SESSION B4

Enhancing Fertility: Letrozole vs. Clomid
Angela C. Thyer, MD

Session Description:

Clomid and Letrozole are both used frequently for ovulation induction and to increase fertility.

Learning Objectives:

Following my presentation, participants will be able to:
1. Describe the difference in mechanism of action between letrozole and clomiphene citrate.
2. Review indications for usage, side effects, and outcomes.
3. Review comparative studies and when one may be more useful than the other.
Objectives

- Describe the difference in mechanism of action between letrozole and clomiphene citrate
- Review indications for usage, side effects, and outcomes
- Review comparative studies and when one may be more useful than the other

Goals of ovarian stimulation

- In oligo or anovulatory women:
  - Single oocyte
- In ovulatory women with unexplained or age-related subfertility:
  - Multiple oocytes

Multiple gestation

- In 2008, multiples made up 3.26% of all births in the US
- Natural rate of dizygotic twinning is 8 in 1000 in the US
- Natural rate of monozygotic twinning is 4 in 1000
- Majority of high-order gestations result from ovulation cycles rather than natural cycles or ART

What is letrozole?

- Non-steroidal aromatase inhibitor
- Inhibitor of estrogen synthesis

ENHANCING FERTILITY: LETROZOLE VS. CLOMID
Angela Thyer, MD
Seattle Reproductive Medicine
Where is aromatase found?
- Ovaries
- Adipose
- Brain
- Muscle
- Liver
- breast

What are the indications for letrozole?
- Extended adjuvant treatment of early breast cancer in postmenopausal women following 5 years of tamoxifen therapy
- First line treatment of postmenopausal women who are ER+ or hormone receptor status unknown advance or metastatic breast cancer
- Treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy

Pharmamacokinetics
- Letrozole doses of 2.5-5 mg/day inhibit estrogen levels by 75-95%
- Half-life: 45 hrs
- Clearance: liver
- Pregnancy category X

Letrozole: Side Effects
- Side effects vs. placebo in postmenopausal women:
  - nausea (8.6% vs. 8.2%)
  - hot flashes (50% vs. 43%)
  - joint pain (22% vs 18%)
  - muscle pain (7% vs 5%)
  - fatigue (34% vs 32%)

Letrozole for ovulation induction
- Aromatase inhibition
- Blocks estradiol production
- Releases hypothalamic/pituitary axis from negative estrogenic feedback
- Increases gonadotropin secretion

Casper RF, Fert Ster, Dec 2003 (80;6, 1335-1337)
Letrozole for OI in PCOS

- Excessive androgens are aromatized to estrogen
- Constant elevation of estrogen suppresses FSH secretion
- Aromatase inhibition releases that suppression

Secondary mechanisms of action

- Increased follicular sensitivity to FSH
- Elevation in intra-ovarian testosterone has been shown to augment FSH receptor expression in primates
- Androgen accumulation stimulates IGF-1 which promotes folliculogenesis

Endometrial effects of Aromatase Inhibitors

- Suppression of estrogen
- Upregulation of ER in the endometrium
- More rapid proliferation of endometrium once estrogen secretion is restored

Clomiphene Citrate

- Nonsteroidal triphenylethylene derivative
- Estrogen agonist and antagonist properties (SERM activity)
- Racemic mix of 2 isomers, enclomiphene and zuclomiphene

Clomiphene Citrate

- 1st use in 1961
- Most commonly used ovulation induction agent
- Long half-life, 5 days to 3 weeks
- Acts mainly as an antiestrogen except when estrogen levels are very low
- Pregnancy category X

Clomiphene Citrate

- CC binds to estrogen receptors for extended periods
- Leads to ER depletion
- Estrogen levels perceived as falsely low in the hypothalamus leading to increased GnRH secretion, and subsequent FSH and LH secretion
Clomiphene Citrate

- Increases GnRH pulse frequency in ovulatory women
- Increases pulse amplitude in women with PCOS
- Supraphysiologic levels of estradiol are common

Cumulative Pregnancy Rate with Clomid

A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women

Fisher SA, Reid RL, Van Vugt DA, Casper RF
Fertility and Sterility - August 2002 (Vol. 78, Issue 2, Pages 280-285)

- 19 Normal volunteers, 18-35, not fertility patients
- Primary outcome: # of mature follicles ≥ 18 mm at the time of LH surge
- Daily blood, interval ultrasounds

<table>
<thead>
<tr>
<th></th>
<th>Natural</th>
<th>Clomid</th>
<th>Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td># fol &gt; 18</td>
<td>1</td>
<td>2.2 + 0.7</td>
<td>1.7 + 0.5</td>
</tr>
<tr>
<td>E2 on the day of LH surge</td>
<td>623 pmol/L</td>
<td>2047 ± 930</td>
<td>399 ± 167</td>
</tr>
</tbody>
</table>
Randomized study: CC vs. letrozole in women with PCOS
- Clomiphene 100 mg CD 3-7 (n=55)
- Letrozole 2.5 mg CD 3-7 (n=51)
- With letrozole, the # of follicles was less
- Endometrial thickness, ovulation, and pregnancy rates were higher


Randomized study: CC vs. letrozole
- Clomiphene 100 mg CD 3-7 (n=95)
- Letrozole 2.5 mg CD 3-7 (n=91)


Randomized study: CC vs. letrozole in PCOS with TIC
- 438 women with PCOS
- Clomiphene 100 mg CD 3-7 (n=523 cycles)
- Letrozole 5 mg CD 3-7 (n=540 cycles)

Randomized study: CC vs. letrozole

Atay V, 2006

Randomized study: CC vs. letrozole in PCOS

Bayar U, 2006
Randomized study: CC vs. letrozole

Badawy, 2009
Meta-Analysis 2011

- He D. et al
- 6 RCTs
- 841 patients
- Letrozole showed decreased # of mature follicles
- No difference in PR, SAB, Multiples

He D and Jiang F, Reprod Biomed Online, 23(1): 91-6; 2011

Letrozole—Neonatal Outcome

- ASRM 2005
- Follow up of 150 babies after letrozole OI
- Comparison group 36,000 spontaneous conceptions
- Congenital anomaly rate 3-4%
- Increased cardiac and locomotor anomalies
- Low birth weight in patients with gestational diabetes

Result: Novartis issued warning that femara is contraindicated in premenopausal women

Neonatal Outcome—Clomiphene Citrate

- National Birth Defects Prevention Study
  - Human Reproduction 2011; 26:451-7
  - ~25,000 women
  - Increased OR for cardiac defects with CC
- Davies, et al
  - NEJM 2012; 366:1803-13
  - OR for CC 3.19 (1.32 – 7.69)

Human Reprod 2011; 26:451-7

Neonatal Outcome—Letrozole vs. CC

- Multicenter Canadian study
- Outcome in 911 babies
- Rate of congenital anomalies
  - Letrozole 2.4% (n=514)
  - Clomiphene 4.8% (n=397)
- Cardiac defects
  - Letrozole 0.2%
  - Clomiphene 1.8%

*p=0.02


Results of Randomized Studies—Letrozole vs. Clomiphene

<table>
<thead>
<tr>
<th>Author</th>
<th>Let/CC (n)</th>
<th>Ovulation Rate</th>
<th>Pregnancy Rate</th>
<th>Multiple Rate</th>
<th>SAB Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atay, et al (2006)</td>
<td>51/55</td>
<td>82/64*</td>
<td>22/9*</td>
<td>0/20</td>
<td>NR</td>
</tr>
<tr>
<td>Badawy et al, (2009)</td>
<td>54/523</td>
<td>68/71</td>
<td>15/18</td>
<td>0/3</td>
<td>12/10</td>
</tr>
<tr>
<td>Bayer, et al (2006)</td>
<td>99/95</td>
<td>69/75</td>
<td>9/7</td>
<td>0/0</td>
<td>1/0</td>
</tr>
<tr>
<td>Kar (2012)</td>
<td>51/52</td>
<td>73/51</td>
<td>22/9*</td>
<td>0/0</td>
<td>NR</td>
</tr>
</tbody>
</table>

*p<0.05

Meta-analysis 2012

- AI for PCOS, 6 RCTs
- No difference in ovulation rate, pregnancy, live birth, multiple rate, or SAB rate

Conclusion- AIs should not be recommended as first line

Misso ML et al, Hum Repr Update, 18(3): 301-12; 2012
RCT CC or AI for unexplained

- 100 mg CC d 3-7 (207 pts, 404 cycles)
- 5 mg letrozole d 3-7 (205 pts, 400 cycles)
- IUI 36 hrs +/- 4 hrs after hcg injection

No superiority between letrozole and CC for inducing ovulation in women with unexplained infertility

Badawy et al, Fert Ster 92(4): 1355-9; 2009

Letrozole vs CC for OI with unexplained infertility

- 214 patients
- Letrozole 2.5 mg/day days cd1-9 (211 cycles)
- CC 100 mg/day cd 3-7 (210 cycles)
- IUI 36-40 hrs after hcg trigger

Fouda UM, Sayed Reprod Bio Endo 21:9:84; 2011

CC vs. extended letrozole in unexplained infertility

Fouda UM and Sayed AM, 2011

Letrozole v. Clomiphene for PCOS

- Richard Legro, MD, lead author
- NEJM July 10, 2014
- Double-blind, multicenter trial

Letrozole v. Clomiphene for PCOS

- 750 women in each arm, 1:1 ratio
- Letrozole or clomiphene
- Up to 5 treatment cycles
- 18-40 yo, at least 1 open tube, male partner with sperm concentration of > 14 mil/ mL

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coullias, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haasenieder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dansu Ohii, M.D., Nanette Santoro, M.D., Esther Eitemberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network™
Letrozole v. Clomiphene for PCOS

- Primary outcome: live birth: 103 of 374 (27.5%) with letrozole vs 72 of 376 (19.1%) with clomiphene
- Ovulation rates: 62% of cycles with letrozole, 48% with clomiphene
- Twins, lower with letrozole, (3.4% vs 7.4%) but not adequately powered to detect a difference

Letrozole v. Clomiphene for PCOS

- Congenital anomalies:
  - In clomiphene group, 1 infant had a ASD, VSD, and pulmonary stenosis
  - In letrozole group, 1 infant had cerebral palsy with arrested hydrocephalus, 1 infant had an imperforate anus with spina bifida, 1 infant had right hemimegalencephaly and dysgenesis of the left frontal and temporal lobes, 1 infant had VSD.

Letrozole v. Clomiphene for PCOS

- Side Effects
  - Clomiphene: Hot flushes 33%
  - Letrozole: Fatigue 21.7%, Dizziness: 12.3%

What is the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole? An analysis of 988 cycles

Anna Palatnik, M.D., Estil Strawn, M.D., Aniko Szabo, Ph.D. and Paul Robb, M.D.

Fertility and Sterility

Volume 97, Issue 5, Pages 1089-1094.e3 (May 2012)

DOI: 10.1016/j.fertnstert.2012.02.018

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Kaplan-Meier Curves for Live Birth

Figure 1
We estimated that each additional millimeter of endometrial thickness is associated with an increase in the optimal follicular size by 0.5 mm.

For an endometrial lining of 9 mm, which was the mean thickness in our study, the optimal follicular size was 24 mm with CC and 24.7 mm with letrozole.

For both drugs, higher pregnancy rates were achieved with the leading follicle being in the range of 23 to 28 mm.

| OI IUI costs with US monitoring                     |
|---------------------------------------------|--------|
| CC or Letrozole                             | $25    |
| US CD12-14                                  | $175   |
| Ovulation Predictor Kit                     | $25    |
| HCG injection                               | $75    |
| IUI next day                                | $450   |
| TOTAL                                       | $750 (average) |

How many cycles should you do?

- CC and IUI, analysis of >4100 cycles from Boston IVF
- PR per cycle is higher for 1st two cycles than cycles 3-9
- Difference in success is related to age

Dovey et al. Fert Ster 90(6):2281-6, 2008
Letrozole vs Clomiphene: Summary

- Letrozole has fewer side effects

### Side effects/ adverse effects

<table>
<thead>
<tr>
<th>Clomiphene</th>
<th>Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
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</tr>
<tr>
<td>Vaginal dryness</td>
<td>Arthalgias</td>
</tr>
<tr>
<td>Headaches</td>
<td>Fatigue</td>
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<tr>
<td>Mood swings</td>
<td>Dizziness</td>
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<tr>
<td>Blurry Vision</td>
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<tr>
<td>Dry cervical mucus</td>
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<tr>
<td>Thin endometrial lining</td>
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<td>Ovarian Cysts</td>
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### Half life

<table>
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<th>Clomid</th>
<th>Letrozole</th>
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<tr>
<td>Up to 3 weeks</td>
<td>About 45 hours</td>
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### Congenital Anomalies

<table>
<thead>
<tr>
<th>Clomid</th>
<th>Letrozole</th>
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<tbody>
<tr>
<td>2.0%</td>
<td>2.0%</td>
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Anomalies vary based on the study
FDA indications

<table>
<thead>
<tr>
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<th>Clomid</th>
<th>Letrozole</th>
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<tbody>
<tr>
<td>Labeling</td>
<td>Indicated for fertility treatment</td>
<td>Off-label</td>
</tr>
<tr>
<td>Duration of experience for ovulation</td>
<td>50+ years</td>
<td>10+ years</td>
</tr>
</tbody>
</table>

Letrozole vs Clomiphene: Summary

- Ovulation rates and pregnancy rates favor letrozole in most studies
- Possibly lower risk of multiples with letrozole

Ovulation

<table>
<thead>
<tr>
<th></th>
<th>Clomid</th>
<th>Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation rates</td>
<td>48-80%</td>
<td>60-80%</td>
</tr>
<tr>
<td>Pregnancy rates</td>
<td>7-19%</td>
<td>9-28%</td>
</tr>
</tbody>
</table>

*may be lower for higher BMI, 48% in Legro paper

Letrozole: Take Home points

- Similar cost
- Well-tolerated
- Higher ovulation in letrozole
- Improved endometrium with letrozole
- Biggest drawback to wider acceptance is off-label use