

Infertility: The Internist's Role

Anu Munshi
Briar Duffy
Carla Spagnoletti
Rachel Bonnema

Overview

- Background of Infertility
- Preconception Counseling and Advanced Parental Age
- Workup of Infertility
- Ovulation Induction
- At the reproductive endocrinologist's office

Infertility

- Definition: Inability to conceive after one year of unprotected intercourse, regardless of cause
- Affects 15-20% of couples, or 7.5 million reproductive age people in the U.S.

Fertility, Family Planning, and Women's Health: New Data from the 2002 National Survey of Family Growth, Table 49

Infertility

- Females aged 15 to 44 with impaired ability to have children: 11.8%
- Females aged 15-44 needing infertility services:
 - Advice: 6.1%
 - Medical help to prevent miscarriage: 5.5%
 - Tests on woman or man: 4.8%
 - Ovulation drugs: 3.8%
 - Artificial insemination: 1.1%

Fertility, Family Planning, and Reproductive Health of U.S. Women: Data from the 2002 National Survey of Family Growth, 2002

Fertility

- In normal young couples:
 - 25% conceive after one month (fecundity)
 - 70% conceive after six months
 - 90% conceive by one year
- Only an additional 5% will conceive in an additional 6-12 months
- What about the rest?

Current Trend

- More women delaying childbearing into their 30s and 40s
- Increased levels of stress, more STIs
- Increased awareness/acceptance of infertility and its treatment (friends, internet, TV - Jon & Kate, Octomom!)
- Readily available sophisticated infertility interventions

Internists and Infertility

- First in line
- More pts with medical illnesses can bear children or at least hope to - Obesity, PCOS
- Need to familiarize ourselves with interventions
- Assess risk that the interventions pose
- Counsel patients – preconception, during intervention, emotional support

Meet Our Couple

- Well known patients to your practice
- Megan 36 year old white female, nulligravid
- Andrew 37 year old white male, fathered one child with ex-wife
- Both attorneys work for busy law firm in Pittsburgh, PA
- Recently, Megan started having issues with her OCPs, keeps missing doses due to being busy at work

Megan and Andrew

- Megan would like to get an IUD placed
- Worried about fertility as she ages as her friend has had difficulty conceiving
- Career demands that she delay childbearing
- Andrew wants to have children now
- Due to this conflict, they now present to you for advice

Megan and Andrew

1. What do you tell Megan and Andrew?
 - A) Refer them to Gynecology for IUD placement as your patient requested
 - B) Discuss the pros/cons of getting an IUD placed and then refer
 - C) Try to convince Megan to have children sooner rather than later and offer preconception counseling

Megan and Andrew

2. Megan asks you that assuming she is healthy, what are her chances of conception at her age of 36 and at 40?
 - A) 90%, 80%
 - B) 25%, 10%
 - C) 75%, 50%
 - D) 50%, 35%

Preconception Counseling and Advanced Parental Age

Carla Spagnoletti MD, MS
Assistant Professor of Medicine
Section of Women's Health
University of Pittsburgh School of
Medicine

Preconception Counseling

- Preconception counseling allows the internist to:
 - Identify and counsel patients about modifiable risk factors that may impact pregnancy outcomes
 - Educate patients on ways to maximize their chances of becoming pregnant
 - Identify conditions that may predispose to infertility and begin evaluation

Behavioral Modifications to Enhance Fertility

- Female factors associated with infertility:
 - Advanced maternal age (≥ 35 years)
 - Obesity and underweight
 - Caffeine ($>250\text{mg/day}$ is associated with a significant decrease in fertility)
 - 250mg caffeine = 1 Starbucks "Tall" coffee or 7 cans of Coke/Pepsi
 - Smoking
- Males factors
 - Tight-fitting undergarments and use of hot tubs decrease sperm count
 - Sperm life cycle=3 months
- Couples should avoid use of lubrication products during intercourse

Discontinuing Contraception and Return of Fertility

- Combined hormonal contraception (OCPs, patch, vaginal ring):
 - Rapid return of fertility upon discontinuation
 - Women should expect an average 1-2 week delay of ovulation.
 - Rarely, amenorrhea can last up to 6 months
- Depo-Provera:
 - Delayed return of fertility after the last injection with an average ovulation delay of 9-10 months
 - There is no increase in delay with increased duration of use
- Intrauterine device (IUD) and Implanon:
 - Immediate return of fertility after removal
- Barrier devices (diaphragm, cervical cap, condom):
 - Immediate return of fertility after removal

Optimal Timing of Intercourse to Achieve Pregnancy

- Women should keep an accurate record of their menses.
- The "Window of Fertility" refers to the days of the menstrual cycle during which intercourse is most likely to result in pregnancy
 - 5 days before and through the day of ovulation
- Intercourse on multiple days during the fertile window is suggested, no benefit to $>1\text{x/day}$
- If the fertile window is unknown, intercourse consistently 2-3 times per week will likely result in 1-2 acts occurring during the window.

Prospective Methods of Identifying Ovulation

- Expected to result in higher conception rates
- Utilize the known physiologic changes that occur during the menstrual cycle
 - Fertility charting of cervical mucus
 - Over-the-counter fertility monitors that measure urinary estrogen metabolites and luteinizing hormone (LH) to identify upcoming ovulation

Effects of Age on Fertility: Advanced Maternal Age

Advanced Maternal Age

- Advanced Maternal Age (AMA) can negatively impact five pregnancy-related factors:
 - **Fertility**
 - Miscarriage
 - Chromosomal abnormalities
 - Hypertensive complications
 - Stillbirth

Maternal Age

- Maternal age ≥ 35 confers a decline in fertility due to the progressive depletion of eggs and decline in egg quality
- The diagnosis of infertility greatly depends on maternal age:
 - Women < 35 years old are usually allowed up to one year to conceive
 - Women ≥ 35 years old are usually allowed 6 months prior to initiation of infertility work-up

Effects of Age on Fertility: Advanced Paternal Age

Paternal Age

- Impact of paternal age on fertility is less clear, due to confounding related to age of female partners
- Paternal age > 40 is associated with decline in semen volume, sperm motility, and sperm morphology

Back to the case...

- At Megan's current age, she has about a 50% chance of getting pregnant
- At age 40, her chances drop to about 35%
- She should be counseled about the effects of age on fertility and attempts should be made to convince her to start trying to conceive now to optimize her chances of pregnancy

Workup of Infertility

Rachel Bonnema, MD, MS
University of Nebraska Medical Center

Megan and Andrew

- They listen to your advice and decide that they are ready to have children.
- They have been trying to conceive for 6 months without any success despite following your pre-conception counseling.

Megan and Andrew

- Andrew has a normal history and physical exam.
- While interviewing Megan you learn she really doesn't have normal menses unless she is on OCPs. Since stopping her OCPs, she notes quite a bit of variation in her cycles. On exam the only significant findings are: BMI 41, scattered acne noted of her face and back.
- What, if any, labs will you do for Megan?
 - A. TSH, fasting glucose, oral glucose tolerance test
 - B. TSH, testosterone, 17 α -hydroxyprogesterone
 - C. TSH, FSH, prolactin
 - D. None, proceed to imaging

Evaluating the Couple

- Obtaining the complete history
 - Medical/surgical history
 - Confirming ovulation, etc.
- Physical exam
- Laboratory data

Use of Vaginal Lubricants

- 25% of couples trying to conceive report always using vaginal lubricant
- Lubricants affect sperm motility and function decreasing fertilization potential
 - Likely due to nonphysiologic osmolality and pH
- Options:
 - Pre~Seed
 - Canola oil/baby oil

Agarwal A, et al. Fertility and Sterility, May 2007

Evaluation of the Male

Unknown	40-50%
Primary Hypogonadism -Androgen insensitivity -Cryptorchidism -Medication -Congenital testicular disorder -Orchitis -Radiation -Systemic disorder -Varicocele	30-40%
Altered Sperm Transport -Erectile dysfunction -Obstruction of vas deferens/epididymis -Retrograde ejaculation	10-20%
Secondary Hypogonadism	1-2%

Fertil Steril. 2004;82(suppl 1):S123-30.

Components of the H&P: Male

- History
 - Developmental history
 - h/o mumps orchitis, severe trauma, CF
 - Medications
 - Substance use
- Physical
 - Signs of androgen deficiency
 - Assessment of genitalia
 - Size and location for urethral meatus and prostate
 - Testes – bilaterally descended
 - Varicocele
 - Hernia
 - Testicular mass

Laboratory Evaluation: Male

- Semen analysis
- Other labs based on clinical suspicion
 - Hypogonadism → Prolactin, FSH, testosterone
 - Retrograde ejaculation → postejaculatory U/A
 - Chemistry/LFTs
- Ultrasound to investigate any scrotal or testicular abnormalities

Laboratory Evaluation: Male

- Semen analysis
 - Early in work up → allows for prompt identification and treatment

Volume	>2ml
pH	7.2-8
Sperm Concentration	>20 x10 ⁶ spermatozoa/ml
Total Sperm Count	>40 x10 ⁶ spermatozoa/ejaculate
Motility	>50% with forward progression >25% with rapid progression
Morphology	>30% with normal forms

Evaluation of the Female

Ovulation Disorders -Aging -Endocrine disorder -PCOS -Diminished Ovarian Reserve	40%
Tubal Factors -Obstruction (h/o PID)	30%
Endometriosis	15%
Other	~10%
Uterine/Cervical factors -Congenital uterine abnormality -Fibroids -Polyps -Poor cervical mucus quantity/quality -Uterine synechiae	~3-5%

Fertil Steril. 2004;82(suppl 1):S169-72.

Components of the H&P: Female

- History
 - Details of the menstrual cycle
 - Confirm that ovulation occurs!
 - Medications
 - STD exposure
 - Surgical history
 - Substance use → caffeine
 - High levels of caffeine associated with lower fertility rates
- Physical
 - Signs of hyperandrogenism
 - Galactorrhea

Laboratory Evaluation: Female

- Rule out “medical” factors
 - Thyroid
 - DM, PCOS
 - Autoimmune disorders – antiphospholipids
- GC/Chlamydia
- Document ovulation
 - Basal Body Temp (BBT), Urinary LH using home kits
- Ovulation dysfunction
 - FSH, prolactin, TSH
 - 17 α -hydroxyprogesterone, testosterone

Evaluation of the Female

- If initial history/physical suggest tubal dysfunction can obtain hysterosalpingogram
 - Assess uterine cavity and tubal patency
 - Even when normal HSG can increase pregnancy rates in next 6 months
- Ultrasound can also be used
- If not suggested by history/physical, imaging can be postponed

Back to the case

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Ovulation Induction

Anuradha Munshi, MD
University of Pittsburgh Medical
Center
VA Pittsburgh Health System

Back to Megan

- After a thorough H+P and workup, you diagnose Megan with PCOS
- Megan asks whether weight loss could help her restore ovulation
- How much weight loss is known to help with restoring ovulation?
 - A) 1-5% of total body weight (TBW)
 - B) 5-10% TBW
 - C) 10-15% TBW
 - D) 30+% TBW

Back to Megan

- What is the first line of medical treatment for infertility due to PCOS?
 - A) Weight Loss
 - B) Metformin
 - C) Clomid
 - D) Aromatase Inhibitors

Focusing on Ovulation

- Thyroid Disorders
- Hypothalamic dysfunction
- Hyperprolactinemia
- Tumors of the pituitary or adrenal glands or ovaries
- Ovarian Failure
- Unexplained Infertility
- **Obesity**
- **Polycystic ovarian syndrome (PCOS)**

Weight Loss

- Cornerstone in treating obesity-related anovulation/infertility
- 30% reduction of visceral adiposity and
- 5-10% total body weight loss can improve insulin sensitivity and restore ovulation
- Not always enough, so must be part of total fertility treatment

Despres J.-P., Lemieux I., Prud'homme D.: Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 322: 716-720.2001
Moran L.J., Noakes M., Clifton P.M., et al: Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88: 812-819.2003

Ovulation Induction Agents

1. Metformin
2. Clomid
3. Injectable gonadotropins
4. Aromatase Inhibitors

Metformin

- Hyperandrogenism, Hyperinsulinemia, & Insulin resistance in PCOS
- Metformin thought to induce ovulation as it helps with insulin resistance
- Help with ovulation in those who want it and those who don't → birth control?

Clomid

- Clomiphene, Serophene
- SERM
- Inhibits action of estrogen on hypothalamus
- Body perceives 'low estrogen' leading to ↑FSH and thus, ovulation
- First-line for anovulatory/irregular cycles (ie. PCOS)

Why Clomid?

- Ease of treatment - pill
- Given on cycle days 3-7 to induce ovulation on day 14
- Low cost - \$ 0.60 to \$2.50 per pill
- Minimal side effects:
 - Hot flushes
 - Dizziness
 - Nausea
 - Headache
 - Bloating

Clomid

- Usually use up to 4 cycles as 85% of couples conceive by 4th ovulatory cycle
- Can go from 50mg to 100mg dose for second or third cycle

Garcia J, Jones GS, Wentz AC. The use of clomiphene citrate. *Fertil Steril.* Jul 1977;28(7):707-17

Clomid and Unexplained Infertility

- No evidence of clinical benefit of using Clomid for unexplained infertility

Cochrane Database Review 2010 January 20;(1):CD000057.Clomiphene citrate for unexplained subfertility in women.

Clomid vs. Metformin for PCOS

- 2007 - RCT of 626 PCOS females with anovulatory infertility
- Primary outcome - live births
- 3 arms: Clomid, Metformin and Clomid plus Metformin

Legro RS, et al. 2007 Clomiphene, metformin or both for infertility in the polycystic ovary syndrome. N Engl J Med 356:551-566

Clomid vs. Metformin for PCOS

	Clomid	Metformin	Clomid+Metformin
Live Birth Rate	22.5%	7.2%	26.8%

- Clomid vs. Metformin - statistically significant
- Clomid vs. Both - not statistically significant

Legro RS, et al. 2007 Clomiphene, metformin or both for infertility in the polycystic ovary syndrome. N Engl J Med 356:551-566

To Metformin or not to Metformin?

- Cochrane Database review in 2009
- 31 RCTs which investigated the effect of insulin sensitising drugs compared with either placebo, no treatment, or ovulation induction agent (for PCOS)
- Pregnancy rates improved with metformin vs. placebo (Pooled OR = OR 3.86, 95% C.I. 2.18 to 6.84)
- No evidence that metformin is better than Clomid or Clomid+Metformin...but...
- Better than placebo

Injectable Gonadotropins

- LH/FSH combination
- Best for 1° amenorrhea (hypopit), 2° amenorrhea (Clomid resistant pts)
- Side effects
 - Multiple pregnancy
 - Ectopic/Miscarriage
 - Ovarian torsion/rupture
 - Ovarian Hyperstimulation Syndrome (OHSS)

Aromatase Inhibitors

- Letrozole, Anastrozole
- Inhibit aromatase (converts androgens to estrogens)
- Estrogen levels ↓ and therefore, stimulate hypothalamus-pituitary axis
- Not FDA approved for ovulation induction
- Side Effects: hot flushes, nausea, vomiting, headaches, leg cramps

Requena A, Herrero J, Landeras J, et al. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Hum Reprod Update. Nov-Dec 2008;14(6):571-82

Back to the Case

- Given the diagnosis of PCOS, she would be an ideal candidate for a diet/weight loss program and Metformin treatment at your office
- She could also start Clomid once she sees a reproductive endocrinologist
- Use ovulation predictor kit to time intercourse

Infertility—at the reproductive endocrinologist's office

Briar Duffy

Megan and Andrew

- Megan has been tried on Metformin and Clomid without any success. She is frustrated and is wondering what she should expect when she goes to the Reproductive Endocrinologist's office again.

Megan and Andrew

- What is the correct order of procedures Megan may undergo at the reproductive endocrinologist's office?
 1. ICSI, HSG, post-coital testing
 2. HSG, IUI, IVF
 3. ZIFT, ovarian drilling, U/S
 4. IUI, GIFT, HSG

Visit with Reproductive Endocrinologist

- Pre-visit
 - Do BBT and/or home ovulation testing kits
- First visit
 - History and Physical
 - Labs: FSH, LH, Estrogen, Progesterone, Testosterone, Prolactin, Thyroid
 - Male testing: sperm count, motility, morphology
 - Procedures: possibly hysterosalpingogram (HSG)
- Subsequent visits
 - Advanced testing and labs

Goal—figure out source of infertility diagnosis

- Is woman ovulating?
- Does woman have anatomic pathology?
- Is sperm adequate?
- Does man have anatomic pathology?

Other testing possibilities

- If hysterosalpingogram normal:
 - 29% of couples conceive without laparoscopy
 - Most of conceptions were in next 3 months
 - If no conception, 50-60% of women have pelvic pathology; consider laparoscopy
- If hysterosalpingogram abnormal:
 - Likely to have hysteroscopy

Carr B, "Infertile Couples with a Normal Hysterosalpingogram," Journal of Reproductive Medicine, January 1995; 40:19-23.

Other testing possibilities

- If ovulating normally:
 - Ultrasound: evaluate endometrium, uterus, ovaries
 - Consider post-coital testing
- If not ovulating normally:
 - PCOS
 - Metformin
 - Ovarian drilling
 - Not PCOS....

Not ovulating (but not due to PCOS)

- Clomiphene
 - 80% of women will then ovulate
 - 50% of ovulating women will conceive
- Superovulation: gonadotropins (FSH, hMG) +/- clomiphene
 - Intercourse
 - Intrauterine insemination (IUI)
 - need at least 11 million sperm in ejaculate
- If 38 years old or more:
 - In vitro fertilization

What next?

- If all of this didn't work
- i.e. if still no viable pregnancy after
 - producing ovulation
 - optimizing anatomy
 - putting viable sperm where it needs to be
- Assisted reproductive technologies

Assisted reproductive technology

- IVF (in vitro fertilization): >99% of procedures
 - Ovulation stimulated and eggs removed surgically
 - Eggs fertilized in lab
 - Developing embryo with dividing cells inserted in uterus
- GIFT (gamete intrafallopian transfer)
 - After egg retrieval, eggs and sperm placed laparoscopically into fallopian tube
 - No confirmation of fertilization
- ZIFT (zygote intrafallopian transfer)
 - Egg fertilized in lab and transferred into fallopian tubes
 - No ability to analyze developing embryo

If male testing abnormal

- ICSI (intracytoplasmic sperm injection)
 - A single sperm inserted in egg with microinstruments
- Can be used even if sperm have no/abnormal motility or do not reach maturity

Success rates

- Vary widely among clinics and procedures
- Depends on age of patient
 - 36 yo patient, 2007 national rate: 30.5% of IVF cycles result in live births
- Important to know rates of your local clinic before agree to be patient there
- www.cdc.gov/art/
- Resource: National Infertility Organization
www.resolve.org

Megan and Andrew

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