Infertility

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DEFINITIONS

• Primary Infertility - Couple has not conceived after one year of unprotected intercourse
• Secondary Infertility - Couple with previous conception who have not conceived after one year of unprotected intercourse

INCIDENCE

INFERTILITY affects approximately 15% of couples
Incidence increases with maternal age
Increasing rates of infertility? - delayed childbearing, environmental, lifestyle
Infertility is Common

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Infertility Rate</th>
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<tbody>
<tr>
<td>30-34</td>
<td>5%</td>
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<tr>
<td>35-39</td>
<td>8%</td>
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<tr>
<td>40-41</td>
<td>16%</td>
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<tr>
<td>42-43</td>
<td>30%</td>
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<td>44-46</td>
<td>60%</td>
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Age and Fertility

The Age Factor
As you can see by the graph below, the older a woman’s chances of conceiving per month is decreased by half. The downward slope continues until age 40, but by age 40 the menstrual cycle rate of conception is approximately 9%.

Maternal age       Pregnancy loss rate
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< 30              5%
30-34             8%
35-39             16%
40-41             30%
42-43             40%
44-46             60%
FEMALE CAUSES OF INFERTILITY

- Ovulation disorders - 40-50% depending on geographic location. PCOS prevalent in South
- Endometriosis - 30-40%. Highly dependent on stage of disease
- Tubal Factors - Endometriosis, STD’s - 10-15%
- Unknown – 10%-immune, endometrial receptivity?

MALE CAUSES OF INFERTILITY

- Low sperm count and/or motility and/or morphology
- Medical contributing factors:
  - Varicoceles
  - Surgical procedures (hernia repair)
  - Infections or fever post pubery
  - STD’s
  - Blockage of vas deferens
- Lifestyle contributing factors:
  - Drugs and medications - calcium channel blockers, Rx meds, illegal drugs, alcohol, marijuana
  - Excessive heat and exercise
  - Environmental and work
CONDITIONS NECESSARY FOR FERTILITY

- Normal motile sperm
- Ejaculation
- Sperm needs to penetrate mucous and swim to oocyte
- Oocyte quality
- Ability to fertilize oocyte
- Ability to form good embryos

CONDITIONS NECESSARY FOR FERTILITY

- Ability of embryo to pass into uterus
- Receptive endometrium for implantation
- Normal hormonal and anatomic milieu to foster healthy pregnancy

EVALUATION OF THE FEMALE

- TSH, FSH, Estradiol, Prolactin and mid luteal Progesterone level
- With androgen excess or obesity- Endocrine panel-LH/FSH ratio, SHBG, Testosterone, Androstenedione, DHEAS-If abnormal assess adrenal function
- Insulin and Glucose

EVALUATION OF THE FEMALE

- Cervical cultures where symptomatic
- Temperature Charts/Ovulation kits
- Assessment of Tubal Patency- Hysterosalpingogram/Chromopertubation
MEDICAL THERAPIES: FEMALE
- If anovulatory-oral ovulation agents. Clomiphene citrate, Aromatase inhibitors. If refractory gonadotrophin therapy
- IUI

OVULATION INDUCTION
- Clomiphene citrate-stimulates endogeneous FSH by lower estrogen feedback to pituitary
- Aromatase inhibitors-inhibits peripheral estrogen production without as much antiestrogenic effect.

MEDICAL THERAPIES: FEMALE
- If anovulatory-oral ovulation agents. Clomiphene citrate, Aromatase inhibitors. If refractory gonadotrophin therapy
- IUI

OVULATION INDUCTION
- Gonadotrophins-original agents derived from urine of menopausal nuns. Human menopausal gonadotrophins (HMG) 75u FSH, 75u LH
- Next generation purified FSH products-LH removed with immunoaffinity columns
**OVULATION INDUCTION**

- Most recent products - Recombinant FSH. Genetic engineering involve genome of Chinese hamster ovary cell line. Alpha and beta forms.
- Less acidic FSH isoforms with shorter half life
- Highly efficient for ovulation induction

**Efficacy of Treatment Modalities**

- Clomiphene - 80% ovulation 40% pregnancy
- Letrozole - 80% ovulation 50% pregnancy
- Bromocriptine - 90% ovulation 70-80% pregnancy
- Gonadotrophins - 80-90% ovulation 50-80% pregnancy
- Ovarian drilling - 70-80% ovulation 50% pregnancy

**SURGICAL THERAPIES: FEMALE**

- Tubal or Ovarian adhesions - Laparoscopic lysis.
- Microsurgery - rarely
- Endometriosis - Laparoscopy with ablation of endometriosis, removal of endometriomas.
- Laparotomy - rarely with stage 3 or 4 disease involving bowel
- Tubal reanastomosis

**EVALUATION OF THE MALE**

- History and Physical exam
- Semen analysis - Kruger vs WHO criterion
- Endocrine testing
- Testicular biopsy
MEDICAL TREATMENTS: MALE

- Clomiphene citrate
- Vitamin C 1000 mgm daily
- Herbal supplements: Carnitene, Acetylcarnitene plus vitamins and minerals

Surgical Treatments: MALE

- Outpatient surgery: Varicoele repair, Vas reversal, Microsurgery for Ductal obstruction.
- Sperm extraction for IVF with ICSI-epididymal vs testicular

Reasons for doing Insemination (IUI)

- Unexplained fertility
- Stage 1 or 2 Endometriosis
- Mild adhesions
- Male factor
- Negative postcoital test

Sperm Wash for Insemination

- Swim-up
- Gradient prep
- Procedure can be coordinated with Natural cycle, Clomiphene or Letrazole or with Gonadotrophins
- Timing most often day after LH surge or 36 hours after HCG injection
Success with Insemination

- Clomiphene and Letrezole approximately 10% with 1 insemination vs 10-20% with two
- Gonadotrophic plus IUI 19-25% with one insemination vs 52% with two

Sperm Donation

- Regulated by FDA
- Semen analysis
- Freeze thaw/Post thaw Analysis
- Lab work: HIV, Hepatitis B, C & RPR
- Seminal fluid cultures, UA
- CMP, TSH, Glucose

Second Level Testing

- Karyotyping
- CF Screening, Tay-Sachs, Sickle cell
- Secondary thaw with additional cultures
- Sample quarantined x6 months. Repeat HIV, Hepatitis B, C, RPR

Staircase Approach to Empirical Infertility Treatment

Psychologic Aspects

- Education and Support
- Resolve (National Organization)
- Relaxation training
- Acupuncture
- Counseling-Individual and Couples
- Extreme Cases-Crisis Intervention, Psychotherapy

In Vitro Fertilization

- Required in approximately 5-10% of fertility patients
- National Success Rates in range of 35% take home baby rate. See CDC-SART reports
- Offers both diagnostic and therapeutic benefits

IVF

- Patient selection-Under 35 years of age-3 to 4 cycles of unsuccessful ovulation (properly monitored)
- 6 months after attempting surgery for Tubal Factor or endometriosis (consider age)
- Failed COH plus IUI
- Known tubal or male factor

IVF

- Over 35-Baseline FSH and estradiol levels
- Diminishing success rates where FSH>8
- If FSH elevated-Clomiphene Challenge test, AMH, Inhibin B
- If compromised Donor oocyte, Donor embryo, adoption
IVF

- Stimulation
- Retrieval
- Transfer
- Cryopreservation of embryos

**Conventional IVF Process**

- **Aspiration**
- **Fertilization**
- **Transfer**

IVF

- Stimulation - varied protocols.
- Can involve midluteal start, suppression of ovaries with O.C and Lupron, GnRh Antagonists
- Combine with Gonadotrophins-Urinary vs recombinant.
- Various protocols to address normal, poor and high responders

IVF

- Retrieval-in operating room.
- Usually involves monitored anaesthesia-propophol. Anaesthesia machine (not for home use!)
- Versed?
- Pre-op antibiotics
- IV
IVF

- Wash vagina with human tubal fluid
- Sterile probe cover and sterile Norfolk needle
- Ultrasound guided entry into follicle.
- Complications include bleeding, infection, damage to adjacent organs

Hormones may be administered to the woman to produce multiple eggs. The eggs are then retrieved from the ovary.

In IVF, eggs are harvested from the woman’s ovary and fertilized in the laboratory with sperm. The embryos are then transferred into the uterus.
**IVF**

- Conventional IVF - Normal semen parameters:
  - Greater than 20 million sperm/ml
  - Greater than 40% motility
  - Greater than 14% normal morphology
  - Fair to good forward progression

**ICSI Selection Criterion**

- Severe male factor - less than 5 million total sperm. Genetic testing to rule out microdeletions on short arm of Y.
- Less than 20 million total sperm with <30% motility and poor morphology.
- Unknown or suspected egg quality issues.
- Previous IVF cycle with poor fertilization.
**IVF**

- EMBRYO TRANSFER
  - Insert speculum
  - Cleanse cervix with side washing catheter and HTF
  - Place outer catheter
  - Place inner catheter to within 1 centimeter of fundus and withdraw 0.5 cm.

**IVF**

- Ultrasound visualization (full bladder)
- Suture if necessary
- Try and avoid tenaculum
**IVF**

- **CRYOPRESERVATION OF EMBRYOS:**
  - Reduces risk of multiple births with IVF
  - Less invasive than ovulation induced cycles
  - Costs much less than repeat IVF cycle
  - We vitrify embryos at blastocyst stage
  - The future: Oocyte freezing

- **COMPLICATIONS:**
  - Surgical: Damage to bowel, bladder, blood vessels, ureter and bony structures
  - Haemorrhage
  - Infection
  - Ovarian hyperstim
• OVARIAN HYPERSTIMULATION:
  Iatrogenic
  Mild, Moderate, Severe
  Increase in capillary permeability
  resulting in a fluid shift from intravascular to extravascular space

• TREATMENT OF OVARIAN HYPERSTIMULATION:
  Mild: Oral analgesics, rest and fluids
  Moderate: Monitor daily weight, urinary output, abdominal girth.
  Evaluations include CBC, electrolytes, creatinine. Push fluids including electrolyte solutions. Limit activity.

  Severe: Severe pain, rapid weight gain, tense ascites, hemodynamic instability, respiratory difficulty, progressive oliguria and hypotension.
  Hemoconcentration with risk of thromboembolism, renal failure, adult RDS, haemorrhage from ovaries
IVF

- TREATMENT FOR SEVERE OVARIAN HYPERSTIMULATION:
  - Hospitalize for fluid replacement,
  - Careful monitoring of I & O, chest x-ray, echocardiogram
  - Ultrasound guided paracentesis
  - Thoracentesis if indicated
  - DIURETICS CONTRAINDICATED

REGULATORY:
- CLIA
- CAP
- AATB
- State Licencing
- CDC/SART
- FDA-All donor materials