


# INFERTILITY



NDAFP Big Sky Meeting  
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Reproductive Endocrinology and Infertility



1

## DISCLOSURES:

- I have no disclosures.

2


## LEARNING OBJECTIVES:

1. Review the etiologies and evaluation of infertility.
2. Discuss the impact of exogenous testosterone use on male fertility.
3. Understand option to optimize fertility including lifestyle modification, weight management, and nutrition.

3

## Most Common Causes of Infertility


- Age
- PCOS
- Amenorrhea/ Oligomenorrhea
- Obesity
- Endometriosis
- Uterine Polyps, Fibroids
- Male factor infertility
- Unexplained infertility



4

## \*\*FERTILITY TESTING\*\*


- When is it indicated?
  - Women <35 years
    - Failure to achieve successful pregnancy after 12 months.
  - Women 35-40 years
    - Failure to achieve successful pregnancy after 6 months.
  - Women >40 years
    - Failure to achieve successful pregnancy after 3 months.
- Right away if:
  - History of oligo/amenorrhea, PCOS
  - Hx chemotherapy/radiation either partner
  - Known or suspected uterine issues, tubal disease, or stage III-IV endometriosis
  - Known or suspected male infertility
  - Recurrent pregnancy loss
  - Special instances: Same sex couples



5

## STEPS OF EVALUATION

- Evaluation of both partners should begin at the same time



6

### HISTORY

- In addition to the usual PMH, Surg Hx, Meds, Fam Hx, Soc Hx, ROS:
  - Pregnancy History
    - Time to conceive, New partner?
    - Miscarriages, ectopic, # of term/preterm,
    - Complications with pregnancy/delivery
  - Previous Fertility evaluation and treatments
  - Extensive Gyn hx
    - Age at menarche
    - Cycle regularity, PCOS
    - Cycle characteristics (duration of bleeding, molimina, dysmenorrhea)
    - Previous Methods of Contraception/ coital frequency
    - Sexual Dysfunction (decreased libido, dyspareunia)

7

### HISTORY

- History continued
  - Sexually transmitted infections/PID
  - Hx fibroids, polyps, endometriosis, ovarian cysts
  - SX Endocrine disease
    - Thyroid, Galactorrhea, Hirsutism, Acne, hot flashes
  - Abnormal paps/subsequent treatment
  - Family history of birth defects, delayed development, early menopause, RPL
  - Occupation & exposure to environmental hazards (chemo tx, radiation tx)
- Eliminate Tobacco, Nicotine, and drugs**
- Avoid ETOH**
- Caffeine <200mg per day**

8

### FERTILITY DECREASES WITH INCREASING FEMALE AGE

Peak fertility

Decline in fertility

\*Hutterites, Geneva Bourgeoisie, Normandy, Norway, Canada populations : 1600-1930

Menken, Trussel, Larsen et al. Science 1986

Adapted from Practice Committee of American Society for Reproductive Medicine, 2008

9

### IMPACT OF MATERNAL AGE

- OVARIAN RESERVE DECLINES WITH AGE**

Non Growing Follicle Number

Upper 95%  
Median  
Lower 95%

Birth Puberty 20's 30's 40's

10

### ANTIMULLERIAN HORMONE (AMH)

- Serum antimullerian hormone (AMH)
  - Produced by granulosa cells of early follicles.
  - Gonadotropin-independent.
  - Relatively consistent between menstrual cycles.
  - More accurate in follicular phase of cycle.
  - AMH decreases starting around age 25 until undetectable at menopause.

AMH (ng/mL)

Age (years)

Seifer DB et al. Fertil Steril 95(2):747-50, 2011

11

### AMH

- Normal adult female values
  - 1.5 - 10ng/mL
- Preferred marker for ovarian reserve.
- Lower levels = diminished ovarian reserve (DOR).
- Higher levels associated with PCOS.
- Useful for determining response to fertility meds, IVF protocols, & med dosing.

Functional ovarian reserve

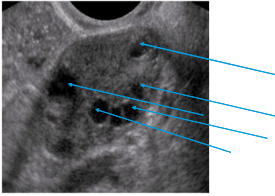
AMH levels

J Clin Endocrinol Metab 2020 Nov; 105(11):3361-3373.

12

### ANTRAL FOLLICLE COUNT

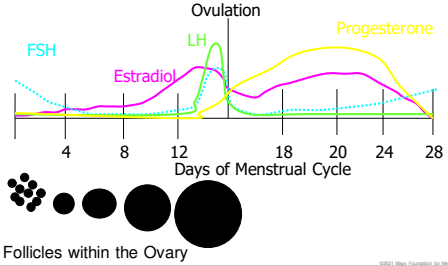
- Sum of the number of small follicles in both ovaries measuring 2–10 millimeters in diameter during an early follicular phase transvaginal scan.
- Measure of ovarian reserve
- The AFC correlates with the size of the remaining follicular pool
- AFC <5 is low
- AFC- 12-15 is normal
- AFC > 25 associated with PCOS



J Clin Endocrinol Metab 2020 Nov; 105(11):3361-3373. Fertility and Sterility, 103(3), 2015: 0015-0282.

13

### NORMAL MENSTRUAL CYCLE




Days of Menstrual Cycle

Follicles within the Ovary

14

### ANOVLUTION

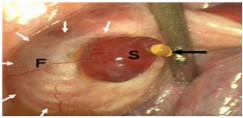
- 40% of infertility in women
- Common causes:
  - Polycystic ovary syndrome
  - Obesity
  - Weight gain or loss
  - Strenuous exercise
  - Thyroid dysfunction
  - Hyperprolactinemia



15

### OVULATORY FUNCTION

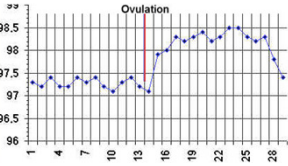
- Methods of determining ovulation:
  - History
  - Basal Body Temperature (BBT)
  - Ovulation predictor (LH) kits
  - Serum progesterone



16

### OVULATORY FUNCTION

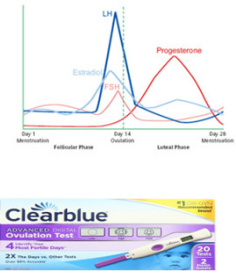
- Basal Body Temperature (BBT)
  - Cannot determine time of ovulation.
  - 0.4-1.0°F 24 hours **AFTER** ovulation.
  - Period of highest fertility 5-7 days prior to temp rise.



17

### OVULATORY FUNCTION

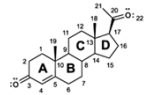
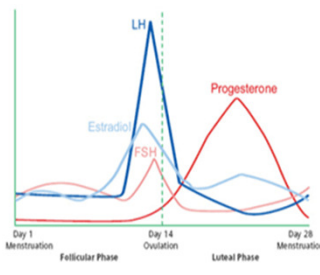
- Ovulation Predictor (LH) kits
  - Detect urinary LH.
  - Identify the midcycle LH surge that precedes ovulation by ~36 hours.
  - Best chance of conceiving:
    - Day of LH surge and following 2 days.
  - Correlate well with the peak in serum LH (midday or evening urine).



18

### OVULATORY FUNCTION


- Midluteal serum progesterone concentration.
  - Check one week after ovulation.
  - Often cycle day 21.
  - Progesterone greater than 3 ng/mL corresponds with ovulation.

19

### LABS



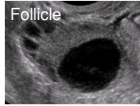

- Need to be drawn on the appropriate day of Menstrual cycle.
- Call office on Cycle day 1
- Hormone evaluation on Day 2,3 or 4:
  - Anti-Mullerian hormone (AMH)
  - Day three labs : FSH, E2, LH,
  - Prolactin
- Routine Health Screening: TSH, CBC, comp panel, HgbA1c, Vit D
- Prenatal labs: Blood type, Rubella/varicella titers, Infect Disease screening
- Carrier Screening- optional
- Hormone evaluation on Day 21 progesterone



20

### ANATOMICAL ISSUES

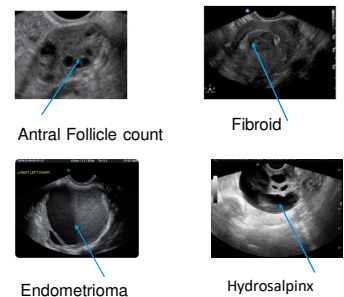
- Ideally schedule Vag ultrasound at start of menstrual cycle Day 2-5
  - Appearing of lining
  - Endometrium Thickness
  - Normal <6mm
  - >10mm= eval
- Ovaries
  - Presence of follicles
  - Presence of cysts

Follicular Phase	Luteal Phase
 <p>Trilaminar</p>	 <p>Hyperechoic</p>
 <p>Follicle</p>	 <p>Corpus luteum</p>

21

### ULTRASOUND

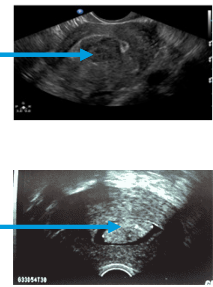
- Antral Follicle Count (AFC)
- Ovarian cysts
- Uterine Fibroids
- Uterine polyps
- Hydrosalpinx
- Uterine anomalies



22

### UTERINE ABNORMALITIES

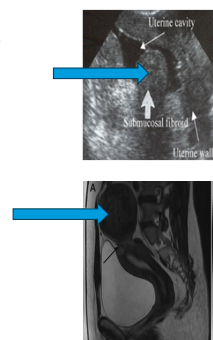
- Fibroids
  - Common
  - Location, location, location
  - Generally, try to ignore
  - May need surgical intervention, esp if large, located in cavity, or submucosal
- Polyps
  - Benign growths in endometrial cavity, cervix
  - Spotting abnormal bleeding
  - INFERTILITY
  - Common with PCOS and Oligomenorrhea
  - Interfere with implantation
  - May be precancerous
  - Treatment- operative hysteroscopy



23

### UTERINE ABNORMALITIES

- Transvaginal saline sonogram (SIS)
  - Better defines the size and shape of the uterine cavity- uterine anomalies
  - High PPV (>90%) and NPV for detection of intrauterine pathology
- Pelvic MRI
  - Useful for mapping fibroids prior to surgery
  - Useful to diagnose uterine anomalies
- Hysteroscopy

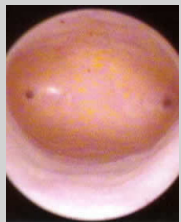


24

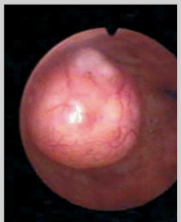
### HYSTEROSCOPY

DEFINITIVE METHOD FOR THE DIAGNOSIS AND TREATMENT OF INTRAUTERINE PATHOLOGY INCLUDING: FIBROIDS, POLYPS

Normal

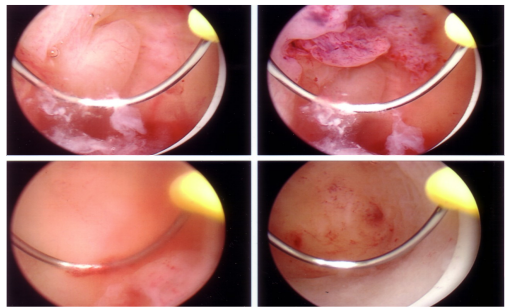


Fibroid



25

### Uterine Polyps

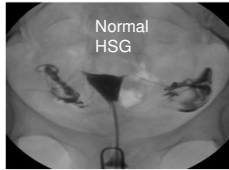


26


### ANATOMICAL ISSUES

- Hysterosalpingography (HSG)
  - Defines the size and shape of the uterine cavity
- Uterine anomalies
  - Unicornuate
  - Septate
  - Bicornuate
  - Didelphys
- Acquired abnormalities
  - Endometrial polyps
  - Submucous myomas
  - Synechia (Asherman's Syndrome)

Normal HSG



Uterine septum




27

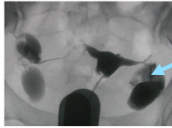
### ANATOMICAL ISSUES

- Methods for evaluation Tubal patency
  - HSG
- SIS for fluid in the cul de sac
- Laparoscopy/chromotubation
  - Adhesions
  - Endometriosis
  - Hydrosalpinx
  - Cysts

Proximal tubal occlusion



Hydrosalpinx

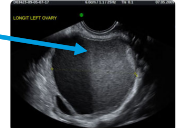


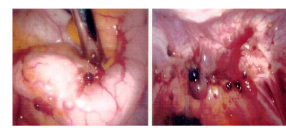
28

### ENDOMETRIOSIS

- Diagnosis-
  - History- severe dysmenorrhea, cyclic pain, chronic pain
  - Surgery- classic appearance, biopsy
    - 4 stages of classification
- 3-10% of women, 25-35 % women w infertility
- Treatment-
  - Treat with birth control pills, Orilissa, Norethindrone, Lupron
  - Ablation of endometriosis surgically, resection of adhesions

Endometrioma

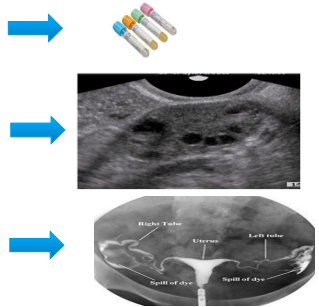




29

### Summary of Female Evaluation

- Blood Draw**
  - AMH
  - FSH/LH/Estradiol
  - TSH, prolactin, CBC, comp panel
  - Blood type, Rubella/Varicella titer
  - Infectious disease testing
  - Day 21 progesterone
  - Optional- carrier testing
- Baseline ultrasound**
  - Antral follicle count (AFC)
  - Fibroids, hydrosalpinx
  - Endometrial lining
- Uterine Cavity/Tubal Evaluation**
  - HSG/ Saline sonogram



30

### OTHER FACTORS THAT AFFECT FERTILITY

- Extremes of weight adversely impact egg quality
- Risk of pregnancy loss and stillbirth are increased with BMI > 30
- Reduced fertility treatment success with BMI > 35 and < 18

Category	BMI (kg/m <sup>2</sup> )
Underweight	Less than 18.5
Normal	18.5 to 24.9
Overweight	25.0 to 29.9
Obesity, Grade I	30.0 to 34.9
Obesity, Grade II	35.0 to 39.9
Obesity, Grade III	≥ 40.0

Note: BMI = body mass index.  
\* WHO 2004.  
Practice Committee. Obesity and reproduction. Fertil Steril 2015.

31

### INCREASING RATES OF OBESITY IN THE US

Risks of obesity in pregnancy

- \*50% greater odds of developing Diabetes
- Chronic hypertension, CV disease
- \*35% increased risk of premature mortality
- \*Increased likelihood of ovarian and endometrial cancer.

Figure 4. Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over: United States, 1999-2000 through 2017-2018

32

### OBESITY AND PREGNANCY

**Risks to the Baby:**

- Increased risk of Macrosomia
- Increased risk of Stillbirth and neonatal death (Kalliala et al. 2017)
- For children who are large for gestational age (LGA)
  - 2- to 5-fold higher risk of childhood and adult obesity
- Increased risk of cardiovascular risk factors in young adulthood
  - Glucose intolerance
  - Insulin resistance
  - Hypertension
  - Dyslipidemia
- Increased risk of cardiovascular mortality in offspring

33

### NUTRITION AND EXERCISE

- WELLNESS is the foundation of success
- Team approach- Consider nutrition consult
- No Specific Diet Recommended (Try to eat a rainbow everyday)
  - 5-7 vegetables and fruits per day
  - Healthy fats- avocado, nuts, olives
  - Whole grain foods and Lean meats
  - Eliminate empty calories (sodas, sugary snacks)
  - Avoid highly processed foods
  - Vegetarian /Vegan eating plans are fine
  - During fertility treatments, avoid Ketosis plans
- Exercise –
  - 30 minutes 5 days per week
  - 2 days of weights /resistance training

34

### EATING HEALTHY DOESN'T HAVE TO BE SCARY

Focus on all the great-tasting foods that power your body rather than sugary/salty snacks that “you can’t eat”

Go for the 90/ 10 rule (or even 80/20 rule)

Enlist a friend/spouse/partner or even coach for support

35

### WHAT ABOUT SUPPLEMENTS??

- Not regulated by FDA
- Do not need to prove their claims or SAFETY
- Not well-studied, rely on paid endorsements
- Buyer Beware- some are scams**
- Many make claims that are simply not true
- Some supplements may be contaminated with
  - Harmful chemicals (lead, mercury)
  - Dessiccated animal organs
- May contain hormones that interfere with fertility Tx
- Unwanted side effects (increased risk of bleeding)

**\*\*\*RED FLAGS\*\*\***

“This statement has not been evaluated by the U.S. Food and Drug Administration (FDA). This product is not intended to diagnose, treat, cure, or prevent any disease.”

36

### RECOMMENDED SUPPLEMENTS

**Prenatal Vitamin**


- No preferred brand
- Tablet or chewable form
- No prescription is necessary
- Should contain at least **0.8 mg or 800 micrograms (mcg) of folic acid**

**Vitamin D (also known as Vitamin D3 or Cholecalciferol)**

- 1000 - 2,000 IU per day**
- No prescription is necessary

**Omega 3 Fatty Acids (also known as Fish Oils, DHA, and/or EPA)**

- 1000 mg per day (Many prenatal include DHA)**
- No prescription is necessary



37

### ADDITIONAL SUPPLEMENTS

**Vitamin C**


- 500 -1000 mg per day**
- Usually included in prenatal or multivitamin
- Beneficial effects as an antioxidant and for immunity

**Co-Enzyme Q10- "Improvement in egg quality"**

- 400 mg to 600 mg per day**
- No prescription is necessary
- Ubiquinol** is also another form of Co-Enzyme Q10
- Mouse studies have shown improvement in egg quality
- Caveat-** no human studies have shown this
- Unlikely to be harmful

**Acai**

- Promising results for beneficial antioxidant effects
- Frozen or powder forms provide highest potency



38

### SUPPLEMENTS: NOT ALWAYS BENEFICIAL

- Myo-Inositol** - improve menstrual cycle regulation in women with PCOS
  - No good data on pregnancy outcomes
  - No good data on women with decreased AMH
- L-Arginine- Amino Acid**
  - too much may be harmful
- Magnesium/Zinc**- already in most prenats
- Selenium**- found in most vitamins
  - Taking too much can be harmful
- Melatonin**- sleep aid
  - May increase risk of bleeding in some people
  - Stop prior to surgeries
- NAC (N-acetyl-L-cysteine)**- Amino acid with some antioxidant properties. May be helpful with PCOS data to support
- DHEA**- can lead to premature elevated in progesterone
  - May have an adverse effect in some women
- St. John's Wort, Chaste Tree berry**
  - Don't recommend

39

### Tips For Men

- Same nutrition recommendations
- Obesity is detrimental to male fertility
  - Increased estrogen levels
- Start a Multivitamin
- Helpful: Vit D, E, C, fish oil
- Avoid:**
  - Antihistamines
  - Herbal supplements
- NO TESTOSTERONE**
- Exercise in moderation
  - Limit biking
- Avoid heat exposure
  - Hot tubs, saunas, laptops




- Limit Alcohol < 5 drinks per wk
- No Smoking
- No Vaping
- Caffeine < 3 per day
- No chewing tobacco/Nicotine pouches
- No drugs



40

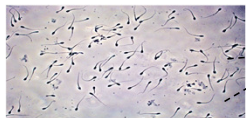
### MALE FACTOR INFERTILITY


- Male factor**
  - Common
  - Sole factor in 30% couples
  - Contributes in an additional 30%–40% of couples
- Men with normal semen parameters can have sperm that are incapable of fertilizing an egg.
- Men with obesity and men > 50 demonstrate lower sperm counts and higher rates of infertility.
- Men are starting testosterone supplementation without understanding implications to fertility.
- Testosterone supplementation eliminates sperm production.**



41

### MALE EVALUATION





Semen analysis

Abstinence interval 2–4 days

Collection:

Masturbation into a specimen cup

3 major parameters

- Concentration (mil/mL)
- Motility %
- Morphology %

42



### SA: NORMAL VALUES

**TABLE 1**

**Lower limits of the accepted reference values for semen analysis.**

Parameter	Reference value
On at least two occasions	
Ejaculate volume	1.5 mL
pH	7.2
Sperm concentration	15 × 10 <sup>6</sup> spermatozoa/mL
Total sperm number	39 × 10 <sup>6</sup> spermatozoa/ejaculate
Percentage motility	40%
Forward progression	32%
Normal morphology	4% normal
And	
Sperm agglutination	Absent
Viscosity	≤ 2 cm thread after liquefaction

Parameters that actually predict male fertility:

- Concentration >48 million/mL
- Motility >63%
- Morphology >8 %
- Always obtain the report

Note: Data from World Health Organization, 2010 (10).  
Practice Committee. Evaluation of the infertile male. Fertil Steril 2015.

43

- ### OVULATION INDUCTION
- Femara/Letrozole
    - Well-tolerated
    - FDA approved treatment for Breast Cancer
    - Risks of birth defects if taken during pregnancy
    - Risks of multiple pregnancy
    - **Not FDA approved for ovulation induction**
    - Must have a negative pregnancy test each month before starting
    - First line recommendation for PCOS
  - Clomid
    - SERM more commonly used for unexplained infertility
    - FDA approved for ovulation induction
    - Increased side effects compared to letrozole and higher risks of multiples
    - May develop thin lining. Must have negative pregnancy test each month before starting
  - Metformin
    - **Not FDA approved for ovulation induction**
    - May regulate cycles and lead to ovulation in women with PCOS
    - GI Side effects. Use with birth control for women who do not want to conceive.
  - Injectable gonadotropins- very risky
    - These should only be administered by a physician experienced with these medications under close ultrasound monitoring due to risks of multiple follicular recruitment and
      - Risk multiples (25% twins, 5% triplets, <1% 4+)
      - Risk of severe OHSS

44

- ### WHEN TO START CLOMID OR LETROZOLE
- Patients having menstrual cycles:
    - Early follicular phase
      - Negative pregnancy test
      - Start Clomid Day 3-5. 50 mg-100 mg po daily for 5 days
      - Start Letrozole Cycle day 3-5. 2.5- 7.5 mg po daily for 5 -7 days
  - Anovulatory PCOS patients:
    - Induce a menstrual cycle
      - Consider EMB if prolonged unopposed estrogen exposure first
    - Neg bhcg. Then Prometrium 400 mg for 10 days

45

- ### WHEN TO TIME INTERCOURSE?
- Use LH predictor kits
  - Ultrasound monitoring on cycle day 10-14 and give Ovidrel 250mcg with dominant follicle
  - Or simply prescribe intercourse cycle days 10, 12, 14, 16
    - Sperm survive 72 hours in the reproductive tract
  - Midluteal progesterone > 5 confirms ovulation
  - Among anovulatory women who ovulate with CC, the cumulative conception rates for 50 mg/d, 100 mg/d, or 150 mg/d at 3 months are 50%, 45%, and 33%, respectively

46

- ### SIDE EFFECTS
- Mood swings are the most common side effect
    - 64%–78%
  - Vasomotor flushes
    - 10%
  - Visual disturbances (Clomid only)
    - Blurred or double vision, scotomata, and light sensitivity, generally are uncommon (<2% prevalence)
    - Reports of optic neuropathy
    - If these symptoms occur must STOP CLOMID
  - Less specific side effects (2-5%)
    - Breast tenderness
    - Pelvic discomfort
    - Nausea

47

### INTRAUTERINE INSEMINATION (IUI)

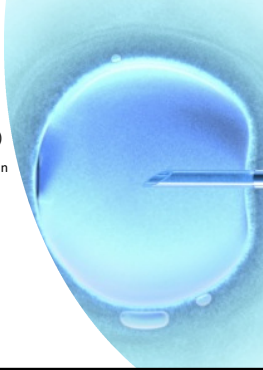
- IUI is one of the simpler treatments for infertility
- Increases the chances of sperm reaching the egg(s)
- Similar to pap smear
- Low risk
- IUI is only utilized after fertility evaluation and after it has been demonstrated that at least one fallopian tube is open
- Most patients will only undergo up to 3 IUIs.
- IUI can be completed with follicle stimulation with the use of medications called Clomid, Letrozole and ultrasound monitoring with trigger shot (Ovidrel)

48



## IN VITRO FERTILIZATION (IVF)

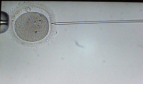
- A form of Assisted Reproductive Technology (ART) which consists of removing eggs from the ovary, fertilizing the eggs with sperm outside the body (in vitro) and transferring a resulting embryo into a uterus.
- Options with donor egg, donor sperm, adopted embryos and/ or gestational carriers.
- Nearly 30 million babies born from IVF procedures worldwide




49

## INDICATIONS FOR IVF


- Women
  - Decreased ovarian reserve
  - Polycystic ovarian syndrome
  - Tubal occlusion
  - Advanced age
  - Recurrent pregnancy loss
  - Heritable Genetic Disorders
  - Endometriosis
  - Failure of success from other types of fertility treatment
- Men
  - Male factor infertility
  - Mechanical factor (blockage)
  - Heritable disorders




### STAGES OF EMBRYO DEVELOPMENT



Day 1  
2 pronuclei



Day 3  
Cleavage stage




Day 5 or 6  
Blastocyst

50

## RESOURCES

- Fertile Hope: financial assistance & information
  - A national nonprofit organization providing reproductive information, support, and hope to cancer patients and survivors whose medical treatments present the risk of infertility.
  - [www.fertilehope.org](http://www.fertilehope.org)
- Everlasting Hope: Support group and resource for ND patients
- American Society of Reproductive Medicine: ASRM
  - [www.asrm.org](http://www.asrm.org)
- Resolve: The national infertility association
  - [www.resolve.org](http://www.resolve.org)



51