Infertility: A Generalist’s Perspective

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UCSF Center for Reproductive Health

Learning Objectives

- Fertility and Lifestyle: Patient education
- Describe the basic infertility workup
- Basic treatment strategies
  - unexplained
  - anovulatory
- When to refer

Case

- 34 yo
- Here for routine care
- Interested in conceiving in the future

Patient Education

- Age
- Smoking
- Body Weight
Knowledge Gap: Age and Fertility

Survey by American Fertility Association 2001

- 12,382 women responded to 15 questions
- 1 responded correctly to all
- More than ½ of all questions answered incorrectly
- 85% overestimated by 5-10 years the point at which fertility declines

Fecundability decline with age


Apparent fecundability and natural fertility in humans


Chance of Natural Conception per Month

Chance of Natural Conception per Month

Percent chance per month

Age
Live birth from IVF by age

<table>
<thead>
<tr>
<th>Age</th>
<th>26</th>
<th>28</th>
<th>30</th>
<th>32</th>
<th>34</th>
<th>36</th>
<th>38</th>
<th>40</th>
<th>42</th>
<th>44</th>
</tr>
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<tbody>
<tr>
<td>Rate</td>
<td>44%</td>
<td>45%</td>
<td>44%</td>
<td>42%</td>
<td>41%</td>
<td>35%</td>
<td>30%</td>
<td>23%</td>
<td>14%</td>
<td>7%</td>
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</tbody>
</table>

Miscarriage Rate by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>15-19</th>
<th>20-24</th>
<th>25-29</th>
<th>30-34</th>
<th>35-39</th>
<th>40-44</th>
<th>&gt;45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>12%</td>
<td>18%</td>
<td>34%</td>
<td>54%</td>
</tr>
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</table>


Abnormalities in the oocyte increase with age

Patient Education

- Information on fertile window can be delivered during routine gynecologic care
- Convey non-directional, factual information
Patient Education

- Age
- Smoking
- Body Weight

Smoking and Fertility

- Average age of menopause 3-4 years earlier than non-smokers
- Numerous studies indicate longer time to conception in smokers

Percent of women with knowledge of health association with smoking

<table>
<thead>
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<th>Health Association</th>
<th>Percentage</th>
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<tr>
<td>Respiratory Diseases</td>
<td>99%</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>99%</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>90%</td>
</tr>
<tr>
<td>Pregnancy complications</td>
<td>91%</td>
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Roth and Taylor (Am J Obstet Gynecol 2001;184:934-9.)

Smoking and Fertility

- Nicotine and Cotinine found in follicular fluid
- Direct damage to oocytes/follicles suspected
Smoking and Fertility

**Average Time to Conceive by Smoking Status**

- No Smoking: 2.6 months
- <10 per day: 3.2 months
- >10 per day: 3.9 months

**Metanalysis: smoking and fertility**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensity (no/day)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Case-control studies:</td>
<td></td>
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<tr>
<td>Tobin (1995)</td>
<td>32/157</td>
<td>15/165</td>
<td>2.0 (1.0, 3.9)</td>
</tr>
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<td>Fisch (1991)</td>
<td>38/140</td>
<td>24/136</td>
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<td>24/136</td>
<td>2.0 (1.0, 3.9)</td>
</tr>
<tr>
<td>Greenland (1980)</td>
<td>103/189</td>
<td>48/112</td>
<td>2.0 (1.0, 3.9)</td>
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<td>Cohort studies:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Convisser (1986)</td>
<td>11/135</td>
<td>12/134</td>
<td>2.0 (1.0, 3.9)</td>
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<tr>
<td>Saha (1987)</td>
<td>14/135</td>
<td>20/134</td>
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</tr>
<tr>
<td>Allred (1981)</td>
<td>33/10</td>
<td>10/100</td>
<td>2.0 (1.0, 3.9)</td>
</tr>
<tr>
<td>Overall (1980)</td>
<td>95/140</td>
<td>55/120</td>
<td>2.0 (1.0, 3.9)</td>
</tr>
<tr>
<td>Meta-analysis (95% CI)</td>
<td>1.45 (1.2, 1.79)</td>
<td>0.04</td>
<td></td>
</tr>
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</table>

Odds Ratio of infertility in smokers: 2.27 (1.34, 1.91)

**Patient Education**

- Advise women of the connection between infertility and smoking.
- Future fertility is a strong motivator to quit for many women.
Body Weight and Fertility

- 1,200 consecutive pregnant women.
- A questionnaire inquiring about time to pregnancy
- Contraceptive use, pregnancy planning, previous subfertility/pregnancies, age, and lifestyle characteristics examined

<table>
<thead>
<tr>
<th>BMI</th>
<th>Adjusted Months to Conception</th>
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<tr>
<td>&lt;19</td>
<td>25</td>
</tr>
<tr>
<td>19-25</td>
<td>6.9</td>
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Lifestyle Factors

- **Alcohol**
  - Evidence that >7 drinks per week is deleterious to fertility

- **Exercise**
  - No evidence that moderate exercise is deleterious

### Adjusted Months to Conception

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<th>Adj RR Infertility</th>
<th>p</th>
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<tr>
<td>&lt;19</td>
<td>4.8 (1.2-19.7)</td>
<td>.03</td>
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<tr>
<td>19-25</td>
<td>1.0</td>
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<td>25 – 39</td>
<td>2.2 (1.6-3.2)</td>
<td>&lt;0.001</td>
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<td>6.9 (2.9-16.8)</td>
<td>&lt;0.001</td>
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Case

- 35 yo
- Trying to conceive two months
- No success.
Optimal Timing

Two days prior to and day of ovulation have highest chance of conception

Wilcox et al NEJM 1333;1517-1521, 1995

Average Time to Conceive

From Guttmacher, JAMA 161:855, 1956

Fecundability over time

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<tr>
<th>Cycle</th>
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Adapted from Zinaman et al, ferti sterl,1996

The Infertility Evaluation

- <35 years old: after one year of trying to conceive
- >35 years old: after six months
Causes of Infertility

- Tubal
- Ovulatory
- Male
- Age
- Uterine
- Endometriosis
- Unexplained

The Basic Infertility Work-up

- Ovary
- Tubes
- Semen
- Lifestyle

Ovulation

- Regular Cycles with minimal symptoms
- Timing of ovulation:
  - Basal body temperature
  - Ovulation predictor kits
- Anovulation suggested by cycle length 36
- Lack of minimal symptoms

Endocrine

- TSH
- Prolactin
- Day 21 Progesterone
# The Basic Infertility Work-up

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<th>Ovary</th>
<th>Tubes</th>
<th>Semen</th>
<th>Lifestyle</th>
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- **Ovulation**
- **Ovarian Reserve**
  - Antral Follicle Count
  - Day 3 FSH/ Estradiol
  - Clomid Challenge Test

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## FSH levels and pregnancy outcome

![Graph showing FSH levels and pregnancy outcome](image)

- Relative hazard of no ongoing pregnancy without treatment (log)
- Basal FSH level (UL), cycle days 2-4

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## Ovarian Reserve

- Antral Follicle Count
- Day 3 FSH/ Estradiol
- Clomid Challenge Test
**Tubal/Uterine Factor**

- Normal
- Filling Defect
- Blocked Tube
- Septum

**Semen Analysis**

- Volume 1.5-5ml
- Concentration > 20 million/ml
- Motility > 50%

If Abnormal → Repeat

**The Basic Infertility Work-up**

- Ovary
- Tubes
- Semen
- Lifestyle

**Semen Analysis**

**The Basic Infertility Work-up**

- Smoking
- Coffee
- Alcohol
- Hot tubs (male)
- Biking (male)
- Weight

**WHO, 1992**
Treatment

Treatment: Anovulation/PCOS

- Weight Loss and Lifestyle Change
- Clomid
- Letrozole
- Metformin

Ovulation Induction: Mechanism

- Metformin
- Weight Loss
- Improve insulin sensitivity

Treatment

- Male Factor
- Tubal Factor

Referral

- Oligoovulatory/PCOS
- Unexplained

Pituitary Gland

FSH

LH

Clomid

Tamoxifen

Letrozole

E2
Lifestyle Changes

87 women
- obese
- 79% PCOS

67 patients completed program
- Mean change in BMI -3.7
- 27% spontaneous conception
- 53% conceived with assistance
- Increased self esteem
- Decreased anxiety/depression

6 month group program
- regular exercise
- gradual dietary changes

20 patients dropped out
- No changes in BMI
- No conceptions

Results from the Reproductive Medicine Network (RMN)

626 women with PCOS

Clomiphene
Metformin
Metformin and Clomiphene

Note: relatively large (BMI = 34-3) and androgenized (FM 76-86) population

Legro et al NEJM 2007

Treatment of Anovulatory Infertility

- Medications:
  
  Clomid: taken for five days
  
  Metformin: taken continuously

Treatment of Anovulatory Infertility: RMN Trial

Percent chance of conception

30% Clomid
12% Metformin
38% Clomid and Metformin

p < .001
p < .001

Legro et al NEJM 2007
Treatment of Anovulatory Infertility: RMN Trial

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<th>Miscarriage Rate</th>
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<td>26%</td>
</tr>
<tr>
<td>Metformin</td>
<td>40%</td>
</tr>
<tr>
<td>Clomid + Metformin</td>
<td>30%</td>
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Non-significant

Legro et al NEJM 2007

Treatment of Anovulatory Infertility

Clomid more effective than Metformin in ovulation induction in PCOS population

Clomid continues to be first line

Unexplained Infertility

Failure to find abnormalities in sperm, tubes, ovulation, ovarian reserve

Stepwise Approach

- Expectant Management
- Clomid
- Clomid + IUI
- Injectable FSH/LH with IUI
- IVF

- Minimal efficacy
- Lower cost
- Minimal invasiveness
- Minimal Risk
- Increasing efficacy
- Higher cost
- More invasive
- More Risk
Mechanism of Ovarian stimulation drugs

FSH
LH
Pituitary Gland
Clomid
Tamoxifen
E2
Letrozole

Clomid for Unexplained Infertility

- 100 mg for five days (typical: 3-7)
- Acts as estrogen antagonist
- Assist in production >1 oocyte

Risks/Side Effects:
- Headache
- Hot Flash
- Mood Changes
- Ovarian Cysts
- Twins

Practice committee ASRM, Fertil Steril, 2004

Unexplained Infertility: Clomid & Intercourse

Three comparable randomized controlled trials: Meta-analysis

Pregnancy rate per Cycle

<table>
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P=0.02

- Modest Treatment Effect
- Number of cycles to achieve one pregnancy: 40 (95% CI, 20–202)

Practice committee ASRM, Fertil Steril, 2006

Unexplained Infertility: Clomid & IUI

Randomized Controlled Trial
- 298 cycles
- 67 patients with unexplained infertility

Pregnancy rate per Cycle

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Deaton et al, Fertil Sterility 54:1083 1990

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Treatment of Unexplained Infertility

- Treatment effect of clomid without IUI is quite modest compared to timed intercourse
- Recommend for patients if:
  - No time constraints (ie young)
  - Patients who wish to avoid additional intervention

Treatment of Unexplained Infertility

- Treatment effect of clomid with IUI has more reasonable efficacy. Due to low cost and relative ease, recommend as first step.

Final Points

- Education regarding factors impacting fertility is important in routine gynecologic care
- Basic evaluation of infertility includes: tubes, ovulation, ovarian reserve, semen analysis
- Initial treatment of anovulatory and may be lifestyle

Final Points

- Clomid alone remains a useful first step in the treatment of ovulatory infertility
- Clomid alone (no IUI) has only marginal benefit in unexplained infertility. Consider adding IUI’s
Thank You

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