Infertility

Review and Update

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Intrauterine Inseminations

- Beneficial effects of IUI not consistently documented in studies
- No deleterious effects on fertility
- 3-4 cycles of IUI should be considered
- No benefit found if washed specimen contains less than 1 million motile sperm

Phase 2 – Evaluation and Treatment

- Indicated for patients with unexplained infertility
- Indicated for patients who have failed to conceive on previous therapy
- Indicated for patients with more complex infertility disorders

Phase 2

- Laparoscopy
- Clomiphene therapy with IUI
- Gonadotropin therapy with IUI
- Assisted reproductive technologies
• Usually performed 6 months after normal HSG
  – delay allows for fertility enhancing effect of HSG
• Laparoscopic findings agree with HSG in 2/3 of cases
• 50% of normal infertile patients will have pelvic pathology, usually adhesions or endometriosis
• can surgically correct certain abnormalities

  Tubal Disease

• Peritubal adhesions
• Proximal tubal obstruction
• Distal tubal obstruction
• Endometriosis

  Laparoscopy
  Laparoscopy
  Laparoscopy
  Laparoscopy

  Lysis of adhesions: 60-80% pregnancy rate
• Fimbrioplasty (neosalpingostomy):
  – mild disease: 30-40% pregnancy rate
  – moderate disease: 15-20% pregnancy rate
  – severe disease (large hydrosalpinges): 5% pregnancy rate

  Gonadotropins

• Should be administered by reproductive endocrinologist due to risks, expense, and backup options
• Requires close monitoring: estradiol levels and transvaginal ultrasound

• Multiple gestation rate: 30% twins, 8% triplets or more

• Severe ovarian hyperstimulation is greatest risk

  Unexplained Infertility
  Pregnancy rate / cycle

• No treatment: 1-4%

• Intrauterine insemination (IUI): 4%

• Clomiphene citrate: 6%

• Clomiphene citrate and IUI: 8%

• Gonadotropins: 8-14%

• Gonadotropins and IUI: 15-20%

• In-vitro fertilization (IVF): 30-35%

  Assisted Reproductive Technology

• IVF: in-vitro fertilization

• GIFT: gamete intrafallopian transfer

• ZIFT: zygote intrafallopian transfer

• ICSI: intracytoplasmic sperm injection

• TESA: testicular epididymal sperm aspiration

  IVF Advantages

• Fallopian tube is unnecessary
• fertilization is confirmed
• endometrial thickness is increased
• may treat male factor, ovulatory dysfunction, tubal disease, or unknown causes

ART - 1998

• Male factor – 27.1%
• Endometriosis – 25.8%
• Ovulatory dysfunction – 22.5%
• Tubal factor – 25.3%
• Uterine factor – 19.3%
• Unexplained – 25.4%

IVF Disadvantages

• cost
• multiple gestation rate
• ovarian hyperstimulation
• ovarian cancer risk

Intracytoplasmic Sperm Injection (ICSI) Advantages

• requires only a single sperm per egg

Intracytoplasmic Sperm Injection (ICSI) Advantages

• bypasses many requirements of sperm function
• avoids polyspermy
• fertilization rates comparable to standard IVF (60-70%)
• pregnancy rates similar to standard IVF

ICSI Disadvantages
• No natural sperm selection
• Entire sperm is intracytoplasmic
• Damage to egg membrane
• Microdeletions of Y chromosome passed on to male children
• Slight increase in congenital anomalies (1.5%)

ART Cycles – 1998
• 61,650 cycles started
• 53,154 retrievals (86.3%)
• 49,837 transfers (80.8%)
• 18,800 pregnancies (30.5%)
• 15,367 live births (24.8%)

ART Cycles – 1998
• 68.9% - no pregnancy
• 18.7% - single fetus pregnancy
• 11.8% - multiple fetus pregnancy
• 0.6% - ectopic pregnancy
  ART Cycles - 1998
  Outcomes

• 50.9% - singleton births

• 30.9% - multiple infant births

• 16.9% - miscarriages

• 1.6% - induced abortions

• 0.5% - stillbirths
  ART Cycles - 1998
  Outcomes
  PCO Syndrome
  PCO Syndrome

• No consensus at present for definition

• A state of chronic anovulation associated with hyperandrogenism

• A heterogeneous disorder in which ovarian and possibly adrenal androgen excess is present

• Most common endocrine disorder of women (6%)
  Clinical Features

• Infertility - 75% (35-94%)

• Hirsutism - 56% (17-83%)

• Amenorrhea - 47% (19-77%)

• Obesity - 33% (16-49%)

• Virilization - 17% (0-28%)
Ovulatory Dysfunction

• majority of women will have ovulatory dysfunction
• dysfunction ranges from menometrorrhagia to amenorrhea
• primary amenorrhea is rare

Ultrasound Findings

• Numerous 6-10 mm sonolucent follicles
• Enlarged ovaries bilaterally
• Thickened endometrial stripe

• Recent ultrasound definition - more than 10 follicles between 2-8 mm in diameter and demonstrating increased ovarian stroma

Laboratory Features

• elevated serum androgens
• increased LH:FSH ratio
• insulin resistance
• hyperprolactinemia

Serum Androgens

Glucose Levels
Insulin Levels
Insulin Resistance
• Fasting glucose and insulin levels
  – elevated glucose (non-insulin dependent DM)
  – elevated insulin (insulin resistance - IR)
  – glucose/insulin ratio: 4.5 or greater (IR)
• 2 hour glucose after 75 g glucose load
  – < 140 mg/dl - normal
  – 140-200 mg/dl - impaired
  – > 200 mg/dl - NIDDM

Polycystic Ovary Syndrome
Treatment

• Clomiphene citrate
  – Dexamethasone
  – Midcycle HCG
• Metformin
• Gonadotropins
• Ovarian drilling
• In-vitro fertilization
• Tamoxifen

Ovarian Drilling
Polycystic Ovary Syndrome

Gonadotropin therapy
• Minimal stimulation protocol
• Oral contraceptive pretreatment
• GnRH agonist pretreatment
• Conversion to IVF
  Gonadotropin Therapy
  Fertility in Women 35 years of age and older

• Gradual decrease in fertility after the age of 35
• Decrease in fecundity
• Increase in spontaneous abortion rate
• Increase in chromosomal and other abnormalities
  Fertility in Women over 35 years
  Fertility in Women over 35 years
  Changes with Advanced Maternal Age

• Decrease in serum inhibin levels
• Subtle increases in serum FSH levels
• Decreased length of the proliferative phase
• Elevations in early proliferative phase estradiol levels
• Decreased fertility
• Increased rate of spontaneous abortions

Workup for Older Patient

• Careful history: length of infertility
Day 2: serum estradiol and FSH

Clomiphene citrate Challenge Test
- a bioassay of FSH response
- 100 mg/day on days 5-9
- Estradiol and FSH levels on day 3 and 10
- FSH levels above 26 IU/L - poor prognosis
- Abnormal response increases with age >35
- 85% of women with increased FSH respond poorly to ovarian stimulation
- Test more sensitive than basal FSH level

Recent Advances
- Recombinant FSH
- Recombinant LH
- Recombinant HCG
- Y microdeletions testing
- GnRH antagonists

Objectives
- normal reproductive physiology
- diagnosis and treatment of infertility
- role of ultrasound
- discuss PCO Syndrome
• discuss advanced maternal age
• assisted reproductive technology
• recent advances

Infertility

* inability to conceive after 12 months of unprotected intercourse *

Fertility

Infertility

• Approximately 15% of couples
• 6.1 million women
• 1.2 million women sought infertility treatment in 1994

Infertility: Causes

• Ovulatory disorders (15-20%)
• Tubal disease (30-35%)
• Male disorders (30-35%)

Miscellaneous Causes

• cervical factor
• endometriosis
• luteal phase deficiency
• uterine disease (myomata, synechiae)
• immunologic
• unexplained

Reproductive Physiology
• follicle maturation and oocyte release
• capture of oocyte in the fallopian tube
• deposition of motile sperm in the vagina
• transport of sperm to the ampullary tube
• fertilization
• transport of the embryo to the uterus
• implantation

Sperm Formation and Function
• pulsatile GnRH from hypothalamus
• LH stimulates testosterone production
• FSH stimulates spermatogenesis
• transport of sperm from epididymus to the ejaculatory duct and release

Ovulation
• oocytes resting in prophase I
• follicular growth stimulated by FSH
• dominant follicle selected by day 5-7
• midcycle LH surge and oocyte release
  
  Fertilization
  
  • sperm must reach the oocyte
  • bind to the zona pellucida
  • penetrate the zona pellucida and bind to the oocyte membrane
  • initiate the cortical granule reaction
  • act in concert with the oocyte to complete meiosis
  
  Implantation
  
  • embryo must be transported to the uterine cavity
  • blastocyst must break out of zona (hatch)
  • cells from the embryo must invade the endometrium
  
  Absolute Requirements For Normal Fertility

• Ovulation

• Motile sperm

• Patent fallopian tubes
  
  Initial Evaluation

• Conference
  – detailed history
  – discussion of reproductive physiology and infertility workup
  – answer questions

• Physical examination

• Order appropriate diagnostic tests
  
  Keys to Patient Rapport
•Time
•Clear information
•Shared decision making
•Respect
•Understanding

Initial Workup – Phase 1

•Evaluate ovulatory status
•Evaluate tubal patency
•Evaluate male factor (semen analysis)

Ovulation

•Serum TSH, Prolactin, and HCG
•BBT charts
•midluteal serum progesterone level
•urine LH kits
•endometrial biopsy
•ultrasonography

Ovulatory Status
BBT
Progesterone Levels

•Levels above 5 ng/ml consistent with ovulation
• Levels above 15 ng/ml consistent with normal luteal phase
• Draw levels on cycle days 21-24
• Convenient but expensive
  Endometrial Biopsy
• Reliable assessment of ovulation
• Performed 2-3 days prior to expected period
• Superior for diagnosing luteal phase defects if performed in midluteal phase
• Expensive, painful, limited clinical usefulness
  Ultrasound

• Evaluate ovarian follicles
  – Number
  – Size (mature follicles: 18-22 mm)

• Evaluate endometrium
  – Thickness
  – Texture

  Follicles
  Endometrium
  Tubal Factor

• Hysterosalpingography - Phase 1
• Laparoscopy - Phase 2
  Hysterosalpingography
• Evaluate the uterine cavity
  – myomata
  – synechiae
  – anomalies

Hysterosalpingography

• Evaluate tubal patency

Hysterosalpingography

• Evaluate tubal patency
  – proximal obstruction
  – distal obstruction

Hysterosalpingography

• Evaluate tubal patency
  – salpingitis isthmica nodosa

Hysterosalpingography

• If distal tube disease, confirm with laparoscopy
• normal HSG does not rule out pelvic pathology
• HSG may enhance fertility:
  – mechanical lavage of tube
- straighten tubes and breakdown adhesions
- stimulatory effect for the cilia
- may improve cervical mucus
- bacteriostatic effect of iodine
- Ethiodol decreases macrophage phagocytosis of sperm

Semen analysis

- Volume: 1-5 cc
- Sperm count: 20 million or more per cc
- Motility: 50% or more
- Morphology: 30% or more normal forms

Phase 1 - Treatment

- Attempt to treat specific abnormalities
- Utilize the safest and most cost-effective modalities
- Discuss with the patient the costs, risks, success rates, and alternatives

Treatment
- Ovulatory dysfunction

- clomiphene citrate
  - dexamethasone
  - midcycle HCG administration
- tamoxifen
- gonadotropins
bromocriptine - hyperprolactinemia

Clomiphene Citrate

- 50-200 mg q day cycle days 5-9
- 75% of pregnancies occur in first 3 ovulatory cycles (90% in 6 cycles)
- Multiple gestation rate: 5-8%
- Must document response to therapy
- 50% of patients will conceive

Clomiphene citrate

- After 4 unsuccessful cycles, discuss with the patient further evaluation and treatment
- Midcycle transvaginal ultrasound is valuable diagnostic tool
- Important to evaluate follicular and endometrial response
- Consider midcycle HCG administration and/or intrauterine insemination (IUI)

Tamoxifen

- 10-60 mg q day cycles days 5-9
- Pregnancy and ovulation rates similar to clomiphene
Multiple pregnancy rate increased

Extensive experience in Europe since the mid 1970’s

Considered an ‘off label” use in the U.S. and comprehensive consent should be obtained

Tamoxifen v Clomiphene
Boostanfar et al Fertil Steril 75:1024, 2001

86 anovulatory patients randomized to CC or TMX

Ovulation rate: 44% TMX v 45% CC

Pregnancies: 10 TMX v 6 CC

Conclusion: TMX and CC have similar ovulation and pregnancy rates

Tamoxifen
Tamoxifen
Treatment
Male

varicocele repair

artificial insemination - IUI (intrauterine)

clomiphene citrate

assisted reproduction

–IVF or GIFT

–ICSI- sperm injection

donor insemination Fertility in Women over 35 years