

# Polycystic ovarian Syndrome and subfertility

## 多囊卵巢綜合症與不孕症

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### 案例: 梁小姐

28歲

已婚2個月, 未有計劃懷孕

過往沒有懷孕史

美容師

沒有過往病史/ 藥物史

由於閉經6個月, 轉診到婦產科

月經初潮 : 12-13歲

週期Q60-95天

流量正常

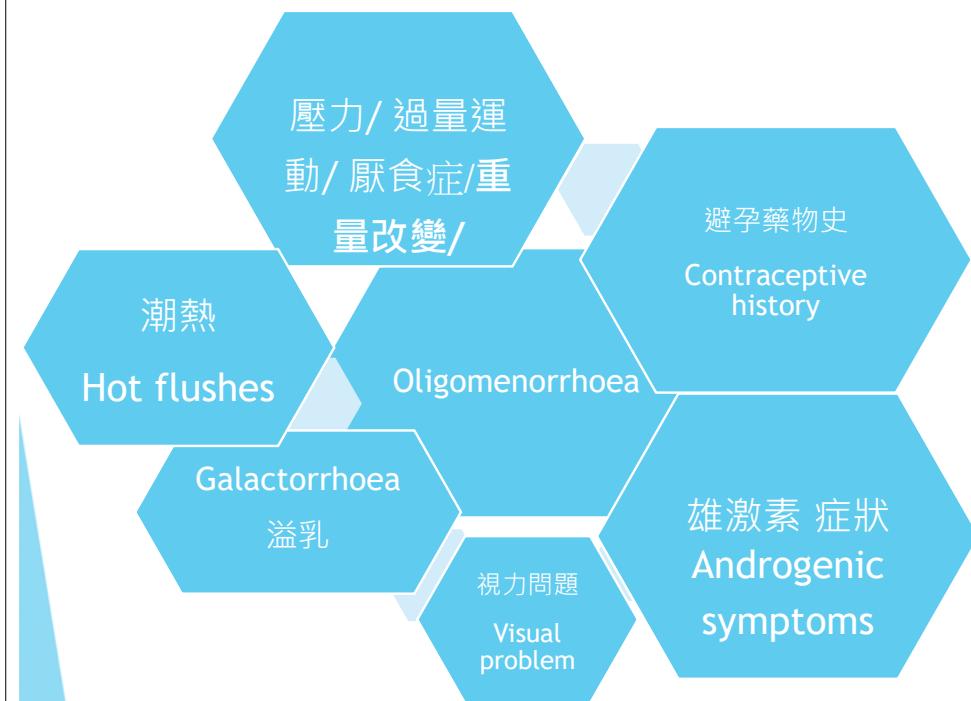
沒有痛經

月經間期沒有出血

月經週期  
不規律的  
原因是?

# 問診 History taking

Rule out  
Pregnancy 懷孕  
Lactation 授乳



## 案例: 梁小姐: 臨床檢查

- ▶ General examination
  - ▶ 身高體重指數 (BMI) -- 30
  - ▶ 血壓 / 脈搏--- 120/80
- ▶ 腦下垂體瘤徵狀 (prolactinoma)
  - ▶ 管視角 tunnel vision - Nil
  - ▶ 溢乳 Galactorrhea - Nil
- ▶ 甲狀腺檢查 (thyroid examination)- normal
- ▶ 雄激素過多症狀 (hyperandrogenism)
  - ▶ 體毛分佈 (多毛症 evidence of hirsutism) 1年前已做全身脫毛
  - ▶ 暗瘡 (acne)- +++



## 案例: 梁小姐: 臨床檢查

### ► 腹部檢查 abdominal examination

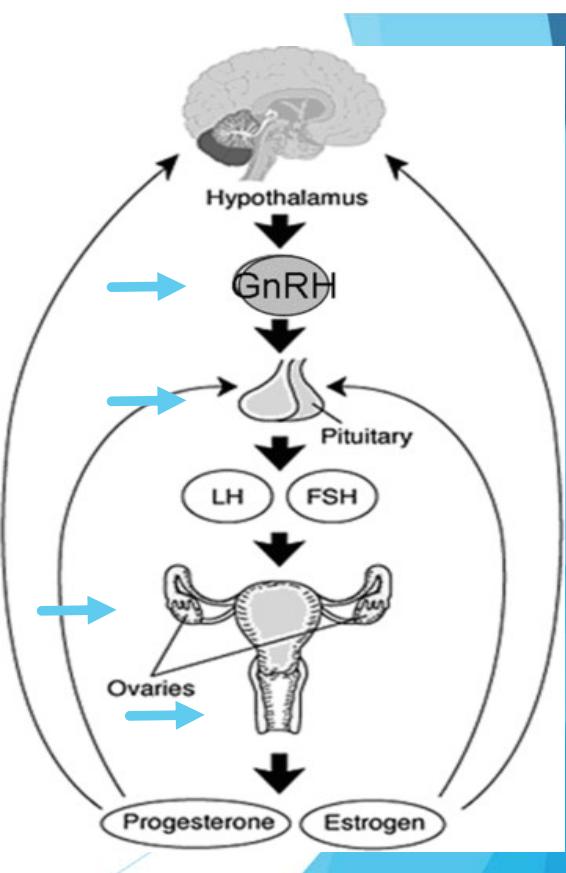
- 傷疤 Scars- **nil**
- 肿塊 mass **Nil**
- 痛楚Tenderness **Nil**

### ► 盆腔檢查 pelvic examination : **Normal**

- 外陰Vulva/ 陰道 vagina
- 子宮頸 Cervix
- 子宮 Uterine size
- 卵巢Ovary / Adnexal mass

## 案例: 梁小姐: 臨床檢查

- 實驗室檢查
- 後續的檢查應針對下丘腦、垂體、卵巢、子宮和生殖道的問題去安排

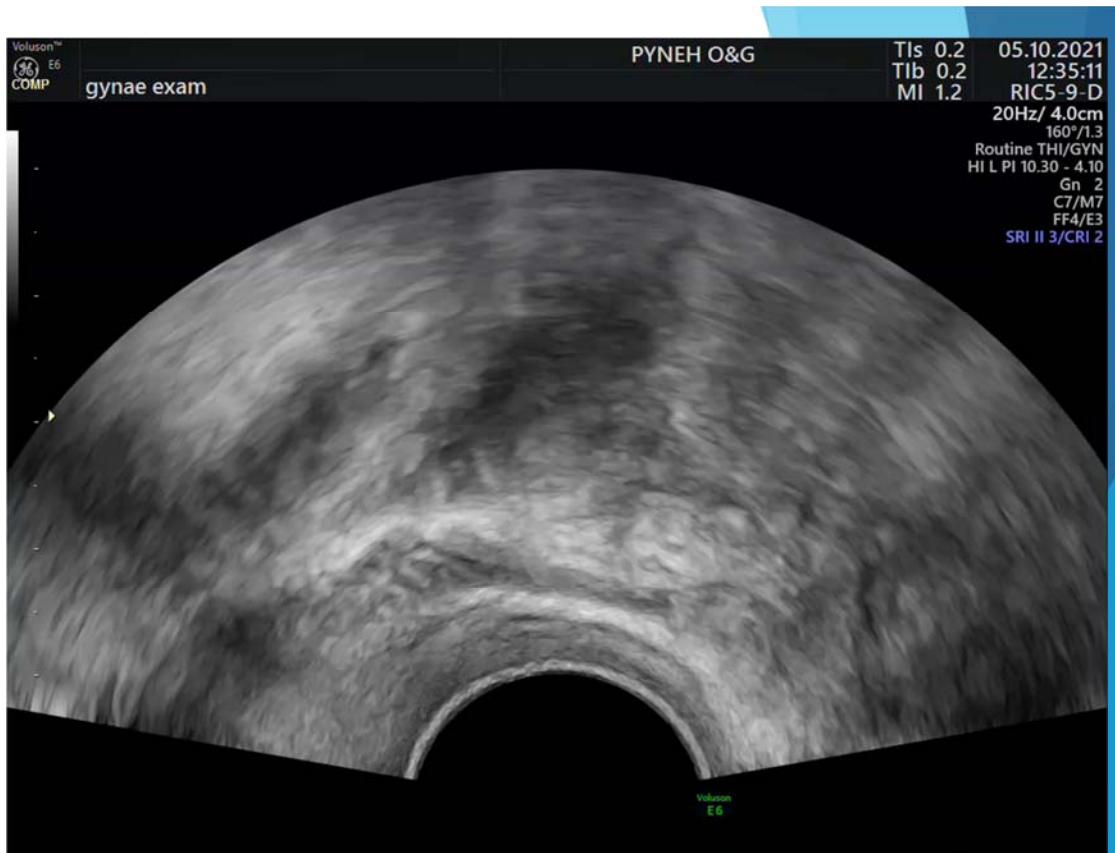


## 案例: 梁小姐: 實驗室檢查 Investigations

- ▶ 懷孕測試: 未懷孕
- ▶ 血液檢查
  - ▶ 甲狀腺素 (thyroid function test)- 正常
  - ▶ 催乳素 (prolactin)- 正常
  - ▶ 荷爾蒙水平檢查
    - ▶ 促卵泡生成激素(FSH)- 正常
    - ▶ 促黃體生成素(LH) - 正常
    - ▶ 雌激素(E2)- 正常
    - ▶ 雄性激素 (testosterone)- 正常

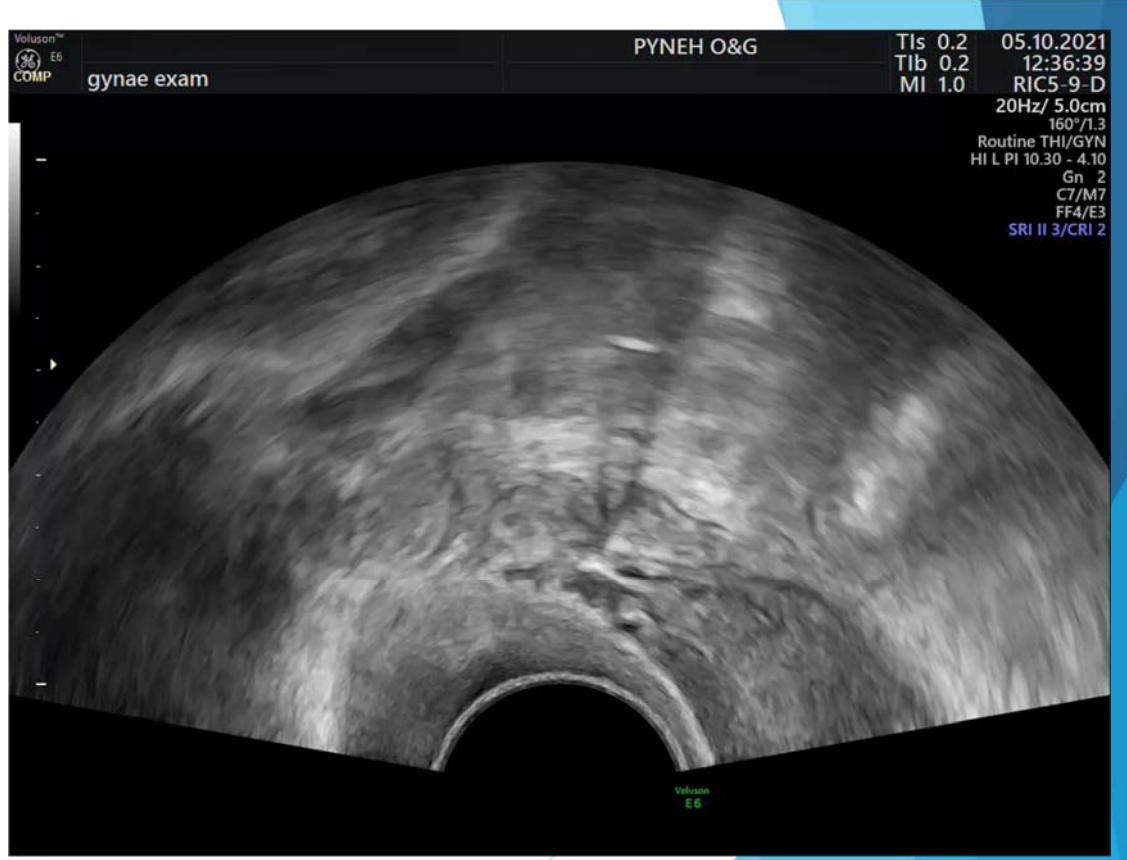
## 案例: 梁小姐

- ▶ 盆腔超聲波檢查



## 案例: 梁小姐

- ▶ 盆腔超聲波檢查



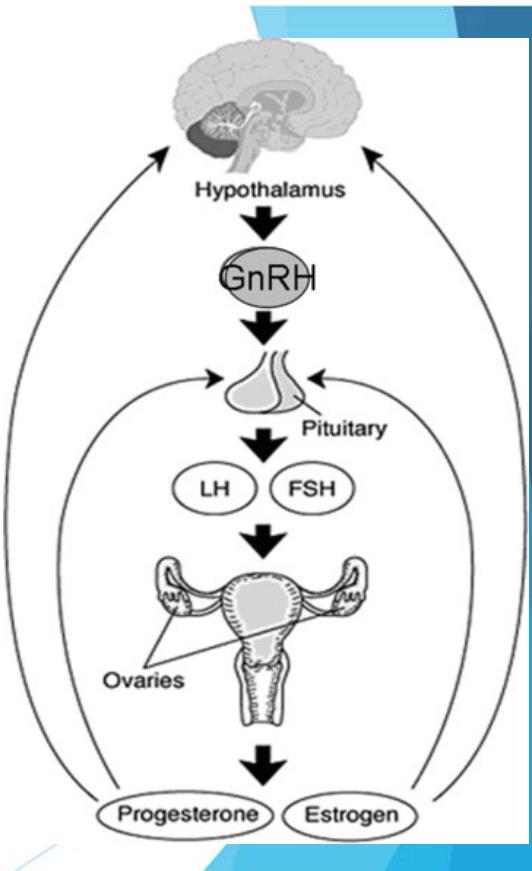
## 案例: 梁小姐

- ▶ 診斷: 多囊性卵巢症候群
- ▶ Diagnosis: Polycystic Ovarian Syndrome

## Polycystic Ovarian Syndrome (多囊性卵巢症候群)

### ► Pathophysiology 病理生理學

- Dysfunction of the Hypothalamic Pituitary Ovary Axis function (由下丘腦和腦垂體-卵巢軸系功能失調引起)
- Unknown 未有確實真正病因



Popat, Vaishali & Prodanov, Tamara & Calis, Karim & Nelson, Lawrence. (2008). The Menstrual Cycle A Biological Marker of General Health in Adolescents. Annals of the New York Academy of Sciences. 1135. 43-51.  
10.1196/annals.1429.040.

## Definition and Diagnosis

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

#### The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group

Revised 2003 criteria (2 out of 3)

1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries

and exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing's syndrome)

符合下列症狀中兩項，就可確定是多囊性卵巢症候群：

- 不排卵、很少排卵或月經不正常（月經不來、偶爾來，或者雖來了，量不是很少就是很多，或拖很久）
- 出現雄性素過多的表徵，例如長青春痘、身體過多毛髮生長等等。
- 超音波發現卵巢多囊腫的現象

## Hirsutism: 多毛症

Modified Ferriman Gallwey score  
9 body parts

Ethnicity	Score
US black and whites	≥8
Mediterranean Hispanic Mid-Eastern	≥9
South American	≥6
Asian	≥2



## Definition and Diagnosis

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  3. Polycystic ovaries
- and exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing's syndrome)

#### 必須排除

- Hyperprolactinaemia 高泌乳素血症
- Acromegaly 肢端肥大症
- CAH 先天性腎上腺增生症
- Cushing syndrome 庫欣綜合徵
- Other androgen secreting tumours 雄激素分泌性腫瘤
- Hypothyroidism 甲狀腺機能低下症

Testosterone level in PCOS is usually < 5nmol/L

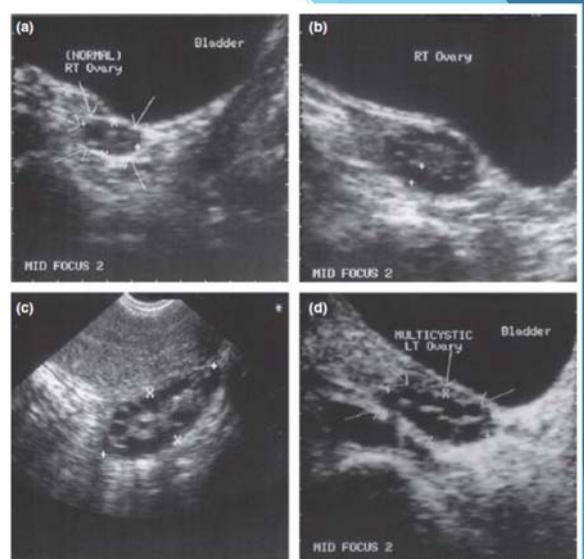
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# International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018



## Pelvic Ultrasound 盆腔超聲波檢查

- ▶ 卵巢多囊是常見的發現
- ▶ 月經初潮後 8 年內：不建議使用超聲波檢查診斷
- 盆腔超聲波檢查多囊卵巢定義 (2018)
  - 經陰道盆腔超聲波檢查
    - 20 or more follicles, 2-9mm each
    - Or increased ovarian volume  $\geq 10\text{ml}$
  - 經腹超聲波檢查 (Transabdominal scan)
    - increased ovarian volume  $\geq 10\text{m l}$



## 治療手段 Treatment

- ▶ 徵狀 Symptoms
  - ▶ 月經不正常 irregular menses
  - ▶ 雄激素過多症狀 (hyperandrogenism): 多毛症 (hirsutism)/ 青春痘
- ▶ 生育意願 Fertility wish
- ▶ 減低健康風險 Reduce subsequent health risk
  - ▶ 心理 Psychological
  - ▶ 高血壓, 糖尿病, 高脂血症 hypertension Diabetes, dyslipidaemia Metabolic syndrome
    - ▶ 5x increase risk of metabolic syndrome
  - ▶ 肥胖, 睡眠窒息症 Obesity, Obstructive sleep Apnea
  - ▶ 子宮內膜增生, 子宮癌風險 Risk of endometrial hyperplasia/CA Corpus

## 治療手段 Treatment

月經不正常	黃體素 口服避孕藥
雄激素過多症狀 (hyperandrogenism): 多毛症 (hirsutism)/ 青春痘	激光Laser/剃毛shaving/衛生 hygiene/ 藥物 medications
肥胖	營養師Dietician/ 運動 exercise
不育	Fertility specialist - 排卵藥ovulation induction as 1 <sup>st</sup> step
心理	臨床心理學家 (Clinical psychologist)
高血壓, 糖尿病, 高脂血症, 睡眠窒息症, 子宮內膜增生, 子宮癌風險	定期檢查Regular monitoring 定期撤回性出血 Regular withdrawal bleeding

## 治療手段 Treatment



International PCOS guideline, recommend COCs as the first-line treatment in adult women with PCOS. Using the lowest effective dose (20 to 30 µg of EE or equivalent). It is also emphasized that a minimum duration of 6 months is required to assess treatment response <sup>18</sup> regarding hirsutism. Ovarian and endometrial cancer is reduced by 30% compared to non-user

## 治療手段 Treatment

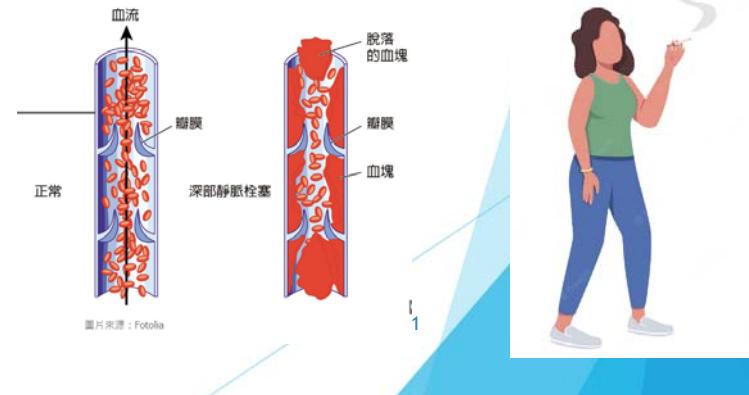
- ▶ 荷爾蒙治療

# 黃體素 VS 口服避孕藥



## 1.) 口服避孕藥: Before initiating hormones..

- ▶ 口服避孕藥: 禁忌症:
- ▶ 排除潛在的靜脈血栓和心臟代謝風險
- ▶ e.g. 吸煙者 + 或35歲以上 Smoker >15 cig per day (older than 35 yo)
- ▶ e.g. 靜脈血栓的病史
- ▶ e.g. 缺血性心臟疾病/ 中風
- ▶ E.g. 乳腺癌



PRESNTATION TITLE

## 哪種口服避孕藥?

- ▶ Mercilon (Desogestrel 150µg/EE 20µg)
- ▶ Marvelon (Desogestrel 150µg/EE 30µg)
- ▶ Microgynon (Levonorgestrel 0.15mg/EE 30µg)
- ▶ Yasmin (Drospirenone 3mg/EE 30µg)
- ▶ Harmonet (Gestodene 7.5µg/EE 20µg)



## 1.) 黃體素 Progestogen

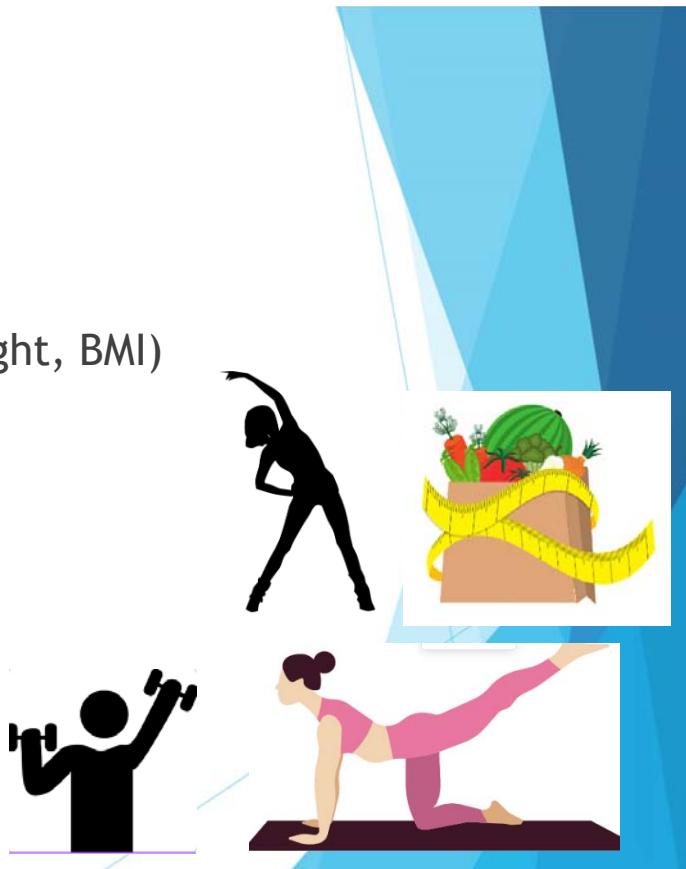
- ▶ “通經藥”
- ▶ 誘發每兩個月來一次月經 (撤退性出血) Withdrawal bleeding
- ▶ E.g. Provera 10mg 10 days every 2 months of amenorrhea

PRESNTATION TITLE

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## 案例：梁小姐

- ▶ 通經藥每(2個月)
  - ▶ 使用額外的避孕措施
  - ▶ 服用通經藥前，應驗孕
- ▶ 每次就診時檢查血壓和體重 ( BP, Weight, BMI)
- ▶ 定期檢查血糖 / 膽固醇
- ▶ 轉介營養師
- ▶ 建議減肥，維持正常 BMI, 做運動
- ▶ 如果日後想懷孕，可能需要藥物幫助



## 案例: 梁小姐--- 3年後

31歲

計劃懷孕 Plan for pregnancy

2年未避孕

嘗試懷孕2年 Tried for 2 years

BW 65kg, BMI 26

月經週期 Q 40-60 days ( sometimes spontaneous, sometimes provera withdrawal)

## 不孕症 ( subfertility)

- 骨盆腔的問題：
  - 輸卵管阻塞或粘黏、骨盆腔粘黏
- 子宮的問題
  - 子宮腫瘤、子宮畸形、子宮內膜粘黏、子宮頸狹窄或閉鎖、子宮內膜異位症
- 卵巢的問題：
  - 排卵障礙、多囊性卵巢、卵巢腫瘤、卵巢過早衰竭
- 內分泌的問題：
  - 泌乳激素過高症、雄性激素過高症、黃體激素缺乏症

### 女性不孕的常見原因

- |         |       |
|---------|-------|
| 卵巢因素    | 不孕症原因 |
| 輸卵管因素   |       |
| 其他子宮因素  |       |
| 其他女性因素  |       |
| 子宮內膜異位症 |       |

# 不孕症 (subfertility)

1. 陰莖的問題：尿道上裂、尿道下裂、陰莖彎曲
2. 睾丸的問題：隱睾症、睪丸扭轉、睪丸萎縮症、精索靜脈曲張、意外傷害
3. 輸精管的問題：先天性輸精管缺損、精道感染發炎
4. 內分泌的問題：性腺功能低下症、泌乳激素過高症



## 男性不孕的常見原因

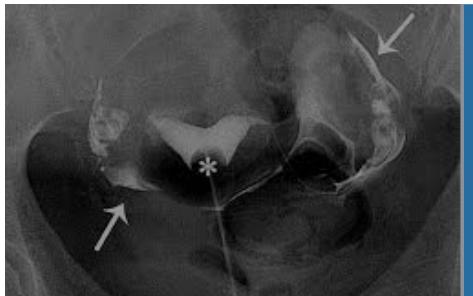
- 陰莖的問題
- 睪丸的問題
- 輸精管的問題
- 內分泌的問題
- 其他原因



1. 免疫因素：先生的抗精蟲抗體或太太的抗卵子抗體
2. 其他因素：高齡、過重、壓力大、環境污染、不良生活習慣、性氾濫、抽煙、藥物濫用

## 案例：梁小姐

- 不孕診所
- 行房沒有問題, 2-3x/week
- 子宮輸卵管造影(hysterosalpingogram)：正常
- 丈夫
  - 35歲，文員，戒菸3年，
  - 無麻疹、腮腺炎病史
  - 外陰無外傷
  - 精液分析 (semen analysis): 正常



## 案例：梁小姐

### 1.) 體重控制 Weight control

- 肥胖增加先天性畸形和妊娠並發症的風險
- 降低對生育治療的反應/成功率
- 推遲生育治療直到  $BMI < 35\text{kg}/\text{cm}^2$
- $BMI \geq 40\text{kg}/\text{cm}^2$ ：考慮減肥手術治療，減肥手術後應避免懷孕 12 個月

### 2.) 孕前葉酸 preconception folic acid

- 預防先天神經管缺陷
- 劑量： $\geq 400\mu\text{g}$  daily；如肥胖， $5\text{mg}$  daily

### 3.) 血液檢查 Baseline blood tests

### 4.) 陰道超音波檢查( Transvaginal Ultrasound of pelvis)

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## 多囊卵巢綜合症 與排卵障礙

### 1.) 藥物治療

- ▶ 排卵誘導：可透過服用或注射激素，促使卵巢釋放成熟的卵子

### 2.) 手術治療

- ▶ 卵巢鑽孔術 (ovarian drilling)

### 3.) 輔助生殖科技: e.g. 體外受精 (試管嬰兒 IVF )

IVF

藥物治療

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# 多囊卵巢綜合症 與排卵障礙

## 1.) 藥物治療

► 排卵誘導: 可透過服用或注射激素，促使卵巢釋放成熟的卵子

### ► 口服排卵藥

► 克羅米酚 Clomiphene citrate

► 來曲唑 Letrozole – first line

► 注射型排卵針 Gonadotrophin

► Metformin

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### Clomiphene citrate 克羅米酚/來曲唑 Letrozole – first line

► 從第 2 天到第 3 天開始

► Clomiphene : 每天劑量 50-150mg

► Letrozole: 每天劑量 2.5-7.5mg

► 使用超聲波監測卵巢反應

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# 多囊卵巢綜合症 與排卵障礙

## 1.) 藥物治療

### ▶ 副作用

- ▶ 大多數使用者並沒有明顯症狀
- ▶ 主要有輕度的嘔心、頭痛、消沉、視力模糊、腹脹、掉髮、體重增加等

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# 多囊卵巢綜合症 與排卵障礙

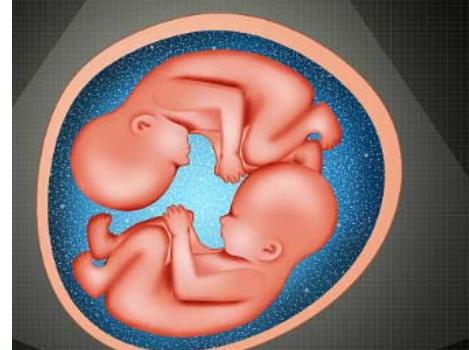
## 1.) 藥物治療

### ▶ 併發症

- ▶ 接受超排卵和人工授精的治療相當安全，也甚少出現併發症
  - 多胎妊娠發生率大約是百分之十至二十。
  - 卵巢過度刺激症 (Ovarian hyperstimulation syndrome)
    - 約有百分之一屬嚴重程度。病人可能出現腹脹及腹痛、嘔吐、卵巢囊腫、腹水、胸水及下肢靜脈閉塞。
  - 如果胎兒有三個或以上，可選擇性減少胎兒的數目。但此程序的風險就是有可能引起發炎及最終導致所有胎兒小產。因此不能輕視選擇性減少胎兒數目所帶來的心理影響



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# **Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline**

Practice Committee of the American Society for Reproductive Medicine  
American Society for Reproductive Medicine, Birmingham, Alabama

Metformin alone compared with placebo increases the ovulation rate in women with polycystic ovary syndrome (PCOS) but should not be used as first-line therapy for anovulation because oral ovulation induction agents such as clomiphene citrate or letrozole alone are much more effective in increasing ovulation, pregnancy, and live-birth rates in women with PCOS. There is fair evidence that metformin alone does not increase rates of miscarriage when stopped at the initiation of pregnancy and insufficient evidence that metformin in combination with other agents used to induce ovulation increases live-birth rates.

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*Fertil Steril.* 2017 Sep;108(3):426-441. doi: 10.1016/j.fertnstert.2017.06.026.

# **Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline**

Practice Committee of the American Society for Reproductive Medicine  
American Society for Reproductive Medicine, Birmingham, Alabama

- ▶ Metformin is better than Placebo, but does not increase livebirth
- ▶ Metformin is inferior to other OI agents, like Clomiphene or letrozole
- ▶ Fair evidence that pretreatment with metformin 3 months prior to OI increases live birth
- ▶ May consider in women who are clomiphene resistant

No answer:

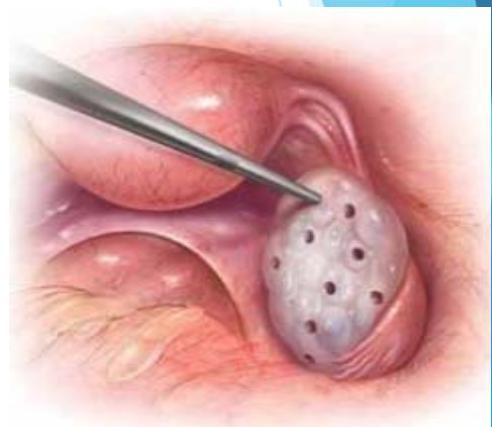
- ▶ Is metformin more effective in lean vs obese PCOS patient?
- ▶ Is it more effective if given long term? (typically, <6 months in the studies)

# 多囊卵巢綜合症 與排卵障礙

## ► 手術治療

### ► 卵巢鑽孔術 (ovarian drilling)

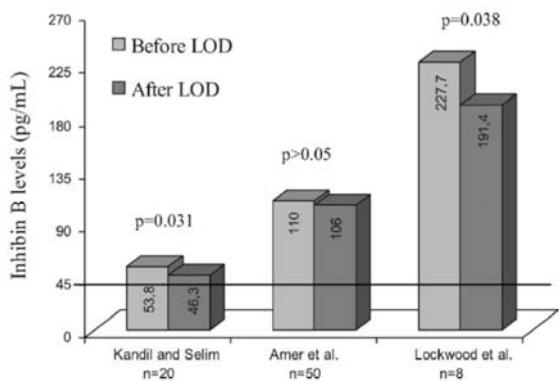
- ▶ 利用小切口引入電針穿刺並電灼卵巢 4 次，用以銷毀部份卵巢組織及平衡體內之荷爾蒙，籍此誘發排卵
- ▶ 70%至 80%的患者能自發地排卵
- ▶ 自然懷孕的概率為 50%至 60%。
- ▶ 不會增加多胞妊娠或卵巢過度刺激綜合症的風險。



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## Is ovarian reserve diminished after laparoscopic ovarian drilling?

Ovarian reserve after LOD 163



NO

Figure 1. Inhibin B levels before and after laparoscopic ovarian drilling (LOD) in polycystic ovarian syndrome. *p* values on each consecutive bars represent significance of mean inhibin B values (shown on each bar) in each studies. *n* values under the names of the authors of each study represent the number of subjects whose inhibin B levels available before and after LOD. Horizontal reference line at 45 pg/ml is the normal lowest level of inhibin B.

## 多囊卵巢綜合徵與妊娠

- ▶ 增加妊娠糖尿病和先兆子癇的風險  
( gestational diabetes)
  - ▶ 5 fold increased risk in Asian
- ▶ 增加先兆子癇的風險 (pre-eclampsia)
- ▶ 增加早產的風險 (preterm birth)
- ▶ 增加嬰兒出生後進入 NICU 的風險



### 案例: 梁小姐--- 再10年後

Age 41

Para 1 SVD x1 (Letrozole induced pregnancy)

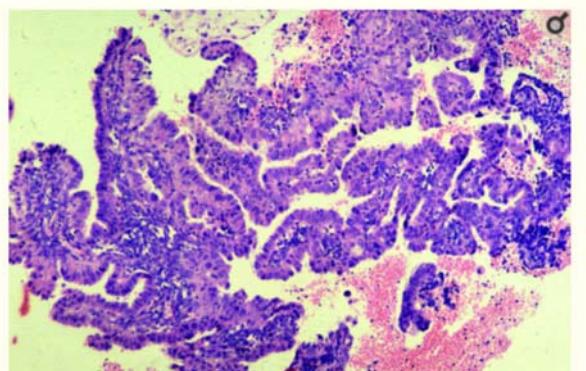
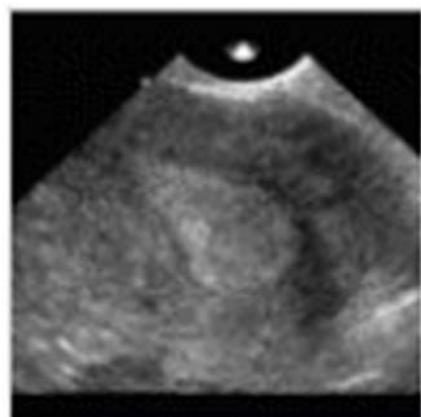
Type II DM on metformin, diagnosed 2 year ago

月經過多, 貧血

每 2 -3 個月的不規則周期

盆腔超聲波檢查: 多囊卵巢

子宮內膜取樣: 非典型子宮內膜增生



## 多囊卵巢綜合徵與癌症

- 2-6X higher risk of endometrial malignancy
- Increase risk of endometrial hyperplasia
- Prolonged endometrial exposure to unopposed estrogen
- Endometriums in PCOS may exhibit progesterone resistance
- Atypical endometrial hyperplasia: up to 40-50 % of concurrent Ca Corpus

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### Department of Obstetrics and Gynaecology

Generalists  
Adolescent-gynae

Irregular Menstruation

Reproductive medicine

Infertility

Fetal maternal Medicine

High risk pregnancy

Gynaec-oncology

Endometrial cancer

Urogynaecology

Urinary incontinence assoc with obesity

Metabolic or cardiovascular problem

→ endocrinologist

## 總結

- ▶ 多囊卵巢綜合症：很常見
- ▶ 主要症狀是月經失調、高雄激素血症、不孕、和心理問題
- ▶ 治療：主要是症狀處理
- ▶ 肥胖會加重多囊卵巢綜合症的影響，尤其是生育方面
- ▶ 以口服排卵藥 (Letrozole- first line) ,作不孕治療