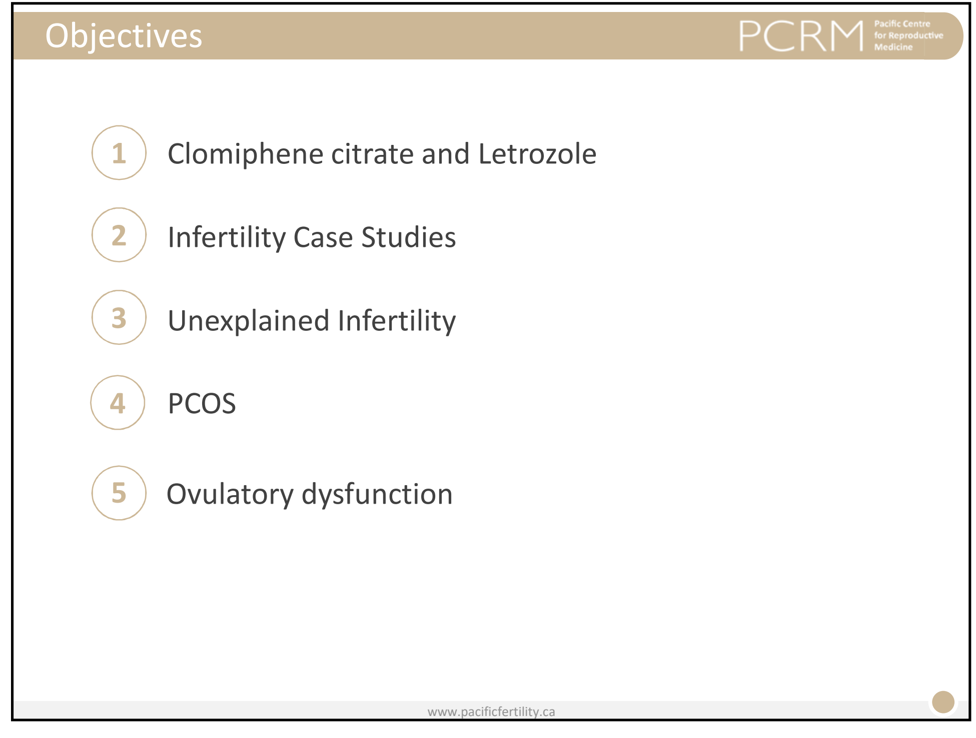
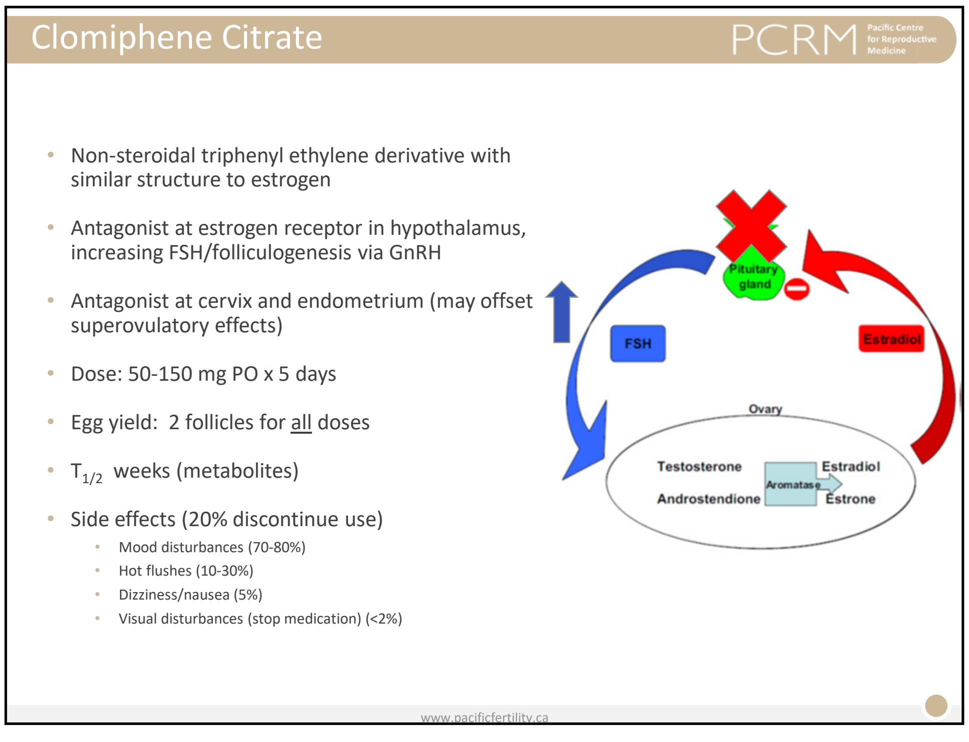
STILL A PLACE FOR PILLS – DON'T IVF EVERYTHING
PCRM Pacific Centre for Reproductive Medicine
Jeff Roberts M.D.
Co-Director, Pacific Centre for Reproductive Medicine


Objectives
PCRM Pacific Centre for Reproductive Medicine
1 Clomiphene citrate and Letrozole
2 Infertility Case Studies
3 Unexplained Infertility
4 PCOS
5 Ovulatory dysfunction
www.pacificfertility.ca


Clomiphene Citrate
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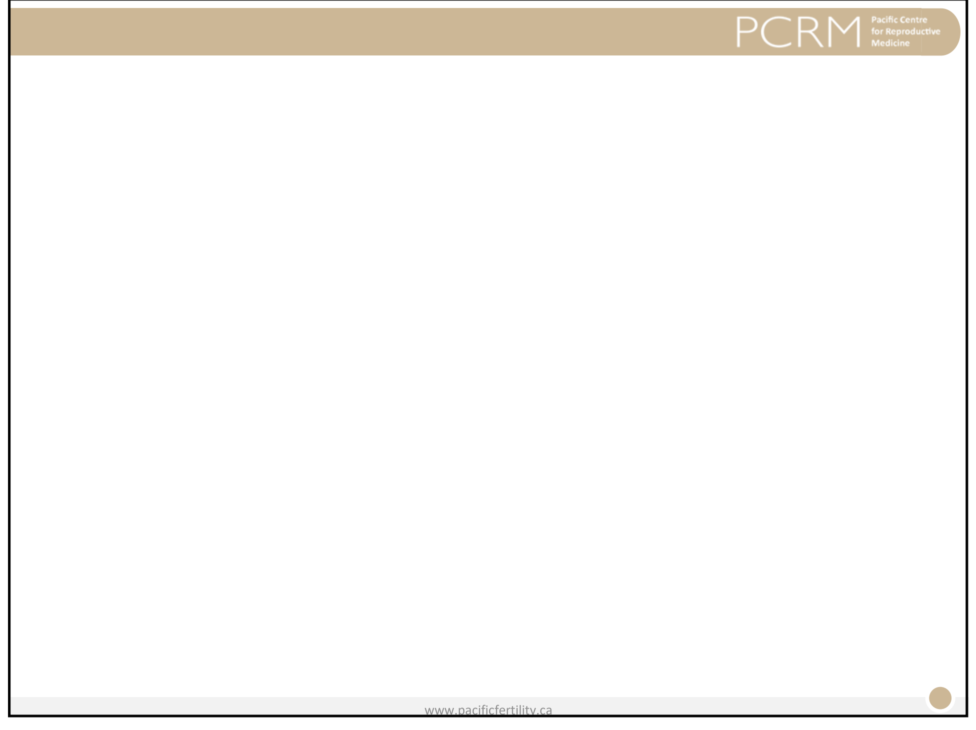
Non-steroidal triphenyl ethylene derivative with similar structure to estrogen
Antagonist at estrogen receptor in hypothalamus, increasing FSH/folliculogenesis via GnRH
Antagonist at cervix and endometrium (may offset superovulatory effects)
Dose: 50-150 mg PO x 5 days
Egg yield: 2 follicles for all doses
T1/2 weeks (metabolites)
Side effects (20% discontinue use)
Mood disturbances (70-80%)
Hot flushes (10-30%)
Dizziness/nausea (5%)
Visual disturbances (stop medication) (<2%)
Pituitary gland
FSH
Estradiol
Ovary
Testosterone
Androstendione
Aromatase
Estradiol
Estrone
www.pacificfertility.ca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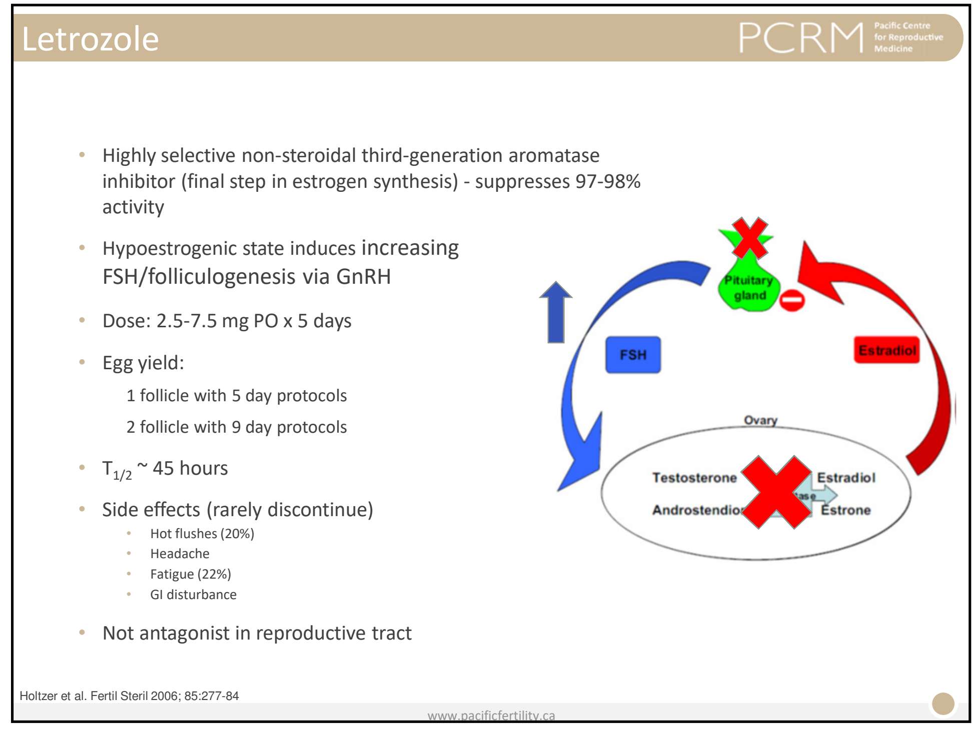

Letrozole

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- Only FDA-approved as adjuvant hormone therapy for post-menopausal breast cancer
- Malformation concerns never appear in peer reviewed publication but Novartis issued a black label warning regardless in response to a single abstract suggesting risk
- Health Canada will not officially approve use of letrozole for fertility, but taking position of non-refusal (unofficially supportive)

Case # 1

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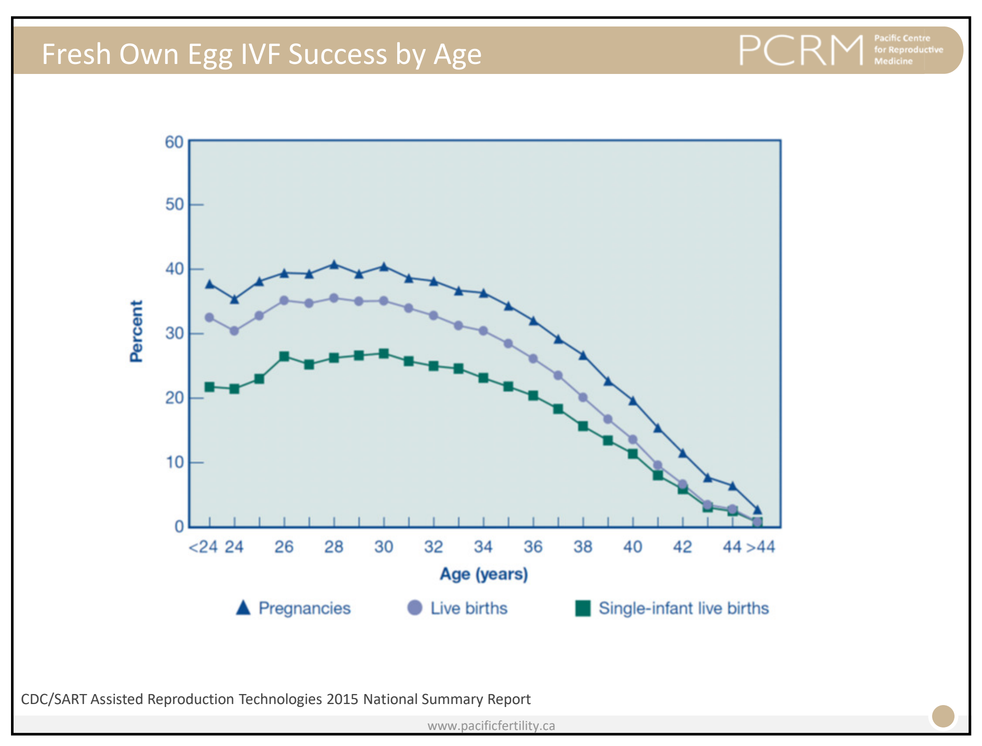
- 37 y.o. G1A1
- 2 years infertility
- SAB x 1 uncomplicated
- Regular cycles q 28 days
- Positive OPKs most months and timing ok
- Investigations:
  - SA: normal
  - HSG: normal
  - Ovarian reserve testing: AMH 9 pmol/L, FSH 8 IU/L, AFC 10

Unexplained Infertility

- Traditionally diagnosis made after basic infertility evaluation fails to reveal an obvious abnormality (ovulation, adequate sperm and patent tubes)
- Up to 30% of infertility couples
- Average cycle fecundity 2 to 4%
- Pregnancy rates decline with increasing age and duration of infertility
- Egg aneuploidy likely cause in most cases - no test

Practice Committee of the American Society for Reproductive Medicine Fertil Steril; 86, Suppl 4:S111-S114


Fresh Own Egg IVF Success by Age
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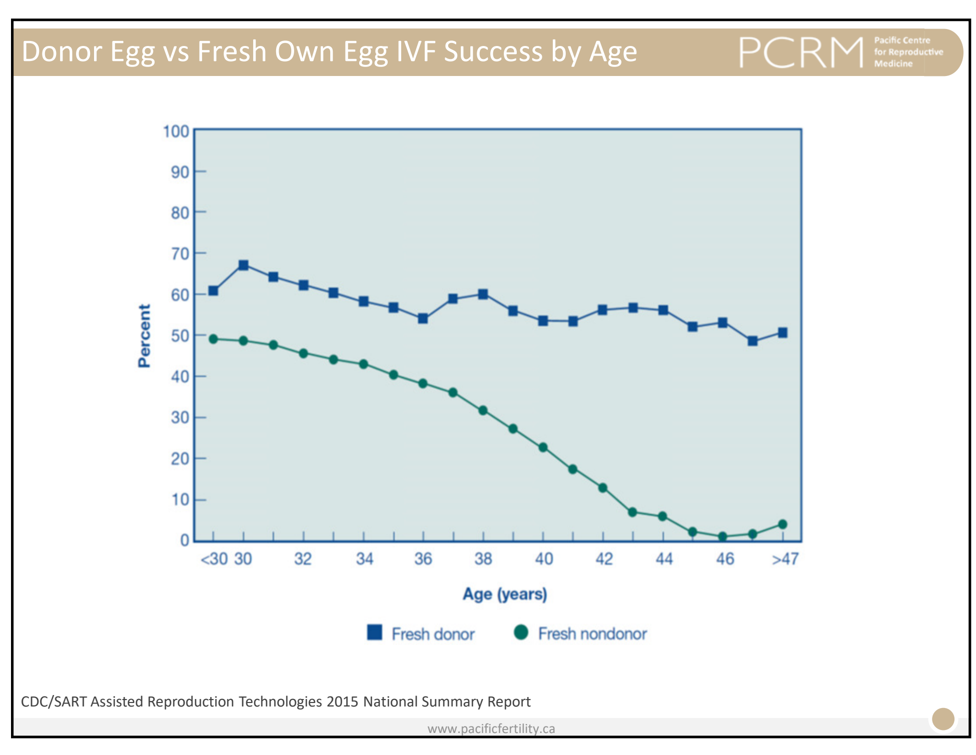
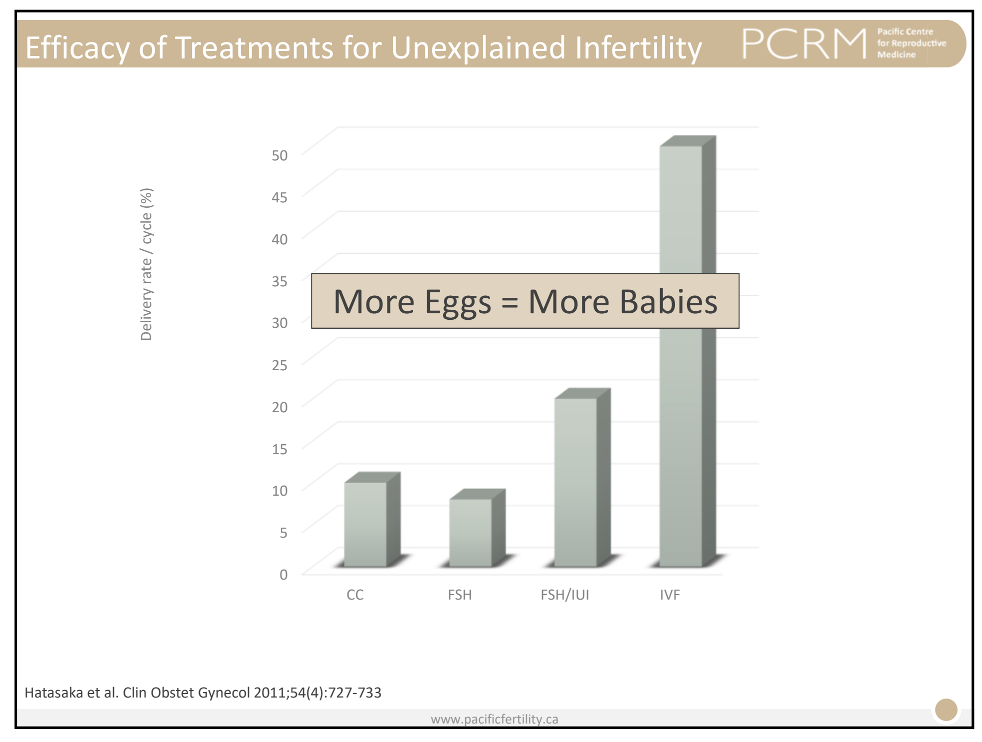
60
50
40
30
20
10
0
Percent
<24 24 26 28 30 32 34 36 38 40 42 44 >44
Age (years)
Pregnancies
Live births
Single-infant live births
CDC/SART Assisted Reproduction Technologies 2015 National Summary Report
www.pacificfertility.ca


Donor Egg vs Fresh Own Egg IVF Success by Age
PCRM
Pacific Centre for Reproductive Medicine
100
90
80
70
60
50
40
30
20
10
0
Percent
<30 30 32 34 36 38 40 42 44 46 >47
Age (years)
Fresh donor
Fresh nondonor
CDC/SART Assisted Reproduction Technologies 2015 National Summary Report
www.pacificfertility.ca



Efficacy of Treatments for Unexplained Infertility
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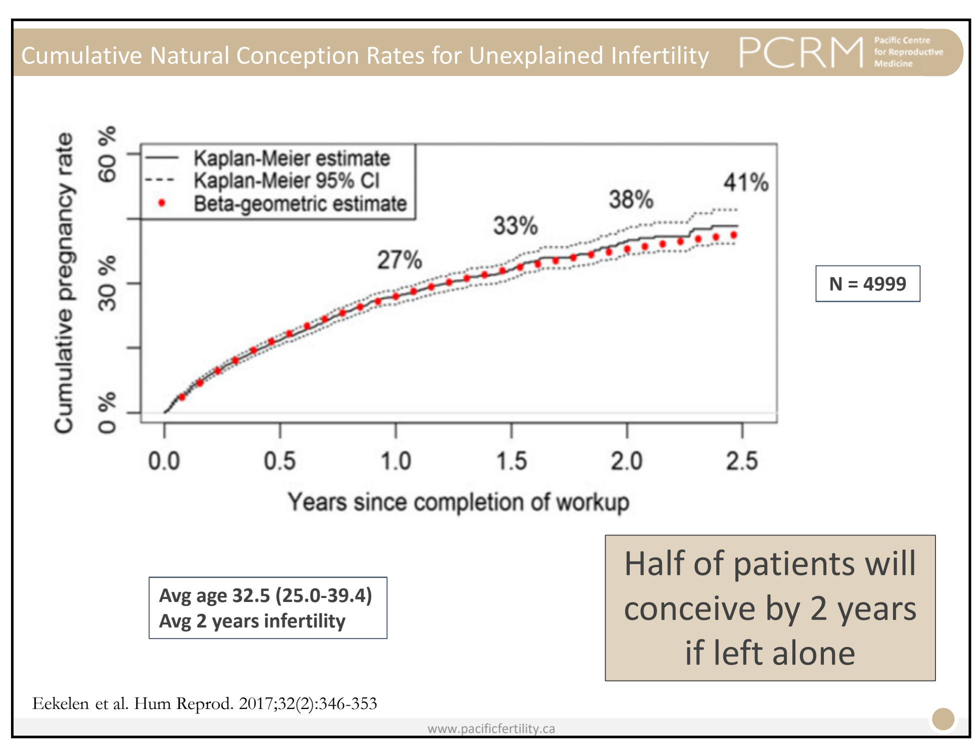
Delivery rate / cycle (%)
50
45
40
35
30
25
20
15
10
5
0
More Eggs = More Babies
CC
FSH
FSH/IUI
IVF
Hatasaka et al. Clin Obstet Gynecol 2011;54(4):727-733
www.pacificfertility.ca



Cumulative Natural Conception Rates for Unexplained Infertility
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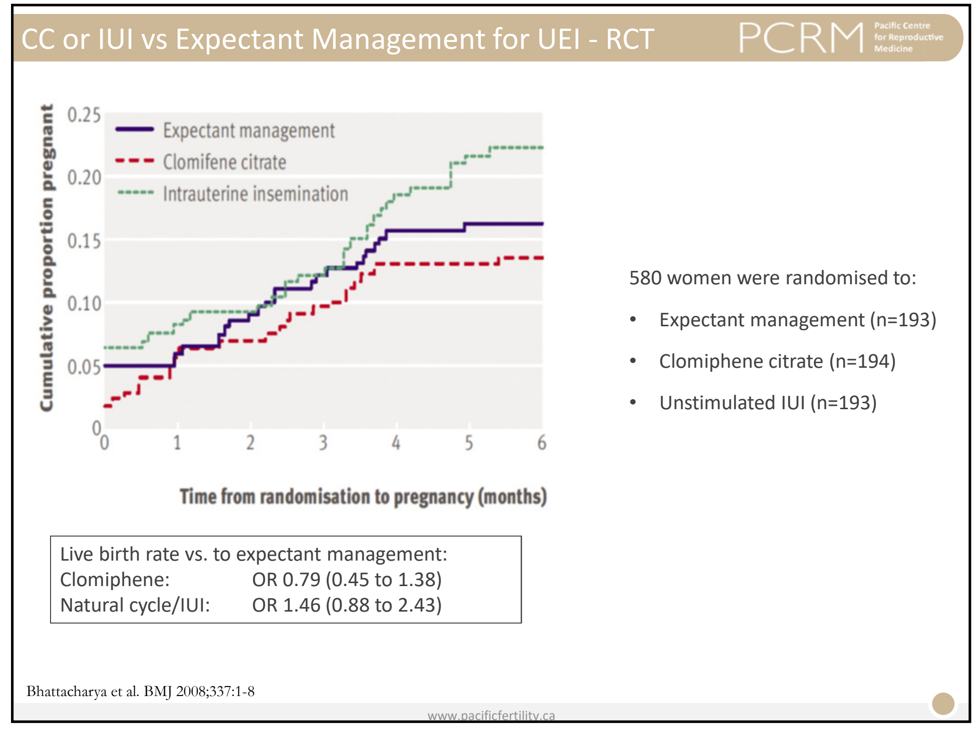
Kaplan-Meier estimate
Kaplan-Meier 95% CI
Beta-geometric estimate
Cumulative pregnancy rate
60 %
30 %
0 %
27%
33%
38%
41%
0.0
0.5
1.0
1.5
2.0
2.5
Years since completion of workup
N = 4999
Avg age 32.5 (25.0-39.4)
Avg 2 years infertility
Half of patients will conceive by 2 years if left alone
Eekelen et al. Hum Reprod. 2017;32(2):346-353
www.pacificfertility.ca


CC or IUI vs Expectant Management for UEI - RCT
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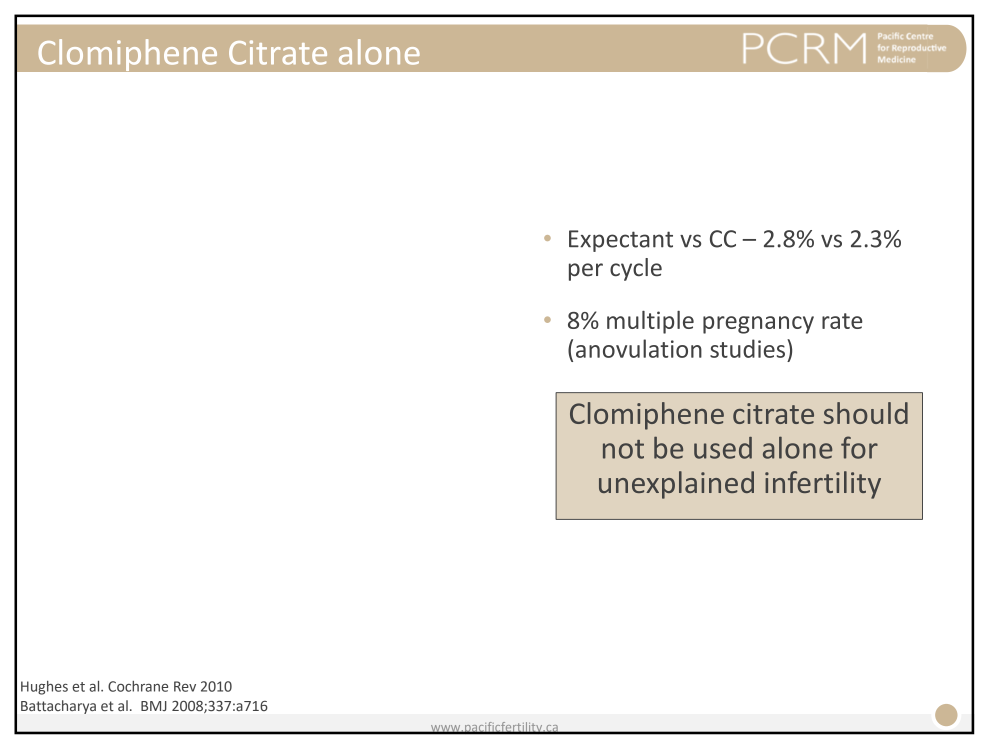
0.25
0.20
0.15
0.10
0.05
0
Cumulative proportion pregnant
Expectant management
Clomifene citrate
Intrauterine insemination
0 1 2 3 4 5 6
Time from randomisation to pregnancy (months)
580 women were randomised to:
• Expectant management (n=193)
• Clomiphene citrate (n=194)
• Unstimulated IUI (n=193)
Live birth rate vs. to expectant management:
Clomiphene: OR 0.79 (0.45 to 1.38)
Natural cycle/IUI: OR 1.46 (0.88 to 2.43)
Bhattacharya et al. BMJ 2008;337:1-8
www.pacificfertility.ca


Clomiphene Citrate alone
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• Expectant vs CC – 2.8% vs 2.3% per cycle
• 8% multiple pregnancy rate (anovulation studies)
Clomiphene citrate should not be used alone for unexplained infertility
Hughes et al. Cochrane Rev 2010
Battacharya et al. BMJ 2008;337:a716
www.pacificfertility.ca

Clomiphene + IUI

PCRM Pacific Centre for Reproductive Medicine

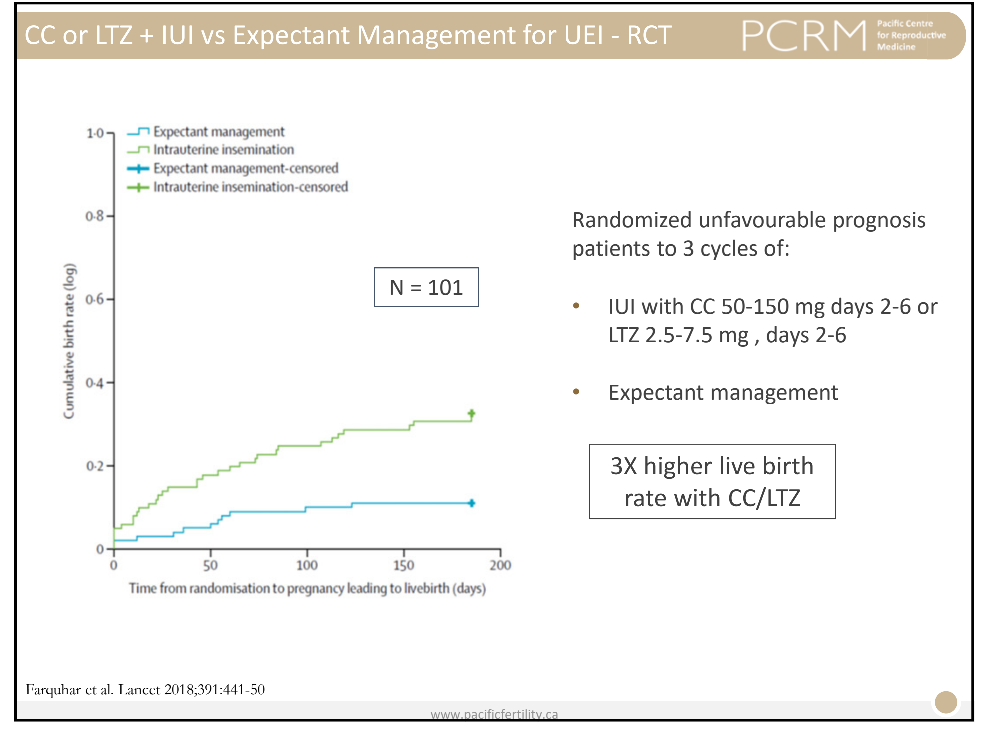
- IUI may counter cervical factor created by CC
- Clinical pregnancy rate 8%/cycle compared to 2-4% with expectant[1]
- Meta-analysis (6 RCTs) demonstrate 4-5X higher pregnancy rates compared to natural cycle[2]
- Cochrane review (2016) (14 RCTs) – no difference between CC/IUI or FSH/IUI and natural cycle

"Given ease, cost and low rate of multiple pregnancy CC/IUI has become a standard 1st line therapy for UEI" - *CFAS CPG Committee*

1. Guzick et al Fertil Steril. 1998;70(2):207-13
2. Costello et al. Aust NZ J OBGYN 2004;44:93-102
3. Veltman-Verhulst et al. Cochrane Rev 2016

CC or LTZ + IUI vs Expectant Management for UEI - RCT

PCRM Pacific Centre for Reproductive Medicine

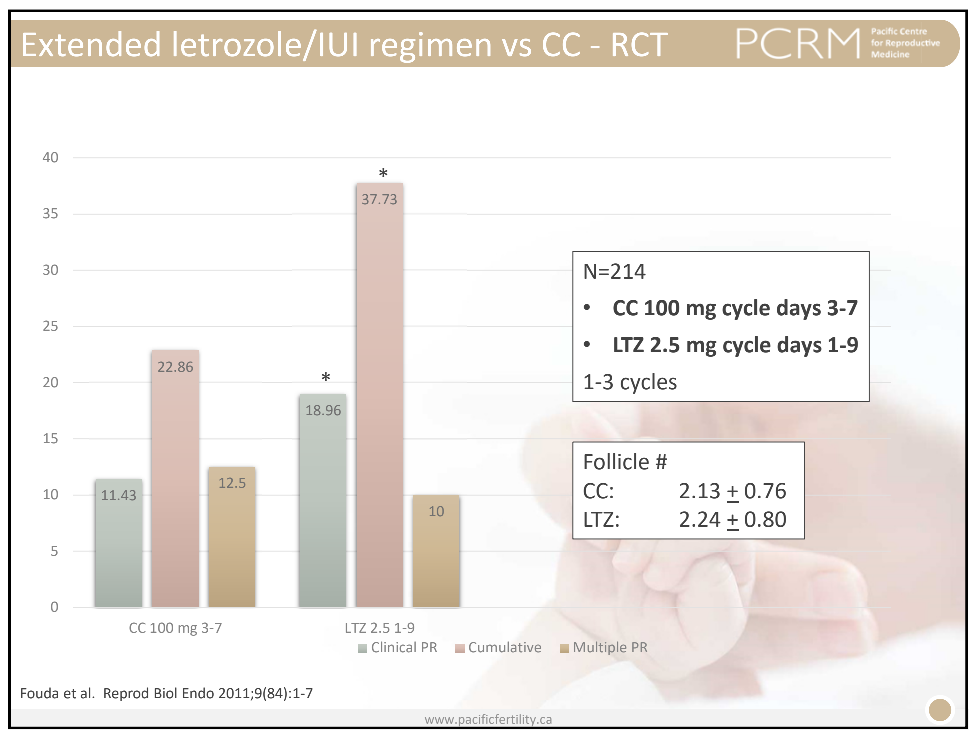


Randomized unfavourable prognosis patients to 3 cycles of:

- IUI with CC 50-150 mg days 2-6 or LTZ 2.5-7.5 mg , days 2-6
- Expectant management

3X higher live birth rate with CC/LTZ

Farquhar et al. Lancet 2018;391:441-50



Extended LTZ for Unexplained Infertility

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- Retrospective analysis of PCRM experience with extended LTZ ± IUI for UEI
- N = 141
- 2.5 mg PO cycle days 1 to 9
- Midcycle ultrasound assessment
- Average age 35.3
- Maximum of 6 cycles, average 3.2
- Cumulative pregnancy rate: **14.3%**
- Multiple pregnancy rate: 10.0%
- Mean # follicles 1.9

Harjee et al. CFAS Annual Meeting 2017

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Management of Unexplained Infertility

- Consider expectant management after completion of work-up, particularly if there has been a surgical correction (e.g. polyp)
- Letrozole 2.5 mg PO QD cycle days 1 to 9 ± IUI
- Clomiphene citrate 100 mg PO QD cycle days 3 to 7 + IUI

Case # 2

- 29 y.o. G0
- Irregular cycles, q 3-4 months
- Complaints of oily skin and acne
- Difficulty detecting ovulation
- Investigations:
    - SA: normal
    - HSG: patient declined
    - Ovarian reserve testing: AMH 29 pmol/L, FSH 4 IU/L, AFC 25

Polycystic Ovary Syndrome

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- Criteria (2 of 3)[1]
  - Anovulation – oligo (>70%), poly (<2%), or eumenorrhea (20-30%)
  - Polycystic ovaries
  - Hyperandrogenism (clinical or biochemical)
- 80% of women with anovulatory infertility
- Clinical features broader
  - Reproductive (infertility, pregnancy-related risks)
  - Metabolic (obesity, insulin resistance, GDM, cardiovascular risks)
  - Psychological (anxiety, depression, impaired quality of life)

1. ESHRE/ASRM, 2004 Rotterdam Criteria
2. National Institute of Health (NIH) 1990 criteria

Polycystic Ovary Syndrome - Work up

- Menstrual history
  - Irregular cycles (>35 or <21) continuing for >2 years after onset of menarche
- Pelvic ultrasound
  - PCO = >12 antral follicles per ovary, volume >10cm^3
- No HSG?
- Assessment of ovulation
  - Mid-luteal progesterone (<10 nmol/L)
  - Follicle tracking
- Early follicular FSH, LH and estradiol
- AMH (>35 pmol/L)
- Assessment for hyperandrogenism
  - Clinical
  - Biochemical (testosterone, DHEAS, 17OHP)
- DM screen

Polycystic Ovary Syndrome - Treatment

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- Weight loss (5-10%)
  - Lower risk pregnancy
  - Improved response to ovulation induction and natural conception
- Bariatric surgery (suggested with BMI >35 and failed weight loss > 1 yr)
- Clomiphene citrate (no IUI)
  - 50-150 mg PO cycle days 3 to 7
- Aromatase inhibitors (no IUI)
  - 2.5-7.5 mg PO cycle days 3 to 7
- Metformin
- Gonadotropins
- Laparoscopic ovarian drilling

Balen et al. Hum Reprod Update 2016;22(6):6687-708

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Goals of Ovulation Induction

- Restoration of a normal menstrual cycle
  - Predictable ovulation
  - Regular menses
- Singleton pregnancy/monofollicular response
- Avoidance of gonadotropins

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Clomiphene Citrate

- Starting dose 50 mg PO cycle days 3-7 or 5-9, with incremental 50 mg increase if no response
- 75% of pregnancies occur in first three cycles and few occur after 6 months
- 10-15% multiple pregnancy rate
- Ovulation rate 60-90% but only 10-40% conceive
  - Co-release of LH with FSH
  - Anti-estrogenic effects on endometrium and cervical mucous

Kousta et al. Hum Reprod Update 1997;3:359-365

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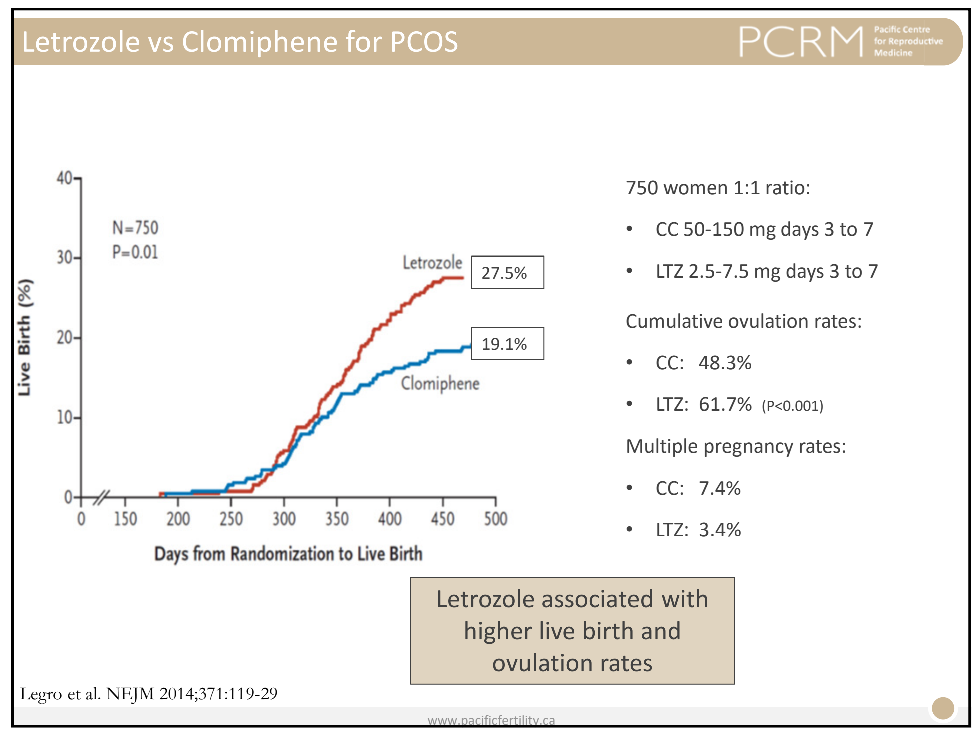
Letrozole vs Clomiphene for PCOS



750 women 1:1 ratio:

- CC 50-150 mg days 3 to 7
- LTZ 2.5-7.5 mg days 3 to 7

Cumulative ovulation rates:

- CC: 48.3%
- LTZ: 61.7% (P<0.001)

Multiple pregnancy rates:

- CC: 7.4%
- LTZ: 3.4%

Letrozole associated with higher live birth and ovulation rates

Legro et al. NEJM 2014;371:119-29

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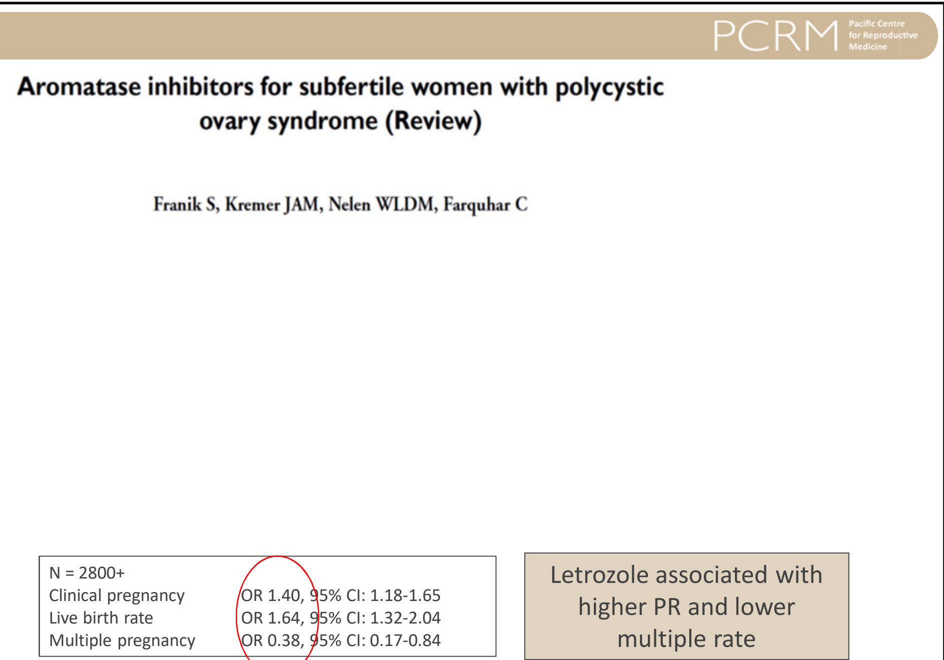

Ovulation Induction Monitoring

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- Ovulation predictor kits
  - False positives if starting too early
- Midluteal progesterone levels (>10 nmol/L)
  - Stop measuring once effective dose established and patient regular
  - Absolute level of no value just + or -
- Monitoring follicular phase (starting cycle days 10):
  - Gold standard for diagnosing anovulation[1]:
    - Establishing lack of response early
    - Useful if patient doesn't get positive OPKs
    - Lowering risk multiple gestation
  - Does NOT increase pregnancy rate
  - Costly
  - Patient fatigue
- Ovulation triggering of no benefit[2-3]

STAY HOME

1. Ecochard et al. BJOG 2001;108:822-9
2. Kyrou et al. RBMO 2012;25:278-283
3. Agarwal et al. Hum Reprod 1995;10:328-331

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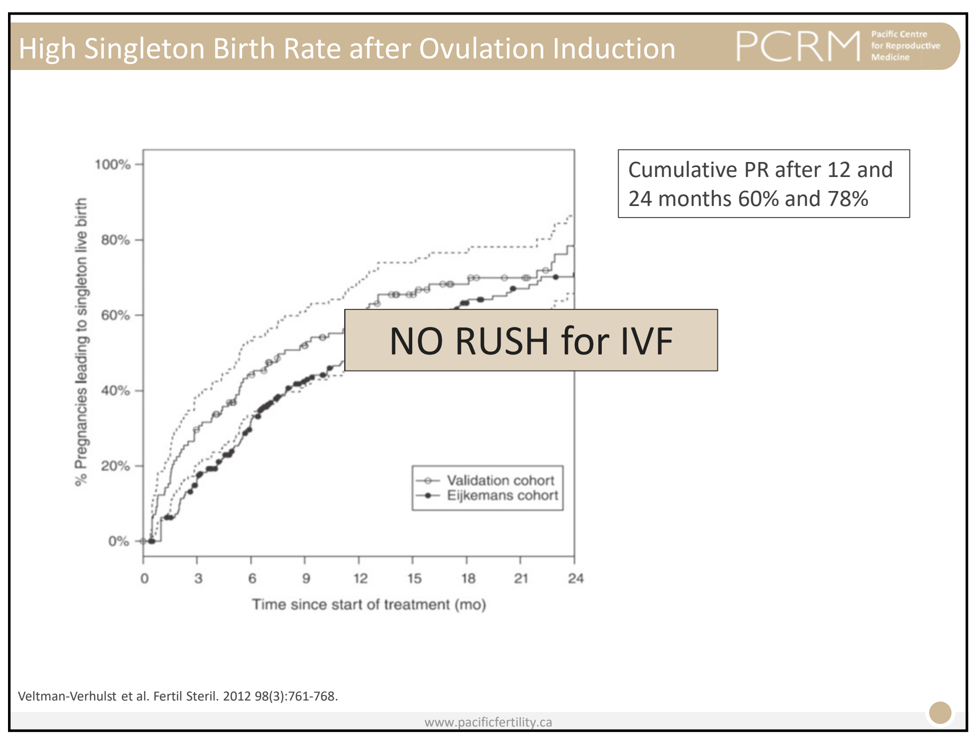
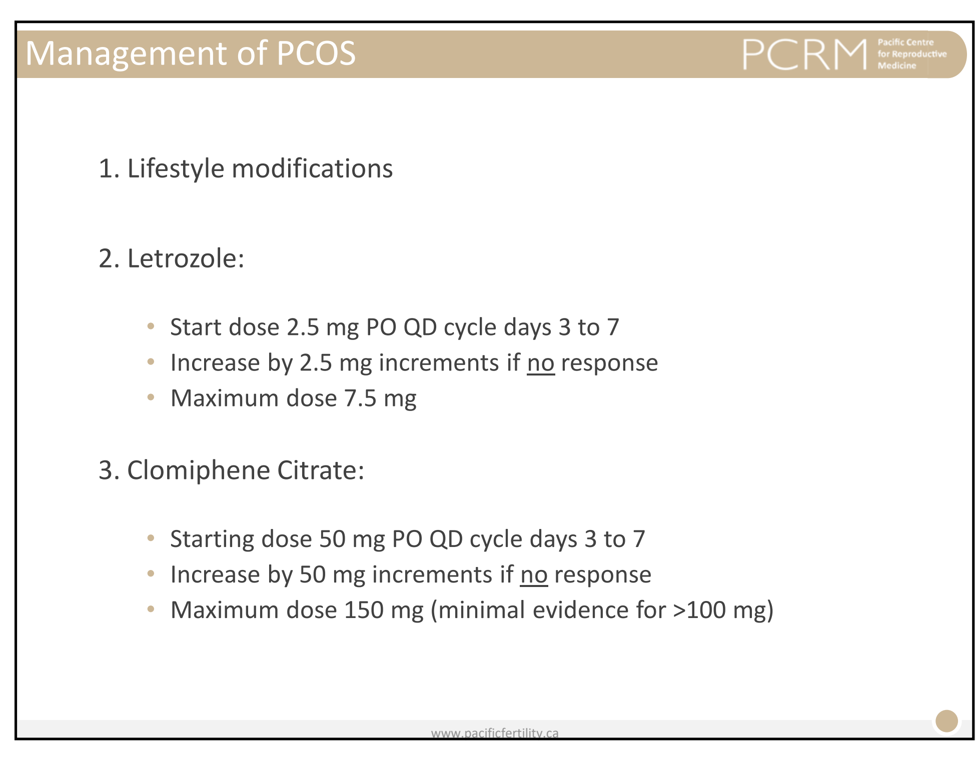

High Singleton Birth Rate after Ovulation Induction
PCRM
Pacific Centre for Reproductive Medicine
Cumulative PR after 12 and 24 months 60% and 78%
NO RUSH for IVF
% Pregnancies leading to singleton live birth
100%
80%
60%
40%
20%
0%
0
3
6
9
12
15
18
21
24
Time since start of treatment (mo)
Validation cohort
Eijkemans cohort
Veltman-Verhulst et al. Fertil Steril. 2012 98(3):761-768.
www.pacificfertility.ca


Management of PCOS
PCRM
Pacific Centre for Reproductive Medicine
1. Lifestyle modifications
2. Letrozole:
Start dose 2.5 mg PO QD cycle days 3 to 7
Increase by 2.5 mg increments if no response
Maximum dose 7.5 mg
3. Clomiphene Citrate:
Starting dose 50 mg PO QD cycle days 3 to 7
Increase by 50 mg increments if no response
Maximum dose 150 mg (minimal evidence for >100 mg)
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Case # 3

- 33 y.o. G0
- Cycles q 26-32 days
- OPKs occasionally faintly positive
- Investigations:
  - SA: low normal morphology
  - HSG: normal
  - Ovarian reserve: AMH 28 pmol/L, FSH 6 IU/L, AFC 32

Traditional Thinking on Ovulation

Ovulatory cycles have regular, predictable and consistent volume and duration

- Eumenorrhea defined by a wide range of lengths (21-35) established through epidemiologic studies

Anovulatory cycles are irregular and unpredictable

- Oligomenorrhea defined as >35 days

Malcolm et al. Obstet Gynecol 2003;102(2):317-318
Cole et al. Fertil Steril 2009;91:522-7

Occult Ovulatory Dysfunction

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- PCOS may be a continuum
- Approximately 20% women have menstrual irregularity 2/3 do not meet criteria for PCOS[2]
- "Regular" menses does not exclude anovulation (mild phenotype in 10-15%)[1]

1. Sjaarda et al. Fertil Steril 2018;109:540-8
2. Soloman et al. JAMA 2001;286:2421-6

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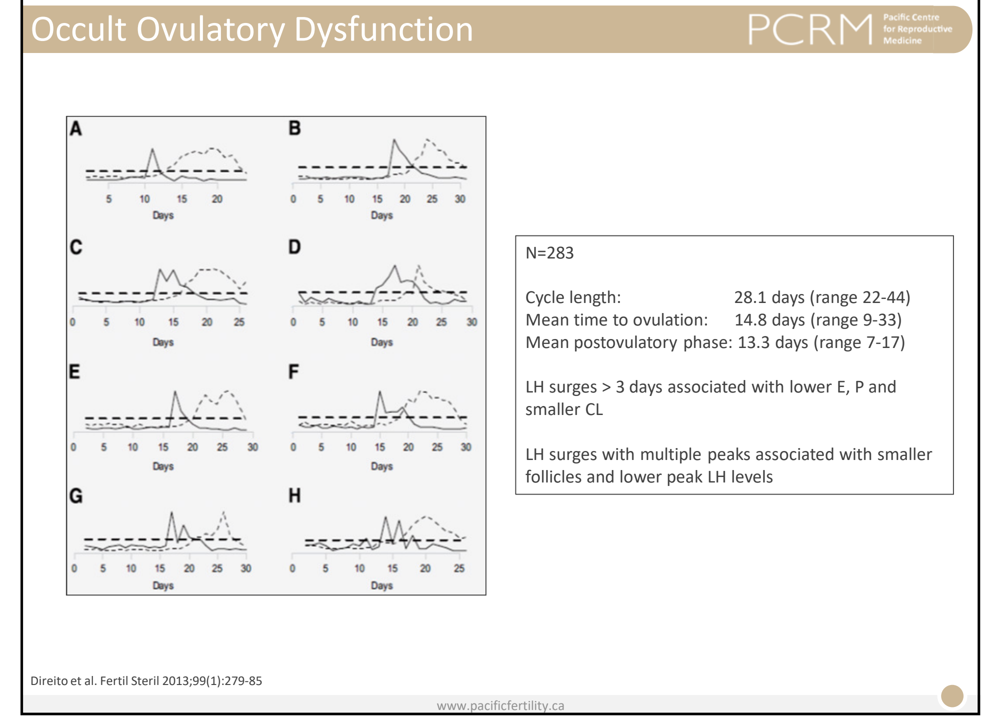

Occult Ovulatory Dysfunction

Luteinized unruptured follicles (LUF) – failure of follicle to rupture at the expected follicular-luteal transition:[1]

- Slower growth as approaches maximum size
- Lower peak FSH and LH levels
- Premature rise of progesterone (premature luteinization)

Luteal phase defect

- Estrogen deficiency will lead to poor priming of endometrium (ER PR upregulation)
- Progesterone deficiency leads to inadequate luteinization
- Short cycles (<25 days) and short luteal phase (<11 days) associated with subfertility[2]
- Women with unexplained infertility have lower progesterone during luteal phase[3]

1. Bashir et al. Hum Reprod 2018;33(6):1130-1140
2. Crawford et al. Fertil Steril 2016;107(3):749-55
3. Blacker et al. Fert Steril 1997;67:437-42

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Occult Ovulatory Dysfunction

Risk factors for oligo/anovulation:

- High AMH (>30 pmol/L)
  - 18-20% rate anovulation
  - AMH reduces sensitivity of granulosa to FSH
  - AMH receptors expressed on GnRH neurons in hypothalamus
- Hyperandrogenism
  - 20-50% have chronic anovulation[1]
- Polycystic ovaries = high ovarian reserve ≠ PCOS[2]
  - 20-30% of population
  - Very common in young patients
  - Approximately 20% have PCOS
- Insulin resistance/metabolic abnormalities – poorly studied but likely an association

1. Chang et al. Fertil Steril 2005;83:1717-23
2. Azziz et al Fertil Steril 2009;91(2):456-88

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Management Occult Ovulatory Dysfunction

1. Lifestyle modifications

2. Letrozole:
   - Start dose 2.5 mg PO QD cycle days 3 to 7
   - Increase by 2.5 mg increments if no response
   - Maximum dose 7.5 mg

3. Clomiphene Citrate:
   - Starting dose 50 mg PO QD cycle days 3 to 7 for anovulation
   - Increase by 50 mg increments if no response
   - Maximum dose 150 mg (minimal evidence for >100 mg)

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Case # 4

- 28 y.o. G0
- Triathelete
- No period since stopping OCs 2 years ago
- No withdrawal bleed to Provera 10 mg x 10 days
- Investigations:
  - SA: normal
  - HSG: not performed
  - Ovarian reserve: AMH 20 pmol/L, FSH <1 IU/L, LH <1 IU/L, AFC 16

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Hypothalamic Amenorrhea

- Limited central function secondary to disrupted GnRH release and low FSH and LH secretion
- Risk factors:
  - Low BMI
  - Exercise
  - Stress
- Diagnosis
  - Failed progestin challenge (hypoestrogenic)
  - Low serum gonadotropin levels, normal prolactin
  - Normal cranial imaging
- Management
  - Lifestyle modification
  - Gonadotropins (FSH + LH)/IUI or IVF
  - Not CC or LTZ

Take Home Messages

- More eggs = more babies but also more risk – optimal number limited by safety
- Consider expectant management after the diagnosis of unexplained infertility
- Clomiphene traditionally first line for ovulatory disorders
- Based on existing evidence, letrozole first line for ovulatory disorders
- Clomiphene/IUI and letrozole acceptable for unexplained infertility
- Have a low threshold for starting letrozole in any patient with suggestion of ovulatory dysfunction

Take Home Messages

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When to refer to REI

- Completion of treatment course:
  - Unexplained infertility: 3-6 months
  - Ovulatory disorders: 6 months of ovulatory cycles
- Hypothalamic amenorrhea
- Advanced age (>37)
- Poor ovarian reserve testing

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