無月經，其間或有偶發性的月經過多合併大量陰道出血。
2. 這種月經的不規則，**通常開始於初經**，因為沒有排卵，所以月經來臨前的一些不適症狀比較不會出現；由於慢性不排卵，子宮內膜便暴露於長期動情素的單向刺激，而**無黃體素的制衡**，發生**子宮內膜增生甚至子宮內膜癌**的機率也就可能增高。
3. 慢性不排卵表示**卵巢濾泡生成的異常**，即或偶有自發性的排卵，其卵子品質也會受到影響，受孕率也隨之下降，所以**容易導致不孕**。

- 二、 雄性素過多(Hyperandrogenemia)：

1. **肥胖(Obesity)**
   大約有**50%**的患者會有肥胖的症狀，這種肥胖與正常婦女的肥胖有些差異，正常婦女的肥胖是下半身的梨子型肥胖，而這些雄性素偏高的婦女肥胖常是**上半身與腹部的蘋果型肥胖**。
2. **多毛症(Hirsutism)**
   多囊性卵巢所導致的多毛症，主要是於**身體的中線**容易發現過多的毛髮生長，就其臨床表徵而言，可能因種族而有不同的變異，例如**西方人**可能有**百分之七十**的多囊性卵巢症候群患者或有多毛的症狀，反之，只有**百分之十的東方人**會出現明顯的多毛症狀。
3. **痤瘡(Acnes)**
   對於一些經由傳統治療無效的痤瘡(Acne) 患者，也常發現有多囊性卵巢症候群的存在。這些**痤瘡主要發生在臉部與和胸骨上方部位**，其他常見的部位包括**胸部，大腿內側與會陰部**等。
4. **黑色棘皮病**
   雄性素過多症的另外一個常見的特徵就是所謂「黑色棘皮病」或「黑色角化病」 (acanthosis nigricans)，也就是在全身，腋下， 胯下，或有皺摺的皮膚處，呈現**過度色素化**(hyperpigmentation)的現象。

多毛症診斷標準





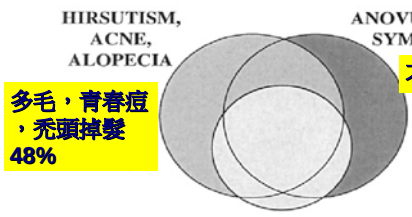
- **midline, scalp, back, chest, abdomen, axillary, and pubic area** and are the type most affected by **androgens**
- **Score≧8** consider hirsutism

Fertility and Sterility 2006

- 三、 抗胰島素(Insulin-resistance)

1. 多囊性卵巢的患者，比較容易形成一種所謂類似糖尿病的狀況，這些病患在以後的日子裡，也**比較容易罹患糖尿病**。
2. 許多研究也顯示，多囊性卵巢症候群和**肥胖、糖尿病，或是心臟血管疾病，有密切的關係**。

多囊性卵巢症候群的臨床表現



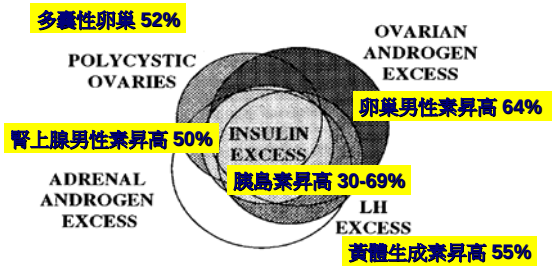
多毛，青春痘，禿頭掉髮 48%

不排卵 52 %

肥胖 50%

(CME vol 12, No. 4, 2002)

多囊性卵巢症候群的抽血賀爾蒙變化



(CME vol 12, No. 4, 2002)

Pathophysiology of PCOS

- **Insulin action and secretion defect**: hyperinsulinaemia and insulin resistance.
- **Neuroendocrine defect**: an exaggerated LH pulse frequency and amplitude ↑.
- **Androgen synthesis defect** :enhanced ovarian androgen production.
- **Cortisol metabolism alteration:** enhanced adrenal androgen production.

多囊性卵巢症候群的致病原因

1. 不適當的「性腺刺激素釋放激素」(GnRH)分泌頻率異常所引發持續性的黃體生成激素(LH)上昇。當LH分泌過多的時候，對濾泡之發育及卵之成熟則有很大的負面影響。
2. 身體組織對對「胰島素產生抗性」(insulin resistance)產生「代償性高胰島素血症」。高胰島素血症容易引起卵巢雄性素製造增加，特別是睪丸酮(testosterone) androstenedione，另外就是會使「血清性腺賀爾蒙結合球蛋白」(SHBG)減少，如此便使血清內游離的睪丸酮濃度上昇。
3. 卵巢與腎上腺所產生的雄性素(androgens)增加。
4. 「泌乳素」(prolactin)的濃度會有輕微上昇的現象。

Insulin resistance

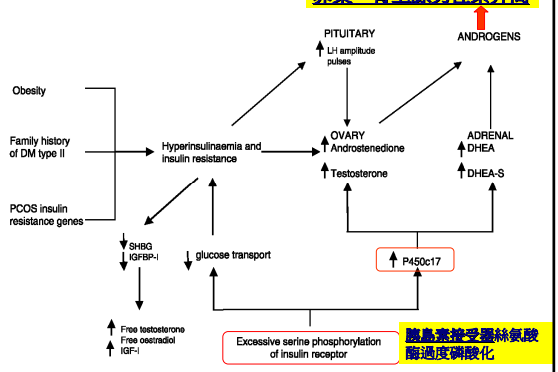
- Insulin sensitivity decreased in PCOS patients both obese and non- obese. (Dunaif *et al,* 1992)
- A negative trend of decreasing IS from lean controls, to lean PCOS, to obese controls, and finally to obese PCOS. (Morales,1996)

Insulin resistance

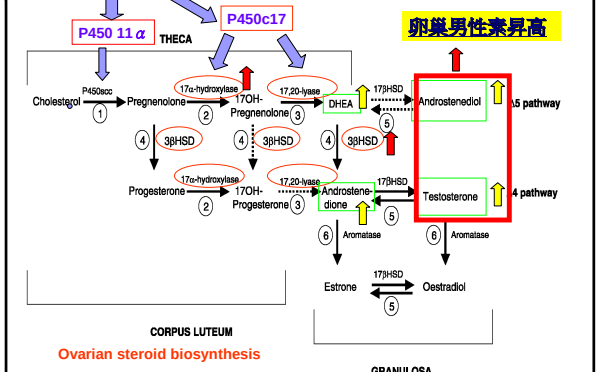
- Insulin action: protein tyrosine kinase receptor. tyrosine autophosphorylation increases activity, serine phosphorylation inhibits it.
- IRS-1 and IRS-2 (insulin receptor substrate-1 and -2) initiating signal transduction and the plieotropic actions of insulin.
- A potential mechanism for IR: at least 50% of PCOS appears excessive serine phosphorylation of insulin receptor.

Insulin resistance

- Serine phophorylation has been shown to increase P450c17 activity and androgen synthesis (Zhang *et al*,1995)
- Proposed insulin-mediated increase of ovarian cytochrome P450c17a activity. (Nestler *et al,* 1996)
- Hyperinsulinaemia may stimulate cytochrome P450c17a activity in andrenal gland- further supports this hypothesis. (Moghetti *et al,* 1996b)
- Insulin → LH pulse amplitude ↑, frequency ↔

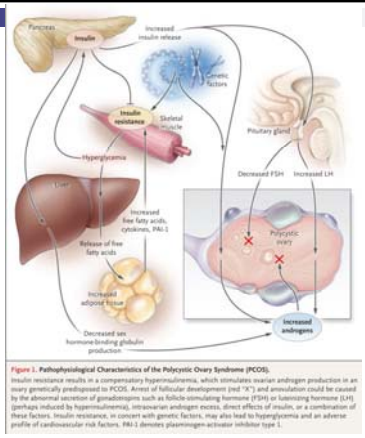


Clinical endocrinology, 2004



Ovarian steroid biosynthesis

Clinical endocrinology, 2004



NEJM, 2008

Neuroendocrine defect

- LH hypersecretion (Yen *et al*,1970; Barnes *et al*,1989)
- Hypersensitivity to GnRH stimulation by increase LH pulse amplitude and frequency (Venturoli *et al*,1970)
- GnRH pulse frequency increased-favor LH synthesis (Waldstreicher *et al*,1988; Cheung *et al*,1997)
- GnRH pulse generator insensitive to estrogen/p4 inhibition. (Pastor *et al*,1998)

Ovarian defect

- Gonadotropin-dependent ovarian hyperandrogenism. (Barnes *et al*,1989)
- Intraovarian hyperandrogenaemia-an intrinsic abnormality of ovarian theca cell steroidogenesis. (Nelson *et al*,2001)
- Dysregulation of steroid biosynthesis and metabolism involved P450c17 enzyme. (Ehrmann *et al*,1995)
- **P450c17** and **3βHSD** activity increased. (Nelson *et al*,2001)

Increased peripheral cortisol metabolism

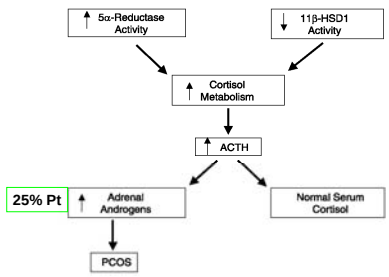


Fig. 3 Increased peripheral cortisol metabolism as a proposed mechanism for the development of PCOS.

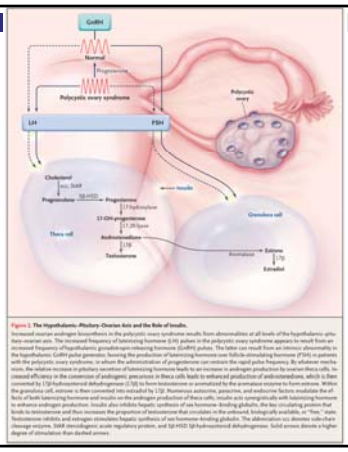
Clinical endocrinology, 2004

Genetics of PCOS

- First degree female relative with PCOS, 46% sisters affected, 50% hyperandrogenaemia. (Logro *et al*,1998)
- CYP17 (Franks *et al*,2001)
- CYP11 α (GAASENBEEK et al, 2004)
- MAPK: MEK and ERK signaling (Mol. Endocrinol. 2004)
- GATA6 (Wood *et al*, 2004)
- Ghrelin (Mclaughlin *et al*, 2004)
- Androgen receptor (Mifsud, *et al*, 2000)

多囊性卵巢症候群和遺傳的關係

1. First degree female(一等親) 有多囊性卵巢症候群, 46% sisters affected, 50% hyperandrogenaemia. (Logro *et al*,1998)
2. 類固醇之合成與作用有關的基因 CYP17 (Franks *et al*,2001)；CYP11 α (GAASENBEEK et al, 2004)
3. 與性激素作用及調控有關之基因 MAPK: MEK and ERK signaling (Mol. Endocrinol. 2004)
4. 與醣類之代謝與利用有關之基因，如Insulin gene (胰島素基因),Insulin Receptor gene (胰島素受器基因),Insulin Receptor substrate gene(胰島素受體受質基因)
5. 男性素接受器異常突變 Androgen receptor (Mifsud, *et al*, 2000)



N Engl J Med 2005; 352:1223-36

Table 2. Representative Candidate Genes with Evidence of Linkage, Association, or Both, with the Polycystic Ovary Syndrome (PCOS).

Pathway and Protein (Gene)	Comments
Insulin secretion and action	
Insulin receptor (*INSR*) region	D19S884, an anonymous marker 1 cM centromeric to *INSR*; evidence for linkage and association with PCOS[46,53]
Insulin variable-number tandem repeats (*VNTR*)	Region involved in transcriptional regulation of insulin gene; evidence for linkage and association with class III allele[54-56]
Insulin receptor substrate 1 (*IRS-1*)	Post-receptor molecule in insulin signaling pathway; association with PCOS[57,58]
Insulin receptor substrate 2 (*IRS-2*)	Post-receptor molecule in insulin signaling pathway; association with PCOS[57,58]
Calpain 10 (*CAPN10*)	Cysteine protease with effect on insulin action and secretion; linkage and association with type 2 diabetes[59,60]
Peroxisome-proliferator–activated receptor γ (*PPARγ*)	The Pro12Ala polymorphism in the *PPARγ* gene is a modifier of insulin resistance in PCOS[61-63]
Protein phosphatase 1 regulatory subunit (*PPP1R3*)	Variant of regulatory subunit of the glycogen-associated form of protein phosphatase-1 derived from skeletal muscle; associated with insulin resistance[64]
Gonadotropin secretion and action	
Follistatin (*FST*)	Acts to inhibit ovarian follicular maturation and androgen production; enhances follicle-stimulating hormone and insulin secretion[65-67]
Androgen biosynthesis, secretion, transport, and metabolism	
Androgen receptor (*AR*)	Number of CAG repeats associated with androgen levels in PCOS[68]
Sex hormone–binding globulin (*SHBG*)	Association of the pentanucleotide (TAAAA)n repeat polymorphism with PCOS[47,48]
Cytochrome P-450c17 (*CYP17*)	Possible association with PCOS[69-71]
Cytochrome P-450 1α (*CYP1α*)	Early analyses revealed association with hyperandrogenemia and PCOS[54,72]; more recently, strength of association has been questioned[73]
11β-Hydroxysteroid dehydrogenase (*11β-HSD*) and hexose-6-phosphate dehydrogenase (*H6PD*)	Mutations in both *11β-HSD* and *H6PD* in a triallelic digenic model of inheritance result in low 11β-HSD expression and NADPH generation with loss of 11β-HSD 1 oxo-reductase activity[74]

N Engl J Med 2005;352:1223-36.

多囊性卵巢症候群的診斷條件

1990 NIH in Bethesda, Maryland, USA 美國

1. 慢性不排卵
2. 抽血顯示雄性賀爾蒙素過多或是臨床上出現雄性賀爾蒙過多的症狀

UK definition of PCOS 英國

1. 超音波檢查時發現多囊性卵巢
2. 慢性不排卵
3. 或是臨床上出現雄性賀爾蒙過多的症狀

多囊性卵巢症候群的診斷條件
2003荷蘭鹿特丹大會

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group

Rotterdam, The Netherlands

Fertil Steril 2004

2003荷蘭鹿特丹大會
多囊性卵巢症候群的診斷條件

(2 OUT OF 3) (三項中出現二項)

- 慢性不排卵
- 抽血顯示雄性賀爾蒙素過多或是臨床上出現雄性賀爾蒙過多的症狀
- 超音波檢查時發現多囊性卵巢

排除其他特定疾病所致，如泌乳素過高、
先天性腎上腺增生、腎上腺腫瘤、與庫欣氏症候群

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TABLE 1

Revised diagnostic criteria of polycystic ovary syndrome.

1990 Criteria (both 1 and 2)
1. Chronic anovulation and
2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies.

Revised 2003 criteria (2 out of 3)
1. Oligo- or anovulation,
2. Clinical and/or biochemical signs of hyperandrogenism,
3. Polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome)

Note: Thorough documentation of applied diagnostic criteria should be done (and described in research papers) for future evaluation.

2003 Rotterdam PCOS consensus. Fertil Steril 2004. Fertil Steril 2004

TABLE 3

Criteria for the metabolic syndrome in women with polycystic ovary syndrome. (Three of five qualify for the syndrome.)

Risk factor	Cutoff
1. Abdominal obesity (waist circumference)	>88 cm (>35 inch)
2. Triglycerides	≥150 mg/dL
3. HDL-C	<50 mg/dL
4. Blood pressure	≥130/≥85
5. Fasting and 2-h glucose from oral glucose tolerance test	110–126 mg/dL and/or 2-h glucose 140–199 mg/dL

2003 Rotterdam PCOS consensus. 小心合併有代謝症候群

Fertil Steril 2004

2009/04/17

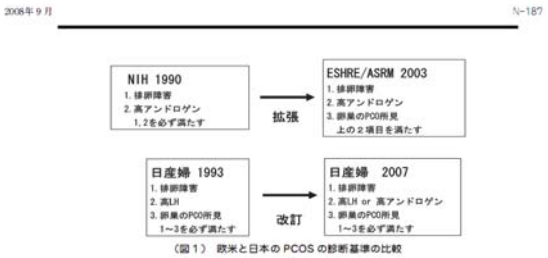
Table 2. Features considered essential for the diagnosis of polycystic ovarian syndrome

	Endo (%) $n = 138$	Gyn (%) $n = 172$	*P*-value
Menstrual irregularity	70	47	< 0·001
Any androgenization	81	59	< 0·001
Clinical (C) androgenization	5	4	0·672
Biochemical (B) androgenization	8	9	0·816
Either C or B androgenization	55	35	< 0·001
Both C and B androgenization	10	10	0·878
Obesity	11	8	0·320
Polycystic ovaries on ultrasound	14	61	< 0·001
Elevated LH / FSH ratio	24	47	< 0·001
Insulin resistance	6	11	0·162

Percentage of endocrinologists (Endo) and gynaecologists (Gyn) who listed these criteria as essential for the diagnosis of PCOS. *P*-value for differences between groups.

Cussons et al., Clin Endocrinol 62:289-95, 2005

PCOS in Japan



（図1） 欧米と日本の PCOS の診断基準の比較

PCOS in Japan

	Control (n=37)	PCOS At diagnosis (n=43)	Early phase (n=25)	Late phase (n=29)
LH (mIU/mL)	4.2 ± 1.6	10.9 ± 3.8	6.9 ± 4.1	10.4 ± 4.5
FSH (mIU/mL)	7.4 ± 1.7	7.1 ± 2.9	7.3 ± 2.1	7.0 ± 3.2
LH/FSH ratio	0.59 ± 0.25	1.73 ± 0.75	0.95 ± 0.49	1.70 ± 0.80
Elevated LH	13.7%	100%	52.0%	82.8%
Elevated LH/FSH ratio	10.8%	100%	52.0%	89.7%

- Early phase: within 10 days from withdrawal bleeding
- Late phase: after more than 10 days from withdrawal bleeding
- Elevated LH: higher than 7 mIU/mL
- Elevated LH/FSH ratio: higher than 1

Iwasa, Irahara et al., JOGR 2008

Diagnostic criteria for polycystic ovary syndrome in Taiwanese Chinese women: comparison between Rotterdam 2003 and NIH 1990

TABLE 1

Clinical and biochemical presentation in various phenotypes of PCOS.

Diagnosis	Number (%)	Interval[a]	T[b]	mFG Score	Hirsutism (%)	Acne (%)	LH (mIU/mL)	LH/FSH	BMI	WHR
PCOS all	170 (100%)	81.5 ± 58.7	3.44 ± 1.60	3.70 ± 3.97	30%	41%	11.21 ± 6.50	1.98 ± 1.20	24.4 ± 6.0	0.81 ± 0.07
Control	45	30.3 ± 3.0	1.42 ± 0.45	0.42 ± 0.72	0	0	3.92 ± 1.94	0.61 ± 0.38	21.2 ± 3.1	0.74 ± 0.04
Non-NIH	67 (39%)	58.1 ± 48.9	2.71 ± 1.42	2.99 ± 3.44	22%	30%	9.26 ± 5.40	1.69 ± 1.01	23.3 ± 5.6	0.80 ± 0.05
O+P	31 (18%)	87.7 ± 59.6	1.91 ± 0.56	1.23 ± 1.50	0	0	10.44 ± 4.34	1.90 ± 1.01	23.5 ± 6.0	0.79 ± 0.05
A+P	36 (21%)	32.5 ± 4.8	3.37 ± 1.60	4.50 ± 3.92	42%	56%	8.25 ± 6.05	1.50 ± 0.98	23.2 ± 5.3	0.80 ± 0.05
NIH	103 (61%)	96.7 ± 59.8	3.92 ± 1.53	4.20 ± 4.23	35%	48%	12.48 ± 6.85	2.17 ± 1.28	25.7 ± 6.1	0.82 ± 0.07
A+O	15 (9%)	81.3 ± 47.2	3.57 ± 1.74	2.93 ± 2.66	27%	46%	9.47 ± 6.04	1.79 ± 1.27	24.9 ± 6.8	0.82 ± 0.06
A+O+P	88 (52%)	99.3 ± 61.5	3.99 ± 1.49	4.42 ± 4.42	36%	48%	13.0 ± 6.88	2.23 ± 1.27	25.8 ± 6.0	0.82 ± 0.07
P value										
NIH vs. non-NIH		.000	.000	NS	NS	.020	.001	.010	.013	.012
O+P vs. control		.000	.002	NS	NS	NS	.000	.000	NS	.000
A+P vs. control		NS	.000	.000	.000	.000	.002	.000	NS	.000
A+O vs. control		.008	.002	.024	NS	.032	.029	.027	NS	.001
A+O+P vs. control		.000	.000	.000	.000	.000	.000	.000	.000	.000

台灣 PCOS p't : 91%PCO (多囊性卵巢) features

TABLE 4

Prevalence of polycystic ovaries (PCO)[a] by transvaginal ultrasonography in the polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. PCOS with PCO	% PCOS with PCO
Rajkhowa et al., 1995	86	153	141	92.20%
Falsetti & Eleftheriou, 1996	88	240	180	75.00%
Khoury et al., 1996	89	112	77	68.80%
Van Santbrink et al., 1997	168	198	148	74.70%[b]
Laven et al., 2001	175	190	154	81.10%
Alborzi et al., 2001	92	371	211	56.90%
Williamson et al., 2001	93	162	161	99.40%
Amer et al., 2002	95	161	93	57.80%
Jonard et al., 2003	176	214	160	74.80%
Orio et al., 2003	97	100	33	33.00%
Hahn et al., 2005	99	200	166	83.00%
Legro et al., 2006	110	626	573	91.50%
Diamanti-Kandarakis & Danidis, 2007	100	634	383	60%
Total		3361	2480	73.79%

[a] Excluding multicystic or multifollicular ovaries.
[b] PCOS defined as oligo-amenorrhea with either increased androgens and/or high LH.

Azziz AE-PCOS Society report on PCOS phenotype. Fertil Steril 2008.

2009/04/17

TABLE 2

Prevalence of menstrual dysfunction in the polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. of PCOS patients with oligo-amenorrhea	% of PCOS patients with oligo-amenorrhea	No. of PCOS patients with eumenorrhea	% of PCOS patients with eumenorrhea
Ferriman & Purdie, 1983	83	280	237	84.60%	43	15.40%
Conway et al., 1989	84	556	395	71.00%	139	25.00%
Kiddy et al., 1990	85	263	203	77.20%	60	22.80%
Ardaens et al., 1991	65	144	105	72.90%	39	27.10%
Rajkhowa et al., 1995	86	153	129	84.30%		
Balen et al., 1995	87	1741	1043	59.90%	517	29.70%
Falsetti & Eleftheriou, 1996	88	240	207	86.30%	24	10.00%
Khoury et al., 1996	89	112	112	100.00%	0	0.00%
Talbott et al., 1998	90	244	229	93.90%	15	6.10%
Carmina et al., 1998	91	332	290	87.30%	42	12.70%
Alborzi et al., 2001	92	371	371	100.00%	0	0.00%
Williamson et al., 2001	93	162	144	88.90%		
Haddad et al., 2002	94	146	120	82.20%	26	17.80%
Amer et al., 2002	95	161	149	92.50%	12	7.50%
Glueck et al., 2003	96	138	138	100.00%	0	0.00%
Orio et al., 2003	97	100	100	100.00%	0	0.00%
Chang et al., 2005	98	316	265	83.90%	51	16.10%
Hahn et al., 2005	99	200	200	100.00%	0	0.00%
Carmina et al., 2006	46	685	538	56.60%	147	15.50%
Diamanti-Kandarakis & Danidis, 2007	100	634	545	85.90%	89	14.10%
Total		6978	5520	79.11%[a]	1204	17.25%

2009/04/17

TABLE 3

Prevalence of hyperandrogenemia and hirsutism in the polycystic ovary syndrome (PCOS).

Study	Reference	Total No. PCOS	No. with elevated Total T	% with elevated Total T	No. with elevated Free T	% with elevated Free T	No. with elevated DHEAS	% with elevated DHEAS	No. with Hirsutism[a]	% with Hirsutism[a]
Ferriman & Purdie, 1983	83	280							230	82.14%
Conway et al., 1989	84	556	110	22.30%[a]					320	57.55%
Kiddy et al., 1990	85	263							129	49.05%
Rajkhowa et al., 1995	86	153							123	80.39%
Balen et al., 1995	87	1741	503	28.90%					1153	66.23%
Norman et al., 1995	109	122							103	84.43%
Falsetti & Eleftheriou, 1996	88	240							92	38.33%
Khoury et al., 1996	89	112							20	17.86%
Talbott et al., 1998	90	244							105	43.03%
Alborzi et al., 2001	92	371							300	80.86%
Williamson et al., 2001	93	162							147	90.74%
Amer et al., 2002	95	161							53	32.92%
Orio et al., 2003	97	100	33	33.00%			27	27.00%	100	100.00%
Azziz et al., 2004	47	873							517	72.20%
Chang et al., 2005	98	316	122	38.60%	216	68.40%	71	22.50%	224	70.89%
Hahn et al., 2005	99	200	162	81.00%			76	38.00%	129	64.50%
Legro et al., 2006	110	626	373	60.80%[b]					505	80.67%
Diamanti-Kandarakis & Danidis, 2007	100	634	535	84.38%			70	11%	441	69.55%
Total		6281	1838	29.26%	216	3.44%	244	3.88%	4691	74.69%

2009/04/17

What is PCOS in 2009?

TABLE 1

All possible phenotypes based on the presence or absence of oligo anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome (PCOS).

Features	Potential Phenotypes A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	–	–	+	–	+	–	+	–	–	–	+	–
Hirsutism	+	+	–	–	+	+	+	+	–	–	+	–	–	+	–	–
Oligo-anovulation	+	+	+	+	+	+	–	–	–	+	–	–	+	–	–	–
Polycystic ovaries	+	–	+	–	+	–	+	+	+	+	–	+	–	–	–	–
NIH 1990 criteria	√	√	√	√	√	√										
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√						
AE-PCOS 2006 criteria	√	√	√	√	√	√	√	√	√							

Azziz AE-PCOS Society report on PCOS phenotype. Fertil Steril 2008.

1. Rotterdam PCOS are less metabolically disturbed compared to NIH PCOS
2. Hyperandrogenemia itself is closely associated with metabolic abnormalities

什麼是多囊性卵巢？

- 在月經來的第 3-5 天使用陰道超音波掃描
- 濾泡大小約2-9mm，數目大於10顆，通常排列於卵巢基質周圍，圍繞成如珍珠項鍊般的特徵(“black pearl necklace” sign)。
- 卵巢體積變大; volume >10 ml

2009/04/17

Diagnostic Criteria

PCO

- Favor TVS
- Early follicular phase (day 3-5)
- 2-9 mm follicle > 10#
- Follicular size <10mm in two sections
- Ovarian volume calculation prolate ellipsoid (0.5 x length x width x thickness); volume >10 ml

TABLE 1

Correlation of each of the ultrasound formulaic methods with 3-dimensional ovarian volume measurements.

Method of measure	Three-dimensional (correlation coefficient)[a]
π/6 (transverse diameter) × (anteroposterior diameter) × (longitudinal diameter)	0.70
π/6 (transverse diameter)^3	0.55
π/6 (anteroposterior diameter)^3	0.61
π/6 (longitudinal diameter)^3	0.10
π/6 [(transverse diameter + anteroposterior diameter)/2]^3	0.72
π/6 [(antero-posterior diameter + longitudinal diameter)/2]^3	0.49
π/6 [(transverse diameter + longitudinal diameter)/2]^3	0.61
π/6 [(transverse diameter + anteroposterior diameter + longitudinal diameter)/3]^3	0.73
π/6 (transverse diameter)^2 (anteroposterior diameter)	0.67
π/6 (anteroposterior diameter)^2 (transverse diameter)	0.73
π/6 (transverse diameter)^2 (longitudinal diameter)	0.61
π/6 (anteroposterior diameter)^2 (longitudinal diameter)	0.51
π/6 (longitudinal diameter)^2 (transverse diameter)	0.49
π/6 (longitudinal diameter)^2 (anteroposterior diameter)	0.30

[a] Pearson's correlation test.

Nardo. PCOS and ultrasound ovarian volume measurements. Fertil Steril 2003.

Fertil Steril 2003

超音波顯示多囊性卵巢的意義何在？

TABLE 1. Baseline characteristics and hormonal values

	Ovulatory women		
	Normal ovaries	Polycystic ovaries	*P* value
n	29	39	
Age (yr)	28.4 ± 1.2	25.6 ± 0.9	0.07
Body mass index (kg/m^2)	23.8 ± 1.2	24.9 ± 0.8	0.56
Ferriman-Gallwey score	4.3 ± 0.4	4.5 ± 0.5	0.62
Ovarian volume (cc)	6.5 ± 0.4	13.2 ± 0.6	<0.001
T (ng/dl)	64.1 ± 3.1	78.3 ± 3.5	<0.01
Δ_4A (ng/ml)	2.4 ± 0.3	3.3 ± 0.3	<0.05
SHBG (nmol/liter)	110.2 ± 9.5	85.5 ± 6.8	<0.05
FT (ng/dl)	0.56 ± 0.05	0.88 ± 0.07	<0.005
DHEAS (μg/dl)	166.5 ± 16.3	242.5 ± 21.2	<0.01

To convert T and FT to nmol/liter, multiply by 0.0346; to convert Δ_4A to nmol/liter, multiply by 3.492; to convert DHEAS to μmol/liter,

超音波檢查時發現有多囊性卵巢即使排卵及月經正常，
但是抽血顯示比沒有多囊性卵巢的女性雄性素升高

(JCEM, 2004)

TABLE 2. Gonadotropin and insulin dynamics

	Ovulatory women	
	Normal ovaries	Polycystic ovaries
n	12	14
Age (yr)	29.1 ± 2.2	25.9 ± 1.7
Body mass index (kg/m^2)	27.1 ± 2.7	27.3 ± 1.7
Pool LH (IU/liter)	6.0 ± 0.8	6.6 ± 0.9
Pool FSH (IU/liter)	10.5 ± 0.7	11.0 ± 0.9
LH/FSH	0.53 ± 0.07	0.59 ± 0.07
LH amplitude (IU/liter)	5.0 ± 1.1	4.9 ± 0.5
LH pulse frequency/24 h	14.7 ± 1.4	15.5 ± 1.4
Fasting glucose (mg/dl)	87.8 ± 2.5	91.7 ± 1.3
Fasting insulin (μU/ml)	3.6 ± 0.5	6.0 ± 0.8[a]
HOMA	0.78 ± 0.12	1.38 ± 0.2[b]

To convert glucose to nmol/liter, multiply by 0.05551; to convert insulin to pmol/liter, multiply by 7.175.

超音波檢查時發現有多囊性卵巢即使排卵及月經正常，
但是抽血顯示比沒有多囊性卵巢的女性胰島素升高

(JCEM, 2004)

Ultrasound diagnosis of polycystic ovaries in women who have no symptoms of polycystic ovary syndrome is not associated with subfecundity or subfertility

如果只有多囊性卵巢沒有其他症狀
受孕能力如何呢？

symptoms of polycystic ovary syndrome.

Design: Case-control study.

Setting: Teaching hospitals in Hull, United Kingdom.

Patient(s): Women with the appearance of polycystic ovaries on ultrasound and women with normal ovaries.

Intervention(s): A questionnaire about previous subfertility, pregnancies, menstrual pattern, features of polycystic ovary syndrome, gynecological history, and individual lifestyle factors.

Main Outcome Measure(s): Time to pregnancy (TTP) and relative risk (RR) of subfertility in symptomatic and asymptomatic subgroups of both groups.

Result(s): Women with PCOs took longer TTP and were significantly less fertile if they were obese (RR = 2.6), had menstrual disturbances (RR = 4.6), hirsutism (RR = 2.5), and/or acne (RR = 2.7). Further reductions in fecundity occurred with an increasing number of symptoms (threefold, sevenfold, and 10-fold longer TTP with two, three, and four symptoms, respectively). The TTP of women with no symptoms was not significantly longer and they were not more likely to be subfertile than women with normal ovaries. These symptoms were not associated with significantly reduced fecundity in women with normal ovaries.

Conclusion(s): The appearance of polycystic ovaries has been shown to have no significant impact on fertility in women with no symptoms. Appearances alone do not reflect the pathological features of polycystic ovary syndrome, and additional diagnostic criteria should be considered. Obesity, menstrual disturbances, and/or hyperandrogenism are factors associated with subfertility in women with polycystic ovaries. (Fertil Steril® 2003;80:966–75. ©2003 by American Society for Reproductive Medicine.)

Fertil Steril 2003

TABLE 1

Symptoms in study and control groups.

Symptoms	No. (%) PCO	No. (%) Normal ov	Odds ratio (CI)	*P*[a]
Subfertility	135 (52.3)	47 (20.3)	4.6 (2.0–3.4)	<.001
Menstrual disturbances	139 (53.9)	35 (15.1)	3.6 (2.6–4.9)	<.001
History of obesity	118 (46.1)	46 (19.8)	2.3 (1.7–3.1)	<.001
Body mass index >29 kg/m^2	93 (38.1)	42 (18.6)	2.1 (1.5–2.8)	<.001
Acne	92 (35.9)	12 (5.2)	6.9 (3.9–12.3)	<.001
Hirsutism	68 (26.6)	33 (14.2)	1.9 (1.3–2.7)	.001
Androgenism	102 (39.8)	42 (18.1)	2.2 (1.6–3.0)	<.001
Diseases (diabetes mellitus, hypertension)	24 (9.4)	10 (4.3)	2.2 (1.1–4.5)	.03
Miscarriage	38 (17.3)	34 (14.8)	1.2 (0.8–1.8)	.5
Family history of subfertility	52 (20.2)	22 (9.5)	2.1 (1.3–3.4)	.001
Family history of miscarriage	42 (16.3)	24 (10.3)	1.6 (1.0–2.5)	.06

Note: CI = 95% confidence interval.

[a] Fisher's exact test.

Hassan. Effect of polycystic ovaries on fecundity. Fertil Steril 2003.

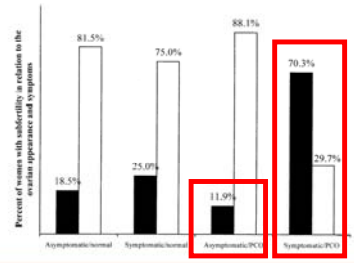
不孕
月經異常
肥胖
青春痘
多毛
雄性素升高症狀

⇒ 不孕機會 52.3%比上20.3%

Fertil Steril 2003

FIGURE 3

The figure illustrates the overall effect of symptoms of menstrual disturbances, obesity, acne, and hirsutism on the proportions of those who experienced subfertility among the women who had PCO appearance and those who had normal ovaries. The *black bars* represent the subfertile proportions, and the *white bars* represent the fertile proportions of each subgroup. $P<.001$.



Hassan. *Effect of polycystic ovaries on fecundity. Fertil Steril 2001.*

不同症狀族群產生不同的不孕機率，沒有症狀最好

多囊性卵巢沒有症狀11.9%不孕比上多囊性卵巢有症狀70.3%不孕

什麼是胰島素抗性？

Insulin resistance

- Euglycemic hyperinsulinemic clamp as a gold standard for insulin sensitivity. (DeFronzo, 1978. Metabolism)
- **Fasting glucose（空腹血糖）/ fasting insulin（空腹胰島素）<4.5（最常用）**
- HOMA index
- QUICKI
- 75gm OGTT

TABLE 1. Equations and references of insulin sensitivity indices derived from fasting and OGTT measurements of glucose and insulin

Index	Equation	Ref. no.
HOMA	$\frac{22.5 \times 18}{\text{fasting insulin} \times \text{fasting glucose}}$	23
QUICKI	$\frac{1}{\log(\text{fasting insulin}) + \log(\text{fasting glucose})}$	5
Belfiore	$\frac{2}{(\text{AUC insulin} \times \text{AUC glucose}) + 1}$	24
Cederholm	$\frac{75{,}000 + (\text{fasting glucose} - 2\text{-h glucose}) \times 1.15 \times 180 \times 0.19 \times BW}{120 \times \log(\text{mean insulin}) \times \text{mean glucose}}$	25
Gutt	$\frac{75{,}000 + (\text{fasting glucose} - 2\text{-h glucose}) \times 0.19 \times BW}{120 \times \log[(\text{fasting insulin} + 2\text{-h insulin})/2] \times [\text{fasting glucose} + 2\text{-h glucose}]/2}$	3
Matsuda	$\frac{10{,}000}{\sqrt{(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})}}$	2
Stumvoll	$0.22 - 0.0032 \times BMI - 0.0000645 \times 2\text{-h insulin} - 0.0037 \times 1.5\text{-h glucose}$	4

> 3.9 molx μ U/L2

(JCEM, 2003)

TABLE 2

Pearson correlations of fasting and postchallenge glucose levels, insulin levels, and glucose-insulin ratios from the glucose tolerance test with the M/I ratios during the final hour of the hyperglycemic clamp.

Value	Glucose vs. M/I ratios		Insulin vs. M/I ratios		Glucose-insulin ratio vs. M/I ratios	
	Correlation	*P* value	Correlation	*P* value	Correlation	*P* value
Fasting	−.022	.953	−.719	.019	.646	.002
2 h	.054	.882	−.618	.057	.574	.003
Sum of 1 h + 2 h values	−.038	.917	−.627	.052	.642	.048
Sum of 1 h + ½ h + 3 h	−.079	.828	−.637	.048	.710	.021
Sum of fasting + 1 h + 2 h + 3 h	−.077	.833	−.642	.046	.735	.016
All	−.188	.603	−.717	.020	.777	.008

Diamond. Fasting insulin predicts insulin action. Fertil Steril 2003.

Fertil Steril 2003

Prevalence and Predictors of Risk for Type 2 Diabetes Mellitus and Impaired Glucose Tolerance in Polycystic Ovary Syndrome: A Prospective, Controlled Study in 254 Affected Women*

多囊性卵巢症候群合併有胰島素抗性的發生率與合併有糖尿病的發生率爲何？

Hospital (A.D.), Boston, Massachusetts 02115

ABSTRACT

Women with polycystic ovary syndrome (PCOS) are insulin resistant, have insulin secretory defects, and are at high risk for glucose intolerance. We performed this study to determine the prevalence of glucose intolerance and parameters associated with risk for this in PCOS women. Two-hundred and fifty-four PCOS women, aged 14–44 yr, were prospectively evaluated at 2 centers, 1 urban and ethnically diverse (n = 110) and 1 rural and ethnically homogeneous (n = 144). The rural PCOS women were compared to 80 control women of similar weight, ethnicity, and age. A 75-g oral glucose challenge was administered after a 3-day 300-g carbohydrate diet and an overnight fast with 0 and 2 h blood samples for glucose levels. Diabetes was categorized according to WHO criteria. The prevalence of glucose intolerance was 31.1% impaired glucose intolerance (IGT) and 7.5% diabetes. In nonobese PCOS women (body mass index, <27 kg/m^2), 10.3% IGT and 1.5% diabetes were found. The prevalence of glucose intolerance was significantly higher in PCOS *vs.* control women ($\chi^2 = 7.0$; $P = 0.01$; odds ratio = 2.76; 95% confidence interval = 1.23–6.57). Variables most associated with postchallenge glucose levels were fasting glucose levels ($P < 0.0001$), PCOS status ($P = 0.002$), waist/hip ratio ($P = 0.01$), and body mass index ($P = 0.021$). The American Diabetes Association criteria applied to fasting glucose significantly underdiagnosed diabetes compared to the WHO criteria (3.2% *vs.* 7.5%; $\chi^2 = 4.7$; $P = 0.046$; odds ratio = 2.48; 95% confidence interval = 1.01–6.48). We conclude that 1) PCOS women are at significantly increased risk for IGT and type 2 diabetes mellitus at all weights and at a young age; 2) these prevalence rates are similar in 2 different populations of PCOS women, suggesting that PCOS may be a more important risk factor than ethnicity or race for glucose intolerance in young women; and 3) the American Diabetes Association diabetes diagnostic criteria failed to detect a significant number of PCOS women with diabetes by postchallenge glucose values. (*J Clin Endocrinol Metab* **84**: 165–169, 1999)

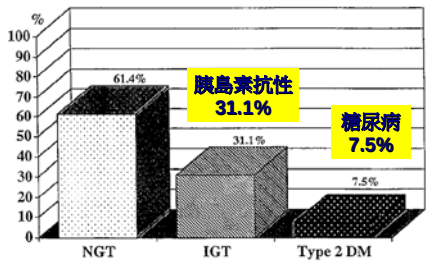


FIG. 1. Combined prevalence of glucose intolerance by WHO criteria in 254 PCOS women. NGT, Normal glucose tolerance; Type 2 DM, type 2 diabetes mellitus.

多囊性卵巢症候群對健康的影響

- Adolescence（青少年）
- Adult（成人）
- Pregnancy（懷孕）
- Long term health（長期健康的影響）

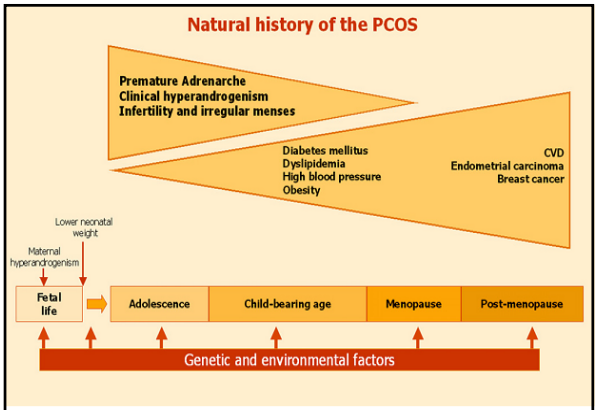


Figure 1 Natural history of the PCOS. Galluzzo *et al.*, 2008

Clinical features

- The fate of this condition changes during life
  - General practitioner
  - Pediatrician
  - Dermatologist
  - Gynecologist
  - Medical endocrinologist
  - Cardiologist
- Doctors usually see just a proportion of the overall spectrum of PCOS

多囊性卵巢症候群對青少年的影響

- 32 % 多毛(Siegberg *et al*, 1986)
- 50 % 青春痘(Apter, 1990)
- 66% 月經異常(2 years after menarche)
- 50% 肥胖(waist-to-hip ratio >0.85)
- 50% 胰島素抗性
- Risk for type II DM(糖尿病)?, CVD(心血管疾病) ?

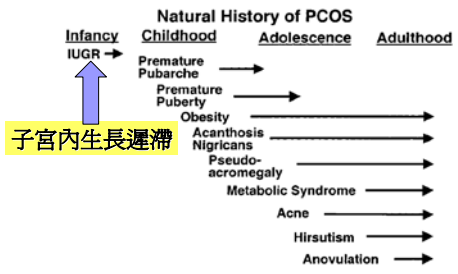


Figure 5. Natural history of PCOS. Intrauterine growth retardation is a risk factor for PCOS, although it occurs in only a minority of patients. Premature pubarche, premature breast development, obesity, acanthosis nigricans, and the metabolic syndrome are common antecedents of adolescent PCOS. Pseudoacromegalic gigantism is a more unusual prepubertal antecedent of PCOS. During adolescence, hirsutism and anovulatory symptoms appear. (CME vol 12, No. 4, 2002)

Early Impairment of Endothelial Structure and Function in Young Normal-Weight Women with Polycystic Ovary Syndrome

患有多囊性卵巢症候群，即使是年輕人，她的血管內上皮組織的健康指標也已經受損

(S.P., T.R., F.Z.), University of Catanzaro "Magna Graecia", 88100 Catanzaro, Italy; and "MeriGen" Laboratory of Molecular Biology (S.D.B., D.L.), 80131 Naples, Italy

The aim of this study was to evaluate the presence of early vascular damage in young normal-weight women with polycystic ovary syndrome (PCOS).

Thirty young normal-weight women with PCOS, who had no additional metabolic or cardiovascular diseases, and 30 healthy women (controls) matched for age and body mass index were studied. A complete hormonal assay was performed in each subject. Serum insulin and glucose levels were measured at baseline and after the oral glucose tolerance test. Plasma endothelin-1 levels and serum lipid profile were also assessed. The endothelial function was studied by flow-mediated dilation on the brachial artery, and arterial structure was evaluated by intima-media thickness measurement using Doppler ultrasound of both common carotid arteries.

A significant ($P < 0.05$) difference in flow-mediated dilation (14.3 ± 1.9% vs. 18.1 ± 2.0% for PCOS patients and controls, respectively) and in intima-media thickness (0.53 ± 0.09 mm vs. 0.59 ± 0.08 mm for PCOS patients and controls, respectively) was found between PCOS and control subjects. Serum endothelin-1 levels were also significantly ($P < 0.05$) higher in PCOS patients compared with controls (1.1 ± 0.4 pmol/liter vs. 0.5 ± 0.2 pmol/liter for PCOS patients and controls, respectively).

In conclusion, our data show that young, normal-weight, nondyslipidemic, nonhypertensive women with PCOS have an early impairment of endothelial structure and function. (*J Clin Endocrinol Metab* 89: 4588–4593, 2004)

(JCEM, 2004)

TABLE 4. Structural and functional parameters of cardiovascular assessment in women with PCOS and controls

	Women with PCOS (n = 30)	Controls (n = 30)
HR (bpm)	78.3 ± 3.9	76.2 ± 4.2
SBP (mm Hg)	111.3 ± 8.2	113.2 ± 6.7
DBP (mm Hg)	74.2 ± 4.7	71.4 ± 4.3
Baseline artery diameter (mm)	3.24 ± 0.3[a]	2.96 ± 0.4
Diameter after reactive hyperemia (mm)	3.7 ± 0.3[a]	3.5 ± 0.2
FMD (%)	14.3 ± 1.9[a]	18.1 ± 2.0
IMT (mm)	0.53 ± 0.09[a]	0.39 ± 0.08
ET-1 (pmol/liter)	1.1 ± 0.4[a]	0.5 ± 0.2

All data (expressed as mean ± SD) were adjusted for chronological age, BMI, WHR, smoking status, glucose and insulin levels, FAI, lipid profile, Hcy concentrations, and SBP and DBP. HR, Heart rate.

[a] $P < 0.05$ *vs.* control group.

(JCEM, 2004)

Increased C-Reactive Protein Levels in the Polycystic Ovary Syndrome: A Marker of Cardiovascular Disease

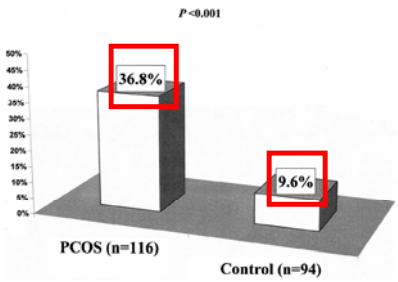
患有多囊性卵巢症候群，即使是年輕人，她的發炎指數《CRP》會升高

The polycystic ovary syndrome (PCOS), one of the most common reproductive abnormalities, shares some components of the metabolic cardiovascular syndrome. Therefore, PCOS patients may represent the largest group of women at high risk for the development of early-onset cardiovascular disease (CVD) and/or diabetes. C-reactive protein (CRP) is a strong independent predictor of future CVD and/or stroke. Only one small published study has looked for such an association (17 PCOS patients *vs.* 15 controls). The objective of this study was to compare the levels of CRP and other risk factors of CVD in a large group of PCOS patients and controls. CRP measurements were undertaken in 116 PCOS patients and 94 body mass index-matched controls with regular menstrual cycles. Whereas 36.8% of the PCOS patients had CRP levels above 5 mg/liter, only 9.6% of the controls exhibited high CRP levels ($P < 0.001$). The mean ± SD was 5.46 ± 7.0 in the PCOS group *vs.* 2.04 ± 1.9 mg/liter in the control ($P < 0.001$). The body mass index, white blood cell count, TSH, glucose, cholesterol, and homocysteine levels were not significantly different between the two groups. CRP levels are elevated in patients with PCOS and may be a marker of early cardiovascular risk in these patients. High CRP levels may explain why some PCOS women may possibly be at an increased risk for the development of early-onset CVD. Consequently, whether treatment regimens directed toward lowering CVD risk factors should be more aggressive for those PCOS women with increased CRP levels, awaits further clinical experience. (*J Clin Endocrinol Metab* 89: 2160–2165, 2004)

(JCEM, 2004)

FIG. 1. The significantly different prevalences of high CRP level (>5 mg/liter) in PCOS *vs.* control groups.

CRP↑



(JCEM, 2004)

The Cardiovascular Risk of Young Women with Polycystic Ovary Syndrome: An Observational, Analytical, Prospective Case-Control Study

患有多囊性卵巢症候群，即使是年輕人，她的心臟超音波顯示功能較一般正常人差

To evaluate the cardiovascular risk of polycystic ovary syndrome (PCOS), we investigated lipid profile, metabolic pattern, and echocardiography in 30 young women with PCOS and 30 healthy age- and body mass index (BMI)-matched women. PCOS women had higher fasting glucose and insulin levels, homeostasis model assessment score of insulin sensitivity, total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels, and TC/high density lipoprotein cholesterol (HDL-C) ratio and lower HDL-C levels than controls. Additionally, PCOS women had higher left atrium size (32.0 ± 4.9 *vs.* 27.4 ± 2.1 mm; $P < 0.0001$) and left ventricular mass index (80.5 ± 18.1 *vs.* 56.1 ± 5.4 g/m^2; $P < 0.0001$) and lower left ventricular ejection fraction (64.4 ± 4.1 *vs.* 67.1 ± 2.6%; $P = 0.003$) and early to late mitral flow velocity ratio (1.6 ± 0.4 *vs.* 2.1 ± 0.2; $P < 0.0001$) than controls. When patients and controls were grouped according to BMI [normal weight (BMI, >18 and <25 kg/m^2), overweight (BMI, 25.1–30 kg/m^2), and obese (BMI, >30 kg/m^2)], the differences between PCOS women and controls were maintained in overweight and obese women. In normal weight PCOS women, a significant increase in left ventricular mass index and a decrease in diastolic filling were observed, notwithstanding no change in TC, LDL-C, HDL-C, TC/HDL-C ratio, and TG compared with controls. In conclusion, our data show the detrimental effect of PCOS on the cardiovascular system even in young women asymptomatic for cardiac disease. (*J Clin Endocrinol Metab* 89: 3696–3701, 2004)

(JCEM, 2004)

TABLE 3. Metabolic profile and cardiovascular risk factors in women with and without PCOS

	PCOS	Controls	*P*
Fasting glucose (mmol/liter)	5.3 ± 2.6	2.6 ± 0.6	<0.0001
Fasting insulin (pmol/liter)	12.9 ± 5.2	2.3 ± 0.9	<0.0001
HOMA	3.2 ± 2.0	0.3 ± 0.1	<0.0001
TC (mmol/liter)	4.2 ± 0.5	3.5 ± 0.4	<0.0001
LDL-C (mmol/liter)	2.3 ± 0.4	1.8 ± 0.3	<0.0001
HDL-C (mmol/liter)	2.5 ± 0.5	2.9 ± 0.3	<0.0001
TC/HDL-C ratio	1.7 ± 0.4	1.2 ± 0.4	<0.0001
TG (mmol/liter)	1.5 ± 0.2	1.4 ± 0.2	0.06

TABLE 4. Echocardiographic findings in PCOS and controls

	PCOS	Controls	*P*
LV diastolic diameter (mm)	46.0 ± 3.9	42.9 ± 1.7	0.1
LV systolic diameter (mm)	26.6 ± 4.3	23.0 ± 1.8	0.001
IST (mm)	8.3 ± 1.2	6.7 ± 0.8	<0.0001
LV posterior wall thickness (mm)	8.1 ± 1.5	6.6 ± 0.8	<0.0001
LVMi (g/m^2)	80.5 ± 14.8	56.1 ± 5.4	<0.0001
Left atrium size (mm)	32.0 ± 4.9	27.4 ± 2.1	<0.0001
Aorta size (mm)	28.9 ± 3.5	28.0 ± 1.3	0.1
LVEF (%)	64.4 ± 4.1	67.1 ± 2.6	0.003
Early to late mitral flow velocity	1.6 ± 0.4	2.1 ± 0.2	<0.0001

IST, Interventricular septum thickness.

(JCEM, 2004)

多囊性卵巢症候群對成人的影響

- 20-50 % 不孕 (慢性不排卵)
- 60%-80% 肥胖
- 50%胰島素抗性
- Risk for type II DM(糖尿病)?, CVD(心血管疾病)？

多囊性卵巢症候群對懷孕的影響

- 30%-50% **早期流產** (Regan, 1990)
- 20-40% **妊娠糖尿病**(Lanzone *et al* 1996),
- Preeclampsia **子癲前症**(Gjonnaess, 1989)?

多囊性卵巢症候群的治療
青少年部分

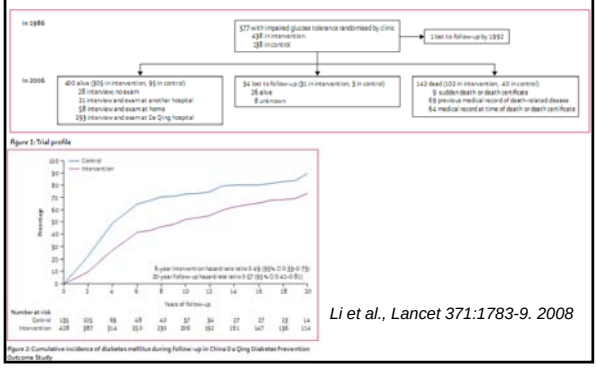
- 改善生活作息，包括良好的飲食習慣與適量的運動
- 適當的減重5-10%
- 避孕藥 Oral contraceptive pill (OCP).
- 抗雄性素的黃體素 Cyproterone acetate
- 降血糖藥物 Metformin
- 抗雄性素藥物 Flutamide
- 抗雄性素藥物 spironolactone

多毛與青春痘與月經異常的治療

適當的減重5-10%

- 改善生活作息，包括良好的飲食習慣與適量的運動，適當的減重 5-10% ，可以在六個月內改善 40-55%多毛與青春痘症狀，50%恢復正常月經.

Long-term effect of lifestyle interventions



Li et al., Lancet 371:1783-9. 2008

月經異常的治療

- 如果沒有懷孕考量，又沒有合併有多毛與青春痘症狀的病人，可以單獨使用黃體素治療。
- 如果沒有懷孕考量但是合併有多毛與青春痘症狀的病人，使用口服避孕藥是一個理想治療方式。
- 如果想懷孕，可以使用口服排卵藥治療。

多毛與青春痘的治療

口服避孕藥

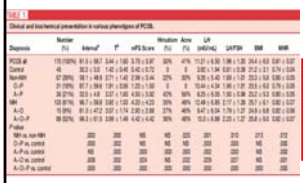
- 黛麗安(Diane-35)
  - 成分組成：21顆 CPA (2mg/day) + EE (35μg/day)
  - 黃體素**Cyproterone acetate**具有抗雄性素作用
  - **青春痘部分**可以在治療**3-5個月**看到效果
  - **多毛部分**可以在治療 **4-9個月**看到效果
  - 可以在治療**9個月**後**改善 50 %多毛症狀與100% 改善青春痘**

(Sairth *et al*, 2001)

多毛形成的原因

- 是否會出現多毛的症狀，與**周邊毛囊組織**中的**5α-還原酶(5α-reductase)的接受器濃度**有關，因為這種5α-還原酶會將睪丸酮轉變為更具活性的DHT(dihydrotestosterone)與3α-diol-G。

台灣多囊性卵巢症候群多毛的盛行率是多少？



- **USA: 77%** had hirsutism and average mF-G scores of 8.0
- **Taiwan: 30%** had hirsutism and average mF-G scores of 4.2
- **Hong Kong: 37%** (33 of 90) had clinical hirsutism

Fertility and Sterility Vol. 88, No. 3, September 2007

HIRSUTISM

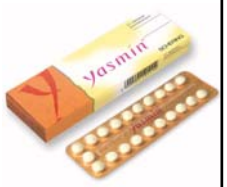
- < 5%
  - Consistent with East Asian p'ts
    Legro RS, et al. *Fertil Steril* 2006;86:914–32
  - Taiwanese：28%
    Ming-I Hsu, et al. *Fertil Steril* 2007;88:727–9.
  - Japanese：8%
    Takashi I, et al. *Endocrine J* 2007;54:233–8.
  - Indian：66%
    Aruna J, et al. *Inter J Obst Gynaecol* 2004;87:237–41

口服避孕藥作用機轉

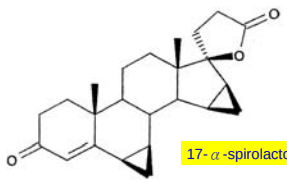
- **動情素(EE)**可抑制腎上腺之活性，**減少雄性激素**的分泌；也會使SHBG增加，所以血清內游離的睪丸酮濃度就會降低。動情素亦可抑制睪固酮在皮膚中活化成DHT，故能改善多毛症、脂溢以及粉刺等相關症狀。
- **黃體素(CPA)**的成分會**直接抑制5-α還原酶的活性**，並會與**男性素的接受器競爭**其結合位置，**抑制男性素的活性**。
- 由於服用口服避孕藥可促使子宮內膜成週期性的剝落，使原本長期不排卵的病人免於子宮內膜癌的威脅。

新一帶口服避孕藥　悅己

- **新一帶口服避孕藥**
- **悅己**(Yasmin)
  - 成分組成：21顆 DRSP (3mg/day) + EE (30μg/day)
  - Drospirenone：最新一代的黃體素
    - **有效保護子宮內膜**
    - **具有PARA效果**（**P**rogestogen with **A**ldosterone **R**eceptor **A**ntagonist activity）
    - **具抗雄性素作用**(anti-androgenic)，**強度為CPA的1/3**



Drospirenone：3 mg 最新一代的黃體素



17-α-spirolactone derivative

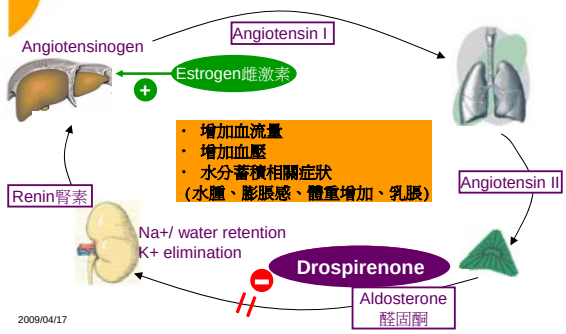
Fig. 1. Chemical structure of drospirenone. Chemical name: 6β,7β,15β,16β-dimethylen-3-oxo-17α-pregn-4-ene-21,17-carbo-lactone (IUPAC). Generic name, drospirenone; molecular formula, $C_{24}H_{30}O_3$; molecular weight, 366.50.

Anti-mineralcorticoid receptor and anti-androgen receptor

抗礦物皮質酮效果有效緩解水份蓄積的問題

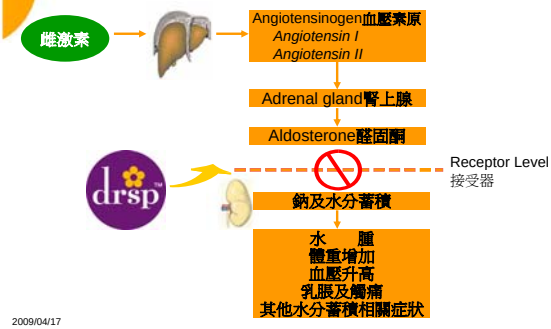
Molecular and Cellular Endocrinology 217 (2004) 255–261

RAAS (Renin-angiotensin-aldosterone-system)



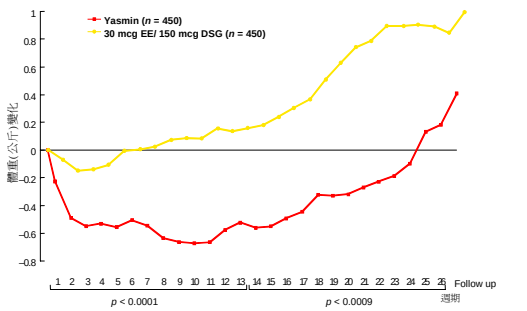
2009/04/17

DRSP如何抑制水分蓄積及相關作用？



2009/04/17

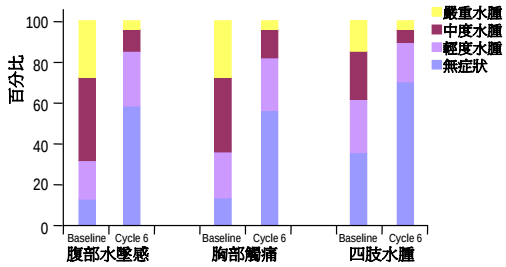
Yasmin®對體重有正面好處



2009/04/17

Foidart JM et al. A comparative investigation of contraceptive reliability,cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel .*Eur J Contracept Reprod Health Care* 2000;5(2):124-34.

Yasmin®有效改善水腫



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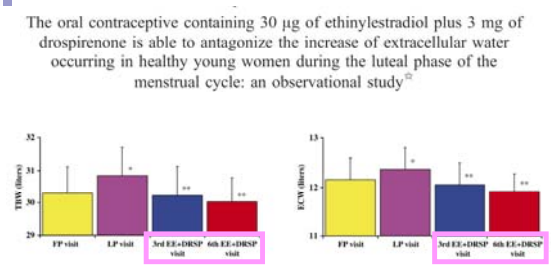
Apter D, *et al. Eur J Contracept Reprod Health Care* 2003;8:37–51



The oral contraceptive containing 30 μg of ethinylestradiol plus 3 mg of drospirenone is able to antagonize the increase of extracellular water occurring in healthy young women during the luteal phase of the menstrual cycle: an observational study☆

Yasmin有效改善水腫

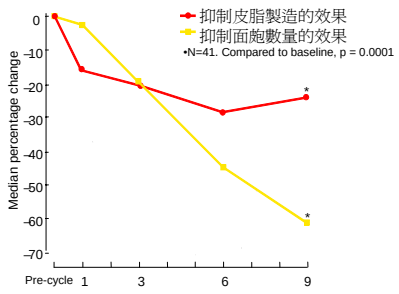
2009/04/17

Contraception 75 (2007) 199– 203

DRSP抗雄性化的作用機轉

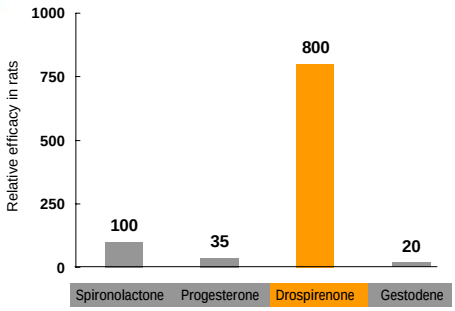
2009/04/17

Yasmin®能降低皮脂及治療痤瘡



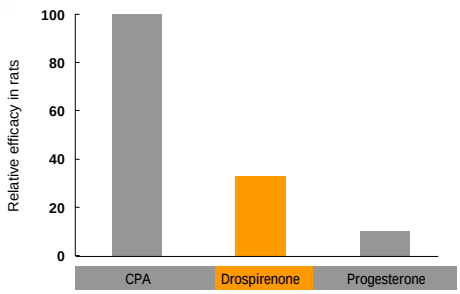
Boschitsch E, Skarabis H, Wuttke W et al. The acceptability of a novel oral contraceptive containing drospirenone and its effect on well-being. Eur J Contracept Reprod Health Care 2000;5(suppl 3):34-40.

抗礦物皮質酮強度比較表



Losert et al. Drug Res 1985;35:459-471

DRSP的抗雄性化效力



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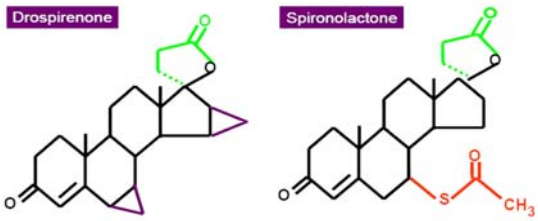
Stölzer W. et al. Tierexperimentelle Charakterisierung des Gestagens Dienogest (STS 557). II. Antigonadotrope, gestagene, estrogene und antiandrogene Wirkungen. III Jenaer Symposium zur hormonalen Kontrazeption, 1985



Drospirenone 3mg
抗男性素效力等於
Spironolactone 25 mg

Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism

TABLE 1
Total and regional hirsutism score of different body parts before and after therapy with oral EE/DRSP.

Region	Hirsutism score: Basal	6 months	12 months	*P* value
Upper lip	2 (0–4)	0 (0–3)	0 (0–2)	<.001
Chin	2 (0–4)	0 (0–3)	0 (0–2)	<.001
Chest	1 (0–4)	0 (0–2)	0 (0–2)	<.001
Back	1 (0–3)	0 (0–2)	0 (0–2)	<.001
Waist	1 (0–4)	0 (0–2)	0 (0–2)	<.001
Thigh	3 (1–4)	1 (0–2)	1 (0–2)	<.001
Arm	1 (0–3)	1 (0–2)	1 (0–2)	<.001
Upper abdomen	1 (0–4)	0 (0–2)	0 (0–1)	<.001
Lower abdomen	2 (0–4)	0.5 (0–2)	0 (0–2)	<.001
Total	15 (8–28)	5 (1–13)	3 (0–8)	<.001

Note: Values are expressed as median (min–max). EE/DRSP = ethinyl estradiol/drospirenone.

Redmond, The effect of Yasmin® in hirsutism. Fertil Steril 2006.

TABLE 3
Hormone levels before and after oral EE/DRSP therapy.

Hormone	Basal	6 months	12 months	*P* value
FSH (mIU/mL)	5.9 ± 2.4	5.8 ± 2.0	5.4 ± 2.1	>.05
LH (mIU/mL)	6.1 ± 3.2	5.8 ± 3.3	6.0 ± 3.2	>.05
E_2 (pg/mL)	67.3 ± 26.1	67.7 ± 30.3	68.2 ± 29.3	>.05
SHBG (nmol/L)	35.8 ± 15.9	45.4 ± 23.5	51.4 ± 30.3	<.0001
DHEAS (μg/mL)	2.6 ± 1.2	2.6 ± 1.1	2.5 ± 1.3	>.05
A (ng/mL)	2.6 ± 0.8	2.4 ± 0.8	2.3 ± 0.8	.007
Total T (ng/dL)	88.7 ± 30.5	74.5 ± 25.1	71.6 ± 28.0	<.0001
Free T (pg/mL)	2.2 ± 1.5	1.9 ± 1.4	1.7 ± 0.9	.002

Fertility and Sterility Vol. 85, No. 2, February 2006

TABLE 2
Changes of mean hirsutism score over 12 months.

	Decrease in mean hirsutism score (%): 6 months	12 months
Upper lip	−71	−88
Chin	−72	−88
Chest	−78	−85
Back	−51	−63
Waist	−66	−76
Thigh	−63	−69
Arm	−56	−61
Upper abdomen	−73	−86
Lower abdomen	−70	−84
Total	−67	−78

使用避孕藥 **6個月** 後達到最大治療效益，連續使用 **12個月** 仍有治療效果

TABLE 3
Hormone levels before and after oral EE/DRSP therapy.

Hormone	Basal	6 months	12 months	*P* value
FSH (mIU/mL)	5.9 ± 2.4	5.8 ± 2.0	5.4 ± 2.1	>.05
LH (mIU/mL)	6.1 ± 3.2	5.8 ± 3.3	6.0 ± 3.2	>.05
E_2 (pg/mL)	67.3 ± 26.1	67.7 ± 30.3	68.2 ± 29.3	>.05
SHBG (nmol/L)	35.8 ± 15.9	45.4 ± 23.5	51.4 ± 30.3	<.0001
DHEAS (μg/mL)	2.6 ± 1.2	2.6 ± 1.1	2.5 ± 1.3	>.05
A (ng/mL)	2.6 ± 0.8	2.4 ± 0.8	2.3 ± 0.8	.007
Total T (ng/dL)	88.7 ± 30.5	74.5 ± 25.1	71.6 ± 28.0	<.0001
Free T (pg/mL)	2.2 ± 1.5	1.9 ± 1.4	1.7 ± 0.9	.002

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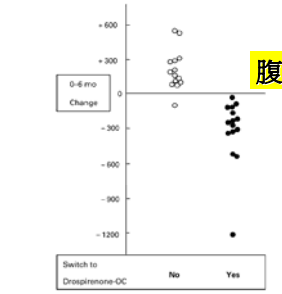
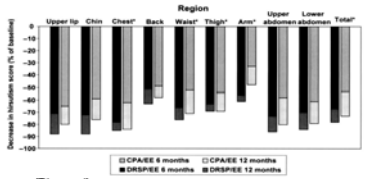


腹部體脂肪減少

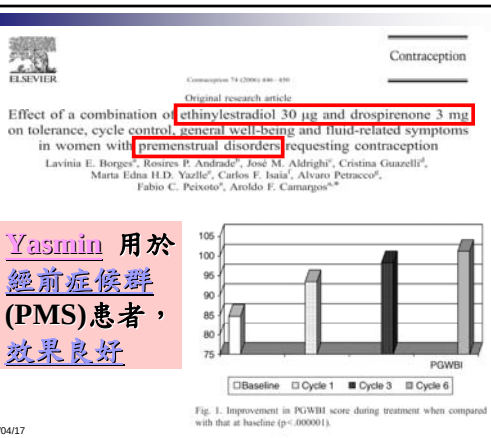
Figure 1. Absolute changes (0–6 months) in the abdominal fat mass (g) of young and non-obese women with PCOS who were randomized (at 0 months) to remain on a gestodene OC (○; $n = 14$) or to switch from a gestodene OC to a drospirenone OC (●; $n = 15$), while background therapy with low-dose flutamide–metformin remained unaltered in both subgroups. The switch from gestodene OC to drospirenone OC was accompanied by a loss of abdominal fat excess, as judged by dual-energy X-ray absorptiometry. See Table I for values and statistics.

Hum Reprod 2004



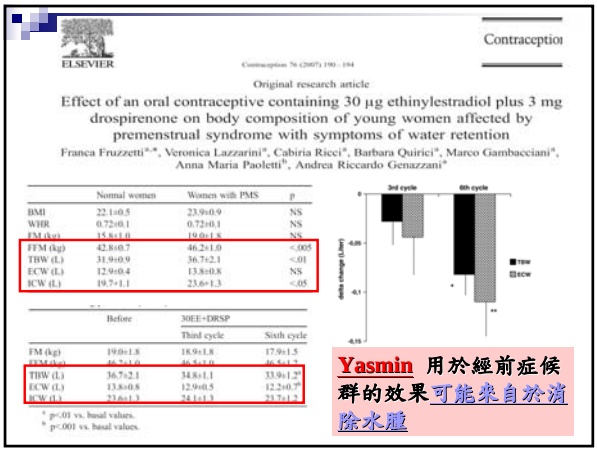
- 悅己 (Yasmin)
- 黛麗安 (Diane-35)
- 在治療多毛症的效果上是一樣好

Gynecological Endocrinology, January 2007; 23(1): 38–44

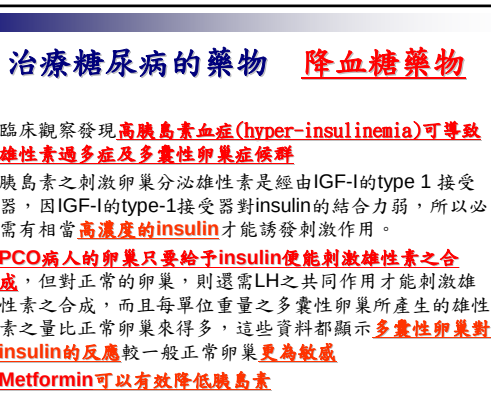


Yasmin 用於經前症候群(PMS)患者，效果良好

Fig. 1. Improvement in PGWBI score during treatment when compared with that at baseline ($p<.000001$).

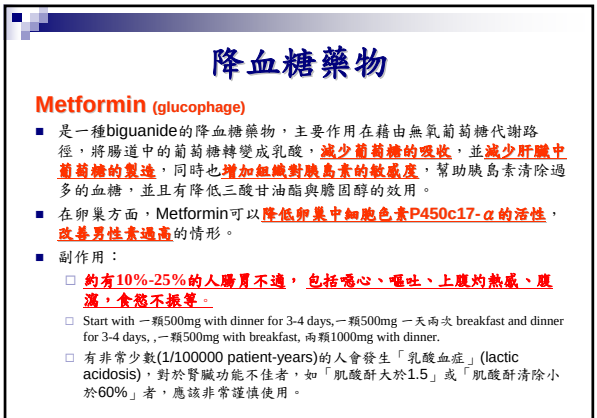


Yasmin 用於經前症候群的效果可能來自於消除水腫



治療糖尿病的藥物　降血糖藥物

- 臨床觀察發現高胰島素血症(hyper-insulinemia)可導致雄性素過多症及多囊性卵巢症候群
- 胰島素之刺激卵巢分泌雄性素是經由IGF-I的type 1 接受器，因IGF-I的type-1接受器對insulin的結合力弱，所以必需有相當高濃度的insulin才能誘發刺激作用。
- PCO病人的卵巢只要給予insulin便能刺激雄性素之合成，但對正常的卵巢，則還需LH之共同作用才能刺激雄性素之合成，而且每單位重量之多囊性卵巢所產生的雄性素之量比正常卵巢來得多，這些資料都顯示多囊性卵巢對insulin的反應較一般正常卵巢更為敏感
- Metformin可以有效降低胰島素



降血糖藥物

Metformin (glucophage)

- 是一種biguanide的降血糖藥物，主要作用在藉由無氧葡萄糖代謝路徑，將腸道中的葡萄糖轉變成乳酸，減少葡萄糖的吸收，並減少肝臟中葡萄糖的製造，同時也增加組織對胰島素的敏感度，幫助胰島素清除過多的血糖，並且有降低三酸甘油酯與膽固醇的效用。
- 在卵巢方面，Metformin可以降低卵巢中細胞色素P450c17-α的活性，改善男性素過高的情形。
- 副作用：
  - 約有10%-25%的人腸胃不適，包括噁心、嘔吐、上腹灼熱感、腹瀉，食慾不振等。
  - Start with 一顆500mg with dinner for 3-4 days,一顆500mg 一天兩次 breakfast and dinner for 3-4 days, ,一顆500mg with breakfast, 兩顆1000mg with dinner.
  - 有非常少數(1/100000 patient-years)的人會發生「乳酸血症」(lactic acidosis)，對於腎臟功能不佳者，如「肌酸酐大於1.5」或「肌酸酐清除小於60%」者，應該非常謹慎使用。

降血糖藥物

Troglitazone(Rezulin)

- 是一種thiazolidinedione的衍生物，可以經由細胞核接受器peroxisome proliferator activated receptors(PPARs)影響脂肪酸的代謝，使其不與葡萄糖競爭氧化代謝，而使**局部細胞組織對胰島素的抗拒力降低**，達到降低血糖與的效果，也同時**減少代償性的高胰島素血症**的發生率。
- 副作用包括：頭痛(11%)，疼痛(10%)，無力(6%)，暈眩(6%)與噁心(6%)

Metformin administration modulates and restores luteinizing hormone spontaneous episodic secretion and ovarian function in nonobese patients with polycystic ovary syndrome

Metformin 對於瘦的多囊性卵巢症候群病人LH分泌的影響

Objective: To evaluate the effects of metformin administration on spontaneous LH episodic release in a group of nonobese polycystic ovary (PCOS) patients.
Design: Controlled clinical study.
Setting: PCOS patients in a clinical research environment.
Patient(s): Twenty nonobese PCOS patients were enrolled after informed consent.
Intervention(s): All patients underwent hormonal evaluations and a pulsatility study (sampling every 10 minutes for 4 hours) before and at the sixth month of therapy (metformin, 500 mg, p.o. b.i.d.). Ultrasound examinations and Ferriman-Gallwey scoring were also performed.
Main Outcome Measure(s): Measurements of plasma LH, FSH, estradiol (E_2), androstenedione (A), 17-hydroxy-progesterone (17-OHP), and testosterone (T), glucose, insulin, and C-peptide concentrations.
Result(s): After 6 months of metformin administration, the plasma LH, 17-OHP, A, and T levels and LH/FSH ratio were significantly reduced. Insulin sensitivity, expressed in the glucose-to-insulin ratio, was significantly improved under glucose load after 6 months of treatment. Spontaneous LH episodic release showed a significant reduction in pulse amplitude with no changes in pulse frequency. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic women. The ovarian volume and Ferriman-Gallwey scores also were significantly reduced.
Conclusion(s): Metformin administration improves reproductive axis functioning in hyperandrogenic nonobese PCOS patients. By acting on the ovary and restoring normal ovarian activity, metformin positively modulates the reproductive axis (namely GnRH-LH episodic release). (Fertil Steril® 2004;81:114–9. ©2004 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, metformin, insulin, leuteinizing hormone, nonobese women

Fertil Steril 2004

TABLE 1

Hormonal characteristics of the patients (n = 20) under study before and during metformin treatment.

Characteristic	Baseline	With metformin
BMI	22.5 ± 1.1	21.7 ± 1.4
LH (mIU/mL)	15 ± 2.3	8.8 ± 1.8*
FSH (mIU/mL)	4.4 ± 0.5	4.5 ± 0.6
E_2 (pg/mL)	75.1 ± 15.6	54.2 ± 9.8
17-OHP (ng/mL)	2.5 ± 0.3	1.7 ± 0.3*
A (ng/100 mL)	386.5 ± 35.2	141.7 ± 26.6*
T (ng/100 mL)	65.5 ± 7.5	45.0 ± 5.5*
LH/FSH	3.5 ± 0.5	1.9 ± 0.2*
Glucose/insulin	9.2 ± 1.8	9.1 ± 1.2
Insulin (μU/mL)	12.0 ± 1.8	12.4 ± 2.4
C-peptide (μg/L)	2.7 ± 0.5	2.9 ± 0.6

* $P<.05$.

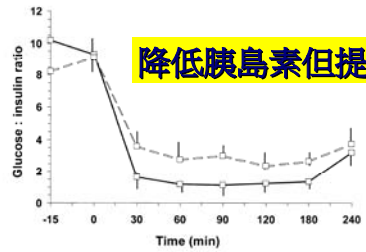
Genazzani. Metformin restores episodic LH secretion in PCOS. Fertil Steril 2004.

降低LH與男性素

Fertil Steril 2004

FIGURE 1

The ratio of glucose to insulin, an index of sensitivity to insulin, was significantly improved by metformin administration. Before metformin: —. During metformin: - - -. ** $P<.01$.



降低胰島素但提高效能

Genazzani. Metformin restores episodic LH secretion in PCOS. Fertil Steril 2004.

Fertil Steril 2004

改善LH的釋放

TABLE 2

LH pulsatile characteristics of patients under study.

	Baseline			With metformin		
	Mean (mIU/mL)	No. of peaks/4 h	Amplitude (mIU/mL)	Mean (mIU/mL)	No. of peaks/4 h	Amplitude (mIU/mL)
PCOS (n = 20)	10.4 ± 1.7	3.5 ± 0.4	5.7 ± 0.5	5.6 ± 1.0*	3.5 ± 0.3	3.4 ± 0.5*

* $P<.05$.

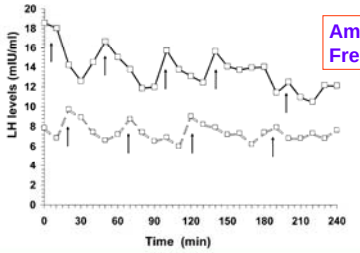
Genazzani. Metformin restores episodic LH secretion in PCOS. Fertil Steril 2004.

Frequency 改變　**Amplitude** 變小

Fertil Steril 2004

FIGURE 2

Episodic LH spontaneous secretion in one PCOS patient under study shows that, after 6 months of treatment, LH pulses were significantly reduced in amplitude with no change in pulse frequency. *Arrows* indicate statistically significant LH pulses detected by the program DETECT. Before metformin: —. During metformin: - - -.



Amplitude ↓
Frequency ↔

Genazzani. Metformin restores episodic LH secretion in PCOS. Fertil Steril 2004.

Fertil Steril 2004

Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin

Metformin 對於瘦的多囊性卵巢症候群治療效果較好

Objective: To determine the clinical, hormonal, and biochemical effects of metformin therapy in obese and nonobese patients with polycystic ovary syndrome (PCOS).

Design: Controlled clinical study.

Setting: Department of Gynecology of Federal University of São Paulo, São Paulo, Brazil.

Patient(s): Twenty-nine patients with PCOS.

Intervention(s): Patients were treated with 500 mg of p.o. metformin t.i.d. for 6 months.

Main Outcome Measure(s): Clinical data as well as serum concentrations of sex steroids, sex hormone-binding globulin (SHBG), gonadotropins, leptin, GH, lipids, insulin, and glucose levels were assessed before and after treatment.

Result(s): In the metformin group of nonobese patients, the mean fasting serum insulin concentration decreased from a pretreatment value of 12.1 ± 2.4 to 6.3 ± 0.6 μU/mL after treatment, and the area under the curve of insulin decreased from 5,189.1 ± 517.4 to 3,035.6 ± 208.9 μU/mL per minute. Also in the metformin group of nonobese patients, the mean basal serum total testosterone, free testosterone, and androstenedione concentrations decreased by 38%, 58%, and 30%, respectively. In the obese patients treated with metformin, only free testosterone showed a statistically significant decrease (1.7 ± 0.2).

Conclusion(s): Our data suggest that nonobese patients respond better than obese patients to a 1.5 g/day metformin regimen. (Fertil Steril® 2004;81:355–60. ©2004 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, metformin, insulin resistance

Fertil Steril 2004

TABLE 2

Metabolic and cardiovascular profile.

	Baseline				Treatment period			
	Placebo		Metformin		Placebo		Metformin	
Serum	Nonobese (n = 8)	Obese (n = 6)	Nonobese (n = 7)	Obese (n = 8)	Nonobese (n = 8)	Obese (n = 6)	Nonobese (n = 7)	Obese (n = 8)
Glucose (mg/dL)	76.8 ± 3	85.3 ± 6.5	81.6 ± 3.3	85.5 ± 3.7	77.5 ± 1.5	84.5 ± 5.7	81.9 ± 4.2	84.6 ± 4.6
G/I ratio	12.1 ± 4.7	4.1 ± 2.3	8.4 ± 1.3	4.9 ± 1.9	11.2 ± 2.8	4.3 ± 0.8	10.5 ± 1.3	5.2 ± 1.4
Insulin (μU/mL)	13.6 ± 3.1	20.9 ± 1.9	12.1 ± 2.4	22.6 ± 4.1	14.1 ± 1.4	25.2 ± 5	6.3 ± 0.6[a]	21.1 ± 3.3
AUCG (mg/dL·min)	12,230.6 ± 629.5	13,393.7 ± 1,117.9	12,681.4 ± 1,176.989	15,298.1 ± 749.7	12,168.1 ± 775.4	12,935.5 ± 1,048.9	13,715.1 ± 1,199.9	14,386.9 ± 1,029.8
AUCI (μU/mL·min)	8,604.5 ± 1,347.1	12,844.3 ± 2,225.8	8,284.1 ± 317.4	12,496.5 ± 1,619.1	8,470.3 ± 1,132.2	10,135.8 ± 984.3	3,035.6 ± 208.9[a]	11,214.2 ± 1,363.1
Cholesterol (mg/dL)	134.2 ± 8.1	138.1 ± 11.4	115.4 ± 14.1	180.8 ± 13.3	141.5 ± 11.5	165.2 ± 17.7	161.6 ± 11.5	181.5 ± 19.2
HDL (mg/dL)	47.6 ± 6	34.5 ± 3.4	40.1 ± 4.2	40.2 ± 7.1	57.5 ± 7	33.3 ± 3	38.3 ± 4.4	45.6 ± 5.4
LDL (mg/dL)	92.3 ± 7.3	102.8 ± 12.9	113.1 ± 14.1	101.6 ± 18	78.1 ± 10	110.8 ± 15.4	100 ± 12.6	115 ± 10.4
VLDL (mg/dL)	14.4 ± 1.8	20.7 ± 4.5	22.1 ± 4.3	30.1 ± 5	11.8 ± 2.4	21.5 ± 3.2	29.4 ± 9.6	26.9 ± 6.1
Triglycerides (mg/dL)	71.8 ± 9	103.2 ± 2.6	111 ± 21.3	150 ± 25	59.8 ± 11.4	106.7 ± 16.4	117.4 ± 26.8	134.9 ± 30.6

* $P<.02$ compared with other groups (two-way).

[a] $P<.01$ compared with other groups.

Macedo, Metformin

瘦的人藥物反應在降低胰島素的效果上比較好

Fertil Steril 2004

TABLE 3

Hormonal profile.

	Baseline				Treatment period			
	Placebo		Metformin		Placebo		Metformin	
Serum	Nonobese (n = 8)	Obese (n = 6)	Nonobese (n = 7)	Obese (n = 8)	Nonobese (n = 8)	Obese (n = 6)	Nonobese (n = 7)	Obese (n = 8)
Testosterone (ng/dL)	97.4 ± 11.8	101.5 ± 28.4	105.6 ± 11.7	116.8 ± 8.2	102.9 ± 8.5	101.6 ± 18.3	65.0 ± 7.5[a]	107.6 ± 8.1
Free testosterone (pg/dL)	3.2 ± 0.3	3.4 ± 0.7	3.1 ± 0.6	3.2 ± 0.7	3.2 ± 0.4	3.6 ± 0.6	1.3 ± 0.2[a]	1.7 ± 0.2[a]
Androstenedione (ng/dL)	2.1 ± 0.3	2 ± 0.4	2.6 ± 0.3	2.2 ± 0.3	2.3 ± 0.5	2.1 ± 0.4	1.4 ± 0.2[a]	2.3 ± 0.3
GH (ng/mL)	2 ± 0.7	0.6 ± 0.3	1.2 ± 0.7	1.3 ± 1.1	1.2 ± 0.4	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
SHBG (nmol/L)	239.3 ± 25.7	175.5 ± 55.6	183.6 ± 36.3	153.4 ± 24.7	274.3 ± 26.5	236.5 ± 54.7	169.5 ± 25.4	194.1 ± 39.2[a]
DHEA (ng/mL)	8.9 ± 1.1	8.9 ± 1.9	11.2 ± 2	9.4 ± 2.1	9.5 ± 1.6	7.4 ± 0.8	7 ± 1.4	7.6 ± 1.1
17OH-progesterone (ng/mL)	1.1 ± 0.1	1.3 ± 0.3	1.3 ± 0.3	1.1 ± 0.2	1.0 ± 0.2	1.3 ± 0.3	1.2 ± 0.4	1.1 ± 0.8
PRL (ng/mL)	15.9 ± 2.4	12 ± 2.5	10.3 ± 2.6	18.2 ± 5.2	17.6 ± 4.2	9.7 ± 0.9	18.2 ± 5.2	16.5 ± 4.8
Leptin (ng/mL)	11.8 ± 2	26.2 ± 7.5	12.5 ± 0.6	10.7 ± 1.5	14.5 ± 2.1	39.9 ± 12.7	10.7 ± 1.5	29.7 ± 2.1
FSH (mUI/mL)	5.8 ± 1.2	5.7 ± 1	7.4 ± 1.3	7.1 ± 1	6.6 ± 0.5	6.3 ± 1.3	7.1 ± 1	7.3 ± 1.1
LH (mUI/mL)	4.3 ± 0.9	5.5 ± 1	6 ± 1.3	7.4 ± 2.3	5.1 ± 1.1	9.7 ± 3.3	7.4 ± 2.3	7.4 ± 1.8

* $P<.01$ compared with other groups.

瘦的人藥物反應在降低男性素的效果上比較好

Fertil Steril 2004

A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study

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University of Rochester School of Medicine and Dentistry and School of Nursing, Rochester, New York

Objective: To obtain data from a pilot randomized trial on the effect of metformin therapy and lifestyle modification on ovulation and androgen concentrations in women with polycystic ovary syndrome (PCOS).

Design: Prospective, randomized, placebo-controlled pilot trial.

Setting: Academic medical center.

Patient(s): Thirty-eight overweight or obese women with PCOS.

Intervention(s): All subjects were randomized to one of four 48-week interventions: metformin 850 mg two times per day, lifestyle modification plus metformin 850 mg two times per day, lifestyle modification plus placebo, or placebo alone.

Main Outcome Measure(s): Recruitment, dropout, and compliance with a long-term lifestyle intervention in PCOS; preliminary estimates of treatment effect on ovulation, as measured by weekly urinary pregnanediol glucuronide, and on total T and free androgen index.

Result(s): It was necessary to screen seven women to have one subject randomized. The dropout rate was 39%, with the majority of dropouts occurring within the first 24 weeks. Mean body mass index was >39 mg/kg². Modest weight reduction was found in all treatment groups, with the most significant reduction occurring with the combination of metformin and lifestyle intervention. Significant androgen reduction occurred in the combination group only. Ovulation rates did not differ significantly between groups. However, when data were analyzed by presence or absence of weight reduction in subjects, independent of treatment group, the estimated odds ratio for weight loss was 9.0 (95% confidence interval 1.2-64.7) with respect to regular ovulation. If weight loss occurred during metformin therapy, the odds ratio for regular ovulation was 16.2 (95% confidence interval 0.4-660.2).

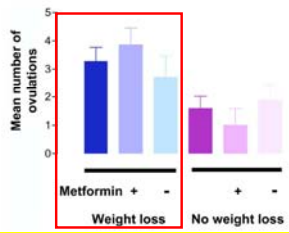
Conclusion(s): Key methodologic issues for a large-scale, randomized trial of lifestyle intervention in PCOS include minimizing early dropout from the lifestyle intervention and including a range of body mass index that is not skewed toward severe obesity. Weight reduction might play the most significant role in restoration of ovulation in obese women with PCOS. (Fertil Steril® 2004;82:421–9. ©2004 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, obesity, ovulation

Fertil Steril 2004

FIGURE 4

Mean number of ovulatory episodes over 24 weeks, displayed by subjects experiencing weight loss (*blue bars*) and not experiencing weight loss (*red bars*). Use of metformin is noted within each weight-loss group by a + or − sign.



有成功減重再加上Metformin，恢復排卵功能效果最好

Fertil Steril 2004

抗雄性素藥物

Spironolactone

- Spironolactone有對抗男性素的效果，主要作用是在毛囊細胞內抑制DHT的接受器。

Cyproterone acetate CPA

- 為合成黃體素hydroprogesterone：它對抗男性荷爾蒙主要的機轉是經由阻礙男性荷爾蒙與細胞核位置形成複合體，並與男性荷爾蒙在細胞質接受器上行競爭性抑制，同時它亦具有抗性腺激素的特性，故可少男性荷爾蒙的製造。

Flutamide

- 它對抗男性荷爾蒙主要的機轉作用在雄性素接受器上，經由在攻擊的組織上抑制雄性素的攝入或細胞核的結合。

2009/04/17

Current Opinion in Pediatrics 2007, 19:389–397

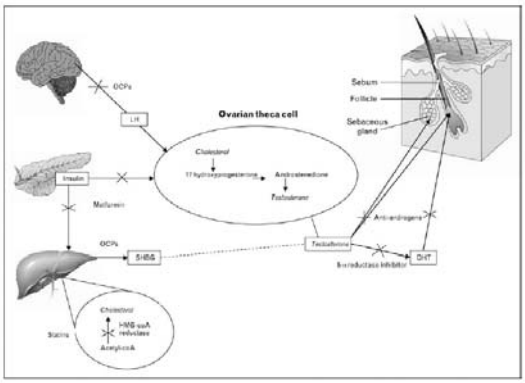


Figure 1 Schematic of pathophysiology of polycystic ovary syndrome and mechanism of different drugs

DHT, dihydrotestosterone; LH, luteinizing hormone; OCP, oral contraceptive pill; SHBG, sex hormone binding globulin.

要治療多久呢?

2009/04/17

Determining the time androgens and sex hormone-binding globulin take to return to baseline after discontinuation of oral contraceptives in women with polycystic ovary syndrome: a prospective study

TABLE 1

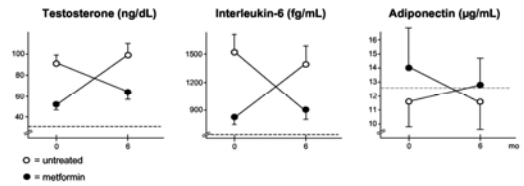
Hormonal parameters before and after 12 weeks of treatment with OCP and during the follow-up period.

Hormone	Baseline	Week 12 of treatment	*P* value	Week 4 of follow up	*P* value	Week 8 of follow up	*P* value
Total testosterone (ng/dL)	119.0	55.0	.002	107.0[a]	.3	91.0[a]	.06
Free testosterone (ng/dL)	0.28	0.11	.002	0.15	.01	0.22[a]	.13
DHEAS (μg/mL)	1.64	1.05	.01	1.40[a]	.13	1.54[a]	.27
SHBG (nmol/L)	59.0	311	.001	78.0	.03	54.0[a]	.34

使用避孕藥三個月後達到治療效果，但是停藥一個月後Total testosterone, DHEAS就回復原狀，停藥二個月後Free testosterone, SHBG 就回復原狀

2009/04/17

Insulin Sensitization for Girls with Precocious Pubarche and with Risk for Polycystic Ovary Syndrome: Effects of Prepubertal Initiation and Postpubertal Discontinuation of Metformin Treatment



使用Metformin六個月後達到治療效果，但是停藥六個月後Total testosterone, IL-6, Adiponectin 就回復原狀

2009/04/17

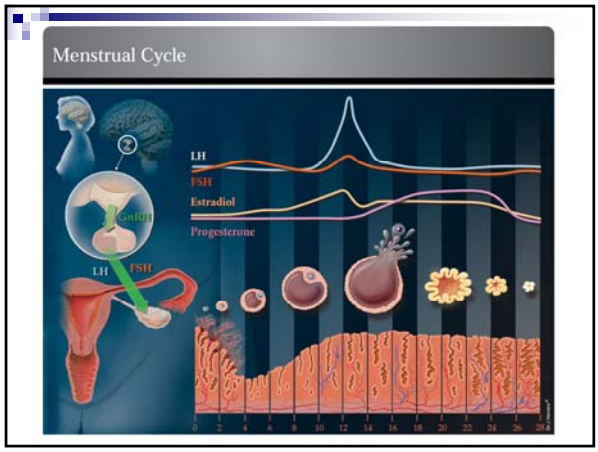
(JCEM, 2004)

不孕症(慢性不排卵)的治療

- 口服排卵藥 Clomid
- 降血糖藥物 Metformin
- 腹腔鏡卵巢燒灼術 Laparoscopic ovarian diathermy (LOD, laparoscopic ovarian drilling)
- 注射型排卵藥
- 合併多種治療Combined

2009/04/17

2009/04/17

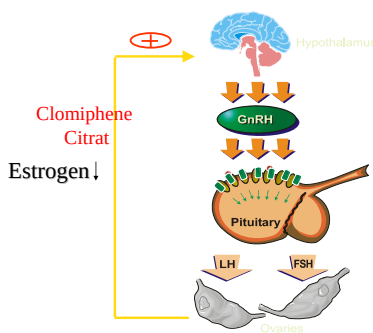


口服排卵藥 Clomiphene Citrate

- 對未排卵狀態病患之誘導排卵的第一線藥物
- 作用機制
  - 增加下視丘釋放GnRH脈衝的頻率
  - 增加腦下垂體對GnRH的敏感程度
  - 增加卵巢對FSH的敏感程度
- 總合作用
  - 增加腦下垂體對性腺激素的分泌

2009/04/17

口服排卵藥 Clomiphene Citrate 機轉



2009/04/17

用藥方式

- 月經**第3-5天**開始給 Clomid,連續5天.通常在給完藥後第5至10天會排卵，**最常在給完藥後第7天排卵**.
- 建議劑量:

  每天50 mg(一顆) ~ 100 mg（二顆）.最高劑量為250 mg.
- Clomid 可使**80% ~90%**的病人達到**排卵**的目的,持續治療**6個月**後,**40%~45%**的病人**懷孕**.

Clomiphene Citrate 副作用

- 子宮頸黏液黏稠
- 子宮內膜厚度變薄
- 潮紅
- 視覺不適
- 產生卵巢囊腫（ovarian cyst）
- 在動物試驗中有導致胎兒異常的報告

Insulin-sensitizing agents as primary therapy for patients with polycystic ovarian syndrome

降血糖藥物 **Metformin**可以**增加排卵率**，
如果**合併口服排卵藥 Clomid**更可以**增加懷孕率**

*To whom correspondence should be addressed. E-mail: sakashyap@ohri.ca and skashyap@ottawahospital.on.ca

BACKGROUND: This paper is a systematic review of metformin versus clomiphene citrate (CC) in women with polycystic ovary syndrome (PCOS). **METHODS:** Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and QUality Of Reporting Of Meta-analyses (QUOROM) guidelines were followed. A systematic computerized literature search was done of seven bibliographic databases. Inclusion criteria included cohort and randomized controlled trials (RCT) of women with PCOS and the following medications: metformin versus placebo; metformin versus CC; metformin plus CC versus placebo plus CC. Rev-man 4.1 and Metaview 4.0 were used to analyse data. Relative risk (RR) estimates were presented. A χ^2-test determined the significance of the association. Heterogeneity was determined by the Cochran *Q*-test. **RESULTS:** Metformin was 50% better than placebo for ovulation induction in infertile PCOS patients [RR 1.50; 95% confidence interval (CI) 1.13, 1.99]. Metformin was also of benefit in non-infertile (i.e. patients with PCOS who were not complaining of infertility) PCOS patients for cycle regulation compared to placebo (RR 1.45; CI 1.11, 1.90). Metformin was not of confirmed benefit versus placebo for achievement of pregnancy (RR 1.07; CI 0.20, 5.74). Metformin plus CC may be 3-4-fold superior to CC alone for ovulation induction (RR 3.04; CI 1.77, 5.24) and pregnancy (RR 3.65; CI 1.11, 11.99) in women with PCOS. **CONCLUSIONS:** Metformin is effective for ovulation induction and cycle regulation in this group of patients. Metformin plus CC appears to be very effective for achievement of pregnancy compared to CC alone. No RCTs directly compare metformin to CC but the need for such a trial exists.

Hum Reprod 2004

Suppression of granulosa proliferation
Follicular atresia (nondominant follicles)
Premature luteinization (preovulatory follicle)
Oocyte development compromised

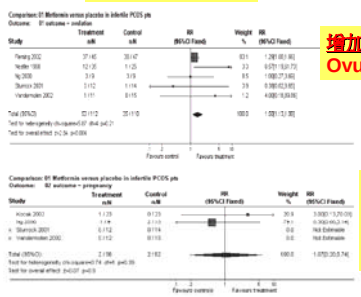
LH ceiling

Normal follicular growth and development
Paracrine signalling activated by FSH and LH
Adequate granulosa proliferation and functional maturation
Normal androgen and estrogen biosynthesis
Full follicular and oocyte maturation

LH threshold

Follicular growth by FSH action (granulosa cell proliferation)
Induction of granulosa cell aromatase activity by FSH
No paracrine signalling between granulosa and theca
No androgen (and estrogen) synthesis
No full oocyte maturation

metformin



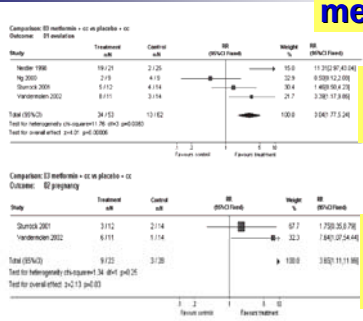
增加排卵率1.5倍
Ovulation: RR 1.5

懷孕率沒有增加
Pregnancy
RR 1.07 ↔

Figure 2. Comparison of metformin versus placebo in infertile polycystic ovarian syndrome (PCOS) patients. The upper panel shows the outcome ovulation and the lower panel the outcome pregnancy. RR = relative risk; CI = confidence interval. Generated from Meta-view 4.0.

Hum Reprod 2004

metformin



Metformin合併口服排卵藥 Clomid
增加排卵率3.04倍
Ovulation: RR 3.04

Metformin合併口服排卵藥 Clomid
增加懷孕率3.65倍
Pregnancy
RR 3.65

Figure 4. Comparison of metformin + clomiphene citrate (CC) versus placebo + CC in infertile patients. The upper panel shows the outcome ovulation and the lower panel the outcome pregnancy. RR = relative risk. Generated from Meta-view 4.0.

Hum Reprod 2004

Table IV. Metformin in polycystic ovarian syndrome (PCOS): comparison of meta-analyses results

	Kashyap *et al.* (in press) RR (95% CI)	Lord *et al.* (2003) OR (95% CI)
Ovulation		
Metformin versus placebo		
Infertile	1.50 (1.13, 1.99)	3.88 (2.25, 6.69)
Non-infertile	1.45 (1.11, 1.90)	
Metformin + CC	3.04 (1.77, 5.24)	4.41 (2.37, 8.22)
Pregnancy		
Metformin versus placebo[a]	1.07 (0.20, 5.74)	2.76 (0.85, 8.98)
Metformin + CC versus CC	3.65 (1.11, 11.99)	4.40 (1.96, 9.85)

[a] Not significant.
RR = relative risk; OR odds ratio; CI = confidence intervel; CC = clomiphene citrate; non-infertile = patients with PCOS who were not complaining of infertility.

Metformin合併口服排卵藥 Clomid效果好

2009/04/17

Hum Reprod 2004

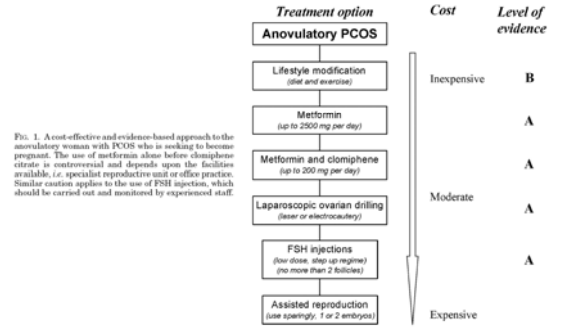


FIG. 1. A cost-effective and evidence-based approach to the anovulatory woman with PCOS who is seeking to become pregnant. The use of metformin alone before clomiphene citrate is controversial and depends upon the facilities available, *i.e.* specialist reproductive unit or office practice. Similar caution applies to the use of FSH injection, which should be carried out and monitored by experienced staff.

2009/04/17

(JCEM, 2004)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2007 VOL. 356 NO. 6

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

Table 2. Rates of Ovulation, Pregnancy, and Pregnancy Loss.*

Variable	Clomiphene Group (N = 209)	Metformin Group (N = 208)	Combination-Therapy Group (N = 209)	Absolute Difference between Combination Therapy and Metformin
	no./total no. (%)			% (95% CI)
Ovulation	462/942 (49.0)	296/1019 (29.0)	582/964 (60.4)	31.4 (24.7 to 38.0)
Conception	62/209 (29.7)	25/208 (12.0)	80/209 (38.3)	26.3 (18.4 to 34.2)
Pregnancy	50/209 (23.9)	18/208 (8.7)	65/209 (31.1)	22.4 (15.0 to 29.8)
Singleton	47/50 (94.0)	18/18 (100.0)	63/65 (96.9)	-3.1 (-7.3 to 1.1)
Twins	2/50 (4.0)	0	2/65 (3.1)	-3.1 (-10.1 to 16.3)
Triplets	1/50 (2.0)	0	0	0 (-12.7 to 12.7)
Other	0	0	0	0 (-12.7 to 12.7)
Live birth	47/209 (22.5)	15/208 (7.2)	56/209 (26.8)	19.6 (12.6 to 26.6)
Pregnancy loss				
Total losses among subjects who conceived	16/62 (25.8)	10/25 (40.0)	24/80 (30.0)	-10.0 (-31.7 to 11.7)
Loss in first trimester	14/62 (22.6)	10/25 (40.0)	20/80 (25.0)	-14.5 (-35.9 to 6.9)
Biochemical factor or no fetal heart motion	10/62 (16.1)	7/25 (28.0)	13/80 (16.2)	-11.7 (-31.1 to 7.7)
Ectopic pregnancy	2/62 (3.2)	0	2/80 (2.5)	2.5 (-7.8 to 12.8)
Loss after observed heart motion	2/62 (3.2)	3/25 (12.0)	5/80 (6.2)	-5.7 (-19.5 to 8.1)
Loss in second or third trimester	2/62 (3.2)	0	4/80 (5.0)	5.0 (-5.7 to 15.7)

2007最新結論：口服排卵藥 Clomid效果還是比Metformin好

2009/04/17

NEJM, 2007

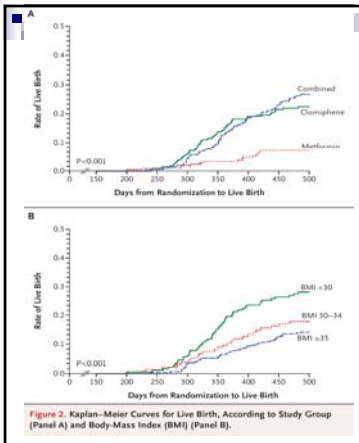


Figure 2. Kaplan–Meier Curves for Live Birth, According to Study Group (Panel A) and Body-Mass Index (BMI) (Panel B).

- 口服排卵藥 Clomid效果比 Metformin好
- 瘦的人治療的效果上比較好

NEJM, 2007

Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial

Murizah Mohd Zain, M.D., M.Med. (O&G),[a,c] Ridzuan Jamaluddin, M.D.,[b] Adibah Ibrahim, M.D., M.Med. (O&G),[b] and Robert J. Norman, M.D., F.R.A.N.Z.C.O.G., F.R.C.O.G., F.R.C.P.A.[c]

[a] Department of Obstetric and Gynaecology, Alor Setar Hospital, Kedah, and [b] Department of Obstetric and Gynaecology, Science University Hospital, Kelantan, Malaysia; and [c] Research Centre of Reproductive Health, School of Paediatrics and Reproductive Health, University of Adelaide, South Australia, Australia

TABLE 1
Baseline characteristic of women with polycystic ovary syndrome.

Characteristics	Metformin group (n = 38)	CC group (n = 39)	Combination group (n = 38)	
Age, mean (SD)	27.8 (3.6)	29.6 (4.35)	29.3 (4.95)	
WHR, mean (SD)	0.78 (0.1)	0.76 (0.45)	0.77 (0.14)	
BMI, mean (SD)	33.9 (3.6)	32.9 (4.2)	33.0 (4.1)	
Primary infertility, n (%)	29 (76.3)	28 (71.8)	34 (89.5)	
Length of infertility (y), mean (SD) Race	3.1 (0.26)	2.9 (0.15)	3.3 (0.14)	
Malay n (%)	33 (86.8)	35 (89.7)	33 (86.8)	
Morphology feature of PCO on U/S, n (%)	38 (100)	39 (100)	38 (100)	NS
Oligomenorrhea, n (%)	28 (73.7)	30 (76.9)	30 (78.9)	NS
Amenorrhea, n (%)	10 (26.3)	9 (23.1)	8 (21.1)	
Significant hirsutism (Ferriman-Gallway >16)	1 (2.6)	2 (5.1)	1 (2.6)	

Note: *P*=not significant.
CC = clomiphene citrate; BMI = body mass index; WHR = waist-to-hip ratio; U/S = ultrasound.

2009/04/17

Fertil Steril 2009;91:514–21

TABLE 3
Rates of ovulation, pregnancy, pregnancy loss, and live birth.

	Metformin (n = 38)	CC (n = 39)	Combination (n = 38)	CC vs. Metformin P & OR (CI)	Combination vs. Metformin P & OR (CI)	CC vs. Combination P & OR (CI)
Ovulation	9/38 (23.7%)	23/39 (59%)*	26/38 (68.4%)*	.002* 4.63 (1.7-12.7)	.001* 6.98 (2.5-19.3)	.742
Pregnancy	3/38 (7.9%)	6/39 (15.4%)	8/38 (21.1%)	.306 2.12 (0.5-9.2)	.103 3.11 (0.5-19.3)	.416
First trimester loss	0	0	1/8 (12.5)			
Ectopic	0	0	0			
Second trimester loss	0	0	0			
Multiple gestation	0	0	0			
Live birth	3/38 (7.9%)	6/39 (15.4%)	7/38 (18.4%) 2.12 (0.5-9.2)	.306 2.64 (0.3-11)	.175	.126

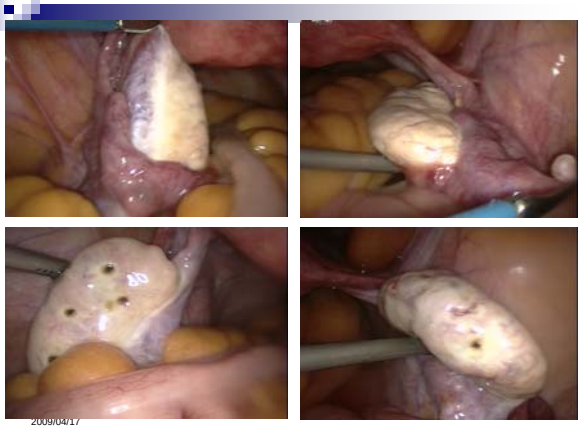
Note: OR = odds ratio; CI = confidence interval.
*Ovulation rate significantly higher in CC vs. metformin and combination vs. metformin.

2009/04/17

Fertil Steril 2009;91:514–21

腹腔鏡卵巢燒灼術

- Laparoscopic ovarian diathermy (LOD)



A prospective dose-finding study of the amount of thermal energy required for laparoscopic ovarian diathermy

根據英國雪菲爾大學Amer *et al*的研究認為**兩側卵巢各燒4個洞**，每個洞使用的電燒能量為30瓦特持續5秒為150焦耳，
4個洞之總能量為**600焦耳**，可達到**67 % 的排卵率**。

*To whom correspondence should be addressed. E-mail: s.amer@sheffield.ac.uk

BACKGROUND: This prospective dose-finding study was undertaken to determine the optimal amount o thermal energy required for laparoscopic ovarian diathermy (LOD) in women with polycystic ovary syndrom (PCOS). **METHODS:** Thirty women with clomiphene-resistant PCOS were included in the study. All women underwent LOD. A modified Monte Carlo up-and-down design was utilized. Women were treated in groups o three (10 groups). The amount of energy applied was standardized at 150 J/puncture. The number of punctures i each group was decreased/increased according to the number of responders in the previous group. The main outcome was ovulation as defined by a serum progesterone concentration of >30 nmol/l. **RESULTS:** Four groups (n = 12) were treated with four punctures/ovary, three groups (n = 9) with three punctures, two group (n = 6) with two punctures and one group (n = 3) with one puncture. Ovulation occurred in 67, 44, 33 and 33% o women treated with four, three, two and one puncture/ovary respectively. The corresponding pregnancy rate were 67, 56, 17 and 0%. The reductions in the free androgen index and the serum concentrations of testosteron and androstenedione after LOD were observed only in women treated with three and four punctures/ovary **CONCLUSION:** The clinical response to LOD seems to be dose-dependent, with an increase in the frequency of ovulation and conception with an increasing dose of thermal energy up to 600 J/ovary.

Hum Reprod 2003

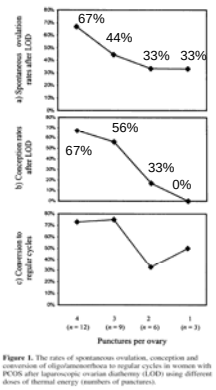


Figure 1. The rates of spontaneous ovulation, conception and conversion of oligo/amenorrhoea to regular cycles in women with PCOS after laparoscopic ovarian diathermy (LOD) using different doses of thermal energy (numbers of punctures).

4 puncture holes, 30W X 5sec X 4=600J Amer *et al*

40 W X 2 sec X 10-12 holes =800-1200 J Tulandi *et al*

Hum Reprod 2003

Laparoscopic treatment of polycystic ovaries: is it time to relinquish the procedure?

加拿大多倫多大學的Tulandi *et al*的建議為**兩側卵巢各燒10-12個洞**，每個洞使用的電燒能量為**40瓦特持續2秒為80焦耳**，10-12個洞之總能量為**800-1200焦耳**亦可達到**67 % 的排卵率**。

Design: A literature search was conducted using the keywords *laparoscopy, laparoscopic ovarian drilling, laparoscopic ovarian diathermy, PCOS, metformin,* and *ovulation.* The MEDLINE and EMBASE databases and the Cochrane Database of Systematic Reviews were searched.

Result(s): No randomized comparisons have been done between laparoscopic ovarian drilling and metformin therapy. However, the ovulation and pregnancy rates appear to be similar for both techniques. Both treatments decrease the incidence of ovarian hyperstimulation and the cancellation rate of IVF cycles. However, unlike laparoscopic ovarian drilling, metformin may decrease the incidence of type 2 diabetes and coronary heart disease.

Conclusion(s): Given the similar magnitude of the results without the potential risks and complication of surgery, we propose that laparoscopic ovarian drilling should be used sparingly in favor of less invasive treatment with metformin. (Fertil Steril® 2003;80:241–51. ©2003 by American Society for Reproductive Medicine.)

Fertil Steril 2003

TABLE 1

Comparison between laparoscopic ovarian drilling and metformin treatment.

	Laparoscopic ovarian drilling	Metformin therapy
Ovulation rate	74% up to 20 years after LOD (34)	82% after 16 weeks of treatment (94)
Pregnancy rate	50–70% 12 months after LOD (27, 28, 51)	55% with metformin + clomiphene for 6 months (112)
Miscarriage rate	17% vs. 54% in the control group (69)	8.8% vs. 41.9% in the control group (104)
Hirsutism	Improvement up to 9 years after surgery (25, 69)	Conflicting results (106, 107)
In vitro fertilization	Decreased cancellation, decreased risk of hyperstimulation	Decreased cancellation, decreased risk of hyperstimulation
Follow-up	Up to 20 years	Up to 26 months

Firouzi. Laparoscopic ovarian drilling and metformin in PCOS. Fertil Steril 2003.

腹腔鏡卵巢燒灼術的治療效果維持比較久

Fertil Steril 2003

Vol 13. No 2. 2006 194-197 Reproductive BioMedicine Online; www.rbmonline.com/Article/2234 on web 17 May 2006

Article

Use of metformin for prevention of ovarian hyperstimulation syndrome: a novel approach

針對多囊性卵巢症候群婦女，Metformin雖不能增加整體懷孕率，但卻能減少卵巢過度刺激症候群發生率(OR:0.21、P<0.0009)

Dr Sherif Khattab

Abstract

In the present study, which includes 287 participants, metformin has been used by women undergoing IVF/intracytoplasmic sperm injection for more than 5 weeks before and during treatment and during luteal phase. There was no significant difference in number of gonadotrophins used, days of stimulation, number of oocytes retrieved, and number of embryos replaced. There was no significant difference in clinical pregnancy rate between both groups but there was significant reduction in the incidence of ovarian hyperstimulation syndrome (OHSS) in the group taking metformin. Metformin is a safe, cheap drug that can help in prevention of OHSS.

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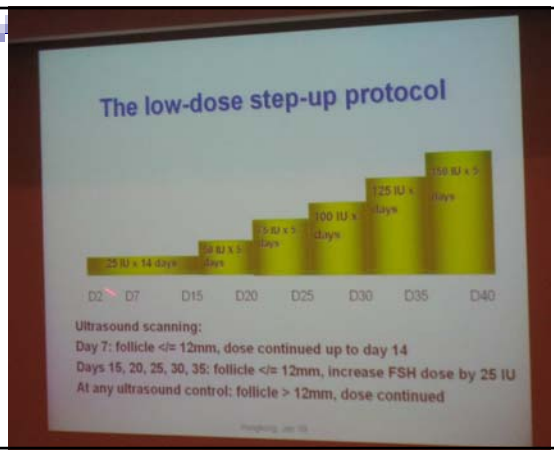
對於PCOS患者的誘導排卵建議

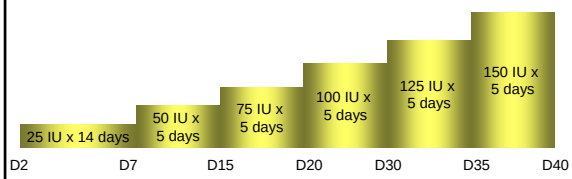
- 哈佛大學Barbieri等學者建議的流程循序使用：
  1. 如果BMI過高，儘可能減重，即使減少5%的體重，也可以增加許多自然排卵的機會
  2. 使用clomiphene(如果DHEAS比較高可以再加上glucocorticoid)
  3. 單獨使用胰島素活化物如Metformin
  4. 胰島素活化物加上clomiphene
  5. 性腺激素
  6. 胰島素活化物加上性腺激素
  7. 卵巢手術
  8. 試管嬰兒。

Gonadotrophins in East Asia

- CC-resistant PCOS patients
- Yong EL, 1997 (Singapore), n=51,
  - Chronic low dose step-up (PR=21.6%)
- Kazumichi A, 1998 (Japan), n=61,
  - Fixed dose (PR=21%)
  - Step down (PR=21%)
  - Low dose step-up (PR=20%)
- Lan VTN 2009 (Vietnam), n=183
  - Chronic low dose step-up (PR=35.5%)



The low-dose step-up protocol



Ultrasound scanning

D7 follicle </=12mm, dose continued up to day 14

D15, 20,25,30,35 follicle </=12mm, increased FSH dose by 25 IU

At any ultrasound control follicle>12mm, dose continued.

對懷孕的影響

GDM(妊娠糖尿病)

- Using 75g OGTT and WHO criteria
  - 3% (Anglo-Celtic)
  - 7.3% (Arabic)
  - 9.6% (Vietnamese)
  - 10.1% (Australia)
  - 16.7% (India)
- HKU: 5.9% in 1988, 10.2% in 2002, 11.2% in 2006

Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome

C. J. Glueck, M.D., Ping Wang, Ph.D., Suichi Kobayashi, M.D., Harvey Phillips, M.D., and Luann Sieve-Smith

Cholesterol Center, Jewish Hospital, Cincinnati, Ohio

- Metformin with a 10-fold reduction in GDM (31% to 3%) (Glueck, *et al,* 2002, Fertil steril)
- 使用**Metformin**可以**減低10倍妊娠糖尿病**的發生率

Effects of Metformin on Early Pregnancy Loss in the Polycystic Ovary Syndrome

使用**Metformin**可以**減少流產**的發生率

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Polycystic ovary syndrome is the most common form of female infertility in the United States. In addition to poor conception rates, pregnancy loss rates are high (30–50%) during the first trimester. We hypothesized that hyperinsulinemic insulin resistance contributes to early pregnancy loss in the syndrome, and that decreasing hyperinsulinemic insulin resistance with metformin during pregnancy would reduce the rate of early pregnancy loss.

We conducted a retrospective study of all women with polycystic ovary syndrome who were seen in an academic endocrinology clinic within the past 4.5 yr and who became pregnant during that time.

Sixty-five women received metformin during pregnancy (metformin group) and 31women did not (control group). The early pregnancy loss rate in the metformin group was 8.8% (6 of 68 pregnancies), as compared with 41.9% (13 of 31 pregnancies) in the control group ($P < 0.001$). In the subset of women in each group with a prior history of miscarriage, the early pregnancy loss rate was 11.1% (4 of 36 pregnancies) in the metformin group, as compared with 58.3% (7 of 12 pregnancies) in the control group ($P = 0.002$).

Metformin administration during pregnancy reduces first-trimester pregnancy loss in women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 87: 524–529, 2002)

(JCEM, 2002)

TABLE 2. Rates of early pregnancy loss among women with polycystic ovary syndrome who either received (metformin group) or did not receive (control group) metformin during pregnancy[a]

Cohort	Early pregnancy loss rate		*P* value
	Metformin group[b] (n = 65)	Control group (n = 31)	
All women	8.8% (6/68)	41.9% (13/31)	<0.001
EPL+ women	11.1% (4/36)	58.3% (7/12)	0.002
EPL− women	6.3% (2/32)	31.6% (6/19)	0.04

[a] EPL−, Women with no prior history of miscarriage (either nulliparous women or women with pregnancies completed to term).

[b] Among the 65 women in the metformin group, there were a total of 68 pregnancies. Of these, 36 pregnancies occurred in the context of a history of prior miscarriage, and 32 pregnancies occurred in the

使用**Metformin**可以**減少流產**的發生率

尤其是之前有流產過的

(JCEM, 2002)

Insulin resistance and spontaneous abortion

TABLE 1. Demographic characteristics of the patients

	Whole group	IR	Non-IR	*P*
Age (yr)	30.8 ± 3.99	31.26 ± 3.96	30.70 ± 3.88	>0.05
Etiology				
Tubal blockage	51.4% (55/107)	52.2% (12/23)	51.2% (43/84)	>0.05
Male factor	25.2% (27/107)	17.4% (4/23)	27.4% (23/84)	>0.05
PCOS	12.1% (13/107)	21.7% (5/23)	9.5% (8/84)	>0.05
Others	11.2% (12/107)	8.7% (2/23)	11.9% (10/84)	>0.05
No. of embryos transferred	2.38 ± 0.54	2.39 ± 0.58	2.38 ± 0.54	>0.05
FI (μIU/ml)	14.54 ± 6.01	22.74 ± 3.78	12.29 ± 4.32	<0.001
FG (mmol/liter)	5.05 ± 0.56	5.31 ± 0.43	4.98 ± 0.57	<0.05
FG/FI	0.43 ± 0.26	0.24 ± 0.04	0.47 ± 0.27	<0.001
BMI	22.09 ± 2.87	22.46 ± 2.89	21.99 ± 2.87	>0.05
Testosterone (nmol/liter)	1.75 ± 1.25	1.75 ± 0.99	1.78 ± 1.31	>0.05
Spontaneous abortion	17.8% (19/107)	47.8% (11/23)	9.5% (8/84)	<0.001
Previous pregnancy	37.4% (40/107)	45.5% (10/22)	35.3% (30/85)	>0.05
Previous spontaneous abortion	4.7% (5/107)	0% (0/22)	5.9% (5/85)	>0.05
Previous delivery	4.7% (5/107)	0% (0/22)	5.9% (5/85)	>0.05
n	107	21.5% (23/107)	78.5% (84/107)	

Data represent mean ± SD and percent. All continuous variables were tested by Student's *t* test and the categorical variables by χ^2 or Fisher's exact test where the cell size was less than 5.

Tian et al., JCEM 92:1430-3, 2007

結論

- **多囊性卵巢症候群的臨床症狀變化多端、表現也是相當的異質性，沒有一致的診斷標準，原因還不是很清楚**
- **基因問題：**
  - **與類固醇之合成與作用的基因有關：** P450c17; CYP11α
  - **與醣類之代謝與利用之基因有關**
  - **與男性素接受器異常突變**
- 目前無法治本，只能根據病人的症狀與需要來治療
- **適當的減重5-10%** 是治療的第一選擇
- 如果**沒有懷孕考量**但是合併**有多毛與青春痘症狀**的病人，使用口服**避孕藥**是一個理想治療方式。

- **胰島素抗性**IR可以使用metformin
- 如果**治療多毛與青春痘等症狀效果不好時，**可以合併使用抗男性素藥物 **Spironolactone**
- 腹腔鏡卵巢燒灼術適用於對排卵藥物反應不好的病患（Ovulation Refractory）
- 要治療多久？How long?
- 心血管疾病CAD ?糖尿病DM?
- 糖尿病可否預防？Metformin Long term use for prevention of type 2 DM ?
- 多囊性卵巢症候群合併有不孕問題：**最適當的誘導排卵方式？**

Thanks for your attention