多囊性卵巢症候群

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Introduction

- Polycystic ovary syndrome (PCOS) is defined as **hyperandrogenism and reduced frequency of ovulation** in the absence of other hyperandrogenic disorders.
- The clinical manifestations of PCOS are **cosmetic** and **reproductive**. These patients present with **hirsutism, acne**, and irregular **menstrual** periods; ovulation may be infrequent or absent, and **infertility** can occur.
- When assessing a patient with possible PCOS, the physician must rule out other conditions that can produce clinical hyperandrogenism, such as **androgen-secreting tumors** and nonclassic **congenital adrenal hyperplasia**.
- It is also necessary to identify patients whose hirsutism or acne results from **increased sensitivity** to normal androgen levels.

PCOS

- The most common cause of hyperandrogenism and hirsutism
- Stein-Leventhal syndrome (1935)

  Triad: hirsutism, amenorrhea, obesity
- Extremely heterogenous clinical pictures
- Multifactorial in etiology
- Dx Criteria (NIHCHHD consensus)

  Major: chronic anovulation; hyperandrogenemia/genism; other etiologies excluded (CAH, pituitary, neoplasm)

  Minor: IR; perimenarchal onset of hirsutism and obesity; elevated LH/FSH; intermittent anovulation (oliogoovulation) with hyperandrogenemia (free T, DHEAS); ultrasonographic evidence of PCO

Epidemiology

- PCOS is one of the most common endocrine disorders of women. In three population-based studies, the average prevalence of PCOS in women of reproductive age was reported to be about 6%. Among anovulatory women, the prevalence of PCOS is approximately 30%.

Clinical profile

- ***Hirsutism*: denotes an increase in terminal hair in a male-pattern distribution.**
  - **Ferriman-Gallwey score**
  - **Caucasian 70%; Orientals 10-20%**
- ***Acne*: acne, like hirsutism, reflects both circulating androgen concentrations and genetic makeup.**
- ***Menstrual dysfunction*:**
  - **Oligomenorrhea to amenorrhea**
- ***Obesity*: Over 50%**
  - **Android obesity; higher waist-to-hip ratio**
- ***IGT & DM* :**
  - **Obese PCOS One third IGT; 7.5-10% type 2 DM**
  - **Nonobese PCOS 10% IGT; 1.5% type 2 DM**
  - **General population 7.8% IGT; 1% type 2 DM**

Clinical profile

- **Abnormal lipoprotein**
  - Elevated cholesterol, TG, LDL
  - Decreased HDL, apoprotein A-I
  - Most characteristic: decreased HDL_{2a}
- **Impaired fibrinolysis**

- Increased **Hypertension**: 40% by MP
- Increased **Atherosclerosis** & **CVD**
- Increased **MI (7-fold)**

Long-term Cancer Risk

- Increased risk of **endometrial carcinoma** (chronic hyperestrogenic state uninterrupted by progesterone)
- Increased risk of **breast cancer** (greater risk for nonobese patients and those not taking OCs)
- Increased risk of **ovarian cancer**: 2~3-folds (greater risk for nonobese patients and those not taking OCs)

Pathology and Pathophysiology

- **Ovaries: 2~5 times the normal size, thickened cortex**
  USG > 5 microcysts (0.5~0.8 mm) / ovary
- **Ovary: most consistent contributor of androgen**

  Dysregulation of CYP17 enzyme

  Hyperandrogenism are stimulated by LH

  Serum total testosterone usually no more than twice the upper normal range (20-80 ng/dl)
- **Adrenal: DHEAS increased in about 50% of patients**
- **Peripheral: E1 level increased due to peripheral aromatization of ASD**
- **H-P: increased GnRH & LH pulse frequency**

  25% patients with elevated prolactin
- **Genetic origin ?**

Pathophysiology

- PCOS is caused by abnormally **increased** secretion of **LH, insulin**, or both.
- Increased levels of those hormones stimulate the ovarian **theca and stroma** to produce excess quantities of **androgen**, including testosterone and androstenedione.
- Elevated ovarian androgen secretion tends to block the growth of a dominant ovarian follicle. Instead, many **small follicles accumulate**; these follicles range in size from 4 to 8 mm in diameter.
- In the absence of a dominant follicle, an LH surge is not triggered, and ovulation does not occur regularly.

Pathophysiology

- About 95% of women with PCOS have elevated levels of LH secretion, and 50% have hyperinsulinemia. Those rates are influenced by body mass and genetics.
- There may be two major phenotypes of PCOS: (1) lean women with markedly elevated levels of LH secretion and minimal or no insulin resistance and (2) obese women with slightly elevated or normal levels of LH secretion and insulin resistance and with markedly elevated levels of insulin

- Women with PCOS show an abnormal increase in both the amplitude and the frequency of LH pulses
- Underlying increase in the pulse frequency of gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus;
- The insulin resistance in women with PCOS has many possible causes, including genetic mutations in the insulin receptor and autoantibodies to the insulin receptor. The most common cause, however, is obesity.
- results in a compensatory and chronic hypersecretion of insulin.
- Why insulin resistance develops in muscle and fat but not the ovary remains unclear.
- insulin stimulates ovarian androgen secretion indirectly by binding to the insulinlike growth factor-1 receptor in the theca and the stroma.

Diagnosis

- No single feature is pathognomonic for PCOS. The history, physical examination, and laboratory evaluation can all provide evidence that establishes the diagnosis of PCOS and that excludes other conditions associated with those features.
- Clinical evidence of hyperandrogenism includes hirsutism, acne, and menstrual irregularity. Laboratory evidence of hyperandrogenism includes an elevated total or free serum testosterone concentration.

History for Dx & (DDx)

- ***Age of Onset*:** oligomenorrhea, hirsutism, and acne typically begin in the **perimenarchal** or teenage years. (onset of severe hirsutism in menopause suggests an ovarian neoplasm.)
- ***Menstrual History*:** typically experience irregular menstrual cycles starting at **menarche**. (Regular cycles are more consistent with familial or **idiopathic hirsutism**) (history of initially regular periods followed by onset of oligomenorrhea or amenorrhea and hirsutism with virilization in adult life suggests an androgen-secreting **tumor**)
- ***Pace of Progression of Hirsutism:*** tends to **progress slowly**, over many years. (rapid progression to severe hirsutism suggests a virilizing **tumor**).
- ***Family History*: ~50% have a family history** of PCOS, type 2 DM, or both. (**familial hirsutism** begins at puberty accompanied by regular MC and normal androgens.)
- ***Medication History*** Long-term use of the **anticonvulsant valproate** is strongly associated with the onset of PCOS.
- ***Smoking History*** **Smoking** may contribute to hyperandrogenism.

PE for Dx & (DDx)

- Hirsutism can be assessed objectively with the Ferriman-Gallwey scoring system
- Various physical findings point to insulin resistance: specific but not sensitive
- BMI of greater than 27 (overweight)are often IR ; BMI of greater than 30 (Obese) are almost always IR.
- waist-to-hip ratio greater than 0.85 and a waist circumference greater than 90 cm
- presence of acanthosis nigricans or achrochordons (skin tags)
- HAIR-AN syndrome is the most severe form of the insulin-resistant phenotype of PCOS
- Mild IR is difficult to detect
- (Virilization): (clitoromegaly, increased upper body muscle mass, and male pattern baldness.)

Lab test for Dx & (DDx)

- Goals: to rule out an adrenal and ovarian tumor, assess the severity, and determine the source is adrenal or ovarian
- most useful include determination of the total serum testosterone level; the 8 A.M. follicular phase 17-OHP; DHEAS (if fertility is an issue); and prolactin (if the patient has amenorrhea).
- *Testosterone:*
- total testosterone not fully reflect the degree especially if the overproduction is mild. Many women with mild PCOS have total testosterone in the upper end of the normal range.

  (total testosterone level > 200 ng/dl: probably has ovarian stromal hyperthecosis or an adrenal or ovarian tumor; needs imaging studies)
- free testosterone measurement is more sensitive in detecting mild androgen overproduction, but more expensive, measurement of free testosterone is not routinely indicated.
- *17-OHP* ~ 2% of women who present with PCOS have nonclassic CAH due to 21-hydroxylase deficiency. (17-OHP > 4 ng/ml must R/O CAH; confirmed by a 60-minute ACTH stimulation test, A post-ACTH > 10 ng/ml confirms CAH)

- ***DHEAS*** **normal is 0.12 ~ 5.35 ug/dl**

  If > 10.7 ug/dl should R/O adrenal tumor. Many women with PCOS have a DHEAS level in the upper range of normal, f PCOS whose DHEAS level is > 2 ug/ml, add glucocorticoid to clomiphene

- ***Prolactin***

  to rule out a pituitary tumor, many clinicians also routinely measure FSH and TSH in amenorrheic patients.

- ***Luteinizing Hormone***

  measurement of LH in clinical practice is of only modest utility (pulsatile) A normal LH value does not necessarily exclude PCOS, as BMI increases, the normal range for LH decreases

- ***Pelvic Imaging***

  Demonstration of polycystic ovaries on pelvic ultrasonography is not essential for the diagnosis of PCOS. Pelvic imaging is indicated only if the ovaries are palpable on PE or the total testosterone concentration is > 200 mg/dl.

- ***Insulin Resistance and Hyperinsulinemia*** **~ 50% of women; fasting insulin or a fasting insulin-to-glucose ratio of less than 4.5 is diagnostic of IR, but many IR women do not have fasting hyperinsulinemia. clinicians should use clinical findings and, if necessary, simple laboratory tests — such as assessment of fasting insulin levels or insulin response to an oral glucose challenge — to identify women with IR**

B-cell function & Insulin sensitivity index

- Fasting glucose / insulin < 4.5 (mg/dl//uU/ml)
- HOMA-IR (Fasting glucose x insulin) / 22.5 > 3.2
- Fasting insulin > 24 uU / ml
- One hour insulin post OGTT-75 gm > 150 uU/ml

Insulin Resistance & PCOS

- Most common cause of IR and hyperinsulinemia is obesity
- IR in PCOS is **independent** of IR in obesity alone
- IR in PCOS is **not due to** hyperandrogenism
- **Acanthosis nigricans**: vulva, axilla, nape, below breast, inner thigh
- **HAIR-AN syndrome**: severe IR

  testosterone > 150 ng/dl

  fasting insulin > 25 uIU/ml (normal < 20-24)

  insulin response to glucose load > 300 uIU/ml (normal < 160)
- Defect in insulin receptor mediated signaling in 50% patients

PCO(S)多囊性卵巢(症候群)

Diagnosis

- **PCO: Readily based on ovarian morphology**
- **Polycystic ovaries: ten or more cysts 2-8 mm in diameter, arranged around a dense stroma or scattered throughout an increased amount of stroma**
- **Prevalence of polycystic ovaries: 20-25% in young adults**
- **PCOS: polycystic ovaries found in association with menstrual disturbance, the complications of hyperandrogen and obesity.**

US consensus on the diagnosis of PCOS 美國定義- NIH 1990

Two criteria:

- **Chronic oligo-/anovulation**
- **Hyperandrogenism**

  Hirsutism

  Hyperandrogen **Total testosterone > 89 ng/dl**

  Free testosterone > 0.66 ng/dl

  Androstenedione > 2.97 ng/ml

  SHBG

Excluding: Hyperprolactinemia, Thyroid dysfunction, LOCAH, Cushing's, Androgen secreting tumor

UK definition of the diagnosis of PCOS 英國定義

- **Polycystic ovaries (PCO)**
  - Ovarian area > 5.5 cm2
  - Ovarian volume > 11 ml
  - 12 Follicles: 2-9 mm (mean of both ovaries)
- **Associated clinical or biochemical features**
  - Oligo-/amenorrhea
  - Hyperandrogenism
  - Obesity
  - Elevated serum testosterone
  - Elevated serum LH

Proposed protocol 流程 for the diagnosis of PCOS Homburg 2002 HR

- 1. Symptoms

  menstrual disturbance, hirsutism, acne

  anovulatory infertility

- → 2. Ultrasound examination : If (+) Dx confirmed

  ≥ 8 follicles (<10mm) in one plane

  stroma > 25% volume or > 34% area

  If (-): proceed to

- → 3. Biochemical examination

  elevated serum testosterone, elevated LH,

  elevated free androgen,

  fasting glucose: insulin < 4.5

  If any one (+): Dx confirmed

New consensus on diagnosis of PCOS 2003 最新診斷共識

At least two out of the following three criteria

- (1) Chronic oligo-/anovulation
- (2) Hyperandrogenism
- (3) Polycystic ovaries

Subsets: (1)+(2); (3)+(2); (3)+(1); (1)+(2)+(3)

Excluding hyperprolactinemia, thyroid dysfunction, LOCAH, Cushing's , androgen secreting tumor

Differential Diagnosis

IDIOPATHIC HIRSUTISM

- Hirsutism in a woman with regular, ovulatory menstrual cycles. Circulating testosterone and androstenedione at the upper limit of the normal range. Mild form of PCOS ? Or Overactive skin conversion of weak precursor androgen ? treated with the same approach as that for hirsutism in PCOS

VIRILIZATION SYNDROMES

- Rapid onset of virilization or testosterone > 200 ng/dl.

  MRI to screen for an adrenal tumor and pelvic sonography to screen for an ovarian tumor

OVARIAN HYPERTHECOSIS

- Islands of luteinized, steroid-secreting stromal cells (stromal hyperthecosis) in the medullary portion of the ovary that are not associated with follicular structures
- Only a small subset of HA women
- Patients presents with virilization, a total testosterone > 200 ng/dl, a normal LH level, and marked IR and hyperinsulinemia.
- Not have significant suppression of circulating testosterone when treated with OCPs alone *
- treatment with a GnRH analogue (e.g., lupron depot) plus an OCPs often results in the normalization of circulating androgens

Treatment for PCOS

Treatment for PCOS may be general—directed at the underlying hormonal imbalance—or specific to a particular manifestation (e.g., hirsutism or infertility). PCOS should be treated, because it poses long-term risks of endometrial cancer, diabetes mellitus, and possibly cardiovascular disease

Patient's goal:

contraception or desiring pregnancy ?

- Hyperandrogneism
- Hirsutism
- Induction of ovulation
- Surgery
- ART

DM screening, Caloric restriction, Quit smoking

- It is appropriate to screen obsese PCOS women for glucose intolerance on a regular basis, once or twice a year.
- Caloric restriction that reduce BW will reduce abnormal glucose metabolism, reduce insulin resistance, reduce androgen production and restore ovulatory function
- 10-kg weight loss -> reduce 40% insulin level , reduce 35% testosterone level
- Treatment of PCOS in a woman who smokes cigarettes includes smoking cessation

Treatment of Hyperandrogenism and Hirsutism (regimens)

Weight Reduction (壹)

- Initial recommendation
- 5% ~ 7% over 6 Months
- Reduce free testosterone significantly
- Restore ovulation & fertility in over 75% patients

Hormonal suppression

- OCPs
- MPA
- GnRH-a
- Glucocorticoids

Treatment of Hyperandrogenism and Hirsutism

Steroidogenic enzyme inhibitors

- Ketoconazole

5a-reductase inhibitors

- Finasteride

Antiandrogens

- Spironolactone
- Cyproterone acetate
- Flutamide

Mechanical

Treatment of Hyperandrogenism and Hirsutism

Oral contraceptives (貳)

- Decrease ovarian and adrenal steroids
- Reduce hair growth < 10% ~ two thirds
- N.B. androgenicity of progestin
- Newer generation favored
- Iinsulin resistance may be enhanced
- Yasmin (drosperinone) provides good cycle control for women with PCOS, with an improvement in acne over 6 months but not in other symptoms of the syndrome. J Fam Plann Reprod Health Care. 2004 Jul;30(3):163-5

Treatment of Hyperandrogenism and Hirsutism

Medroxyprogesterone acetate (叁)

- **20-40 mg po qd or 150 mg im q6w~q3m**
- **Total and free androgen decreased**
- **Hair growth reduced ~ 90% patients**
- **SE: amenorrhea, headache, fluid retention, BW gain, depression, hepatic dysfunction**

GnRH-a (肆)

- **Leuporlide acetate im q28d**
- **Ovarian androgen selectively reduced**
- **Add back with OCPs or ERT not affect, nor potentiate, hirsutism-reducing effect**

Treatment of Hyperandrogenism and Hirsutism

Glucocorticoids (伍)

- **Dexamethasone 0.25 mg QN or QON**
- **Avoid dosage > 0.5 mg QN**
- **Maintain morning cortisol > 2ug/dl**
- **Suppress DHEAS to < 400 ug/dl**

Ketoconazole (陸)

- **Ketoconazole 200 mg QD**
- **Significantly reduce ASD, T and free T**

Treatment of Hyperandrogenism and Hirsutism

Finasteride (柒)

- Inhibit 5a-reductase, T rising
- 5-mg for BPH and 1-mg for male baldness
- Finasteride 5 mg QD similar effectiveness to spironolactone 100 mg QD
- 6 months of Rx with 7.5 mg QD
- Not prevent ovulation nor cause mense problem
- More effective while combined with OCPs
- Need contraception (feminize male fetus)

Treatment of Hyperandrogenism and Hirsutism

Spironolactone (捌)

- Aldosterone antagonist, K-sparing diuretic, T reduced
- 100 mg QD for 6 months, modest improvement in 70 ~ 80% patients
- Common dosage 25 ~ 100 mg BID
- Electrolysis commence after 9 ~ 12 Months Rx
- SE: metrorrhagia (~50% patients), mastodynia, scalp hair loss
- Contraindicated in renal insufficiency & hyperkalemia
- Mense return normal (60% patients) in amenorrheic
- Need contraception (feminize male fetus)

Treatment of Hyperandrogenism and Hirsutism

Cyproterone acetate (玫)

- Competitive inhibition at AR level
- Diane-35 (E.E. & cyproterone) / Climen
- **Reverse sequential regimen**

  Cypro 100 mg D5~D15 + E.E. 30~50 ug D5~D26 effective in severe hirsutism and acne, **tapered gradually**
- SE: decreased libido, irregular bleeding, nausea, headache
- **Not approved by FDA** (liver tumor in beagles)

Treatment of Hyperandrogenism and Hirsutism

Flutamide (拾)

- Inhibit nuclear binding of androgen
- 250 mg BID to TID
- Flutamide alone for 3 months -> hirsutism improved
- Flutamide combined with LD-OCPs -> significant drop in ASD, DHT, Gn
- SE: dry skin (50~75%) decreased libido, liver toxicity, breast tenderness, hot flashes etc
- Not routine option

Treatment of Hyperandrogenism and Hirsutism

Insulin sensitizer (拾壹)： Metformin (Glucophage)

- Target at postreceptor level
- Class B, no teratogenicity, reduced miscarriage rate
- Potential increased preeclampsia & PNM
- **500 mg TID** in obese PCOS -> **90%** ovulation rate
- SE: GI, lactic acidosis
- Contraindication: **elevated serum creatinine**

Step-by-step approach (Kim 2000 FS)

- **Primary intervention** : recommend and assist BW loss (5~10% BW)

  Orlistat 羅氏鮮 120mg PO TID : helpful

TABLE 1

A step-by-step approach to ovulation induction in women with PCOS.

Step	Approach
1	If BMI is elevated, loss of at least 5% of current body weight
2	Ovulation induction with clomiphene (+/− glucocorticoid if elevated DHEA-S)
3	Insulin sensitizer as a single agent
4	Insulin sensitizer in combination with clomiphene
5	Gonadotropin therapy
6	Insulin sensitizer in combination with gonadotropin therapy
7	Ovarian surgery
8	IVF

Kim. Insulin sensitizers for infertility. Fertil Steril 2000.

Treatment of Hirsutism

Mechanical（拾貳）

- Depilatory cream

  Eflornithine hydrocloride (DFMO) cream

  Percutaneous absorption and pharmacokinetics of eflornithine HCl 13.9% cream (Vaniqa)in women with unwanted facial hair. J Clin Pharmacol. 2001 41(9):972-8.

- Shaving
- Waxing / plucking
- Bleaching : 6% hydrogen peroxide
- Electrolysis
- Laser photoablation

PCOS and Ovulation Induction

- The most common cause of oligoovulation and anovulation
- It may be prudent to perform an endometrial biopsy before beginning ovulation induction
- Restoration of the release of one egg per cycle
- Avoid ovulation of more than two eggs to minimize the risk of OHSS and multiple pregnancy
- There is no fixed protocol
- Continue a successful regimen for at least 3 cycles

  (cycle fecundity of 20-25%)

Ovulation Induction in PCOS

Weight Reduction (壹)

- **Keep BMI < 27 kg/m2**
- **Weight loss 10 kg/m2 -> spontaneous ovulation 90% , spontaneous pregnancy 30%** (HR 1998, Clark et al, 13: 1502)

  Miscarriage rate dropped from 75% to 18%
- **Multidisciplinary efforts including dietitian, exercise program**
- **Pursue medical options in parallel with lifestyle change**

Ovulation Induction in PCOS

Clomiphene Citrate (貳)

- First-line intervention
- Functional HPO axis is required
- Antiestrogenic effect at endometrium and cervix
- 75%~ 80%~85% ovulate, 40%(35~50%) will conceive
- Most pregnancies occur during the first 6 months
- Should be promptly DC if with visual abnormalities
- Multiple gestation: 5% ~ 8% (mostly twins)
- Spontaneous abortion / teratogenicity not increased
- Low success in patients with IR and obesity
- Add dexamethasone 0.25 ~ 0.5 mg HS in patients with elevated DHEAS

Ovulation Induction in PCOS

Clomiphene Citrate (貳)

- Starting dosage **50 mg/d** begun in **D5 through D9**
- Or begun on D2 to D6
- Ovulation should be **documented** (urine LH kit or BBT)
- FDA recommend maximal dose 100 mg/d, but 11.8% ovulated at 150 mg/d, dosage of **up to 250 mg/d** is safe
- Ovulation occurs 5 to 10 days after last dose
- Intercourse **every other day for one week** beginning one or two days before anticipated ovulation or intercourse **for 3 days** beginning on the day of positive urine LH kit
- HCG could be used for triggering and timing (USG)
- Number of **CC treated ovulatory** cycle **not exceed 6**

Ovulation Induction in PCOS

Insulin sensitizer (參)

- **IR** in subset of PCOS patients with increased **BMI (>27kg/m2), W-T-H ratio > 0.85, waist > 100 cm, AN,** hyperinsulinemia and significant hyperandrogenism
- **Troglitazone** withdrawn due to 1:50000 fatal hepatic failure
- **Rosiglitazone** and **pioglitazone** safety and efficacy not fully assessed
- **Metformin for 12 weeks**: significantly decreased insulin, T, BMI, W-T-H ratio, hirsutism and acne
- **89% ~ 90% ovulated** after combination with CC
- Typically DC once pregnancy established

Ovulation Induction in PCOS

Insulin sensitizer (叁) Metformin regimen

- subset of PCOS patients:
  CC failure is indicated but not required
- Normal liver / renal function (Cr < 1.4 mg/dl)
- Metformin 500 mg QD with BF for 4 days

  Metformin 500 mg BID with BF/D for 4 days

  Metformin 500 mg with BF and 1000 mg with D for 4 days

  Metformin 1000 mg BID with BF/D thereafter
- May take 2 months before spontaneous ovulation
- Add CC 50-100 mg when full dose reached, if spontaneous ovulation not occur
- Keep ovulatory regimen for 3 ~ 6 cycles

Ovulation Induction in PCOS

Gonadotropin therapy (肆)

- Failed to ovulate or conceive after surgery or medical treatment with CC and metformin
- With or without down regulation
- Daily Gn injection and **close monitoring** with E2 and TVU by experienced physician
- **IUI often is recommended** using such intense regimen
- risk of OHSS and multiple pregnancy are significantly increased

Ovulation Induction in PCOS

Surgical treatment (伍)

Ovarian wedge resection (伍-1)

- **Decreased T, resumption of MC in 91%**
- **Suffer post-op intrapelvic adhesions**

LSC ovarian diathermy (伍-2)

- **Decreased T, DHEAS, ASD, LH, LH/FSH**
- **Spontaneous ovulation 73%, with CC 24%**
- **Cumulative PR 12 M: 54%; 18M:68%; 24M: 82%**
- **Median time to conception: 10.2 months**
- **IVF: higher OGPR (28.6% vs 7.3%), lower peak E2, and trends for decreased spontaneous abortion rate**

Table 1. Ovulation and pregnancy rates after different surgical treatment of polycystic ovarian syndrome.

Authors	Year	Technique	Ovulation rate (%)	Pregnancy rate (%)
Kistner	1969	Wedge resection	9/16 (56)	2/16 (12)
Buttram and Vasquez	1975	Wedge resection	NA	64/150 (43)
Weinstein and Polishuk	1975	Wedge resection	NA	38/57 (67)
Adashi et al	1981	Wedge resection	82/90 (91)	43/90 (48)
Daniell and Miller	1989	CO_2 + KTP*	84/85 (99)	48/85 (56)
Keckstein et al	1989	CO_2 laser*	15/19 (79)	7/19 (44)
Huber et al	1988	Nd:YAG laser*	5/8 (62)	0/8 (0)
Gurgan et al	1991	Nd:YAG laser*	7/10 (70)	4/10 (40)
Gjonnaess	1984	Electrocoagulation*	57/62 (92)	24/35 (80)
Greenblatt and Casper	1987	Electrocoagulation*	5/6 (83)	4/6 (66)
Armar et al	1990	Electrocoagulation*	17/21 (81)	11/21 (52)
Gurgan et al	1991	Electrocoagulation*	5/7 (71)	4/7 (57)
Naether et al	1993	Electrocoagulation*	90/104 (86)	73/104 (70)
Merchant	1996	Electrocoagulation	65/74 (88)	62/74 (84)
Tulandi et al	1997	Electrocoagulation*	30/34 (88.2)	– (70÷)

* Laparoscopy.
÷ Cumulative probability of conception at 12 months.

Table 2. The rate of adnexal adhesion at second-look laparoscopy.

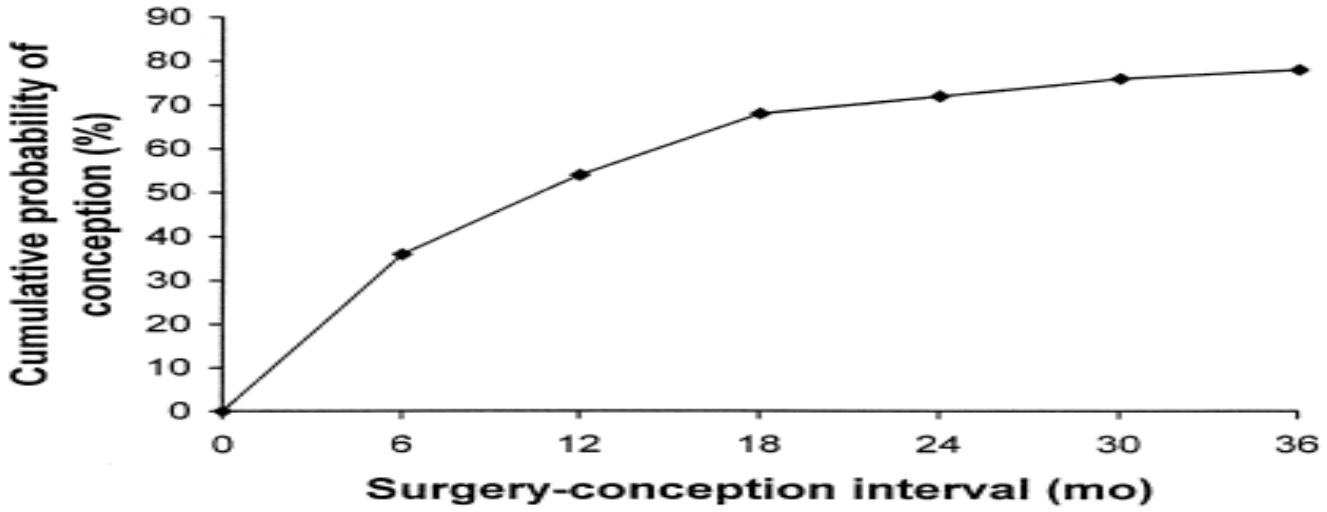
Authors	Year	Technique	Number of patients	Rate of adnexal adhesion (%)
Kistner	1969	OWR by laparotomy	16	16/16 (100)
Buttram and Vasquez	1975	OWR by laparotomy	173	59/59 (100)
Weinstein and Polishuk	1975	OWR by laparotomy	72	8/19 (42)
Toaff et al	1976	OWR by laparotomy	7	7/7 (100)
Adashi et al	1981	OWR by laparotomy	90	7/7 (100)
Portuondo et al	1984	OWR by laparotomy	12	11/12 (91)
Daniell and Miller	1989	CO_2 + KTP	85	0/8 (0)
Gurgan et al	1991	Nd:YAG laser	10	8/10 (80)
Weise et al	1991	Electrocoagulation	39	7/10 (70)
Gurgan et al	1991	Electrocoagulation	7	6/7 (85)
Dabirashrafi et al	1991	Electrocoagulation	31	2/12 (16)
Naether et al	1993	Electrocoagulation	133	7/26 (26)
Naether and Fischer	1993	Electrocoagulation	199	12/62 (19)

Reproduced from Al Took and Tulandi (1997, *Journal of the Society for Obstetricians and Gynaecologists of Canada* **19**: 721–729) with permission.

Laparoscopic treatment of polycystic ovaries with insulated needle cautery: a reappraisal

FIGURE 1

Cumulative probability of conception among 112 clomiphene-resistant anovulatory women with polycystic ovaries (median, 10.2 months).



Felemban. Insulated needle cautery. Fertil Steril 2000.

Ovarian Drilling by Diathermy vs Laser for Ovulation Induction in PCOS

Cochrane review by Farquhar C et al 2001

- OGPR: 6~12 Ms after OD vs 3~6 Ms Gn (OR 1.27 CI 0.77~2.09)
- OGCPR: 6Ms OD vs 6Ms Gn (OR 0.48 CI 0.28~0.81) *

  at 12Ms FU (OR 1.42 CI 0.84~2.42)
- PR: Laser vs Diathermy OD (OR 0.52 CI 0.52~3.42)
- MPR: Gn vs OD (OR 0.61 CI 0.17~2.16) *
- Adhesion formation: insufficient evidence
- There is insufficient evidence (except MPR) that either LOD or ovulation induction with gonadotrophins is superior for the outcomes of pregnancy and ovulation

Laparoscopic Ovarian Drilling

- No single technique proved superior
- Recently advocate diathermy by electrocautery
- Insulated needle insertion 100W cutting
- Coagulation with

  40W x 2 sec up to 10~15 punctures / ovary (Tulandi)
  30W x 5 sec up to 3~10 punctures / ovary (Amer)
- LR/NS 500 ml lavage: adhesion reduced 19.3->16.6%
- Risk of premature ovarian failure eg: 30Wx 2s x 20p

  - 0.4ml ovarian tissue /puncture / avoid if ov < 10 ml
- Impact of postsurgical adhesion?
  Indication for second-look laparoscopy?

Metformin 之臨床療效

India JRM 2004-05

- 66 Patients, 6 Months therapy
- 85.7% responder
- 62.3% responder achieve regular MC
- Significant reduction BMI, mean T, mean fasting insulin
- No significant improvement in hirsutis, acne, LH/FSH, Glucose/Insulin
- Better response in oligomenorrhea, high LH/FSH and low testosterone patients

LOD 之臨床療效

Chi-Mei Tainan, JAAGL, 2004-05

- **CC-R patients, 3 Months after LOD**
- **significant decreases in the free androgen index, total testosterone, LH, LH/FSH levels, significant increase in SHBG**
- **vascularization index and vascularization flow index of the intraovarian stroma significantly decreased**

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Height, weight, and motor–social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy

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BACKGROUND: We prospectively assessed growth and motor–social development during the first 18 months of life in 126 live births (122 pregnancies) to 109 women with polycystic ovary syndrome (PCOS) who conceived on and continued metformin (1.5–2.55 g/day) through pregnancy. METHODS: The lengths and weights of PCOS neonates were compared with gender-specific Centers for Disease Control and Prevention (CDC) infant data. Gestational diabetes (GD) and pre-eclampsia in women with PCOS were compared with 252 healthy women without PCOS who had ⩾1 live birth (262 live births). RESULTS: There were 101 out of 126 (80%) term (⩾37 gestational weeks) PCOS births, which was not significantly different ($P = 0.7$) from controls, 206 out of 252 (81.7%). There were two (1.6%) birth defects. GD occurred in nine out of 119 PCOS pregnancies (7.6%) versus 40 out of 251 (15.9%) controls, $P = 0.027$. The prevalence of pre-eclampsia did not differ in PCOS versus control pregnancies (4.1 versus 3.6%, $P = 0.8$). The birth length and weight of the 52 male neonates did not differ ($P > 0.05$) from those of CDC males; the 74 female neonates were shorter than CDC females (48.9 ± 5.4 versus 50.6 ± 2.7 cm, $P = 0.006$) and weighed less (3.09 ± 0.85 versus 3.29 ± 0.52 kg, $P = 0.04$). There were no systematic differences in growth between PCOS and CDC infants over 18 months. At 3, 6, 9, 12 and 18 months, of a potential 100% motor–social development score, scores (±SD) were 95 ± 13, 98 ± 8%, 95 ± 10, 97 ± 8 and 94 ± 16%; no infants had motor–social developmental delays. CONCLUSIONS: Metformin reduced development of GD, was not teratogenic and did not adversely affect birth length and weight, growth or motor–social development in the first 18 months of life.

Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study

S.B.Kjøtrød[1,3], V.von Düring[1] and S.M.Carlsen[2]

weeks with metformin (1000 mg bid) or placebo ending on the day of HCG injection. RESULTS: No differences were found in the primary end-points: duration of FSH stimulation 14.4 (13.1–15.7) versus 14.2 (12.6–15.7) days or estradiol on the day of HCG injection 6.8 (5.3–8.2) versus 7.6 (5.6–9.6) nmol/l in the metformin and placebo groups, respectively. The secondary end-points number of oocytes, fertilization rates, embryo quality, pregnancy rates and clinical pregnancy rates were equal. However, in the normal weight subgroup (BMI <28 kg/m^2, n = 27), pregnancy rates following IVF were 0.71 (0.63–0.79) versus 0.23 (0.15–0.31) in the metformin and placebo groups, respectively (P = 0.04). Overall clinical pregnancy rates were equal: 0.51 (0.34–0.68) versus 0.44 (0.27–0.62) in the metformin and placebo groups, respectively. However, in the normal weight subgroup, clinical pregnancy rates were 0.67 (0.43–0.91) and 0.33 (0.06–0.60), respectively (P = 0.06). CONCLUSIONS: Pre-treatment with metformin prior to conventional IVF/ICSI in women with PCOS does not improve stimulation or clinical outcome. However, among normal weight PCOS women, pre-treatment with metformin tends to improve pregnancy rates. Further studies in subgroups of PCOS women are required.

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Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study

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Table IV. Pregnancy rates and embryo quality, secondary end-points

Variable	Group	All				BMI <28 kg/m²				BMI ≥28 kg/m²			
		n	Mean/ no.	CI	*P*	*n*	Mean/ no.	CI	*P*	*n*	Mean/ no.	CI	*P*
Spontaneous pregnancies (no.)	Placebo	34	2			15	2			19	0		
	Metformin	35	4		0.4	18	4		0.5	17	0		1.0
Ova (no.)	Placebo	31	13.1	10.7–15.5		12	9.8	6.8–12.7		19	15.2	11.9–18.5	
	Metformin	30	13.9	11.1–16.7	0.7	14	13.1	8.9–17.3	0.3	16	14.6	10.4–18.9	0.9
Fertilization rate	Placebo	31	0.55	0.46–0.63		12	0.54	0.36–0.72		19	0.55	0.45–0.66	
	Metformin	29	0.53	0.45–0.60	0.5	13	0.50	0.40–0.61	0.4	16	0.54	0.42–0.67	0.8
Mean cleavage (only 2PN)	Placebo	28	5.3	4.9–5.7		10	5.2	4.3–6.2		18	5.4	5.0–5.8	
	Metformin	29	5.1	4.7–5.6	0.6	13	5.2	4.5–5.9	0.9	16	5.1	4.4–5.8	0.6
Sum ET and frozen embryos	Placebo	31	3.4	2.1–4.7		12	2.3	1.4–3.2		19	4.1	2.0–6.2	
	Metformin	30	2.6	1.8–3.4	0.7	14	2.4	1.5–3.4	0.6	16	2.7	1.3–4.1	0.3
Pregnancy rate(through IVF)	Placebo	32	0.47	0.39–0.55		13	0.23	0.15–0.31		19	0.63	0.55–0.71	
	Metformin	31	0.58	0.50–0.66	0.7	14	0.71	0.63–0.79	0.04	17	0.47	0.39–0.55	0.6
Clinical pregnancy rate	Placebo	32	0.44	0.36–0.52		13	0.23	0.15–0.31		19	0.58	0.50–0.66	
	Metformin	31	0.48	0.40–0.56	0.8	14	0.57	0.49–0.65	0.12	17	0.41	0.33–0.49	0.5
Live birth rate	Placebo	32	0.34	0.26–0.42		13	0.15	0.07–0.23		19	0.47	0.39–0.55	
	Metformin	31	0.39	0.31–0.47	0.7	14	0.43	0.35–0.51	0.12	17	0.35	0.27–0.43	0.5

Polycystic ovary syndrome in adolescence—a therapeutic conundrum

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The polycystic ovary syndrome (PCOS) often presents in adolescence with menstrual disorders, acne and hirsutism. The early diagnostic signs are sometimes dismissed as 'normal' changes of adolescence, and the opportunity to save the teenager from the stigmata of the syndrome is missed. The finding that the metabolic syndrome is a possible long-term sequela of PCOS now presents a challenge to make an early diagnosis, educate patients regarding the importance of weight control and exercise, and treat accordingly both symptomatically and prophylactically. The use of long-term insulin sensitizers, particularly metformin, for these purposes in adolescents is now the subject of an inter-disciplinary debate. Good, hard supportive data are not yet forthcoming but, as in the adult, the establishment of metformin treatment for the hyperinsulinaemic adolescent with PCOS may precede the evidence.

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Secondary forms of polycystic ovary syndrome

Table 1. Clinical, biochemical and ultrasonographic features in secondary causes of polycystic ovary syndrome[a,b]

Disease	Hirsutism	Anovulation	17-OHPG	E_2	Testosterone	Δ_4	DHEAS	LH	FSH	SHBG	IR	PCO
CAH [19]	+	+	↑↑	↑	↑	↑	↑	↑	→↓	→↓	↑	82%
Virilizing adrenal tumours [10,12,24]	+	+	↑	→↑	↑↑	↑	↑↑	⇌↑	→↓	→↓↑	→↑	25%
Virilizing ovarian tumours	++	+	⇌	↑↑	↑↑	↑↑	↑	→↓	→↓	↑	→	>80%
CS [34]	+	+	⇌	→↓	→↑	→↑	→↓↑	→↓↑	→↓	↓	↑	46%
Acromegaly [35]	+	+	⇌	→↓	⇌	⇌	⇌	→↓↑	→↓	↓	↑	NK
Hyperprolactinaemia [37]	+	+	⇌	→↓	→↑	→	↑	→↓	→↓	→↑	→↑	50–67%
Glucocorticoid resistance [40]	+	+	↑	→↑	↑	↑	↑	→↓↑	→↓	→↑	→↓	NK
Altered cortisol metabolism [42–44]	+	+	→	→↑	→↑	→↑	→↑	→↑	→↓	→↑	→↓	NK
Severe forms of IR [14]	++	++	→	→	↑	↑	→↑	→↑	→	↓	↑↑	80–100%
T2DM [48,49]	+	+	→	→	→↑	→↑	→	→↑	→	→↓	↑	68–82%
Gestational DM [50,51]	−	−	↑	↑↑	→↑	→	→	↓	↓	↑↑	↑	30–50%

[a](+), present; (++), present in severe form; (−): absent; (→), normal; (↑), raised; (↓), decreased.

[b]Abbreviations: 17OHPG, 17-hydroxyprogesterone; Δ_4, androstenedione; CAH, congenital adrenal hyperplasia; CS, Cushing's syndrome; DHEAS, dehydroepiandosterone sulfate; DM, diabetes mellitus; E_2, estradiol; FSH, follicle-stimulating hormone; IR, insulin resistance (lipoatrophic diabetes, leprechaunism, Rabson–Mendenhall, Kahn types A and B insulin resistance); LH, lueinizing hormone; PCO, polycystic ovaries; NK: not known; SHBG, sex hormone-binding globulin; T2DM, type 2 diabetes mellitus.

Review of nonsurgical and surgical treatment and the role of insulin-sensitizing agents in the management of infertile women with polycystic ovary syndrome

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Results. For obese PCOS women weight loss of >5% of pretreatment weight restores menstrual regularity in 89%, of whom 30% achieved spontaneous pregnancy. It was estimated that 75–80% of anovulatory PCOS women will respond to clomiphene citrate (CC) and 35–50% will achieve pregnancy. For CC-resistant PCOS women (20–25%), CC + metformin (1.5 g/day) for 3–6 months has a 70% chance of restoration of regular menses and ovulation, and a 23% chance of pregnancy. Laparoscopic ovarian drilling (LOD) can be offered to CC-resistant PCOS women. There was no statistically significant difference in the ovulation rate following LOD with electrocoagulation and laser [83% vs. 77.5%; odds ratio (OR) 1.4; 95% CI 0.9–2.1], while there was a significantly higher cumulative pregnancy rate at 12 months after surgery (65% vs. 54.5%; OR 1.5; 95% CI 1.1–2.1). *Conclusion.* Diet and exercise followed by CC should be used for nonsurgical ovulation induction. For CC-resistant PCOS women, metformin may be included in a stepwise approach before a surgical approach. LOD with electrocautery is superior to laser drilling and gonadotropin therapy.