



Evaluation and Treatment of Female Infertility

Margareta D. Pisarska, M.D.

Director

Center for Reproductive Medicine

Cedars-Sinai Medical Center

Assistant Professor, David Geffen School of
Medicine at UCLA

Objectives

- Define Infertility
- Identify the various causes of infertility
- Understand the evaluation for infertility

Time Required For Conception

Time of Exposure	% pregnant
3 months	57%
6 months	72%
1 year	85%
2 years	93%

Fertility:

One year of unprotected coitus without conception
Affects 10-15% of couples in reproductive age group

Infertility

(Data from U.S.)

Number of women ages 15-44 with impaired ability to have children: 6.1 million

Number of married couples that are infertile: 2.1 million

Number of women who've ever used infertility services: 9.2 million

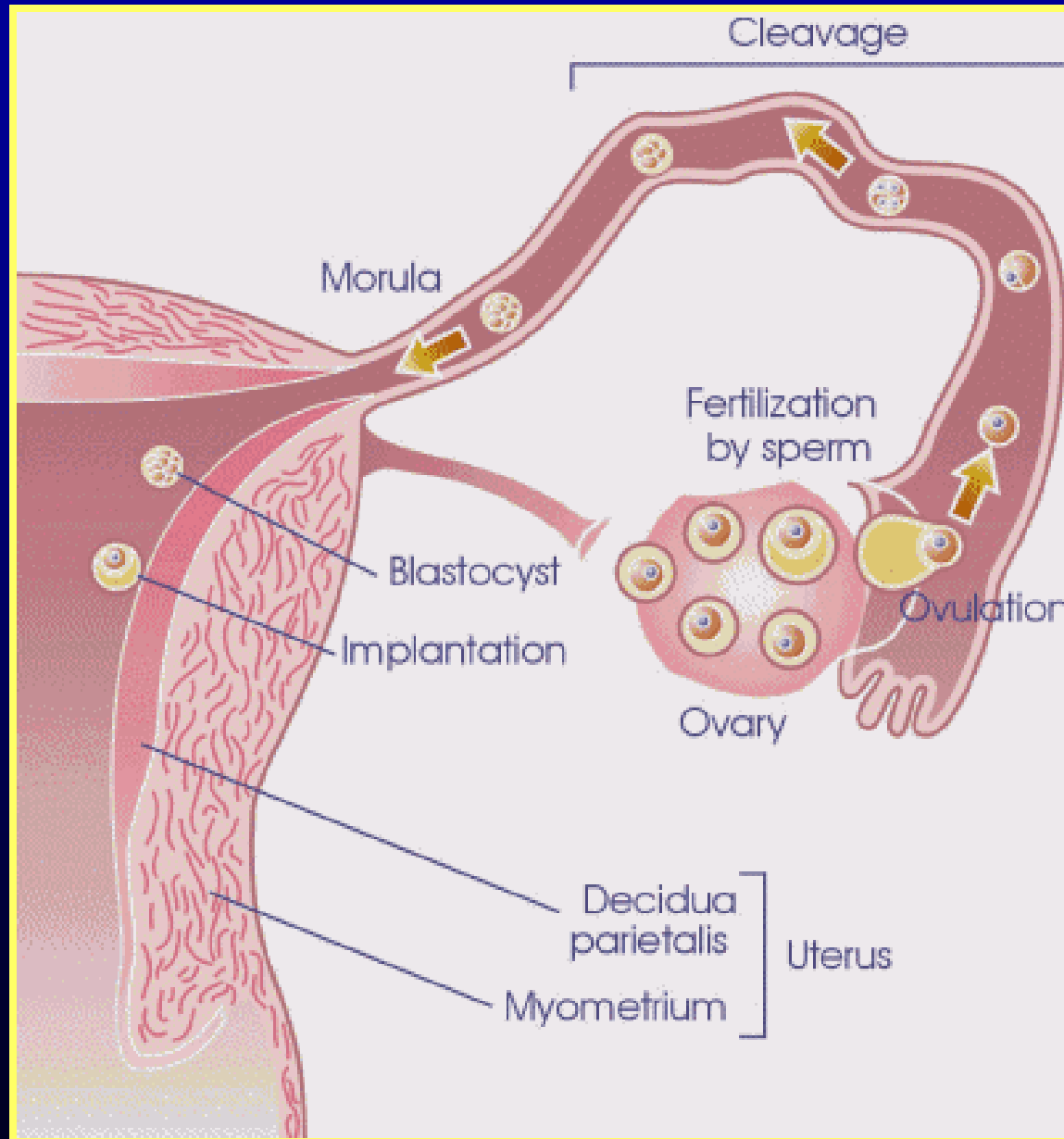
Number of women using infertility services: 9.3 million

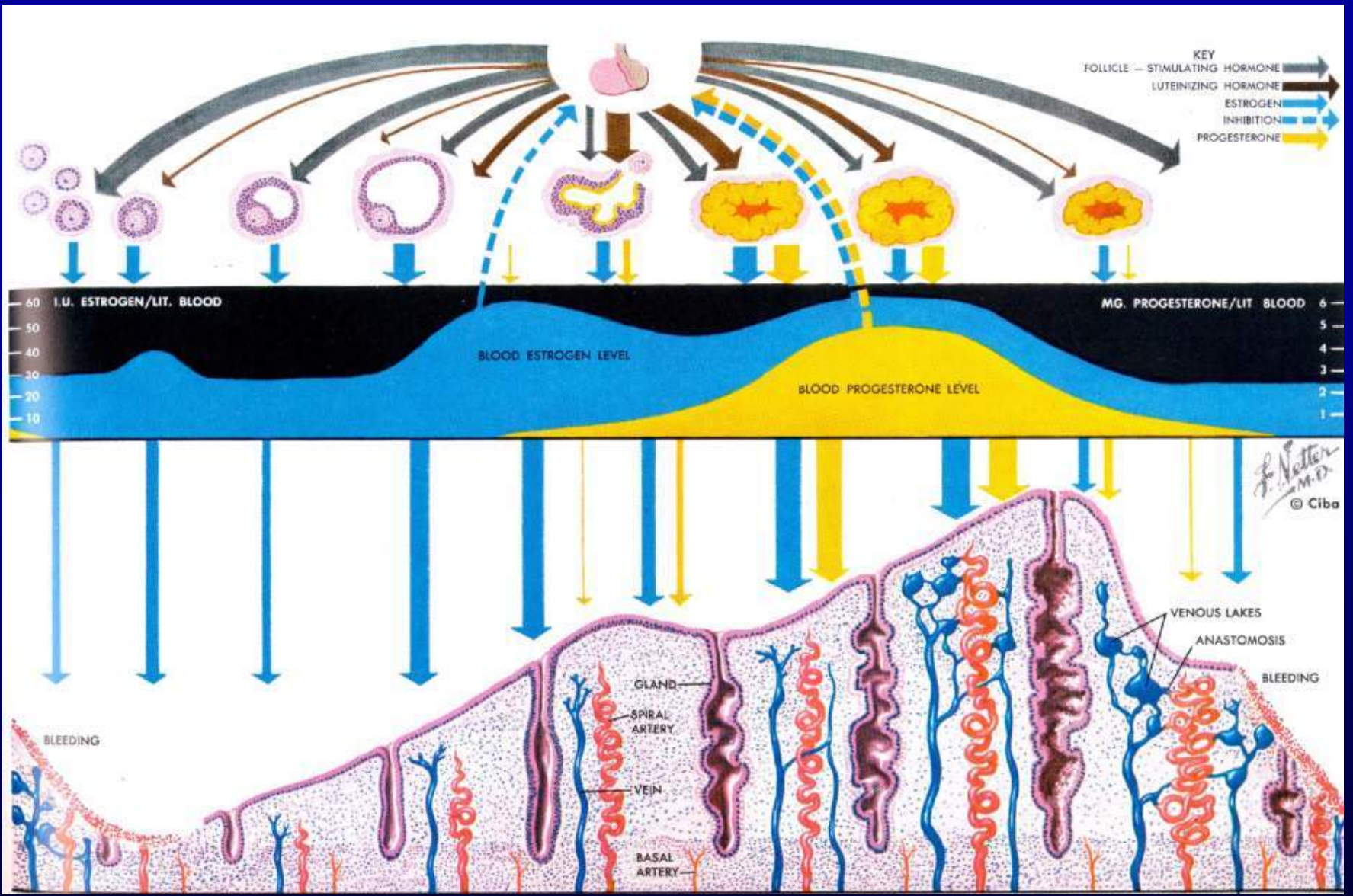
TABLE 8. Effect of assisted reproductive technology (ART) on the total number of infants born in the United States, by plurality — United States, 2003

Plurality	No. of ART infants [†]	(%) of total	No. of total U.S. infants [§]	(%) of total	Contribution of ART to total births in the United States (%)
Infants born in singleton deliveries	22,383	(47.8)	3,953,622	(96.7)	0.6
Infants born in multiple-birth deliveries	24,447	(52.2)	136,328	(3.3)	17.9
Twins	21,057	(45.0)	128,665	(3.1)	16.4
Triplets or higher order	3,390	(7.2)	7,663	(0.2)	44.2
Total no. of infants	46,830		4,089,950		1.1

* SOURCE: Assisted Reproductive Technology Surveillance System.

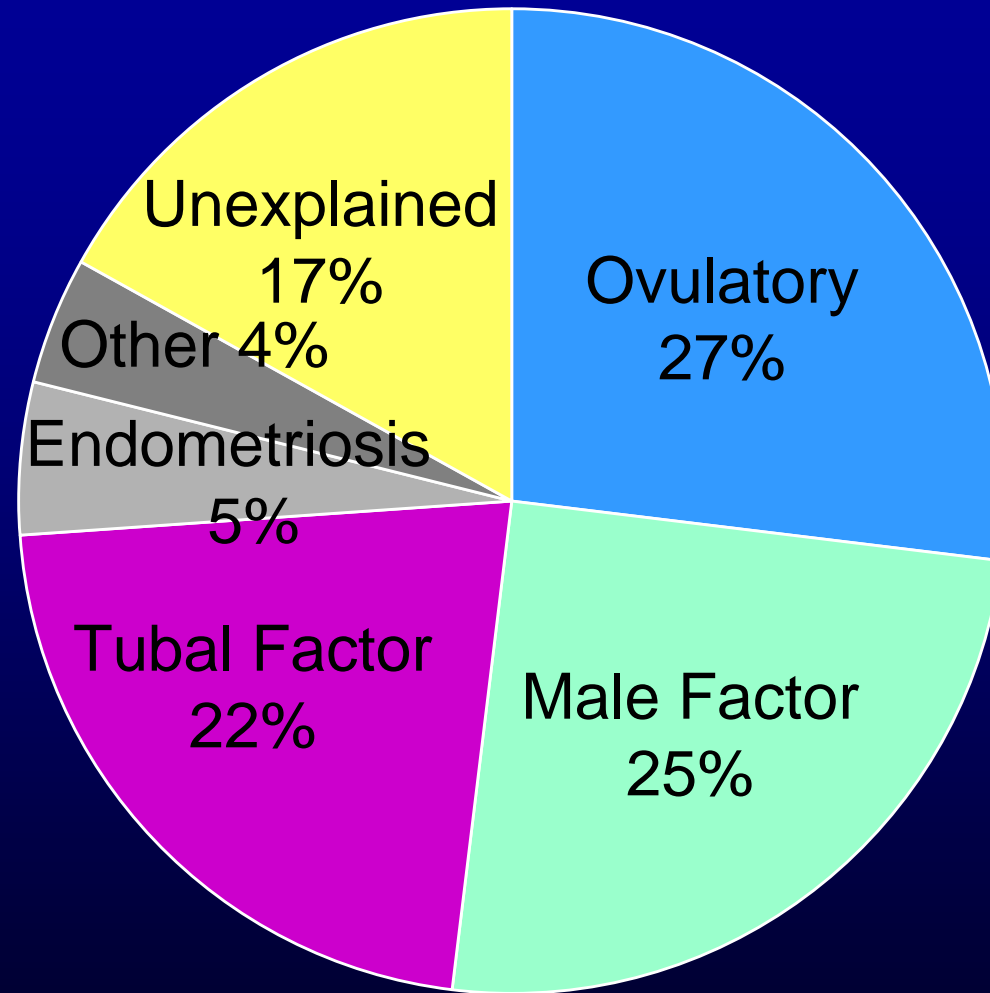
Requirements for Conception





CD 20~24
(LH +6 ~ +10)

Diagnosis in Infertile Couples



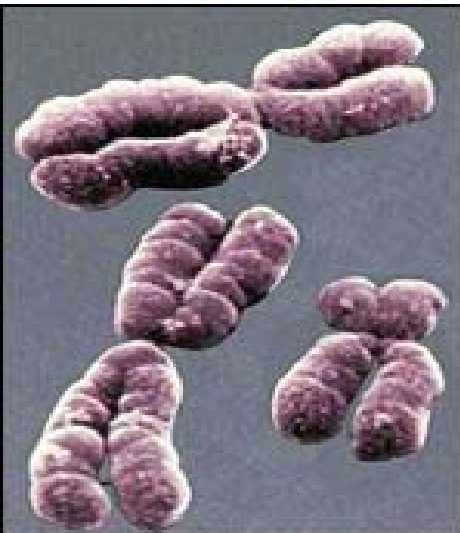
- Collins, JA. Unexplained Infertility. In Keye WE, Chang RJ, Rebar RW, Soules MR (eds). Infertility: Evaluation and Treatment 1995.

History and Physical

- Sexual History – coital frequency
- Gynecologic History
 - menstrual history, pelvic pain, pelvic infections, endometriosis
- Obstetric History
- Medical History
 - Thyroid abnormalities, hair growth and acne, nipple discharge
 - Childhood illnesses, chicken pox, German measles
- Medications
- Surgical History
 - Abdominal and pelvic surgeries
- Social History / Family History

Male History

- Genital History
 - Puberty, testicular development
 - Previous infections
- Medical History
 - Childhood illnesses, mumps
- Surgical History
- Medications
- Social History / Family History



Preconception Counseling

- Genetic Risk Factors
- Vaccinations
 - Rubella
 - Varicella
- Prenatal Vitamins



Preconception Genetic Screening

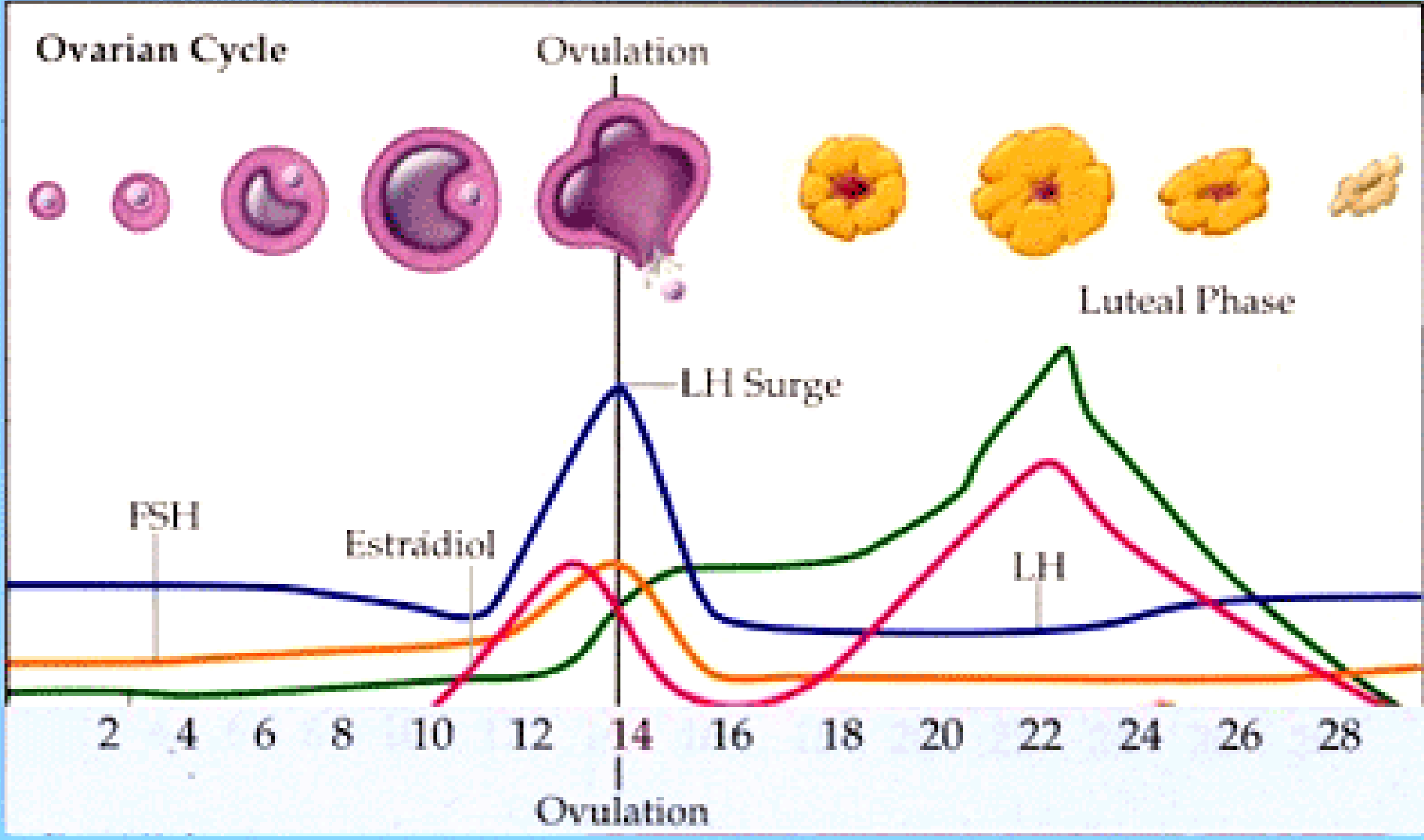
- African-American/Mediterranean/South East Asian
 - *Hemoglobin electrophoresis (sickle cell or thalasemia)*
- French Canadian/Creole - *Tay Sachs disease*
- Caucasian – *Cystic Fibrosis*
- Ashkenazi Jewish
 - *Cystic Fibrosis, Tay Sachs disease, Canavan disease, Familial Dysautonomia, Bloom Syndrome, Fanconi anemia group C, Gaucher disease, Glycogen storage disease type 1a, mucopolysaccharidosis type IV, Niemann-Pick disease type A*
- Family History of Mental Retardation/ Ataxia/ Fragile X Syndrome
 - *Fragile X premutation*

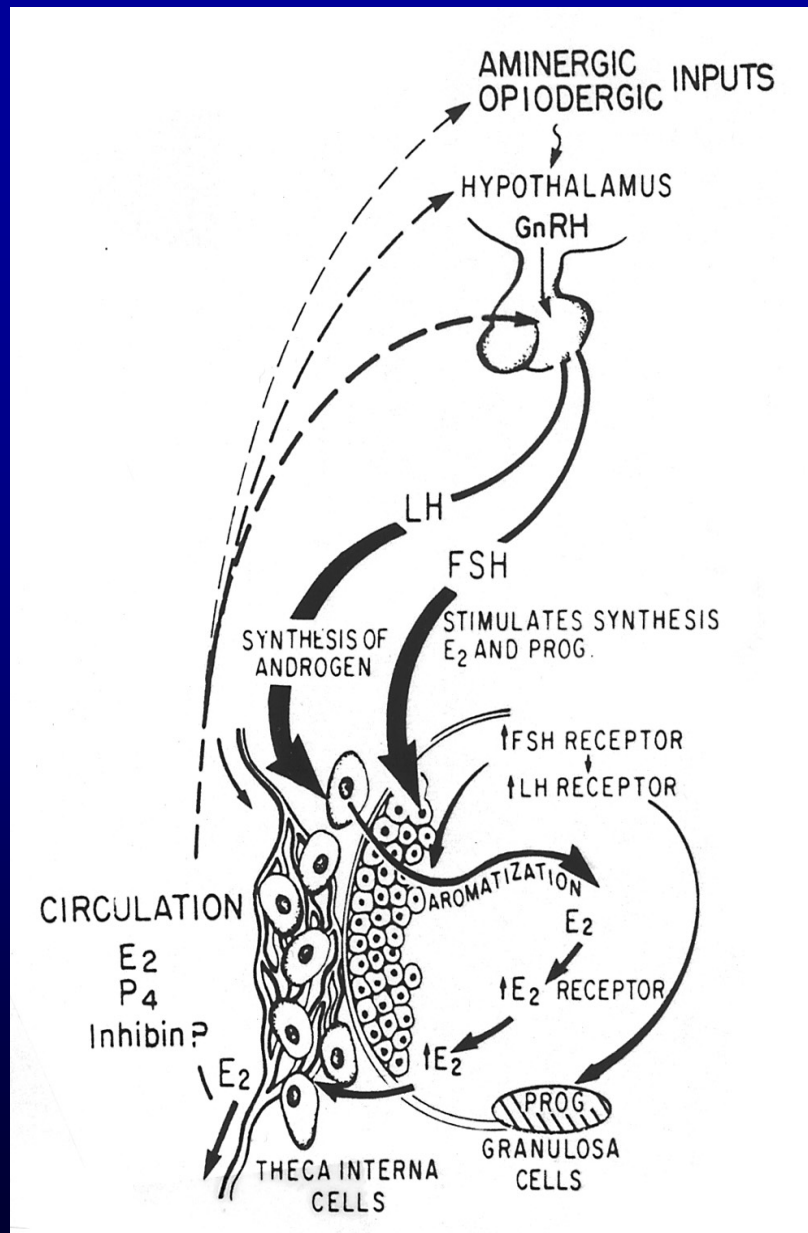
Physical Exam

- General overview
- Pelvic exam
- Ultrasound

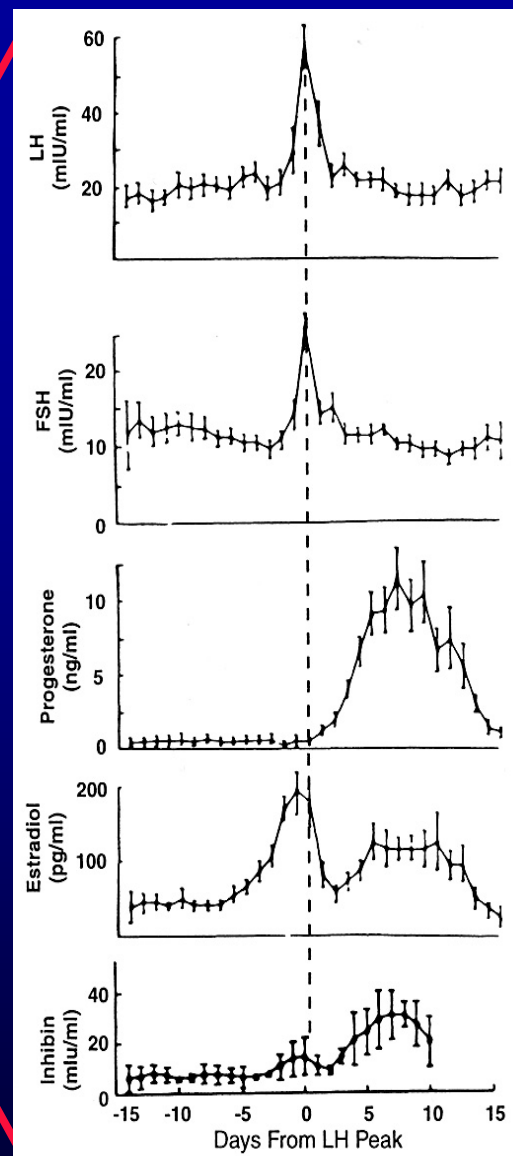
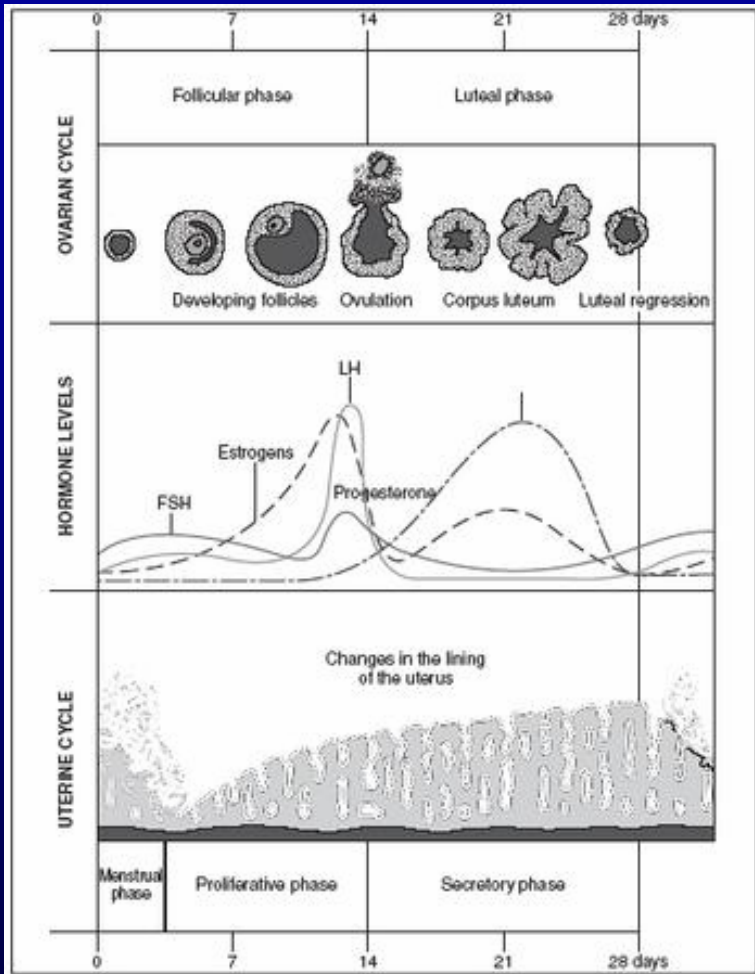


Ovulation





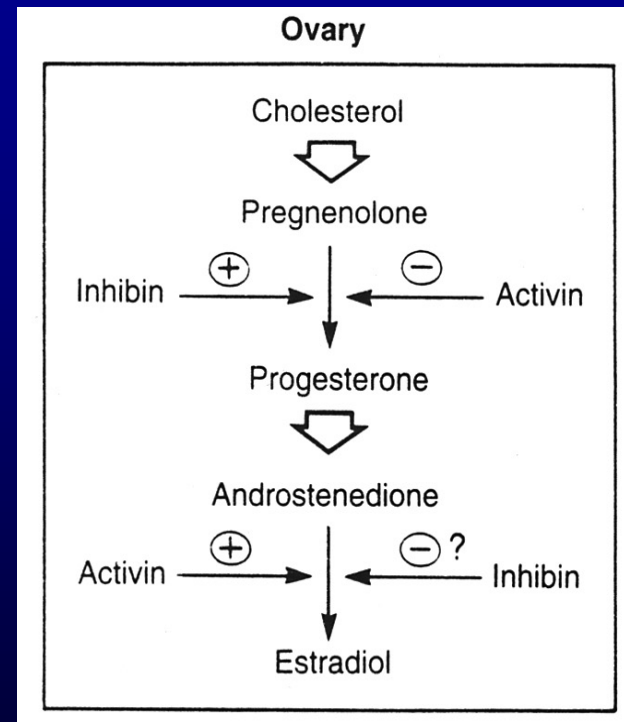
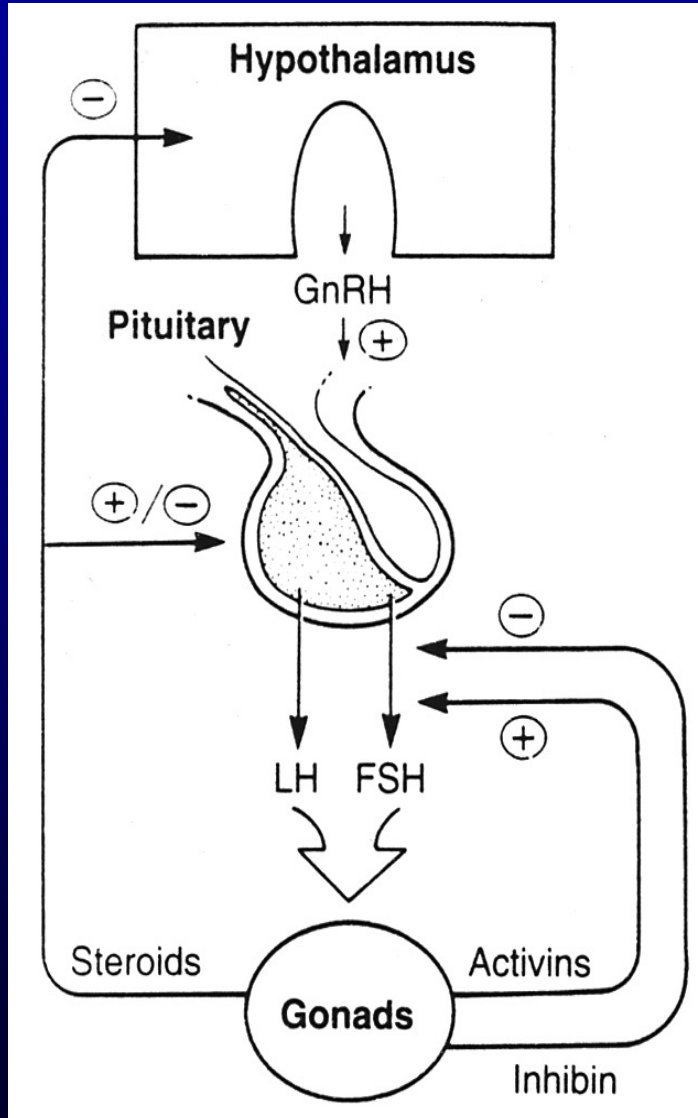
Gonadotropin-ovarian interaction in the regulation of follicular maturation and steroidogenesis (E₂ = estradiol; prog. = progesterone).



• Mean values of LH, FSH, progesterone, estradiol, and inhibin in daily serum samples of women during ovulatory menstrual cycles (mean \pm SE depicted)

*From Thorneycroft et al. Am J Obstet Gynecol 1971;111:947
McLachlan et al. J Clin Endocrinol Metab 1987;65:954*

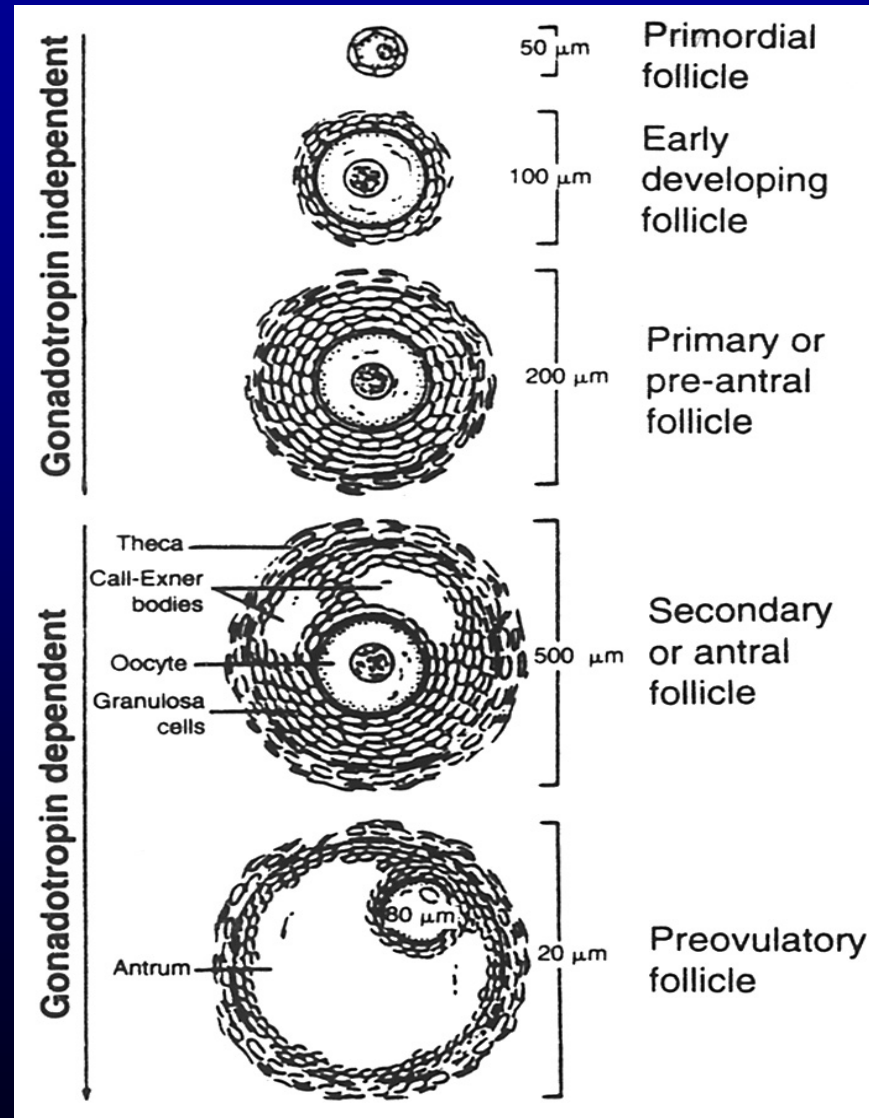
GENERALIZED SCHEMATA SHOWING INVOLVEMENT OF ACTIVINS AND INHIBINS



Hylka VW and di Zerega GS: Reproductive hormones and their mechanisms of action. In Mishell DR Jr, Davajan V, and Lobo RA: Infertility, contraception and reproductive endocrinology, ed 3, 1991, Blackwell Scientific Publications.

Follicle development:

Progress beyond primary follicle stage depends on FSH stimulation

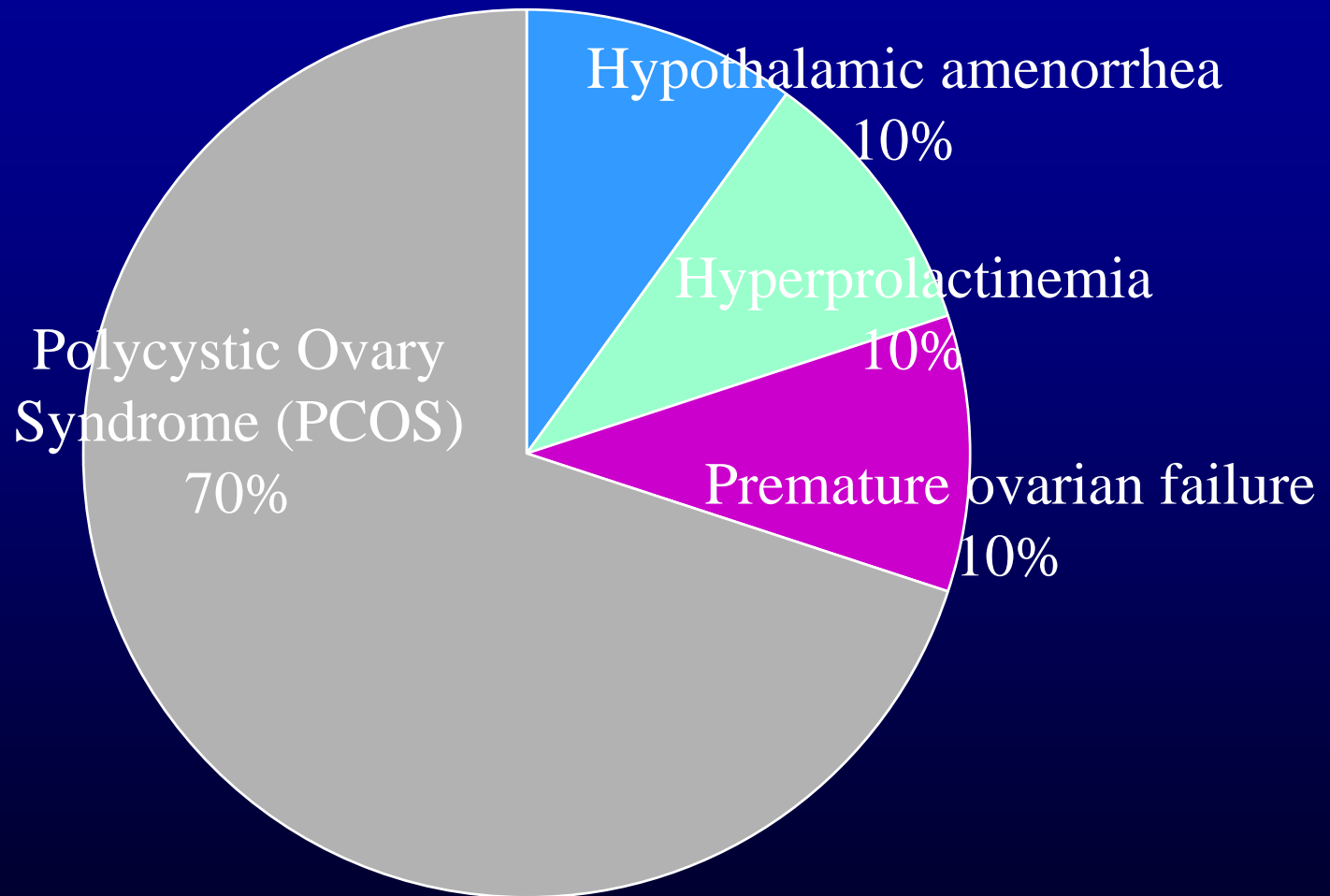


Paulson RJ: Oocytes: from development to fertilization. In Mishell DR Jr, Davajan V, and Lobo RA, editors: Infertility, contraception and reproductive endocrinology, ed 3, 1991, Blackwell Scientific Publications

OVULATION

- E_2 \uparrow pituitary LH synthesis, but inhibits release (\uparrow “reserve pool”)
- As E_2 reaches high levels it causes paradoxical release of all stored LH over a 24-36-hr period (i.e. the LH surge)
- The LH surge triggers ovulation (i.e. the end of follicular phase)
- LH surge \uparrow proteases which digest capsule of ovary, resulting in extrusion of oocyte and surrounding granulosa cells (i.e. cumulus oophorus)
- Oocyte enters Meiosis II, which is again arrested until fertilization
- LH surge typically occurs 14 days into menstrual cycle (counted from first day of bleeding), but can vary (10-17 days)

Ovulatory Dysfunction

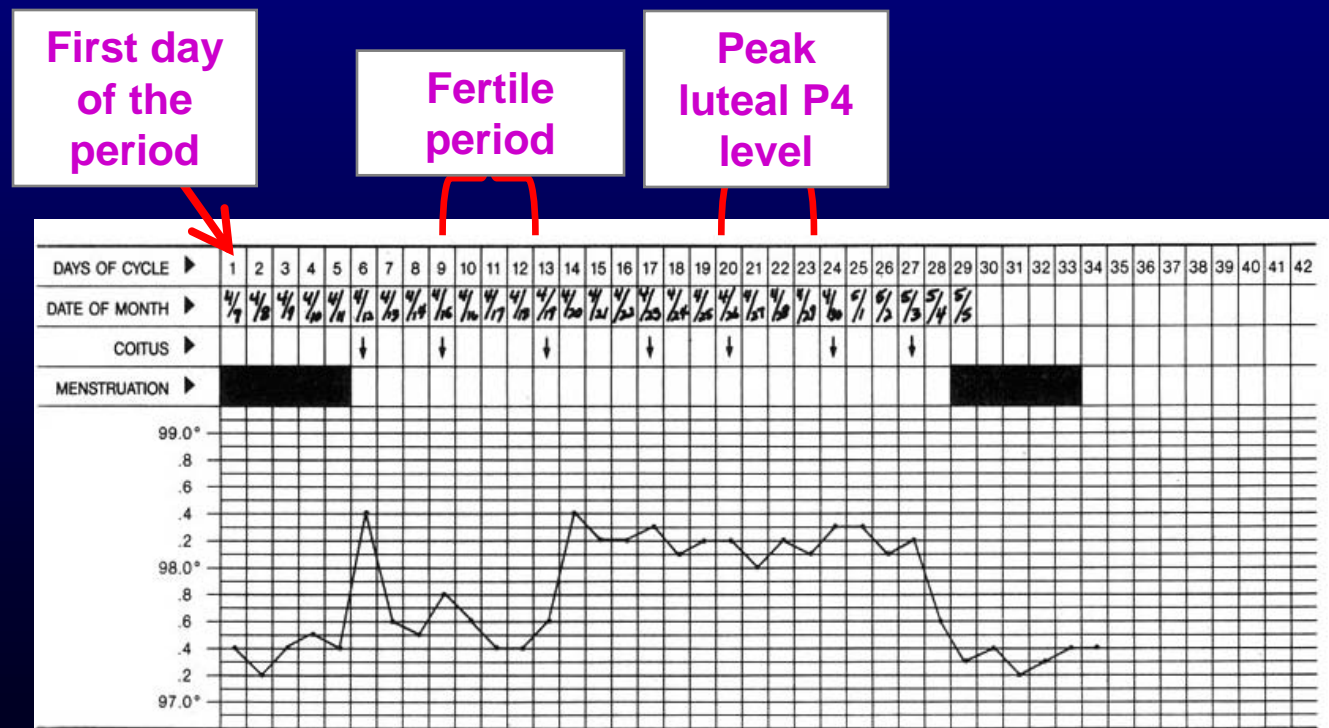


-Reindollar RH, et al. Am J Obstet Gynecol 1986; 155: 531-43

Document Ovulatory Function

Basal Body Temperature

- Temperature increases as a result of progesterone production in the luteal phase of the cycle
- Coincides with an increase in the progesterone level above 4 ng/ml
- A biphasic pattern signifies ovulation
- Temperature taken upon awakening
- Predicts the LH surge only within 2-3 days

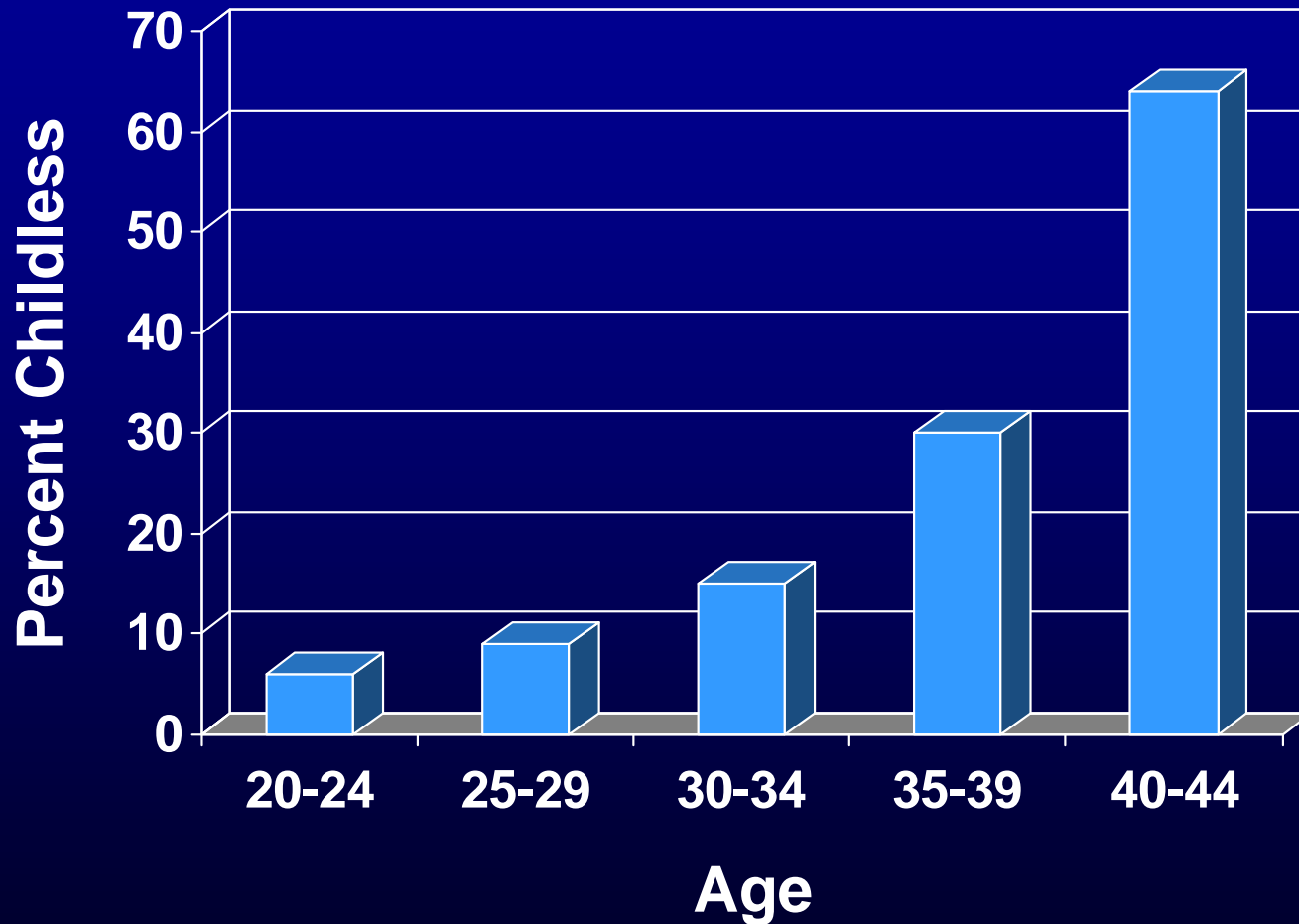


Document Ovulatory Function

- Basal Body Temperature
- Ovulation Predictor Kits
- Day 22-24 Progesterone
 - Midluteal phase $> 3\text{ng/ml}$
 - Preferably $>10\text{ ng/ml}$

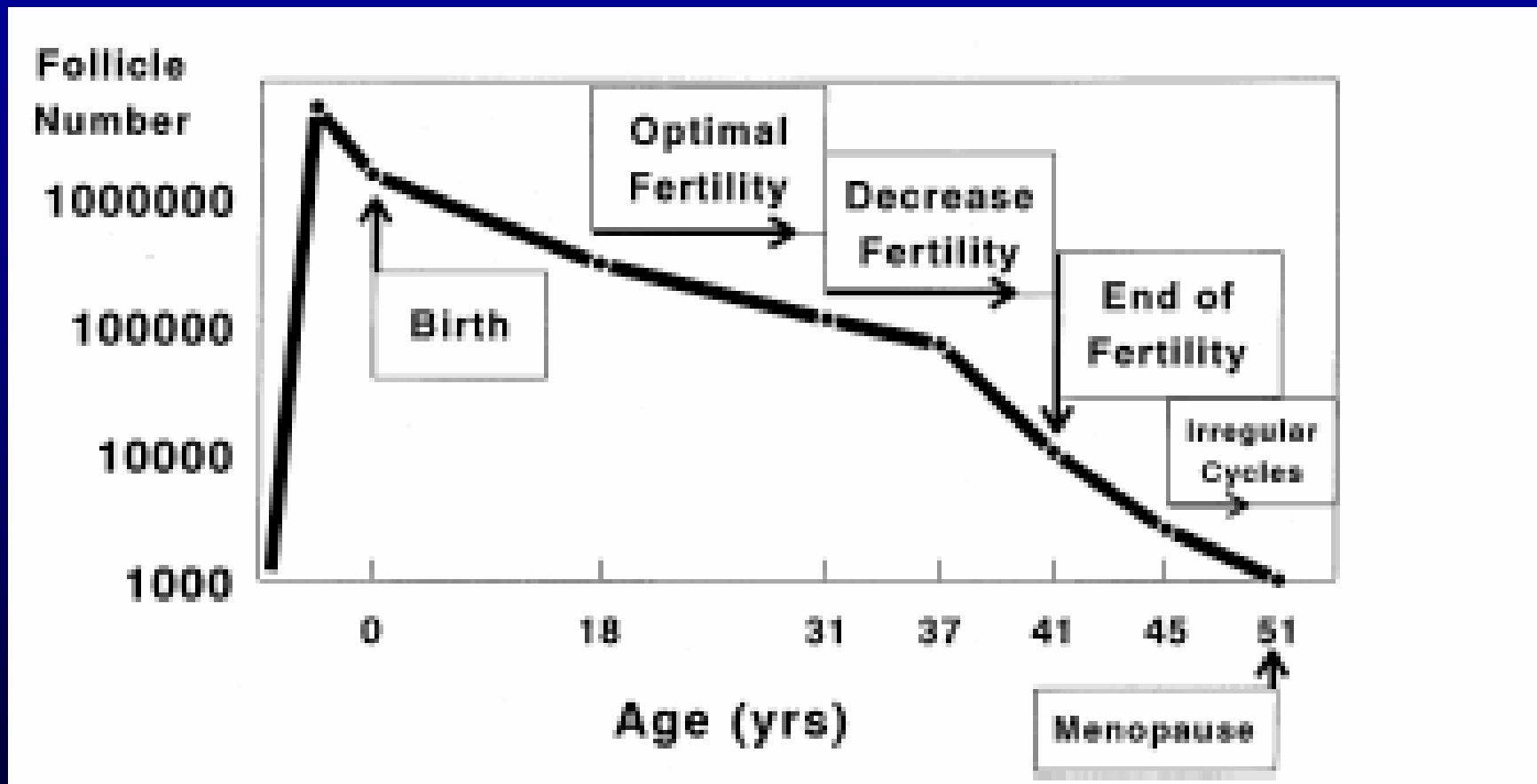


Age and Fertility



-Menken J, et al. *Science*.1986;233:1389-1394

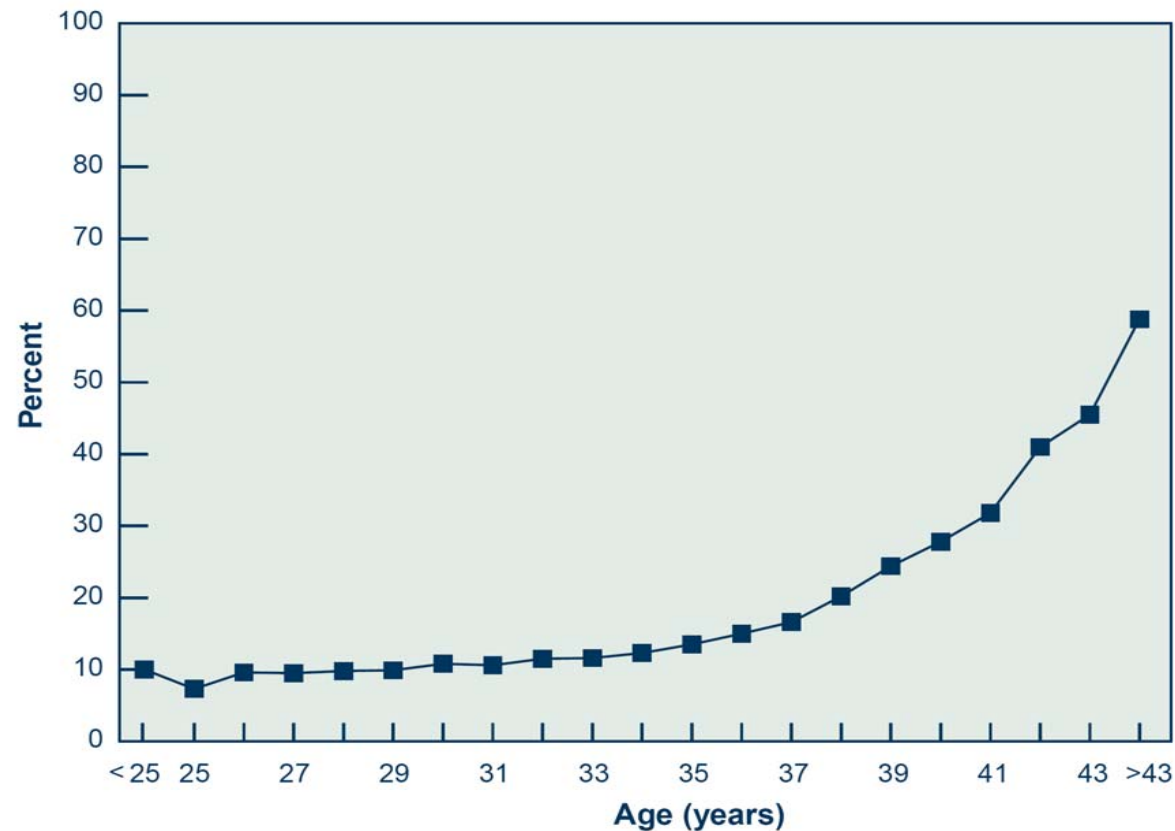
The Declining Follicle Pool



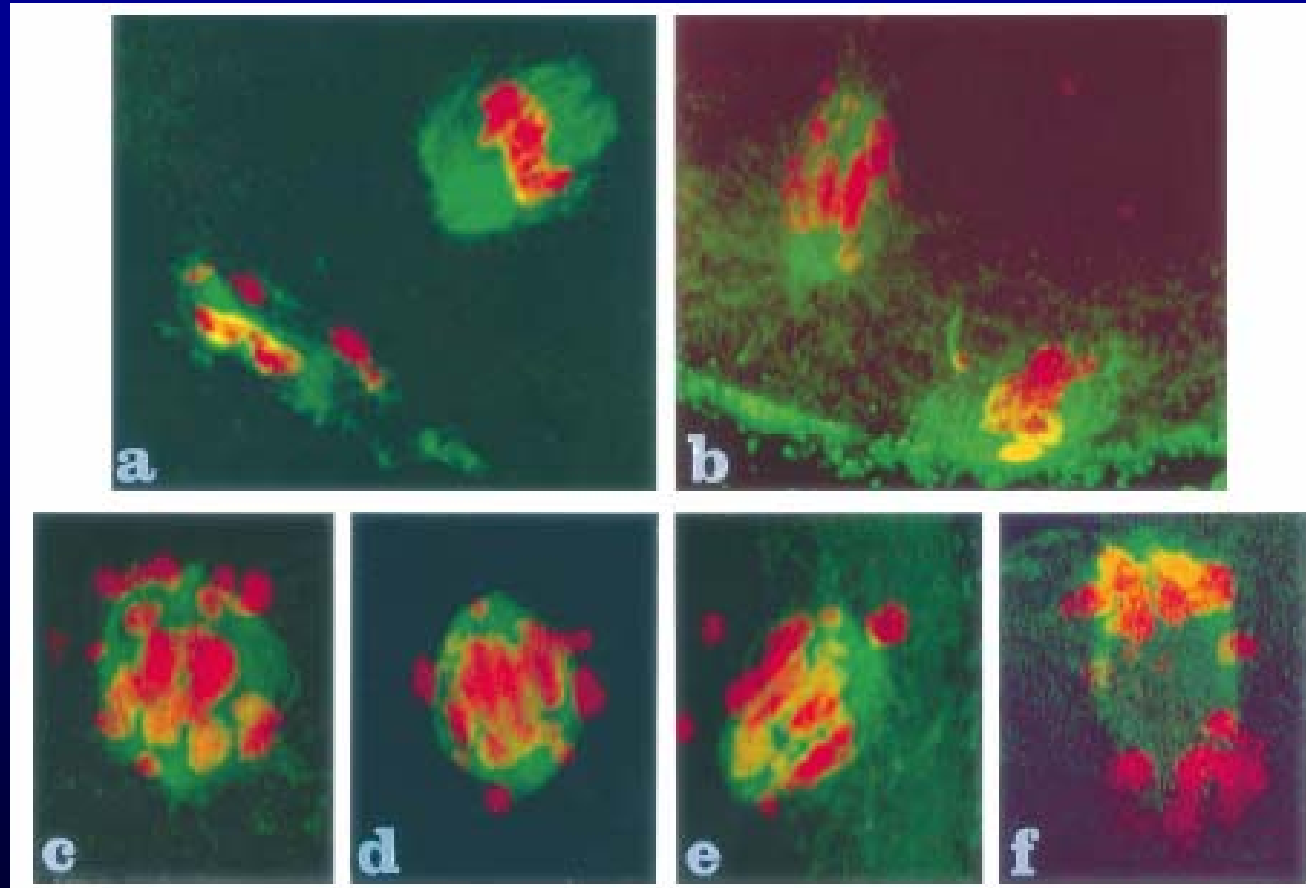
-te Velde ER, et al., Maturitas 30 (1998) 119-125

Age Related Decline of Oocyte Quality

Figure 14
Miscarriage Rates Among Women Who Had ART Cycles Using
Fresh Nondonor Eggs or Embryos, by Age of Woman, 2004



Meiotic Spindle Abnormalities with Advanced Age



-Volarcik K. et al. Hum Reprod. 1998 Jan;13(1):154-60

Diagnostic Evaluation Ovarian Factors

- Cycle Day 3 Follicle Stimulating Hormone (FSH) and Estradiol (E2)
- Thyroid Stimulating Hormone (TSH)
- Prolactin
- Androgens (testosterone; DHEAS and 17-OHP if hirsutism present)

Diagnostic Evaluation Ovarian Factors

Ovarian Reserve:

Day 3 FSH level

> 10-12 IU/L Abnormal

> 25 IU/L Pregnancy Rate Approximates

Day 3 Estradiol

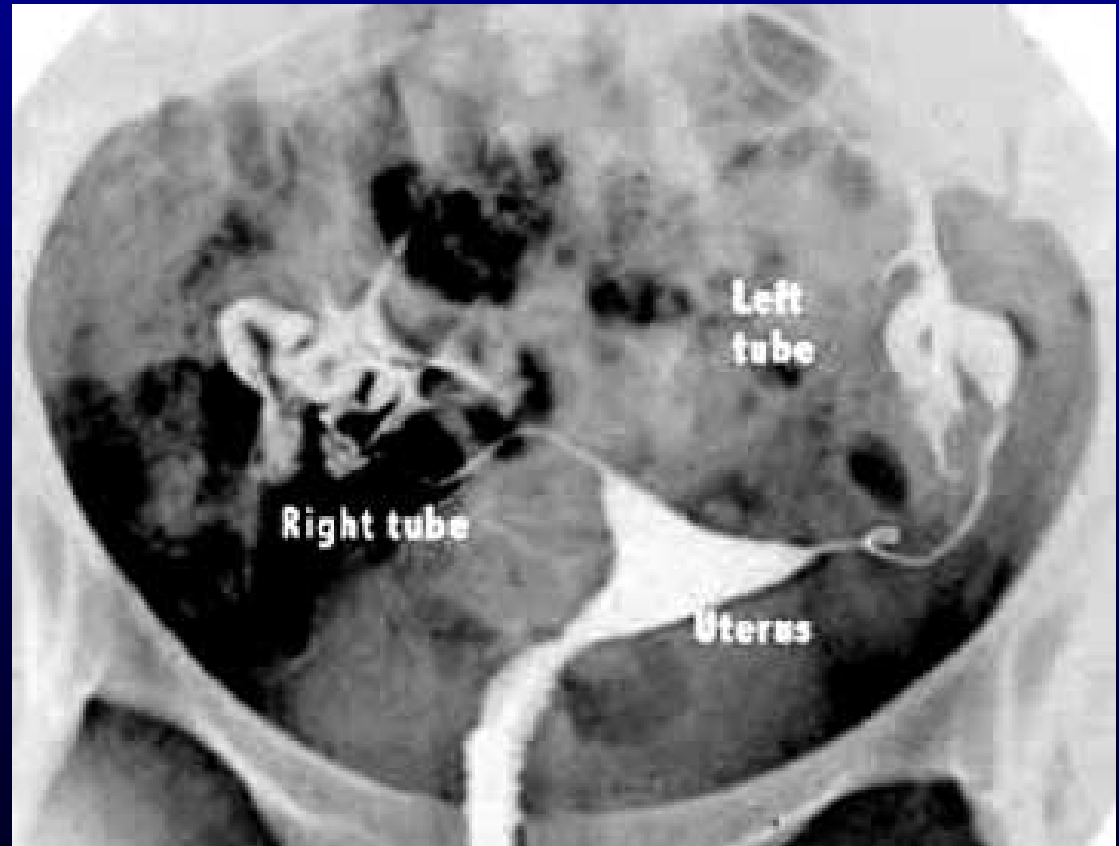
> 80 pg/ml Poor Outcome

Age > 35

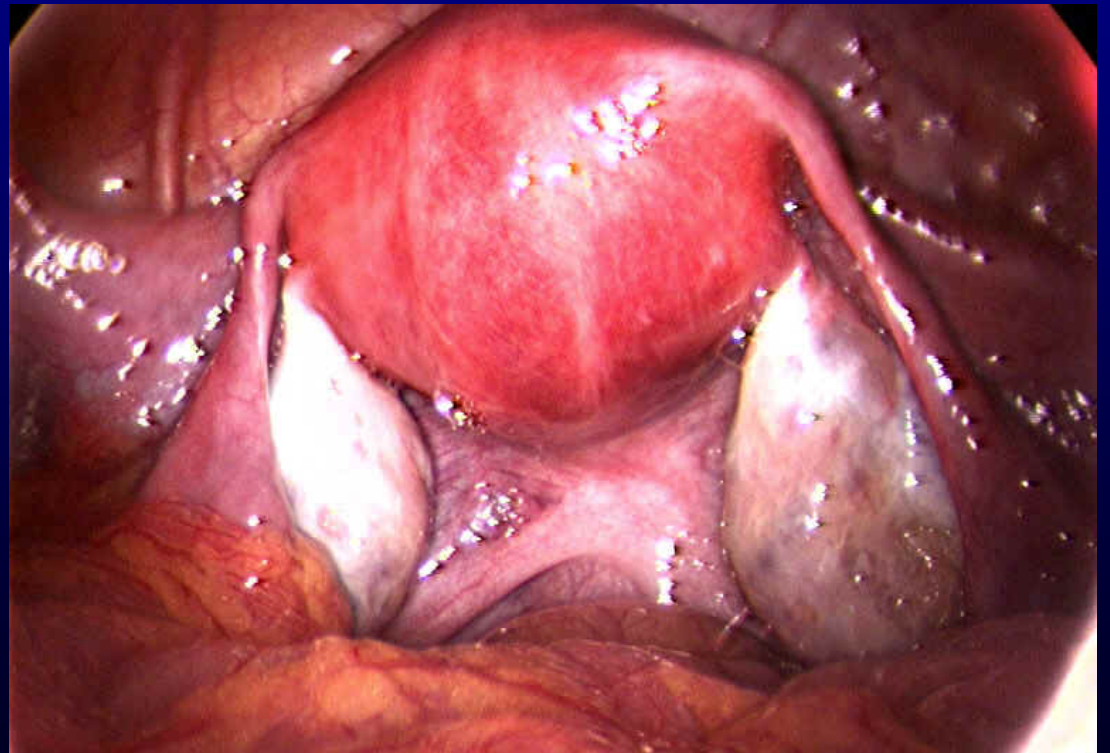
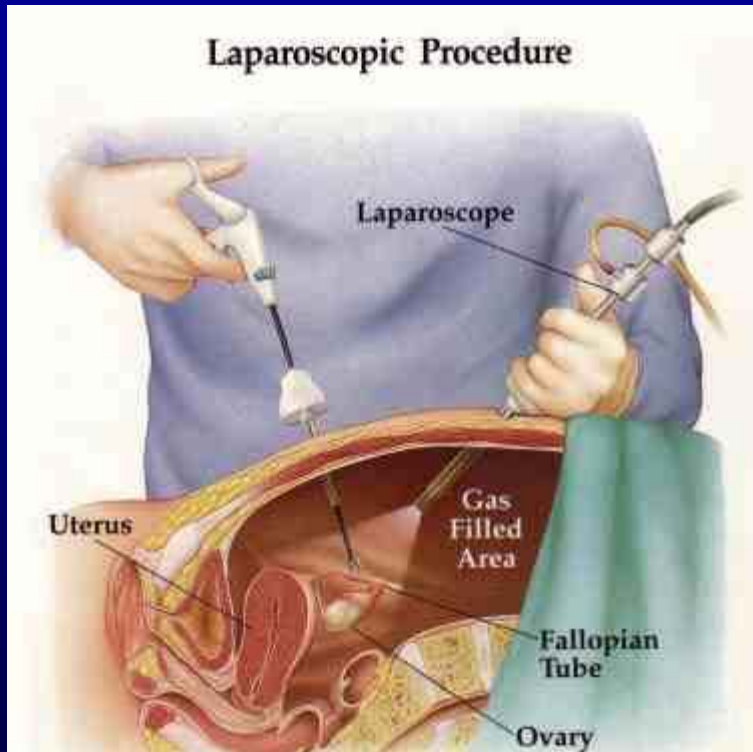
Single Ovary or previous ovarian surgery

Documented previous poor responder to
gonadotropins

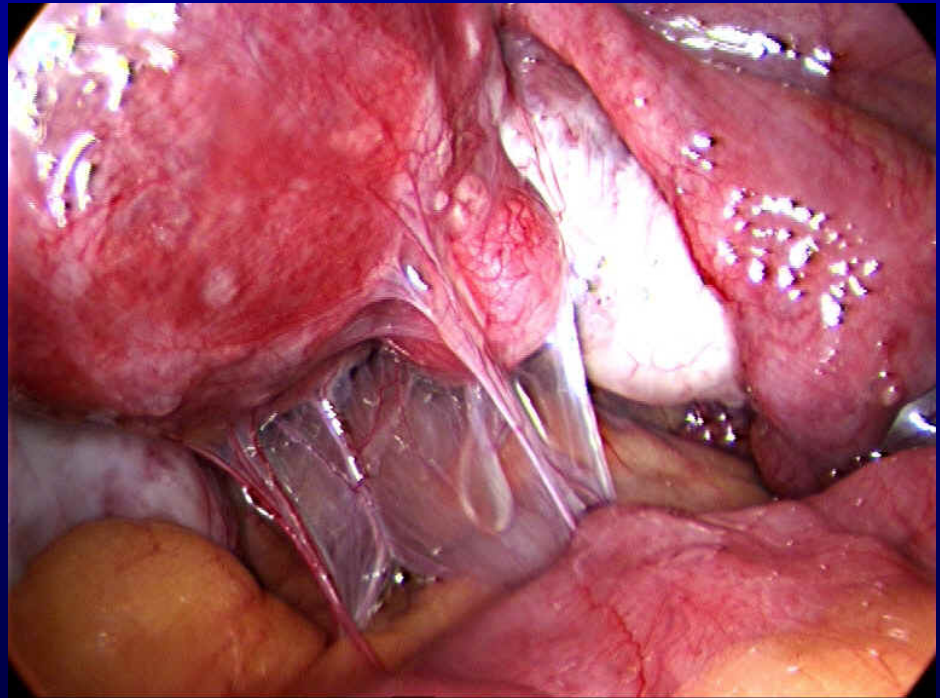
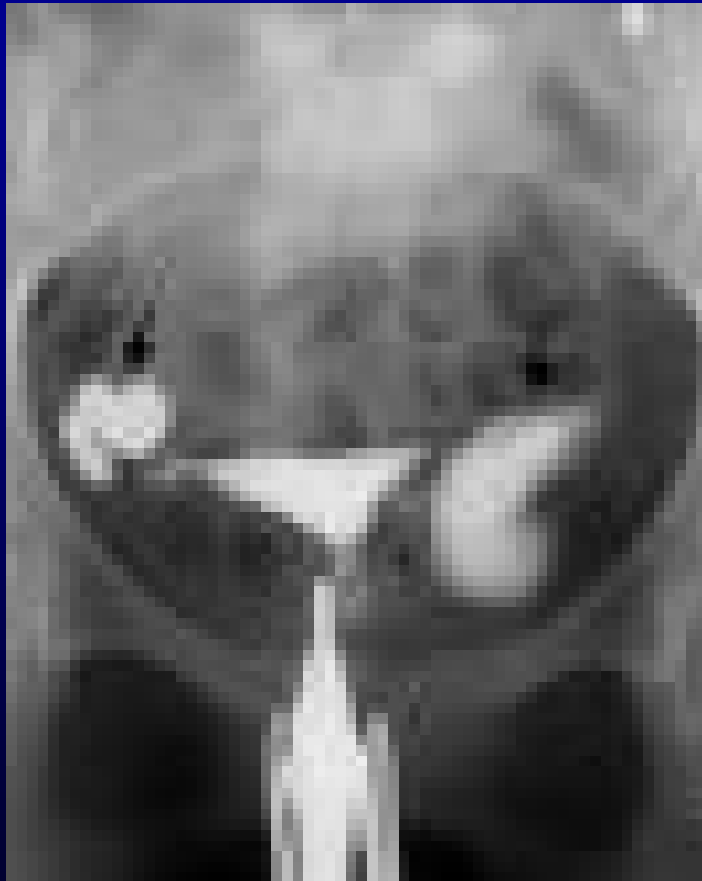
Anatomic Evaluation Hysterosalpingogram (HSG)



Laparoscopy

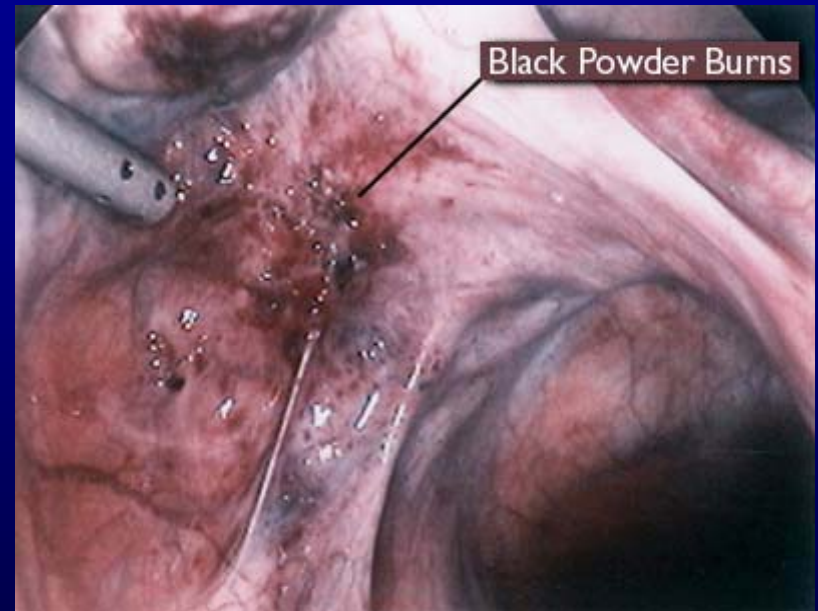
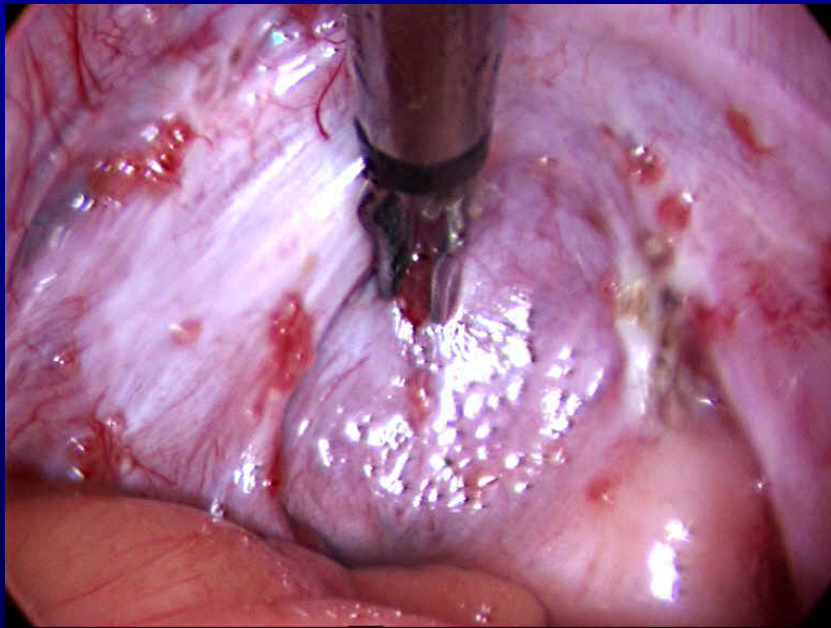


Tubal Disease



- Pelvic Infections
- Endometriosis
- Pelvic Surgery

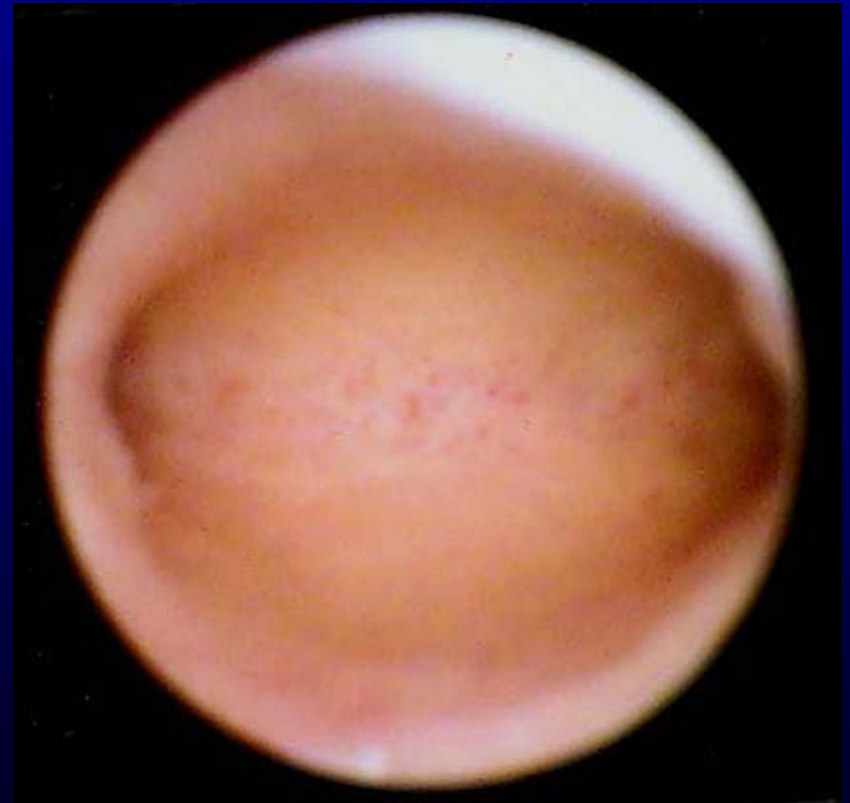
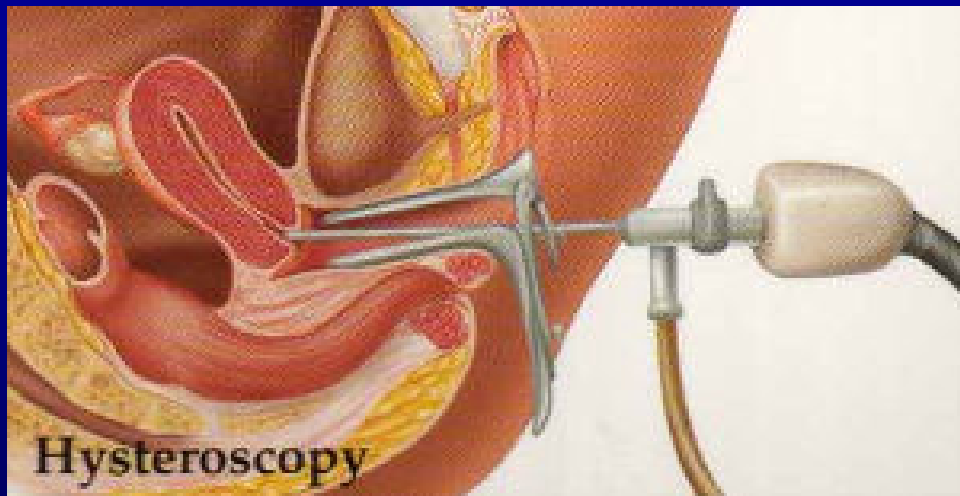
Endometriosis



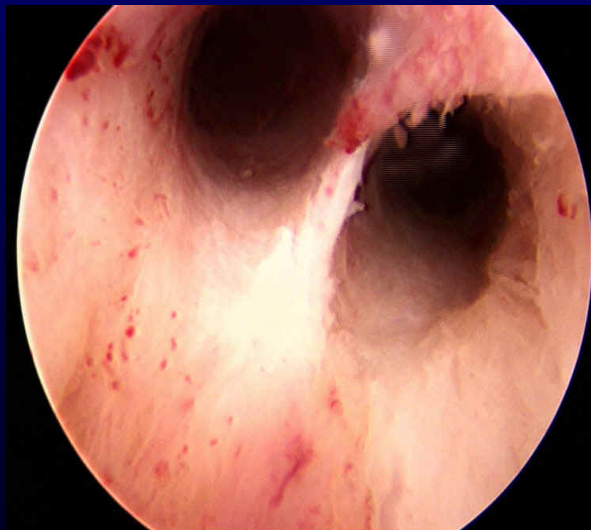
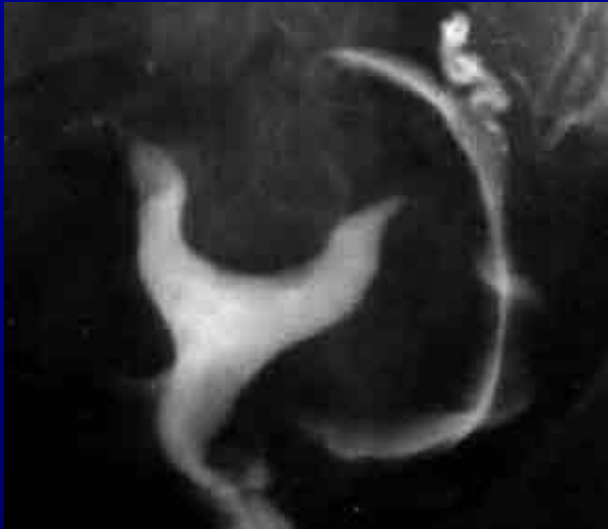
Endometriosis and Infertility

- Fecundity:
Control population:
0.15 — 0.20
Endometriosis population:
0.02 — 0.10
- Association:
Incidence in Fertile/Tubal ligation population:
– 5%
Incidence in Infertility population:
– 48%
- 6 – 8x more likely to have Endometriosis

Hysteroscopy



Uterine Cavity Abnormalities

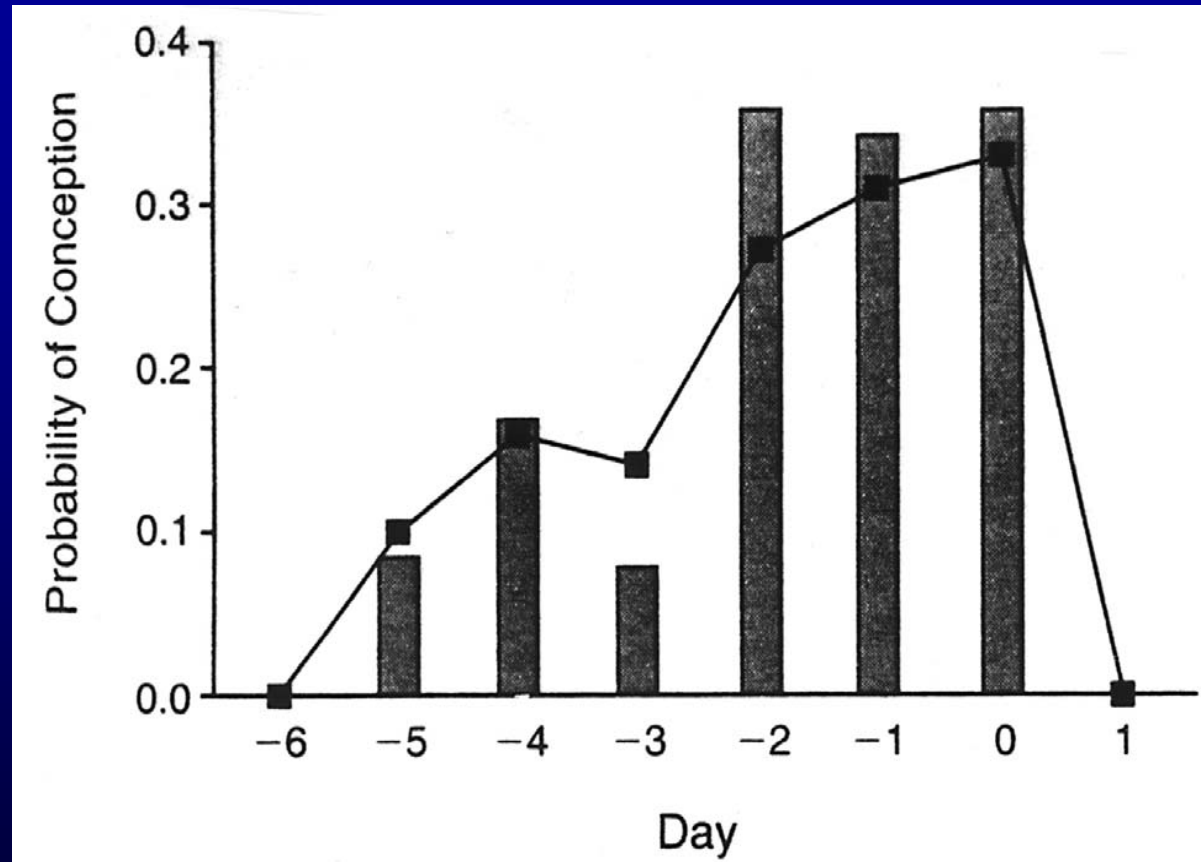


Male Evaluation Semen Analysis

- Volume ≥ 2.0 cc
- Conc. ≥ 20 M/ml
- Motility $> 50\%$
- Conc. Motile >8 M/ml
- Morphology (WHO) $>50\%$
(Kruger's) $>14\%$



PROBABILITY OF CONCEPTION ON SPECIFIC DAYS NEAR THE DAY OF OVULATION



•The bars represent data reported by 129 women who had sexual intercourse on only 1 day in the 6-day interval ending on the day of ovulation (day 0). The solid line shows the probability of conception based on a statistical analysis of data from 625 cycles.

From Wilcox AJ, Weinberg CR, Baird DD. N Engl J Med 333:1517-1521, 1995