BODY OF KNOWLEDGE

History---Reproduction and Infertility

- Important Dates
- Discoveries
    - Scientists

Cell and Molecular Biology: Eukaryotic Cells

Features, organization and proteins

- Features of eukaryotic cells
- Components
  - Nucleus
  - Organelles
  - Chemical components
  - Transport
  - Metabolism
    - Glycolysis
    - Kreb's Citric Acid cycle
    - Electron Transport Chain
  - Organization
  - Cytoskeleton
    - Structure
    - Function
    - Regulation
- Eukaryotic cell membrane
  - Membrane properties
  - Membrane proteins
  - Transport
    - Channels
- Extracellular matrix
- Adhesion proteins
- Proteins
  - Structure
  - Synthesis
  - Properties
  - Transport mechanisms
  - Functions

-- Regulation

Cell Growth and Specialization

- Cell growth
  - Cell cycle
    - Cell division
      - Mitosis
      - Cytokinesis
    - Cell growth
    - Apoptosis
    - Control
  - Cellular Evolution
  - Specialization

Basic Genetics

DNA, Genes, Chromosomes and Genomes

- DNA
  - Structure
  - Function
  - Replication
  - Mutations
  - Repair
  - Recombination
  - Chromosomes
    - Structure
    - Function
  - Meiosis
- Recombination
  - Transposons
- Transcription
- RNAs
  - Regulation
    - editing
- Translation
  - Control
- Genes
  - Regulation
    - Circadian clock
  - Cancer genes

Genomes

- Human genome
- Epigenetics
  - Methods
    - Effects

Immunology: Basic Immunology

Immunity, Immune system, Immunoglobulins, Complement, Detection Methods

- Innate and adaptive immunity
  - Defense mechanisms
- Innate immunity
  - Components
  - Functions
- Active immunity
  - Components
  - Functions
- Immune system
  - Cells, tissues and organs
  - Cellular
    - T cells
    - MHC proteins
  - Antigen processing
  - Humoral
    - Antibodies
- Immunoglobulins (structure, classes, function, location)
  - Activation
  - Complement
  - MHC proteins
  - Tolerance
  - Immune response to
    - Implantation
    - Transplantation
  - Antigen-Antibody detection methods
  - Inflammatory response
  - Flow cytometry
  - Serology to detect infectious diseases

Immunology: Reproductive Immunology

Antibodies, Indications, Diagnostic Testing and Treatment Options

- Antibodies
  - Iso
  - Auto
- Antibodies associated with infertility and fetal loss
  - Male
  - Female
- Immunological response to spermatozoa
- Anti-sperm antibodies
    - Agglutinating, cytotoxic, immobilizing
    - Indicators for anti-sperm antibodies (e.g. findings in andrology lab)
    - Diagnostic testing
      - Screens
      - Testing
        - Methods
          - Direct
          - Indirect
- Anti-sperm antibodies in cervical mucus
  - Implications
  - Treatment(s)

Infection and Microbiology: Basics

Pathogens, Inflammation, Immunity and Infectious Agents

- Pathogens
- Distinguish
  - Infection
  - Disease
- Methods of infection
- Inflammation
  - Inflammatory cells
- Immunity
- Infectious agents
    - Microorganisms
    - Viruses
    - Bactria
    - Fungi
    - Protozoa
  - Prions
      - Detection

Infection and Microbiology: Reproductive Microbiology

Resident flora, Micoorganisms Associated with Infertility, Detection Methods, Transmission, Surveillance

- Resident flora
  - Female reproductive track
  - Male reproductive track
- Microorganisms associated with infertility and reproductive failure
  - Genital ulcer diseases
  - Vaginitis syndromes
  - Genital warts and cervical cancer
  - Urethritis and cervicitis syndromes
    - Male
    - Female
  - Cytomegalovirus (CMV)
  - Blood-borne viruses
  - Prostate syndromes
- Microbiology detection methods
  - Culture
  - Biochemicals
  - Serology
  - Molecular diagnostics
  - Cell culture
- Infectious disease transmission
  - Patient/Intimate Partner
  - Donor
    - FDA requirements
      - Screening
      - Testing
        - Directed donor
        - Anonymous donor
          - Sperm
          - Oocyte
        - Donated embryos
  - Cryopreserved gametes and embryos
- Viral transmission
  - Handling HIV positive patients
    - Positive couples
      - Male
      - Female
    - Discordant couples
      - Facilities/storage
  - Hepatitis patients
    - Treatments
    - Vaccines
  - CMV
    - Males
- Mode(s) of transmission

- Sterility
- Sterile technique

- Laboratory-prevention mechanisms
  - Routine surveillance
  - Organisms potentially transmitted via ART procedures
  -
  - Sterilization methods
    -Physical
    -Chemical
  - Decontamination
  - Disinfectants
    - Toxicity concerns
    - Air quality
    - Clean rooms
    - Biological safety cabinets (BSCs)
    - Packaging biological materials for shipment
    - requirements

Endocrinology: Basic

Endocrine system, hormones, regulation

- Endocrine system
  - Glands
  - Tissues
  - Hormones
    - Local
    - Classes
  - Functions
- Regulation via feedback mechanisms

Endocrinology: Reproductive Hormones

Synthesis, disorders, and control

- Hormone Synthesis
  - Hypothalamus
  - Pituitary
  - Female sex organs
  - Male sex organs
    - Function
- Testosterone
  - Preferred biochemical pathway
  - Metabolites
  - Formation in androgen target tissue
- Androgens
  - Effects on males
    - Testis
    - External genitalia
    - Skin
    - Voice pitch
- Estrogen
  - Preferred biochemical pathway
  - Catabolism in females
  - Clinically important forms
    - Derivation
  - Effects
    - Ovaries
    - Endometrium
    - Skin
    - Adipose tissue
- Hypogonadism
  - Primary
    - Male
    - Female
      - Diagnosis
  - Secondary
    - Male
    - Female
      - Diagnosis
- Inhibin
- Hormonal control
  - Spermatogenesis
    - Oogenesis
    - Menstrual cycle
    - Ovulation
    - Implantation

Development of the Gonads

Ovaries, testes, internal and external systems

- Temporal Development
  - Ovaries
  - Testes
  - Internal Reproductive System
    - Male
    - Female
  - External Reproductive System
    - Male
    - Female

Male Reproductive Track

Testes

- General structure
- Products
  - Exocrine
  - Endocrine
- Accessory glands
  - Products
  - function
- Testicular temperature
  - thermo regulatory
- Seminiferous tubules
  - Histology
- Leydig cell
  - Location
  - Function(s)
- Sertoli cell
  - Function(s)
  - Location
- Blood-testis barrier
  - Location
    Function(s)
    Breach

Spermatogenesis, semen, ejaculatory process

- Spermatogenesis
  - Stages
  - Time Line
  - Hormonal Control
  - Cell Characteristics
    - DNA content
    - Chromosome number
- Spermiogenesis
  - Biochemical changes
  - Biophysical changes
- Onset of puberty

Male Factor Infertility

- Diagnostic categories
  - Evaluation
  - Physical
  - Laboratory
    - General clinical
    - Endocrine
  - Genetics
    - Microbiology
  - Andrology
    - Treatment options
- Semen Analysis
  - Macroscopic examination
  - Microscopic
    - Sperm Concentration
    - Motility
      - Confidence limits
    - Morphology
      - Strict Criteria
      - TZI
      - Round Cells
        - Reference ranges

Infertility Testing

- Test(s) to detect
  - Capacitation
  - Acrosome reaction
  - Zona binding
  - Sperm penetration
- Sperm concentration
  - methods
- Sperm-Cervical mucus interaction
  - Post-coital test
    - Interpretation
  - Sperm-Cervical mucus interaction
    - Testing
    - Interpretation
- Counting chambers
  - Types
    - Methodology
    - Accuracy
    - QC
    - Advantage(s)
    - Disadvantage(s)

Female Reproductive Track

Ovary

- General Structure
  - Products
    - Exocrine
- Menstrual cycle
  - Follicular phase
    - Hormones
      - Source
        - Function
  - Luteal phase
    - Hormones
      - Source
        - Function
  - Menstrual phase
    - Hormones
      - Function

Follicular development, oogenesis, ovulation

- Age of menarche in US
  - Follicular Development
    - Stage
      - Hormonal stimulation (if any)
      - Structure
        - Membranes
        - cells
      - Time line
      - Size
      - Oocyte present
        - Meiotic stage
        - Fate
  - Oogenesis
    - Stages
    - Time line
    - Hormonal Control
    - Characteristics
      - DNA content
      - Chromosome number
  - Primary oocytes
    - Produced
    - Fate
  - Dominant follicle
    - Selection
      - LH
  - Ovulation
    - Events
    - Oocyte
      - Meiotic stage
    - Hormonal control
      - Two-cell theory of hormone production
    - Estrogen
      - Source
        - Pregnant female
        - Non-pregnant female
        - Source
          - Function

Accessory organs

Uterus

- Anatomy
- Histology Cycle phase
  - Follicular
    - Hormones
      - Source(s)
      - Function
    - Uterine phase
      - Appearance
  - Luteal
    - Hormones
      - Source(s)
      - Function
    - Uterine phase
      - Appearance
  - Menstrual
    - Hormones
      - Source(s)
      - Function
    - Uterine phase
- Cervix
  - Anatomy
  - Histology
  - Estrogen dominance
    - Appearance
      - microscopic
    - pH
  - Progesterone
    - Appearance
      - Microscopic
      - pH
- Vagina
  - Anatomy
  - Histology
  - Estrogen
    - Appearance
  - Progesterone
    - Appearance
- Mammary Glands
  - Anatomy
  - Histology
  - Function
    - Lactation

Female Factor Infertility

Diagnostic categories

- Evaluation
  - Physical
  - Diagnostic testing
    - General clinical laboratory
    - Endocrinology
    - Genetics
    - Fertility lab
      - Treatment
- PCOS
  - Physical findings
    - Hirsutism vs. virilization
  - Laboratory findings
- Endometriosis

Diagnostic Testing

- Hysterosalpingogram
  - Procedure
  - Diagnostic for
- Clomid challenge
  - Procedure
  - Diagnostic for
- Laparoscopy
  - Procedure
- Diagnostic for Endometriosis
- Causes

ART Treatments

IVF, GIFT, ZIFT, ICSI, AH

- IVF
  - Patient selection
  - Procedure
  - Indication
  - Advantage
  - Likelihood of success based on
    - Diagnosis
    - Age
  - Procedural
    - Advantage(s)
    - Disadvantage(s)
- Culture to blastocyst stage
  - Selection of embryos
  - Medium
- GIFT
  - Patient selection
  - Procedure
  - Indication
  - Advantage
  - Likelihood of success based on
    - Diagnosis
    - Age
  - Procedural
    - Advantage(s)
    - Disadvantage(s)
  - ZIFT
    - Patient selection
    - Procedure
    - Indication
    - Advantage
    - Likelihood of success based on
      - Diagnosis
      - Age
    - Procedural
      - Advantage(s)
      - Disadvantage(s)
  - ICSI
    - Patient selection
    - Procedure
    - Indication
    - Advantage
    - Likelihood of success based on
      - Diagnosis
      - Age
    - Procedural
      - Advantage(s)

- Disadvantage(s)

- Assisted Hatching
  - Patient selection
  - Procedure
  - Indication
  - Advantage
  - Likelihood of success based on
    - Diagnosis
    - Age
  - Procedural
    - Advantages
    - Disadvantages

Associated Procedures

- PGD
  - Patient selection
  - Procedure
  - Indication
  - Advantage
  - Likelihood of success based on
    - Diagnosis
    - Age
  - Procedural
    - Advantage(s)
- Gender selection
  - Patient selection
  - Procedure
  - Indication
  - Advantage
  - Likelihood of success based on
    - Diagnosis
    - Age
    - Procedural
      - Advantage(s)
      - Disadvantage(s)

- Embryology Assessment criteria
  - Oocyte
  - PN stage
  - Cleavage stage embryos
  - Blastocyst
- Embryo Transfer
  - Quality Control
  - Number of transfer
    - Cleavage stage
    - Blastocysts
- Freezing excess embryos/blastocysts
  - criteria
- Documentation of pregnancy
  - Test
  - Advantage

- Disadvantage

Assisted Reproductive Technology

Routine procedures

- Stimulation protocols
  - Stimulation agents
  - Media
  - Oocyte Donor
    - Patient selection
    - Procedure
    - Indication
    - Advantage
    - Likelihood of success based on
      - Diagnosis
      - Age
    - Procedural
      - Advantage(s)
      - Disadvantage(s)

Third party reproduction, experimental procedures, fetal reduction

- Gestational carrier
  - Patient selection
  - Procedure
  - Indication
  - Advantage
  - Likelihood of success based on
    - Diagnosis
    - Age
  - Procedural
    - Advantage(s)
    - Disadvantage(s)

- Fetal Reduction
  - Procedures
    - Stage of pregnancy

Insemination and Fertilization

Capacitation, Sperm-oocyte interaction, fertilization, corpus luteum

- Approximate time for sequential steps
  - Sperm transport
    - Vagina
    - Cervical mucus
      - Influence of estrogen
      - Influence of progesterone
    - Site(s)
  - Capacitation
    - Biochemical changes
    - Biophysical changes
    - Hyperactivation
      - Site(s)
  - Zona binding
    - Site
  - Acrosome reaction
    - Site
  - Sperm penetration
    - Blocks to polyspermia
  - Sperm-egg interaction
    - Factors
  - Oocyte activation
    - Meiotic events
  - Syngamy
  - Pronuclear formation
- Corpus luteum
  - Development
    - Cellular source
  - Time line
  - Hormonal milieu
  - Function
  - Life span

Early Embryo Development

- Stage
  - Nutritional requirements
    - Cleavage stage
    - Blastocyst stage
  - Embryonic genome becomes active
  - Totipotent
  - Implantation
    - In vivo
    - In vitro
  - Maternal recognition
- Hormonal milieu
  - PN stage embryo
  - Cleavage stage embryo
  - Blastocyst
  - Implanting embryo

Stimulation/ovulation induction agents

- Selective estrogen receptor modulator
  - Examples
  - General mode of action
  - Adverse affects
    - Patient
    - Oocytes
- Gonadotropins
  - Examples
  - General mode of action
  - Adverse affects
    - Patient
    - Oocytes
- HCG
  - Examples
  - General mode of action
  - Adverse affects
    - Patient
    - Oocytes
- GnRH antagonist
  - Examples
  - General mode of action
  - Adverse affects
    - Patient
    - Oocytes
- GnRH agonist
  - Examples
  - General mode of action
  - Adverse affects
    - Patient

- Oocytes

Media/Enzymes/Proteins;Cryoprotectants/Supplements

- Heparin
  - Use
  - Mode of Action
- Dulbecco's phosphate buffered saline
  - Use
  - Mode of Action
- Sperm isolation medium
  - Use
  - Mode of Action
- Test yolk buff Use
  - Mode of Action
  - Use
- Human tubal fluid
  - Use
  - Mode of Action
  - Modified hum Use
  - Mode of Action
- Sequential medium part I
  - Use
  - Mode of Action
- Sequential medium part II
  - Use
  - Mode of Action
- Mineral Oil
  - Use
  - Mode of Action
- PVP
  - Use
  - Mode of Action
- Liquid protein in 5% normal saline
  - Use
  - Mode of Action

ART Laboratory Management

General

- Laboratory math
- Clinical chemistry
    - Hormone measurements

QA, QC

- Quality Control
- Quality Management Program
- Reporting results

Regulations

- CLIA
- HIPAA
- FDA
- OSHA (see safety)

Certification/Accreditation

- Certification
- Accreditation

SART reporting

- Data

Security

- Specimen tracking
- Chain of Custody

Personnel

- Position requirements
- Education/skills/certification or licensure
- Training
- Continuing Education (CE)
- Licensure and Certification
- Evaluation
    - Competency testing
- Legal requirements

Budget

- Types

LIS

- Types
- Concerns
    - Cost
    - Maintenance
    - Going live

Phlebotomy

- Techniques
- Safety
- Contamination
- Collection Devices
- Tubes

Laboratory Safety

- OSHA
- Universal Precautions
- Chemical Hygiene Plan
- Emergency Plan for IVF
- Chain of Custody
- # embryologists needed based on case load
- Infectious disease control (see micro section)

Personnel

- Qualifications
    - Hiring Practices
        - Advertisements
        - Interviews
        - Salary ranges
        - Non-compete contracts
    - Probationary period
    - Evaluations
        - Competency testing
- Scheduling

Cryobiology

Biology/Physics Principles

- Ice crystal formation
- Mazur's theory
- Physical stress
- Damage from Thawing
- Heat of Fusion
  - Seeding
- Cooling methods
  - Rapid cooling
    - Principle
    - General procedure
    - Advantages
    - Drawbacks
  - Slow cooling
    - Principle
    - General Procedure
    - Advantages
      - Drawbacks
  - Vitrification
    - Principle
    - General Procedure
    - Advantages
    - Drawbacks
    -
  - Warming rates
    - Rapid cooling
    - Slow cooling
    - Vitrification
  - Cryoprotectants
    - Intracellular
    - Extracellular

Gamete and Embryo Cryopreservation

- Freezing metaphase II ooyctes
    - Problems
    - Advantages
- Freezing Prophase I oocytes
    - Problems
    - Advantages
    - Problems
- Freezing cleavage stage embryos
    - Selection criteria
    - Advantages
    - Problems
- Freezing blastocysts
    - Selection criteria
    - Advantages

Freezing reproductive tissues/organs

- Problems Freezing Testicular tissue
    - Advantages
    - Problems
- Freezing ovarian tissue
    - Advantages
    - Problems
- Oocyte maturation following vitrification

Cryobanking Management

- Record Keeping
    - Terms of Storage
    - Contracts
    - Fees
    - Regulations
- Cancer patients
    - Timing
    - Considerations
- Reproductive Tissue Banking
    - FDA regulations
    - ASRM guidelines
    - Quality Control
- Donor requirements (FDA)

- Autologous banking
- Management
    - Banking
        - Sperm
        - Oocytes
        - Embryo
        - Reproductive tissues
        - Reproductive organs
            - Ovaries
            - Fallopian tubes
    - Transportation
        - National
        - International

Fertility Cryopreservation

- Fertility Preservation
    - Tissues
        - Whole ovary
        - Cortex
    - Methods
        - Vitrification
        - Orthotopic transplantation
    - Freezing stem cells
        - Adult
        - Embryonic
    - Freeze drying methodology

Research

Tools/Methodology

- Cells
  - Isolation and culture
  - Media
  - Cell lines
  - Cell sorting
  - Patch clamp
- Microscopy
  - Resolution
  - Light
  - Phase-contrast
  - Differential –interference-contrast
  - Dark-field
  - Bright-field
  - Fluorescent
  - Indirect immunocytochemistry
  - Confocal
  - Image deconvolution
  - Transmission electron microscopy
  - Scanning electron microscopy
  - Freeze-fracture electron microscopy
  - EM tomography
  - Fluorescent analog cytochemistry
  - Caged molecules
  - Radioisotopes
  - Stains
- Separation of cellular components
  - Ultracentrifugation
  - Chromotography
  - Gel electrophoresis
  - Mass spectrometry
- Non-amplified Molecular Assays
  - Probe techniques
  - Accuprobe Method for r-RNA Detection
  - Hybrid capture
  - B-DNA technology
  - Gel-based DNA/RNA detection
  - Pulse Field gel electrophoresis
  - Southern hybridization
  - Northern hybridization

- Amplified Molecular Assays
    - PCR with gel analysis
    - Real time PCR applications
    - Luminex analysis
    - Microarray analysis
    - In situ hybridization
- Nucleic Acids
    - Northern Blot
    - In situ hybridization
- DNA
    - Isolation
    - Sequencing
    - PCR; rtPCR
    - Cloning
    - Engineering
- Genes
    - Linkage analysis
    - Microarrays
    - Reverse genetics
    - Engineering
    - Databases
- Protein Structure/Function
    - X-ray diffraction
    - Nuclear Magnetic Resonance Spectrospcop
    - Affinity chromotography
    - Immunoprecipitation
    - DNA Footprinting
- Stem cells
- SCNT
- Somatic cells to gametes
- Restoring non living genomes through nuclear transfer,
- Human cells into animal ooyctes??
- Somatic cells into stem cells
- Animal models
    - Transgenics
    - Knockout models
- Institutional Review Board

Government Regulations, ASRM and SART Guidelines

LAW: Regulations, Laws, Policy, and Guidelines

- Definitions
  - Law
  - Regulation
  - policy
  - Guideline
- Regulations vs. guidelines
- Law and legal
- ***Regulatory agencies***
  - CLIA
  - FDA
  - State
- Regulation
  - Surrogacy
  - Human cloning
  - Laboratory requirements
- Legal Issues
  - Legal issues
    - Terms of storage
    - Cryopreserved embryos
      - ownership
  - Surrogacy
  - Gestational host

Policy: Donors, registry, frozen oocytes (under discussion)

- Tracking donors
- Donor registry
- Quarantine
  - Frozen oocytes

Guidelines

- ASRM
  - Practice Guidelines
    - Gamete and Embryo Donation
    - Emergency Plan for IVF
    - Reducing Risk of Viral Infection
    - Number of Embryos Transferred
    - Human Embryo and Andrology Laboratories
    - Offering Assisted Reproductive Technology
    - Vaccination for Female Infertility Patients

Ethics

- ASRM Ethics Committee
  - Ethical Considerations of Assisted Reproductive Technology
  - Donating spare embryos for stem cell research
  - Interest, obligation and rights of the donor in gamete donation
  - Financial compensation of oocyte donors
  - Access to fertility treatments by gays, lesbians, and unmarried persons
  - Disclosure of medical errors involving gametes and embryos
  - Fertility preservation and reproduction in cancer patients
  - Fertility treatment when the prognosis is very poor or futile
  - Child-rearing ability and provision of fertility services
  - Informing offspring of their conception by gamete donation
  - Family members as gamete donors and surrogates
  - Human immunodeficiency virus and infertility treatment
  - Preconception gender selection for non-medical purposes
  - Human somatic cell nuclear transfer-cloning
  - Sex selection and preimplantation genetic diagnosis
  - Risk-sharing or refund programs in assisted reproduction
  - Informed consent and the use of gametes and embryos for research
  - Disposition of abandoned embryos
  - Oocyte donation to postmenopausal women
  - The use of fetal oocytes in assisted reproduction
  - Posthumous
- IRB
  - When required
- ASRM Committee Opinions

International Practices

- IFFS Reports

Resources

Education, Professional Societies, Industry

- Education Programs
  - National
  - International
- Professional Societies
  - Publications
  - CE
- Industry
  - Support
  - Funding
  - Publications