Aromatase Inhibitors for Ovulation Induction

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Disclosure: Licensing agreement with EMD-Serono
Discussion of off-label use of drugs
Objectives

• Are aromatase inhibitors effective?

• Are aromatase inhibitors safe?
Fisher et al, Fertil Steril 2002
Natural Cycle

CC Cycle
Aromatase Inhibitor Treatment

FSH → ER → E2 → AI → FSH

Day 5

FSH → ER → E2

Day 10
Natural Cycle
Letrozole

FSH level (mIU/mL)

No of Days from LH surge

Fisher et al, Fertil Steril 2002
Are Aromatase Inhibitors Effective?
Randomized Controlled Trials
Letrozole vs CC

- Sammour et al, ASRM abstract 2001 (n=49)
- Fatemi et al, RBM online 2003 (n=15)
- Al-Fozan et al, Fertil Steril 2004 (n=154)
- Sohrabvand et al, Hum Reprod 2006 (n=59)
- Bayar et al, Fertil Steril 2006 (n=74)
- Begum et al, Fertil Steril (in press) (n=64)

Total subjects = 959
Total cycles = 1785
PCOS trials: Weighted Relative Risk

Atay et al, 2006
Badawy et al, in press
Begum et al, in press
Sohrabvand et al, 2006
Average: 1.02 (0.83, 1.26)

662 patients, 1247 cycles
Eight Trials: Weighted Relative Risk

- Al-Fozan et al, 2006
- Atay et al, 2006
- Badawy et al, in press
- Bayar et al, 2006
- Begum et al, in press
- Fatemi et al, 2003
- Sammour et al, 2001
- Sohrabvand et al, 2006

Average: 1.06 (0.87, 1.30)

959 patients, 1785 cycles
Pregnancy Rate per Cycle

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>5%</td>
<td>994</td>
</tr>
<tr>
<td>FSH</td>
<td>15%</td>
<td>772</td>
</tr>
<tr>
<td>Letrozole 2.5mg</td>
<td>20%</td>
<td>310</td>
</tr>
<tr>
<td>Letrozole 5.0mg</td>
<td>25%</td>
<td>432</td>
</tr>
<tr>
<td>CC+FSH</td>
<td>30%</td>
<td>205</td>
</tr>
<tr>
<td>Let+FSH</td>
<td>40%</td>
<td>609</td>
</tr>
<tr>
<td>Natural</td>
<td>5%</td>
<td>423</td>
</tr>
<tr>
<td>Total</td>
<td>25%</td>
<td>3748</td>
</tr>
</tbody>
</table>
Multiple Pregnancy Rate

Mitwally et al, AJOG 2005;192(2):381-6
Spontaneous Abortion Rate per Cycle

Mitwally et al, AJOG 2005;192(2):381-6
Summary

• Letrozole as least as effective as CC for ovulation induction or augmentation
• Low risk of multiple pregnancy when used alone
• Short half-life
• No anti-estrogenic or estrogenic effects
Are Aromatase Inhibitors Safe?
The Outcome of 150 Babies Following the Treatment with Letrozole or Letrozole and Gonadotropins.

M. M. Biljan, R. Hemmings, N. Brassard.
Montreal Fertility Centre, Montreal, PQ, Canada; St. Mary’s Hospital, Montreal, PQ, Canada; Universite´ Laval, Que´bec, PQ, Canada.
Methods

• One hundred and fifty letrozole babies in 130 pregnancies

• Compared with a data-base of 36,050 normal deliveries in a low risk hospital

1. Biljan et al. ASRM October 14-19, 2005; Montreal, Quebec. Abstract O-231
Results

• Incidence of all malformations was not different between the two groups (p=0.25; 95% CI 0.78-4.71).

  The incidence of locomotor malformations  
  p=0.0005; 95% CI 2.64–27.0

  The incidence of cardiac anomalies  
  p=0.0006; 95% CI 3.30–58.1

1. Biljan et al. ASRM October 14-19, 2005; Montreal, Quebec. Abstract O-231
Problems

- Control group not infertility patients
- Delivered in a low-risk hospital
- Controls 5 years younger than the letrozole group
- Twin rate 15% compared to 1.25% in the general population
- Gestational diabetes rate 15%
Problems

• 150 pregnancies in the letrozole group and 36,050 in the control group
• If a rare congenital abnormality (1/1000) happens in a small study group like the letrozole pregnancy group (1/150), its frequency automatically appears 7X as great
Pharmaceutical Company Response

- November 17, 2005
- Novartis issued a Health Canada endorsed letter stating contraindication for the use of letrozole in women with premenopausal endocrine status
- Because of the potential for maternal and fetal toxicity and fetal malformations

New Pregnancy Outcome Data

• 911 pregnancies between 2003 and 2005
• Five clinics
  – TCART, University of Toronto and CREATE, Toronto
  – McGill University, Montreal
  – SOFT, London, Ontario
• Letrozole ± FSH compared with CC ± FSH
• All patients monitored for IUI or TI

### Group Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Letrozole</th>
<th>Letrozole + FSH</th>
<th>CC</th>
<th>CC + FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newborns</strong></td>
<td>252</td>
<td>262</td>
<td>293</td>
<td>104</td>
</tr>
<tr>
<td><strong>Birth weight (grams)</strong></td>
<td>3287 ± 616</td>
<td>3248 ± 639</td>
<td>3159 ± 609</td>
<td>3323 ± 365</td>
</tr>
<tr>
<td><strong>Twins</strong></td>
<td>12 (4.8%)</td>
<td>23 (8.8%)</td>
<td>15 (5.1%)</td>
<td>6 (5.8%)</td>
</tr>
<tr>
<td><strong>Triplets</strong></td>
<td>1</td>
<td>1</td>
<td>1 (fetal reduction to twins)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age of mother (years)</strong></td>
<td>33.1 ± 5.3</td>
<td>32.4 ± 5.4</td>
<td>32.9 ± 4.5</td>
<td>33.9 ± 4.9</td>
</tr>
</tbody>
</table>

Congenital Malformations and Chromosomal Abnormalities

• Overall malformation rate
  – 14 of 514 newborns with letrozole (2.4%)
  – 19 of 397 newborns with CC (4.8%)

• Major malformation rate
  – letrozole 1.2% (6/514)
  – CC 3.0% (12/397)

Cardiac Anomalies

• Letrozole group
  1/514 (0.2%)

• CC group
  7/397 (1.8%)

P = 0.02

## Major Malformations CC

<table>
<thead>
<tr>
<th>Condition</th>
<th>Birth weight (grams)</th>
<th>Age of mother (years)</th>
<th>CC dose (mg)</th>
<th>Other medication</th>
<th>Possible contributing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>2380</td>
<td>32</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VSD</td>
<td>2890</td>
<td>29</td>
<td>50</td>
<td>FSH, Prog</td>
<td>Smoking</td>
</tr>
<tr>
<td>VSD</td>
<td>2060</td>
<td>31</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VSD</td>
<td>1030</td>
<td>39</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transposition of great vessels</td>
<td>3488</td>
<td>29</td>
<td>50</td>
<td>-</td>
<td>Smoking</td>
</tr>
<tr>
<td>Atresia of pulmonary valve and right ventricle</td>
<td>3005</td>
<td>36</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary valve atresia</td>
<td>3740</td>
<td>33</td>
<td>25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyelectasis</td>
<td>2145</td>
<td>34</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>3600</td>
<td>29</td>
<td>150</td>
<td>-</td>
<td>Smoking</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>3327</td>
<td>39</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>3090</td>
<td>38</td>
<td>100</td>
<td>FSH, Prog</td>
<td>-</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>4082</td>
<td>37</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Major Malformations with Letrozole

<table>
<thead>
<tr>
<th>Condition</th>
<th>Birth weight (grams)</th>
<th>Age of mother (years)</th>
<th>dose (mg)</th>
<th>Other medication</th>
<th>Possible contributing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>2650</td>
<td>33</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>3210</td>
<td>36</td>
<td>5</td>
<td>FSH</td>
<td>-</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>2855</td>
<td>24</td>
<td>5</td>
<td>Metformin</td>
<td>Gestational diabetes</td>
</tr>
<tr>
<td>Potter’s</td>
<td>3175</td>
<td>36</td>
<td>5</td>
<td>Prog</td>
<td>-</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>2497</td>
<td>41</td>
<td>2.5</td>
<td>FSH</td>
<td>-</td>
</tr>
<tr>
<td>Down’s</td>
<td>2551</td>
<td>26</td>
<td>7.5</td>
<td>Metformin</td>
<td>Smoking</td>
</tr>
</tbody>
</table>

Fetal Safety of Letrozole and Clomiphene Citrate for Ovulation Induction

Rachel Forman, MD, FRCSC,1 Simmerpal Gill, MSc,2 Myla Moretti, MSc,2 Togas Tulandi, MD CM,3 Gideon Koren, MD, FRCPC,2 Robert Casper, MD, FRCSC1

1Toronto Centre for Advancing Reproduction Technology, Toronto ON
2Motherisk Program, The Hospital for Sick Children, Toronto ON
3Department of Obstetrics and Gynecology, McGill University, Montreal QC


In its ability to induce ovulation, letrozole compares favourably to clomiphene citrate, which has been the first line treatment for ovulation induction in subfertile women.
Follow-up Study
(The McGill Reproductive Centre, and The Toronto Centre for Advanced Reproductive Technology)

- Pregnancies after letrozole or CC for ovulation induction
- Each woman in the letrozole group was age-matched to a control from the Motherisk database
- All Motherisk controls conceived spontaneously
- Centiles for birthweight adjusted for GA were calculated using centile charts (multiples excluded)
# Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Maternal Age [25%, 75%]</th>
<th>Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole (n=92)</td>
<td>33 [30, 37]</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Motherisk (n=92)</td>
<td>33 [30, 37]</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>CC (n=257)</td>
<td>33 [30, 36]</td>
<td>7 (2.6%)</td>
</tr>
</tbody>
</table>
## Birthweight Adjusted for Gestational Age (Singletons only)

<table>
<thead>
<tr>
<th></th>
<th>MEAN CENTILE ± SD [lower 95% CI, upper 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOTHERISK (n=73)</td>
<td>61.7 ± 33.5, [53.8, 69.5]</td>
</tr>
<tr>
<td>LETROZOLE (n=41)</td>
<td>54.8 ± 30.0, [45.3, 64.2]</td>
</tr>
<tr>
<td>CC (n=54)</td>
<td>37.2 ± 30.6*, [28.9, 45.6] (P&lt;0.05 vs Motherisk)</td>
</tr>
</tbody>
</table>
Conclusion

• Letrozole is not a human teratogen when used for ovulation induction
• Major malformations in the CC group not numerically significantly different from the Motherisk control group
• CC use may be associated with small for gestational age infants
Clomiphene Citrate - Problems

- Long tissue half-life
- High multiple pregnancy rate
- Peripheral anti-estrogenic effects
- Thin endometrium (Gonen et al, 1990)
- Unfavorable cervical mucus
- Reduced uterine blood flow
- Lower pregnancy rate than expected from the high ovulatory rate
Day 3 zuclomiphene concentrations. *Solid line*: All subjects with an ovulatory response (n = 6–9). *Stippled line*: Subjects with an ovulatory response to 50 mg CC (n = 3–5). Data are presented as means ± SE. *P < .05 compared with previous point in post hoc analysis.
Advantages of Aromatase Inhibitors in Ovulation Induction

• Relatively short half-life (~45 hrs)
• Intact central feedback mechanisms
• Increase follicular sensitivity to FSH
• No adverse effects on endometrium or cervical mucous
• Safe for community gynaecologists without access to ultrasound monitoring
• No increased risk of congenital anomalies
AIs as First Line Treatment?

• Similar efficacy to CC for ovulation induction
• Short half life and no accumulation from cycle to cycle
• No adverse ER effects
• Low multiple pregnancy rate in PCOS
• No need for monitoring
Acknowledgements

- Mohamed Mitwally – Wayne State University
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- Cliff Librach, U of Toronto
- Gideon Koren, Motherisk, U of Toronto
- Bob Reid, Stephanie Fisher – Queen’s University
- Marinko Biljan – McGill University, Montreal