Surgical treatment of PCOS
2017 status

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Disclosures

Have both served on Advisory Boards and given lectures for

- Teva
- Bayer
- MSD
Are PCO oocytes "inferior"?

Professor Gab Kovacs
FACULTY DISCLOSURE FORM
1st Meeting on the Oocyte: from Basic Research to Clinical Practice

(Barcelona, Spain, November 3-6, 2011)

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Presenter/Faculty Name

Title of Presentation(s)

Date of Presentation(s)
Outline

• History
• Early results and complications
• Superseded by medical treatment
• Surgical treatment – revisited
• Methods/ results/ complications
• Cost comparison
• Advantages
• 2017 Regimen for OI in PCOS
Stein- Leventhal Syndrome
Polycystic Ovarian Syndrome
PCOS

• Irregular menses
• Obesity
• Symptoms of androgen excess
Figure 1. Irving Freiler Stein (1887 – 1976).

Figure 2. Michael Leo Leventhal (1901-1971).
Stein-Leventhal Syndrome

- 1935: Dr. Irving Stein and Dr. Michael Leventhal published the article:
  - Seven women with amenorrhea, hirsutism, obesity, and polycystic appearing ovaries

AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES

Irving F. Stein, M.D., and Michael L. Leventhal, M.D.,
Chicago, Ill.

(From Michael Reese Hospital and Northwestern University Medical School)

According to leading authoritative works on gynecology, the bilateral polycystic ovary is most commonly found in association with uterine bleeding (Fig. 1). This association has been recognized by the medical profession and is not infrequent in occurrence. Endometrial hyperplasia, multiple follicle cysts with granulosa cell lining, and a notable absence of corpora lutea in the ovary are the significant pathologic findings in such cases. The bleeding in these patients is readily explained by the fact that the increase in number of follicles lined by granulosa cells produces an excess of secretion of estrogenic hormone.

According to the same authoritative works, little or no mention is made of bilateral polycystic ovaries accompanied by amenorrhea, and inasmuch as we have encountered a series of cases exemplifying the latter conditions, we desire to present the results of our study of them.

Cyst formation in the follicular apparatus of the ovary is very common and is regarded to some extent as a physiologic process. When these structures are visible to the naked eye, they are regarded as cysts; when not, they are called follicles. When this process becomes excessive, persistent or progressive, the ovary becomes enlarged, tense, tender and painful, and produces what has been termed “cystic degen-

*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.
Surgical treatment of PCOS - history

- By 1964 Stein reported on 108 women who had BOWR over 34 years
  - Return of Cycles in 95%
  - 71 of 83 who wished to conceive did

- Confirmed by Adashi 1981
  - Ovulation in 91%
  - Crude conception rate 47%
  - But 7/10 had adhesions when re-investigated
JOURNAL ARTICLE

Stein-Leventhal Syndrome

Geoffrey Chamberlain and Carl Wood

The British Medical Journal
Vol. 1, No. 5375 (Jan. 11, 1964), pp. 96-98

Published by: BMJ
wedge resection of the ovaries has been preferred as the method of treatment in this series. Operation has the added advantage of excluding the presence of a small masculinizing tumour which could not have been diagnosed otherwise (Siganos, 1961).

At laparotomy a simple wedge of one-third to one-half of each ovary was removed, the cut extending into the hilus; through this incision the numerous subcapsular cysts were punctured. If the ovary was greatly enlarged more tissue was removed so that the reconstituted organ was approximately normal in size. The defect was closed with a catgut suture.

Other forms of ovarian surgery which have been reported to be effective are stripping of the capsule, splitting of the ovaries, or a simple cut into the ovarian substance. Some leave the ovarian wedge everted in order to assist future ovulation (Bailey,
Surgical treatment of PCOS

- Wedge Resection (Stein & Leventhal) in 1935

- BUT
  - Availability of Clomiphene (Greenblatt 1961)
  - Availability of urinary FSH and pituitary FSH (Gemzell 1960)
Complications of BOWR

- **Toaff et al (1976)** laparoscopy on 7 women who failed to conceive after BOWR
  - Found extensive adhesions peritubal/pelvic
- Agreed with **Kistner (1968)** "To relegate surgical approach to a minor position in patients with Stein-Leventhal syndrome"
Laparoscopic approach

• 1972- First report of laparoscopic biopsy and cauterity using Palmar forceps (1972 Cohen J)
  – Several reports from France spontaneous pregnancies after ovarian biopsy/cauterity

• It was noted that biopsy often resulted in subsequent ovulation
Reports of ovarian biopsy/cautery resulting in pregnancy

- Sykes & Ginsburg 1972  70 cases 63% PR
- Minntz & deBrux 1971  157 cases 44% PR
- Tescher et al 1972  85 cases 23% PR
- Cohen & Chassagnard 1974  92 cases 23% PR
- Devaut 1977  32 cases 33% PR
- Scarpa & Malaponte 1978,  29 cases 55% PR
- Fouquet 1978  100 cases 50% PR
Surgical treatment revisited

- **Gjonnaess (1984)** - 62 women treated by ovarian unipolar diathermy
- **Campo et al (1983)** - laparoscopic resection of ovarian fragments in 12 women
- **Greenblatt & Casper (1987)**
- **van der Weiden and Alberda (1987)**
- **Kovacs et al (1991)**
Gjönnaess H.
Polycystic ovarian syndrome treated by ovarian electrocautery through the laparoscope

- 62 women treated by cautery
- 92% ovulated within 3 months
- 51 (86%)- regular menses
- 24 of 35 (69%) who wanted to conceived
- Upto 80% when CC used post cautery
Surgical treatment revisited

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- **Campo et al (1983)** - laparoscopic resection of ovarian fragments in 12 women
- **Greenblatt & Casper (1987)**
- **van der Weiden and Alberda (1987)**
- **Kovacs et al (1991)**
Treatment of anovulation due to polycystic ovarian syndrome by laparoscopic ovarian electrocautery.


• Our experience of ovarian electrocautery for the treatment of polycystic ovarian syndrome (PCOS) in ten women is described.

• We found that nine responded favourably, either ovulating spontaneously or becoming more responsive to ovulation induction.

• There was a significant and persistent fall in serum testosterone levels, and a transient fall with subsequent rise in inhibin.

• We recommend that laparoscopic ovarian electrocautery is considered as an alternative to ovulation induction with gonadotrophins, in women with PCOS who fail to respond to clomiphene citrate.
Gjønnaess H.

Ovarian electrocautery in the treatment of women with polycystic ovary syndrome (PCOS). Factors affecting the results.


- Between 1979 and 1991, Aker University Hospital
- 252 PCOS treated
  - 92 % ovulated
  - 84% pregnant
  - If CC added 89%
- Less likely in obese women to ovulate
- Once ovulating BMI not significant
Methods of laparoscopic ovarian drilling

- Unipolar diathermy - *Corson needle is best*
- Bipolar diathermy - *no suitable instrument*
- Carbon dioxide laser - several craters
- Other lasers
  - Argon, YAG, KTP
Trans-vaginal approaches


- Transvaginal bipolar hydro-laparoscopic drilling (cautery) - Gordts et al, 2009
  - 39 PCOS patients - failed OI
  - 10-15 holes / ovary
  - 25/32 became pregnant (mean 7.2 months)
- Confirmatory study from Naples (Giampaolino Gynecol Endocrinol, 2017) - 123 infertile PCOS women;
  - 82% ovulated within 6/12
  - 28 patients conceived (Pregnancy rate 70.1%)

- Ultrasound guided ovarian needle drilling (UTND)
- 163 CC resistant women
- Randomised lap cauterity or UTND
- Similar results
Bilateral or unilateral?

- First suggested by Balen and Jacobs 1994 (10 women; 4 drills to one ovary would suffice)
- Supported by Roy et al 2009, (5 drills either uni or bilateral)- no difference in 44 women
- Also Youssef and Atallah 2007 (87 women)

Ovulation, pregnancy and miscarriage rates similar
Mechanism of action of Surgical treatment

- Decreased crowding of cortex
- Inhibitory substance from capsule destroyed
- Reduced negative/increased positive feedback
- Transient reduction in inhibin
- Removal of androgenic fluid
- Restoration of putative gonadotrophin surge attenuating factor
- Many theories none proven
Laparoscopic “drilling” or laser for ovulation induction in anovulatory PCOS

- Cochrane review, Farquhar et al, 1999
  - 14 trials identified
  - 8 included (7 RCT)
- Main outcomes measures:
  - Ovulation rate,
  - Pregnancy Rate
- Secondary outcomes:
  - Miscarriage rate, multiple pregnancy, OHSS
Conclusions
Cochrane review 1999

• The value of ovarian drilling as primary treatment is undetermined
• For Clomiphene resistant; insufficient numbers to show difference on PR, Ovn Rate
• None of the modalities of drilling showed any advantage
• Multiple pregnancy rates are reduced in pregnancies after ovarian drilling
Laparoscopic “drilling” or laser for ovulation induction in anovulatory PCOS

- Cochrane review, Farquhar et al, 2001
  - 15 trials identified
  - 6 included (7 RCT)

- Main outcomes measures:
  - Ovulation rate,
  - Pregnancy Rate

- Secondary outcomes:
  - Miscarriage rate, multiple pregnancy, OHSS
Conclusions
Cochrane review 2001

• Insufficient evidence for difference in CPR
• Multiple pregnancy rates are reduced in pregnancies after ovarian drilling
Laparoscopic “drilling” or laser for ovulation induction in anovulatory PCOS

• Cochrane review, Farquhar et al, 2005
  – 15 trials identified
  – 6 included (7 RCT)
• Main outcomes measures:
  – Ovulation rate,
  – Pregnancy Rate
• Secondary outcomes:
  – Miscarriage rate, multiple pregnancy, OHSS
Conclusions
Cochrane review 2005

• No difference in ongoing PR
• Multiple pregnancy rates are reduced in pregnancies after ovarian drilling
• Concerns about long term effects on function
Laparoscopic “drilling” or laser for ovulation induction in anovulatory PCOS

• Cochrane review, Farquhar et al, 2007
  – 16 trials identified
  – 9 included (7 RCT)

• Main outcomes measures:
  – Live birth
  – Ovulation rate,
  – Pregnancy Rate

• Secondary outcomes:
  – Miscarriage rate, multiple pregnancy, OHSS
Conclusions
Cochrane review 2007

• No difference in CPR RR= 1.04
• No difference in LBR
• No difference in miscarriage rates
• Multiple pregnancy rates are reduced in pregnancies after ovarian drilling
Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial 

Bayram N et al BMJ 2004;328:192
Comparative effectiveness of 9 ovulation-induction therapies in patients with clomiphene citrate-resistant polycystic ovary syndrome: a network meta-analysis.
Yu et al, Zhengzhou, PRC

- Network meta analysis 26 RCTs, 2722 women
- Included CC, Metformin (MET), Letrozole (LET), FSH, hMG, Met+LET, CC+MET, Unilateral (ULOD) and bilateral (BLOD) drilling

Difficult to interpret but
- hMG higher PR than BLOD or ULOD or CC
Advantages of laparoscopic ovarian drilling

- No major surgery
- Adhesions less frequent
- Once only treatment for several tries
- No ongoing monitoring
- No increase in multiples
- May convert Clomiphene resistance to responsive
- Decreases gonadotrophin requirements
- Decreased abortion rate in subsequent IVF
Complications of laparoscopic ovarian cautery

Intraoperative

• Anaesthetic
• Gas complications
• Trauma or heat trauma to viscus or vessel
• Bleeding

Postoperative

• Adhesions
• Infection
• Ovarian atrophy
• Premature menopause
  • AMH lower post surgery (Amner et al metanalysis of 442 studies in 2017)
• Failure to respond
• 6 or 12 punctures

• Adhesion formation was detected in 54 of the 90 women (60%) and in 83 of the 180 ovaries treated (46%). Not different in 6 or 12 groups.

• The incidence of ovarian adhesion formation after LOD was high, and their extent and severity was not influenced by the number of ovarian punctures.

- Four articles that specifically reported on the ovarian reserve tests
  - Day 3 FSH
  - Inhibin B
  - Ovarian volume
  - AFC

Before and after cautery

- No concrete evidence of a DOR or POF associated with LOD in women with PCOS
“Show me the money”
Cost comparison
(Australian private system. Kovacs et al 2002)

• The mean of 15 cycles of OI with gonadotrophins was compared to laparoscopic cautery costs
• Included cost of hormones, biochemistry and medical/ surgical costs
• Cost ovarian cautery $A 1180
• Cost of typical cycle OI
  – With HMG $A 1401
  – With rFSH $ 1800
• surgical treatment slightly cheaper
Long-term follow-up of laparoscopic electrocautery of the ovaries versus ovulation induction with recombinant FSH in clomiphene citrate-resistant women with polycystic ovary syndrome: an economic evaluation.  


Economic analysis on 159 randomized women

- 71 of 83 in cautery
- 69 of 85 in FSH group CONCEIVED

• Costs

- Cautery Eu 11,176 (9689-12549)
- FSH Eu 14423 (12239-16606)

• Electrocautery of the ovaries results in significantly lower costs per live birth
An economic evaluation of laparoscopic ovarian diathermy versus gonadotrophin therapy for women with clomiphene citrate-resistant polycystic ovarian syndrome.

Farquhar CM. Curr Opin Obstet Gynecol. 2005

- In the New Zealand trial the costs of a live birth were one-third lower in the group that underwent laparoscopic ovarian diathermy compared with those women who received gonadotrophins (NZ$19,640 and 29,836, respectively).
Can we predict who will respond?

- The role of AMH assay:

  The value of measuring anti-Mullerian hormone in women with anovulatory polycystic ovary syndrome undergoing laparoscopic ovarian diathermy.

  Amer SA¹, Li TC, Ledger WL. (Nottingham) Hum Reprod. 2009 Nov;24:2760-6
Value of AMH assay

- Women with PCOS undergoing LOD (n = 29) or receiving clomiphene citrate (n = 18)
- Before, 1 week, and 3 and 6 months after LOD
- Women who ovulated after LOD (n = 24) had a significantly (P = 0.032) lower pre-operative AMH [5.6 (1.0-21.0) ng/ml] vs [9.0 (6.1-17.1) ng/ml]
- AMH > or = 7.7 ng/ml was associated with a reduced chance of ovulation Following LOD, the median AMH concentration significantly (P = 0.003) decreased to 4.7 (0.3-15.1) ng/ml
Can we predict who will respond?


Preoperative luteinizing hormone levels predict the ovulatory response to laparoscopic ovarian drilling in patients with clomiphene citrate-resistant polycystic ovary syndrome.
Role of preoperative LH level

• 40 infertile Japanese women with CC-resistant PCOS who received LOD using argon-beam electrocoagulation

• Ovulation occurred in 33 (83%) patients; pregnancy occurred in 22 patients (55%).

• Preoperative serum LH levels were significantly higher in women who ovulated after LOD
Suggested management of anovulation in PCOS

1. Diet
2. Clomiphene citrate (+/- glucocorticoid – DHEAS)
3. Metformin
4. Metformin + clomiphene
5. Ovarian cautery (+/- CC; +/- Metformin)
6. FSH
7. IVF
RCOG Guidelines : Grade A

Laparoscopic ovarian drilling with either diathermy or laser is an effective treatment for anovulation in women with clomiphene-resistant PCOS. Value of LOD as primary treatment of anovulatory PCOS is undetermined. No difference in OR or PR when compared to gonadotropins (level 1)
Women with CC resistant PCOS may be offered LOD because it is as effective as gonadotrophin treatment and is not associated with a risk of multiple pregnancy. [A]

LOD is now well established as the treatment of first choice for CC-resistant women with PCOS (Dutch Health Council guideline, 2003; NICE, 2004),
5. **Laparoscopic ovarian drilling** may be considered in women with Clomiphene-resistant PCOS, particularly when there are other indications for laparoscopy. (I-A)

Surgical risks need to be considered in these patients. (III-A).

6. **In vitro fertilization** should be reserved for women with PCOS who fail gonadotropin therapy or who have other indications for IVF treatment (II-2A).
Further reading

• For health professionals
  – Polycystic Ovary Syndrome (2nd Edition)
    *Cambridge University Press*
    *Edited by Gabor T Kovacs and Rob Norman*

• For consumers
  – A Patient’s Guide to the Polycystic Ovary
    *Hill of Content*
    *by Gab Kovacs and Jane Smith*