What have we learned from Multi-Clinical Trials in PCOS: Focus on Infertility

Richard S. Legro, M.D., Penn State College of Medicine, Dept of Ob/Gyn, Hershey, PA, USA
Disclosures

- Consultant: Euroscreen, AstraZeneca, Clarus Therapeutics, Sprout, Millendo, Kindex, Bayer Takeda, JDS, NIH

- Research Funding: Ferring, Astra Zeneca, NIH, Tobacco Settlement Funds PA

Off Label Uses

- Metformin, Other Anti-Diabetic drugs, and Aromatase Inhibitors are not FDA approved to treat infertility and / or PCOS
Learning Objectives

1. Identify preconception issues in women with PCOS that may affect outcomes.
2. Discuss the common side effects, adverse events, and any teratogenicity of aromatase inhibitors in the treatment of reproductive disorders.
3. Identify the relative efficacy of aromatase inhibitors to treat PCOS vs. unexplained infertility.
Preconception Issues in Women with PCOS

- Undiagnosed, untreated, or poorly controlled medical conditions
  - Impaired Glucose Tolerance/Type 2 DM
- Nutritional Issues
- Family History and Genetic Risk
- Tobacco and substance use
- Occupational and Environmental Exposures
- Mental Health Issues

Adapted from ACOG Committee Opinion #313, September 2005
Smoking and EtOH Use is Common Among Women with PCOS

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 626</td>
</tr>
<tr>
<td>Patient had history of smoking</td>
<td>247/626 (39.5%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>107/626 (17.1%)</td>
</tr>
<tr>
<td>Stopped smoking</td>
<td>140/626 (22.4%)</td>
</tr>
<tr>
<td>Patient had history of alcohol use</td>
<td>416/626 (66.5%)</td>
</tr>
<tr>
<td>Currently using alcohol</td>
<td>226/626 (36.1%)</td>
</tr>
<tr>
<td>No current alcohol use</td>
<td>190/626 (30.4%)</td>
</tr>
</tbody>
</table>

Legro et al, Fertil Steril, 2006
Smoking in infertile women with polycystic ovary syndrome: baseline validation of self-report and effects on phenotype

Richard S. Legro¹,*, Gang Chen², Allen R. Kunselman², William D. Schlaff³, Michael P. Diamond⁴, Christos Coutifaris⁵, Sandra A. Carson⁶, Michael P. Steinkampf⁷, Bruce R. Carr⁸, Peter G. McGovern⁹, Nicholas A. Cataldo¹⁰, Gabriella G. Gosman¹¹, John E. Nestler¹², Evan R. Myers¹³, Heping Zhang¹⁴ and Jonathan Foulds², for the Reproductive Medicine Network.
Current smokers are 30% less likely to ovulate than non-smokers

RR and 95% CI (0.70, 0.50-0.99)

Kuang et al, JCEM, 2015
Prevalence of Glucose Intolerance in PCOS

Study Site
- University of Chicago** 122
- Penn State Univ* 144
- Mt Sinai* 110
- Rezulin Collab Grp¥ 408
- TOTAL 784

¥Azziz et al JCEM 2001, Ehrmann et al, JCEM, 2005
Glucose Intolerance Presents Early and Plateaus During Pregnancy in Women with PCOS

Dmitrovic et al, Obstet Gynecol, 2011
Conclusions

● GDM, defined by glucose intolerance is common during pregnancy in women with PCOS (47% vs 12% in controls), and most likely exists prior to pregnancy.

● Pregnancy per se, may not exacerbate pre-existing glucose intolerance in women with PCOS.

Dmitrovic et al, Obstet Gynecol, 2011
The Experts Recommendation

Infertile PCOS

Obese

Lifestyle therapy

Nonobese

Clomiphene

Consensus on infertility treatment related to polycystic ovary syndrome

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

*Group members: B. C. Tarlatzis (Gr), B. C. J. M. Fauser (NL), R. S. Legro (USA), R. J. Norman (Ausi), K. Hoeger (USA), R. Pasquali (It), S. Franks (UK), I. E. Messinis (Gr), R. F. Casper (Can), R. Homburg (Is), R. Lobo (USA), R. W. Rebar (USA), R. Fleming (UK), B. R. Carr (USA), Ph. Bouchard (Fr), J. Chang (USA), J. N. Huges (Fr), R. Azziz (USA), E. M. Koliubianakis (Gr), G. Griesinger (Ger), K. Diedrich (G), A. Balen (UK), C. Farquhar (NZ), P. Devroey (B), P. C. Ho (HK), J. Collins (Can), D. G. Goulis (Gr), R. Eijkemans (NL), P. G. Crosignani (It), A. DeCherney (USA), A. van Steirteghem (B).

Infertile Overweight/Obese Women with PCOS N = 149

Lifestyle Modification
Continuous OCP
Combined

16 Weeks

Ovulation Induction with Clomiphene: 4 cycles

Conception: Follow q trimester

PRIMARY OUTCOME: Live Birth

Clinicaltrials.gov: NCT00704912
Legro et al, F and S, Suppl 2014
Percent Weight Loss After Preconception Intervention of 16 Weeks

No difference between weight loss with sibutramine or orlistat

*P < .0001

Legro et al, JCEM, 2015
Cumulative Ovulation Rates During 4 Cycles of Clomiphene Citrate Ovulation Induction

Relative Rate of Ovulation vs OCP
- Lifestyle: 1.3, 95%CI 1.0-1.7
- Combination RR 1.5, 95%CI 1.1-1.9

Legro et al, JCEM, 2015

* P < .001 vs Combined and P = .06 vs Lifestyle
Kaplan Meier Curve: Live Birth

Primary Outcome

Legro et al, JCEM, 2015
Post Hoc Analysis: Combination of Lifestyle and Combined into One Treatment Group

Legro et al, JCEM, 2015
Conclusions: Clinical Care

Preconception lifestyle modification in overweight/obese women with PCOS improves ovulation rates with clomiphene vs pretreatment with OCP.

- Treatment is relatively simple, safe and well tolerated.
- Larger studies are needed to confirm the benefit on live birth.
Preconception Issues in Women with PCOS

- Undiagnosed, untreated, or poorly controlled medical conditions
  - Impaired Glucose Tolerance/Type 2 DM
- Nutritional Issues
- Family History and Genetic Risk
- Tobacco and substance use
- Occupational and Environmental Exposures
- Mental Health Issues

Adapted from ACOG Committee Opinion #313, September 2005
Mood Disorders in Women with PCOS

- Increased prevalence of depression and anxiety
  - Dokras A et al, Steroids 2012, Obstet Gynecol 2011

- Does Stress Contribute to Infertility in Women with PCOS?
# Quality of Life by PCOSQ*

**Improved in all Groups**

<table>
<thead>
<tr>
<th></th>
<th>OCP</th>
<th>Lifestyle</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Physical Well-Being</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved**</td>
</tr>
<tr>
<td>General Emotional Well-Being</td>
<td>No Change</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Overall General Well-Being</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
</tbody>
</table>

*Only between group difference was improvement vs OCP

*Cronin et al, JCEM, 1998*
How useful is it to screen women with PCOS and their male partners for other infertility factors?

- 10.4% of males have severe oligospermia
- 4.2% of women have bilateral tubal occlusion

Conclusion: They should be screened.

What is the first line treatment agent for infertility in women with PCOS?
Infertility Treatment in PCOS

- Need for low cost, safe, and effective infertility therapies
  - IVF, developed for Tubal Factor Infertility increasingly used for Ovulatory Dysfunction - more expensive with higher multiple pregnancy rate (~30% in the U.S.).

<table>
<thead>
<tr>
<th>Using own Eggs</th>
<th>2005</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of IVF cycles</td>
<td>89,385</td>
<td>101,213</td>
</tr>
<tr>
<td>Ovulatory Dysfunction (%)</td>
<td>8%</td>
<td>14%</td>
</tr>
</tbody>
</table>

CDC Assisted Reproductive Technology National Summary
Infertility in PCOS: Lessons from PPCOS I

- Clomiphene superior to metformin
- Clomiphene resistance: 25% never ovulated once in up to 6 treatment cycles
- Clomiphene Failure Common: 78% did not have a baby

Legro et al, NEJM 2007
Polycystic Ovary Syndrome: Chronic Anovulation with Androgen Excess

A Metabolic Disorder of Insulin Resistance
Borrow Drugs from Type 2 Diabetes

PCOS?

A Reproductive Disorder of Hypothalamic/Ovarian Dysfunction
Borrow Drugs from Breast Cancer and Prostate Cancer
Rationale for Aromatase Inhibitors in Ovulation Induction

- Interferes with inappropriate estrogen feedback at the hypothalamus
  - Corresponding rise in FSH secretion from the pituitary gland
- Shorter half life than clomiphene
  - Less early pregnancy exposure and cumulative effects
- Favorable Reproductive Effects vs. Clomiphene
  - More monofollicular ovulation
  - More favorable endometrial effects

Casper and Mitwally, JCEM, 2005
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 Coutifaris, 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. Haisenleder, 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., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network*
Primary Outcome: Live Birth

Rate Ratio for Live Birth (LTZ vs CC), 1.44; 95% confidence interval, 1.10 to 1.87

Legro et al, NEJM, 2014
Pundits on the Street: Aromatase Inhibitors Work only in American Women with PCOS and Severe Obesity

Aromatase is expressed in a wide variety of tissues including ovary, fat, brain, breast and endometrium (endometriosis)
Tertile Analysis by BMI

Lower Tertile

BMI <= 30.3, n=250
p = 0.394

Mid Tertile

BMI 30.4-39.4
n=249, p=0.027

Upper Tertile

BMI > 39.4, n=251
p = 0.034

Legro et al, NEJM, 2014
Meta-Analysis of Letrozole in PCOS

- 5 prospective RCTs comparing the use of letrozole to CC in PCOS patients
- There was a statistically significant increase in the live birth rates in the letrozole group when compared to the CC group, relative risk $= 1.55$ (95% CI: 1.26-1.90)
- There were no differences in the multiple pregnancy, miscarriage, and ovulation rates between the two groups.

Roque et al, Gynecol Endocrinol, 2015
What is the mechanism of action for Letrozole?
How to treat Infertility in PCOS?

Insulin Sensitizing Agents, Weight loss, Exercise

Other

Clomiphene, GnRH, Aromatase Inhibitor

FSH, Ovarian Surgery

FSH
No Change in Gonadotropins (Baseline, mean (S.D.) [25%, 75% percentiles].

<table>
<thead>
<tr>
<th>Change in Measure from Baseline to Last Visit</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (mIU/mL)</td>
<td>11.3 -1.9 (9.1)</td>
<td>11.0 -2.4 (9.7)</td>
<td>0.502</td>
</tr>
<tr>
<td></td>
<td>[-5.1, 1.6]</td>
<td>[-5.7, 1.9]</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>6.3 -1.6 (2.6)</td>
<td>6.2 -1.5 (2.7)</td>
<td>0.720</td>
</tr>
<tr>
<td></td>
<td>[-3.3, 0]</td>
<td>[-3.0, 0.1]</td>
<td></td>
</tr>
</tbody>
</table>

Legro et al, NEJM, 2014
No Change in Number of Recruited Follicles [Mean with Median [25%, 75% percentiles].

<table>
<thead>
<tr>
<th>Change in Measure from Baseline to Last Visit</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Measurable Follicles ≥ 10 mm</td>
<td>0.7 ± 1.1</td>
<td>0.7 ± 0.9</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>(0.0 to 1.0)</td>
<td>(0.0 to 1.0)</td>
<td></td>
</tr>
</tbody>
</table>

Legro et al, NEJM, 2014
## Multiple Pregnancy By Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>Relative Rate: Letrozole to Clomiphene (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin Pregnancy</td>
<td>6/81 (7.4%)</td>
<td>4/117 (3.4%)</td>
<td>0.46 (0.13 to 1.58)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Legro et al, NEJM, 2014
What did Change?
Significant Change in Key Parameters at Final Midluteal Visit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change with Letrozole Relative to Clomiphene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antral Follicle Count and AMH Level</td>
<td>Decreased</td>
</tr>
<tr>
<td>Endometrial Thickness</td>
<td>Decreased</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Decreased</td>
</tr>
<tr>
<td>Free Androgen Index</td>
<td>Decreased</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Increased</td>
</tr>
</tbody>
</table>
## Significant Change in Ultrasound Parameters During Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Change in Measure from Baseline to Last Midluteal Visit</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antral follicle count (both ovaries)</td>
<td>-3 (23) [-12, 8]</td>
<td>-5 (22) [-16, 5]</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness: sagittal plane (mm)</td>
<td>3 (4) [1, 6]</td>
<td>2 (4) [0, 5]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Legro et al, NEJM, 2014*
Letrozole improves Hyperandrogenism less than Clomiphene

<table>
<thead>
<tr>
<th>Category</th>
<th>Change in Measure from Baseline to Last Midluteal Visit</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum SHBG (nmol/L)</td>
<td>14 (20) [3, 21]</td>
<td>-2 (16) [-5, 3]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Serum Free Androgen Index</td>
<td>-2 (5) [-4, 0.2]</td>
<td>2 (6) [-1, 3]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Legro et al, NEJM, 2014
**Letrozole Site of Aromatase Inhibition is the Ovary**

Legro et al, NEJM, 2014

<table>
<thead>
<tr>
<th>Category</th>
<th>Change in Measure from Baseline to Last Midluteal Visit</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Estradiol (pg/mL)</td>
<td>53 (108) [-2, 92]</td>
<td>9 (60) [-21, 33]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Progesterone (ng/dL)</td>
<td>11 (22) [-0.1, 15]</td>
<td>13 (21) [0.1, 18]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Rationale for Aromatase Inhibitors in Ovulation Induction

- Interferes with inappropriate estrogen feedback at the hypothalamus
  - Corresponding rise in FSH secretion from the pituitary gland
    No, but unable to fully document

- Favorable Reproductive Effects vs. Clomiphene
  - More monofollicular ovulation
    No
  - More favorable endometrial effects
    No

Casper and Mitwally, JCEM, 2005
Why is Letrozole better than Clomiphene?

- Aromatase inhibition achieves a more favorable ovulation/conception/implantation environment
  - Lower estradiol, higher progesterone after ovulation
  - Endometrium is thinner with letrozole
  - Lowers number of small follicles in the ovary (and their hormone-Anti-Mullerian Hormone)
  - Less improvement in parameters of hyperandrogenism, than a SERM (Clomiphene)
    - , incl. burden of body hair, Free Androgen Index, Sebum
Does Ovulation = Live Birth?

Ovulation

Fertilization

Implantation

Fetal Viability

Healthy Liveborn

Legro et al, Hum Reprod, 2004
Fecundity per Ovulation in PPCOS I

* Significant compared to baseline

Legro et al, NEJM, 2007
### Improved Fecundity with Letrozole per Subject who Ovulated

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clomiphene group N=288 (%)</th>
<th>Letrozole group N=331 (%)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception</td>
<td>103/288 (36)</td>
<td>154/331 (47)</td>
<td>1.31 (1.07 to 1.58)</td>
</tr>
<tr>
<td>Singleton pregnancy</td>
<td>75/288 (26)</td>
<td>113/331 (34)</td>
<td>1.31 (1.03 to 1.58)</td>
</tr>
<tr>
<td>Singleton live birth</td>
<td>67/288 (23)</td>
<td>99/331 (30)</td>
<td>1.29 (0.98 to 1.68)</td>
</tr>
</tbody>
</table>

Legro et al, NEJM, 2014
All ovulations are not alike!!

Ovulation is a surrogate outcome for anovulatory infertility
All Infertility Trials should report on Live Births and this is the preferable primary outcome.
Question

• Is Letrozole safe?
## Adverse Events During Treatment

### Significant differences between treatments

<table>
<thead>
<tr>
<th>Event</th>
<th>Clomiphene Group</th>
<th>Letrozole Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes*</td>
<td>117 (33%)</td>
<td>73 (20%)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>53 (15%)</td>
<td>78 (22%)</td>
</tr>
<tr>
<td>Dizziness*</td>
<td>27 (8%)</td>
<td>44 (12%)</td>
</tr>
</tbody>
</table>

### Most common without difference between treatments

1) Headache
2) Abdominal/Pelvic Pain
3) Nausea

*P < .05

Legro et al, NEJM, 2014
November 24, 2005

Subject: Femara* (letrozole) should not be used in women who may become pregnant

Femara* (letrozole) is a medication authorized for use in Canada to treat breast cancer in women who are postmenopausal. Novartis Pharmaceuticals Canada Inc. (“Novartis”) as the manufacturer and distributor of Femara* (letrozole), is aware that Femara* is being used to stimulate ovulation in women who are infertile, or unable to become pregnant, as a treatment to increase their chances of becoming pregnant. Novartis believes it is our responsibility to remind physicians treating infertility and their patients that:

• Femara* is authorized for use in post-menopausal women with breast cancer only.
• The use of Femara* for the purpose of inducing ovulation and increasing the chance of pregnancy is not an authorized use of this drug.
• Femara* is contraindicated and should not be used in women who may become pregnant, during pregnancy and/or while breastfeeding, because there is a potential risk of harm to the mother and the fetus, including risk of fetal malformations.
• If there is exposure to Femara* during pregnancy, the patient should contact her physician immediately to discuss the potential of harm to the fetus and potential risk for loss of the pregnancy.

Novartis has also issued a letter to Canadian obstetricians, gynecologists and fertility specialists advising them of this safety information. This letter can be found on the Health Canada website at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html

Novartis is committed to the delivery of quality pharmaceutical products and to ensuring the timely communication of safety information that is important to patients and health care professionals.
Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate

Togas Tulandi, M.D., M.H.C.M., a James Martin, M.D., b Raedah Al-Fadhli, M.D., a
Nadia Kabli, M.D., a Rachel Forman, M.D., c Jason Hitkari, M.D., c Clifford Librach, M.D., c
Ellen Greenblatt, M.D., c and Robert F. Casper, M.D. c

Results: Overall, congenital malformations and chromosomal abnormalities were found in 14 of 514 newborns in the letrozole group (2.4%) and in 19 of 397 newborns in the CC group (4.8%). The major malformation rate in the letrozole group was 1.2% (6/514) and in the CC group was 3.0% (12/397). One newborn in the letrozole group was found to have a ventricular septal defect (0.2%) compared to 4 newborns in the CC group (1.0%). In addition, the rate of all congenital cardiac anomalies was significantly higher (P: 0.02) in the CC group (1.8%) compared to the letrozole group (0.2%).
### Congenital Anomalies-PPCOS II

<table>
<thead>
<tr>
<th>Event</th>
<th>Clomiphene Group (N =66)</th>
<th>Letrozole Group (N =102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPCOS III</td>
<td>1 (1.5%)</td>
<td>4 (3.9%)</td>
</tr>
<tr>
<td></td>
<td>- atrial/ventricular septal cardiac defect with pulmonary stenosis.</td>
<td>- cerebral palsy with arrested hydrocephalus with polycythemia and neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- imperforate anus with perineal fistula and spina bifida with a tethered spinal cord</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- right hemimegancephaly, and dysgenesis of the left frontal and temporal lobes but no hydrocephalus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- large cardiac ventricular septal defect requiring surgical repair</td>
</tr>
</tbody>
</table>
Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility

## Congenital Anomaly Rates in Two Large RCTs Conducted by the Reproductive Medicine Network

<table>
<thead>
<tr>
<th>Indication</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>Gonadotropins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMIGOS</strong>&lt;br&gt;N = 900 Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>4.2%</td>
<td>3.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>PPCOS II</strong>&lt;br&gt;N = 750 Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>1.9%</td>
<td>3.9%</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

Birth Defect Rate from Assisted Conception | Birth Defect Rate from Pregnancies without Assisted Conception | Adjusted Odds Ratio of Birth Defect with Assisted Conception (95% CI)
---|---|---
8.3% | 5.8% | 1.28 (95% CI, 1.16 to 1.41)
Letrozole: Anomaly Rates Interpretation

- Rates of Congenital Anomalies are higher after infertility treatment than unassisted conception.
- The rate of congenital anomalies with letrozole is comparable to that of clomiphene.
- No peer reviewed data have ever demonstrated a higher anomaly rate or a pattern to anomalies occurring after conception with letrozole.
Learning Objectives

1. Identify preconception issues in women with PCOS that may affect outcomes
   - Smoking, Obesity, Glucose Intolerance, Male Partner Issues, Other Infertility Factors, ? Stress

2. Discuss the common side effects, adverse events, and any teratogenicity of aromatase inhibitors in the treatment of reproductive disorders.
   - Hot Flushes, Dizziness and Fatigue, No known Teratogenicity

2. Identify the first line treatment for infertility in PCOS.
   - Letrozole, Not IVF. Consider Clomiphene
Steering Committee: OWL-PCOS: OCP vs Weight Loss for Pregnancy in Polycystic Ovary Syndrome (R01HD056510)
Steering Committee of the PPCOS II and AMIGOS Trials