Ultrasound in Infertility

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Ultrasound in Infertility

• Disclosures: None

• Learning Objectives
  – Understand the basic process of in vitro fertilization (IVF)
  – Understand process of ovarian follicle development
  – Understand advances in ultrasound technology led to development of modern IVF

Overall Causes of Infertility

- Male Factor 30%
- Unexplained 25%
- Ovulatory Dysfunction 20%
- Tubal and Peritoneal Disease 20%
- Uterine and Cervical Factors 5%

Boston IVF Handbook of Infertility, 2002
Causes of Infertility: Female

- Female factors: 45% of infertility
- Ultrasound can provide insights
  - Tubal and Peritoneal Disease
  - Ovulatory Dysfunction
  - Uterine and Cervical factors

Infertility: Tubal and Peritoneal Disease

- Hydrosalpinx
  - Suggest tubal disease
- Endometrioma
  - Suggest other endometriosis
  - Suggest adhesions

Infertility: Ovulatory Dysfunction

- Polycystic Ovary
  - Suggest irregular ovulation
  - Rule out diminished ovarian reserve
Infertility: Uterine Factors

• Uterine anomalies
• Myomas
• Intra-uterine lesions
  – Polyps or myomas

Assisted Reproduction

• Test tube babies
• In Vitro Fertilization (IVF)
• Infertility treatment in which both oocytes and sperm are handled outside the body and embryos are generated in a laboratory
1978: Human Birth After IVF

- Indication
  - Blocked tubes
- C-Section
  - Pre-eclampsia
  - @ 38.5 wks
- Louise Joy Brown
  - July 25, 1978
  - 5 lb 12 oz

- Steptoe PC, Edwards RG.
  - ‘We hope to publish further medical and scientific details in your column at a later date.’

IVF Procedure: 1978

- Laparoscopic oocyte retrieval (timed with natural cycle)
- Insemination in vitro
- Incubation of the embryo 2.5 days
- Transfer of 1 embryo into uterus
IVF: Early Days

- Lesley Brown conceived with 1st IVF cycle
  - Not typical
- Often no embryos to transfer
  - Oocyte not retrievable
  - 0.3 oocytes per cycle
  - Oocyte does not fertilize
  - Embryo does not divide
- Modern IVF depends on multiple oocytes
  - More oocytes → more embryos
  - Select best embryos for transfer

Follicle Development in the Ovary

- http://medcell.med.yale.edu/histology/ovary_follicle.php

- Besser, GM and Thorner MO, Comprehensive Clinical Endocrinology, 2002

Primordial → Preantral Follicle

- Hormone Independent
  - Granulosa Cells have no FSH receptors
- Continues thru-out life
- Most preantral follicles
  - Undergo atresia
- Preantral follicles
  - Granulosa cells express FSH receptors

- Besser, GM and Thorner MO, Comprehensive Clinical Endocrinology, 2002
FSH “Rescues” Cohort

- Promote Follicle Development
  - Granulosa cell proliferation
  - Development of antrum
  - Follicle growth

Follicle Development in the Ovary

Dominant Follicle Selection

- Day 5-7 → ↓ FSH
- Most follicles → Atresia
- Dominant Follicle Develops

Besser, GM and Thorner MO, Comprehensive Clinical Endocrinology, 2002
Human Menopausal Gonadotropins

- Isolated from urine
  - Pooled from menopausal women
  - Contains FSH and LH
- 1950: Pergonal 25 Serono
  - Registered in Italy

1963: First Pregnancy

HMG Injections → Multiple Ovarian Follicles

- Sextuplets
  - Premature
  - Poor outcome
- Monitoring
  - Physical exam
  - Ultrasound not available

HMG → Ovarian Hyperstimulation Syndrome (OHSS)

- Ovarian Enlargement
- ↑ Capillary Permeability
  - Ascites
  - Pleural effusions
  - Hemo-concentration
  - → thrombosis

1961: 1st Fatality
1980: Tracking Follicle Development: Ultrasound and estradiol


1981: 1st IVF Baby in United States
1st IVF Birth Using Gonadotropins


- Indication
  - Tubal disease
- C-Section
- Elizabeth Jordan Carr
  - December 28, 1981
  - 5 lb 12 oz

LH Surge: Positive Estrogen Feedback

Besser, GM & Thorner MO, Comprehensive Clinical Endocrinology, 2002

- ↑ Estrogen
  - Triggers LH surge
- With IVF
  - Many small follicles
  - High estradiol
- For IVF
  - Need pituitary suppression
    - GnRH Agonist
    - GnRH Antagonist
  - Prevent premature LH surge
**LH Needed for Oocyte Maturation**

- Triggers ovulation
- Triggers final maturation
  - Meiosis resume
  - Cumulus expands
- hCG used for IVF
  - Binds same receptor
  - Issues
    - False positive pregnancy test
    - Risk of ovarian hyperstimulation syndrome

*Speroff L et al, Clinical Gynecologic Endocrinology and Infertility, 1999*

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**IVF Procedure: 1980**

- Ovulation Induction (monitored by ULTRASOUND and estradiol)
- Laparoscopic oocyte retrieval
- Insemination in vitro
- Incubation of the embryo 2.5 days
- Transfer of 1 embryo into uterus

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**IVF: Monitoring Follicle Development**

- Baseline antral follicle count
  - Predict ovarian response
- Avoid Ovarian Hyperstimulation
  - Adjust medications
  - Cancel cycle
- Optimize cycle
  - Adjust medications
- Time oocyte retrieval
  - Maximize # mature eggs
    - Follicles generally 18-20 mm
  - Fewer eggs from
    - Follicles < 12 mm
    - Follicles > 24 mm
Transvaginal Ultrasound and Hormone Levels Guide Clinical Management

- Track daily follicle growth
  - Natural 1.0 – 1.4 mm
  - Gonadotropin 1.7 – 2.0 mm
- Follow hormone levels
  - Estradiol
  - LH
  - Progesterone
- Time hCG trigger
  - Oocyte retrieval in 36 hours
- Track endometrium
  - Freeze embryos or transfer?

Endometrial Changes in Response To Estrogen and Progesterone

IVF: Monitoring Endometrium

- Endometrial Thickness
  - No consensus regarding minimal thickness for pregnancy
    - > 6 mm, 7 mm, 8 mm?
  - Pregnancy reported with 4 mm
  - Thicker with gonadotropin tx
  - > 14 mm? < 18 mm?
- Endometrial Pattern
  - Optimal is “triple-line”
  - Positive and negative predictive values for endometrial echo patterns are low
1980: 
- Ovulation Induction (monitored by ULTRASOUND and estradiol)
- Laparoscopic oocyte retrieval
- Insemination in vitro
- Incubation of the embryo 2.5 days
- Transfer of 1 embryo into uterus

1981: Ultrasound Guided Oocyte Retrieval
- Transabdominal/Transvesical
  - Painful
  - 1981: Sector Scanner

1983: Transvaginal Oocyte Retrieval
  Guided by Transabdominal Ultrasound
  - 1983: case report
    - Gleicher N et al, Egg Retrieval for in vitro fertilization by sonographically controlled vaginal culdocentesis. Lancet 2: 508
  - 1985: 124 retrievals
    - Full bladder; void after procedure
    - 2.2 oocytes/patient
    - Less pain than transabdominal
    - Simpler than laparoscopy
    - BUT: precise location and puncture NOT possible

1983:
- Collection of human oocytes for in vitro fertilization by ultrasound-guided follicular puncture.
1986: Transvaginal Oocyte Retrieval Guided by Transvaginal Ultrasound

- 1986: 61 patients
  - Transvaginal sector scanner
  - Empty bladder
  - 4.5 oocytes/procedure
  - Oocytes collected from 86% follicles


Transvaginal Ultrasound Guided Retrieval

- Surgical Procedure
  - Follicle punctured
  - Fluid aspirated
  - Oocytes collected in tube


Ovaries on Day of hCG Trigger

IVF Procedure: 1986

- Ovulation Induction (monitored by ULTRASOUND and estradiol)
- Transvaginal ULTRASOUND guided oocyte retrieval
- Insemination in vitro
- Incubation of the embryo 2.5 days
- Transfer of 1 embryo into uterus

IVF: Embryo Culture

- 1978 IVF: Embryo transfer on day 2-3
- In Vivo
  - Fertilization: in Fallopian tube
  - Uterine implantation: Day 5-6 blastocyst embryo
- 1998: Commercial media for blastocyst culture

Ultrasound to Guide Embryo Transfer

- Results
  - Improve pregnancy and live birth rate (10 RCT)
  - May decrease ectopic pregnancy
- Catheter placement
  - More than 1 cm from fundus in upper/middle area of uterine cavity
- Disadvantages
  - Full bladder
  - 2nd operator

ASRM Guideline: Performing the embryo transfer, 2017
Modern IVF Procedure

- Ovulation Induction (monitored by ULTRASOUND and estradiol)
- Transvaginal ULTRASOUND guided oocyte retrieval
- Insemination in vitro
- Incubation of embryos 5-6 days
- Transfer of embryo(s) into uterus (with ULTRASOUND guidance)

Robert G. Edwards - Facts

2010
- The Nobel Prize was awarded to Robert G. Edwards "for development of in vitro fertilization"

2010: Assisted Reproductive Technology in United States

- 443 Clinics
- 147,260 IVF Procedures
  - 16,531 Egg Donor Cycles
  - 859 Gestational Carrier Cycles
  - 1% used pre-implantation genetic diagnosis
- Births
  - 1.5% births in United States
  - 47,090 Deliveries
  - 61,564 infants

http://www.cdc.gov/art/ART2010/section1.htm
https://www.sartcorsonline.com/prCSR_PublicMultiYear.aspx?ClinicPKID=0
2010: Pregnancy Rate for Cycles Using Fresh Non-donor Eggs or Embryos

Ultrasound for Assisted Reproduction: Future Directions

- Time oocyte retrieval better to optimize number of mature eggs
  - Follicle volume?
  - Follicle vascularity?
- Assess uterine receptivity to optimize implantation and live birth rate
  - Endometrial volume?
  - Uterine blood flow?

Louise Brown and Elizabeth Carr to meet in Chicago on June 16, 2017

First test-tube babies in world, US to meet

By The Associated Press

MIDDLETOWN, Va. — The world’s first test-tube baby and America’s first test-tube baby, whose parents lived in Winchester, Massachusetts, are meeting face-to-face for the first time this year.

The Virginia Pilot reports that 19-year-old Louise Brown and 18-year-old Elizabeth Carr are scheduled to meet at a fertility conference in June in Chicago.