Assisted Reproduction

Background

1. Assisted Reproduction
    - The use of medical techniques to achieve fertility
    - Medications and procedures to achieve and maintain a pregnancy in an infertile couple
    - 1% of children born in US are conceived using ART (assisted reproductive techniques - defined as ICF, ICSI, ZIFT, GIFT)[1]

Pathophysiology

1. Female factors
    - Ovulatory disorders
    - Tubal factors
    - Endometriosis
    - Uterine factors
    - Cervical factors
2. Male factor
    - Hypogonadism
    - Testicular disease
    - Sperm transport disorders
    - Unexplained
3. Industrialized counties
    - 17% of couples seek services[2]
    - US Prevalence
        - 11.9% of all women sought treatment for infertility
        - 7.1% of all childless women
        - 7.5% of married women have sought treatment for infertility[3]
        - 7.6% of all men have sought treatment for infertility[4]
4. Risk factors
    - Increasing age
    - Smoking
    - Alcohol use
    - Obesity
5. Morbidity/ mortality
    - Maternal
        - Psychological stress of infertility
        - Ovarian hyperstimulation syndrome
        - Ovarian cancer
    - Paternal
        - Psychological stress of infertility
    - Fetal
        - Cerebral palsy
            - OR 2.18 for all IVF, OR 1.82 for IVF singletons
            - Related to but not entirely explained by preterm delivery[5]
        - Low birthweight disproportiately associated with ART
            - ART responsible for 2% of births but 7% of low birthweight[6]
        - Birth defects

            - 30-40% increase in all birth defects compared to baseline rate, number needed to harm 60-250[7]
    - Both maternal and fetal
        - Multiple birth due to transfer of multiple embryos[8]
            - ART accounts for 17% of all multiple births
            - Over 95% of triplets or higher order multiples will be born preterm and have low birth weight

Diagnostics

1. History
    - Coital practices, developmental history including puberty, chronic conditions (genetic, endocrine); medications, STI history or current symptoms, medications, previous fertility, surgical history (pelvic, hernia), substance use (tobacco, alcohol, drugs) family history (genetic conditions), toxin exposure (chemo/radiation)[9]
    - Male specific
        - Genital trauma
        - Recent high fever
    - Female specific
        - Menstrual history
2. Physical exam
    - Male
        - Genital infection, hernia, varicocele, testicular mass, presence of vas deferens, Tanner stage, focal neurological signs (visual field impairments)
    - Female
        - Genital infection, Tanner stage, signs of virilization, galactorrhea, pelvic examination, focal neurological signs (visual field impairments)
3. Diagnostic testing
    - Male
        - Sperm analysis (obtain second sample if first is abnormal), FSH/testosterone (hypogonadism)
    - Female
        - Confirm ovulation (basal body temp chart or home LH surge kit or measure progesterone level 7 days before expected menses, normal >5); FSH, TSH (ovulatory impairment add testosterone and 17-hydroxyprogesterone if signs of virilzation), assess ovarian reserve (FSH and estradiol level on day 3 of menstrual cycle , normal FSH <10)
4. Diagnostic imaging
    - Male
        - Scrotal ultrasound
    - Female
        - TVU and HSG to evaluate tubes, uterus
5. Other studies
    - Male
        - Post ejaculatory U/A or transrectal U/S

Therapeutics

1. Medications
    - Oral
        - Clomiphene citrate
        - Metformin
        - Bromocriptine
        - Tamoxifen
        - Aromatase inhibitors
    - Injectable
        - Gonadotropins (FSH,hMG)
        - GnRH
        - hCG (to trigger ovulation)
        - Progesterone (luteal phase support)
2. Techniques
    - Intrauterine Insemination (IUI): washing and concentration of sperm and injecting it via a catheter in the cervix to the upper uterine cavity; timed to occur just before ovulation
    - In Vitro Fertilization (IVF): induction of ovarian hyperstimulation through gonadotropins, removal of oocytes and subsequent fertilization (through mixing with sperm or ICSI), transfer of resulting embryos back into upper uterine cavity
        - Transfer with ultrasound guidance and 5 days post fertilization in couples with good prognosis improved success[10]
        - Assisted hatching in couples with previous failure improved success[11]
    - Intracytoplasmic sperm injection (ICSI) – direct injection of a single sperm into an oocyte
    - GIFT (gamete intrafallopian transfer) and ZIFT (zygote intrafallopian transfer) – placing either mixed sperm and oocytes (GIFT) or a zygote (ZIFT) directly into a woman's fallopian tube - not often used
3. Other considerations
    - Gamete donation
        - Oocytes or sperm
    - Gestational surrogate
        - A woman outside the couple completes a pregnancy
    - Acupuncture at time of embryo transfer for IVF cycles
        - Improves rates of pregnancy (NNT 10) and live birth (NNT 9)[12]
4. Male factor – specific treatments
    - Hypogonadism
        - Dopamine agonist such as bromocriptine if caused by hyperprolactemia from an adenoma; then testosterone replacement if still hypogonadal
    - Varicocele
        - Varicocele repair has not been shown to increase the likelihood of conception (SORT A)[13]
    - Vasectomy
        - Reversal more successful and cost effective compared with IVF and ICSI

- Sperm disorders
    - ICSI recommended for men with severe low sperm counts, low sperm motility or high rates of sperm abnormalities

5. Female Factor
    - Ovulatory disorder
        - Ovulation induction via clomiphene citrate or injectable gonadotrophins
        - PCOS
            - Clomiphene citrate or metformin; can use both if women fail to respond[14]
            - Laproscopic drilling for ovulation induction in women with PCOS
        - IVF
        - Oocyte donation in ovarian failure
        - Bromocriptine if anovulation caused by hyperprolactemia
    - Tubal
        - IVF
        - Tubal flushing with oil soluble media
        - Tubal surgery prior to IVF
    - Endometriosis[15]
        - IUI plus gonadotropins
        - IVF
        - Laproscopic surgery

Follow-up

1. Refer to specialist
    - To Reproductive Endocrinologist if natural conception unsuccessful after 1 year if under 35, after 6 months if over 35
    - If sperm abnormalities
        - Immediately to Reproductive Endocrinologist

Prognosis

1. Rates of pregnancy with treatment
2. Ovulatory disorders best prognosis -50%
3. Tubal Factor - 21%
4. Endometriosis – 17%

Prevention

1. Preventing STIs, counseling on decreasing fertility with age, decreasing smoking rates and alcohol use, addressing obesity

Patient Education

1. The National Infertility Association http://www.resolve.org/
2. CDC website for ART clinic success rates http://www.cdc.gov/art/ARTReports.htm

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