

# Infertility for the Generalist

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## Commercial affiliations/Disclosures

Nothing to report

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## Learning Objectives

- At the end of this lecture the audience should be able to:
  - Explain the frequency of infertility and its impact on patients
  - Be able to perform a complete infertility evaluation on the first office visit
  - Be able to address common infertility counseling issues and initiate therapy or referral

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## Infertility is common

- World-wide couples view infertility as a tragedy which carries social, economic and psychological consequences
  - interferes with “one of the most fundamental and highly valued human activities—building a family.”
  - in Latin America, 21 percent of women are more likely to be divorced or separated if they suffer primary infertility
- Effects 10-15% of all couples, >6 million Americans
  - 700,000 Canadians
- infertility increases sharply with age
  - WHO Demographic and Health Surveys (DHS) Comparative reports No. 9 2004

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## Embryo Implantation Rate by Age

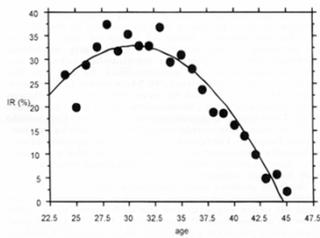


Fig. 3. The actual data points for implantation rate as determined by age are demonstrated by the circles. The curved line represents the calculated implantation rates as a function of age as demonstrated by the following equation:  
 Implantation Rate = -119.352 + (9.985 × Age) - (0.164 × Age<sup>2</sup>)

Spandorfer, 2000

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## Infertility

- 'a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse'
- 6 months of failure to conceive in women ≥35 years
  - Massachusetts, Rhode Island, insurance coverage for infertility starts as above
    - Treatment is expensive and less effective with advancing maternal age
- Occurs equally in men and women, with male factors and female factors each accounting for about one-third of infertility problems

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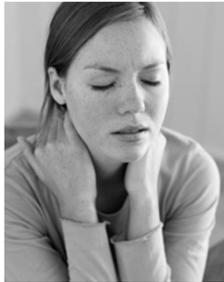
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Many of the feelings that infertility brings on are similar to depression

- ❑ Loss of interest in activities
- ❑ Strained relationships
- ❑ Anxiety
- ❑ Difficulty in thinking about anything other than having a baby
- ❑ Difficulty with concentration
- ❑ Disturbed sleep patterns



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Infertility patients

- ❑ Needy?
- ❑ Sense loss of control
- ❑ Searching education, reassurance, professional relationships, provider confidence
- ❑ They want answers and find comfort in an organized, thoughtful, and efficient approach

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The infertility patient

- ❑ What do they want from their visit?
- ❑ How much time do you have in your schedule to service their needs?
- ❑ How can make the most effective use of your time and theirs?

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### A Standard approach to testing

- ❑ Every infertility patient needs an assessment of four things:
- ❑ Sperm
- ❑ Eggs/Ovulation
- ❑ Uterus and tubes
- ❑ General Health/ pre-natal Labs

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### Sperm

- ❑ Semen analysis
- ❑ Simple
- ❑ Ideally after abstinence for a couple of days
- ❑ Ideally by a lab that assesses morphology (shape)
- ❑ If abnormal, repeat, and/or refer to a urologist for a testicular exam and some endocrine testing or genetic testing

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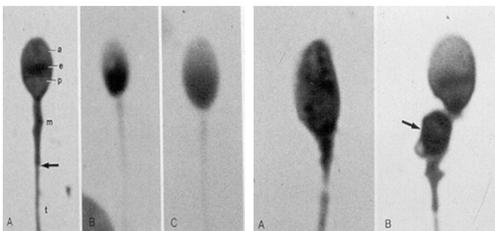
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### Sperm Morphology



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### Abnormal SA

- ❑ Ovarian stimulation/IUI combined if not too low
- ❑ Total motile sperm after prep 4 to 10 M
  
- ❑ IVF or ICSI if < 10 M total motile sperm on SA or < 4% normal morphology
  
- ❑ IVF with Intra-cytoplasmic sperm injection
  - 50% of IVF cycles in the US are with ICSI
  - >50,000 ICSI cycles/year in US

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### ICSI VIDEO



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### Assessment of Ovulation

- ❑ History- standard questionnaire?
- ❑ Hirsutism -consider androgen assessment
- ❑ High Prolactin causes short luteal phase or anovulation
- ❑ Thyroid disorders cause irregular menses, DUB, infertility and miscarriage (TSH)
  - Above problems relatively easy to fix from a fertility perspective

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### Elevated TSH in the first Trimester

- ❑ 4657 patients screened at 11 weeks gestation with TSH testing
- ❑ Two groups compared
  - ❑ TSH < 2.5 vs. TSH 2.5-5.0 (all neg anti-TPO Ab)
- ❑ Miscarriage rate 3% vs 6%, P<0.006
  
- ❑ If TPO -Ab Pos- Miscarriage rate is 13.8%
  
- ❑ The increased incidence of pregnancy loss in pregnant women with TSH levels between 2.5 and 5.0 mIU/liter provides strong physiological evidence to support redefining the TSH upper limit of normal in the first trimester to 2.5 mIU/liter
  
- ❑ Negro et al. J Clin Endocrinol Metab 95: E44-E48,2010

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### Ovarian reserve/egg quality

- ❑ Day 3 FSH testing
  - Typically done with E2 and LH
- ❑ A high E2 (>70) indicates the test was done at the wrong time
- ❑ A high FSH (>12) indicates that there is diminished ovarian reserve
- ❑ Clomiphene citrate Challenge test for patients over 39
  - Day 3 E,FSH,LH. CC 100 D5-9, Day 10 FSH

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### Diminished Ovarian Reserve

- ❑ Low egg potential for pregnancy
  - Lower monthly PR
  - Higher miscarriage rate
- ❑ Low ovarian response to FSH stimulation
- ❑ Low egg numbers left in ovary

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Oocytes from Older Women are Chromosomally Fragmented.

283 Oocytes Karyotyped From 3 Age Groups

Age (years)	% Chromosomal Fragmentation
<34	24%
35 to 40	52%
> 40	95%

*Lim & Tsakok, Fertil Steril, 1997*

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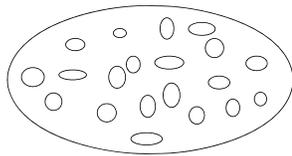
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30 year old ovary

24% Abnormal Oocytes



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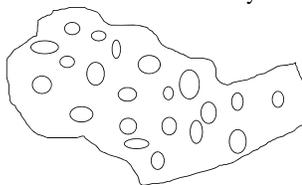
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41 Year Old Ovary

95% Abnormal Oocytes



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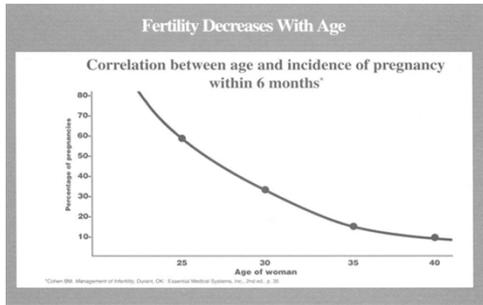
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## Fertility and Age




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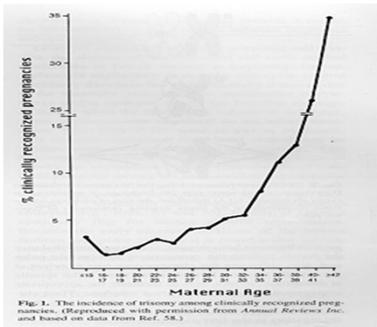
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## Risk of Trisomy with Advancing Maternal Age




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## Transvaginal Ultrasound

- Assess ovarian anatomy
  - Antral follicle count
    - Most predictive marker for ovarian response to gonadotropins
- Look for fibroids
  - Size
  - Proximity to endometrium
- Hydrosalpinges

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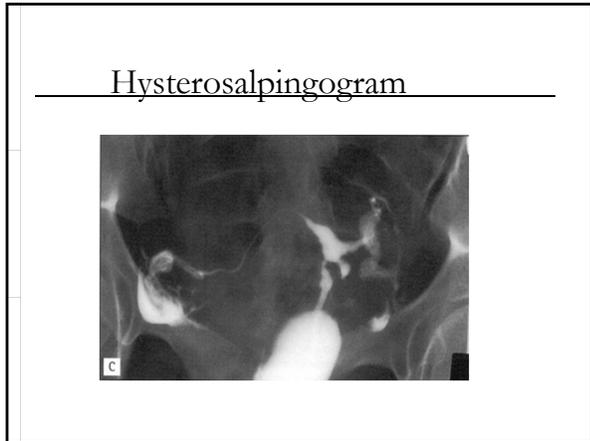
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- ### Hysterosalpingogram
- Assess tubal patency
    - If Proximal tubal occlusion
      - No suspicious history, repeat
      - 60% of the time open on subsequent HSG
    - If distal occlusion (hydrosalpinx)
      - Laparoscopy
      - Removal or repair or referral

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- ### Hysterosalpingogram
- Uterine cavity assessment
    - Mullerian anomalies
      - Septate most common
        - Hysteroscopic septal incision
    - Fibroids or polyps
      - Need Sonohysterogram to guide therapy

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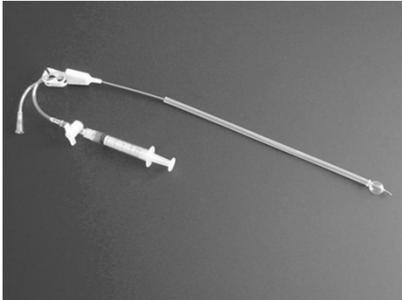
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HSG catheter

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Prenatal Labs

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- Blood type and Rh
- Rubella
- Hep B Sag
- HIV
- Cervical cultures
- Pap if needed
- RPR

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Summary of Labs ordered at first infertility office visit

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- Semen analysis
- HSG
- Day 3 E,FSH,LH or CCCT
- TSH, Prolactin
- Prenatal Labs
- Pap, cervical cultures
- RTO in one month to review

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## Infertility history

- A standard form to be filled in by the patient in the waiting room or ahead of time is very helpful available online from ASRM
- Assessment of:
  - Pregnancy history
  - menstrual cycle
  - Duration of infertility
  - Previous testing
  - Previous treatment
  - Male health/issues
  - ROS
  - Environmental exposures
  - Etc.

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## Counseling Issues

- Timing of intercourse
- Frequency of intercourse
- Age and fertility
- Male factor issues
- Toxins
  - Tobacco, alcohol,
- Obesity

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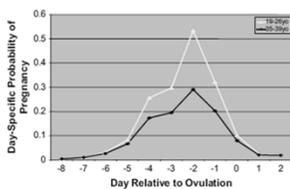
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## Timing intercourse

Probability of pregnancy by cycle day, involving recurrent intercourse, by age. Data from Stanford and Dunson 2007 (15).



ASRM Practice Committee. *Optimizing natural fertility*. Fertil Steril 2008.

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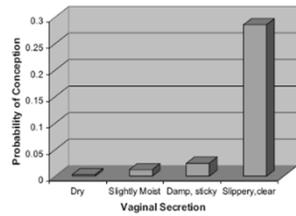
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## Timing Intercourse

Estimates of the probability of conception according to vaginal secretion observations on the day of intercourse. Data from Scarpa et al. 2006 (17).



ASRM Practice Committee. Optimizing natural fertility. *Fertil Steril* 2008.

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## Lifestyle and fertility

### Lifestyle factors that may impact fertility.

Factor	Impact on fertility	Study
Obesity (BMI >35)	Time to conception increased two-fold	Hassan and Killick, 2004 (72)
Underweight (BMI <19)	Time to conception increased four-fold	Hassan and Killick, 2004 (72)
Smoking	RR of infertility increased 60%	Clark et al., 1998 (37)
Alcohol (>2 drinks/day)	RR of infertility increased 60%	Eggert et al., 2004 (48)
Caffeine (>250 mg/day)	Fecundability decreased 45%	Wilcox et al., 1998 (53)
Illicit drugs	RR of infertility increased 70%	Mueller et al., 1990 (59)
Toxins, solvents	RR of infertility increased 40%	Hruska et al., 2000 (62)

Note: BMI = body mass index; RR = relative risk.  
ASRM Practice Committee. Optimizing natural fertility. *Fertil Steril* 2008.

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## Alcohol and fertility

- ❑ In women who drink at least 4 drinks per week, the odds of a live birth after IVF decreased by 16% OR 0.84 [CI 0.71-0.99]
- ❑ In couples who drank at least 4 drinks/week, OR for live birth was decreased 21%
- ❑ Men drinking beer daily had a greater likelihood of failed implantation, OR 1.36[1.07-1.8]
  - Obstet Gynecol 2011; 117:136-42

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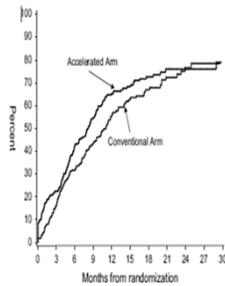
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### Idiopathic infertility- FASTT trial

- FASTT trial
  - 500 patients aged 21-39 randomized to:
    - CC/IUI x3, FSH/IUI x3, IVF x 6
    - Or
    - CC/IUI x3, IVF x 6
- FSH/IUI added no value
- Accelerated arm resulted in delivery three months sooner and infertility costs \$2600 less per couple, \$9800 less per delivery
- Per cycle pregnancy rates CC-7.6%, FSH-9.8%
- IVF- 30.7%




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### Ovulation induction basics

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| <ul style="list-style-type: none"> <li>□ Clomiphene Citrate</li> <li>□ 50-100 mg days 5-9</li> <li>□ Ovulation 5-7 days after last pill</li> <li>□ OPK (LH) testing</li> <li>□ IUI/IC</li> <li>□ [P] level Day 21</li> <li>□ Side effects                             <ul style="list-style-type: none"> <li>■ Vasomotor, headache, breast tenderness, visual, irritability</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>□ Letrozole</li> <li>□ 2.5 - 5 mg days 5-9</li> <li>□ Ovulation 5-7 days after last pill</li> <li>□ OPK (LH) testing</li> <li>□ IUI/IC</li> <li>□ [P] level Day 21</li> <li>□ Side effects                             <ul style="list-style-type: none"> <li>■ Minimal</li> <li>■ Luteal phase defect may require progesterone supplementation</li> </ul> </li> </ul> |
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□ Tredway et al. Fertil Steril 2011;95:1549

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### Referral Relationships

- Establish a good relationship with a local Reproductive Endocrinologist
  - Helpful by telephone
  - Complicated reproductive surgery
  - Endocrine issues
  - IVF
    - Know program success rates
    - www.SART.org

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### Treating Infertility can be very rewarding

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- ❑ Standard questionnaire
- ❑ Standard evaluation (completed in one month)
  - Sperm, eggs, uterus, health
- ❑ Follow-up
- ❑ Treatment/referral
- ❑ Many happy patients



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### Important Websites

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- ❑ <http://www.reproductivefacts.org>
- ❑ <http://www.ASRM.org>
- ❑ <http://www.resolve.org>
- ❑ <http://www.theafa.org>
- ❑ <http://www.sart.org>

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### Suggested Readings

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- ❑ 2008 Compendium of Practice Committee Reports-American Society of Reproductive Medicine. Fertil Steril Vol 90, No. 5, 2008. Supplement
  - Optimizing natural fertility S1-6
  - Obesity and reproduction: an educational bulletin S21-29
  - Smoking and infertility S254-9
- ❑ Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010 Aug; 94(3):888-99. Epub 2009 Jun 16
- ❑ Dessole S, Meloni GB, Capobianco G, Manzoni MA, Ambrosini G, Canalis GC. A second hysterosalpingography reduces the use of selective technique for treatment of a proximal tubal obstruction. Fertil Steril. 2000 May; 73(5):1037-9.

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Contact information:

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