Optimizing Ovulation and Fertility in the Polycystic Ovary Syndrome (PCOS)

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OBJECTIVES

At the conclusion of the presentation, the participant should be able to…

1. Understand the impact of PCOS on anovulatory infertility.
2. Discuss the potential benefits of lifestyle changes on ovulation in PCOS women.
3. Describe ovulation induction options in PCOS.
   - Clomiphene citrate
   - Letrozole
   - Adjuncts & new protocols (metformin, glucocorticoids, CoQ10, myo-inositol)
4. Discuss ovarian drilling in PCOS
5. In vitro fertilization

DIAGNOSIS OF PCOS:
Historical Perspective

- Originally described by Drs. Irving Stein and Michael Leventhal at Rush Medical College in 1935.
- Case series of 7 patients (4 obese) with amenorrhea, hirsutism and enlarged, polycystic ovaries on exploratory laparotomy.
- On ovarian biopsy, thickened ovarian tunica thought to impair ovulation.

DIAGNOSIS OF PCOS: (NIH/NICHD Conference, 1990)

- Clinical hyperandrogenism/hyperandrogenemia
- Ovulatory dysfunction
- Exclusion of other disorders:
  - non-classic adrenal hyperplasia
  - androgen secreting tumors
  - hyperprolactinemia/thyroid disorder
- Presence of polycystic-ovaries was felt to be suggestive, but not diagnostic of PCOS

Zawadski & Dunaif, 1992

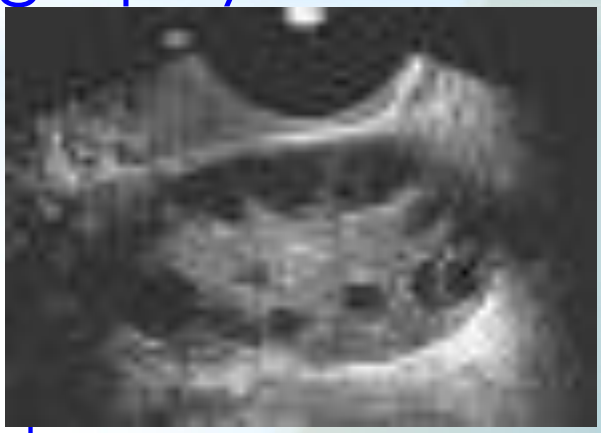
DIAGNOSIS OF PCOS (Rotterdam Criteria, 2003)

Presence of at least 2 of 3 criteria:

- Clinical and/or biochemical signs of hyperandrogenism
- Oligo and/or anovulation dysfunction
- Polycystic ovaries on ultrasonography

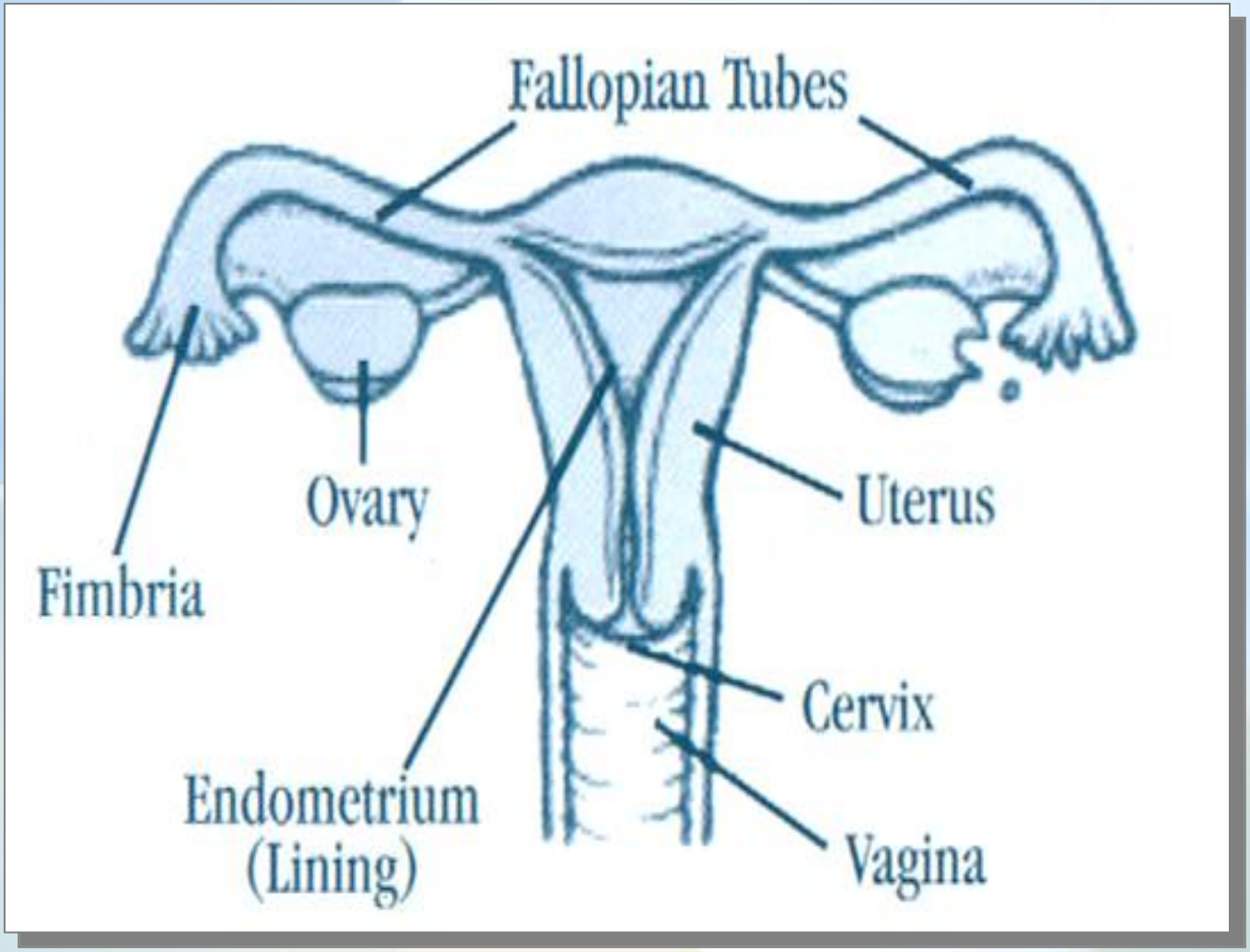
and

- Exclusion of other disorders:
  - non-classic adrenal hyperplasia
  - androgen secreting tumors
  - hyperprolactinemia/thyroid disorder

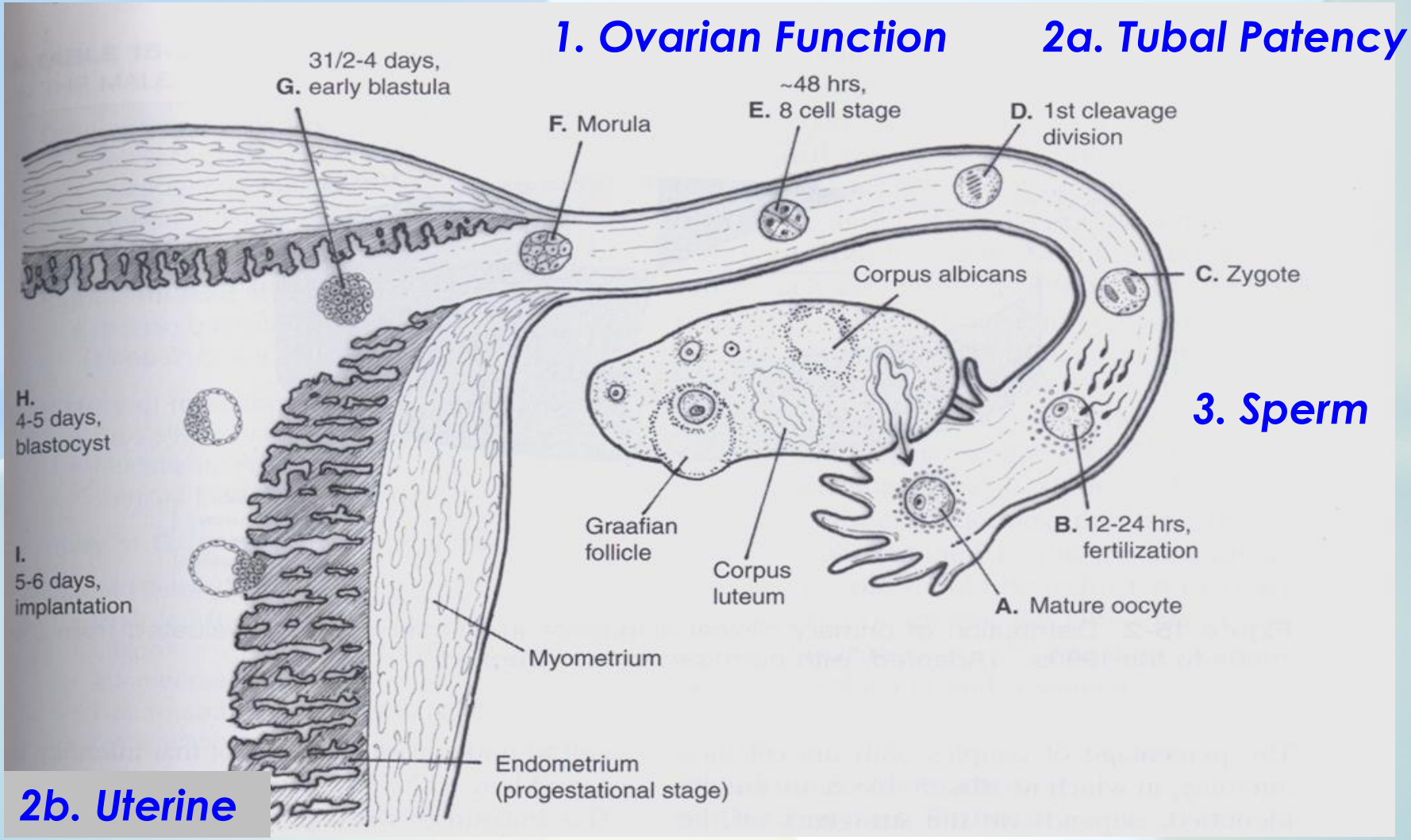


Fertil Steril. 2004;81:19.

Fertility 101: The Basics



Basic Fertility 101

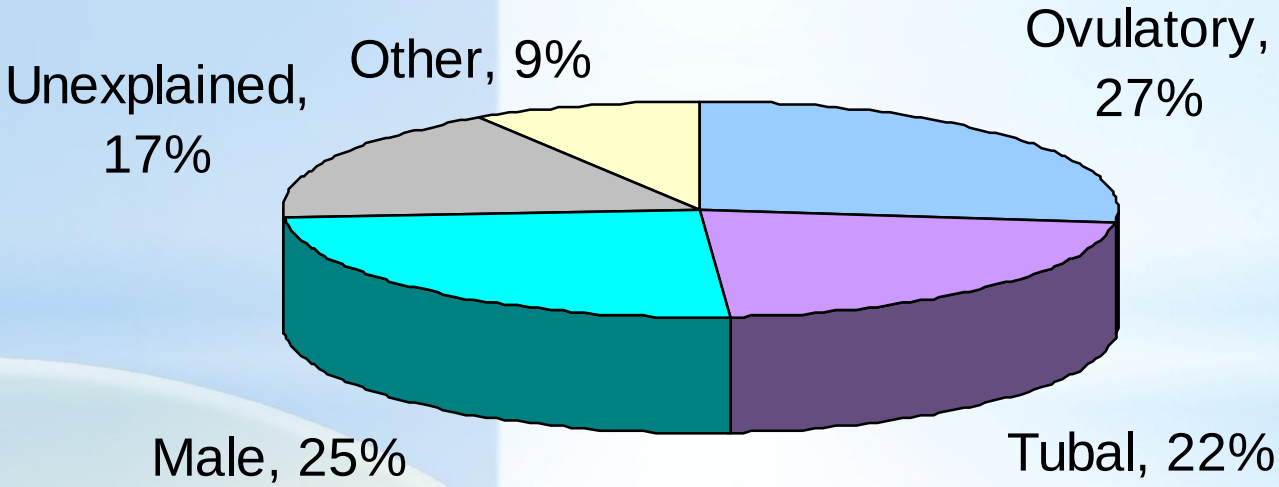


Adapted from Barbieri RL, Reproductive Endocrinology 4th ed. 1999; 562.

Definitions of Infertility

- Infertility : inability to conceive after 12 months of regular intercourse in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older
- Affects approximately 15% of reproductive aged couples in the United States
- History of risks factors should prompt earlier evaluation:
  - Irregular menses
  - Previous pelvic surgery/ injury
  - Previous cancer treatment (chemo, radiation)
  - Significant pain, mass

Causes of Infertility

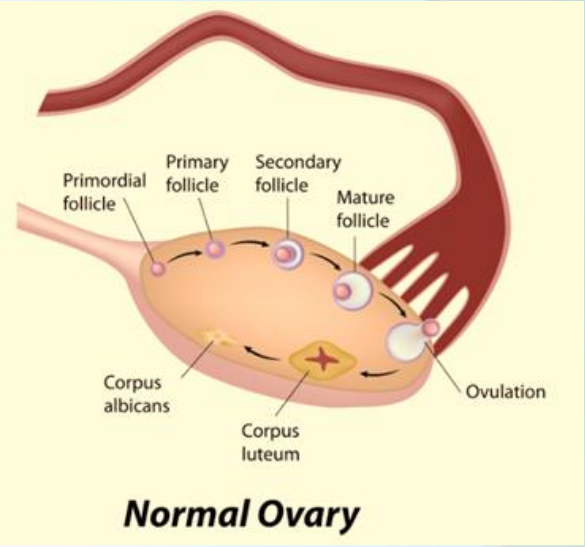


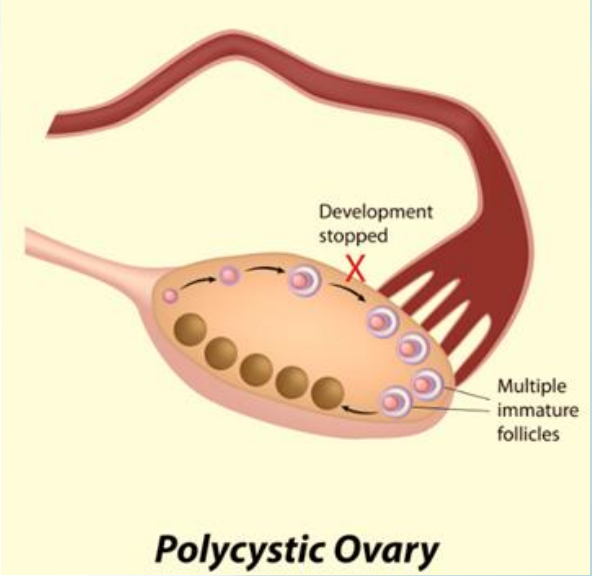
Collins et al., *Can Med Assoc J* 1

Collins et al., *Can Med Assoc J* 1984; 130:269.

PCOS and Anovulatory Infertility

- ***PCOS is the most common cause of anovulatory infertility***
- Multiple etiologies of ovulatory dysfunction in PCOS
  - Excess intraovarian 5α-reduced androgens inhibit granulosa cell aromatase and inhibit follicle growth
  - Elevated insulin levels worsen follicular arrest
    - Stimulates increased theca cell androgen
    - Promotes premature luteinization , arresting granulosa cell proliferation and follicle growth
  - Overproduction of AMH by granulosa cells antagonizes FSH action in small follicles





Prevalence of Infertility in PCOS

	Percentage frequency of symptom or sign			
	Balen et al[44]	Franks[14]	Goldzieher et al[53]	
	n = 1741 (%)	n = 300 (%)	n = 1079 (%)	No. of cases[a]
Menstrual cycle disturbance				
Oligomenorrhoea	47	52	29	547
Amenorrhoea	19	28	51	640
Hirsutism	66.2	64	69	819
Obesity	38	35	41	600
Acne	35	27	–	–
Alopoecia	6	3	–	–
Acanthosis nigricans	3	<1	–	–
Infertility (primary/secondary)	20	42	74	596

Hart et al., Best Pract Res Clin Ob Gyn 2004;18:671.

Economic impact of Evaluating and Treating PCOS-Related Infertility

- Approximately 33-75% of PCOS women report having infertility
- An estimated 50% of PCOS women actively seen infertility services during their reproductive years
- Using standard treatment algorithms in the United States, the cost per live pregnancy in varies from $5,600 - $9,600 in 1997
- Average cost per pregnancy in 2005, adjusted for inflation, was approximately $8000
- ***Average annual cost of infertility care for PCOS***

  ~ $533 Million not including increased risk of pregnancy complications (GDM, PET, PIH, SAB)

Azziz et al., JCEM 90(8): 4650-4658

LIFESTYLE MODIFICATION: Preconceptional Counseling

- Preconceptional counseling and lifestyle modification should take precedence
- Identify risk factors
  - Folate supplementation
  - Insulin resistance and diabetes
  - Blood pressure
  - Genetic screening
  - Vitamin D levels
  - Alcohol intake
  - Tobacco use
- ***Opportunity for patient optimization: the goal of counseling is to identify and ideally correct risk factors prior to starting treatment***

LIFESTYLE MODIFICATION: Weight Loss in Obese PCOS Patients

- Approximately 50% of PCOS women are overweight to obese
- Obese women demonstrate greater PCOS severity:
  - Worsened ovulatory dysfunction
  - Greater severity of hirsutism, insulin resistance
  - Lower rates of spontaneous or unassisted pregnancy
  - Greater risk of pregnancy complications
- Weight loss is considered *first-line* treatment in obese PCOS women seeking pregnancy
- Multifaceted approach: behavioral counseling, diet, exercise, sometimes medical and surgical

Lifestyle Modification: Weight Loss

- Loss of as little as 5% initial body weight results in improved metabolic parameters:
  - Reduced total cholesterol and triglyceride levels
  - Reduced LDL cholesterol
  - Reduced fasting and post-load insulin levels after 2-hr OGTT
  - Increased SHBG
  - Decreased testosterone levels
  - Improved menstrual regularity
  - Increased ovulatory cycles

Hoeger K, Best Pract Res Clin Endocrinol Metab. 2006; 20:293.

OVULATION INDUCTION IN PCOS: Diet

- Case series of 33 anovulatory overweight patients with PCOS enrolled in 1200 kcal/d diet
- >5% reduction in initial body weight resulted in:
  - Significant reduction in WHR, BMI
  - Reduction in ovarian volume and #microfollicles
  - 67% had resumption of regular cycles
  - 56% had spontaneous ovulation
  - 10 spontaneous pregnancies occurred (30%)

Crosignani et al., Hum Reprod 2003;18:1928.

OVULATION INDUCTION IN PCOS: Diet

- Case series of 14 obese PCOS patients treated for approximately 8-mo with hypocaloric diet
- >5% reduction in initial body weight resulted in:
  - 35% decrease in plasma testosterone levels
  - Significant improvement in AN and hirsutism
  - 40% had significant improvement in menstrual regularity
  - Four pregnancies occurred

Pasquali et al., JCEM 1989;68:173.

OVULATION INDUCTION IN PCOS: Diet

- RCT of 35 obese PCOS patients studied
- Short term effects of two energy-restricted diets:
  - High protein (30% protein, 40% carbs, 30% fat)
  - High carb (15% protein, 55% carbs, 30% fat)
- Of 26 women completing study:
  - No difference between the two diets in mean weight loss, androgen levels, glucose metabolism, and leptin levels
  - High prevalence of menstrual bleeding during diet (54%)

Stamets et al., Fertil Steril 2004;81:630.

OVULATION INDUCTION IN PCOS: Diet

- Disagreement on optimal diet for PCOS women
- Recommended diet for obese PCOS women is to one that patient can follow to achieve ≥ 5% weight loss
- Goal is hypocaloric (with ~500 kcal/day deficit)
- Recent data suggests hypocaloric diet with reduced glycemic load improves androgen levels, metabolic changes, cardiovascular risk factors markers

Mehrabani et al., 2012; Marsh et al., Am J Clin Nutr 2010

OVULATION INDUCTION IN PCOS: Exercise

- Exercise reduces insulin resistance and visceral fat
- May increase muscle cell metabolism and insulin sensitivity
- Shown to improve menstrual irregularity and restore ovulation in obese PCOS patients
- Duration of type of exercise not important: just do it!

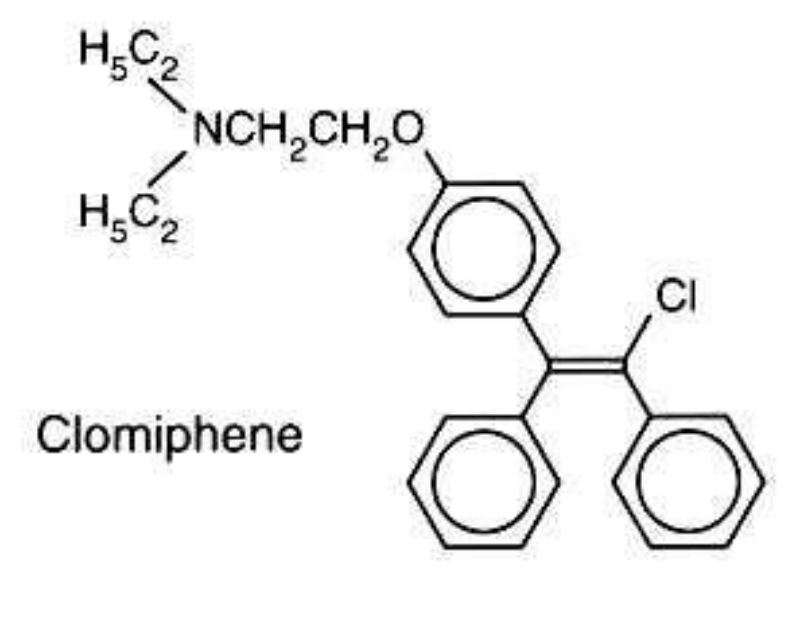
Panidis et al., Endocrine 2013. 44:583-590

OVULATION INDUCTION IN PCOS: Exercise

- Exercise can restore menstrual regularity in 60%; ovulation in 50%; and pregnancy in 35% of PCOS patients with irregular ovulation!
- No guidelines for type, frequency , intensity or duration.
- Greatest metabolic improvement seen in obese PCOS women seen after at least 30 mun daily for at least 5 days per week; in combination with diet.

Panidis et al., Endocrine 2013. 44:583-590

MEDICAL OVULATION INDUCTION: Clomiphene citrate



- First line for ovulation induction in PCOS
- Nonsteroidal E-R agonist-antagonist
- Prolonged binding and depletion of E-R in hypothalamus
- Increases GnRH pulse amplitude
- Increases FSH, LH secretion

MEDICAL OVULATION INDUCTION: Clomiphene citrate

- Available as 50-mg tablets
- Empirically administered starting at 50mg x 5d starting days 2-5 after spontaneous or induced menses
- Increase dose by 50-mg until ovulation
- FDA-approved for up to 150-mg QD x 5d, for up to 3 cycles
- 7-10% multiple gestation rate

MEDICAL OVULATION INDUCTION: Clomiphene citrate

- Majority of women with anovulatory infertility ovulate in response to clomiphene
- Approximately 70% ovulate in response clomiphene; of responders ~70% respond to 50 – 100 mg doses
- Up to 30% remain anovulatory
- Only 50% of ovulatory responders conceive

Garcia et al.,Fertil Steril 1977;28:707.

Predictors of Poor Response to Clomiphene

- Obesity and higher body mass index (BMI)
- Higher androgen/ testosterone levels
- Increased ovarian volume (measured by ultrasound)
- Severity of menstrual abnormality
- Severity of insulin abnormality
- Older age
- Higher AMH levels

INSULIN RESISTANCE & PCOS

- Hyperinsulinemic insulin resistance appears to affect 25-70% of women with PCOS
- PCOS is associated with a profound form of insulin resistance that is intrinsic to the syndrome, independent of obesity
- Hyperinsulinemic insulin resistance occurs in obese and nonobese women with PCOS
- Appears related to a post-receptor defect

Dunaif et al., Diabetes 1989; 38:1165.

Ciaraldi et al., JCEM 1992; 75:577.

Diabetes and IGT in PCOS

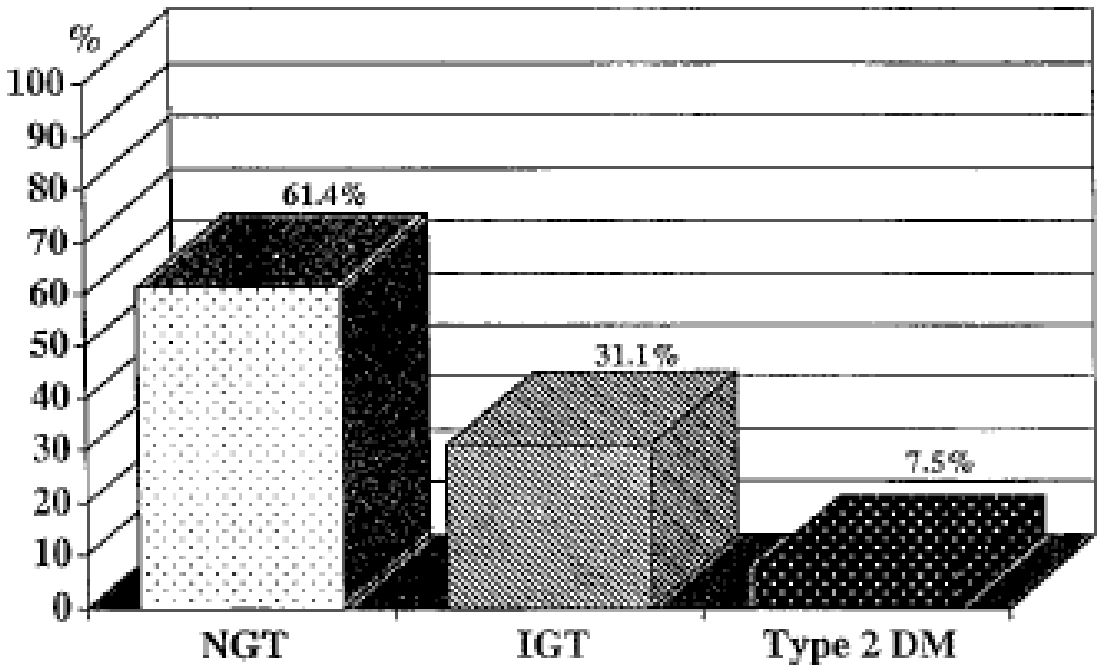
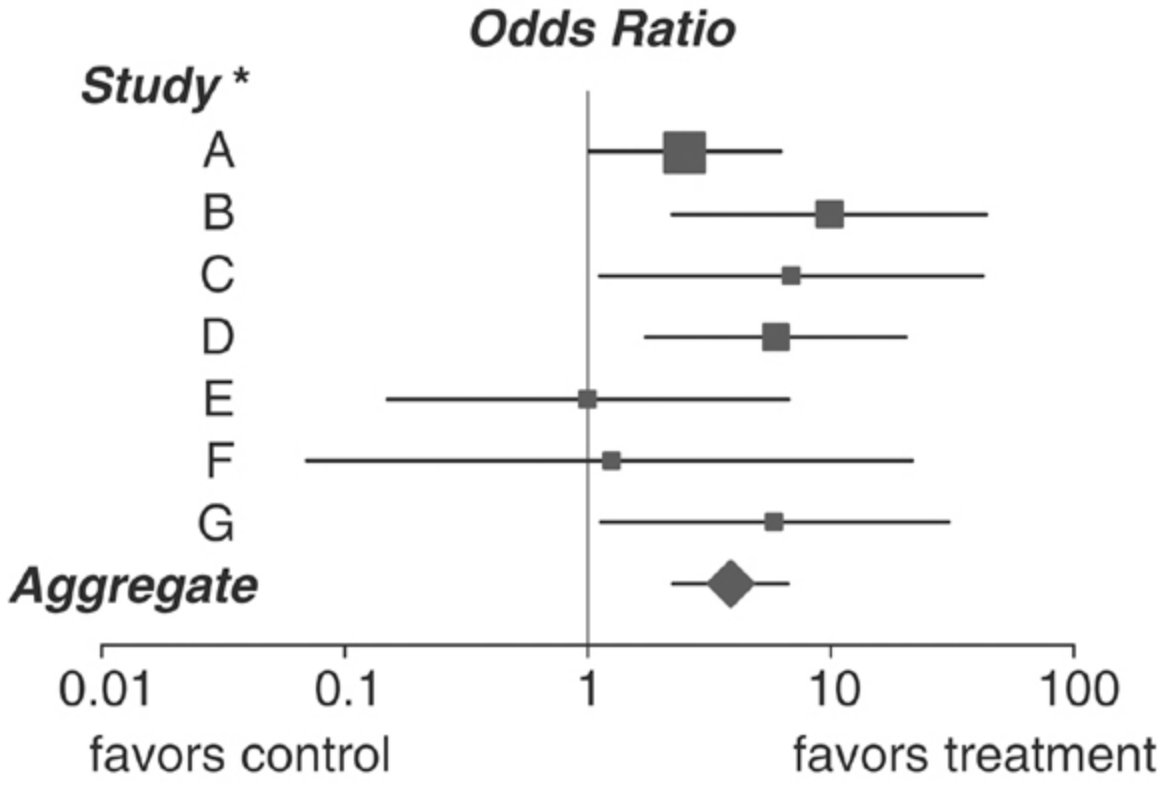


FIG. 1. Combined prevalence of glucose intolerance by WHO criteria in 254 PCOS women. NGT, Normal glucose tolerance; Type 2 DM, type 2 diabetes mellitus.

Legro et al., JCEM 1999: 84; 165.

MEDICAL OVULATION INDUCTION
Insulin Sensitizer: Metformin

- Gastrointestinal
  - Diarrhea (53%) , nausea,/vomiting (26%), flatulence, indigestion, abdominal discomfort
- Rare cases lactic acidosis
  - Check chem panel pre-Rx: r/o hepatic disease
  - Intravascular iodinated contrast may change renal function and increase r/o lactic acidosis
- Cimetidine competes for renal clearance
- Vit B12 malabsorption in 10-30%
  - Anemia rare, but check B12 levels annually



* Details regarding individual studies are summarized in Lord, et al. (27)

Clomiphene, Metformin or Both:

Cooperative Multicenter Reproductive Medicine Network:

- Multicenter, randomized trial of 626 subjects
- PCOS diagnosed by older, strict criteria
  - Oligomenorrhea (<8 spontaneous menses/year)
  - Hyperandrogenemia by local lab standards
  - Exclusion of hyperPRL, CAH, thyroid disease, POF
- Three arms followed for up to 6 cycles
  - Glucophage XR 2000 mg daily / matching placebo
  - Clomiphene 50 mg tablets daily / matching placebo
  - Both

Legro et al., N Engl J Med 2007;356:551.

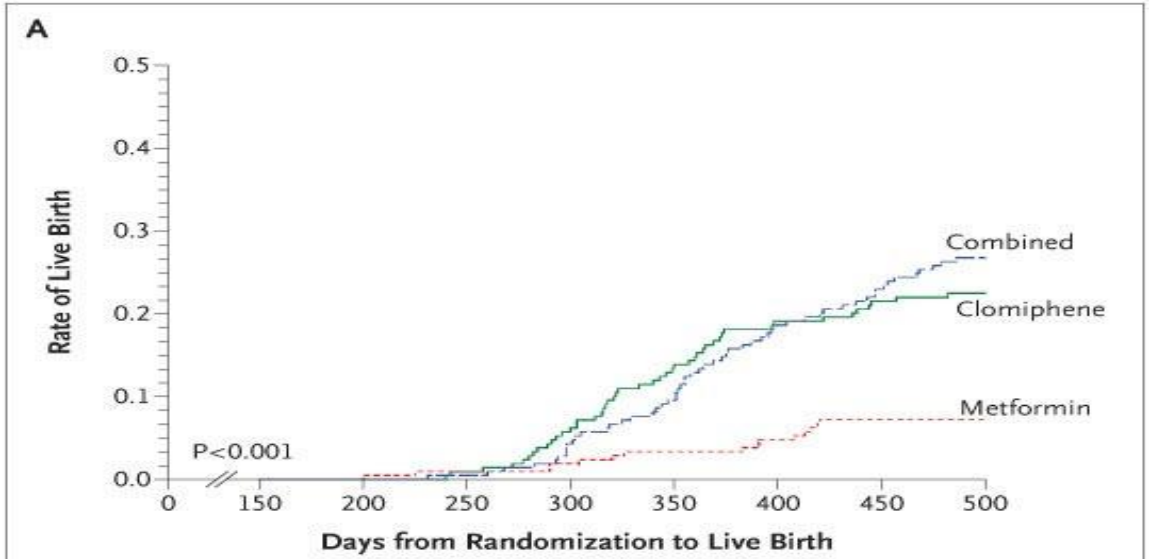
Clomiphene, Metformin or Both:

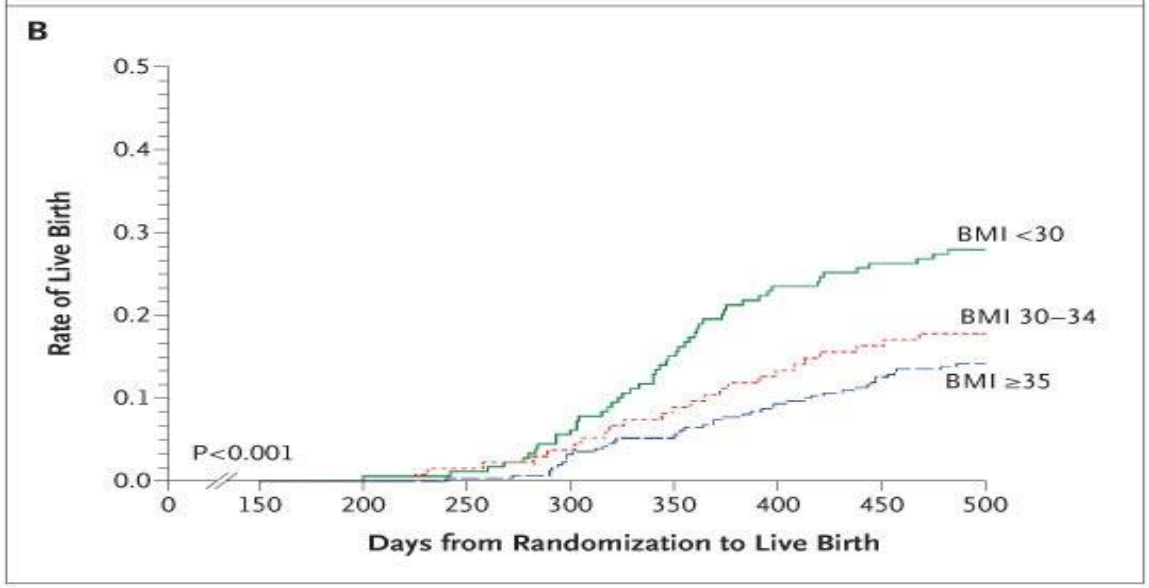
Cooperative Multicenter Reproductive Medicine Network:

- Baseline characteristics similar in age, BMI, degree of hirsutism, race, fertility history and prior conception.
- No significant difference in ultrasound findings
  - %PCO morphology
  - Ovarian volume
- Metabolic parameters similar
  - Insulin levels
  - SHBG
  - Testosterone levels

Legro et al., N Engl J Med 2007;356:551.

Clomiphene, Metformin or Both:





Clomiphene vs. Metformin Pregnancy Loss

- Single center randomized, double blinded controlled trial
  - Total of 92 subjects studied over 426 cycles in 6 months
  - Randomized to Metformin 850 BID + placebo or to placebo + Clomid 150 mg x 5 days
- Followed ovulation, pregnancy, LB and SAB rates
- Metformin associated with significantly lower spontaneous abortion rate compared with clomid (9.7% vs 37.5%, p=0.045)

Palombo et al., JCEM 2005;90:4068.

Metformin and Fetal Malformation

- Meta-analysis of 13 studies from 1966-2004
  - Control: disease matched women without metformin exposures
  - Disease: women exposed to metformin during the first trimester
- OR for major malformation in women exposed to metformin was 0.50 (95% CI 0.15-1.60)
- Mean malformation rate in the metformin group was 1.7% vs 7.2% in the untreated group
- Subanalysis to separate diabetic vs PCOS subjects showed no increase malformation after metformin

Gilbert et al., Fertil Steril 2006;86:685.

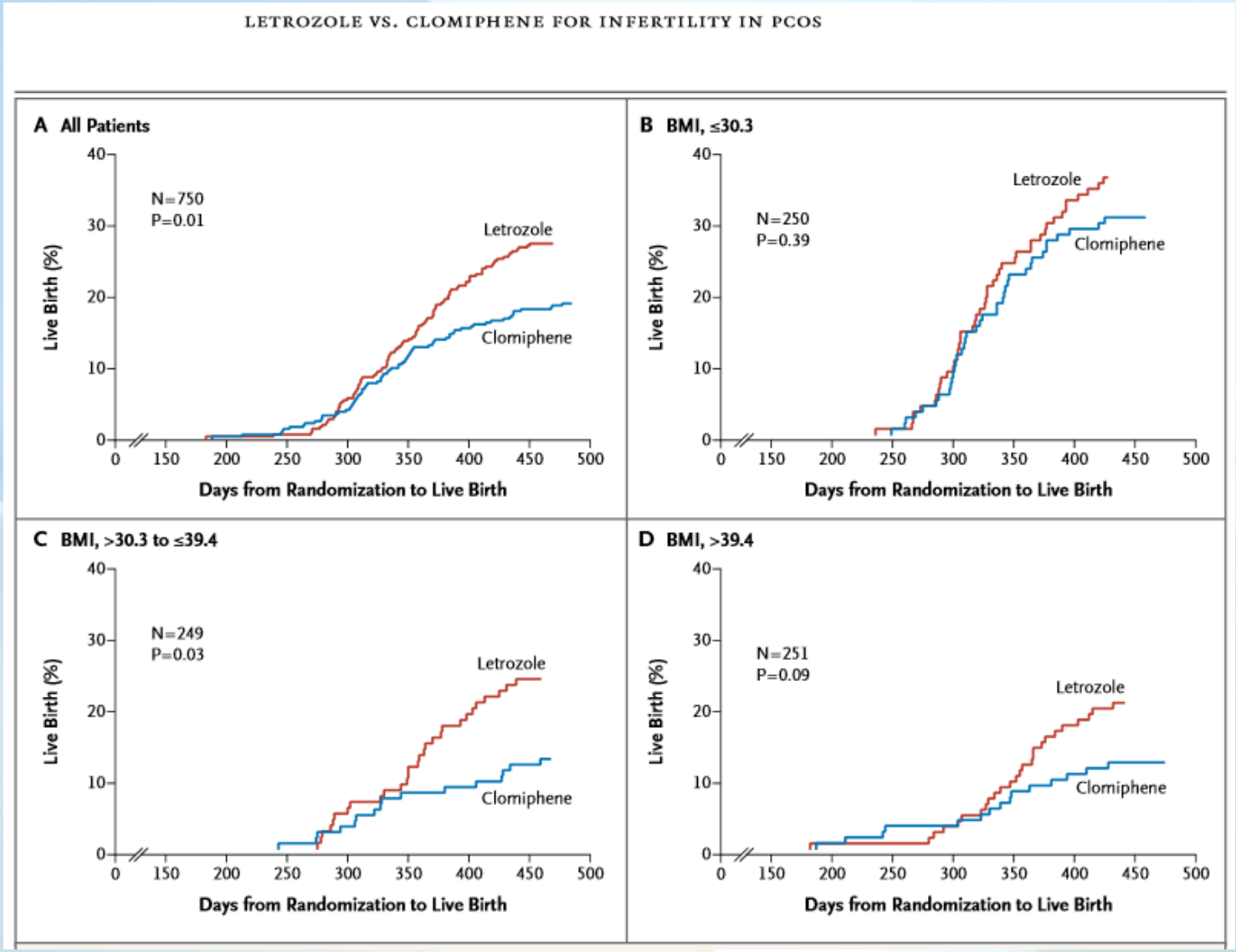
OVULATION INDUCTION IN PCOS: Letrozole

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Clomiphene Group (N=376)	Letrozole Group (N=374)
Age — yr	28.8±4.0	28.9±4.5
Body-mass index†	35.1±9.0	35.2±9.5
Ferriman–Gallwey hirsutism score‡	16.9±8.5	17.0±8.6
Race or ethnic group — no. (%)§		
White	302 (80.3)	288 (77.0)
Black	44 (11.7)	56 (15.0)
Asian	12 (3.2)	12 (3.2)
Mixed race	12 (3.2)	15 (4.0)
Hispanic or Latino	68 (18.1)	60 (16.0)
Fertility history		
Duration of time attempting to conceive — mo	42.5±37.6	40.9±38.0
Previous live birth — no. (%)	73 (19.4)	75 (20.1)
Ultrasonographic findings		
Antral follicle count in both ovaries	46.5±28.5	47.4±27.4
Polycystic ovaries according to modified Rotterdam criteria — no./total no. (%)¶	349/374 (93.3)	354/369 (95.9)
Endometrial thickness in sagittal plane — mm	6.7±2.9	6.8±3.0
Fasting serum biochemical values		
Total testosterone — ng/dl	56.3±30.1	53.8±27.4
Sex hormone–binding globulin — nmol/liter	33.2±23.7	34.5±22.4
Free androgen index‖	8.2±6.2	7.4±5.6
Estradiol — pg/ml	55.7±40.5	54.6±32.6
Progesterone — ng/ml	1.5±2.9	1.5±3.3
Antimüllerian hormone — ng/ml	8.1±6.9	8.0±7.1

Legros et al., N Engl J Med 2014;371:119-29.

OVULATION INDUCTION IN PCOS: Aromatase Inhibitors Letrozole



Legros et al., N Engl J Med 2014;371:119-29.

OVULATION INDUCTION IN PCOS:
Glucocorticoids in Clomiphene Resistant Patients

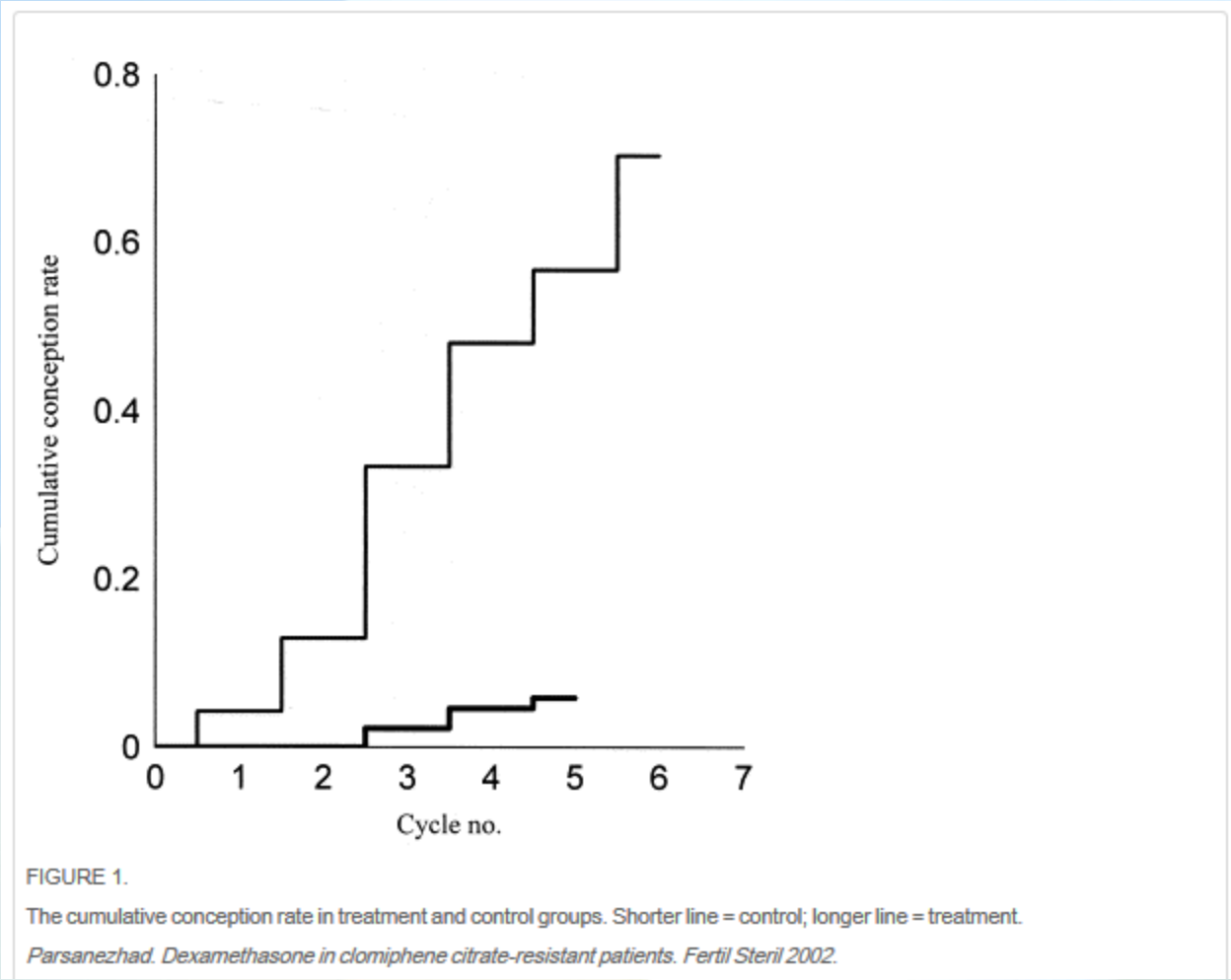


FIGURE 1.

The cumulative conception rate in treatment and control groups. Shorter line = control; longer line = treatment.

Parsanezhad. Dexamethasone in clomiphene citrate-resistant patients. Fertil Steril 2002.

Elnashar et al., Hum. Reprod. (2006) 21 (7): 1805-1808.

OVULATION INDUCTION IN PCOS:
Glucocorticoids in Clomiphene Resistant Patients

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 Pregnancy rate (per woman)						
Daly 1984	17	32	8	32	48.2%	3.40 [1.18, 9.81]
Elnashar 2006b	16	40	2	40	15.4%	12.67 [2.67, 60.05]
Parsanezhad 2002a	46	111	5	119	36.3%	16.14 [6.11, 42.65]
Subtotal (95% CI)		**183**		**191**	**100.0%**	**9.46 [5.05, 17.70]**
Total events	79		15			
Heterogeneity: $Chi^2 = 4.88$, df = 2 (P = 0.09); $I^2 = 59\%$						
Test for overall effect: Z = 7.03 (P < 0.00001)						
3.3.2 Ovulation rate (per woman)						
Daly 1984	23	32	14	32	48.3%	3.29 [1.16, 9.30]
Elnashar 2006b	30	40	6	40	18.4%	17.00 [5.52, 52.36]
Parsanezhad 2002a	98	111	24	119	33.3%	29.84 [14.36, 62.02]
Subtotal (95% CI)		**183**		**191**	**100.0%**	**14.65 [8.76, 24.49]**
Total events	151		44			
Heterogeneity: $Chi^2 = 11.64$, df = 2 (P = 0.003); $I^2 = 83\%$						
Test for overall effect: Z = 10.24 (P < 0.00001)						
3.3.3 Multiple pregnancy (per woman)						
Daly 1984	3	32	0	32	100.0%	7.71 [0.38, 155.64]
Elnashar 2006b	0	40	0	40		Not estimable
Subtotal (95% CI)		**72**		**72**	**100.0%**	**7.71 [0.38, 155.64]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						

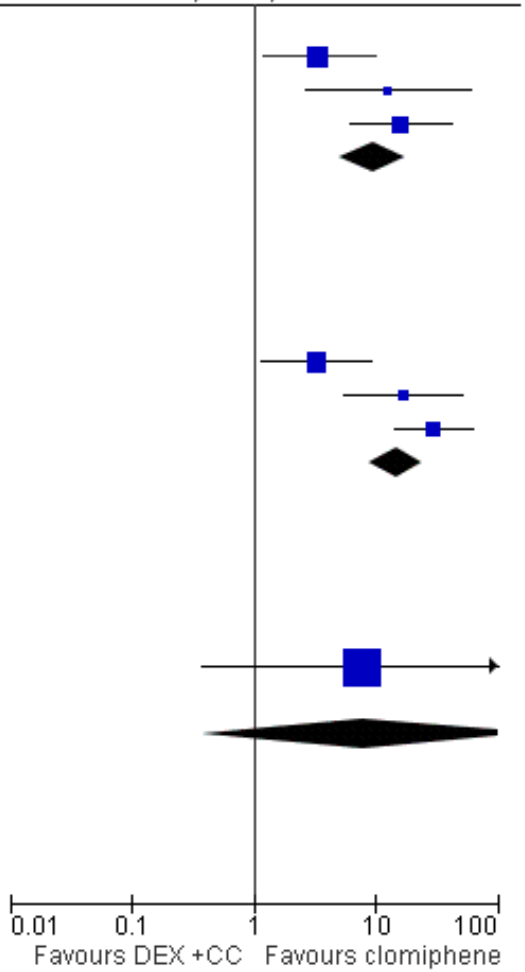


Figure 7. Forest plot of comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, outcome: 3.3 Clomiphene plus dexamethasone versus clomiphene.

Elnashar et al., Hum. Reprod. (2006) 21 (7): 1805-1808.

Ovulation Induction in PCOS
Injectable Hormones aka Gonadotropins

- Synthetic or urinary hormones secreted by pituitary
- Injected into subcutaneous fat or muscle
- Requires careful monitoring due to potential for multiple eggs to develops and multiple gestation
- May requires several weeks to develop mature egg follicle
- Higher risk of ovarian hyperstimulatio syndrome (OHSS)

OVULATION INDUCTION IN PCOS: Coenzyme Q_{10}

Table 2 Treatment outcomes.

	CoQ10-clomiphene citrate (n = 51)	*Clomiphene citrate (n = 50)*	*P-value*
No. of follicles >14 mm	1.94 ± 0.25	0.13 ± 0.29	<0.05
No. of follicles ≥18 mm	1.85 ± 0.27	1.30 ± 0.32	<0.001
Endometrial thickness on day of HCG (mm)	8.82 ± 1.49	7.03 ± 0.74	<0.001
Serum oestradiol on the day of HCG (pg/ml)	168.93 ± 75.01	138.32 ± 70.24	<0.05
Midluteal progesterone (pg/ml)	10.2 ± 1.03	8.9 ± 0.91	<0.001
Ovulation per cycle	54/82 (65.9)	11/71 (15.5)	<0.001
Clinical pregnancy per patient	19 (37.3)	3 (6.0)	<0.001

Values are mean ± SD or *n* (%).

Ovulation Induction in PCOS:
The Role of Supplements

- D-chiro-Inositol
- Myo-Inositol
- Proposed mechanisms of action
- No randomized controlled trial examining the potential fertility benefits
- Not routinely recommended by physicians
- Recommend discontinuation upon positive pregnancy test

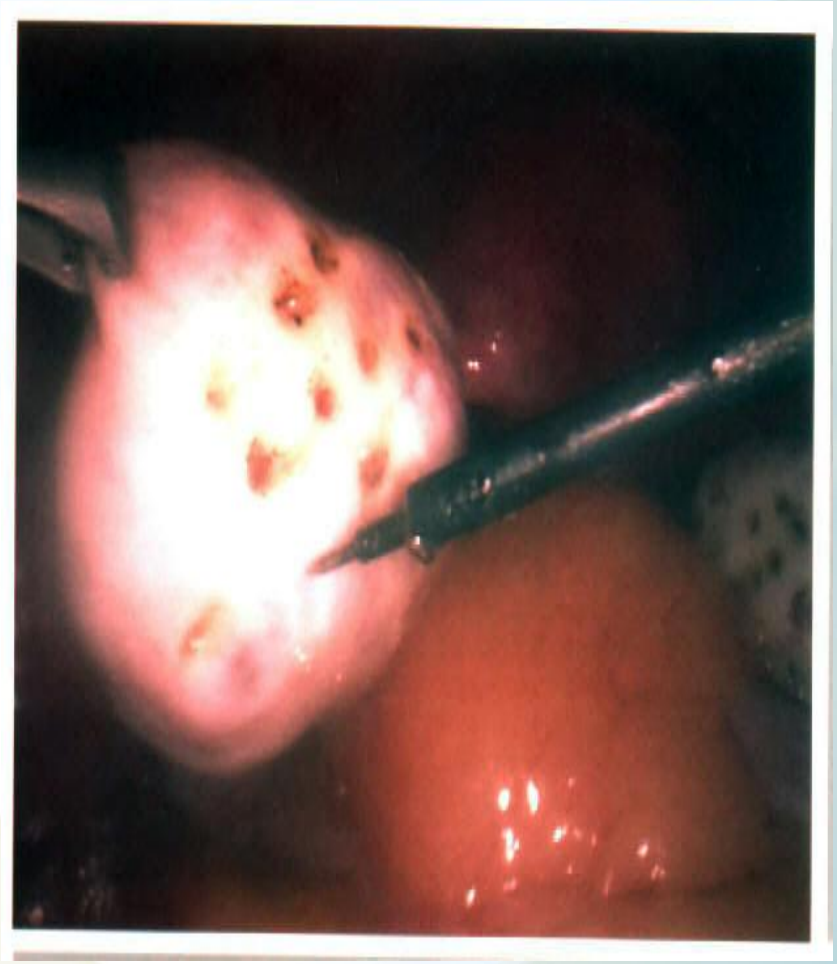
SURGICAL OVULATION INDUCTION

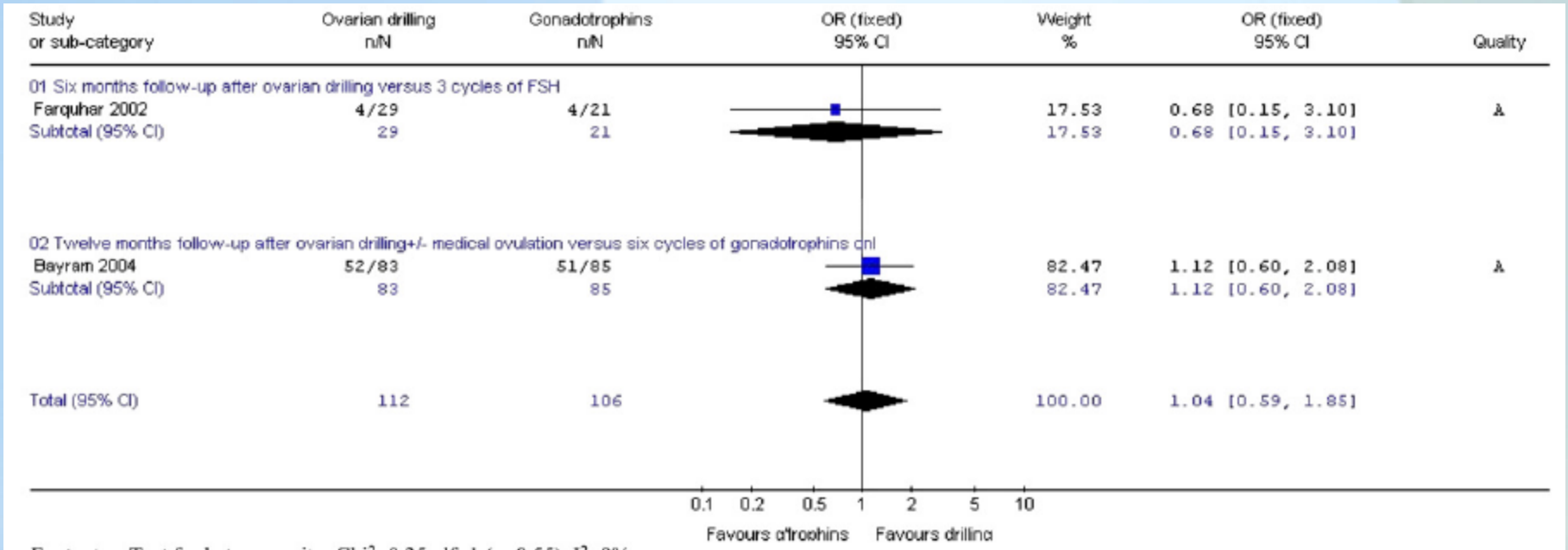
Laparoscopic ovarian drilling (LOD)

- Decreased adhesion formation compared with laparotomy
- Laparoscopy routine part of infertility evaluation
- No increase in risk of OHSS
- Lower risk of multiple gestation compared with gonadotropins
- Single procedure results in multiple ovulatory cycles

SURGICAL OVULATION INDUCTION
Laparoscopic ovarian drilling (LOD)

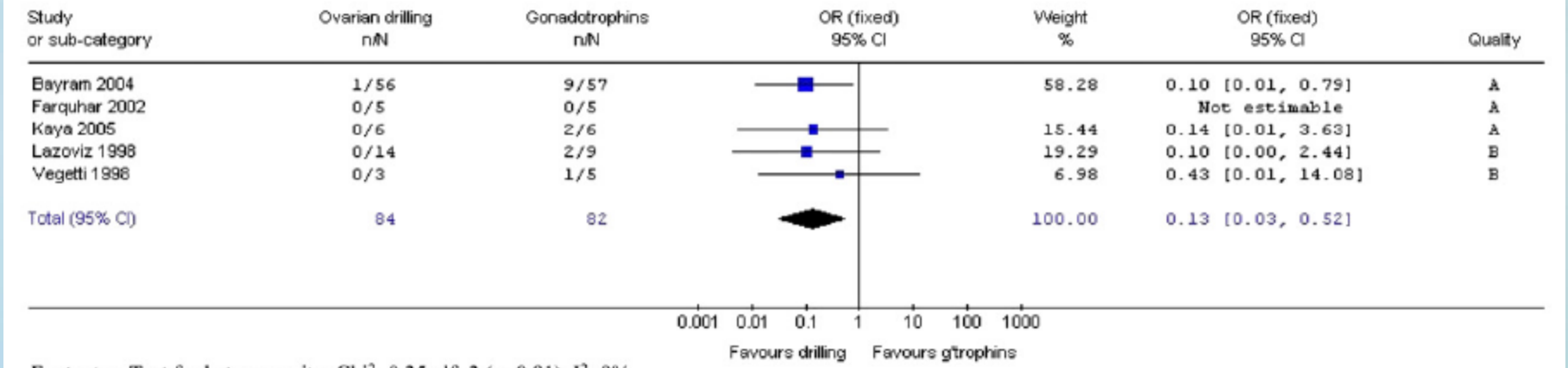
- Ovarian biopsy
- Electrocautery
  - Unipolar needlepoint
- Laser
  - Carbon dioxide
  - KTP
  - Nd-YAG





Footnotes: Test for heterogeneity: $Chi^2=0.35$, df=1 (p=0.55), $I^2=0\%$
Test for overall effect: Z=0.14 (p=0.89)

(b)

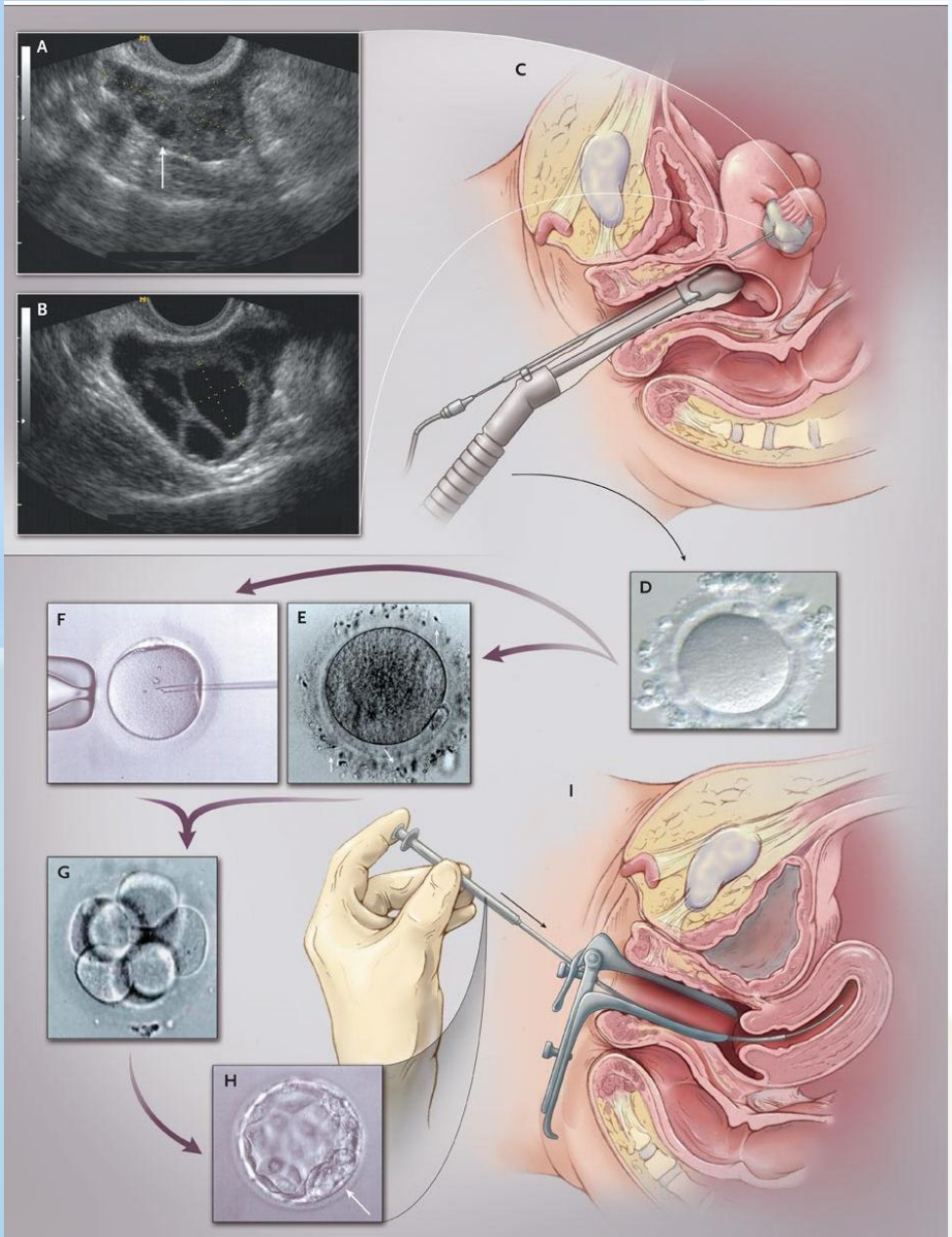


Footnotes: Test for heterogeneity: $Chi^2=0.35$, df=3 (p=0.91), $I^2=0\%$
Test for overall effect: Z=2.89 (p=0.91)

SURGICAL OVULATION INDUCTION
Laparoscopic ovarian drilling (LOD)

- Cochrane analysis of 6 RCT LOD vs. Gn
  - Similar cumulative ongoing PR after 6 -12 months after LOD vs. 3-6 cycles Gn
  - LOD advantage: monofollicular ovululation and reduction in multiple PR
- Multicenter study comparing LOD vs. Gn
  - 12-month PR in 168 CC-resistant PCOS patients
  - PR similar in LOD vs. Gn groups
    - 3-6 months Gn
    - 12 months LOD, LOD + CC, + Gn; multiple pregnancy rates lower

IN VITRO FERTILIZATION (IVF): SUMMARY



A. Ovaries are examined at baseline;

B. Patient takes injectable hormones (FSH & HMG) to stimulate ovaries;

C. Oocytes are retrieved under ultrasound guidance;

D. Oocyte is recovered from follicular fluid and is inseminated (E) or injected with sperm via ICSI (F);

G-H. Embryos are frozen and subsequently transferred at the cleavage or blastocyst stage.

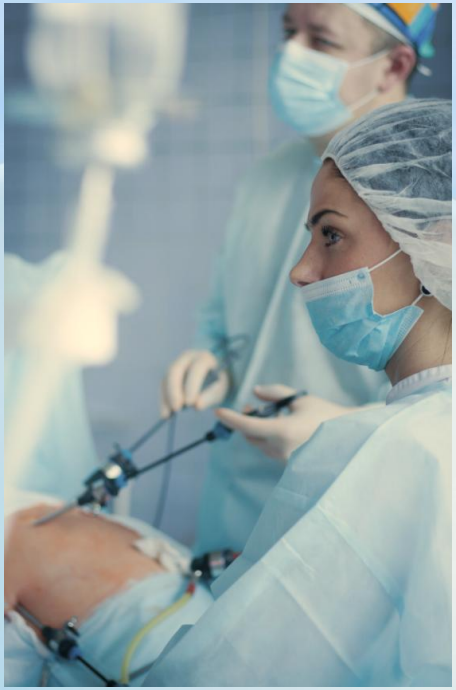
Van Voorhis 356 (4): 379, Figure 1
January 25, 2007

IVF OUTCOMES: PCOS versus Non-PCOS

- Significantly increased chance of cycle cancellation in PCOS (12.8% versus 4.1%)
- Higher number of oocytes retrieved in PCOS
- Lower fertilization rate in PCOS
- No difference in clinical pregnancy rates per started cycle (37.4% versus 32.3%)
- No difference in live birth rates per cycle

Heijnen et al., Hum Reprod Update 2006 12(1):13-21


Clomid
Tablets
50 mg



Thank you for your time
and attention!