PCOS
First line ovulation induction

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The health economic impact of PCOS in the USA has been estimated at up to $1.77 billion

(Azziz 2005)

UK : 16-22 million £ for diagnosis and treatment per year (Hum Reprod 2000)

PCO	70-80%
Hirsutismus	30-80%
Obesity	20-60%
Anovulation	80-90%
Oligo/amenorrhea	50-70%
Acne	15-20%
Androgenic alopesi	5-10%

PCOS AND FERTILITY

- What are the expectations from ovulation induction?

Aim

- Ovulatory cycle ended with singleton pregnancy
- Low abortion rate

. First line medications

. Second line options

(ACOG, 2002)

1. Weight loss: If BMI >30 kg/m^2
2. Clomiphene citrate (CC)
3. CC + corticosteroids if DHEAS > 2ug/ml
4. CC + Metformin
5. Low dose FSH injection
6. Low dose FSH injection + Metformin
7. Ovarian drilling

PCOS obesity : 35-50%

Central Obesity

Negative effects of obesity

Early menarch

Oligo-amenorrhea

High risk of Abortion

Lower ART chance

Pregnancy complications

Pasquali et al., Human Rep 2003

Weight loss

- Improve ovulatory function
- Regular menses
- Elevate SHBG concentrations
- Lower free testosterone levels
- Improve lipids
- Improve insulin sensitivity

From Hoeger et al. Best Pract Res Clin Endocrinol Metab 2006; 20:293

Trials of dietary intervention and impact on key features in overweight/obese women with PCOS

Studies (not controlled) (n = 20):

*Bates 1988, Pasquali 1986, Kiddy 1989, Pasquali 1989, Dessole 1990, Kiddy 1992, Hamilton-Fairley 1993, Nicolas 1993, Andersen 1995, Holte 1995, Hollman 1996, Jacubowicz 1997, Hernadez-Garcia 1999, Butzow 2000, van Dam 2002, Crosignani 2003, van Dam 2004, Tolino 2005, Moran 2007, Thomson 2008, Thomson 2009 *.*

Patients: 319

Duration: 1-7 months

Major findings:

Weight loss: all

Decreased testosterone (or FAI): 11/20

Improvement in menses: 10/20

Improvement in ovulation (no pregnancies included): 1/20

Occurrence of spontaneous conception: 7/20

Improved hirsutism: 3/20

Increased SHBG: 7/20

Improved insulin resistance or insulin (fasting, OGTT): 12/20

Anti-Mullerian hormone (AMH) 1/1* (no change)

General comment: heterogeneity in the pts response (particularly on androgens, menses, ovulation)

Modified and adapted from: Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Fertil Steril. 2009; 92:1966-82.

Weight loss is cheap, non complicating method

For anovulatory PCOS obes patients may be the ***FIRST LINE*** therapy

Homburg R 2003

Clomiphene citrate

- Since 1962
- minimal adverse effects
- triphenylethylene derivative
- dihydrogen citrate salt (clomiphene citrate)
- Two stereoisomer: zu-clomiphene (38 %) and en-clomiphene (62 %)

- Primary indication: oligoovulatory or anovulatory infertility

- normogonadotropic, normoprolactinemic, euthyroid women (WHO group 2)

Pharmacology

- Selective estrogen receptor modulator
- Competitive inhibition of estrogen for binding to estrogen receptors

- En-clomiphene faster elimination
- Zu-clomiphene **longer
- Zu-clomiphene higher estrogenic effect than en-clomiphene

- Oral dose elimination

- 50% in five days,
- Radioactive labelled CC has been showed as long as to six months in faeces

Mechanism

- Hypophisis: Increased sensitivity to GnRH
- Ovary: stimulation for follicle grow up secondary to FSH, LH increase
- Uterus, cervix, vagina: anti-estrogenic,
- cervical mucus: negative effects with 100 mg

Ovary

- Estrogen agonistic effects if estrogen is low,
- Stimulation of LH receptors in granulosa cells with FSH
- Direct effect to the aromatase activity

CC ADMINISTRATION

- For 5 days
- Onset on days 2-5
- No difference between different days of onset
- Starting dose 50 mg/day per os

CC: Monitoring the treatment

- No consensus
- Progesterone assay
- Ultrasound
- Estradiol assay
- Basal body temperature chart

CC vs PLACEBO

4 studies (cross-over)

- CC increased ovulation (OR: 6.8) (3 studies) and pregnancy rate (OR: 3.41) (2 studies)

(Hughes et al., 2000 Cochrane Database Syst. Rev. (2): CD000056)

3 RCTs

- CC increased pregnancy rate (OR 5.8, 95% CI 1.6 to 21.5)

(Beck et al., 2005 Cochrane Database Syst. Rev. (1): CD002249)

Table I. Results of treatment with clomiphene citrate: a collection of published data

	No of patients	Ovulation	Pregnancy	Abortion	Live birth
McGregor *et al.* (1968)	4098	2869	1393	279	1114
Garcia *et al.* (1977)	159	130	64	16	48
Gysler *et al.* (1982)	428	364	184	24	160
Hammond (1984)	159	137	67	10	57
Kousta *et al.* (1997)	128	113	55	13	42
Messinis and Milingos (1998)	55	51	35	4	31
Imani *et al.* (2002)	259	194	111	11	98
Total (% of patients)	5268 (100)	3858 (73)	1909 (36)	357	1550 (29)

Table II. Outcome of pregnancy following treatment with clomiphene citrate

	Pregnancies	Abortion	Live births
Total data from Table 1	1909	357	1550
Ahlgren *et al.* (1976)	159	18	141
Adashi *et al.* (1979)	86	23	62
Correy *et al.* (1982)	156	16	140
Dickey *et al.* (1996)	1744	413	1331
Total (% of pregnancies)	4054 (100)	827 (20.4)	3224 (79.5)

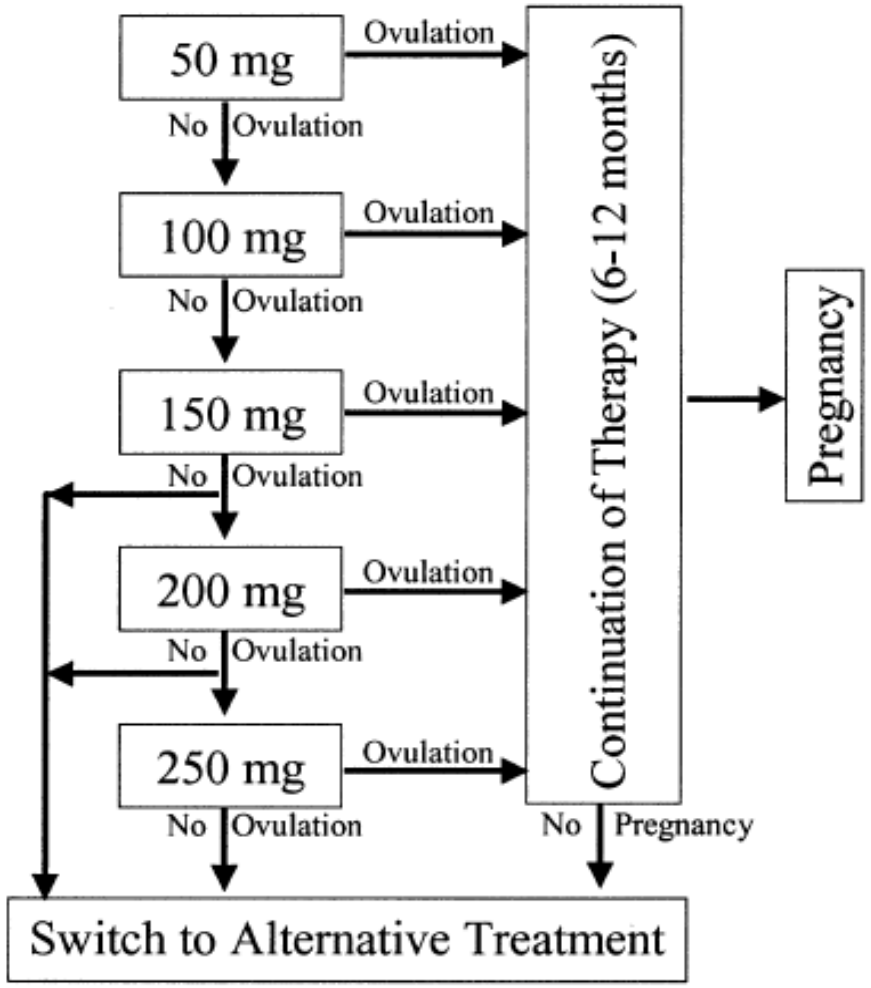
Homburg R, Human Reprod 2005

Effective dose

- Most of the pregnancies occurs in the first 6 ovulatory cycles
- Approx 50% occurs with the dose of 50 mg/day
- Other 25% occurs with 100 mg/day

FIGURE 1

Schematic representation of the algorithm used currently for dose adjustment in the treatment of infertile women with clomiphene.



Rostami-Hodjegan. Clomiphene dose individualization. Fertil Steril 2004.

OVULATION INDUCTION WITH CLOMIPHENE

- Response (ovulation – conception)
- Response (ovulation – no conception) **CLOMIPHENE FAILURE**

- No response (no ovulation) **CLOMIPHENE RESISTANCE**

Factors effecting the pregnancy rates with CC

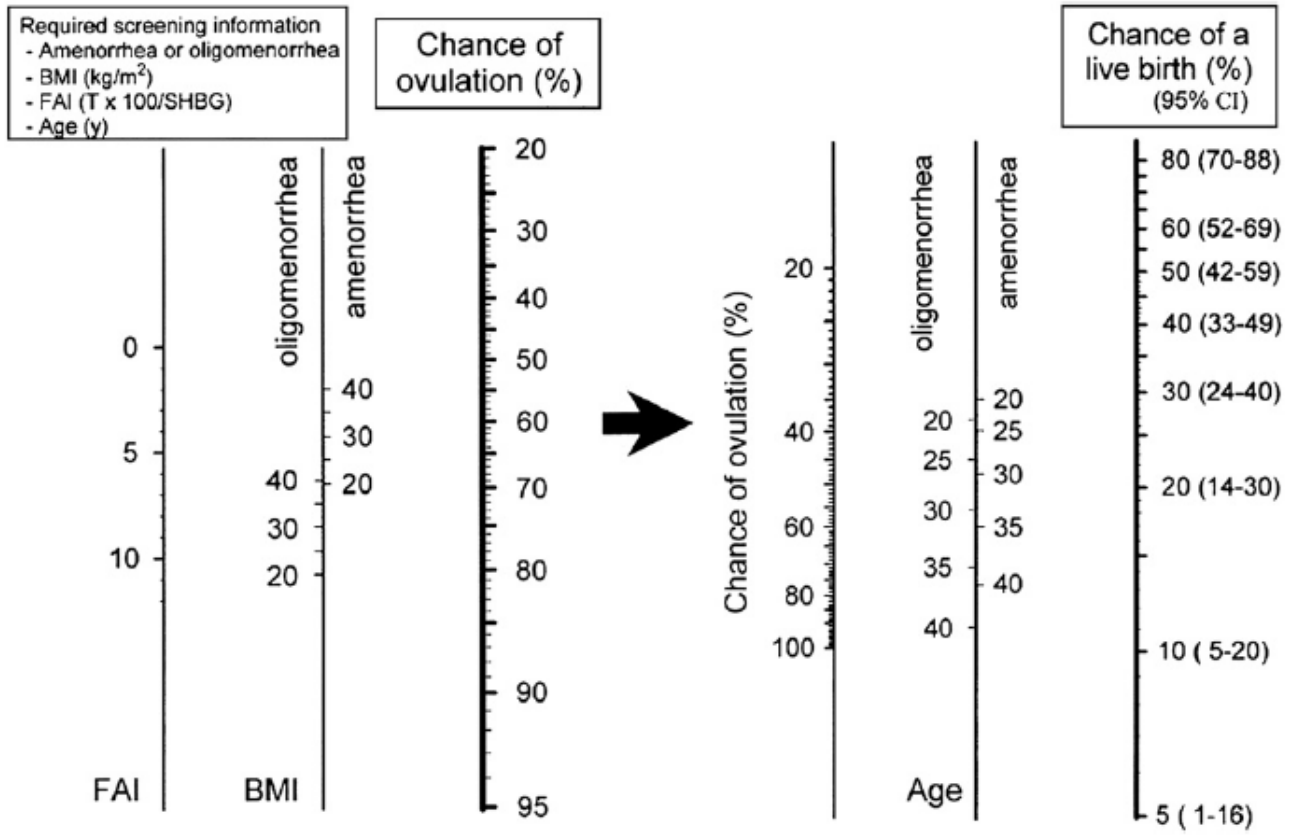
- baseline free androgen index (FAI),
- baseline proinsulin level,
- body mass index (BMI)
- duration of attempting conception

(Rausch *et al., 2009*)

Chances of live birth in CC ovulation induction

FIGURE 2

Nomogram designed to predict chances for live birth in clomiphene citrate induction of ovulation. Note the two different steps. (Imani et al., Fertil Steril 2002;77:91–7. Used with permission.)



Tarlatzis. Consensus on infertility treatment related to PCOS. Fertil Steril 2008.

The predictive value of circulating anti-Müllerian hormone in women with polycystic ovarian syndrome receiving clomiphene citrate: a prospective observational study

Mahran et al. UK Clin Endocrinol Metab. 2013 Oct;98(10):4170-5

Serum AMH concentrations were significantly ($P < .001$) lower in responders (achieving ovulation) vs nonresponders (mean ± SEM, 2.5 ± 0.1 vs 5.8 ± 0.7 ng/mL, respectively).

Similarly, serum AMH concentrations were significantly ($P = .046$) lower in pregnant (3.0 ± 0.4 ng/mL) vs nonpregnant patients (4.4 ± 0.5 ng/mL)

Ovulation and pregnancy rates were significantly higher (97%, $P < .001$, and 46%, $P = .034$) in patients with low AMH (<3.4 ng/mL) vs women with AMH 3.4 ng/mL or greater (48% and 19%)

CONCLUSION

PCOS women with high circulating AMH (≥ 3.4 ng/mL) seem to be resistant to CC and may require a higher starting dose

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

- Clomiphene citrate remains the treatment of first choice for induction of ovulation in most anovulatory women with PCOS.
- Selection of patients for CC treatment should take into account body weight/BMI, female age, and the presence of other infertility factors.
- The starting dose of CC should be 50 mg/day (for 5 days), and the recommended maximum dose is 150 mg/day.
- Results of large trials suggest monitoring by ultrasound or progesterone is not mandatory to ensure good outcome.
- Life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in women ovulating while on CC.
- Further studies should demonstrate efficacy and safety of aromatase inhibitors.

Ovulation inducing drugs and ovarian cancer risk: results from an extended follow_up of a large United States infertility cohort

Trabert B et al. Fertil Steril 2013 Dec 100(6)

- 9825 women treated between 1965 and 1988 follow up through 2010
  No association of cancer risk ever use of CC
- Women who used CC and remained nulligravid did demonstrate much risk RR 3.63
- Remains to be determined

CC FAILURE
Can we improve?

- Patients selection
- Combinations of clomiphene with other drugs
- Second line treatment

CC RESISTANCE
Is it possible to sensitize?

- Higher doses (up to 250 mg)
- Extended treatment (~ 20 days)
- Combinations with other drugs

Alternatives as first line?

- Insulin sensitizers (Metformin)
- Aromatase inhibitors (Letrozole)
- Laparoscopic ovarian drilling (LOD)
- Low-dose FSH

METFORMIN vs CC
First line

626 women with PCOS

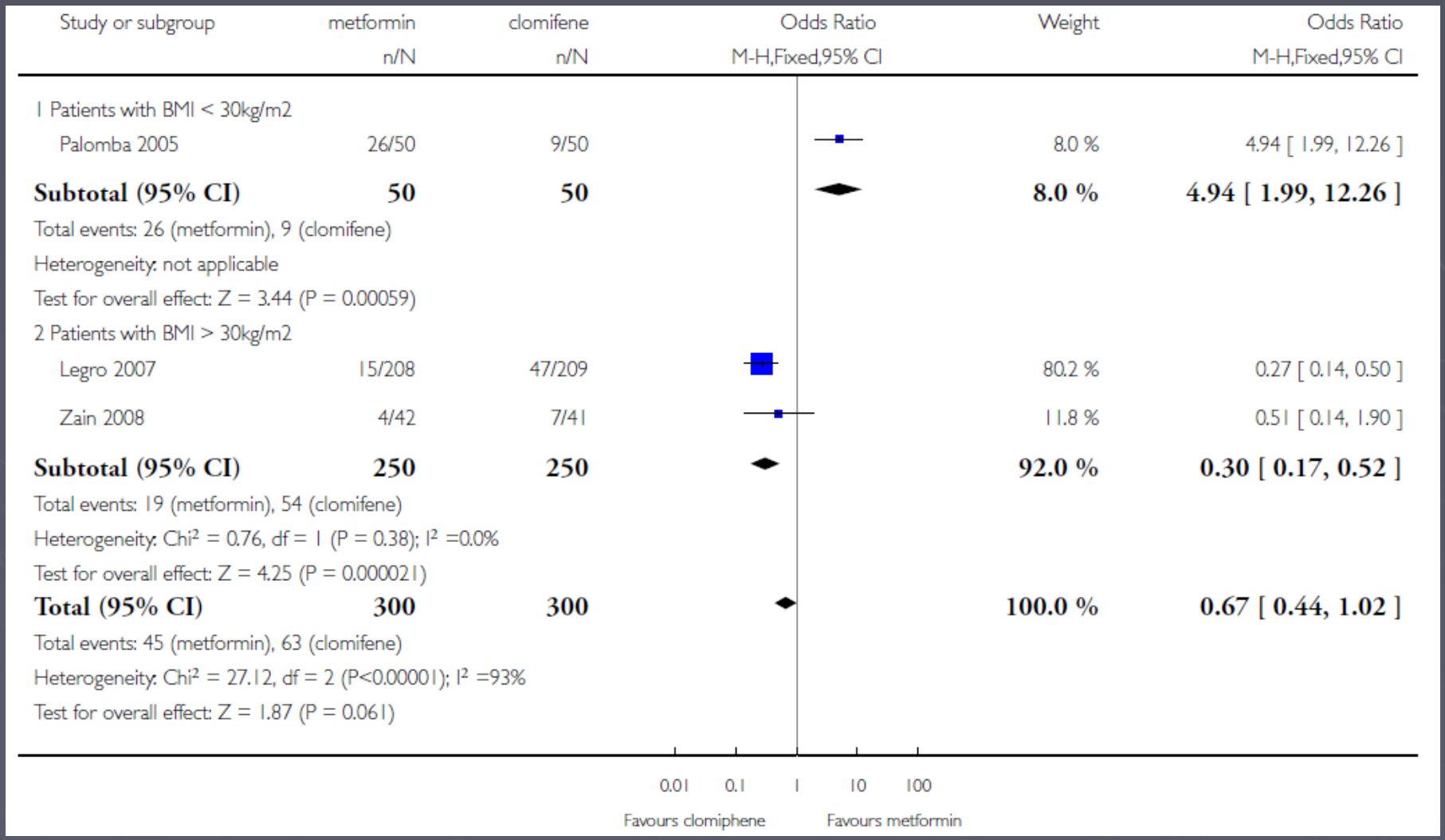
	Conception rate	Live-birth rate
CC	39.5%	47/209 (22.5%)
CC + M	46.0%	56/209 (26.8%)
M	21.7%**	5/208 (7.2%)*

**P<0.001*

***P=0.002*

Legro et al., 2007
N. Engl. J. Med. 356, 551-66

Analysis 3.1. Comparison 3 Metformin versus clomiphene citrate, Outcome 1 Live birth.



From Tang et al. Cochrane Library 2010

CC+Metformin
First-line (Dutch study)

- CC+M vs CC+P (228 PCOS women) No difference in:
  - Ovulations (64% vs 72%)
  - Ongoing pregnancies (40% vs 46%)
  - Miscarriages (12% vs 11%)

Moll et al., 2006.BMJ 332, 1485

CC+Metformin
Systematic review

- CC is still first choice therapy
- In CC-resistant women, CC+M is the preferred treatment before moving to LOD or FSH

Moll et al., 2007
Hum. Reprod. Update 13, 527-537

LETROZOLE IN PCOS
Meta-analysis

- **4 RCTs**

Letrozole vs CC

- Ovulation (OR 1.17, 95% CI 0.66 to 2.09)
- Pregnancy/cycle (OR 1.47, CI 0.73 to 2.96)
- Pregnancy/patient (OR 1.37, CI 0.70 to 2.71)

Requena et al., 2008
Hum. Reprod. Update 14, 571-82

Aromatase inhibitors for subfertility treatment in women with PCOS

Franik S, Kremer JAM, Nelen WLDM, Farquhar C

Cochrane summaries, 24 February 2014

Over the last ten years clinical trials have reached differing conclusions as to whether the AI letrozole is at least as effective for treating subfertility as the most commonly used treatment, clomiphene citrate.

26 randomised controlled trials (RCT) with 5560 women

Letrozole appears to improve live birth and pregnancy rates compared to clomiphene citrate.

However the quality of this evidence was low and findings should be regarded with some caution

Conclusion

Weight loss, exercise, and lifestyle modifications should be the first-line option for these women

- Clomiphene citrate has been proven effective in ovulation induction for women with PCOS and should be considered the first-line therapy
- Patients should be informed that there is an increased risk of multiple pregnancy with ovulation induction using clomiphene citrate