HUMAN REPRODUCTION:
CLINICAL,
PATHOLOGIC AND PHARMACOLOGIC
CORRELATIONS

2004

Course Co-Director
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Department of Obstetrics and Gynecology
Welcome to the course on Human Reproduction. This syllabus has been recently revised to incorporate the most recent information available and to insure success on national qualifying examinations. This course is designed to be used in conjunction with our website which has interactive materials, visual displays and practice tests to assist your endeavors to master the material. Group discussions are provided to allow in-depth coverage. We encourage you to attend these sessions.

For those of you who are web learners, please visit our web site that has case studies, clinical/pathological correlations, and test questions.

http://medstat.med.utah.edu/kw/human_reprod
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March 10, 2004
To: UUMC Sophomores
Re: Sophomore Reproductive Organ Systems Course

Hello, and welcome to the upcoming Reproductive Organ Systems Course. This 8 day course is designed to provide you with information about reproductive biology and some of its clinical consequences.

Medical Students learn in different ways, and have different commitments to various topics. In view of this, we have designed the course to have a base content (the syllabus) from which the examination questions are taken (except the pathology questions). This is the **minimum** we expect you to know and be able to use to pass the exam. In addition to the syllabus, we have lectures, workshops, and lunch-time seminars. We also have a website for more material, visual displays, and practice tests.

The lectures are meant to be clinical correlates to the syllabus. They are **NOT** designed to follow the syllabus but are designed to be additive to help bring the physiology to clinical relevance.

The workshops are designed to help you use what you have learned. The expectation is that students who attend the workshop have read the syllabus material **IN ADVANCE** and are ready to work to solve clinical problems. This is **NOT** a passive learning session – it is to see if you can use what you have learned. If you have not read the syllabus in advance, you could use your time, your fellow students time, and the faculty time more efficiently by using this workshop time to read. This year the Pathology and Ob/Gyn Faculty will be working together to provide clinical and pathological correlates in the Pathology Workshops on Thursday, April 1, and Tuesday, April 6. **All students should visit the human reproduction website below and go to the Ovarian Tumor Seminar in preparation for this workshop.** Although attendance is not mandatory for the other workshops, the Pathology Department has required attendance for their workshops, including this one.

The websites (medstat.med.utah/kw/human_reprod and med.utah.edu/andrology) are for those of you who are web learners and seek more information on female and male reproduction and advanced reproductive technology.

The lunch-time brown bag (bring your own lunch or eat later) seminars are to introduce ethical and controversial issues in our field, or to provide information you probably will not receive at another time during medical school. There is no syllabus (you will not be tested on the content), but these are informational or interactive sessions on topics that may be new to you and are in the news.

We look forward to this upcoming Sophomore Reproductive Organ Systems Course

Kirtly Parker Jones MD
Reproductive Organ Systems Coursemaster
LECTURES/EXAMINATION

All lectures will be held in classrooms as noted. Seminars will be as listed in the schedule. The Ob/Gyn Conference Room is 2B243.

There is no single textbook that the department recommends for medical students in obstetrics and gynecology. During your junior clerkship a text is provided on loan to all students (*Danforth's Obstetrics and Gynecology*, Scott JR, DiSaia PH, Hammond CB, Spellacy WN, eds). Several are in the library for your optional use. Texts we recommend to our residents include the following:

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<tr>
<td>Comprehensive</td>
<td><em>Current Obstetric and Gynecologic Diagnosis and Treatment</em>, Lange Series, VIII Edition</td>
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**Grading and Evaluation:** The final examination, which will incorporate the pathology and pharmacology exams, will account for 100% of your grade.

Final examination schedules for sophomore students will be made by the Office of Student Affairs with the consultation of course directors. The sophomore examination schedules will be approved by the specific Curriculum Committee. The examination schedule will not be altered without the written consent of the course director, 100 percent approval of the class involved, and formal approval of the specific Curriculum Committee. All final examinations must be administered during the regularly scheduled examination period of that particular class unless otherwise approved by the specific Curriculum Committee.

**Missed Examinations by Students:** Departments and/or course directors should establish their own policy concerning missed examinations by students due to brief illness, death in the family, etc. Consideration might be given to the following options:

1. Allow the student to take the original examination at a specified time with the agreement that the student will not discuss the examination with anyone prior to taking the exam.
2. Allow the student to take a make-up examination prepared by the department which is different from the original exam.
3. Not allow the student to take a make-up examination and give him either a zero grade or calculate the final overall grade by using an average of all other exams.
4. Require the student to take a National Board subject examination at the end of the quarter at his own expense, giving it the proper weight when determining the overall grade.

If such an occasion arises, the student should contact the course director before the exam and make appropriate arrangements.
### Sophomore Organ System Course Schedule 2004

#### Monday, March 29

**Classroom A**

8:10 – 9:00 am  Kirtly Parker Jones, M.D.  
Introduction to Sophomore Reproductive Organ Systems Course: Life Cycle of the Ovary: Puberty to Menopause

9:10-10:00 am  Kirtly Parker Jones, M.D.  
Birth to Menopause

10:10-11:00 am  Thomas Abbott, M.D.  
Introduction to Pathology

11:10-12:00  Thomas Abbott, M.D.  
Trophoblastic Disease/GYN Cytology

**Classroom D**

12:10 pm  Brown Bag Seminar  
Kirtly Parker Jones, M.D.  
Taking a Sexual History

1:00-5:00 pm FREE

#### Tuesday, March 30

**Classroom A**

8:10 – 9:00 am  Harry H. Hatasaka, M.D.  
Fertilization, Early Pregnancy and it’s Disorders

9:10-10:00 am  C. Matthew Peterson, M.D.  
Prolactin and Pathologic Associations

10:10-12:00  Thomas Abbott, M.D.  
Pathology of the Genital Tract

12:10-1:00 pm  Brown Bag Seminar  
Kirtly Parker Jones, M.D.  
Egg and Sperm Donation

1:00-5:00 pm FREE

#### Wednesday, March 31

**Classroom A**

8:10-9:00 am  Michael L. Draper, M.D.  
Physiology of Pregnancy

9:10-10:00 am  M. Sean Esplin, M.D.  
Physiology of Labor and Delivery

10:10-12:00  PIH/OB Hemorrhage Workshop  
OB/Gyn 2B329  Student Group A  M. Sean Esplin, M.D.  
Tyler Conf 4A440  Student Group D  Bob Silver, M.D.  
Pediatric 2B475  Student Group C  Robert Andres, M.D.  
MREB 408  Student Group B  Michael Belfort, M.D., Ph.D.  
6th Floor Eccles Conf. Rm  Student Group E  Antonio Frias, M.D.
Classroom A
12:10-1:00 pm  Brown Bag Seminar  Human Cloning in
Kirtly Parker Jones, M.D.  Reproduction and Therapy

1:00-5:00 pm FREE

**Thursday, April 1**
Classroom A
9:10-10:00 am  Doug Carrell, Ph.D.  Male Reproduction

10:10-12:00  Infertility Workshop
OB/Gyn  2B329  Student Group A  C. Matthew Peterson, M.D.
Tyler Conf  4A440  Student Group D  Harry H. Hatasaka, M.D.
Old CVMB Library 5C310  Student Group E  Kirtly Parker Jones, M.D.
Women/Child  2A097  Student Group B  Mark Gibson, M.D.
Blue Room  AB193  Student Group C  Kenneth Wong, M.D.

Classroom B
12:10-1:00 pm  Brown Bag Seminar  Medical Abortion
Katie Morgan, N.P.
Kirtly Parker Jones, M.D.

3C310
1:10-3:00 pm  Pathology Workshop  Pathology Staff

3:00-5:00 pm FREE

**Friday, April 2**
Classroom A
8:10-9:00 am  Thomas Abbott, M.D.  Male Genital Tract

9:10-10:00 am  Thomas Abbott, M.D.  Pathology of the Breast

10:10 – 12:00 pm  Contraception Workshop
Pediatric  2B475  Student Group C  Kirtly Parker Jones, M.D.
Women/Child  2A097  Student Group B  Katie Morgan, NP
OB/Gyn  2B329  Student Group A  D. Yvette LaCoursiere, M.D.
Old CVMB Library 5C310  Student Group E  Karen Miller, MD
6th Floor Eccles Conf Rm  Student Group D  TBA

Classroom B
12:10 pm  Brown Bag Seminar  Emergency Contraception
Katie Morgan, N.P.

1:00-5:00 pm FREE
**Monday, April 5**
Classroom A
8:10-9:00 am  Paul R. Summers, M.D.  Sexually Transmitted Diseases
9:00-5:00 FREE

**Tuesday, April 6**
Classroom A
8:10-9:00 am  Peggy A. Norton, M.D.  Menstrual Disorders and Common GYN Problems
9:10-10:00 am  William Crowley, Ph.D.  Pharmacology of Gonadal Steroids
10:00-12:00 FREE
Classroom C
12:10-1:00 pm  Brown Bag Seminar  Issues in Contraceptive Counseling
Joseph Stanford, M.D.
Classroom A
1:10-3:00 pm  D. Yvette LaCoursiere, M.D. – cases 1-2  Pathology Seminar
Kirtly Parker Jones, M.D. – cases 7-8
Howard T. Sharp, M.D. – cases 5-6
GYN Oncologist TBA – cases 3-4
3:00-5:00 pm FREE

**Wednesday, April 7**
Classroom A
8:10-9:00 am  Janice L.B. Byrne, M.D.  Clinical Perinatal Genetics
9:10-10:00 am  Lester Partlow, Ph.D.  Teratology
10:00-12:00 FREE
Classroom D
12:10-1:00 pm  Brown Bag Seminar  Rape
Diane Fuller, N.P.
1:00-5:00 pm FREE

**Friday, April 9**
9:10 am-12:00 pm  Classroom A and D  Reproductive Organ Systems Exam
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<td>Thomas Abbott, M.D.</td>
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<td>Robert Andres, M.D.</td>
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<td>William Crowley, Ph.D</td>
<td>Department Chair</td>
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<td>M. Sean Esplin, M.D.</td>
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<td>Diane Fuller, PA-NP</td>
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<td>Mark Gibson, M.D.</td>
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<td>Harry Hatasaka, M.D.</td>
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<td>Jay Marshall, M.D.</td>
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# SOPHOMORE REPRODUCTIVE ORGAN SYSTEMS
## STUDENT GROUPS

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LIFE CYCLE OF THE OVARY: PUBERTY, THE MENSTRUAL CYCLE, AND MENOPAUSE

"A chicken is only an egg's way of making another egg" --Samuel Butler

Objectives

1. To describe normal and abnormal puberty in males and females
2. To understand the hypothalamic, pituitary, ovarian, and uterine functions in the normal menstrual cycle
3. To understand the normal transition from regular menstrual function to menopause and describe menopausal symptoms

Definitions

Adrenarche: The increase in secretion of androgens by the adrenal gland, occurring from about age 5 to age 20

Gonadarche: The initiation of production of significant amount of sex steroids by the testis or the ovary related to stimulation by gonadotropins

Puberty: The physical and biochemical changes associated with maturation of the hypothalamic/pituitary/gonadal axis which lead to the development of secondary sex characteristics and reproductive function (usually the coordinated consequences of adrenarche and gonadarche)

Menopause: The final spontaneous menstrual period (occurring at about 51 years of age in American women)

Climacteric: The period of transition from predictable ovarian function through the postmenopausal years, a period marked by waning ovarian function and dramatic decline in estrogen production

Perimenopause: The period before and after the final menstrual period marked by fluctuating ovarian function (a period of about four years on average)

Ontogeny of the Reproductive System in Human: Fetal Life

Although puberty occurs when increased gonadotropin secretions by the pituitary stimulate the gonads, the stage has been set during fetal life. In males, the earliest secretion of testosterone at 7 to 8 weeks gestation occurs independent of gonadotropins and continues with stimulation of hCG. The hypothalamic/pituitary axis completes development at about 20 weeks gestation. After the development of the portal system at 20 weeks, gonadotropins become sensitive to estrogen feedback suppression and fall to undetectable levels.

Neonatal Life

Immediately after birth, the stimulatory effect of hCG on the male testis and the suppressive effect of placental estrogens and progesterone on the pituitary and hypothalamus are withdrawn, leading to a rapid rise in gonadotropins. The withdrawal of placental hormones may actually lead to scant vaginal bleeding in females as well as temporary nipple discharge. The subsequent pattern of gonadotropin hormone levels
and gonadal response differs in infant boys and girls. In girls, there is a fall in estradiol levels in the first week of life and then a gradual minimal rise that continues for one to two years. In boys, testosterone levels rapidly decrease in the first week of life and then increase to pubertal levels for two to four months before declining.

Childhood

The period between infancy and puberty are marked by very low levels of gonadotropins and gonadal steroids. Even in children without functioning gonads (Turner's Syndrome, XO gonadal dysgenesis), the gonadotropins remain low suggesting a profound suppression of the hypothalamic GNRH center. Classic experiments in the rhesus monkey by Nobil (for which the Nobel Prize in medicine was awarded) reveal that the administration of pulsatile GNRH to the prepubertal monkey can initiate puberty.

Errors in Suppression-Precocious Puberty

The finding that the administration of pulsatile GNRH can initiate puberty and experimentally induced lesions in the anterior hypothalamus in animals and can cause precocious puberty suggests that there is an active "off" center that suppresses the pulsatile release of GNRH. Accidents in nature in humans (hypothalamic tumors, hydrocephalus, epilepsy) can lead to precocious puberty in boys and girls. To date, no specific locus of suppression, which is destroyed by tumors or turned "off" at puberty, has been found in humans.

Normal Puberty

Human puberty is defined as the transition between the juvenile state and the mature reproductive state when secondary sex characteristics develop and fertility is achieved. It is composed of the relatively synchronous processes of adrenarche and gonadarche. Adrenarche occurs usually one to two years before gonadarche and is independent of gonadarche. Children without functioning gonads will achieve adrenarche. Puberty includes the adolescent growth spurt, growth of pubic and axillary hair in males and females, and specific secondary sex characteristics for males and females.

The age of puberty has been decreasing over the past several hundred years of written documentation in Europe and the United States. Although the age of male puberty is not as well documented as females, suggestions from Northern European village records suggest that the age of menarche may have declined from as late as 18 to the current 12.2 years. There are clear differences in racial norms of puberty with African-Americans and Latinos achieving puberty at a slightly earlier age on average than European-Americans.

Females

The earliest manifestation of puberty in females is adrenarche. The rise in serum DHEA and DHEAS may have no clinical signs or symptoms; therefore, the first sign of puberty in females is usually defined as the initiation of breast buds. The breast develops under unopposed low dose estrogen stimulation for about two years before the first menses. During this time, pubic and axillary hair become evident and there is a growth spurt. Weight gain occurs with increase in height, but there is also an increase in body fat as distributed in the breasts, mons pubis, hips and thighs. The vagina lengthens and becomes rugated, and the labia majora and minora become thickened and rugated.
The first menses occurs about two years after breast bud development and is usually the result of fluctuating estrogens associated with follicle development without ovulation. Ovulation usually occurs within six months from the first episode of vaginal bleeding. The breast and pubic hair development as well as vertical growth and fat deposition continue for several years after the first menses.

Males

As in females, puberty begins with adrenarche that also has limited clinical manifestations in boys. The first clinical manifestation is testicular enlargement, which begins at a mean age of 11.6 and is followed in the next two years by pubic hair. Adult size and shape of the penis and scrotum is achieved between ages 12 and 17 with an average of about 15 years of age, and pubic hair completes development at about the same time.

The testosterone effect on the vocal cords leads to the beginnings of voice changing at an average age of 13, accompanied by the onset of spermatogenesis. The growth spurt continues with 45 % of the adult skeletal mass acquired between age 11 and age 18. Prior to puberty, males and females have similar muscle mass; but by the end of puberty, the average male has more muscle mass than the average female.

The emotional responses to the changes in gonadal steroid are poorly understood, although all families and societies describe a marked change in pubertal children with respect to their relationships with their parents, peers and members of the opposite gender. Violent events by males increase dramatically in adolescence, but whether this is a direct effect of gonadal steroids on behavior or a function of the individual adolescent's character and societal roles is not clear.

Errors in Puberty (Delayed Puberty)

Delayed puberty may be due to dysfunction of the hypothalamic/pituitary axis, end organ failure, or may be idiopathic. Constitutional delay of puberty may be due to chronic severe medical illness, weight loss or malnourishment, or physical stress (including chronic strenuous exercise).

Adrenarche usually occurs, but gonadarche does not follow. Delayed puberty may also be due to pituitary or hypothalamic tumors, pituitary failure, or congenital absence of GNRH neurons.

Gonadal failure in boys or girls may be due to chromosomal anomalies (Turner's syndrome), exposure to high dose chemotherapy or radiation to the pelvis in childhood, autoimmune or idiopathic. Adrenarche also still occurs (except in those children with pituitary and subsequent adrenal failure), but development of secondary sex characteristics does not follow. An evaluation of delayed puberty should be evaluated in girls who have no evidence of breast development by age 14 and in boys who have no evidence of genital growth by age 15.

The Normal Menstrual Cycle

Overview

One can analyze the menstrual cycle from many different points of view. The lay person is primarily aware of episodic uterine bleeding, the more or less regular interval between the bleeding episodes, and the interruption of the cycles by pregnancy. The hypothalamus and the pituitary, however, orchestrate a month-long interaction of the hypothalamic-releasing factors, pituitary gonadotropins, and steroid hormones. In the ovary, the morphologic and endocrine events of dominant follicle maturation and ovulation contrast sharply with the more sedate background of relentless early follicle development and
subsequent atresia (only one follicle ovulates out of every 999 which initiate development). Meanwhile, the endometrium sees and responds to the cyclic and sequential appearances of estradiol and progesterone. The biochemist measures the concentrations of the relevant hormones in plasma throughout the cycle and wonders how these circulating hormones reflect or cause the key events in the menstrual cycle. Thus, the view that a person, or an organ, has of the menstrual cycle is highly relative to the position from which it is observed.

Interaction of Hypothalamus, Pituitary, and Ovary

Circulating concentrations of sex steroids and gonadotropins throughout the menstrual cycle are depicted in Figure 1. It is logical to begin an analysis of the hormonal interactions with the observation that as the corpus-luteum involutes after a cycle in which conception has not occurred, pituitary FSH release is increased in response to declining estrogen and progesterone concentration. The resulting rise in circulating FSH stimulates follicle growth and induces activity of the aromatase enzyme system necessary for estradiol synthesis. This process of recruiting a cohort of follicles from among which one will typically become dominant takes place by about the fifth day of the average menstrual cycle. More intense gonadotropin stimulation before this time in the cycle usually leads to multiple follicle maturations such as the use of gonadotropins for the treatment of infertility and in-vitro fertilization.

In response to FSH stimulation, the responsive follicles secrete estradiol, which feeds back to suppression FSH release from the pituitary. As depicted in Figure 1, the estradiol concentration continues to rise, ultimately in exponential fashion, throughout the follicular phase of the menstrual cycle despite the declining levels of FSH. The explanation of this phenomenon lies within the micro environment of the ovarian follicle. By the last few days before ovulation, virtually all of the ovarian estradiol secreted is produced by the ovary, and primarily by the follicle destined to ovulate. The surge of estradiol secretion at this time is responsible for the mid-cycle surge of LH, a positive feedback of estradiol. In women, the amount of estradiol necessary to produce a positive feedback effect on LH release is a concentration of 200 pg/ml or more sustained for about 50 hours. Long-term high concentrations of estrogens lead to pituitary suppression (as with oral contraceptive pills). Ovulation occurs about 29 to 39 hours after the LH surge begins.

After ovulation, the corpus luteum secretes progesterone at the rate of about 25 mg/day, yielding serum concentrations of the hormone typically between 5 and 25 ng/ml. This rate of steroid production by the early corpus luteum is roughly equal to the entire steroid output of both adrenal glands. In addition, the corpus luteum also secretes estradiol and 17-hydroxyprogesterone, an intermediate metabolite between progesterone and estrogen. After rupture and release of the ovum, capillaries penetrate the granulosa layer, enabling the delivery of circulating cholesterol, the necessary substrate for progesterone biosynthesis. In the face of these levels of sex steroid secretion, FSH concentration declines even further, whereas LH secretion levels plateau and is important in stimulation of the corpus luteum. If conception does not occur, the potent LH-surrogate, hCG, does not arrive on the scene to sustain corpus luteum function. Through sustained intra-ovarian processes of programmed cell death, the corpus luteum involutes 12 to 14 days after ovulation. Serum sex steroid concentrations fall, and menstruation ensues.

Endometrial Response During the Menstrual Cycle

Estradiol is clearly a mitogen in the endometrium. At histologic analysis of endometrial tissue, glandular mitoses are typically seen. An increased risk of endometriosis of the endometrium is associated with exposure over a period of many years to significant amounts of estrogen, either ingested orally, administered parenterally, or formed endogenously, typically by extraglandular aromatization of circulating androgens. This stimulation, without the naturally occurring progesterone from ovulation, or
the administration of progestin, may lead to a hyperplastic endometrium and potentially, to cancer. Mitoses are almost never seen in endometrial specimens during the postovulatory phase of the menstrual cycle, and the incidence of adenocarcinoma of the endometrium in premenopausal women with normal ovulatory function is nearly zero. This also explains the protective effect of oral contraceptives against endometrial cancer, as these medications always include a progestin.

Falling progesterone in the secretory endometrium leads to the local production of prostaglandin by the decidua (the part of the endometrium which is sloughed each month). Prostaglandin causes vasospasm of the spiral arterioles, and subsequent ischemia and sloughing of the endometrium is what patients experience as a "periods." The uterine cramping associated with the normal ovulatory cycle is caused by this prostaglandin's action and explains the effectiveness of prostaglandin inhibitors (aspirin or ibuprofen) in the treatment of dysmenorrhea.

![Graph of hormone levels during the menstrual cycle]

Figure 1: Sex steroid and gonadotropin concentration during the menstrual cycle.
The End of Reproductive Life in Women

Perimenopause

The reliability of ovarian function, both hormonally and reproductively, peaks in the mid-to-late twenties. Beginning in the early thirties, there is epidemiologic evidence of a decline in fertility. By the mid-thirties, there are subtle changes in the levels of FSH in the early follicular phase that become more marked in the forties. These changes may not be reflected in clearly noticeable changes in the experience of an individual woman's menstrual cycle. As the mid forties arrive, there may be a shortening of the length of the menstrual cycle that is a reflection of a declining pool of oocytes, declining inhibin, rising FSH and earlier efforts at recruitment and ovulation of the dominant follicle. The nature of these changes as perceived by an individual woman will be very different from person to person.

The perimenopause is defined as that period around the menopause that is marked by unpredictable ovarian function and menstrual irregularity. Epidemiologic studies of normal women suggest that this is a period of about four years around the menopause although the variation from woman to woman is large. This time is marked by unpredictable ovulation and periods of both higher and lower than usual estrogen levels. Uterine bleeding may be more or less than "usual" in flow and the timing of uterine bleeding is also unpredictable.

There are numerous physical and psychological phenomena attributed to this time of reproductive life (mood swings, vasomotor flushes, sleep disturbances, headaches, memory problems, decreased libido, urinary incontinence). It is not clear which are related to fluctuations of ovarian function, which are related to aging, and which are psycho-social responses to mid-life which may vary from person to person and culture to culture.
Menopause

The menopause is the retrospective diagnosis of the "final" spontaneous menstrual period. Usually a woman in her fifties who has not had a period for over a year may look back and note that her "menopause" was on a specific date of her last spontaneous period. The average age of menopause in American women is 51. Various inherited and environmental factors influence the age of menopause. Cigarette smoking, living at high altitude, exposure to some chemotherapeutic agents, and hysterectomy tend to slightly lower the age of menopause or final cessation of ovulation.

Climacteric

The climacteric is a term used for the transitional period including the perimenopause and the several years after the menopause. There are specific symptoms that some women may experience which are directly attributable to estrogen withdrawal (vasomotor flushes, urogenital atrophy), and there are some long-term aging and disease processes which are worsened by estrogen withdrawal (osteoporosis, coronary artery disease). There are number of other symptoms of aging which may be worsened by estrogen withdrawal (arthritis symptoms, cognitive function) but the evidence is not so clear.

The postmenopausal ovary is still capable of producing substantial amounts of weak androgens (ovarian stroma stimulated by menopausal levels of LH) that are peripherally converted to estrogens.

Issues in Hormone “Replacement”

The eventual cessation of ovulation is a "normal" event in human development. Until the last several hundred years, human life span was usually less than 50 years of age. The existence of a population of women who predictably lived well beyond the age of reproduction is new in human history. Through epidemiologic studies in aging women, many of whom took estrogen hormones for the treatment of vasomotor flushes, it was noted that long-term estrogen users had a decreased incidence of complications of osteoporosis and coronary artery disease. The health benefits and risks of estrogen therapy after menopause have been continuously evaluated over the past 35 years, and this therapy is now being subjected to prospective randomized trials. Recent prospective randomized trials of initiating continuous estrogen and progestin in older postmenopausal women did not show a health benefit with respect to protection against coronary artery disease, demonstrated a very small increase in the incidence of breast cancer and thromboembolic disease, and showed a decrease in osteoporotic fractures and colon cancer in women who took estrogen/progestin compared to placebo.

Observations from women who had a uterus and took only estrogen after menopause revealed an increased risk of uterine cancer. Unopposed estrogen stimulation of the uterus, whether due to endogenous estrogens or estrogen therapy, causes endometrial hyperplasia and potentially adenocarcinoma of the uterus. The intermittent addition of progestational agents for 12 days each month causing endometrial shedding eliminates this increased risk. For older women, the thought of monthly periods is unattractive and is one of the major reasons for lack of compliance in post- menopausal hormone therapy. Another concern is the possibility of a small increase in the risk of breast cancer in long-term estrogen users. Exogenous estrogens for the menopause may also carry a very small increased risk of deep venous thrombosis and gallstone formation.

Formulations for estrogens and progestins and combinations of both will change dramatically in the years to come as clinical research develops methods and formulations which protect the heart and bone but which do not stimulate the endometrium or breast (Selective Estrogen Receptor Modulators).
Male Climacteric - Does It Exist?

The search for a physiologic event in men that would correlate to the menopause in women has been largely unsuccessful. The "male menopause" as a definable gonadal event does not exist. Although the secretion of testosterone gradually declines with advanced age (the rate after 40 about 1% per year) is not enough to account for any decrease in libido or erectile function. Rather, the problems associated with loss of desire or erectile dysfunction are related to disease states or specific changes related to aging and not testosterone levels, themselves. The concept of a gradual decline in adrenal androgenic steroids (DHEA and DHEAS) which begins in the mid to late 20's and may lead to some decrease in physical vigor and musculoskeletal flexibility has recently received a great deal of press coverage. These hormones are readily available at most super-markets and health food stores without a prescription. As DHEAS levels in men decrease by 50% from 20 years of age to 50 years of age, there is a great deal of interest in these hormones as a potential "fountain of youth" for men. Limited prospective randomized studies suggest that the administration of DHEAS in middle-aged men does increase lean body mass.

With an aging population and the possibility of a generation of physically incapacitated elderly men and women, the search for anabolic agents that will maintain musculoskeletal strength has become more intense. Several studies on the administration of 'growth hormone' in elderly men suggest that it may increase lean body mass and strength in older men.

In numerous cross-cultural studies of men and women, there does not appear to be a well-defined entity called the "mid-life crisis." In both men and women, there is no well-defined increase in major depression or major affective disorders in mid-life. At the time of menopause women do have more concerns about health and aging than do men of similar age. However, the concepts of “involutional melancholia”, “empty nest syndrome”, and “mid-life crisis” do not exist as normative events in the life cycle of men and women.

Summary

1. Puberty is the coordinated sequence of biochemical and physiologic events including adrenarche and gonadarche that result in the growth spurt of adolescence, development of secondary sex characteristics, and reproductive capacity.

2. The CNS activation of puberty may occur prematurely (before the age of 8 in girls or 9 in boys) or may be delayed (age 14 in girls and 15 in boys), often indicating underlying medical disease.

3. The cessation of predictable ovarian function occurs over several years. The menopause is defined as the last spontaneous menstrual period.

4. Estrogen therapy significantly decreases hot flushes and vaginal atrophy and may substantially decrease the risk of postmenopausal osteoporotic fractures. Menopausal estrogen therapy for more than 5 years in women over 50 has been associated with a small increase in the detection of breast cancer.

5. There is no clear rapid decline in gonadal function in men as there is in women, although there is a dramatic decline in adrenal androgens from their peak after puberty to middle age. Whether this is reflected in decreased function is unclear.
Bibliography and Suggested Reading


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FERTILIZATION, EARLY PREGNANCY AND ITS DISORDERS

Harry H. Hataseka, M.D.

Objectives
The student should be able to:

1. Understand the process of ovulation, fertilization and implantation.
2. List the presumptive, probable and positive signs of pregnancy.
3. Understand the basis of pregnancy tests and their limitations.

Ovulation

The ovulation process is important if subsequent fertilization is to take place. This is an exquisitely timed phenomenon dependent on a host of hormonal interactions involving a variety of endocrine glands. Tubal function must also be adequate or the ovum will not be picked up by the fallopian tube to be fertilized within the ampulla.

Fertilization

Following ovulation, the ovum with its cumulus oophorus cells are picked up by the fimbria of the fallopian tube. The ovum has now formed the first polar body. It remains in the ampulla portion of the tube and is viable for about 18 to 24 hours. If fertilization does not occur, the ovum disintegrates and is destroyed by the tube. Sperm will remain viable in the female reproductive tract for about 48 hours, although this can be quite variable. Sperm present in the ampulla meet the cumulus oophorus mass and penetrate by chemical and mechanical means to reach the zona pellucida. One sperm penetrates the zona pellucida, the second polar body is formed, and the nuclear material of the sperm enters the vitelline membrane. The diploid chromosome number is re-established, and mitotic cell division can now occur.

Implantation

After fertilization occurs, the fertilized egg remains in the fallopian tube for about 72 hours. During this time there are several cellular division, but the size of the fertilized ovum does not increase. Around 72 hours the zona pellucida fragments and falls away. The pre-implantation embryo enters the uterine cavity for 60 to 72 more hours, and the central cavity begins to form. A definite cell mass is formed on one side of the blastocyst by the time implantation occurs. The trophoblast cells burrow into the endometrial stroma to form syncytiotrophoblast. Primitive amniotic and chorionic cavities begin to form, and a germ disk is recognizable soon after implantation.

Diagnosis of Pregnancy

Most women suspect pregnancy before seeking confirmation. However, it is sometimes necessary to differentiate pregnancy from other causes of uterine enlargement and/or amenorrhea. The signs and symptoms are as follows:

1. Presumptive
   a. Cessation of menses (amenorrhea).
   b. Breast changes.
   c. Vaginal discoloration.
d. Skin pigmentation.
e. Morning sickness.
f. Perception of fetal movements (quickening).
g. Urinary frequency. h. Fatigue.

2. Probable
   a. Abdominal enlargement.
   b. Uterine and cervical changes (shape, size, consistency).
   c. Intermittent uterine contractions.
   d. Ballottement of fetus.
   e. Palpation of fetal parts.
   f. Positive hormonal (hCG) tests.

3. Positive
   a. Fetal heart tones heard or recorded.
   b. Fetal movements perceived by examiner.
   c. Fetus identified ultrasonically or radiologically.

The diagnosis is substantiated by the appearance of softening of the cervix on pelvic examination (Goodell's sign), a purple hue of the vagina and cervix (Chadwick's sign) and compressibility and softening of the isthmus (Hegar's sign) by six to eight weeks' gestation. Abdominal signs of pregnancy appear somewhat later. From 14 weeks, enlargement of the uterus is palpable abdominally. Fetal movement is felt by 18 to 20 weeks (quickening), and fetal heart tones are heard with the fetoscope slightly later. With the doppler, fetal life can be confirmed much earlier (9 to 12 weeks) than with conventional auscultation methods.

Pregnancy Tests

The biochemical test for pregnancy has evolved from dependence on laboratory animals to rapid accurate assays of human chorionic gonadotropin (hCG) produced by the syncytiotrophoblast.

Pregnancy tests generally available currently are enzyme immunoassays (E.I.A.) utilizing monoclonal antibodies specific for hCG, thus avoiding false positive reactions with luteinizing hormone. Serum or urine may be tested, and both cost about the same and can be run in about ten minutes. It is sensitive to about 25 mIU/mL, making it reliable soon after implantation which occurs seven or eight days after ovulation. At approximately the time a woman expects her menses to begin, her hCG concentration will be about 100 mIU/mL if she is pregnant. Therefore commercial urine home pregnancy tests are generally positive by that time. Home pregnancy tests are considered qualitative (yes or no) tests as opposed to quantitative tests.

Serum radioimmunoassay beta subunit (RIA-hCG-P) testing measures only beta subunit hCG. It is sensitive to approximately 5 mIU/mL and is particularly useful for diagnosing pregnancy very early. Serial quantitative RIA-hCG-P analyses are helpful in diagnosing ectopic pregnancies, distinguishing viable pregnancies from non-viable ones and for monitoring trophoblastic diseases (such as hydatidiform mole).

Differential Diagnosis

Errors may be caused by uterine fibroids and ovarian cysts which may be confusing by their size. Other sources of diagnostic error are premature menopause, obesity, and other endocrine causes of amenorrhea.
Pseudocyesis (a psychiatric condition where a woman feels and fully believes she is pregnant when she is not) may be accompanied by many of the subjective symptoms and signs of true pregnancy, but the pelvic signs of pregnancy are absent and the laboratory tests are negative. Lastly, ectopic or tubal pregnancy should always be kept in mind in any woman of reproductive age who develops menstrual abnormalities and pelvic pain along with symptoms of pregnancy.

**Spontaneous Abortion**

**Definition:** The natural termination of pregnancy prior to the 20th week of gestation or with fetal weight less than 500 gm.

**Clinical Classification:**

1. Threatened Abortion: Uterine bleeding in early pregnancy, with or without cramping.
2. Inevitable Abortion: Symptoms of threatened abortion plus the physical finding of dilatation of the internal os of the cervix.
3. Incomplete Abortion: Passage of a portion of the products of conception from the uterus.
4. Complete Abortion: Passage (grossly) of all of the products of conception from the uterus.
5. Missed Abortion: Retention of the conceptus in the uterus for a clinically appreciable time after death of the embryo or fetus.
6. Habitual Abortion: The usual criterion is three or more consecutive abortions.

**Incidence:** Clinically recognizable spontaneous abortion occurs in 15% to 20% of pregnancies, the majority occurring in the first three months. It is probable that at least as many abortions occur very early in pregnancy without recognition of the event.

**Causes of Abortion:**

A. Fetal factors (most common).
   1. Developmental anomalies in more than 60% of cases (Hertig).
   2. Chromosome abnormalities (22% in Carr's study).
B. Maternal factors (less common, but more often treatable).
   1. Systemic diseases.
      a. Infections transmitted to the fetus (viral, bacterial, protozoal).
      b. Febrile illness without fetal infection.
      c. Peritonitis secondary to infection or surgery.
      d. Hypertensive vascular disease.
      e. Severe metabolic disorders (diabetes, thyroid dysfunction).
      f. Chronic debilitating disease states.
   2. Inadequate progesterone production (corpus luteum or placenta) is a definite probably infrequent cause.
   3. Immunologic Factors - Women expressing serum Lupus anticoagulant and anticardiolipin antibodies in high titers are at increased risk of abortion (antiphospholipid syndrome).
   4. Trauma - a rare factor.
   5. Psychosomatic - suspected but unproven factor.
   6. Uterine abnormalities.
      a. Malformation, especially septate uterus.
      b. Myoma (submucous).
      c. Intrauterine synechiae (bands).
      d. Incompetent cervix.
A uterine abnormality is particularly suspect with repeated late abortion (second trimester).

Complications of Abortion

A. Hemorrhage - More common with late abortions. Continued heavy bleeding indicates retained tissue (incomplete abortion).
B. Infection (septic abortion) seen most commonly with criminally-induced abortion but may ensue in spontaneous or therapeutic abortion. Septic shock may occur in severe instances.
C. If a missed abortion is retained beyond one month, thromboplastin passage into the maternal circulation may result in a clotting disorder (DIC). This risk is greater in late abortion.

Therapy

A. Threatened Abortion - no specific therapy is rational since the majority of abortions result from failure of normal fetal development and the fetus usually is dead by the time of onset of bleeding. Management is directed toward avoiding the complications of infection or excessive blood loss.

Of all women who present uterine bleeding in early pregnancy, fewer than half proceed to abortion.

B. Inevitable and incomplete abortion - the aim of therapy is prompt evacuation of the uterus to prevent hemorrhage or infection.

1. Intravenous oxytocin infusion.
2. Removal of tissue with sponge forceps and uterine curettage (suction or instrumental).

An exception in the management of "inevitable" abortion is that of cervical incompetence. In this condition painless dilatation of the cervix has occurred (without bleeding) in the mid trimester. In this circumstance, a purse-string suture of the cervix (cerclage) may succeed in retaining the pregnancy.

C. Complete Abortion: No further therapy is required, but the patient must be observed closely for continued bleeding or evidence of infection. These complications most often indicate that not all of the tissue has been passed.

D. Missed Abortion: Most missed abortions will evacuate spontaneously and should then be evaluated for completion of the process. If uterine evacuation is delayed beyond four weeks, intervention to empty the uterus should be considered to prevent a coagulation disorder.

Ectopic Pregnancy

A. Defined: Ectopic pregnancy refers to implantation of the zygote outside the uterus or in an abnormal location within the uterus.
B. Incidence.
   1. Varies widely from study to study.
   2. Probably dependent on population base (Jamaica 1:28).
   3. From 1:64 to 1:350, but generally accepted at 1: 130.
   4. Recently has shown increasing frequency.
C. Mortality.
   1. Felt to be responsible for 10% of maternal deaths.
2. Approximate maternal mortality: 1-2/1,000.

D. Etiology.
1. Chronic PID.
2. Tubal damage (previous surgery, endometriosis).
3. Hormonal factors slowing ovum transport.
4. Menstrual bleeding (unsuppressed).
5. Tubal atony or spasm.
6. Blighted conceptus - features of blighted ovum are seen twice as often in tubal pregnancies.
7. Developmental abnormalities of the tube.
8. Extrinsic obstruction.
9. IUD usage.

E. Pathology: "Normal" conceptus but with pathologic site.
1. Uterine changes.
   a. In first two months uterus growth may be comparable to normal pregnancy due to the circulating hormonal changes of early pregnancy.
   b. Decidual changes.
   c. Arias-Stella ("Sturgis-Arias-Stella"): Secondary to hyperstimulation by progesterone and estrogen (occurs in 60%), suggestive of tubal ectopic pregnancy.

2. Pathologic distribution of nidation.
   a. Uterine.
      (1) Cervical - 1.5%
      (2) Diverticular - rare.
      (3) Uterine sacculcation - more rare.
      (4) Intramural.
      (5) Angular.
      (6) Cornual - 2%.
      (7) Rudimentary horn.
   b. Tubal - 95%.
      (1) Interstitial.
      (2) Isthmic.
      (3) Ampullar (most common).
      (4) Infundibular.
      (5) Fimbrial.
   c. Interligamentous.
   d. Ovarian - 1:9,000 to 1:60,000.
   e. Abdominal - 1: 15,000 live births.

F. Diagnosis.
1. Clinical history will give greatest amount of useful information.
   a. Clinical history - negative history of amenorrhea in 25%.
   b. Pain - most common symptom - more than 90%.
   c. Syncope - -33%

2. Physical exam.
   a. Signs of hypovolemia - 3.3 % heart rate - blood pressure.
   b. Pelvic mass - 50%.
   c. Pelvic pain - especially with movement of cervix.
   d. Temperature.
      (1) May be subnormal with acute blood loss.
      (2) May be elevated when patient stable (2%).
   e. Diaphragmatic irritation - 10%.

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3. Lab data.
   a. CBC with differential.
      (1) Hct - Hbg: almost always low.
      (2) Leukocytosis: 50% greater than 15,000/cu mm.
   b. Pregnancy testing: almost always positive with RIA or EIA tests.
   c. Ultrasonography: A gestational sac should be seen using a transvaginal ultrasound probe when the serum quantitative PhCG exceeds 2,500 mIU/mL (even 1,000 at some centers) in a normal intrauterine gestation. The inability to detect an ectopic pregnancy ultrasonographically DOES NOT rule out the possibility of ectopic pregnancy.

4. Surgical Diagnostic Options.
   a. Cullocentesis: quick and simple with extremely high correlation in ruptured ectopics (90% to 95%).
   b. D & C.
      (1) Only 20% will show decidual response.
      (2) Questionable value.
   c. Laparoscopy: especially if diagnosis is only a suspicion.

G. Differential diagnosis.
   1. Ectopic pregnancy
   2. Pelvic inflammatory disease.
   3. Abortion: threatened or incomplete.
   5. Acute appendicitis.

H. Treatment.
   1. Lab: CBC, ABO-Rh, cross match, electrolytes, UA.
   2. Stabilize patient.
   5. Conservative approach.
      a. Resection.
      b. Expression.
      c. Evacuation.
      d. Linear salpingostomy.
   6. Contralateral tube.
   8. The Rh negative patient.

I. Prognosis
   1. Tubal pregnancy interferes with future reproductive ability in 50% to 60%.
   2. Recurrent tubal pregnancy ranges from 7.7% to 20%.

Fertilization, Early Pregnancy and Its Disorders

Major Take Home Points:
- The number one reason for amenorrhea in a woman of reproductive age is pregnancy.
- The diagnosis of early pregnancy is not always straightforward; clinicians from all disciplines must become expert in the methods of diagnosing pregnancy.
- The most common disorder of early pregnancy is abortion in all its varied presentations.
- The most life-threatening disorder of early pregnancy is ectopic pregnancy. High suspicion for ectopic pregnancy should always be maintained for gynecologic patients, and prompt diagnosis and therapy should be reflexive.
Objectives

1. To understand the release and control of prolactin secretion and its actions both physiologically and pathologically.
2. To understand the anatomy, differentiation, and development of the breast and the actions of various endocrine factors resulting in lactation.
3. To appreciate the workup and treatment in a case of hyperprolactinemia and its treatment.
4. To recognize the potential CNS abnormalities that may result in hyperprolactinemia.

Expectations

I would expect all students to know the following definitions and take-home points. I have included additional materials and references for those who desire greater than a superficial knowledge on the subject. The test will come from the definitions and take home points.

Definitions

Prolactin: A product of the anterior pituitary 199 amino acids with glycosylated and nonglycosylated forms. It possesses a myriad of effects with the most noticeable being lactation. Its secretion is inhibited by prolactin-inhibiting factor.

Prolactin-inhibiting factor (PIF): Inhibits the release of prolactin and is purported to be dopamine that is secreted by the tuberoinfundibular neurons.

Lactation: The production of milk through the actions of prolactin on breast tissue to create polyamines, casein, lactose and phospholipids.

Galactorrhea: The secretion of milky fluid from the breast at times other than pregnancy.

Micro/macroadenoma of the pituitary secreting prolactin: Small tumors usually located in the lateral aspects of the pituitary that are surrounded by a pseudocapsule which contains secretory granules of prolactin. Microadenomas are < 1 cm; macroadenomas are ≥ 1 cm. Hypotheses for their origin include reduced pituitary dopamine concentrations and/or a vascular isolation of the adenoma cells.

Take-Home Points

Normal mammary development depends on a critical interplay of appropriate fat deposition, vascular supply, and hormone interactions. Estrogen stimulation of ductal development and progesterone induced development of alveolar growth and the modulating activities of estrogen, progesterone, growth hormone, insulin, cortisol, thyroid and parathyroid hormone with prolactin result in a functional gland. Dopamine, which is secreted by the tuberoinfundibular dopaminergic neurons into the portal hypophyseal vessels, is the primary prolactin-inhibiting factor. Lactation postpartum occurs when the inhibitory activity of progesterone is reduced through its more rapid clearance compared to prolactin.

Progesterone antagonizes the alveolar cell prolactin receptor and inhibits lactation by:

Inhibiting the upregulation of the prolactin receptor
Reducing estrogen binding
Competing for binding at the glucocorticoid receptor.

Galactorrhea occurs with:
- Stimulation of the afferent limb of the neuroendocrine arc
- Decreased dopamine release or transport or binding
- Autonomous prolactin secretion
- Hypothyroidism
- Chronic renal failure

Hyperprolactinemia may cause anovulation through:
- A reduction in granulosa cell number and FSH binding
- Inhibition of granulosa cell 17P estradiol production by interfering with FSH action
- Inadequate luteinization and reduced progesterone
- The suppressive effects of prolactin on GnRH pulsatile release.

The combination of amenorrhea and galactorrhea is associated with hyperprolactinemia in two-thirds of cases. In over one-third of women with hyperprolactinemia, a radiologic abnormality consistent with an adenoma is found. A pituitary microadenoma (< 1 cm) or hyperplasia is the cause of hyperprolactinemia in most patients with hyperprolactinemia. Macroadenomas are larger than 1 cm. Well over 90% of untreated microprolactinomas do not enlarge over a 4-6 year period of time. Both microadenomas and macroadenomas (>1 cm) are monoclonal in origin. MRI is the optimal radiologic technique to evaluate the sella/suprasellar region. Most patients with hyperprolactinemia due to a microadenoma can be reassured that they have a relatively benign condition (pituitary microadenoma or release of pituitary stem cell growth inhibition through activating or loss of function mutations in the pituitary lactotroph) that requires only periodic monitoring. However, it is critical for the physician to exercise vigilance and consider the evaluation of other potential etiologies, particularly sellar/suprasellar tumors. A TSH level should be measured in all cases of hyperprolactinemia. Bromocriptine is the mainstay of therapy for microadenomas and macroadenomas and in hyperprolactinemia without evidence of an adenoma. While bromocriptine is the best initial and potentially long-term treatment option for macroadenomas, transsphenoidal surgery may be required if the adenoma is not responsive to medical management. Breastfeeding is not contraindicated in the presence of microadenomas or macroadenomas.

Chapter on Prolactin Disorders-Novack’s Gynecology 2003 by C. Matthew Peterson, M.D.
NOT REQUIRED – UNDERLINED TEXT CONSIDERED SIGNIFICANT

Prolactin

Prolactin was first identified as a product of the anterior pituitary in 1933 (168). Since that time, it has been found in nearly every vertebrate species. The specific activities of human prolactin (hPRL) have been further defined by the separation of its activity from growth hormone (169) and subsequently by the development of radioimmunoassays (170–172). Although the initiation and maintenance of lactation is the primary function of prolactin, many studies have documented a significant role for prolactin activity both within and beyond the reproductive system.

Prolactin Secretion
There are 199 amino acids within hPRL with a molecular weight of 23,000 daltons (Fig. 25.4). Although human growth hormone and placental lactogen have significant lactogenic activity, they have only a 16% and 13% amino acid sequence homology with prolactin, respectively.

In the basal state, three forms are released: a monomer, a dimer, and multimeric species called “little,” “big,” and “big-big” PRL, respectively (173-175). The two larger species can be degraded to the monomeric form by reducing disulfide bonds (176). The proportions of each of these prolactin species vary with physiologic, pathologic, and hormonal stimulation (176-179). The heterogeneity of secreted forms remains an active area of research. Overall, these studies indicate that “little” prolactin (molecular weight [MW] 23,000) constitutes more than 50% of all combined prolactin production (175,178,179) and is most responsive to extrapituitary stimulation or suppression. The bioactivity and immunoreactivity of “little” prolactin is influenced by glycosylation (180–183). It appears that the glycosylated form is the predominant species secreted, but the most potent biological form appears to be the 23,000 MW nonglycosylated form of prolactin (182). To some degree, the physical heterogeneity of prolactin may explain the biologic heterogeneity of this hormone, but it further complicates the physiologic evaluation of prolactin’s myriad effects.

In contrast to other anterior pituitary hormones, which are controlled by hypothalamic-releasing factors, prolactin secretion is primarily under inhibitory control mediated by dopamine. Multiple lines of evidence suggest that dopamine, which is secreted by the tuberoinfundibular dopaminergic neurons into the portal hypophyseal vessels, is the primary prolactin-inhibiting factor. Dopamine receptors have been found on pituitary lactotrophs (184), and treatment with dopamine or dopamine agonists suppresses prolactin
secretion (185-190). The dopamine antagonist, metaclopramide, abolishes the pulsatility of prolactin release and increases serum prolactin levels (186,187,191). Interference with dopamine release from the hypothalamus to the pituitary routinely raises serum prolactin levels. Gamma-aminobutyric acid (GABA) and other neuropeptides may also function as prolactin-inhibiting factors (Table 25.6) (192–195). Several hypothalamic polypeptides that increase prolactin-releasing activity are also listed (Table 25.6).
### Table 25.6. Chemical Factors Modulating Prolactin Release and Conditions That Result in Hyperprolactinemia

**Inhibitory factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td></td>
</tr>
<tr>
<td>α-Aminobutyric acid</td>
<td></td>
</tr>
<tr>
<td>Histidyl-proline diketopiperazine</td>
<td></td>
</tr>
<tr>
<td>Pyroglutamic acid</td>
<td></td>
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<tr>
<td>Somatostatin</td>
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</table>

**Stimulatory factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ß-Endorphin</td>
<td></td>
</tr>
<tr>
<td>17ß-Estradiol</td>
<td></td>
</tr>
<tr>
<td>Enkephalins</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone</td>
<td></td>
</tr>
<tr>
<td>Vasoactive intestinal peptide</td>
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</tbody>
</table>

**Physiologic conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia</td>
<td></td>
</tr>
<tr>
<td>Empty sella syndrome</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Intercourse</td>
<td>Major surgery and disorders of chest wall (burns, herpes, chest percussion)</td>
</tr>
<tr>
<td>Newborns</td>
<td></td>
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<tr>
<td>Nipple stimulation</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Postpartum (nonnursing: days 1-7; nursing: with suckling)</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td></td>
</tr>
<tr>
<td>Postpartum</td>
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</tbody>
</table>

**Hypothalamic conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachnoid cyst</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td></td>
</tr>
<tr>
<td>Cystic glioma</td>
<td></td>
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<tr>
<td>Cysticercosis</td>
<td></td>
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<tr>
<td>Dermoid cyst</td>
<td></td>
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<tr>
<td>Epidermoid cyst</td>
<td></td>
</tr>
<tr>
<td>Histocytosis</td>
<td></td>
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<tr>
<td>Neutrotuberculosis</td>
<td></td>
</tr>
<tr>
<td>Pineal tumors</td>
<td></td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Suprasellar cysts</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
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</tbody>
</table>

**Pituitary conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Histocytosis</td>
<td></td>
</tr>
<tr>
<td>Lymphoid hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Metastatic tumors (especially of the lungs and breast)</td>
<td></td>
</tr>
<tr>
<td>Multiple endocrine neoplasia</td>
<td></td>
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<tr>
<td>Nelson’s syndrome</td>
<td></td>
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<tr>
<td>Pituitary adenoma (microadenoma or macroadenoma)</td>
<td></td>
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<tr>
<td>Post-oral contraception</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone administration</td>
<td></td>
</tr>
<tr>
<td>Trauma to stalk</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
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</tbody>
</table>

**Metabolic dysfunction**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic production (hypernephroma, bronchogenic sarcoma)</td>
<td></td>
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<tr>
<td>Hepatic cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td>Starvation refeeding</td>
<td></td>
</tr>
</tbody>
</table>

**Drug conditions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ß-Methyldopa</td>
<td>Amoxapine, imipramine, amitriptyline</td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td>Dopamine antagonists (phenoxybenzamine, thioxanthenes, butyrophenone, diphenylbutylpiperidine, dibenzoxazepine, dihydroindolone, procainamide, metaclopromide)</td>
<td></td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>Reserpine</td>
</tr>
<tr>
<td>Sulpiride</td>
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</tbody>
</table>
Hyperprolactinemia

When evaluating prolactin levels, “physiologic” alterations or conditions may result in transient as well as persistent elevations in prolactin levels. Drug-related and physiologic conditions resulting in hyperprolactinemia do not always require intervention.

Evaluation

Plasma levels of immunoreactive prolactin are 5–27 ng/ml throughout the normal menstrual cycle. Samples should not be drawn soon after the patient awakes or after procedures. Prolactin is secreted in a pulsatile fashion with a pulse frequency ranging from about 14 pulses per 24 hours in the late follicular phase to about nine pulses per 24 hours in the late luteal phase. There is also a diurnal variation with the lowest levels occurring in the midmorning. Levels rise one hour after the onset of sleep and continue to rise until peak values are reached between 5:00 and 7:00 AM (196,197). The pulse amplitude of prolactin appears to increase from early to late follicular and luteal phases (198–200). Because of the variability of secretion and inherent limitations of radioimmunoassay, an elevated level should always be rechecked. This is preferably drawn midmorning and not after stress, venipuncture, breast stimulation, or physical examination, which increases prolactin levels.

Prolactin and TSH determinations are basic evaluations in infertile women. Infertile men with hypogonadism also should be tested. Likewise, prolactin levels should be measured in the evaluation of amenorrhea, galactorrhea, amenorrhea with galactorrhea, hirsutism with amenorrhea, anovulatory bleeding, and delayed puberty (Fig. 25.5).
Hyperprolactinemia
Review history, drug use, and physiologic etiologies

Repeat prolactin level

Abnormal
Normal

TSH level

Elevated
Normal

Coned-down view may be appropriate in certain situations. In cases of clear drug-induced hyperprolactinemia, a scan may not be required.

Repeat TSH

MRI or CT scan

Elevated TSH and hypothyroid by thyroid function tests

Treat hypothyroidism

• Repeat prolactin and TSH in 6 to 12 weeks
• Document resolution

• Amenorrhea
• (+) progestin challenge

ERT OCPs

Microadenoma
• Decreased prolactin
• Absent CNS signs or symptoms

Macroadenoma
• Prolactin levels and CNS symptoms return to normal

Micro or Macroadenoma
• Prolactin remains elevated or recurs
• CNS symptoms persist or recur

No further scans required unless CNS signs or symptoms develop or prolactin level increases

Initially scan at six months and 1-4 years thereafter

Neurosurgery

Microadenoma
Discuss risks with pregnancy

Macroadenoma
• Formal visual field test
• Neurosurgical consultation
• Discuss risks with pregnancy

Medical management

Bromocriptine
• Insure periods
• Resume or replace

Regular periods or (+) progestin challenge every 3 months

Expectant management
• Repeat MRI in 6-12 months
Physical Signs. Amenorrhea without galactorrhea is associated with hyperprolactinemia in approximately 15% of women (201-203). The cessation of normal ovulatory processes attributed to elevated prolactin levels may be related to the following gonadal and hypothalamic-pituitary effects: reduction in granulosa cell number and FSH binding (204); inhibition of granulosa cell 17-β estradiol production by interfering with FSH action (204-206); inadequate luteinization and reduced progesterone (207-209); and the suppressive effects of prolactin on GnRH pulsatile release, which may mediate most of the anovulatory effects (210-222).

Although isolated galactorrhea is commonly considered indicative of hyperprolactinemia, prolactin levels are within the normal range in nearly 50% of such patients (223–225) (Fig. 25.5). In these cases, an earlier transient episode of hyperprolactinemia may have existed, which triggered galactorrhea. This situation is very similar to nursing mothers in whom milk secretion, once established, continues despite normal prolactin levels. Repeat testing is occasionally helpful in detecting hyperprolactinemia. Approximately one-third of women with galactorrhea have normal menses. Conversely, hyperprolactinemia commonly (66%) occurs in the absence of galactorrhea, which may result from inadequate estrogenic or progestational priming of the breast.

In patients with both galactorrhea and amenorrhea (including the syndromes described and named by Forbes, Henneman, Griswold, and Albright, 1951; Argonz and del Castilla, 1953, and Chiari and Frommel, 1985), approximately two-thirds will have hyperprolactinemia; and in that group, approximately one-third will have a pituitary adenoma (226). In anovulatory women, 3–10% with the diagnosis of polycystic ovarian disease are noted to be hyperprolactinemic (227, 228) (Fig. 25.6).
In all cases of delayed puberty, pituitary abnormalities, including craniopharyngiomas and adenomas, must be considered. Additionally, the multiple endocrine neoplasia type 1 syndrome should be considered, particularly in patients with a family history of multiple adenomas (229). Prolactinomas are noted in approximately 20% of patients with multiple endocrine neoplasia.
type 1 (MEN-1). MEN-1 gene is localized to chromosome 11q13 and appears to act as a constitutive tumor suppressor gene. An inactivating mutation results in the tumor development. It is thought that prolactinomas that present in patients with MEN-1 may be more aggressive than sporadic prolactinomas (230). Prolactin and TSH levels should be measured in all patients with delayed puberty.

Once an elevated prolactin level is documented, the gynecologist must be familiar with neuroanatomy as well as imaging techniques and their interpretation (see Chapter 7). Patients can be reassured that hyperprolactinemia usually is associated with a relatively benign condition (pituitary microadenoma or release of pituitary stem cell growth inhibition through activating or loss of function mutations in the pituitary lactotroph) that requires only periodic monitoring. However, it is critical for the physician to exercise vigilance and to consider the evaluation of other potential etiologies, particularly sellar/suprasellar tumors. A TSH level should be measured in all cases of hyperprolactinemia. (Figure 25.5)

**Imaging Techniques**

Prolactin levels in patients with larger microadenomas and macroadenomas are usually higher than 100 ng/ml. However, levels lower than 100 ng/ml may be associated with smaller microadenomas and other suprasellar tumors that may be easily missed on a “coned-down” view of the sella turcica. In patients with a clearly identifiable drug-induced or physiologic etiology for hyperprolactinemia, scanning may not be necessary. MRI imaging of the sella and pituitary gland with gadolinium enhancement appears to provide the best anatomic detail (231) (Fig. 25.7). The cumulative radiation dose from multiple CT scans may cause cataracts, and the coned-down views or tomograms of the sella are very insensitive and likewise expose the patient to radiation. The clinician must keep in mind that even modest elevations of prolactin can be associated with microadenomas or macroadenomas, nonlactotroph pituitary tumors, and other central nervous system abnormalities; and pituitary imaging must be considered (Table 25.7). For patients with hyperprolactinemia who desire future fertility, MRI is indicated to differentiate a pituitary microadenoma from a macroadenoma as well as to identify other potential sellar-suprasellar masses. Although infrequent, when pregnancy-related complications of a pituitary adenoma occur, they occur more frequently with macroadenomas (Table 25.7).

Well over 90% of untreated microprolactinomas do not enlarge over a 4-6 year period of time. For that reason, the argument that medical therapy will prevent a microadenoma from growing is false. While prolactin levels correlate with tumor size, both elevations and reductions in prolactin levels may occur without any change in size. If during follow-up a prolactin level rises significantly or CNS symptoms (headache, visual changes) are noted, repeat scanning may be indicated.
Dopamine was the first of many substances demonstrated to be produced in the arcuate nucleus. Dopamine-releasing neurons innervate the external zone of the median eminence. When released into the hypophyseal portal system, dopamine inhibits prolactin release in the anterior pituitary. Lesions that disrupt dopamine release can result in hyperprolactinemia. Such lesions may arise from the suprasellar area, pituitary gland, and infundibular stalk, as well as from adjacent bone, brain, cranial nerves, dura, leptomeninges, nasopharynx, and vessels. Numerous pathologic entities and physiologic conditions in the

Hypothalamic Disorders

Dopamine was the first of many substances demonstrated to be produced in the arcuate nucleus. Dopamine-releasing neurons innervate the external zone of the median eminence. When released into the hypophyseal portal system, dopamine inhibits prolactin release in the anterior pituitary. Lesions that disrupt dopamine release can result in hyperprolactinemia. Such lesions may arise from the suprasellar area, pituitary gland, and infundibular stalk, as well as from adjacent bone, brain, cranial nerves, dura, leptomeninges, nasopharynx, and vessels. Numerous pathologic entities and physiologic conditions in the
hypothalamic-pituitary region can disrupt dopamine release and cause hyperprolactinemia (Table 25.7).

<table>
<thead>
<tr>
<th>Table 25.7. Sellar and Suprasellar Tumors and Conditions That May Result in Hyperprolactinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
</tr>
<tr>
<td>Aneurysm</td>
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<tr>
<td>Arachnoid cyst</td>
</tr>
<tr>
<td>Cephalocele</td>
</tr>
<tr>
<td>Chloroma (granulocytic sarcoma)</td>
</tr>
<tr>
<td>Colloid cyst</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
</tr>
<tr>
<td>Dermoid</td>
</tr>
<tr>
<td>Ectopic neurohypophysis</td>
</tr>
<tr>
<td>“Empty” sella</td>
</tr>
<tr>
<td>Epidermoid tumor</td>
</tr>
<tr>
<td>Germinoma</td>
</tr>
<tr>
<td>Hamartoma (tuber cinereum/hypothalmus)</td>
</tr>
<tr>
<td>Histiocytosis</td>
</tr>
<tr>
<td>Hyperplasia</td>
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<tr>
<td>Hypophysitis</td>
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</table>

**Pituitary Disorders – Microadenoma**

In over one-third of women with hyperprolactinemia, a radiologic abnormality consistent with a microadenoma is found. Release of pituitary stem cell growth inhibition via activating and/or loss of function mutations result in cell cycle dysregulation and are critical to the development of pituitary microadenomas and macroadenomas. Microadenomas (<1 cm) are monoclonal in origin. Genetic mutations are thought to release stem cell growth inhibition and result in autonomous anterior pituitary hormone production, secretion and cell proliferation. Additional anatomic factors which may contribute to adenoma formation include reduced dopamine concentrations in the hypophyseal portal system, vascular isolation of the tumor and/or both. Recently, the heparin-binding secretory transforming gene (HST) has been noted in a variety of cancers as well as in prolactinomas (232). Patients with microadenomas (<1 cm) can generally be reassured of a benign course (233,234).

Both microadenomas and macroadenomas (>1 cm) are monoclonal in origin. Pituitary prolactinomas or lactotrope adenomas are sparsely or densely granulated histologically. The sparsely granulated lactotrope adenomas have trabecular, papillary or solid patterns. Calcification of these tumors may take the form of a psammoma body or a pituitary stone. The densely granulated lactotrope adenoma is a strongly acidophilic tumor and appears to be more aggressive than the sparsely granulated lactotrope adenoma. The unusual acidophil stem cell adenoma can be associated with hyperprolactinemia with some clinical or biochemical evidence of growth hormone excess.

Microadenomas rarely progress to macroadenomas. Six large series of patients with microadenomas reveal that with no treatment, the risk of progression for microadenoma to a macroadenoma is only
approximately 7% (235). Therapies include expectant, medical, or, rarely, surgical therapy. All affected women should be advised to notify their physician of chronic headaches, visual disturbances (particularly tunnel vision consistent with bitemporal hemianopsia), and extraocular muscle palsies. Formal visual field testing is rarely necessary.

Expectant Management. In women who do not desire fertility, expectant management can be utilized for both microadenomas and hyperprolactinemia without an adenoma if menstrual function remains intact. Hyperprolactinemia-induced estrogen deficiency, rather than prolactin itself, is the major factor in the development of osteopenia (236). Therefore, estrogen replacement or oral contraceptives are indicated for patients with amenorrhea or irregular menses. Patients with drug-induced hyperprolactinemia can also be managed expectantly with attention to the risks of osteoporosis. In the absence of symptoms, repeat imaging for microadenomas may be performed in 12 months to rule out further growth of the microadenoma.

Medical Treatment. Ergot alkaloids are the mainstay of therapy. In 1985, bromocriptine was approved for use in the U.S. to treat hyperprolactinemia caused by a pituitary adenoma. The ergot alkaloids increase dopamine levels, thus decreasing prolactin levels. Bromocriptine decreases prolactin synthesis, DNA synthesis, cell multiplication, and tumor growth. Bromocriptine treatment results in normal prolactinemia or return of ovulatory menses in 80-90% of patients.

Because ergot alkaloids, like bromocriptine, are excreted via the biliary tree, caution is required in the presence of liver disease. The major adverse effects include nausea, headaches, hypotension, dizziness, fatigue and drowsiness, vomiting, headaches, nasal congestion, and constipation. Many patients tolerate the drug on the following regimen: one-half tablet every evening (1.25 mg), one-half tablet morning and evening in the second week (1.25 mg q am and q hs), and an increase of one-half tablet every evening in the third week (1.25 mg q am, 2.5 mg q hs) and every morning in the fourth week (2.5 mg twice a day). The lowest dose that maintains the prolactin level in the normal range is continued. Pharmacokinetic studies show peak serum levels occur three hours after an oral dose with a nadir at seven hours. There is little detectable bromocriptine in the serum by 11-14 hours. Therefore, twice-a-day administration is required. Prolactin levels can be checked soon (6 to 24 hr) after the last dose.

One rare, but notable adverse effect of bromocriptine is a psychotic reaction. Symptoms include auditory hallucinations, delusional ideas and changes in mood that quickly resolve after discontinuation of the drug (237).

Many investigators report no difference in fibrosis, calcification, prolactin immunoreactivity, or the surgical success in patients pretreated with bromocriptine compared to those not receiving bromocriptine (238).

An alternative to oral administration is the vaginal administration of bromocriptine tablets, which is well tolerated (239). Cabergoline, another ergot alkaloid, has a very long half-life and can be given orally once per week. Its long duration of action is attributable to slow elimination of pituitary tumor tissue, high affinity binding to pituitary dopamine receptors, and extensive enterohepatic recirculation.

Cabergoline, which appears to be as effective as bromocriptine in lowering prolactin levels and in reducing tumor size, has substantially fewer adverse effects. Very rare patients experience nausea and vomiting with cabergoline; they may be treated with intravaginal caberoline just as with bromocriptine. Although caberogline appears to be safe during pregnancy; more extensive data regarding the use of
bromocriptine in pregnancy is available and is therefore preferred in pregnant patients.

When bromocriptine or cabergoline cannot be used, other medications such as pergolide or methergoline may be used. In patients with a microadenoma who are receiving bromocriptine therapy, a repeat MRI scan may be performed at 6-12 months after prolactin levels are normal. Normal prolactin levels and resumption of menses should not be considered absolute proof of tumor response to treatment. Further MRI scans should be performed if new symptoms appear.

Discontinuation of bromocriptine therapy after 2-3 years may be attempted because some adenomas undergo hemorrhagic necrosis and cease to function.

**Pituitary Disorders-Macroadenomas**

Macroadenomas are pituitary tumors that are larger than 1 cm in size. Bromocriptine is the best initial and potentially long-term treatment option, but transsphenoidal surgery may be required. Evaluation for pituitary hormone deficiencies may be indicated. Symptoms of macroadenoma enlargement include severe headaches, visual field changes, and, rarely, diabetes insipidus and blindness. After prolactin has reached normal levels following ergot alkaloid treatment, a repeat MRI is indicated within six months to document shrinkage or stabilization of the size of the macroadenoma. This may be performed earlier if new symptoms develop or if there is no improvement in previously noted symptoms. Normalized prolactin levels or resumption of menses should not be taken as absolute proof of tumor response to treatment.

**Medical Treatment.** Macroadenomas treated with bromocriptine routinely show a decrease in prolactin levels and size; nearly one-half show a 50% reduction in size, and another one-fourth show a 33% reduction after six months of bromocriptine therapy. Because tumor regrowth occurs in over 60% of cases after discontinuation of bromocriptine therapy, long-term therapy is the rule.

After stabilization of tumor size is documented, the MRI scan is repeated 6 months later and, if stable, yearly for several years. Serum prolactin levels are measured every 6 months. Because tumors may enlarge despite normalized prolactin values, a reevaluation of symptoms at regular intervals (6 months) is required.

**Surgical Intervention** Tumors that are unresponsive to bromocriptine or that cause persistent visual field loss require surgical intervention. Some neurosurgeons have noted that a short 2-6 week course of preoperative bromocriptine increases the efficacy of surgery in patients with larger adenomas (239). Unfortunately, despite surgical resection, recurrence of hyperprolactinemia and tumor growth are not uncommon. Complications of surgery include cerebral carotid artery injury, diabetes insipidus, meningitis, nasal septal perforation, partial or panhypopituitarism, spinal fluid rhinorrhea, third nerve palsy, and recurrence. Periodic MRI scanning after surgery is indicated, particularly in patients with recurrent hyperprolactinemia.

**Metabolic Dysfunction**

Occasionally, patients with hypothyroidism exhibit hyperprolactinemia with remarkable pituitary enlargement due to thyrotroph hyperplasia. These patients respond to thyroid replacement with reduction in pituitary enlargement and normalization of prolactin levels (240).

Hyperprolactinemia occurs in 20–75% of women with chronic renal failure. Prolactin levels are not normalized through hemodialysis but are normalized after transplantation (241-244). Occasionally,
women with hyperandrogenemia also have hyperprolactinemia. Elevated prolactin levels may alter adrenal function by enhancing the release of adrenal androgens such as DHEAS (245).

**Drug-Induced Hyperprolactinemia**

Numerous drugs interfere with dopamine secretion (Table 25.6). The same principles utilized in the management of pituitary microadenomas or hyperplasia can be applied in these situations. If discontinuation of the drugs is feasible, resolution of hyperprolactinemia is uniformly prompt.

**Use of Estrogen in Hyperprolactinemia**

In rodents, rapid pituitary prolactin-secreting adenoma (prolactinoma) occurs with high-dose estrogen administration (246). However, even conditions associated with high estrogen levels, such as pregnancy, do not cause prolactinomas in humans. Indeed, pregnancy may have a favorable influence on preexisting prolactinomas (247-24). Studies (249-251) and autopsy surveys (228) indicate that estrogen administration is not associated with clinical, biochemical, or radiologic evidence of growth of pituitary microadenomas or the progression of idiopathic hyperprolactinemia to an adenoma status. For these reasons, estrogen replacement or oral contraceptive use for hypoestrogenic hyperprolactinemic patients secondary to microadenoma or hyperplasia is appropriate.

**Monitoring Pituitary Adenomas in Pregnancy**

Prolactin-secreting microadenomas rarely create complications during pregnancy. However, monitoring of patients with serial gross visual field examinations and fundoscopic examination is recommended. If persistent headaches, visual field deficits, or visual or fundoscopic changes occur, MRI scanning is advisable. Because serum prolactin levels are elevated throughout pregnancy, prolactin measurements are of no value.

Although not recommended, bromocriptine use during pregnancy in women with symptomatic (visual field defects, headaches) microadenoma enlargement has resulted in resolution of deficits and symptoms (253-256).

Pregnant women with previous transsphenoidal surgery for microadenomas and/or macroadenomas may be additionally monitored with monthly Goldman perimetry visual field testing. Periodic MRI scanning may be necessary in women with symptoms or visual changes. Bromocriptine has been used on a temporary basis to resolve symptoms and visual field deficits in symptomatic macroadenoma patients to allow completion of pregnancy before initiation of definitive therapy. Breastfeeding is not contraindicated in the presence of microadenomas or macroadenomas (253–256).

**Chapter References – Prolactin Disorders**

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46. Moul PJA, Rees LH, Besser GM. Pulsatile gonadotrophin secretion in hyperprolactinaemic


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NORMAL MATERNAL PHYSIOLOGY: IMPLICATIONS FOR PRENATAL CARE

Objectives

1. List pertinent normal physiologic changes in the maternal cardiovascular, respiratory, renal, hematologic, gastrointestinal, and reproductive systems.
2. Describe the implications for these changes for normal and abnormal pregnancies.
3. List the nutritional requirements for calories, protein, iron, calcium, and folic acid for a normal pregnancy in a healthy gravid woman.
4. Describe the medical evaluation at the first prenatal visit and then subsequent visits for a normal pregnant woman.
5. List at least five routine laboratory tests obtained early in pregnancy and the rationale for each.

Definitions

1. Dilutional anemia of pregnancy: lower hematocrits are seen in pregnancy because the expansion of plasma volume is greater than the increase in red blood cell mass.
2. Hypercoagulable state of pregnancy: increased predilection for pregnant women to have clotting episodes.
3. MSAFP (Maternal serum alpha-fetoprotein): Screening test of maternal blood done in the early second trimester to screen pregnant women for fetal anomalies and chromosomal abnormalities.
4. Estimated delivery date (EDD): the estimated date of delivery based on either dating or ultrasound parameters.
5. Bacterial vaginosis: a bacterial infection of the vagina associated with preterm labor and birth.
7. Rhogam: an antibody preparation of anti-Rh factor given to Rh (-) women to prevent Rh isoimmunization.
8. Neural tube defect (NTD): an abnormality in closure of the neural tube, resulting in a spectrum of anomalies from anencephaly (no cranium or cerebrum) to spina bifida.
10. Small-for-gestational age (SGA): the lower 10% of birthweights.
11. Large-for-gestational age (LGA): the upper 10% of birthweights.
12. Macrosomia: an abnormally large infant (usually > 4000 gm).

I. Introduction
The primary goal of prenatal care is to deliver a healthy term infant without impairing the mother’s health and to identify and optimally treat the high-risk parturient.

II. Pertinent Changes in Normal Maternal Physiology
A. Cardiovascular system
   1. Cardiac (see table 1)
      a. Cardiac output increases about 30-50% (from 4.5 to 6.0 L/min, see figure 1)
      b. Stroke volume increases about 10 to 15%
c. Pulse increases about 15-20 bpm
d. Systolic ejection murmur and S3 gallop is common (about 90% of pregnant women)

2. Blood pressure
   a. Peripheral vascular resistance falls
   b. There is normally a fall in BP during the second trimester (5-10 mmHg systolic, 10-15 mmHg diastolic), and then returns to normal during the third trimester

Pertinence: Many of the effects of the altered cardiovascular system mimic heart failure (edema, gallops, dyspnea, distended neck veins, abnormal cardiac silhouette on CXR, EKG changes).

B. Respiratory system (see figure 2)
   1. Unchanged: respiratory rate, vital capacity, inspiratory reserve volume
   2. Decreased: functional residual capacity (by 20%), expiratory reserve volume (by 20%), residual volume (by 20%), total lung capacity (by 5%)
   3. Increased: inspiratory capacity (by 5%), tidal volume (by 30-40%)

Pertinence: A normal pregnant woman has a compensated respiratory alkalosis and a diminished pulmonary reserve.

C. Renal system
   1. Anatomic: increase in kidney size and weight, ureteral dilatation (Right > left), bladder becomes an intra-abdominal organ
   2. Hemodynamics:
      a. GFR increases 50%, renal plasma flow increases by 75%
      b. Creatinine clearance increases to 150-200 cc/min
   3. Metabolic changes
      a. BUN and serum creatinine decreases by about 25%
      b. Plasma osmolarity decreases about 10 mOsm/kg H2O
      c. Increase in tubular reabsorption of sodium
      d. Marked increase in renin and angiotensin levels, but markedly reduced vascular sensitivity to their hypertensive effects
      e. Increase in glucose excretion

Pertinence: Pregnant women are more prone to pyelonephritis and bladder rupture during abdominal trauma.

D. Hematologic System
   1. Plasma volume and RBC mass (see figure 3)
      a. Plasma volume increases by about 50%
      b. RBC volume increases by about 30%
      c. The result: the "dilutional anemia of pregnancy", such that the mean hemoglobin during pregnancy is about 11.5 g/dl
   2. WBC and platelets
      a. WBC count increases during pregnancy
      b. Platelet count decreases, but stays within normal limits
   3. Coagulation system: pregnancy as a "hypercoagulable state"
      a. Increased levels of fibrinogen, factor VII-X
      b. The placenta produces a plasminogen activator inhibitor

Pertinence: Blood loss is well-tolerated during labor, but maternal vital signs do not change for blood loss of 1500 cc, so vital signs cannot be trusted as an indicator of blood loss. Also, serious thromboembolic disease is more common during pregnancy.

E. Gastrointestinal System
   1. Decreased motility, probably due to influence of progesterone
2. Reduced gastric acid secretion

*Pertinence:* A pregnant woman is considered to have a full stomach even if she has had nothing to eat or drink for several hours. Peptic ulceration is rare during pregnancy.

F. Reproductive System

1. The Uterus (see figure 4)
   a. Weight: increases from 70 gm to 1100 gm
   b. Blood flow: increases to about 750 cc/min, or about 10-15% of cardiac output

*Pertinence:* Laceration of the uterine arteries can result in massive hemorrhage in a short period of time.

2. The Cervix
   a. Increase in water content and vascularity (Hegar's sign)
   b. Increase in cervical mucous secretions

III. Nutritional Considerations in the Normal Pregnancy

A. Weight gain: both weight gain and pre-pregnancy weight are directly related to infant birthweight

1. Average weight gain (no one knows optimal weight gain)
   a. Normal weight for height: about 20 lbs
   b. Underweight women: about 30 lbs
   c. Overweight women: about 16 lbs

2. Average weight gain by organ system
   a. Fetus-7 1/2 lbs
   b. Placenta and amniotic fluid-3 lbs
   c. Blood volume-4 lbs
   d. Breasts-1 to 2 lbs
   e. Maternal fat--4 lbs

B. Daily dietary requirements for common nutrients

1. Calories: increased 15% kcal/day, or you need about 2200 cal/day
2. Protein: an additional 10 to 30 gm/day (about 75 gm/day total)
3. Iron: supplement 30 to 60 mg of elemental iron per day
4. Calcium: 1200 mg needed per day, usually provided by a quart of milk per day (can use 2 Tums per day, each have 600 mg of calcium carbonate)
5. Folate: supplement 200 to 400 mcg per day (most vitamins have 1 mg)
   a. In women with a prior history of having a baby with a neural tube defect, supplementing with 4 mg per day has been shown to decrease the risk of a recurrence in the next pregnancy

C. The pregnant patient is best served by having a healthy balanced diet with iron and folate supplementation. Only rarely are other vitamin supplements needed.

IV. Prenatal Care for the Normal Pregnancy

A. The first visit-The basic decision: normal vs. high-risk

1. History
   a. Menstrual history: confirm the pregnancy
      (1) Regularity, interval, duration
      (2) Last normal menstrual period (LMP): characteristics and bleeding since then
      (3) Assign an estimated date of delivery (EDD): it is inappropriate for a patient to be past 20 weeks of pregnancy without a definite EDD
   b. Past obstetric history (if any): for many conditions, if the patient had an abnormality in the first pregnancy, then she is predisposed to a recurrence in subsequent
pregnancies
  (1) Length of gestation
  (2) Birth weight: low (IUGR/SGA) vs. high (LGA/macrosomia)
  (3) Fetal/neonatal outcome: alive vs. dead, impairments
  (4) Length of labor
  (5) Type of delivery: vaginal vs. cesarean, breech vs. cephalic
  (6) Other complications
  (7) Type of anesthesia used
c. Past medical history
  (1) Significant past illnesses
  (2) Permanent conditions: hypertension, diabetes, seizure disorder, thyroid
disease, and so on
  (3) Previous surgeries: C/S, gynecologic/abdominal surgery
  (4) Medications: prolonged therapy
d. Family history
  (1) Look for conditions with familial predilection: hypertension, diabetes, cardiac
disease, genetic abnormalities
e. Social history
  (1) alcohol use, smoking, drug abuse
  (2) 8-9% of pregnant women in the Salt Lake Valley have a positive urine for at
least one drug of abuse
  (3) occupational hazards
f. Genetic screening: evaluate from patient and family history the risk for genetic
abnormalities (is it above the usual 2-3% of all pregnancies)
  (1) Risk of chromosomal abnormalities increases with maternal age:

<table>
<thead>
<tr>
<th>Age</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>1/204</td>
</tr>
<tr>
<td>38</td>
<td>1/103</td>
</tr>
<tr>
<td>40</td>
<td>1/65</td>
</tr>
<tr>
<td>42</td>
<td>1/40</td>
</tr>
<tr>
<td>44</td>
<td>1/25</td>
</tr>
</tbody>
</table>

2. Physical examination
a. Vital signs: are they normal or not
b. General physical examination: are there any concurrent undiagnosed medical conditions
c. Abdominal exam: scars, enlarged uterus, other masses
d. Pelvic examination: uterine size (confirm dates), cervical examination, Pap smear,
clinical pelvimetry
  (1) uterine size large for dates: think twins or incorrect dates
  (2) uterine size small for dates: think IUGR or incorrect dates
  (3) the next step: ultrasound evaluation of the pregnancy

3. Laboratory data
a. CBC: make certain the patient is normal for pregnancy
b. Serology for syphilis: RPR, VDRL, confirm with FTA
c. Blood type, Rh, and indirect Coomb's test: evaluate for blood group
   isoimmunization
d. Rubella titer
e. Hepatitis B screen. HIV screen offered
f. Maternal serum alpha-fetoprotein (MSAFP) at 15-18 weeks
  (1) If elevated, then the patient should be evaluated with a targeted ultrasound for
fetal anomalies, including neural tube defects and abdominal wall defects
(gastroschisis and omphalocele)
(2) If low, then the patient should be offered a genetic amniocentesis to evaluate the fetus for trisomy 21 (Down's syndrome)
g. Urinalysis and urine culture
h. Pap smear: abnormal smears must be evaluated during pregnancy
i. Bacterial vaginosis (BV) screening: wet mount

B. Subsequent visits
1. Frequency: the usual regimen
   a. Monthly up to 32 weeks
   b. Every two week until 36 weeks
   c. Weekly after 36 weeks until delivery
2. Interval history
   a. General health and well-being
   b. Presence or absence of contractions
   c. Fetal movement increased, decreased
   d. Leaking clear fluid: rule out spontaneous rupture of membranes
   e. Vaginal bleeding: all vaginal bleeding after the first trimester is abnormal and mandates an evaluation
3. Examination
   a. Maternal weight
   b. Blood pressure: get worried if it is much above 120/80
   c. Fundal height, estimated fetal weight, fetal position (see figure 5)
   d. Always confirm the presence of fetal heart tones (FHT's)
   e. Urinalysis for protein and glucose: simple inexpensive screens for pre-eclampsia and diabetes
4. Laboratory evaluation
   a. CBC in the early third trimester: rule out anemia
   b. Glucola (diabetes screen) in the late second trimester
   c. Rhogam at 26-28 weeks if the patient is Rh negative
5. Ultrasound evaluation: routine vs. indicated?
6. Preparation for labor
   a. Childbirth education classes
   b. Physician input

C. Some common complaints during pregnancy: the "Discomforts of Pregnancy"
1. Nausea and vomiting: usually dissipates by 15 weeks or so
2. Constipation: common throughout pregnancy
3. Heartburn: often worsens as pregnancy progresses
4. Vaginitis: treat only if symptomatic
5. Varicose veins and hemorrhoids: treat symptomatically
6. Headaches
7. Edema: lower extremity edema is very common
8. Nasal congestion and nosebleeds,
9. Backache: lordosis is common with change in the center of gravity
10. Leg cramps: especially in lower leg
11. Faintness and light-headedness
12. Breast tenderness
13. Carpal tunnel syndrome

D. Common questions for which you will need to have an answer
1. Activity and exercise: moderation should be encouraged
2. Sexual activity: no problem as long as pregnancy progresses normally
3. Diet: a general balanced diet is usually all that is required
4. Bathing and swimming: no high speed sports or jet skis
5. Douching: OK if pregnancy is normal, best avoided if possible
6. Dentition: a dental check-up is recommended, any work is OK
7. Immunizations: should probably avoid live virus vaccines
8. Travel: no problems, but should have frequent stops to stretch
9. Employment usually no contraindication as long as pregnancy is normal

V. Take-home Points
1. The pregnant patient is best served by a confident and caring physician who vigilantly searches for high-risk features and then treats the patient as is appropriate for each high-risk condition. Most patients have completely normal pregnancies, but the high-risk pregnancy mandates changes in the "normal" evaluation of the pregnant patient.

2. The process of antenatal care is on-going risk assessment:
   a. What is the genetic risk? (maternal age, abnormal MSAFP screening, folate administration for prior NTD)
   b. What is the risk for preterm birth? (BV screening, history of preterm birth)
   c. What is the risk for pregnancy-induced hypertension? (history)
   d. What is the risk for IUGR? (past history, small uterine size for dates)
   e. What is the risk for blood group isoimmunization? (Rhogam for Rh- women NOT previously sensitized)
Fig. 6. Cardiac output during the course of normal gestation. Cardiac output was previously thought to decrease during the latter parts of pregnancy, but measurements taken with the subject in other than supine position indicate that it increases early in gestation and is maintained at an increased level until delivery. (Hyttén F. Chamberlain G: Clinical Physiology in Obstetrics. Boston, Blackwell Scientific Publications, 1960)

Table 5.3 Central Hemodynamic Assessment

<table>
<thead>
<tr>
<th></th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71</td>
<td>83</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne<em>cm</em>sec^-2)</td>
<td>15.50</td>
<td>12.10</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne<em>cm</em>sec^-2)</td>
<td>119</td>
<td>78</td>
</tr>
<tr>
<td>Colloid oncotic pressure (mmHg)</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>86 (NS)</td>
<td>90</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>6.3 (NS)</td>
<td>7.5</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>3.7 (NS)</td>
<td>3.6</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g<em>m</em>min^-3)</td>
<td>41 (NS)</td>
<td>48</td>
</tr>
</tbody>
</table>

(From Gair et al. with permission.)

Fig. 5.1 Lung volumes in nonpregnant and pregnant women.

Figure 4. Uterine blood flow at various stages of gestation. The flow increases significantly with the duration of pregnancy. (Hyttren F, Chambers P: Clinical Physiology in Obstetrics. Boston, Blackwell Scientific Publications, 1980)

Figure 5. Height of fundus at comparable gestational dates varies greatly from patient to patient. Those shown are in common. Convenient rule of thumb is that at five months' gestation, fundus is usually at or slightly above umbilicus.
PHYSIOLOGY OF NORMAL LABOR AND DELIVERY - PART I AND II

Objectives

1. To understand and recognize a normal labor pattern.
2. To understand the mechanism of labor for a cephalic presentation.
3. To understand the meaning of the following germs: Presentation, position, lie, station, effacement, dilatation.
4. To understand the phases and stages of labor.
5. To understand the following abnormalities of labor: Prolonged latent phase, arrest of dilatation, and arrest of descent.
6. To understand the indications for cesarean delivery.
7. To understand the indications for forceps delivery.

Definitions

Attitude: This refers to the posturing of the joints and relation of fetal parts to one another. The normal fetal attitude when labor begins is with all joints in flexion.

Lie: This refers to the longitudinal axis of the fetus in relation to the mother's longitudinal axis (i.e., transverse, oblique, or longitudinal (parallel)).

Presentation: This describes the part on the fetus lying over the inlet of the pelvic or at the cervical os.

Point of Reference of Direction: This is an arbitrary point on the presenting part used to orient it to the maternal pelvis [usually occiput, mentum (chin) or sacrum].

Position: This describes the relation of the point of reference to one of the eight octanes of the pelvic inlet (e.g., LOT: the occiput is transverse and to the left).

Engagement: This occurs when the biparietal diameter is at or below the inlet of the true pelvis.

Station: This references the presenting part to the level of the ischial spines measured in plus or minus centimeters.

Flexion and Engagement: This occurs at various times before the forces of labor begin.

Descent: This occurs as a result of active forces of labor.

Internal Rotation: This occurs as a result of impingement of the presenting part on the bony and soft tissues of the pelvis.

Extension: This is the mechanism by which the head normally negotiates the pelvic curve.

External Rotation (Restitution): This is the spontaneous realignment of the head with the shoulders.

Expulsion: This is anterior and then posterior shoulders, followed by trunk and lower extremities in rapid succession.

I. The Characteristics of Uterine Contraction in Labor

The musculature of the pregnant uterus is arranged in three strata:

1. An external hood-like layer which arches over the fundus and extends into the various ligaments.
2. An internal layer consisting of sphincter-like fibers around the orifices of the tubes and internal os.
3. Lying between the two, a dense network of muscle fibers perforated in all directions by blood vessels. The main portion of the uterine wall is formed by this middle layer which consists of an interlacing network of muscle fibers between which extend the blood vessels. As the result of such an arrangement, when the cells contract after delivery, they constrict the vessels and thus act
Uterine contractions are involuntary and, for the most part, independent of extraterine control. It has been demonstrated that the uterus has pacemakers to produce the rhythmic coordinated contractions of labor. These pacemaker sites are found near the uterotubal junctions, although the pacemaker cells do not differ anatomically from the surrounding myocytes as they do in cardiac muscle. The interval between contractions diminishes gradually from approximately ten minutes in early labor to as little as two minutes near the end of labor. In the normal process there is a progressive increment in the strength of contractions from approximately 20 mm of mercury at the onset of labor to 50 to 80 mm late in labor. The effect of uterine contractions of this frequency and intensity is twofold on the uterine cervix. First, effacement consisting of thinning of the cervix with a shortening of the endocervical canal, is produced. Secondly, cervical dilatation concurs, initially slowly as it accompanies the process of effacement of the cervix, and then more rapidly as cervical effacement has been accomplished (see Figure 1).

Progressive contractile activity of the uterus has been demonstrated throughout pregnancy. Most of these contractions are imperceptible to the pregnant individual, but toward the end of pregnancy they may achieve on a sporadic basis strength equivalent to those of early labor. False labor, Braxton-Hicks contractions, and pre-labor contractions are terms that have been applied to this uterine activity. The latter term is probably the most appropriate, and it is this uterine activity, which accomplishes a significant degree of effacement and even some dilatation in the days or weeks prior to the onset of recognizable labor. Descent of the presenting part of the fetus into the birth canal, particularly in a first pregnancy, is another result of pre-labor.

II. The Mechanism of Normal Labor

The definition or clinical diagnosis of labor is a retrospective one. There is no laboratory test that gives a "labor titer" or an x-ray procedure that can define the difference between the laboring and non-laboring patient. Realizing these limitations, the patient is diagnosed as being in labor when a combination of conditions exists. Perhaps a good working definition may be stated as follows: When in the presence of perceived uterine contractions, there is progressive cervical dilatation and descent of the presenting part which leads to the eventual expulsion of the products of conception, the patient is in labor.

The "mechanism of labor" refers to the sequencing of events related to posturing and positioning that allows the baby to find the "easiest way out." For the most part the fetus is a passive respondent in the process of labor, while the mother provides the uterine forces and a structural configuration of the passageway through which the passenger must travel. For a normal mechanism of labor to occur, both the fetal and maternal factors must be harmonious. An understanding of these factors is essential for the obstetrician to appropriately intervene if the mechanism deviates from the normal. The definitions at the beginning of this section should mastered to be able to discuss and understand the mechanism of labor.

The single most important determinant to the mechanism of labor is probably pelvic configuration. The classic work of Caldwell and Maloy is reviewed in the text and should be understood. Their classification of the pelvis into four major types (gynecoid, android, anthropoid, and platypelloid) helps the student understand the possible difficulties that may arise in a laboring patient. A quote that should be remembered is: "No two pelves are exactly the same, just as no two faces are the same. For each pelvis there is an optimum mechanism that may be wholly different from the so-called normal mechanism described."

An important principle is that most pelves are not purely defined but occur in nature as mixed types. Regardless of the shape, the baby will be delivered if size and positioning remain compatible. The
narrowest part of the fetus attempts to align itself with the narrowest pelvic dimensions (e.g., biparietal to interspinous diameters) which means the occiput generally tends to rotate to the "most ample portion of the pelvis."

The mechanical steps the baby undergoes can be arbitrarily divided, and clinically they are usually broken down into six or eight steps for ease of discussion. It must be understood, however, that these are arbitrary distinctions in a natural continuum.

The following six divisions of labor are easy to use:

1. **Flexion and Engagement.** This occurs at various times before the forces of labor begin.
2. **Descent.** This occurs as a result of active forces of labor.
3. **Internal Rotation.** This occurs as a result of impingement of the presenting part on the bony and soft tissues of the pelvis.
4. **Extension.** This is the mechanism by which the head normally negotiates the pelvic curve.
5. **External Rotation (Restitution).** This is the spontaneous realignment of the head with the shoulders.
6. **Expulsion.** This is anterior and then posterior shoulders, followed by trunk and lower extremities in rapid succession.

Abnormal mechanisms of labor do occur, and the operator must be able to recognize these early and intervene when appropriate. Those patients who have undeliverable or uncorrectable problems should be unhesitatingly delivered by the abdominal route because inappropriate operative vaginal intervention may lead to damage to both mother and fetus. Some of the undeliverable situations include persistent mentum posterior, persistent brow presentation, some types of breech presentations, and shoulder presentation.
Principle movements in the mechanism of labor and delivery

1. Head floating, before engagement
2. Engagement; flexion, descent.
3. Further descent, internal rotation.
5. Complete extension.
7. Del. of ant. shoulder.
8. Delivery of posterior shoulder.
III. Physiology of Normal Labor and Delivery

A. Normal labor

Emanuel Friedman in his elegant treatise on labor (1978) stated correctly that “the clinical features of uterine contractions namely frequency, intensity, and duration cannot be relied upon as measures of progression in labor nor as indices of normality. Except for cervical dilatation and fetal descent, none of the clinical features of the parturient patient appears to be useful in assessing labor progression.” Friedman sought to select criteria that would limit normal labor and thus be able to identify significant abnormalities of labor. These limits, admittedly arbitrary, appear to be logical and clinically useful. The graphic representation of labor plotting descent and dilatation against time has become known as the Friedman curve. It, or a modification of it, is used extensively to evaluate laboring patients.

Friedman Curve

Figure 2. Graphic portrayal of the relationship between cervical dilatation and elapsed time in labor (heavy line) and between fetal station and time (light line). Labor has been divided functionally into a preparatory division (including latent and acceleration phases of the dilatation curve), a dilatational division comprising only the linear phase of maximum slope of dilatation, and a pelvic division encompassing the linear phase of maximum descent.
B. Functional classification of labor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preparatory Division</th>
<th>Dilatational Division</th>
<th>Pelvic Division</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functions</td>
<td>Contraction coordinated, polarized, oriented, cervix prepared</td>
<td>Cervix actively dilated</td>
<td>Pelvis negotiated; mechanisms of labor; fetal descent delivery</td>
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<tr>
<td>Interval</td>
<td>Latent and acceleration phases</td>
<td>Phase of maximum slope</td>
<td>Deceleration phase and second stage</td>
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<tr>
<td>Measurement</td>
<td>Elapsed duration</td>
<td>Linear rate of dilatation</td>
<td>Linear rate of descent</td>
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<td>Diagnosable disorders</td>
<td>Prolonged latent phase</td>
<td>Protracted dilatation; protracted descent</td>
<td>Prolonged deceleration; secondary arrest of dilatation; arrest of descent; failure of descent</td>
</tr>
</tbody>
</table>

C. Abnormal labor

Dystocia (literally difficult labor) is characterized by abnormally slow progress in labor. It is the consequence of four distinct abnormalities that may exist singly or in combination.

1. Uterine forces that are not sufficiently strong or appropriately coordinated to efface and dilate the cervix.
2. Forces generated by voluntary muscles during the second stage of labor that are inadequate to overcome the normal resistance of the bony birth canal and maternal soft parts.
3. Faulty presentation or abnormal development of the fetus of such character that the fetus cannot be extruded through the birth canal.
4. Abnormalities of the birth canal that form an obstacle to the descent of the fetus.

<table>
<thead>
<tr>
<th>Labor Disorders</th>
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<tr>
<td>Pattern</td>
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<tr>
<td>Diagnositic Criterion</td>
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<td>--------------------------------------------------</td>
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<tr>
<td>Prolonged latent phase</td>
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<tr>
<td>Protracted active phase dilatation</td>
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<td>Protracted descent</td>
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<tr>
<td>Prolonged deceleration phase</td>
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<tr>
<td>Secondary arrest of dilatation</td>
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<tr>
<td>Arrest of descent</td>
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<tr>
<td>Failure of descent</td>
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</table>
1. Prolonged latent phase of labor

Etiologic factors that appear to be responsible for the development of prolonged latent phase disorders in multiparas most often include excessive sedation administered during the course of the latent phase and poor prelabor soft-tissue preparation. In addition, false labor and myometrial dysfunction are found but can be diagnosed only retrospectively.

Arrest disorder

A - Secondary arrest of dilatation pattern with documented cessation of progression in the active phase
B - Prolonged deceleration phase pattern with deceleration phase duration greater than normal limits
C - Failure of descent in the deceleration phase and second stage
D - Arrest of descent characterized by halted advancement of fetal station in the second stage.
These four abnormalities are similar in etiology, response to treatment, and prognosis, being readily differentiated from the normal dilatation and descent curves (broken lines).

Etiology of arrest disorders are: Power (inadequate uterine contractions), Passage (cephalo-pelvic disproportion – pelvis too small or inadequately shaped for delivery), and Passenger (fetus too large or presenting abnor

IV. Forceps delivery

Figure 5. Showing line of axis traction perpendicular to the plane of the pelvis at which the head is stationed.
Immediately after incising the uterus and fetal membranes, the operator’s fingers are insinuated between the symphysis pubis and the fetal head until the posterior surface is reached. The head is carefully tilted anteriorly and, as necessary, superiorly to bring it from beneath the symphysis forward through the uterine and abdominal incisions.

V. Cesarean delivery
PIH/OBSTETRICAL HEMORRAGE WORKSHOP

I. Preeclampsia and Eclampsia

Case Presentation – A 22-year-old Primigravid patient at 32 weeks of gestation presents with a blood pressure of 140/96, a urinalysis showing 2 + protein, and a 5 lb (2.27 kg) weight gain in two weeks. Her cervix is 1 cm dilated, uneffaced with a floating cephalic presentation. She is admitted to the hospital for a nonstress test (NST) which is reactive. Her laboratory values are within normal limits. She is observed at rest, and over the course of the next 24 hours her blood pressure increases to 150 to 160/100 to 110. She develops 3+ proteinuria and complains of epigastric pain.

Terminal Objective – Given a patient with hypertension, the student should be able to make an appropriate diagnosis and establish a plan of management.

Enabling Objectives – The student should be able to:

1. Define the various hypertensive disorders in pregnancy and the underlying pathophysiology.
2. Know the incidence, clinical course, prognosis, prophylaxis and general management including pharmacologic agents used for these disorders.

II. Late Pregnancy Bleeding

Case Presentation - A 32-year-old, gravida 6, para 5-0-0-5 at 28 weeks of gestation presents with vaginal bleeding to the emergency room. Her obstetrician is out of town. Her vital signs show a blood pressure of 100/50, a pulse of 98, and respiratory rate of 24. She is extremely anxious. Her obstetrical history and current prenatal course is unremarkable.

Terminal Objective – Given a pregnant patient in the third trimester who is bleeding per vagina, the student should be able to evaluate the case and discuss the management.

Enabling Objectives – The student should know.

1. The most common obstetrical and non-obstetrical causes and overall incidence of bleeding late pregnancy.
2. If the unsuspected diagnosis is abruptio placentae, know the pathophysiology, clinical characteristics, maternal and fetal complications and management.
3. If the suspected diagnosis is placenta previa, know the classification, incidence and probable mechanism, methods to localize the placenta clinical characteristics and management.

Preeclampsia and Eclampsia

I. Definition – Preeclampsia is that condition occurring only during pregnancy characterized by hypertension, edema and proteinuria. Eclampsia is the occurrence of convulsions, not caused by any coincident neurologic disease in a woman whose condition fulfills the criteria for preeclampsia. The etiology of preeclampsia is unknown. This condition occurs only in humans, and there is no animal model. Preeclampsia, can occur any time after 20 weeks of
gestation but usually becomes clinically evident late in pregnancy. It occurs in 7% of all pregnancies. Another term commonly seen is pregnancy-induced hypertension (PIH) which is divided into three categories, (1) Hypertension alone, (2) preeclampsia, and (3) eclampsia

PIH is classified as mild or severe according to the following:

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Mild</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Diastolic BP</td>
<td>&lt;100 mm Hg or rise</td>
<td>110 mm Hg or greater or rise</td>
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<tr>
<td></td>
<td>&gt;15 mm Hg from</td>
<td>&gt;30 mm Hg from second trimester BP</td>
</tr>
<tr>
<td></td>
<td>second trimester BP</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Trace to 1+</td>
<td>Persistent 2+ or more*</td>
</tr>
<tr>
<td>Headaches</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Visual Disturbances</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>SGOT elevation</td>
<td>Minimal</td>
<td>Marked</td>
</tr>
<tr>
<td>Fetal growth retardation</td>
<td>Absent</td>
<td>Obvious</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

*Significant proteinuria is defined as > 300mg/24 hour collection or 100 mg/dl on two separate urine collections > six hours apart (2+ on a urine dipstick)

II. Incidence-Occurs in 6 to 8% of pregnancies and continues to be one of the leading causes of Maternal morbidity and mortality. It ranks as the second leading cause of maternal death after pulmonary embolism.

III. Risk Factors
1. First pregnancy – 85% of cases of PE/E occur in first pregnancies.
2. Age-PE/E occurs most frequently in teens and women in their late 30’s and 40’s.
3. Chronic hypertension
4. Renal disease
5. Molar pregnancy
6. Previous pregnancy complicated by severe PE/E

IV. Management- While PE does not usually become clinically evident until late in pregnancy it is felt to develop a the time of implantation and is, therefore, directed toward preventing severe complications for the mother or baby. Low-dose aspirin has recently become popular in physician attempts to prevent the occurrence of PE. Conclusive evidence may be forthcoming.
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>THERAPY</th>
</tr>
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<tbody>
<tr>
<td>A. PIH with mature fetus</td>
<td>1. Prevent convulsions</td>
</tr>
<tr>
<td></td>
<td>2. Control BP</td>
</tr>
<tr>
<td></td>
<td>3. Delivery</td>
</tr>
<tr>
<td>B. PIH with immature fetus bet there is:</td>
<td>1. Prevent convulsions</td>
</tr>
<tr>
<td>1. Severe PE or</td>
<td>2. Control BP</td>
</tr>
<tr>
<td>2. Fetal growth retardation or</td>
<td>3. Delivery</td>
</tr>
<tr>
<td>3. Fetal jeopardy</td>
<td></td>
</tr>
<tr>
<td>C. PIH with immature fetus and PIH</td>
<td>Expectant management</td>
</tr>
<tr>
<td>Is mild or moderate</td>
<td></td>
</tr>
<tr>
<td>D. Patients at risk for PIH</td>
<td>Consider low-dose aspirin (15 mg/day)</td>
</tr>
</tbody>
</table>

The indication for hospitalization of women with PE is a systolic blood pressure of 140 mm Hg and greater or a diastolic blood pressure of 90 mm Hg and greater.

Hospital Management:

1. History and physical exam followed by daily search for evidence of development of severe PIH
2. Weight measured every two days.
3. Urine check for proteinuria every two days (24-hour collections)
4. BP check every four hours except at night to allow sleep.
5. Follow labs – CBC, Platelets, SGOT, Creatinine

Drug therapy to prevent convulsions and control BP

1. Magnesium sulfate-typically administered intravenously, monitoring reflexes, respirations and urine output.
2. Hydralazine (Apresoline) – used to control severe HTN and reduce the maternal risk of intracranial hemorrhage, NOT to achieve normotension which can compromise placental perfusion. Several other antihypertensive drugs can be used in this setting (beta blockers). However, the bulk of experience is with hydralazine.

Delivery is achieved by induction of labor and use of cesarean section for fetal or obstetrical indications.

V. Complications-Most serious complications of PE, including eclampsia, DIC, ruptured liver, maternal stroke, and fetal death, are due to failure to recognize the severity of the disease, failure to hospitalize the patient or failure to move to delivery. The goal of management of this disease is to keep the mother healthy and prevent intrauterine fetal demise. The earlier the onset of the illness, the more severe the course with regard to mother and fetus. The overall neonatal mortality rate in 1985 in the USA was 7/1000 live births. When toxemia is not managed, the neonatal death rate can increase 10 to 15 times.
Third Trimester Bleeding

1. Placenta Previa

   A. Definition-Place: Implantation in the lower uterine segment over or near the cervical internal os. Placenta previa is uncommon with the first child. In women who have had a previous cesarean section and present with an anterior low-lying placenta previa, up to 25% of these women may have a placenta acreta caused by the absence of Nitabuch’s layer. This can result in not only a cesarean section but also a postpartum hysterectomy commonly referred to as a cesarean hysterectomy.

   Incidence-approximately 1 in 200 pregnancies.

   Types
   1. Total placenta previa-cervical os completely covered by placenta.
   2. Partial placenta previa-cervical os partially covered by placenta.
   3. Marginal placenta, previa-placental edge is at the margin of the cervical os.
   4. Low-lying Placenta-placental implantation in the lower uterine segment, but the placental edge does not actually reach the internal os.

   B. Signs and Symptoms
   1. Painless hemorrhage- usually occurring toward the end of the second trimester or later
   2. Coagulation defects are rare.

   C. Risk Factors
   1. Multipara
   2. Advanced maternal age
   3. Previous cesarean section
   4. Large placenta such as in multiple gestation and pregnancies complicated by fetal erythroblastosis.
   5. Previous D&C or treatment for Asherman’s syndrome

   D. Diagnosis:
The diagnosis is suspected in the setting of painless bleeding late in pregnancy, a uterus which is soft and nontender, and a presenting part which is high in the uterus. The diagnosis in confirmed by ultrasound. It is dangerous to do a vaginal examination on a patient with third trimester bleeding since this may precipitate uncontrollable hemorrhage. Blood flow to the uterus at term ranges from 400 to 800 cc/minute.

   E. Management
In the setting of a premature fetus and no active bleeding, hospitalization and close observation is standard. Delivery by cesarean section is indicated in the setting of fetal maturity or severe maternal hemorrhage.
2. Placental Abruption

A. Definition
The separation of the placenta from its site of implantation in the uterus before the delivery of the baby.

B. Signs and Symptoms
Very variable, bleeding may be heavy or nonexistent. Pain may be severe or mild, and the baby may die or be unaffected. Placental abruption can be complicated by severe maternal hemorrhage, coagulation defects, renal failure, and fetal demise.

C. Risk Factors
1. Trauma
2. Polyhydramnios
3. Chronic HTN or PIH
4. Short umbilical cord
5. Uterine anomaly or tumor
6. Alcohol or drug use (particularly cocaine)

D. Diagnosis
The diagnosis is made by clinical suspicion. Ultrasound only occasionally confirms the diagnosis.

E. Management
Treatment will vary depending on the well-being of the mother and baby. Cesarean section is indicated for fetal distress and maternal hemorrhage. Close monitoring of fluid balance and coagulation defects is essential to optimize outcome.

III. Other Causes

A. Marginal sinus rupture
B. Uterine rupture
C. Bloody show of labor
D. Vasa Previa
E. Non-obstetric causes-vulvovaginal trauma, cervical lesions
F. Unknown

IV. Initial approach to a patient presenting with third-trimester bleeding

A. Hospitalization
B. Careful abdominal examination, including Leopold maneuvers
C. No internal vaginal or rectal exams
D. Placement of IV access
E. Type and crossmatch 2 to 4 units of PRBC
F. Ultrasound examinations for placental location
G. Close monitoring of mother and baby
MALE REPRODUCTION

Douglas Carrell, Ph.D.

Objectives

1. To understand hypothalamic-pituitary-testicular hormonal axis and the role of hormones in spermatogenesis.
2. To understand the process of sperm production.
3. To know the role of and the markers for epididymis, vas deferens, seminal vesicles, and the prostate.
4. To understand male fertility problems including: (a) diagnosis of male infertility, (b) traditional treatment of male infertility, and (c) advanced reproductive techniques.

Definitions

Aspermia: The failure to produce an ejaculate.
Asthenospermia (azthenozoospermia): The production of an ejaculate in which less than 50% of spermatozoa are motile.
Azoospermia: The production of an ejaculate devoid of spermatozoa.
Oligospermia (oligozoospermia): The production of an ejaculate containing less than 20 million spermatozoa per milliliter of semen.
Teratospermia (teratozoospermia) - The production of an ejaculate in which more than 50% of spermatozoa are of abnormal shape.

Hormones and Male Reproduction

I. Hypothalamus

A. GnRH (LHRH) contributes to the release of both LH and FSH from the pituitary.

III. Pituitary

A. FSH release is controlled by the feedback of inhibin from the testicle.
B. LH release is controlled by the feedback of steroids from the testicle.
C. LH and FSH also control their own release by feeding back to hypothalamus.
D. The target organs for FSH and LH are:
   1. LH acts on the Leydig cells to increase steroidogenesis.
   2. FSH participates in protein synthesis and the initiation of spermatogenesis at the level of the seminiferous tubules.

III. Testicle

A. LH binds to Leydig cells and increases cAMP which increases protein secretion and the side-chain cleavage of cholesterol, as well as other likely steps, to increase steroidogenesis and the production of testosterone and other androgens. Regulated by steroid feedback. The Leydig cells produce the testicular steroids, lie between the seminiferous tubules, and assist in the transportation of steroids in the blood, lymph and seminiferous tubules.
B. FSH binds to the Sertoli cells of the seminiferous tubules, increases cAMP and protein
synthesis, androgen binding in the tubules, etc. Regulated by inhibin produced by the Sertoli cells. Sertoli cells secrete proteins that are important to spermatogenesis and have been called the "director cells of spermatogenesis." They comprise the blood-testis barrier.

C. Prolactin may increase Leydig cell response to LH and/or prostate sensitivity to androgens.
D. Steroids and other hormones may aid in the movement of sperm from the testicle by causing smooth muscle contractions.
E. Normal hormone values:
   \[
   \begin{align*}
   \text{FSH} &= 1-10 \text{ mIU/ml} \\
   \text{LH} &= 1-10 \text{ mIU/ml} \\
   \text{Testosterone} &= 3-10 \text{ ng/ml} \\
   \text{Estradiol and dihydrotestosterone} &= \text{extremely low in normal males.}
   \end{align*}
   \]
F. Spermatogenesis occurs with the following steps:

1. Yolk sac endoderm gives rise to primordial germ cells which give rise to more type A cells, some of which degenerate.
2. Type A stem cells form additional type A cells or differentiate into type B spermatogonia cells during early puberty.
3. Type B cells differentiate during late puberty and in the adult to form primary spermatocytes, secondary spermatocytes and spermatids. These events occur initially through mitosis and then reduce the chromosomes to one-half through meiosis.
4. Spermiogenesis transforms early spermatids into late spermatids and form what we recognize as morphological normal sperm.
5. The above process takes 72 to 74 days in the human.
6. Sperm are released into the lumen through spermiogenesis which involves a gradual
7. Disorders of spermatogenesis can occur and can include:
   a. Azoospermia including Sertoli cell only syndrome
   b. Maturation arrest at one of a number of possible stages
   c. Hypospermatogenesis
8. Sperm transport from the testicle occurs through:
   a. Seminiferous tubule contractions of the myoid cells (hormone dependent)
   b. Fluid build up and pressure
   c. Testicular capsule contractions

IV. Epididymis

A. Responsible for sperm maturation and motility.
B. Usually two-thirds of the epididymis is needed for sperm transport in the human for normal sperm fertilization capacity.
C. Potential markers of epididymal function include carnitine and glycerol phosphocholine.
D. Sperm take approximately two weeks to get through the epididymis.
E. Sperm are stored near the tail portion and in the vas deferens until they are ejaculated.

V. Accessory organs

A. Seminal vesicles
   1. Contribute prostaglandins and fructose.
   2. Contribute two-thirds of volume of ejaculate.
   3. Qualitative fructose is useful for verifying presence and the presence of the vas
deferens.

B. Prostate
1. Contributes acid phosphatase, Zn and citric acid
2. Chronic inflammation may contribute to infert
3. Many markers including PSA

C. Vas deferens
1. Sperm storage and transport organ
2. Adrenergic innervation

VI. Male infertility

A. Contributes to about 50% of infertility.
B. Many potential causes including:

Varicocele
Idiopathic
Testicular failure
Obstruction
Cryptorchid
Volume
Agglutination
Sexual dysfunction
Viscosity
Ejaculatory failure
Endocrine
High density
Necrospermia
Combination of sperm defects

C. Varicocele contributes to about 40%; idiopathic causes are about 25%

D. Diagnosis

1. Physical exam
   a. Testicular size and consistency
   b. Varicocele - usually on the left side; on both sides or right about 10% of the time.
2. Semen quality
   a. Two or more complete semen analyses
   b. Should evaluate volume, agglutination, viscosity, quantitative motility and morphology, count, viability and membrane quality.
3. Blood hormones
   a. FSH
   b. LH
   C. Testosterone
   d. Prolactin
4. History

E. Treatment of male infertility
1. Specific medical problems
   a. Gonadotropins - HCG, Pergonal, Metrodin
   b. Other - thyroid, adrenal, etc.
2. Non-specific medical therapy  
   a. Gonadotropins - 2500 IU HCG 2X weekly - 10 to 12 weeks  
   b. Testosterone rebound therapy  
   c. Clomiphene citrate - 25 mg daily for 3 to 4 months  

3. Varicocele – Semen pattern of low motility, high tapered and immature sperm  
   Post-surgery correction yields pregnancy rates of 30% to 60% and semen improvement rates of 60% to 80%.  

4. Laboratory improvement of sperm with insemination  
   a. Can make semen quality better with lab manipulation techniques and then utilize with intrauterine insemination.  

5. Laboratory improvement with advanced reproductive techniques  
   a. GIFT techniques  
   b. IVF techniques  
      (1) Regular IVF  
      (2) ICSI techniques for poor sperm quality  
      (3) Sperm aspiration or testicular biopsy with ICSI  

Take-Home Points  

The history, physical exam, and laboratory investigations will detect an etiology for male factor infertility in approximately 50% of cases. Serum FSH levels provide an important diagnostic parameter in determining the pathological basis of azoospermia. Karyotypic analysis is most helpful in males with azoospermia and small testes. Obstruction of the ejaculatory ducts can be diagnosed by ultrasound. The absence of the vas deferens can be detected by the absence of fructose in the semen sample.  

The most common congenital abnormality resulting in testicular dysfunction is cryptorchidism. The longer the testis remain outside the scrotum, the greater the degree of spermatic disruption. The most common chromosomal abnormality resulting in deficient testicular function is Klinefelter's syndrome. The frequency of this abnormality is 1 in 500 live births. The 47,XX7 karyotype results in the destruction of all germ cells with seminiferous tubules causing small, firm testes and azoospermia. Gynecomastia and various degrees of androgen deficiency are usually noted. The most common vascular abnormality associated with infertility is a varicocele. The higher frequency of varicocele in infertile men (21% to 41%) compared to men in the general population (4% to 23%) has been interpreted as supporting a causal relationship between varicocele and infertility. Theories to account for adverse testicular function with a varicocele include: vascular stasis, back pressure, interference with oxygenation, reflux of renal or adrenal products into the pampiniform plexus and interference with heat exchange function of the pampiniform plexus.
GOALS OF THE ASSESSMENT AND TREATMENT: Objectives

a) Establish a diagnosis efficiently
b) Educate the infertile couple
c) Establish a prognosis
d) Establish and effect a realistic plan
e) Emotional support for the couple
f) Advise when discontinuation of treatment should be considered

DEFINITIONS (see also glossary on the last page)

Infertility: The inability to conceive following 12 months of regular coitus without contraception. In couples who conceive normally, 50% do so following 3 months whereas about 92% conceive following 12 months.

Fecundity: The monthly probability of pregnancy. (Normally 20-25% at best)

Primary infertility: Conception has never taken place.

Secondary infertility: At least one previous conception has been documented.

Sterility: The etiology of infertility is established and there is no possibility for conception.

DEMOGRAPHICS

Over the past two decades, the number of patient visits for infertility have soared. This does not appear to be caused by an increased proportion of infertility within age groupings. Rather, factors contributing to the demand include: a higher absolute number of couples of reproductive age ("baby boomers"), decreasing availability of babies for adoption (largely due to legalized abortion and increasing social acceptance of single parenthood), less stigma regarding infertility, increasing tubal disease due to sexually transmitted disease, and better and more plentiful medical care providers for infertility services. However, the most important contributor to the increased prevalence of infertility visits is delayed childbearing with consequent attrition of ovarian function.

Approximately 10-15% of all married couples in the United States are infertile. A systematic approach should be used to evaluate the cause(s) of infertility for a couple, while the emotional stress that accompanies infertility for both partners must be constantly addressed.

The etiology of infertility can be divided into three major categories: (1) female factor, (2) male factor, and (3) undetermined etiology. Approximately 40% of infertility cases, where the etiology has been determined, are due to female factor, 40% to male factor, and the remaining 20% are due to mixed male/female factors. In 10-20% of couples presenting for evaluation, no diagnosis can be made after standard investigation (unexplained infertility).

INVESTIGATION PLAN

Investigation of infertility should be designed to be completed as efficiently as possible. All couples should have a complete history and physical. The most information can be obtained if both partners are present initially. A sexual history should be obtained, including the frequency and timing of intercourse, the use of potentially spermicidal lubricants and a complete menstrual history.
Female Infertility Etiologies
Central (CNS)
Tubal
Pelvic/peritoneal
Endometrial/uterine
Cervical/mucus
Unexplained

The entire reproductive axis (hypothalamus, pituitary, ovary, pelvis, fallopian tubes, uterus, and vagina) must be intact and integrated for the success of the reproductive system. Systematic consideration of major risk factors for each component should be considered during history taking. Examples of some of the principal dysfunctions for each component of the reproductive system are given:

Sperm- childhood mumps, testicular injury/sexually transmitted diseases, varicocele, sexual dysfunction, exposure to toxins, endocrinopathies

Hypothalamus- extremes of weight, stress, excessive exercise, CNS lesions, Kallman's Syndrome, eating disorders

Pituitary- tumors (Prolactinoma, Cushing's Disease, Acromegaly), Postpartum panhypopituitarism (Sheehan's Syndrome).

Ovaries- tumors, surgical trauma, endometriosis, radiation / chemotherapy damage, dysgenetic gonads, polycystic ovary syndrome

Gametes/ folliculogenesis- age, smoking, medications. illicit drug / alcohol use (either partner), exposure to radiation, toxic chemicals, premature ovarian failure, obesity

Pelvis/Fallopian Tubes- IUD use, pelvic inflammatory disease, ruptured appendix, previous ectopic pregnancy, prior pelvic surgery, endometriosis

Uterus- embryologic malformations (e.g. septate uterus), luteal phase inadequacy, intrauterine synechiae (Asherman's Syndrome), leiomyomata uteri

Cervix- history of diethystilbesterol exposure, previous cervical surgery

Vagina- embryologic malformations e.g. imperforate hymen

Systemic disease- diabetes, renal failure, thyroid dysfunction, anorexia nervosa, etc.

REVIEW OF SECTION I

Be aware of the most important factors in society that have contributed to infertility as major health care concern.
Realize that each anatomical component of the reproductive system must function appropriately for a successful pregnancy; and the easiest way to take a careful history is to consider each component systematically.
II. PHYSICAL EXAMINATION AND LABORATORY INVESTIGATION

The goals of this section are to learn to look for clues on physical examination to common infertility causes. Also, the basic tests used to evaluate each component of the reproductive system will be reviewed.

PHYSICAL EXAMINATION

As with history taking, the physical examination is best directed toward uncovering manifestations of pathology involving each individual component of the reproductive system. In particular, attention is paid to the patient's weight, thyroid palpation, evidence of acne, hirsutism and seborrhea, as well as a search for galactorrhea. The degree of development of secondary sexual characteristics is also noted. Pelvic exam offers many clues including assessment of ovarian estrogen production (via observation of cervical mucus production and vaginal cytology). Mullerian abnormalities, leiomyomata uteri, and other pelvic masses and observation of any pelvic pain. A nonmobile retroverted uterus may signify the presence of pelvic adhesions from previous PID, surgeries, appendicitis or endometriosis that are fixing the uterus in the pelvic cul-de-sac.

LABORATORY INVESTIGATION OF INFERTILITY

Rubella immunity status, chlamydia and gonorrhea cultures are generally pursued on the initial visit. Folate supplementation should be considered if an inadequate diet is ascertained (ingesting 0.4 mg of folic acid daily before conception, decreases the probability of a neural tube defect by 50%). Then, an efficient general approach is to begin with a semen analysis followed by presumptive documentation of ovulation usually by temperature charting, and a hysterosalpingogram (HSG). Attention must be paid to the time during the menstrual cycle when the tests are performed since most have an optimal window during which they should be done. Depending on the outcome of the aforementioned tests, the following additional tests may be offered: endometrial biopsies to establish the diagnosis of inadequate luteal phase and, a postcoital test to determine sperm survival and movement within cervical mucus, and lastly, diagnostic laparoscopy.

a) Examination of Semen

Semen analysis should be the first step in the investigation before expensive and invasive female testing is performed. Semen specimens are best collected at the andrology lab. If this is not possible, specimens can be collected at home if they can be brought to the laboratory within 30 minutes. The semen should be collected by masturbation in a clean, detergent-free container. The interval of abstinence should be 48 to 72 hours. Since most of the spermatozoa are found in the first milliliter of the ejaculate, the man should be instructed to be careful to include this fraction.

At least two specimens should be examined at least several weeks apart since there can be considerable variability in quality. Like the female, the entire male reproductive axis must be evaluated depending upon the particular sperm abnormality. Abnormal results deserve referral to a urologist skilled in the male infertility evaluation.

While the individual parameters of the semen analysis are not particularly sensitive predictors of fertility, the overall semen quality does have predictive value. Minimum normal values have been suggested: sperm concentration > 20 million per ml, total count > 60 million, ejaculate volume > 1.5 ml, total motile count > 30 million, viable sperm > 50%, normal shapes (morphology) > 60%.
A host of specialized sperm function tests are available when indicated, for example:

- Antisperm antibody assays
- Hamster egg penetration test (HEPT) - to predict fertilizing capability of spermatozoa
- Hypoosmotic swelling test (HOS) - to assess sperm membrane function

b) Presumptive Documentation of Ovulation

The vast majority (98%) of women who give a history of regular menstrual cycles combined with premenstrual symptoms are probably ovulating. When in doubt, several practical tests offer presumptive evidence of ovulation: BBT, serum progesterone, and urinary LH surge testing. Endometrial biopsies and serial ultrasound examinations to ascertain the collapse of ovarian follicles are other ways to make the presumptive diagnosis of ovulation, but are less practical and very expensive.

**Basal Body Temperature**

Under the influence of circulating progesterone, the BBT rises in the luteal phase of the cycle. A mean increase of at least 0.4°F over the proliferative-phase temperature is considered normal. The patient should be instructed to take her temperature each morning prior to getting out of bed. The BBT is free, and answers the question of whether there is ovulation or not for the majority of women. Also, the length of the luteal phase can be assessed. Drawbacks include the fact that it can not predict prospectively when ovulation will occur, and it can be bothersome to record. Digital electronic thermometers have made this early morning task more palatable.

**Serum Progesterone**

A single serum progesterone value above 4 ng/ml obtained between days 19 and 23 of the menstrual cycle is presumptive evidence of ovulation.

**Urinary LH Surge Testing**

Serum estradiol is released from ovarian follicles in increasing amounts during the follicular phase. When the serum estradiol concentration exceeds a threshold level for a particular duration, positive feedback to the hypothalamic-pituitary axis initiates the release of a surge of LH. This LH surge triggers the events leading to ovulation approximately 40 hours after the start of the surge. LH is excreted into the urine where is can be measured simply by any number of commercially available ELISA home test kits. The major advantage over BBTs and serum progesterone determinations is the ability to prospectively predict the presence and timing of ovulation. LH kits are used in our clinic twice daily to ascertain optimal timing of artificial inseminations.

When a woman is found to be anovulatory, the underlying etiology must be sought and corrected if possible. In brief, some of the more common causes of anovulation include: extremes of weight, polycystic ovary syndrome (chronic hyperandrogenic anovulation), emotional stress, medications, systemic illness, and structural lesions of the hypothalamic-pituitary-ovarian axis. The initial blood evaluation includes obtaining TSH and prolactin values routinely and an FSH if ovarian failure is suspected. Total testosterone and DHEAS are obtained if a hyperandrogenic condition is suspected clinically.
c) Hysterosalpingogram

In most clinics, 30-40% of female infertility can be attributed to the pelvic abnormalities (such as tubal occlusion, adhesions, and endometriosis). An evaluation of the patency of the fallopian tubes involves transuterine contrast instillation under fluoroscopic visualization. The study should be performed in the follicular phase of the cycle prior to ovulation. Water-soluble contrast material is generally used as it offers better detail and less risk than oil-based contrast. An HSG should be obtained relatively early in the infertility investigation following semen analysis. HSG also serves to assess the contour and adequacy of the uterine cavity. Pathology such as intrauterine leiomyomata, polyps and synechiae (Asherman's Syndrome) and well as embryologically abnormal uterine cavities can be evaluated.

d) Postcoital Test

The couple is asked to have intercourse at least eight hours prior to but less than 24 hours prior to presenting to clinic. Postcoital testing (PCT) should be performed at midcycle when cervical mucus has a high water content secondary to the midcycle estrogen surge. At other times the mucus is thick and doesn't allow spermatozoa to penetrate. The sperm are then destroyed by the acidic vaginal environment.

Several characteristics will indicate whether the timing of the sample and the quality of the mucus is good. Copious amounts of alkaline mucus are generally observed emanating from the cervix at midcycle. A sample of cervical mucus is aspirated and placed on a glass slide. A coverslip is applied and lifted. The degree to which the mucus stretches (the spinnbarkeit) is measured. Columns of 8 or more centimeters is considered optimal. Good mucus appears acellular microscopically, and when dried the high sodium chloride content of midcycle mucus precipitates into a microscopic fernleaf-like pattern.

In a normal PCT, there should be at least several progressively motile spermatozoa per high power field. If only a few dead sperm or no sperm are found, the most common reason is a poorly timed PCT. Other reasons include oligospermia, inadequate coital technique, hypospadias, antisperm antibodies or possibly insufficient mucus. When sperm are seen to clump together and flagellate without progressive motility, this is often associated with the presence of antisperm antibodies originating either from the mucus or the semen. This test should not be used in place of a good semen analysis. The PCT is now used sparingly due to its poor predictive value for conception, but it remains a reasonable screen for antisperm antibodies.

e) Endometrial Biopsy

Approximately one week after ovulation, the now fertilized ovum (zygote), implants. The endometrium must be of sufficient quality to allow implantation. If not, it is termed luteal phase inadequacy (LPI) or luteal phase defect (LPD)—a rare cause of infertility. Correct maturation of endometrium requires sufficient sequential hormonal stimulation, primarily with progesterone, as well as normal end organ responsiveness to these signals. Therefore, a single progesterone assay alone is insufficient to diagnose LPI. Furthermore, it is important to differentiate between inadequate luteal phase and short luteal phase. In a short luteal phase, the duration of BBT temperature rise is less than ten days. Shortened luteal phases are not associated with infertility.

Histological "dating" of the endometrium. (based on the development of endometrial glands and stroma) can assess maturation. It has become the principal means of diagnosing LPI. Optimally, an office biopsy performed with a disposable Pipelle' should sample endometrium from high in the uterus as soon before the onset of menses as possible. This allows the full effect of the hormonal stimulation during that
menstrual cycle to exert its effect on the endometrium. When the histologic appearance of the endometrium shows a discrepancy of 2 or more days from the norm for the day on which the biopsy was taken, then the procedure is repeated in the subsequent cycle. Two such out-of-phase biopsies establishes the diagnosis of luteal phase inadequacy. Due to the rarity of LPI and the inherent inaccuracy and inconvenience of pursuing the diagnosis, biopsies are now done only when there are risk factors for LPI such as hyperprolactinemia, or when other infertility factors have been ruled out.

f) Laparoscopy

Diagnostic laparoscopy is an outpatient surgical technique in which a fiberoptic scope, is inserted through a 1 cm incision into the abdominal cavity to inspect the pelvis under general anesthesia. A number of surgical procedures can also be performed through accessory abdominal incisions using the scope for visualization. Dye can be passed through a canula via the cervix transvaginally. Patent Fallopian tubes exhibit the passage of dye through the fimbriated ends seen laparoscopically. During the procedure a hysteroscope can also be used to examine the uterine cavity. (This is an even more sensitive test than the hysterosalpingogram.)

Due to the expense and invasiveness, diagnostic laparoscopy is reserved as the last step of an infertility workup if no other salient etiologies are identified, and if conservative treatments are unsuccessful. In some circumstances, a minimally invasive laparoscopy procedure can be done under local analgesia.

REVIEW OF SECTION II

In evaluating the causes of infertility, it is helpful to consider the reproductive system segmentally such that no stone is unturned. Think of the hypothalamic, pituitary, peritoneal, ovarian, tubal, uterine, and vaginal compartments as well as systemic illnesses that can contribute to infertility. Each compartment has its typical dysfunctions and tests.

III. TREATMENT

Goals of this section are to understand the tools available to treat or circumvent the specific etiologies ascertained during the evaluation.

Therapy depends upon the etiologies identified. Anatomical defects, such as damaged tubes and Mullerian anomalies, are corrected surgically if possible. Endocrinopathies and systemic illnesses are treated specifically. For example, luteal phase insufficiency may often be corrected by supplementing progesterone during the luteal phase, and ovulation may resume spontaneously when a hyperprolactinemic woman is treated with the dopamine agonist bromocriptine.

ANOVULATION

Approximately 10-15% of infertile females are anovulatory. If potential causes of anovulation have been addressed and the woman remains anovulatory, attempts at medical induction of ovulation are reasonable. Furthermore, when the etiology of delayed fertility can not be identified after complete evaluation, and the ovaries are known not to have undergone premature failure, ovulation induction may also be attempted empirically ("superovulation"). The rationale is to drive more than one oocyte to ovulate with each cycle in order to increase the odds of a pregnancy. Likewise, intrauterine insemination of washed sperm increases the number of male gametes potentially reaching the oocyte(s).
OVULATION-INDUCING DRUGS

A number of medications have been used to help initiate ovulation including clomiphene citrate, human menopausal gonadotropins (hMG), GnRH, glucocorticoids and bromocriptine mesylate.

Clomiphene Citrate - Relatively inexpensive, taken by mouth with few side effects (except a multiple gestation rate of 7% in anovulatory women and the rare possibility of inducing hyperstimulation syndrome). Requires an intact hypothalamic-pituitary-ovarian axis. Mechanism of action is primarily within the hypothalamus as an "antiestrogen". It occupies estrogen receptors and "deceives" the hypothalamus into sensing a low estrogen environment. The hypothalamus in turn signals the pituitary via pulsatile GnRH to increase gonadotropin (FSH and LH) release to produce more follicular development and subsequent estrogen release. With an intact hypothalamic-pituitary axis, clomiphene has been successful in inducing ovulation in over 90% of cases. However, pregnancy rates approach only 65%. Eighty percent of patients treated with clomiphene who get pregnant do so within three cycles of therapy. Therefore judicious, limited use under physician care is recommended. Be aware that higher doses or prolonged usage can exert antiestrogen effects by thinning the endometrium and thickening cervical mucus and therefore can be counterproductive.

Human menopausal gonadotropins, (hMG; Pergonal, Humegon, Metrodin, Fertinex Gonal-F) Extremely expensive, given daily IM or SQ, and involves much more risk. The multiple gestation rate is about 15-35%, and overdosage may produce a potentially life-threatening ovarian hyperstimulation syndrome. Therefore, close monitoring with serial ovarian ultrasound and serum estradiol levels is necessary. hMG consists of LH and FSH, therefore it can bypass a non-functional hypothalamic-pituitary axis. Recombinant FSH (Gonal F) is used as above with some risks but has no contaminating protein found in the menopausal gonadotropins.

GnRH- Must be given subcutaneously or IV via a continuous pump. Therefore it is cumbersome and expensive. It requires an intact pituitary ovarian axis. It has few risks.

Glucocorticoids- Act by suppressing ACTH and therefore adrenal androgen production. This may occasionally be helpful in facilitating ovulation because circulating androgens cause ovarian follicular atresia. Used primarily in polycystic ovary syndrome with a component of elevated adrenal androgen secretion, and in women with congenital adrenal hyperplasia.

Metformin – an insulin sensitizing agent which may be used primarily or as an adjunct to clomiphene or hMG in insulin resistant patients with polycystic ovary syndrome.

Bromocriptine mesylate (Parlodel)- Anovulatory women with hyperprolactinemia should be treated initially with bromocriptine before considering ovulation induction medications. Excess prolactin inhibits normal hypothalamic pulsatile GnRH release.

A reasonable strategy in some circumstances is to attempt to compel more than the usual one oocyte to ovulate, by using ovulation induction medications. This is termed "superovulation" and is a tactic often used for couples with unexplained infertility and other situations of low estimated fecundity prior to resorting to expensive artificial reproductive technologies.
ENDOMETRIOSIS

Endometriosis is the ectopic growth of endometrium. It is diagnosed by the histologic confirmation of both endometrial glands and stroma in an ectopic location.

Establishing the diagnosis usually requires laparoscopy. Common symptoms may include infertility, dyspareunia, dysmenorrhea and dyschezia. Common sites include ovaries, broad ligament and pelvic peritoneum, cul-de-sac and bowel. The ectopic tissue is hormonally responsive, growing in the presence of estrogen. Sloughing endometriosis may result in pelvic lesions of a variety of colors, older lesions appear as "gunpowder" lesions due to sequestered hemosiderin. Endometriosis may incite inflammation with resulting adhesion formation. Such adhesions can distort the delicate reproductive anatomical relationships resulting in infertility. Endometriosis is clinically staged into minimal, mild, moderate and severe categories (stages I-IV).

Although found in approximately 5-10% of the general population, endometriosis has been noted in 30-40% of women presenting to infertility clinics. Endometrial tissue secretes a number of abnormal cytokines which have been implicated in aberrant ovulation, fertilization and tubal function. Nonetheless, minimal and mild endometriosis have not been definitively proven to cause infertility.

Both medical and surgical techniques have been used to treat endometriosis. Only total abdominal hysterectomy and bilateral salpingo-oophorectomy has resulted in high rates of cure. All other treatments offer high rates of temporary diminution of pain but should be considered suppressive only. Medical treatment is designed to inhibit ovulation and concomitant estrogen secretion because estrogen is "fertilizer" for endometriosis growth. A variety of agents including oral contraceptives, progestins, GnRH agonists and danazol have been employed for this purpose.

Ultimately, except for mechanical restoration of pelvic anatomy, medical and surgical treatment of endometriosis has NOT been shown to increase pregnancy rates. Treatment may theoretically, however, slow the progression to higher stage disease.

MALE FACTOR INFERTILITY

Unfortunately, few cases of male factor reproductive disorders can be remedied. Evaluation for male factor infertility is analogous to that of the female. Attention is paid to the hypothalamic-pituitary-testicular hormonal axis (LH, FSH, testosterone), and to the patency of the vas deferens. Particular abnormalities identified by semen analysis may suggest evaluation for specific presumptive causes of male-factor infertility. For instance, elevated percentages of tapered shaped sperm heads on morphologic examination suggest varicocele. Varicoceles are abnormal dilatations (varices) of scrotal veins. They are commonly found within the left scrotum superior to the testicle and feel like a "bag of worms". They are usually caused by deficient valves in the left internal spermatic vein and are noted in about 40% of men presenting to infertility clinics. Treatment is by ligation of the internal spermatic vein, but such treatment has resulted in only marginal increases in pregnancy rates rendering varicocelectomy controversial.

Occasionally, vas occlusion can be surgically corrected and in cases of hormonal deficiency, replacement hormonal therapy can restore testicular function. Recent technology allows in some instances the aspiration of sperm directly from the epididymis in cases of blockage or absence of the vas deferens. However, the few (usually compromised) spermatozoa obtained are usually subjected to micromanipulation techniques during in vitro fertilization procedures so the wife must become subjected
to a procedure as well. Formerly, most cases of severe male factor abnormalities have required consideration of donor sperm, but a dramatic advance has been the widespread utility of a micromanipulation technique called intracytoplasmic sperm injection (ICSI). A single motile sperm can be captured and injected into an oocyte resulting in normal fertilization. Therefore men with extremely low sperm counts and quality can potentially achieve a pregnancy using their own genetic sperm.

ASSISTED REPRODUCTIVE TECHNOLOGIES

Sperm and Oocyte Donation- If inadequate gametogenesis is the cause of infertility, couples are offered therapeutic donor insemination, donor oocytes, or both.

In vitro fertilization / embryo transfer - Irreparable tubal disease requires consideration of in vitro fertilization and embryo transfer (IVF-ET). Endogenous gonadotropin release is first down-regulated using a GnRH agonist to prevent interference with the ovulation induction process. Then the ovaries are stimulated to produce maximal numbers of oocyte-containing follicles using hMG. Oocytes are then aspirated transvaginally under ultrasound guidance during an outpatient procedure using local anesthesia. The oocytes are incubated with sperm in vitro. If fertilization occurs, embryos are transferred back into the uterus. Beside tubal disease or absence, IVF-ET has been used for other indications such as male factor infertility, endometriosis and unexplained infertility. Success rates average 20% but some centers are now achieving > 45 % success rates ("take-home baby rate" per embryo transfer procedure) depending on the age and infertility diagnoses of the candidates.

Zygote Intra-Fallopian Transfer (ZIFT)- Same procedure as IVF except embryos (zygotes) are transferred into the Fallopian tubes rather than the uterus with the rationale that exposure to normal tubal physiology facilitates pregnancy rates. Disadvantages include the need for normal tubes and the need for laparoscopy under general anesthesia for tubal embryo transfer. The ability to fertilize can be ascertained as in IVF.

Gamete Intra-Fallopian Transfer (GIFT)- Same procedure as ZIFT except gametes (instead of embryos) are transferred into the tubes immediately after retrieval of the gametes. This does not allow documentation of the ability of the gametes to fertilize.

Oocyte cryopreservation- Unlike sperm, oocytes are extremely sensitive to cryopreservation and do not survive the process. Once fertilization has occurred, however, about one half of cryopreserved embryos may survive the freeze/thaw process and can be transferred into the uterus.

Gamete micromanipulation- When fertilization proves defective, the oocyte zona pellucida, can be mechanically opened via micromanipulation techniques to facilitate sperm entry. Or, a single sperm can be injected directly into the cytoplasm of the oocyte (ICSI, intracytoplasmic sperm injection).

Ultimately, only about 50% of couples who seek help for infertility eventually report a pregnancy. However, amongst the group that does conceive, ectopic pregnancy, miscarriage and perinatal mortality surpass what would be expected in the general population. Therefore, of the original infertile population presenting for treatment, over half will eventually confront biologic childlessness. Many times financial and emotional stresses cause the cessation of infertility treatments even though there may still be efficacious medical treatments available to the couple.

A major responsibility of the physician is to suggest to a couple when to discontinue attempts at conception.
REVIEW OF SECTION III

Each treatment plan must be custom designed based upon etiology(ies), patient age, resources, desires etc. Note that available treatments are often designed to bypass certain irreparable obstacles in the reproductive system. For example, hMG bypasses hypothalamic/pituitary dysfunction by directly stimulating the ovaries. IVF bypasses tubal and peritoneal disease, and optimizes sperm function. And, artificial insemination bypasses cervical mucus dysfunction.

Understanding the mechanisms of action of the ovulation inducing agents is critical to rationally treat anovulatory women. There are treatments available to circumvent almost all problems with the reproductive system with the following three prerequisites: functional spermatozoa, functional oocytes and a normal uterus. Even these circumstances can be skirted if the couple is willing to use donated gametes and/or surrogacy when necessary.

IV. GLOSSARY

AI Artificial insemination
ART: Artificial reproductive technologies (including Al, TDI, ZIFT, GIFT, IVF-ET, ED)
BBT: Basal body temperature
Clomiphene citrate (Clomid, Serophene): An oral antiestrogen that initiates FSH and LH release from the pituitary
Danazol: A synthetic testosterone derivative that prevents ovulation by inhibiting the midcycle surge of LH, used in the treatment of endometriosis
Dyschezia: Painful bowel movements
Dysmenorrhea: Painful menses
Dyspareunia: Painful intercourse
ED: Embryo donation
Gonadotropins: FSH and LH
Gonadotropin releasing hormone agonist (GnRHa): Medications which cause first stimulation of, then downregulation of pituitary gonadotropes resulting in low FSH and LH secretion.
hMG (human menopausal gonadotropins: Pergonal, Metrodin, Humagon): Injectable LH and FSH
ICSI: Intracytoplasmic sperm injection
IVF-ET: In vitro fertilization and embryo transfer
LPD: Luteal phase defect (inadequacy)- The presence of endometrium inadequate to support implantation and growth
Lupron: An injectable brand of GnRH agonist
Parlodel: Bromocriptine mesylate, dopamine agonist that inhibits prolactin secretion
PCT: Post-coital test
Spinnbarkeit: The stretchability of cervical mucus at midcycle
Superovulation: The use of ovulation induction agents to purposefully ovulate more than the usual single monthly oocyte.
TDI: Therapeutic donor insemination
Varicocele: Abnormal testicular vascular configuration associated with decreased sperm
GYNECOLOGY SEMINAR
CONTRACEPTION

Case Presentations

A 20-year-old, nulligravid, single woman has been sexually active for six months. She states that she has been using condoms, coitus interruptus, and chance to keep from getting pregnant. She requests an IUD for contraception because she "doesn't want to mess with things ... and I don't remember too good."

A 31-year-old, gravida 3, para 3 who is six weeks postpartum requests a method of contraception. She is breastfeeding and plans to continue for one year. She requests contraceptive advice and is considering sterilization but is unsure whether she wants to limit her family to the three children she has.

Terminal Objective

Given a patient requesting contraception, the student should obtain the appropriate database and provide sufficient information and counseling to enable the patient to choose a satisfactory method of contraception.

Enabling Objectives

The student should be able to:

1. List seven methods of contraception and the effectiveness of each.
2. Discuss the physiologic or pharmacologic basis for each of the methods listed above
3. List and discuss the absolute and relative contraindications, advantages, disadvantages and complications of each method

Definitions

Efficacy—percentage of women experiencing an unintended pregnancy within the first year of use

Perfect use: how effective methods can be when used consistently and correctly
Typical use: how effective methods are for the average person

Breakthrough bleeding - nonorganic endometrial bleeding during the use of oral contraceptives. It may be due to estrogen or progestin deficiency or missing pills.

OCP - oral contraceptive pill, usually refers to combined oral contraceptive pill containing both progestin and estrogen.

Contraceptives can be divided into groups, depending on their perfect use effectiveness, their relation to the act of intercourse, and the general approach.

1. Efficacy. There is no perfect method of contraception. Each patient must be approached individually. However, the options available to women now are vast compared to those two generations ago. Methods differ in their effectiveness, side effects, participation of the users, expense, availability, ability to be concealed, and
Pregnancy rates are 85 to 100 woman-years (85% per year) without contraception.

Table. Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year: United States

<table>
<thead>
<tr>
<th>Method</th>
<th>% of Women Experiencing an Unintended Pregnancy within the First Year of Use</th>
<th>% of Women Continuing Use at One Year</th>
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<tbody>
<tr>
<td></td>
<td>Typical Use¹</td>
<td>Perfect Use²</td>
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<tr>
<td>Chance</td>
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<td>85</td>
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<tr>
<td>Spermicides</td>
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<td>6</td>
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<tr>
<td>Periodic Abstinence</td>
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<td>9</td>
</tr>
<tr>
<td>Ovulation Method</td>
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<td>3</td>
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<td>Symptothermal⁶</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Post-ovulation</td>
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<td></td>
</tr>
<tr>
<td>Cap⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parous Women</td>
<td>40</td>
<td>26</td>
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<tr>
<td>Nulliparous Women</td>
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<td>9</td>
</tr>
<tr>
<td>Sponge</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Parous Women</td>
<td>40</td>
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<tr>
<td>Nulliparous Women</td>
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<td>9</td>
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<tr>
<td>Diaphragm³⁷</td>
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<tr>
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<tr>
<td>Male</td>
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<tr>
<td>Pill</td>
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<td>Combined</td>
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<tr>
<td>IUD</td>
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<tr>
<td>Progesterone T</td>
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</tr>
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<td>LNg 20</td>
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<tr>
<td>Depo-Provera</td>
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<tr>
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</tr>
<tr>
<td>Male Sterilization</td>
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</tr>
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</table>

2. Coital independent - coital dependent - coital inhibiting - postcoital
ORAL CONTRACEPTIVES

The era of modern contraception dates from 1960 when oral contraception was first approved by the US Food and Drug Administration, and intrauterine devices were re-introduced. A few catastrophes attributable to oral contraceptive pills (OCP) usage, particularly from the older higher-dose pills, caused considerable public alarm in the 1970's. Now the birth control pill has become safer and better tolerated, with reduced dosage of both the estrogen and the progestin components. The 1990's are seeing multiple reports on the health benefits of the Pill. According to the 1988 Ortho Survey, approximately 14 million women in the United States use the pill; about 60 million women worldwide use OCPs. ("OCP" usually refers to combined oral contraceptive pills containing both estrogen and progestin).

Few women are not candidates to take OCPs. Table 1 lists absolute and relative contraindications. Most of the contraindications are related to the estrogen component. Risks of hormonal contraception must always be weighed against risks of pregnancy and acceptability of other options. A woman is 15 to 20 times more likely to die from continuing a pregnancy than from using oral contraceptive pills.

OCP Contraindications

Absolute Contraindications:

1. Thromboembolic disorder (or history thereof)
2. Cerebrovascular accident (or history thereof)
3. Coronary artery disease (or history thereof)
4. Impaired liver function (current)
5. Hepatic adenoma (or history thereof)
6. Breast cancer, endometrial cancer, other estrogen-dependant malignancies (or history hereof)
7. Pregnancy
8. Undiagnosed vaginal bleeding
9. Tobacco user over age 35
10. Migraine headache with focal neurologic deficits

Relative Contraindications:

1. Hypertension
2. Diabetes mellitus
3. Surgery with immobilization (suggest 1 - 3 months discontinuation)
4. Seizure disorder, anticonvulsant use
5. Obstructive jaundice in pregnancy

Studies to look at the complications of oral contraceptive pills are confounded by the higher-dose pills used in the 1960's and 1970's. Estrogen and progestin doses have been steadily lowered, with attendant lowered morbidity. The currently prescribed low-dose pills (<50 micrograms of ethinyl estradiol cause cardiovascular complications (myocardial infarction, cerebrovascular accident, thromboembolism) almost exclusively in women over age 35 who smoke, or in some women with underlying medical problems, particularly with conditions predisposing to thrombosis. Healthy OCP users who undergo surgery with immobilization are at increased risk of venous thrombosis and pulmonary embolism. Pills should be discontinued prior to surgery and reinstated six to eight weeks postoperatively. This, too, should be balanced against the risk of pregnancy.
Side Effects

Breakthrough bleeding is the most common side effect for which women discontinue OCP usage. This may be due to estrogen or progestin deficiency or to missing pills. Estrogen excess side effects may include nausea, water retention, vascular headaches, and chloasma. Progestin excess may lead to increased appetite and weight gain, acne, depression, and pill amenorrhea. With current low-dose formulations, most women experience mild or no side effects.

Benefits

Benefits of taking contraceptive pills have been under-publicized. Long-term use is not only safe, but it is protective against many serious disorders and nuisance complaints. There is no need for a pill-free interval for reproductive or general health.

Noncontraceptive Benefits of OCPs

Effective contraception
  --less need for therapeutic abortion
  --less need for surgical sterilization
Less endometrial cancer (50% reduction)
Less ovarian cancer (40% reduction)
Less benign breast disease
Fewer ovarian cysts (50% to 80% reduction)
Fewer uterine fibroids (31% reduction)
Fewer ectopic pregnancies
Fewer menstrual problems
  --more regular
  --less flow
  --less dysmenorrhea
  --less anemia
Less salpingitis (pelvic inflammatory disease)
Less rheumatoid arthritis (60% reduction)
Increased bone density
Probably less endometriosis

Besides providing protection from the above medical disorders, OCPs are used to manage many gynecologic disorders.

Noncontraceptive Uses of OCPs

Definitely beneficial:
  --Dysfunctional uterine bleeding
  --Dysmenorrhea
  --Mittelschmerz
  --Endometriosis prophylaxis
  --Acne and hirsutism
  --Hormone replacement
  --Prevention of menstrual porphyria

Beneficial in many cases:
The OCP has over 25 preparations, using two different estrogens and several different progestins. The available pills contain fixed and variable-dose ratios. All can claim > 99% theoretical effectiveness. Combination pills, using both estrogen and progestin, are taken for 21 days, with a seven-day hiatus between cycles, during which time withdrawal bleeding occurs. The "minipill", or progestin-only pill, is taken continuously without a break; bleeding may occur irregularly, not at all, or occasionally as regular menstrual cycles. Additional information can be found under "progestins".

The principle mechanisms of action of OCP's appear to be:

1. Blockage of ovulation, which is mediated through hypothalamic suppression of FSH, and the LH surge.
2. Creation of "hostile" (viscid) cervical mucus to hamper the transport of sperm and decrease sperm penetration.
3. Prevention of implantation by altering the endometrium so that it is not receptive to the blastocyst.
4. Other probable factors of decreased tubal transport and sperm capacitation.

Choosing an oral contraceptive is simpler than it may seem. All pills protect against pregnancy in most women. Start with a preparation containing 30 or 35 mcg of ethinyl estradiol. The "newer" progestins, norgestimate and desogestrel, are reported to have equal progestin but less androgen effect than the traditional progestins (norethindrone, levonorgestrel, etc.). For new starts, ethinyl estradiol-plus-norgestimate (Ortho-Cyclen, Ortho Tri-Cyclen) may be the best option, per the theory that less androgen effect will be better for the cardiovascular system. Older low-dose oral contraceptive pills which have been well studied and proven safe and effective, are also recommended (Norinyl 1+35, Ortho-Novum 7-7-7, Demulen 1/35, Ovcon 35, Loestrin 1.5/30, etc.). One study reported that desogestrel-containing oral contraceptive pills's (OrthoCept, Desogen) cause a slightly higher incidence of thrombotic events. These data have not been corroborated, and these oral contraceptive pills's do not need to be discontinued but are not recommended for new starts. All tri-phasic pills have the same amount of estrogen throughout the month, but varying doses of progestin. This is formulated to provide less total monthly progestin exposure, theoretically enhancing cardiovascular health.

New Methods of Administration of Combination Estrogen/Progestin for Contraception

Within the past 2 years, there have been new methods of administering estrogens and progestins for contraception. In an effort to increase compliance and decrease the need for daily administration of an oral pill, new products have been introduced to try to lower the user-failure rate of combination hormonal contraception:

Contraceptive transdermal patch – changed weekly, administered for three weeks with one week off

Contraceptive vaginal ring – an intravaginal ring which releases continuous estrogen and progestin which is changed monthly (three weeks of ring use with one week off)
Women may discontinue usage for side effects such as breakthrough bleeding, amenorrhea or nausea, or for side effects with possible relationships to pill use such as weight gain, headaches or acne. Many women in the United States are unable to pay for contraceptives, and instead find themselves dealing with the much more expensive problem of childrearing. Better education improves compliance. A patient should know when to contact her physician, with the potential danger signals listed below. She should also be thoroughly informed about the safety of the pill and of its benefits.

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**EARLY PILL DANGER SIGNS**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Abdominal pain (severe)</td>
</tr>
<tr>
<td>C</td>
<td>Chest pain (severe), cough, shortness of breath</td>
</tr>
<tr>
<td>H</td>
<td>Headache (severe), dizziness, weakness, or numbness</td>
</tr>
<tr>
<td>E</td>
<td>Eye problems (vision loss or blurring), speech problems</td>
</tr>
<tr>
<td>S</td>
<td>Severe leg pain (calf or thigh)</td>
</tr>
</tbody>
</table>

See your clinician if you have any of these problems, or if you develop depression, yellow jaundice or a breast lump.

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**Progestin Administration**

Progestins can be administered on a continuous basis in oral (progestin only pill), or injectable form (Depo-Provera). Progestin only contraceptives work by inhibiting ovulation, thickening cervical mucous, and causing atrophy of the endometrial lining. The main drawback to all these methods is unpredictable, irregular bleeding in many users. The advantages of the injectable form is effectiveness, lack of use responsibility, and lack of impact on lactation. In comparison to the combination birth control pill, the progestin only birth control pill is less effective (except when combined with lactation), associated with more break through bleeding, and fewer serious side effects. Women must be compulsive about taking the pill at the same time each day for maximum efficacy. This is no pill free interval.

Health concerns revolve around changes in lipid levels. In general, some lowering of HDL (high-density lipo-protein, the "good" cholesterol) can be measured, but this has not been shown to contribute clinically to heart disease. Progestins do not promote clotting, therefore, they do not increase the risks of heart attack or stroke regardless of age or smoking status. Despite this, the FDA requires the same thrombosis precautions on all hormonal contraceptives because of the technical approval process.
Table 3. Brand Names of Progestin-Only Pills

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Dose (mg)</th>
<th>Number of Tablets Per Package</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethindrone (Norethisterone)</td>
<td>350</td>
<td>42/28</td>
<td>Micronor, NOR-QD Noriday, Norod</td>
</tr>
<tr>
<td>Norethindrone (Norethisterone)</td>
<td>75</td>
<td>35</td>
<td>Micro-Novum</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>75</td>
<td>28</td>
<td>Ovrette, Neogest</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>30</td>
<td>35</td>
<td>Microval, Noregeston, Microlut</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
<td>500</td>
<td>28</td>
<td>Femulen</td>
</tr>
<tr>
<td>Lynestrenol</td>
<td>500</td>
<td>35</td>
<td>Exluton</td>
</tr>
</tbody>
</table>

Depo-Provera is medroxyprogesterone acetate in a sustained-release suspension, 150 mg IM every three months. It is extremely effective with a failure rate of 0.3% during the first year of use. Fifty percent of women using depo-provera will experience amenorrhea after one year of use. The most common side effects are irregular bleeding and a slight increase in weight. The average return to fertility is 9-10 months.

Intrauterine Devices

Intrauterine devices are plastic, polyethylene devices impregnated with barium sulfate to make them radiographic, now containing copper or progesterone, which stay in the uterine cavity. They cause a sterile spermicidal inflammatory reaction. Very few sperm reach the oviducts, and fertilization usually does not occur. If it should occur, the inflammatory reaction is also toxic to the blastocyst, and implantation is prohibited. There are two IUD's currently marketed in the United States. "ParaGard" (TCu-380A) is a copper-containing IUD with an efficacy lasting ten years. “Mirena” is a progestin-releasing IUD which must be replaced every 5 years.

First-year IUD failure rates range from < 1 % to 3.7 %. Pregnancy usually follows spontaneous expulsion of the IUD, occurring most commonly shortly after insertion. Cumulative four to six year pregnancy rates are less than 1 % per year. An experienced clinician has fewer failures, due mainly to correct high-fundal insertion.

The advantage of the IUD include its use in women unable to take estrogen, lack of systemic side effects, immediate high efficacy, a rapid return to fertility after removal, the necessity for a single motivational act, and a lack of interference with lactation. The disadvantages are a slight increased risk of infection...
during the month following insertion, an increase in menstrual bleeding and cramping with the copper IUD (the progestin IUD decreases blood loss and dysmenorrhea), the rare complications of expulsion and perforation.

Pregnancies may occur with the IUD in place. This carries about a 55% risk of spontaneous abortion. Removal of the IUD after pregnancy is diagnosed, lowers this risk to about 25%. There may be a higher risk of septic (spontaneous) abortion, but with modern IUD's this is not certain. IUDs substantially decrease the risk of ectopic pregnancies compared to not using contraception, but they are more effective at preventing intrauterine than preventing ectopic pregnancies. If a woman using an IUD does become pregnant, she has a higher chance of having an ectopic pregnancy (3-4% with the copper IUD 1.5% in the general population).

Concerns regarding the safety of the IUD relate mostly to pelvic inflammatory disease (PID) and subsequent infertility. These concerns are largely unwarranted with modern IUD's. The Dalkon Shield was found to be the main offender and was removed from the market. Other IUD's were removed from the market because of the cost of defending against multiple malpractice suits. The incidence of PID in monogamous IUD users is slightly greater than background risk only shortly after insertion. Exposure to more than one sexual partner greatly increases infectious risks. The ideal patient for an IUD is a monogamous woman who thinks she may be finished with childbearing.

Contraindications for IUD use include:
- Known for suspected pregnancy
- Active, recent (three months), recurrent pelvic infection including postpartum endometritis, septic abortion, PIH, cervicitis
- Distorted uterine cavity from leiomyomata, uterine anomalies, etc.
- Risk factors for infection including multiple partners, history of recurrent sexually transmitted infections
- Impaired immune response from chronic steroid use, HIV, etc.
- Undiagnosed abnormal vaginal bleeding
- Known or suspected cervical or uterine malignancy, including an unresolved abnormal PAP smear
- History of pregnancy, perforation with prior IUD

In addition, the copper IUD should not be used in women with a copper allergy or Wilson’s disease. The progestin containing IUD (“Mirena, containing levonorgestrel) should not be used in a woman with a previous adverse reaction to levonorgestrel).

Surgical Sterilization

Surgical sterilization is increasing in popularity as a form of contraception. 10.7 million women in the United States rely on female sterilization, 4.2 million on vasectomy.

Bilateral tubal ligations may be performed postpartum using the Pomeroy, Parkland, Uchida, or Irving techniques through a small infraumbilical incision. Interval bilateral tubal ligations are usually performed with the laparoscope using electrocautery, silastic bands, or spring clips.

The U.S. Collaborative review of Sterilization (CREST) study is the largest U.S. study on female sterilization. It reports a 10-year cumulative failure rate of 18.5 pregnancies for every 1000 procedures. This is higher than previously thought. Failures may occur as long as a woman is fertile, not just in the first 1-2 years following the procedure. Failure rates were higher in young women and with specific methods (spring clips and bipolar electrocautery compared to postpartum sterilization). However,
sterilization remains the most effective method of contraception (regardless of technique) for women >34 years. It is important to note that longterm hormonal contraceptive methods (implants and Depo-Provera) and IUD’s have annual failure rates of about 2/1000 – very close to the failure rates of sterilization.

The advantages of sterilization include permanence, effectiveness, lack of side effects. The disadvantages are surgical risk (mortality 1-2/100,000), risk of regret, risk of ectopic if pregnancy should occur.

A bilateral tubal ligation protects against ectopic pregnancy compared to not using contraception. However, in the few pregnancies which do occur, there is an increased risk (33% compared to 1.5% in the general population). Regret occurs more often in young patients, in postpartum or postabortion tubals, and when patient’s life situation changes. Tubal reversal is expensive and successful in only 43-80% of cases. In vitro fertilization is a very successful options for young women who with a child after tubal ligation (about 50%/IVF cycle) but is quite expensive. Therefore, a patient should be certain that she doesn’t want more children prior to having a bilateral tubal ligation.

Vasectomy is safer, less expensive, and more effective than female sterilization. The one year failure rate is 0.15% compared to 0.5%. The cost is about 1/3 that of bilateral tubal ligation. Vasectomies are performed in the office with local anesthetic. Two semen analyzes must be negative for sperm (approximately 15-20 ejaculations) after the procedure.

**Fertility Awareness Methods**

Fertility awareness methods are based upon identifying the days in each menstrual cycle in which intercourse is most likely to result in a pregnancy. This is termed fertility awareness combines methods (FACE) if pregnancy is avoided by using barrier methods or coitus interruptus. Natural family planning (NFP) refers to abstaining from intercourse during fertile days. Typical use failure rates are 25% during the first year. With perfect use failure rates of 1-9 % occur.

Four indicators may be used to predict periods of fertility.

1. Cervical secretions increase and become clear and stretchy near ovulation.
2. The cervix itself, becomes softer and wider near ovulation.
3. Basal body temperature (BBT) rises under the influence of progesterone after ovulation
4. Calendar calculations may be made based on the length of a women’s menstrual cycle.

Most couples initially require an instructor to help interpret signs of fertility. Fertility awareness methods are more difficult to interpret if a women has recently been on a hormonal form of contraception, if she is near menarche or menopause, or is he is recently postpartum or breastfeeding.

**Barrier Methods**

Barrier methods of contraception include the condom, diaphragm, cervical cap, and vaginal spermicides.

The male condom offers the most effective method of preventing sexually transmitted infections. Male condoms are manufactured from latex, lamb caecum, or polyurethane. All prevent pregnancy. Naturally membrane condoms do not offer the same protection against sexually transmitted disease. Small pores may permit the passage of viruses, including HIV, hepatitis B, and HSV. Polyurethane condoms may be used for patients with latex allergies. With latex condoms, only water-based lubricants (KY jelly,
spermicidal agents) should be used. Oil based lubricants (lotion, petroleum jelly, massage oil) may damage the condom. The failure rate with condom use the first year is 3% with perfect use and 14% with typical use. Failures occur more commonly because condoms are not used with every act of intercourse, rather than from slippage or breakage. The advantages of condom use include protection from STDs, low cost accessibility, and lack of side effects. All patients at risk for sexually transmitted infections should be counseled to use condoms. The first female condom, call Reality, was approved by the FDA in 1993.

Vaginal spermicides are used with the diaphragm and cervical cap. They may be used alone, but have a wide range of failure rates, from 5-50% in the first year. Spermicides consist of a base (gel, foam, cream, film, suppository) and an active chemical agent (nonoxynol-9) in the United States. Suppositories and film must be placed at least 15 minutes before intercourse to allow adequate dispersion. Spermicides might slightly decrease the risk of sexually transmitted infection (by approximately 25%). The advantages of spermicides are their accessibility, ease of use, and ability to augment other forms of contraception. They are not good options if a patient is allergic to the base or spermicidal agent or if she has abnormal vaginal anatomy (such as a septum).

The diaphragm is a dome shaped cup that rests between the pubic symphysis and in the posterior fornix. Diaphragms are manufactured in different sizes, from 50 mm to 95 mm. A patient should be fitted with the largest size that is comfortable. The diaphragm is used with a spermicidal cream or jelly. It may be placed up to 6 hours before intercourse, should be left in place for at least 6 hours before intercourse, and should not be worn more than 24 hours total. A diaphragm should be refitted after a weight gain or loss of 10 pounds and postpartum. The diaphragm has a 20% failure rate with typical use, a 6% failure rate with perfect use over the first year.

The cervical cap is as smaller that fits snugly over the cervix. The cervical cap is manufactured in 4 sizes. Because of the limited number of sizes, 6-10% of women are unable to be fitted properly. The cap may be left in place for up to 48 hours total, and should be left in place for at least 6 hours after intercourse. It also is used with a spermicidal preparation. The cervical cap is more efficacious in nulliparous women. The failure rate is 20% for typical use, 9% for perfect use in nulliparous women. In parous women the failure rate is 40% for typical use, 26% for perfect use.

The advantages of the diaphragm and cervical cap include a lack of systemic side effects and potential protection against STDs. They are good choices for women who need contraception intermittently. They should be used with caution in women who have allergies to latex or spermicides, vaginal anatomy abnormalities, a history of Toxic Shock Syndrome, or recurrent urinary tract infections.

Coitus Interruptus (Withdrawal)

Coitus interruptus is used as the primary means of contraception by at least 2% of couples in the United States. In some countries, it is the most commonly used form of contraception. With perfect use there is a 4% failure rate during the first year, with typical use 19%. This is similar to barrier methods. It’s advantages are its cost and lack of side effects. It is unforgiving if used inconsistently and does not offer STD protection.
**Postpartum Contraception**

Breastfeeding women will have a longer period of postpartum infertility than will nonbreastfeeding women. Women who solely breast-feed who continue to experience amenorrhea are 98% protected from pregnancy in the first six months following delivery. In nonlactating women, the first ovulation occurs on average 45 days postpartum. Good contraceptive options for lactating women include barrier methods (the diaphragm and cervical cap should be refit at six-weeks postpartum), progestin only methods, the IUD (may be placed immediately postpartum, but more often is placed at 6-8 weeks postpartum), and male or female sterilization. The combination birth control pill is not a good option because estrogens decrease milk supply but may be given after 3 months when the milk supply is well established. In women who are not breastfeeding, the combination birth control should not be started until 2-3 weeks postpartum because the risk of thromboembolism is increased during this time. Fertility awareness methods may be difficult to practice until regular cycles are established.

**Emergency Contraception**

Emergency contraception is defined as methods women may use after intercourse to prevent pregnancy. The available regimens include combination oral contraceptives, oral progestin, and the IUD. Two tablets of Ovral, or four tablets of Nordette, Levelen, Lo/Ovral, Triphasil, or Tri-Levlen taken as two doses, 12 hours apart, within 72 hours of unprotected intercourse. “Preven” is a product with ethinyl estradiol and levonorgestrel which is specifically approved for emergency contraception. This reduces the risk of pregnancy by 74%. Nausea and vomiting are the most common side effects. Women should be counseled about STD screening, contraceptive options (emergency contraception is not as effective as other methods), and the need to check a pregnancy test if there is a delay in menstruation. The IUD may be inserted within five days of unprotected intercourse. A progestin only regimen of two doses of levonorgestrel (0.75 mg) given 12 hours apart is also effective, with less nausea than the combined oral contraceptive regimens. “Plan B” is a product with levonorgestrel which is specifically approved for emergency contraception.

**Major Take Home Points**

1. Surgical sterilization of women and oral contraceptive use by women are the most common methods of contraception in the U.S., and are some of the most effective methods.

2. Contraindications to combined estrogen/progesterin OCP use are thromboembolic disorders, cerebrovascular accidents, coronary artery disease, liver abnormalities, estrogen dependent cancers, pregnancy, undiagnosed vaginal bleeding and tobacco use over age 35.

3. Noncontraceptive benefits of combined oral contraceptives include decreased endometrial cancer, uterine cancer, benign breast disease, ovarian cysts, uterine fibroids, ectopic pregnancy, menstrual irregularities, salpingitis, rheumatoid arthritis, endometriosis, atherosclerosis, and increased bone density.

4. Intrauterine devices are safe and effective contraceptive methods especially for monogamous females near the end of their reproductive careers.

5. Barrier methods and rhythm methods are highly dependent on the individuals involved.

6. Pregnancies in women who have undergone a surgical sterilization should be considered ectopics.
until proven otherwise. Likewise, a positive pregnancy in a woman with an IUD may be an ectopic pregnancy.

7. Good contraceptive options for lactating women include barrier methods, progestin only methods, the IUD, and sterilization.

8. Emergency contraception reduces the risk of unintended pregnancy by at least 74% after unprotected intercourse or contraceptive failure.

References

Sexually Transmitted Diseases
Paul R. Summers, M.D.
Department of Obstetrics and Gynecology

Without exception, the spread of disease during sexual contact requires a sequence of events that involve the infectious source, as well as the new host. Exposure to a critical number of microbes is an essential requirement before disease transmission can occur. To invade through the protective layer of the stratum corneum, these microbes first must be able to adhere to the exposed epithelium. Adherence requires the presence of specific binding sites that are generally native protein sequences within the skin. Skin microtrauma during sexual relations may compromise the skin barrier by increasing the number of exposed binding sites. The integrity of the local skin barrier and mucosal immunity act as the chief defenses against the sexual transmission of infection. Failure of this defense system in the genital area allows sexual transmission of disease.

I. What is a Sexually Transmitted Disease

A wide variety of microbes are transmitted by sexual contact. The majority of these microbes can colonize the genital area, but do not cause disease. A disorder attributed to one of the limited number of microbes that can produce disease is termed a sexually transmitted disease (STD). To be considered an STD, the origin of the infectious microbes as well as the site of microbial invasion in the new host must be the reproductive organs.

Contrary to reasonable expectations, STD transmission usually does not result in symptomatic disease. Thus, many more individuals are STD carriers than symptomatic cases. This frequent delay or failure to develop symptoms is problematic for STD prevention and control. Most infected individuals are not aware of their STD, do not seek treatment, and may spread the infection unknowingly.

Factors that influence development of symptomatic disease are only partially understood. Herpes simplex infection is likely to remain unrecognized because of decreased visibility of the lesions if the vagina or cervix is the primary site of infection. Trichomonas infection is typically symptomatic in the female, but asymptomatic in the male. This may be due to a smaller number of the estrogen-dependent trichomonas binding sites in the male genital epithelium. In contrast, there is no explanation why chancroid is generally less severe for the female and is diagnosed 10 times more frequently in the male.

II. Who is at Risk

The physical contact required for reproduction provides an opportunity for transfer of microbes. Any life form that replicates sexually is then theoretically at risk for STDs. Table I gives some examples of non-human STDs.

Consistent with the observation that humans suffer from many more diseases than lower life forms, the largest majority of recognized STDs afflict humans. The small number of STD’s that have been recognized in non-primates are generally viral. Some pathogenic plant viruses infect pollen, and infection can then be spread from plant to plant by pollinating insects. Of the few known STDs in lower mammals, canine herpesvirus infection most accurately mimics the manifestations of its counterpart in humans. The canine virus is biochemically similar to human herpes simplex virus, but dogs are its only host. Bacteria that are significant sexually transmitted pathogens in humans, such as Neisseria gonorrhoea and Treponema pallidum, have no pathologic significance for dogs or cats. Thus, it is difficult to find animal models to study human STDs.

Populations that are at higher risk for STDs have been identified. Human STD risk factors include youth, low socioeconomic status, drug abuse, multiple sexual partners, or a partner with risk factors. In popular literature, STDs have been inaccurately characterized as a problem limited to night clubs and
prostitutes, but these social factors only contribute a relatively small number to the large group at risk. Careful investigation may reveal evidence of microbes that cause STDs in 30% of the general population during the reproductive years. Yet, the range varies widely among different groups, from under 5% to over 90%. Many in the high risk groups have markers for multiple STDs.

III. Consequences of Sexually Transmitted Diseases

Infertility as a result of STDs is a problem unique to humans, specifically women. STD-associated infertility is generally due to fallopian tube occlusion from untreated chlamydia or gonorrhea. A chlamydia antibody screen may be part of the routine female infertility evaluation.

When symptomatic, the majority of STDs have local manifestations. Generally, the genital lesions are annoying but not life-threatening. Some are only transient and may resolve spontaneously after a few months (warts and molluscum contagiosum), but others may be recurrent (herpes) or persistent (trichomonas, lymphogranuloma venereum, granuloma inguinale). Table II lists STDs that may have systemic manifestations, often associated with significant disability. These diseases are occasionally life-threatening.

Immunocompromise from chemotherapeutic agents, immunosuppressant drugs or acquired immunodeficiency syndrome results in more dramatic manifestations of STDs. Genital lesions are larger, more destructive, and are often resistant to therapy. Systemic symptoms progress more rapidly and are more severe.

Antepartum or intrapartum spread to the neonate occurs with some STDs. The manifestations of disease are often more severe in the neonate than in the mother. This is partially due to the immaturity of the fetal immune system. Several of these diseases disrupt organogenesis as well, and can lead to significant congenital anomalies and mental retardation. Table III lists some STDs that have an adverse fetal effect during pregnancy.

IV. What is not an STD

Many microbes are transmitted by intimate contact, yet all do not qualify as STDs. Our current understanding of the pathophysiology of vulvovaginal candidiasis is best characterized by limited truth but extensive folklore. Thus, the popular belief that candida infection is an STD has little scientific basis. Sexual partners typically are colonized with the same DNA serotype of *Candida albicans* but symptomatic candidiasis are most likely associated with local factors other than intercourse. Similarly, genital group B streptococcal colonization is sexually shared, but it is asymptomatic and it is not generally viewed as an STD.

Vulvodynia, chronic vulvar pain often made worse during intercourse, is not characteristic of any STD. The cause for this unfortunate pain often remains obscure, but may be related to vulvar irritant dermatitis or some other dermatopathology. The exacerbation of pain by sexual intercourse often raises the false concern that there may be an STD.

V. Alternate Means of STD Transmission

It is possible for some STDs to be spread by non-sexual contact. Syphilis, HIV, and HBV can be transmitted to laboratory and hospital personnel by blood contact. Blood banks routinely screen donor blood for these diseases. Improperly sterilized surgical instruments may also transmit these disorders. Hand contact with HSV and HPV lesions may spread these infections to other body sites as well as to other individuals. Most STD pathogens are not hardy enough to persist on inanimate objects. Although the theoretical possibility exists at least for HPV and molluscum contagiosum, it is unlikely that an STD will be contracted from contaminated door knobs or toilet seats.

VI. STD Treatment versus Eradication

Pharmaceutical research is providing better agents for STD treatment. New antibiotics that are effective as a single oral dose, such as azithromycin, substantially improve compliance with therapy. There is renewed interest in vaccines for STD prevention. As research reveals the mechanisms of STD pathophysiology, drugs that inhibit adhesion or improve the immune defenses may become available.
Unfortunately, STDs can not be eliminated by antimicrobial protocols alone. The more optimal management of STDs includes lifestyle changes that would eliminate exposure. Social planning that could eradicate STDs is unrealistic because of the necessary restrictions of free agency, and community education programs are expensive. STD clinics are often poorly funded, work with high volumes of patients, and use primitive equipment. In this setting, adequate STD therapy remains challenging, and STD prevention often appears impossible. Thus, STDs remain a social problem with no easy solution. The advocacy of abstinence or condom use to limit microbial exposure is the only social planning that has achieved general approval. Even with our expanded technology, social considerations suggest that STDs are likely to persist as a significant health threat.

**GENERAL CONCEPTS**

**Etiology and Epidemiology**

1. The popular understanding of sexually transmitted diseases (STDs) has inaccurately characterized STDs as a problem limited to night clubs and prostitutes. The majority of cases have some other history.
2. Most cases are associated with youth, an unstable life style, drug abuse, low socioeconomic status, multiple sexual partners, or a partner with risk factors.
3. On the average, one adult out of three has evidence of an STD. The prevalence of STD markers varies widely, from less than 5% to greater than 90%.
4. Many in the high risk groups have markers for more than one STD.
5. Immunocompromise (AIDS, chemotherapy, leukemia) results in more dramatic manifestations of STDs. Lesions are larger, with more tissue destruction. Systemic symptoms progress more rapidly and are more severe. Resistance to standard therapy is common.
6. Some STDs can be spread by non-sexual contact.
   a. Syphilis, AIDS, and hepatitis B can be transmitted by blood contact. Intravenous drug abusers, emergency rescue workers, and laboratory or hospital personnel are at risk. Blood banks routinely screen donor blood for these diseases. Inadequately sterilized surgical instruments also may transmit these disorders.
   b. Hand contact with herpes or warts may spread these infections to other body sites as well as to other individuals.
   c. Most STD pathogens are not hardy enough to persist on inanimate objects, although the possibility exists at least for human papilloma virus and for the virus of molluscum contagiosum. It is unlikely that an STD will be contracted from contaminated door knobs or from toilet seats. Mites (scabies and pediculosis pubis) persist in clothing and bedding.

**Symptoms**

1. The majority of STD cases are asymptomatic and many who are infected do not seek treatment. Thus, more individuals are STD carriers than symptomatic cases.
   a. Females with trichomonas infection and bacterial vaginosis are typically symptomatic, but men are not.
   b. Chancroid is generally less symptomatic for the female and is diagnosed 10 times more frequently in the male.
   c. Lesions in the vagina or on the cervix often are not detected.
   d. Thus, STDs are typically spread unknowingly.
2. Some STDs are annoying, but are not life-threatening (trichomonas, bacterial vaginosis, genital warts, molluscum, scabies, pediculosis pubis).
4. STDs can cause birth defects (syphilis), or serious infection in the newborn (syphilis, herpes, gonorrhea, chlamydia).
5. Some STDs may cause infertility from fallopian tube occlusion (gonorrhea, chlamydia). Infertility as a result of STDs is a problem unique to humans. A chlamydia antibody screen may be part of the routine female infertility evaluation.

Clinical Findings
Typical manifestations of symptomatic cases follow:
1. Generalized rash: Initial infection with human immunodeficiency virus, secondary syphilis, disseminated gonorrhea. A rash in an adult should be considered to be syphilis until proven otherwise.
2. Localized ulcer: Syphilis, chancroid, herpes.
3. Localized papules: Warts, molluscum, scabies.
6. Inguinal lymphadenopathy: Chancroid, syphilis, primary herpes, lymphogranuloma venereum, granuloma inguinale.
7. Pubic pruritus: Pubic lice, scabies.
8. Dysuria: Chlamydia, gonorrhea, trichomonas, herpes.

Laboratory Tests
Initial diagnosis is often based upon clinical findings, but laboratory tests can be confirmatory, as follows:
1. Blood tests: Syphilis (RPR confirmed by FTA), Human immunodeficiency virus infection (HIV antibody screen, confirmed by Western blot).
2. Microscope examination of material from an ulcer or lesion: Chancroid, herpes, syphilis, scabies.
5. Biopsy of lesion: Lymphogranuloma venereum, granuloma inguinale, warts.

Differential Diagnosis
The working differential diagnosis is based upon clinical manifestations, such as genital ulcers, lymphadenopathy, vaginal discharge or rash. See clinical findings section above.

Treatment
1. Use single dose antibiotic agents if possible. Compliance is poor with 7 day therapy.
2. Many patients have more than one STD. For such cases, simultaneous therapy with 2 or more antibiotics is appropriate. Adverse antibiotic interactions are rare.
3. Empiric therapy may be started for any presumed diagnosis if confirmatory tests are not immediately available.
4. Empiric therapy should consider the most consequential diagnoses in differential if labs not immediately available.
5. Test all primary sexual contacts of identified cases, but primary contacts should be treated even if tests are negative.
6. Test all secondary contacts (other sexual partners of primary contacts) and treat if tests are positive or if disease is suspected.
7. Patient education regarding abstinence, monogamous relationships, or condom use to limit microbial exposure are the only social planning measures that have achieved general approval.

Follow-up
1. Repeat cultures to test for cure 3 weeks after chlamydia or gonorrhea therapy.
2. Serology should be repeated for syphilis (RPR titer) and for HIV infection (HIV antibody) after 3 to 6 months if initial tests are negative.
3. Annual screening is recommended for the population at risk for syphilis, gonorrhea, chlamydia, cervical dysplasia, and HIV.
MENSTRUAL DISORDERS AND OTHER COMMON
GYNECOLOGY PROBLEMS

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Objectives:
At the end of this lecture, you should be able to:

1. Discuss the etiology, pathophysiology, and treatment of the three common menstrual disorders: dysmenorrhea, abnormal menstruation, menorrhagia, metrorrhagia, intermenstrual bleeding.
2. Identify the major causes of urinary incontinence in women, and be familiar with their treatments.
3. Discuss the pathophysiology of uterine leiomyomata (fibroids), its clinical presentation, and treatment options.

I. Menstrual Disorders

Definitions:
- dysmenorrhea: pelvic pain during menstruation
- polymenorrhea: frequent but regular episodes of uterine bleeding, usually at intervals of 21 days or less.
- menorrhagia (hypermenorrhea): uterine bleeding excessive in amount and duration of flow, occurring at regular intervals.
- metrorrhagia: uterine bleeding, usually not excessive, occurring at irregular intervals.
- intermenstrual bleeding: uterine bleeding occurring between otherwise regular menstrual periods.
- "normal": every 24-32 days, lasting 3-7 days, average loss 30cc, 80% blood loss occurs in first two days.

A. Dysmenorrhea affects over 50% of all postpubescent women, 5% are incapacitated for 1-3 days each month.

1. Primary dysmenorrhea is painful menses without evidence of an organic lesion or cause, usually brief, and worst on the first day of menstruation. This type of dysmenorrhea is seen in ovulatory menstrual cycles, usually within five years of menarche, and improves with age. Most theories center around excess prostaglandin PGF2alpha, resulting in smooth muscle contraction. The role of estrogen and progesterone is unclear: estrogen is a stimulator of uterine activity, and progesterone is an inhibitor. Yet women with high levels of estrogen, such as those with anovulatory cycles and obesity, typically do not experience much dysmenorrhea.

Treatment of primary dysmenorrhea usually is aimed at prostaglandin inhibition or suppression of cycles. Other non-specific measures such as heat, mild analgesics, and exercise should be encouraged, but narcotics are not used.

Does the patient need contraception: Does she have other complains which make suppression of menses favorable?
If yes,
   1. oral contraceptives
   2. continuous progesterone (Depoprovera)

If no,
   1. non-steroidal anti-inflammatory agents: mefenamic acid (Ponstel 500mg t.i.d.), naproxen (naprosyn, anaprox 550mg stat, then 275 mg q.i.d.)
   2. if not helpful, consider suppression of menses

2. **Secondary dysmenorrhea** accounts for 20% of all dysmenorrhea, usually develops later than primary, and is due to an underlying condition. Treatment is aimed at correcting the underlying condition:
   a. adenomyosis: gland-like growth into myometrium
   b. endometriosis: ectopic endometrial tissue
   c. fibroids: (covered separately)
   d. intrauterine devices (IUD)
   e. endometritis: chronic infection of uterus
   f. congenital uterine anomalies: menstrual flow may lack an outflow tract.
   g. other: ovarian cysts, pelvic varicosities

B. Abnormal Uterine Bleeding is defined as any bleeding which is considered excessive in frequency, duration, or amount **by the patient**, and as such should be evaluated. The pathophysiology involves hormonal balances, pregnancy, structural abnormalities, and cancer. In general, we worry about bleeding more often than 21 days, lasting seven days or longer, or with large clots.

1. If the patient is **ovulatory**, causes include:
   a. endometrial polyps
   b. submucous fibroids
   c. chronic endometritis

2. If the patient is **anovulatory**, causes include:
   a. dysfunctional uterine bleeding (DUB)
   b. menarche
   c. extrinsic hormone effects
   d. perimenopausal bleeding: hyperplastic, neoplastic

Dysfunctional and perimenopausal bleeding merit further discussion. DUB is the result of persistent anovulation where the endometrial lining does not shed in a synchronous fashion. Consider exogenous or endogenous sources of excess estrogen, such as peripheral conversion of androgens to estrone in obese individuals. Unopposed estrogen can lead to endometrial hyperplasia: we usually sample the endometrial lining in women aged 35 years or older who experience DUB. Perimenopausal bleeding is also anovulatory bleeding and should be evaluated for hyperplasia.

The evaluation includes a pelvic exam, and may include an endometrial biopsy. Hysteroscopy visualizes the endometrial lining to identify polyps, fibroids, anomalies, and direct biopsies. Blood work includes a hematocrit, thyroid studies, prolactin, and pituitary hormones (LH, FSH) in select individuals. **Don't forget pregnancy as a cause of abnormal uterine bleeding**! To biopsy or hysteroscope such a patient would be disastrous.
Treatment of abnormal uterine bleeding:

1. If the abnormality is anatomic, surgically remove polyps or fibroids. Antibiotic therapy is used for chronic endometritis, or an IUD may be removed. Failing these, the patient may be considered for endometrial ablation or hysterectomy.

2. If the abnormality is anovulation, exogenous progestins, estrogens, or combination therapy are used.
   a. acute severe bleeding is an emergency, seen in menarchal girls and perimenopausal women. Stabilize the patient with fluids, consider pregnancy and bleeding dyscrasias. IV Premarin (conjugated equine estrogens) is used, and is thought to stabilize the spiral arteries of the endometrium. A dilation and curettage (D&C) in the operating room is rarely used.
   b. in less severe cases, a "chemical D&C" is accomplished with a progesterone shot, 10 days of medroxyprogesterone 10 mg, or oral contraceptive pills in high doses (2-4 per day.) The progesterone effect is to shut down estrogen receptors, and withdrawal from progesterone triggers the shedding of the endometrium. The patient is then cycled on oral contraceptives for several months thereafter.
   c. chronic anovulatory bleeding may be managed by observation, oral contraceptives, cyclic progesterone, or ovulation induction. If hyperplasia has been diagnosed in high risk individuals, progesterone must be used to reverse the effects of chronic anovulation. Only hyperplasia with atypia is considered a premalignant lesion.

3. Premenstrual Syndrome (PMS)

This is felt to be an exaggerated presentation of molimina, the symptoms that many women experience in the luteal phase of the cycle and which accompany ovulatory cycles. An important attribute is that symptoms are found in the luteal phase, and absent in the postmenstrual week. Although many hypotheses exist, the etiology is essentially unknown.

Several key points in PMS:

   a. all that cycles is not PMS. Some conditions vary with the menstrual cycles, including thyroid size, basal body temperature, and alcohol metabolism. Other conditions are exacerbated, but not caused by phases of the menstrual cycles: migraine, seizure disorders, asthma, genital herpes, and even angina. Mood disorders may commonly be exacerbated in the luteal phase.

   b. all premenstrual changes may not be PMS. Molimina should not be labelled as PMS unless they are severe enough to disrupt daily life and family interactions, or affect alcohol, drug use, or suicidal thoughts.

   c. PMS may be more than one entity. It is unclear why some women have emotional effects (depression, emotional lability), while others experience physical effects (water retention, pain, breast tenderness.)

Evaluation is usually made by history alone; there are no specific physical findings or laboratory abnormalities. A calendar of symptoms should clearly demonstrate a luteal phase effect, with absence of symptoms after menstruation.
Management is empiric, since the etiology is unknown. Even recent textbooks of gynecology suggest that most women suffering from PMS are somehow "causing it" and that successful treatment depends on a "responsive and cooperative patient who wants to get better." Overcoming these stigma and acknowledging symptoms as real pathology is an important part of therapy.

FLOW DIAGRAM FOR TREATMENT OF PMS

Conservative measures, little evidence
- non-steroidal anti-inflammatory agent
- no caffeine (forever)
- low sodium diet 7-10 days prior to menses
- exercise
- six feedings a day Q meals, 3 protein/complex carbo snacks
- vitamin B6, calcium
- family or marital counseling

Evidence-based treatment
- Prozac
- oral contraceptives

II. Urinary incontinence in women

A. Stress urinary incontinence is the loss of urine with coughing, sneezing, laughing, or other increases in intra-abdominal pressure. The pathophysiology is incomplete transmission of intra-abdominal pressure to the bladder neck (where the bladder meets the urethra.) Baseline bladder pressure 10 cm H20 baseline urethral pressure 50 cm H20

1. Good transmission, no stress incontinence

2. Poor transmission, stress incontinence
Evaluation includes history, exam excluding large post void residuals, and hypermobility of the bladder neck. Because symptoms may be confusing or mixed, further urodynamic testing may be needed. A cystometrogram (CMG) measures pressures in the bladder, urethra, and vagina, and can distinguish stress from urge incontinence.

Treatment is driven by the patient's needs: mild-to-moderate stress incontinence treated with
a. pelvic floor exercises
b. devices to stabilize the bladder neck
c. medications to increase intraurethral resting pressure.

Moderate-to-severe stress incontinence is often treated by surgery aimed at supporting and stabilizing the bladder neck. This is the only type of incontinence to improve with surgery; compromised voiding is a common adverse outcome. Surgical procedures include Burch colposuspension and pubovaginal sling.

B. Urge incontinence (detrusor overactivity, unstable bladder) is the sudden loss of urine associated with a uninhibitable detrusor contraction, mediated by parasympathetics. Clinically, patients experience urgency, frequency, nocturia, and nocturnal enuresis. Common antecedents are listening to running water, or arriving home and unlocking the door. Evaluation is as above, but looking for neurologic abnormalities. A bladder diary may show excess fluid output, small voided volumes, etc.

Treatment of urge incontinence is NOT surgical. Patients are offered bladder retraining, timed-voiding, and behavior modification. Some patients need anticholinergic agents such as tolterodine (Detrol)
4 mg qd or oxybutynin (Ditropan) 5-15 mg qd.

III. Leiomyomata uteri (fibroids)

This condition is seen in 20-30% of women 35 years and older. It is often asymptomatic and should be followed clinically. Uterine enlargement should be noted, and the adnexae may need to be evaluated with ultrasound because the size of the uterus limits palpation of other structures. Because the condition is common and malignant degeneration is rare (less than 0.2%), it is not necessary to perform ultrasound or endometrial sampling. The tumors are smooth muscle, and are estrogen responsive. Therefore, most fibroids will regress postmenopausally even with hormone replacement therapy.

Bleeding may result from submucosal fibroids: the endometrium is distorted over the mass, and normal mechanisms of shedding are compromised. In women with abnormal uterine bleeding unresposive to hormonal management, a hysteroscopy or ultrasound may reveal a submucosal Fibroid. Hysteroscopic resection or hysterectomy is the usual treatment after failure of medical management. GnRH agonists may be used short-term to shrink fibroids for easier surgical management. Fibroids which outgrow their blood supply may become painful. Myomectomy is usually reserved for women who wish to preserve fertility, since other fibroids are likely to grow. The most common clinical manifestation of fibroids is discomfort due to the mass itself. Although hysterectomy was previously recommended for enlargement the size of a twelve week pregnancy or greater, now most fibroids are followed clinically until menopause.
IV. Major take-home points:
1. Dysmenorrhea is very treatable with NSAIDs or oral contraceptives.
2. Abnormal uterine bleeding needs to be evaluated, especially in women aged 35 years or older.
3. PMS is not in her head. Prozac is a recognized, very effective treatment.
4. Not all urinary incontinence is the same: stress incontinence and urge incontinence are treated very differently.
5. Fibroids are common, and may be followed clinically in most cases.
PHARMACOLOGY 6040

PHARMACOLOGY OF ESTROGENS AND PROGESTINS
Dr. Crowley

References

Objectives
A. To review the physiological actions and pharmacological effects of estrogens and progestins that are relevant to their clinical uses.
B. To review the adverse effects and contraindications to use of estrogens and progestins.
C. To review the current strategies for the use of estrogens and progestins in oral contraceptives and in hormone replacement therapy in menopause.
D. Review the pharmacology and clinical uses of estrogen and progestin antagonists.

I. PHARMACOLOGY OF THE ESTROGENS
(The naturally occurring estrogens are estradiol 17β (E2), estrone (E1) and estriol (E3).

A. PHYSIOLOGICAL ACTIONS OF THE ESTROGENS

1. Reproductive actions:
   a. Growth and development of primary and secondary female sex characteristics
   b. Physiological changes at puberty (e.g., growth, epiphyseal closure of bones)
   c. Neuroendocrine regulation of the menstrual cycle; negative feedback and positive feedback
   d. Stimulates growth (proliferation) of uterine endometrium
   e. Stimulates secretion of thin cervical mucous (facilitates sperm transport)
   f. Induces thickening, maintains structure of vaginal mucosa

2. Metabolic actions:
   a. Increases circulating High Density Lipoproteins (HDL), decreases low density lipoproteins (LDL)
   b. Increases cholesterol saturation of bile
   c. Increases blood pressure via increased synthesis of renin substrate
   d. Increases synthesis of clotting factors, increased # of platelets and platelet aggregation
   e. Decreases bone resorption
   f. Increases liver weight, synthesis of various transport proteins

   3. Higher CNS functions:
      a. Positive effects on mood, cognition, memory

KEY CONCEPT: These actions are relevant for beneficial and adverse estrogen effects in oral contraceptives and hormone replacement therapy in menopause.
B. PHARMACOKINETICS

1. Biological Activity: E2 > E1 >>> E3
2. Well absorbed from GI tract and transdermally; substantial first pass metabolism of estrogens in liver after oral administration
3. E2 is metabolized mainly to E1 and conjugated; E2 is more rapidly metabolized than the congeners (e.g. ethinyl E2)
4. Pharmacokinetic drug interactions:
   a. Agents that induce cytochrome P450 enzymes can enhance metabolism and interfere w/ therapeutic actions (e.g. unwanted pregnancies). Examples: rifampin, phenytoin, carbamezepine, phenobarbital, topiramate, St. John’s Wort
   b. Some antibiotics may reduce bioavailability.

C. CLINICAL USES OF ESTROGENS

1. As a component of combined oral contraceptives (COC); mainly ethinyl estradiol
2. In HRT during menopause (Premarin ® most widely used)
3. HRT in hypogonadism in women
4. Rx of dysmenorrhea, dysfunctional uterine bleeding (oligomenorrhea) and some amenorrheic states; perimenopause
5. Rx of delayed puberty
6. Rx of acne

D. REPRESENTATIVE ESTROGENS AND PREPARATIONS
(OC, oral contraceptives; HRT, hormone replacement therapy)
(Note: those in bold on UUHSC Commonly Used Drugs List)

1. Estradiol and derivatives
   a. ethinyl estradiol (OC, HRT)
   b. micronized estradiol (Estrace ®) (HRT)
   c. transdermal estradiol (Vivelle®, CombiPatch® ) (HRT)
   d. Also in topical creams and vaginal ring

2. estrone and derivatives
   a. conjugated equine estrogens (Premarin®) (HRT)
      1. mainly estrone sulfate and equilin sulfate in Premarin
      2. conjugated human and equine estrogens (Cenestin ®)
   b. piperazine estrone sulfate, estropipate (Ogen® HRT)

3. Synthetic estrogen: diethylstilbestrol (DES) (OC, HRT)

4. Herbals, dietary supplements, phytoestrogens
   a. black cohosh (or kohosh)
   b. estrogens from soy (phytoestrogens)

E. Anti-estrogens and mixed agonist-antagonists
1. clomiphene (Clomid®) (fertility induction)
2. tamoxifen (Nolvadex®) (breast cancer)
3. reloxifene (Evista ®) (osteoporosis)
II. PHARMACOLOGY OF THE PROGESTINS
The naturally occurring progestin is progesterone.

A. PHYSIOLOGICAL ACTIONS OF PROGESTERONE

1. Neuroendocrine regulation of the menstrual cycle; esp. negative feedback during luteal phase
2. Transforms estrogen-primed proliferative uterine endometrium to secretory endometrium; essential for implantation of fertilized ovum (nidation)
3. Transforms cervical mucus to thick and viscous (inhibits sperm transport)
4. Increase in body temperature (0.5-1.0° F) at ovulation and during luteal phase
5. Essential for maintenance of pregnancy; Inhibits uterine contractility during pregnancy
6. Stimulates development of mammary gland in preparation for lactation
7. Antagonizes some, but enhances other, actions of estrogens

B. PHARMACOKINETICS OF PROGESTINS

1. Progesterone is poorly absorbed after oral administration; other progestins better
2. Drug interactions: similar to the estrogens

C. CLINICAL USES OF PROGESTINS

1. As OC alone, or a component of COC; mainly the 19-norT derivatives
2. In HRT during menopause (mainly medroxyprogesterone)
3. Rx of dysmenorrhea (OC)
4. Rx of dysfunctional uterine bleeding (OC)
5. Rx of endometriosis

D. REPRESENTATIVE PROGESTINS

1. C-21 progestins: medroxyprogesterone (HRT)
2. 19-nortestosterone derivatives: l-norgestrel, norethindrone, norgestimate, desogestrel, norethinodrel (in OC’s)
   (note: 19 nor-T derivatives have some androgenic actions, but norgestimate and desogestrel have less)
3. drospirenone: spironolactone derivative in Yasmin ®, OC

E. Anti-progestin: mifepristone (RU-486)

1. progestin (and glucocorticoid) receptor antagonist
2. abortifacient in first trimester

III. PHARMACOLOGY OF ORAL CONTRACEPTIVES

A. Combination preparations (see table in Katzung p 688; Goodman and Gilman p. 1433)

KEY CONCEPTS: Combination OC’s consist of an estrogen (usually, ethinyl estradiol) and a progestin (usually, one of the 19-nortestosterone derivatives). All (except 1) are taken for 21 days, w/ 7 days off. Estrogen doses range from 20 µg/day to 50 µg/day; P dose from 50 µg/d to 1.5 mg/day
1. **Efficacy**: approx. 0.1% incidence of accidental pregnancy during first year of use.

2. **Mechanism**: primarily via inhibition of gonadotropin secretion, preventing follicular development and ovulation (mimics luteal phase); Plus, progestin component thickens cervical mucus, inhibiting sperm transport

3. **Examples**
   a. Combination monophasic: combination of fixed dose estrogen and fixed dose progestin
      Example: Lo/Ovral 28 ®; 30 µg of ethinyl E2 plus 0.3 mg of levo-norgestrel
      Seasonale ®, a “new” approach. Combination of 30 µg ethinyl estradiol and 150 µg levo-norgestrel taken for 84 days, followed by 7 days placebo
   
   b. Combination biphasic: combination of fixed dose of estrogen and two different doses of progestin
      Example: Ortho-Novum 10/11 ®; 35 µg of ethinyl E2 plus 0.5 mg norethindrone for first 10 days followed by 1 mg norethindrone for next 11 days
   
   c. Example, Combination triphasic: combination of fixed or variable ethinyl E2 and variable progestin
      Examples: Ortho-Tri-Cyclen ®: 21 days of 35 µg ethinyl E2 plus norgestimate; 7 days @ 180 µg, next 7 days @ 210 µg and then 7 days @ 250 µg.
      Triphasil-21 ®: Days 1-6: 30 µg ethinyl E2 plus 50 µg levonorgestrel
      Days 7-11: 40 µg ethinyl E2 plus 75 µg levonorgestrel
      Days 12-21: 30 µg ethinyl E2 plus 125 µg levonorgestrel

4. **Adverse Effects of Combination OC’s:**

   KEY CONCEPT: Early OC preparations contained high doses of estrogen and progestins and were associated with increased incidence of thromboembolic disease, increased risk of MI and stroke, and increased blood pressure,. The estrogenic component was primarily responsible. These risks have been markedly reduced with modern low-dose OCs.

   a. nausea and vomiting (E)
   b. breast tenderness (mastalgia) (E)
   c. exacerbation of migraine headache (E or P)
   d. melasma, chloasma (E)
   e. water retention (E or P)
   f. weight gain (E)
   g. acne (P)
   h. decreased glucose tolerance (E)
   i. breakthrough bleeding (too low E)

5. **Absolute contraindications to use of combination OCs**

   a. Past or present history of thromboembolic disease, thrombophlebitis
   b. Past or present history of cardiovascular disease, esp. cerebrovascular disease, coronary artery disease, and MI
   c. Heavy smokers (1 pack +) over 35
   d. Past or present history of estrogen-dependent neoplasia, esp. carcinoma of the breast and endometrium*
   e. Undiagnosed abnormal vaginal bleeding
f. Impaired liver function, jaundice, hepatic adenoma

g. Pregnancy or lactation

**Note:** In absence of known or suspected breast cancer, OC use does not appear to increase risk of breast or endometrial cancer

6. Relative contraindications to use of combination OCs

   a. migraine headache (esp. w/ aura)
   b. hypertension
   c. diabetes
   d. gall bladder disease
   e. major surgery

7. Health Benefits of Combination OCs

   a. menstrual improvements: predictable menses; deceased dysmenorrhea; decreased anemia; regularizes dysfunctional uterine bleeding
   b. Rx symptoms in perimenopausal transition
   c. protective against ovarian, endometrial and colorectal carcinoma
   d. protective against ovarian cysts
   e. protective against fibrocystic and other benign breast disorders
   f. protective against pelvic inflammatory disease
   g. protective against rheumatoid arthritis
   h. positive effect on bone density; may decrease risk of osteoporosis in menopause

**B. Progestin only contraceptives**

1. Examples
   a. Oral (minpill) Examples: norethindrone (Micronor®, Nor-QD®) levo-norgestrel (Ovrette®, Microval ®)
   b. Long-acting injectable progestin: Depo-Provera® (medroxyprogesterone acetate)
   c. Progestin implant: Norplant ® (levo-norgestrel)
   d. Progestin-containing IUD (Progestasert® ; Mirena ®)
   e. vaginal ring (Crinone®)

2. **Efficacy:** failure rates between 0.1% (Norplant) and 0.5% (minipills)

3. **Mechanism:** some inhibition of ovulation; mainly changes in cervical mucus that inhibit sperm transport and fertilization
   IUD: also inflammatory reaction that inhibits sperm transport

3. **Adverse effects:**
   a. irregular, unpredictable bleeding
   b. weight gain*
   b. acne*
   c. unfavorable lipid profile, decrease HDL and increase LDL*
   d. mood changes, esp depression
e. nausea
f. headache
* esp in androgenic progestins

**Note:** Progestin-only contraceptives are a good choice during lactation; estrogens may interfere with milk production

**C. Emergency (post-coital) contraception**

1. **Mechanism:** When administered within 72 hr of unprotected intercourse, high doses of ovarian steroids may, depending on timing, 1) inhibit ovulation, 2) inhibit sperm transport, 3) inhibit implantation of the blastocyst (nidation)

2. **Regimens:**
   a. (Yuzpe regimen): Two pills of COC taken within 72 hrs of intercourse followed 12 hours later by a second dose; Example is Preven ®: ethinyl estradiol plus levo-norgestrel
   b. levonorgestrel only, e.g., in Plan B®, or Ovrette; same regimen as Yuzpe method

3. **Efficacy:** 75-90 % inhibition of pregnancy

4. High doses associated with **adverse effects:**
   a. nausea and vomiting
   b. headache, dizziness
   c. mastalgia
   d. abdominal and leg pain

**IV. HORMONE REPLACEMENT THERAPY IN MENOPAUSE**

**A. Physiology of Menopause:** defined (retrospectively) as the last menstruation; diagnostically if one year since last menses and plasma FSH > 25 mIU/ml.

(Avg. age in U.S. fitting this definition: 51 yrs w/ large variation; range 40-58 years)

1. Physiological basis: exhaustion of supply of ovarian follicles, loss of cells that secrete estradiol, progesterone; estradiol reduced to castrate levels; less active estrone from conversion of androgens; removal of negative feedback elevates the gonadotropins, no cycles

2. Perimenopause: transition to menopause, early onset of symptoms, esp. vasomotor, insomnia, mood changes, irregular cyclicity; may begin in late 30’s, early 40’s

**KEY CONCEPT:** Most adverse events in menopause result from estrogen deficiency.

<table>
<thead>
<tr>
<th>Early symptoms</th>
<th>Physical changes (intermediate)</th>
<th>Disease development (Longer term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor instability (70%)</td>
<td>Urogenital atrophy (60%)</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Insomnia (55%)</td>
<td>Urinary incontinence</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Fatigue (90%)</td>
<td>Recurrent genital tract infection</td>
<td>Dementias (?)</td>
</tr>
</tbody>
</table>
Mood changes (90-95%) | Skin atrophy, loss of collagen
---|---
(% reporting)

B. Major indications for HRT in menopause:
1. vasomotor instability (hot flashes or flushes, night sweats)
2. mood changes
3. urogenital atrophy
4. prevention and Rx of osteoporosis

C. HRT preparations commonly used:
1. conjugated equine estrogens (Premarin®, Cenestin®), usually 0.625 mg/day, po
2. micronized estradiol (Estrace®), po
3. E2-17β in skin patch (Vivelle®)
4. Medroxyprogesterone (Provera®, Cycrin®), po
5. Combination products: Prempro®, Premphase®, Premarin® plus Cycrin®, po
6. CombiPatch®: transdermal E2-17β plus medroxyprogesterone

**KEY CONCEPT:** The progestin component is included only to prevent uterine hyperplasia and carcinoma.

D. Some typical regimens

1. Daily estrogen only (ERT): only appropriate for women w/o uterus
2. Cyclic estrogen and progestin (Cyclic sequential): estrogen for days 1-25; Cycrin on days 14-25; no drugs days 26-28.
   withdrawal bleeding will occur after P, menopausal symptoms may reoccur on days 26-28.
3. Cyclic combined: estrogen plus Cycrin on days 1-25; no drugs days 26-28.
   withdrawal bleeding will occur after P, menopausal symptoms may reoccur on days 26-28.
4. Continuous estrogen, cyclic progestin (Continuous sequential): estrogen every day, 5 mg Cycrin on days 1-12.
   withdrawal bleeding will occur after P
5. Continuous estrogen and progestin: estrogen and 2.5 mg Cycrin every day.
   - amenorrhea in most

E. Androgens in HRT
1. may improve symptom relief; improves skin tone, muscle mass and strength
2. Estratest®: esterified estrogens plus methyltestosterone; Premarin with methyltestosterone combination

E. Effects of HRT

1. reduces incidence and severity of vasomotor instability episodes; alternative, medroxyprogesterone
2. reduces vaginal atrophy; reduces urinary incontinence, urinary frequency, reduces incidence of urogenital infections
3. Reduces fatigue and depression

4. FDA-approved for prevention of osteoporosis; inhibits bone resorption and prevents bone loss and increases bone density; reduces incidence of wrist, vertebral and hip fractures
   Women’s Health Initiative results lead FDA to recommend that HRT be used to prevent osteoporosis if benefits outweigh risks
   The Women’s Health Initiative (2002) and additional studies since then show no cardioprotective effect and perhaps a small increase in risk of cardiovascular disease; the women’s Health Initiative Memory study shows no protective effect on, and a significant increase in risk of Alzheimer’s Disease.

F. Common adverse effects of HRT

**KEY CONCEPTS:** Biological activities of estrogens used in HRT are generally lower than in OCs. The relative and absolute contraindications to estrogen use are similar to those for OCs.

1. estrogen component assoc w/ nausea, mastalgia, headache, fluid retention
2. progestin component assoc w/ weight gain, headache
3. androgen component assoc w/ acne, hirsutism

G. HRT and Cancer

1. Unopposed estrogen taken for 5 years increases the risk of endometrial hyperplasia and cancer by 5-fold, and by 8-fold if taken for longer than 5 years. Nearly eliminated by addition of progestin.

2. Reports on risk and incidence of breast cancer w/ HRT. Little or no increased risk for HRT < 5 yrs.; for 10-15 yrs RR ~1.3, from US. studies
   Progestin component now believe to contribute significantly

3. Results from the Million Women Study (UK) (see Lancet 362: 414-427, 2003):
   a. Overall relative risk for breast cancer incidence in current users vs. never-users was 1.66
   b. Overall relative risk of breast cancer death was 1.22, same comparison
   c. Risk increase with duration of use
   d. No risk for past users
   e. Risk was higher in estrogen+progestin vs. estrogen alone
   f. No differences continuous v. sequential regimens or specific compounds; no difference oral vs. transdermal

4. Reduces risk of colon cancer

Check out the North American Menopause Society web page ([www.menopause.org](http://www.menopause.org)) for a well written up to date summary of the current literature and recommendations.
CLINICAL GENETICS

Objectives
1. To know and understand pertinent areas to cover when eliciting a genetic history from a patient.
2. To know and understand the different types of genetic abnormalities: chromosomal, single gene defects (Mendelian disorders), multifactorial polygenic.
3. To know and understand the indications, advantages, and disadvantages of several prenatal invasive diagnostic procedures.
4. To be familiar with several molecular techniques used for prenatal diagnosis.

Definitions
Aneuploid: A haploid gamete or diploid cell lacking the expected number of chromosomes (n or 2n)

Translocation: Following the chromosomal breakage, material may be exchanged between two or more chromosomes. When no genetic material is lost, the translocation is balanced. Translocations may be reciprocal or robertsonian (acrocentric chromosomes: chromosomes 13, 14, 15, 21, 22).

Single gene: The DNA sequence encoding a single protein.

Mendelian Inheritance: Genetic traits that follow the Mendelian laws of segregation and independent assortment.

Multifactorial/polygenic: A combination of genetic and environmental factors must be invoked for anomalies whose recurrence risks are greater than the general population but less than that expected on the basis of a single recessive or dominant gene (25% and 50% respectively).

Polymerase chain reaction (PCR): Amplification of short sequences (up to 2kb) of DNA without the need for cloning. This method is based on the use of DNA primers that are complementary to sequences on either side of the DNA of interest. Approximately 35 cycles of denaturation (95oC), primer annealing (60oC) are then performed.

Genetic amniocentesis: The prenatal diagnostic procedure involving a needle puncture into the amniotic sac and obtaining amniotic fluid which contains cells of fetal origin. These cells can then either be used directly for fetal DNA analysis or cultured for fetal karyotype.

Percutaneous umbilical cord blood sampling (PUBS): The prenatal diagnostic procedure involving a needle puncture into the fetal umbilical blood vessels and obtaining fetal blood. The fetal blood then may be used directly for fetal DNA analysis, cultured for fetal karyotype, a fetal blood count, or assessment of fetal acid base status.

I. Genetic History-Taking and Genetic Counseling

A. American College of Obstetricians and Gynecologists (ACOG) recommendations 21.4% of couples will show at least one positive response, with 7.8% requiring
formal genetic counseling. Advanced maternal age is the most common
indication for further testing.

B. The genetic history
1. Inquire about the health status of 1st, 2nd, and 3rd degree relatives.
   Record abnormal reproductive outcomes such as repetitive spontaneous
   miscarriage, stillbirths, and anomalous fetuses.
2. Record maternal and paternal drug exposure.
3. Record maternal and paternal ages.
4. Record maternal and paternal ethnic origins.

C. Principles and prerequisites of genetic screening
   Screening programs versus case detection programs
   1. Voluntary
   2. One does not expect to detect all affected cases in a given population
   3. Establishing technical feasibility for screening a given disorder alone
does not justify screening.
      a. Capacity to alter clinical management
      b. Cost-effectiveness
      c. Reliable means of assessment
      d. Capacity to handle problems
      e. Specific indications for heterozygote genetic screening

D. Principles of genetic counseling
   1. Communication
   2. Nondirective

II. General Principles

A. Cytogenetics – Numerical Chromosomal Abnormalities
   1. Karyotype
   2. Aneuploidy – lacks the expected number of chromosomes (n or 2n)
      a. Trisomy (2n +1) Meiotic or mitotic nondisjunction
      b. Polysomy – additional sex chromosome (ex: 47XXY)
      c. Monosomy (2n – 1)
      d. Polyploidy – more than two haploid sets of chromosomes
         Triploidy – (3n = 69) most common
         Large Placenta such as in multiple gestation and pregnancies
         complicated by fetal erythroblastosis. Dispermy most
         common mechanism.

B. Cytogenetics – Structural Chromosomal Abnormalities
   1. Karyotype and chromosomal banding patterns
      a. Types
         i. Deletion
         ii. Translocation
            1. Reciprocal
            2. Robertsonian
         iii. Inversions
            1. Pericentric – includes the centromere
            2. Paracentric – does not include the centromere
         iv. Isochromosomes
         v. Dicentric chromosomes
         vi. Ring chromosomes

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vii. Duplications
  1. Etiology – Originate after chromosomal breakage which may be caused by radiation, chemicals, or viruses

C. Single Gene Defects (Mendelian Disorders)
  1. Eukaryotic gene structure and expression
  2. Mendelian Inheritance
     a. Autosomal dominant inheritance
     b. Autosomal recessive inheritance
     c. X-linked inheritance
  3. DNA Technology
     a. Polymerase Chain Reaction (PCR)
     b. Restriction fragment length polymorphisms
     c. Allele-specific hybridization (Dot Blots)
  4. Examples of single gene defects
     a. Hemoglobinopathies
        i. Thalassemia – Quantitative variants
        ii. Sickle cell anemia – Structural variants
     b. Coagulopathies
        i. Hemophilia A – X-linked defect
        ii. Hemophilia B – X-linked defect
     c. Metabolic disorders – autosomal recessive
        i. Phenylketonuria – Deficiency of phenylalanine hydroxylase
        ii. Congenital adrenal hyperplasia – Deficiency hydroxylase
        iii. Alpha-1-antitrypsin deficiency
     d. Neurologic disorders
        i. Duchenne muscular dystrophy
        ii. Huntington’s disease
        iii. Neurofibromatosis

D. Multifactorial/Polygenic Defects

Characteristics
  1. The trait, the incidence of which usually 1/1000 live births, usually involves a single organ system or embryologically related organ systems.
  2. The frequency of similarly affected cotwins is higher among monozygotic than dizygotic twins.
  3. Unlike mendelian inheritance, the recurrence risk increases after more than one progeny is affected. The risk rarely approaches the 25% expected for recessive traits or the 50% expected for dominant traits.
  4. The more serious the defect, the higher the recurrence risk. Bilateral cleft palate carries a higher recurrence risk than unilateral cleft palate.
  5. If the trait occurs more frequently among members of one sex, the risk for relatives is higher if the proband (index case) is of the less frequently affected case. Pyloric stenosis occurs more frequently in males; thus, the recurrence risk is higher if the proband is female.
  6. As the degree of relation decreases, the recurrence risks for relatives decreases more rapidly than that observed for autosomal dominant traits.
Multifactorial / Polygenic Traits
- Neural tube defects
- Cleft lip with or without cleft palate
- Cardiac defects
- Diaphragmatic hernia
- Omphaloclele
- Renal agenesis
- Ureteral anomalies
- Hypospadias
- Posterior urethral valves
- Incomplete muellerian fusion
- Hip dislocation
- Limb reduction defects
- Talipes equinovarus (clubfoot)

E. Teratogens
1. Fetal warfarin syndrome
2. Fetal hydantoin syndrome

III. Procedures for Prenatal Diagnosis
A. Amniocentesis
   1. Indications – 15-17 weeks gestation evaluation of genetics
   2. Risks – 1/200 fetal loss rate
B. Chorionic villus sampling
   Transcervical vs. Transabdominal
   1. Indications – 9-12 weeks gestation evaluation of fetal genetics
   2. Risks – 0.6-0.8% fetal loss rate, limb reduction defects, 1% confined placental mosaicism, performed prior to MSAFP screening
C. Percutaneous umbilical blood sampling
   1. Indications – evaluation of fetal genetics, blood count, acid/base status
   2. Risks – 1% fetal loss rate, 5% preterm labor/delivery
D. Fetoscopy
   1. Indications
   2. Risks – 1-3% fetal loss rate, 5% preterm labor/delivery
E. Fetal skin sampling
   1. Indications – Dermatologic disorders
   2. Risks – 2-3% fetal loss rate
F. Fetal liver sampling
   1. Indications – Metabolic disorders
   2. Risks – 2-3% fetal loss rate
G. Fetal muscle sampling
   1. Indications – Becker-Duchenne muscular dystrophy assay for dystrophin
   2. Risks – 2-3% fetal loss rate

IV. Prenatal Diagnostic Techniques Just Around the Corner
A. Fluorescent in situ hybridization (FISH)
B. Isolating and analyzing fetal cells in maternal blood
C. Stem cell transplantation
References:

Take Home Points

The genetic history is part of the obstetric history and includes the family history, reproductive outcomes, maternal and paternal ages, maternal and paternal ethnic origins, and drug exposures.

Be familiar with common genetic syndromes and teratogens.

There exist a number of prenatal diagnostic procedures, amniocentesis, chorionic villus sampling, percutaneous umbilical blood sampling, and fetoscopy, that have their indications, advantages, and disadvantages.

Be familiar with advancing molecule technology and its utility in the clinical setting. It is our responsibility as physicians to keep up with rapidly advancing diagnostic techniques. Techniques such as FISH, isolation of fetal cells in maternal circulation, and fetal stem cell transplantation are in our patients near future.
Abortion: Termination of pregnancy before the 20th week of gestation, when the fetus weighs less than 500 grams.
  Complete: Expulsion of entire product of conception.
  Elective: Intentional abortion without specific medical indication.
  Habitual or Recurrent: Three or more consecutive spontaneous abortions.
  Incomplete: Incomplete expulsion, with some products of conception retained in uterus.
  Threatened: Vaginal bleeding in the presence of closed cervix.
  Abruptio placenta: Separation of the normally located placenta from its uterine attachment between the 20th week of pregnancy and the birth of the infant. Occurs mainly in the third trimester.
  Acromegaly: Over growth of the terminal parts of the skeletal system after epiphysial fusion, as a result of over production of growth hormone.
  Adenomyosis: Presence of endometrial tissue within myometrium as a result of direct extension.
  Adnexa: Uterine appendages, including the fallopian tubes, ovaries, and associated ligaments.
  Adrenal hyperplasia: Congenital or acquired increase in the number of cells of the adrenal cortex, occurring, bilaterally and resulting in excessive excretion of 17-ketosteroids with signs of virilization.
  Al: Artificial insemination (AIH = homologous, AID = donor).
  Amenorrhea: Absence or cessation of menstruation.
    Primary: Failure of the menarche to occur by the 16th year of life.
    Secondary: Absence of menses for three or more months occurring after the menarche.
  Amniocentesis: Aspiration of amniotic fluid, usually transabdominally, for diagnostic or therapeutic purposes.
  Amniotic fluid: The fluid confined by the amnion.
  Androgen Insensitivity: A syndrome of androgen insensitivity characterized by primary amenorrhea, a female phenotype, testes (abdominal or inguinal) instead of ovaries, the absence of a uterus, and a male genotype.
  Anemia, megaloblastic: Anemia with excessive megaloblasts in circulation, caused primarily by deficiency of folic acid, Vitamin B12 or both.
  Anorexia nervosa: Marked reduction in the intake of food, caused by psychogenic factors and leading to malnutrition and amenorrhea.
  Anovulatory period: Uterine periodic bleeding without ovulation.
  Antepartum: Before labor or delivery.
  Anti-D gamma globulin: Immunoglobulin for prevention of Rh-sensitization.
  Apgar score: The physical assessment of the newborn, usually at one and five minutes after birth.
  Arrhenoblastoma: Uncommon ovarian neoplasm associated with androgen production, causing amenorrhea, dereminization, and virilization.
  Atony, uterine: Loss of uterine muscular tonicity, which may result in failure of progress of labor or postpartum hemorrhage.
  Barr bodies: Sex chromatin masses on the nuclear membrane. The number of Barr bodies is one fewer than the number of X chromosomes in that cell.
  Bartholin's glands: A pair of glands located at the 4 o'clock and 8 o'clock positions on the vulvovaginal rim. Homologues of bulbourethral glands in males.
  Basal body temperature: Temperature reading at rest used for detection of ovulation.
  Basophilic adenoma: Benign tumor of the pituitary composed of basophilic cells.
  BBT: Basal body temperature.
  Benign cystic teratoma: The most common germ-cell tumor, consisting of mature elements of all three...
germ layers (often called dermoid cyst).

**Biphasic temperature curve:** A graph showing basal body temperature rise in the luteal phase 0.4 to 1.0 degrees F higher than that of follicular phase and indicating ovulation.

**Blood flow, uteroplacental:** The circulation by which the fetus exchanges nutrients and waste products with the mother.

**Breakthrough bleeding:** Nonorganic endometrial bleeding during the use of oral contraceptives.

**Breech:** The buttocks (often refers to a fetal presentation).

**Cesarean section:** Delivery of the fetus through an incision in the uterine wall.

**Chloasma:** “mask of pregnancy.” Irregular brownish patches of varying sizes appearing on the face during pregnancy and sometimes during the use of oral contraceptives.

**Chorioamnionitis:** Inflammation of the fetal membranes.

**Choriocarcinoma:** A malignant tumor composed of sheets of cellular and syncytial trophoblast.

**Chromophobe adenoma:** Adenoma of the pituitary gland, consisting of cells that are neither acidophilic nor basophilic.

**Climacteric:** The syndrome of endocrine, somatic, and psychic changes occurring at the termination of the reproductive period in woman.

**Clomiphene:** Synthetic nonsteroidal compound that stimulates the maturation of follicles, resulting in ovulation, as a result of its antiestrogenic effect on the hypothalamus.

**Coitus interruptus:** Withdrawal of penis during coitus before ejaculation.

**Contraception:** The means of preventing conception.

**Hormonal Contraception:** Contraception by means of estrogen, progestational agents or both.

**Corpus luteum:** Yellow endocrine structure formed in the ovary at the site of a ruptured ovarian follicle.

**Counseling, premarital:** Advice given to a couple before marriage, dealing with medical, psychologic, sexual, and social matters.

**Cryptomenorrhea:** A condition in which the menses occur without external bleeding, as with an imperforate hymen.

**Cul-de-sac:** The pouch like cavity formed by a fold of peritoneum between the rectum and uterus.

**Culdocentesis:** Needle aspiration of intraperitoneal fluid or blood through a puncture of the posterior vaginal fornix into the cul-de-sac.

**Curettage:** Scraping of the interior of a cavity or other surface with a curette.

**Cushing's syndrome:** A symptom complex caused by hypersecretion of glucocorticoids, mineralocorticoids, and sex hormones of adrenal cortex.

**Danazol:** A synthetic testosterone derivative that prevents ovulation by inhibiting the midcycle surge of LH, used in the treatment of endometriosis.

**Dermoid cyst:** (See benign cystic teratoma).

**Dilatation:** Physiologic or instrumental opening of the cervix.

**Dilutional anemia of pregnancy:** Lower hematocrits are seen in pregnancy because the expansion of plasma volume is greater than the increase in red blood cell mass.

**Double set-up:** The simultaneous availability of two sterile set-ups for both vaginal and abdominal operations.

**Dyschezia:** Painful bowel movement.

**Dysgerminoma:** Solid germ-cell tumor of the ovary.

**Dysmenorrhea:** Painful menstruation.

**Dyspareunia:** Difficult or painful intercourse.

**Dystocia:** Abnormal or difficult labor.

**Dysuria:** Painful urination.

**Eclampsia:** The convulsive form of pregnancy induced hypertension.

**ED:** Embryo donation.

**Effacement:** Taking up, or shortening, of the cervix.
Endometrial biopsy: The procedure of obtaining endometrial tissue for diagnostic purposes.
Endometriosis: The presence of endometrial implants outside the normal intrauterine location.
Estimated delivery date (EDD): The estimated date of delivery based on either dating or ultrasound parameters. Also known as the estimated day of confinement (EDC)
Estrogen replacement: Exogenous administration of estrogen or estrogenic substances employed to overcome a deficiency or absence of the natural hormone.
Estrogen, unopposed: Continuous and prolonged effect of estrogen on the endometrium resulting from a lack of progesterone.
ET: Embryo transfer.
Ferning: The microscopic pattern of dried cervical mucus, resulting from the influence of estrogen.
Fibrocystic disease (breast): Mammary disease characterized by fibrosis and formation of cysts in the fibrous stroma.
Functional ovarian Cyst: A physiologic cyst arising from the graafian follicle or the corpus luteum.
Galactorrhea: Spontaneous flow of breast milk in the absence of a recent pregnancy.
Glucola: A screening test performed on maternal blood for gestational diabetes.
Gonadal agenesis: Congenital malformation with absence of ovarian tissue or its presence only as a rudimentary streak.
Gonadal dysgenesis: Congenitally defective development of the gonads.
Gonadotropic: FSH and LH.
Gonadotropin releasing hormone agonist (GnRHa): Medications which cause first stimulation of, then down regulation of pituitary gonadotropes resulting in low FSH and LH secretion.
Gonadotropin:
Human chorionic: A glycoprotein hormone that is produced by the syncihtrophoblast. It is immunologically similar to luteinizing hormone. Abbreviated as hCG.
Human menopausal: A preparation isolated from the urine of menopausal women that consists primarily of FSH with variable amounts of LH. Abbreviated as hMG.
Pituitary: Gonad-stimulating anterior pituitary hormone (FSH and LH).
Granulosa cell tumor: A feminizing, estrogen-producing ovarian tumor.
Gravida: A pregnant woman.
Gravidity: The pregnant state, or the total number of pregnancies a woman has had including the current pregnancy.
Hemoperitoneum: Blood in the peritoneal cavity.
Hilus cell tumor: An uncommon ovarian tumor usually associated with deferninization or virilization. and having a low incidence of malignancy.
Hirsutism: The development in a woman of various degrees of hair growth of male type and distribution.
hMG (human menopausal gonadotropins): Injectable LH and FSH.
Hot flashes: A vasomotor symptom characterized by transient hot sensations that involve chiefly the upper part of the thorax, neck and head. They are frequently followed by sweats and are associated with cessation or diminution in ovarian secretion of estrogen.
Hydatidiform mole: A pathologic condition of pregnancy characterized by hydropic degeneration of the chorionic villi and variable degrees of trophoblastic proliferation.
Hydramnios: Excessive amounts of amniotic fluid (more than two liters at term).
Hypercoagulable state of pregnancy: Increased predilection for pregnant women to have venous clotting episodes.
Hyperplasia, endometrial: Adenomatous: Abnormal proliferation of the endometrium with a marked increase in the number of glands with increased and often abnormal mitotic activity. These changes may be related to prolonged, unopposed estrogen stimulation. Adenomatous hyperplasia is sometimes a precursor of carcinoma of the endometrium.
Cystic glandular: Endometrial proliferation with dilated glands but very little nuclear atypia, seldom progressing to endometrial carcinoma.

Hypoestrogenism: A condition of subnormal estrogen production with resultant atrophy or failure of development of estrogen-dependent tissues.

Hypofibrinogenemia: A deficiency of circulating fibrinogen, usually below 100 mg percent. It may be seen in conditions such as abruptio placentae, amniotic fluid embolism, fetal death, and occasionally intraamniotic instillation of hypertonic saline, in which the fibrinogen is consumed by disseminated intravascular coagulation.

Hypogonadism: Subnormal production of hormones by the gonads.

**Hysterectomy:**
- **Abdominal:** Removal of the uterine corpus and cervix through an incision in the abdominal wall.
- **Radical:** Removal of corpus, cervix, and parametrium, with dissection of the ureters, usually combined with pelvic lymphadenectomy.
- **Subtotal:** Removal of the corpus, leaving the cervix in situ.
- **Total:** Removal of the corpus and cervix (without regard to tubes or ovaries).
- **Vaginal:** Removal of the uterus through the vagina.

**Hysterosalpingography:** Roentgenography of the uterus and tubes after injection of radiopaque contrast medium through cervix. Useful in ascertaining irregularities of the uterine cavity and patency of the fallopian tubes.

**Hysteroscopy:** Transcervical endoscopic visualization of the endometrial cavity.

**Hysterotomy:** Surgical incision of the wall of the uterus.

**ICSI:** Intracytoplasmic sperm injection.

**Imperforate hymen:** Failure of a lumen to develop at a point where the budding vagina arises from the urogenital sinus.

**Infertility:** Inability to achieve pregnancy within a stipulated period of time, often considered to be one year.

**Intermenstrual bleeding:** Uterine bleeding occurring between otherwise regular menstrual periods.

**Intervillous space:** The in the placenta in which maternal blood bathes chorionic villi, thus allowing exchange of materials between the fetal and maternal circulations.

**Intrauterine device (IUD):** A mechanical or hormonal device inserted into the uterine cavity for contraception.

**Intrauterine growth restriction (IUGR):** Pathological condition of abnormal placentation resulting in an undergrown fetus.

**IVF-ET:** In vitro fertilization and embryo transfer.

**Karyotype:** A photographic reproduction of the chromosomes of a cell in metaphase arranged according to standard classification.

**Labor:** The process of expulsion of the fetus from the uterus:
- **Induced:** Labor that is initiated artificially.
- **Stimulated:** Labor that is stimulated, usually with oxytocin.

**Lactation:** The production of milk through the actions of prolactin and other hormones on appropriately prepared breast tissue to create polyamines, casein, lactose and phospholipids.

**Lactogen, human placental (chorionic somatomammotropin):** A polypeptide hormone produced by the synctiotrophoblast. It bears similarity to prolactin and somatropin from the pituitary and is intimately involved in carbohydrate metabolism of the mother and fetus. Abbreviated as hPL or hCS.

**Laparoscopy:** Transabdominal endoscopic examination of the peritoneal cavity and its contents after inducing pneumoperitoneum.

**Large-for gestational age (LGA):** The Upper 10% of birthweights.

**Leiomyoma:** A benign tumor derives from smooth muscle. Colloquially referred to as a fibroid.

**Leiomyosarcoma:** An uncommon malignant tumor of smooth muscle.
Levator muscle: The muscular sheet, consisting of the iliococcygeus, pubococcygeus, and puborectalis muscles, which forms most of the pelvic floor (pelvic diaphragm) and acts to support the pelvic viscera.

Lie: (See presentation).

Ligation, tubal: Surgical interruption of the continuity of the fallopian tubes for the purpose of permanent contraception.

LMP: Last menstrual period.

LNMP: Last normal menstrual period.

LPD: Luteal phase defect (inadequacy) - The presence of endometrium inadequate to support implantation and growth.


Macrosomia: An abnormally large infant (usually >4000 gm).

Mastitis: Inflammation of the breast.

Membranes, premature rupture: Rupture of the amniotic membranes before the onset of labor.

Menarche: Onset of the menses.

Menopause: Permanent cessation of the menses, naturally caused by ovarian failure.

Menorrhagia (hypermenorrhea): Excessive or prolonged uterine bleeding in amount and duration of flow occurring at regular intervals.

Metrorrhagia: Uterine bleeding occurring at times other than the expected menses; for example, intermenstrual bleeding; usually not excessive.

Micro/Macroadenoma of the pituitary secreting prolactin: Refers to tumors usually located in the lateral aspects of the pituitary which are surrounded by a pseudo capsule which contain secretory granules of prolactin. Microadenomas are <1 cm, and macroadenomas are >1 cm. Hypotheses for their origin include reduced pituitary dopamine concentration and/or a vascular isolation of the adenoma cells.

Midpelvis: An imaginary plane that passes through the pelvis and is defined by three points: the inferior margin of the symphysis pubis and the tips of the ischial spines on either side. This plane usually includes the smallest dimensions of the pelvis.

Mosaicism: The presence in an individual of cells of differing chromosomal constitutions.

MSAFP (Maternal serum alpha-fetoprotein): Screening test of maternal blood done in the early second trimester to screen pregnant women for fetal anomalies and chromosomal abnormalities.

Mucus, cervical: The secretion of the cervical mucous glands; its quality and quantity are influenced by estrogen and progesterone. Estrogen makes it abundant and clear, with spinnbarkeit and a fern pattern on drying. Progesterone makes it scant, opaque, and cellular without a fern pattern on microscopic examination.

Neonatal: Referring to the first 28 days of life.

Neural tube defect (NTD): An abnormality in closure of the neural tube, resulting in a spectrum of anomalies from anencephaly (no cranium or cerebrum) to spina bifida.

Normal Menstrual bleeding: every 24-32 days, lasting 3-7 days, average loss 30 cc, 80% blood loss occurs in first two days.

Oligomenorrhea: Infrequent menstruation.

Osteoporosis: Atrophy of bone caused by demineralization.

Ovulation, induction of: Achievement of ovulation by medications.

Oxytocin: An octapeptide formed in the hypothalamus and stored in the posterior lobe of the pituitary. It has stimulant effects on the smooth muscle of the uterus and mammary glands.

Papanicolaou smear: Cytologic smear of exfoliated cells (for example, from the cervix, endometrial cavity, or vagina) used in the early detection of cancer or the evaluation of the hormonal status of the patient.

Parity: The number of pregnancies of a particular woman in which the fetus has reached viability.

Parlodol: Bromocriptine mesylate, dopamine agonist that inhibits prolactin secretion.
PCT: Post-coital test.

Pelvic floor: The floor or sling for the pelvic structures located at the level of the pelvic outlet. The most important structures are the levator ani muscle and the fascial sheaths.

Pelvic inflammatory disease (PID): An infection of the pelvic viscera, usually by ascending routes. The most frequent primary etiologic agent is Neisseria gonorrhoea. Other important causative organisms include coliform bacilli and streptococci.

Pelvic inlet: An imaginary plane passing through the pelvis that represents the upper boundary of the true pelvis. It is bounded posteriorly by the promontory and alae of the sacrum, laterally by the linea terminalis, and anteriorly by the horizontal rami of the pubic bones and the upper margin of the symphysis pubis.

Perinatal: Pertaining to the combination of fetal and neonatal periods, currently considered to begin after 20 weeks' gestation and to end 28 days after birth.

Perineum: The pelvic floor and associated structures occupying the pelvic outlet.

Placenta previa: A condition in which the placenta is located in the lower portion of the uterus, extending to or covering part or all of the internal os.

PMP: Previous menstrual period.

Pneumoperitoneum: The presence of air in the peritoneal cavity.

Polycystic ovary syndrome: (Stein-Leventhal syndrome) A syndrome of secondary oligomenorrhea and infertility, associated with multiple follicle cysts of the ovary and failure to ovulate.

Polymenorrhea: Frequent but regular episodes of uterine bleeding, usually at intervals of 21 days or less.

Position: The relationship of a designated point on the presenting part of the fetus to the anterior, transverse, or posterior portion of the maternal pelvis. Example: occiput left anterior (OLA).

Postmenopausal bleeding: Bleeding from the uterus, cervix, or vagina that occurs after the menopause.

Post partum: After delivery, or childbirth.

Preeclampsia: A specific hypertensive disorder of pregnancy with the diagnosis made on the basis of hypertension with proteinuria, edema, or both. It occurs after the 20th week of pregnancy.

Pregnancy, ectopic: A pregnancy outside the usual locations in the corpus uteri.

Prematurity: The condition of a fetus born at less than 37 weeks gestation.

Presentation: The relationship of the long axis of the fetus to the long axis of the mother. The presentation is either longitudinal (head or breech) or transverse.

Presenting: The portion of the fetus that is felt through the cervix on vaginal examination. The presenting part determines the presentation.

Primigravida: A woman who is pregnant for the first time.

Prolactin: A product of the anterior pituitary 199 Amino acids with glycosylated and nonglycosylated forms. It possesses a myriad of effects, the most noticeable being lactation controlled by prolactin inhibiting factor.

Prolactin Inhibiting Factor: Inhibits the release of prolactin and is probably dopamine which is secreted by the tuberoinfundibular neurons.

Prolapse:

Cord: The condition in which the umbilical cord precedes the presenting part.

Uterine: Prolapse of the uterus, usually due to the loss of supporting structures. It is related to injuries of childbirth, advanced age, or congenital weakness.

Pseudocyesis: False pregnancy, in which some of the signs and symptoms of pregnancy are present although no conception has taken place.

Puberty: The period of time between the beginning of the development of secondary sexual characteristics and the completion of somatic growth.

Precocious: The onset of sexual development and menstrual bleeding before ten years of age.

Puerperium: The period of time after delivery in which the reproductive tract returns to its normal,
nonpregnant condition.

Quickening: The first perception by the mother of fetal movement, usually around the 20th week of gestation.

Resection, tubal: Surgical removal of a segment of fallopian tube for the purpose of permanent contraception.

Rhogam: An antibody preparation of anti-Rh factor given to Rh (-) women to prevent Ph isoinmunization.

Rhythm: Practice of contraception in which coitus is avoided when ovulation is likely.

Salpingectomy: Surgical removal of the fallopian tube.

Salpingo-oophorectomy: Surgical removal of a fallopian tube and ovary.

Secondary sexual characteristics: The physical and emotional changes in the pubertal girl before and after the menarche.

Semen analysis: Evaluation of the components of the semen, especially spermatozoa, as a means of evaluating male fertility.

Sims-Huhner test: A test for infertility in which cervical mucus is aspirated after coitus and examined for quality and presence or absence of infection. The motility, normality, and number of sperm are noted. Also known as post-coital test.

Small-for-Gestational age (SGA): The lower 10% of birth weights.

Somatomammotropin, chorionic: Same as lactogen (human placental).

Sonography: A diagnostic aid in which high-frequency sound waves are used to detect the presence of normal and abnormal pregnancies and pelvic tumors. It is used also to locate the placenta and to measure the fetal biparietal diameter.

Spinnbarkeit: Ability of the cervical mucus to be drawn out into a thread, characteristically greater in the preovulatory and ovulatory phases of the menstrual cycle.

Station: Position of the fetal presenting part relative to the level of the ischial spines. Station +2 means the presenting part is 2 cm below the ischial spines. Station -1 means the presenting part is 1 cm above the ischial spines.

Sterility: Absolute inability to procreate.

Stress incontinence: Involuntary leakage of urine during, increase in intraabdominal pressure as a result of a weakness of the supports of the internal vesical sphincter and bladder neck.

Striae gravidarum: Streaks or lines seen on the abdominal skin of the pregnant woman.

Superovulation: The use of ovulation induction agents to purposefully ovulate more than the usual single monthly oocyte.

Supine hypotensive syndrome: A hypotensive syndrome often characterized by sweating, nausea, and tachycardia. It occurs in some pregnant women in the supine position and is related to obstruction by the pregnant uterus of venous return.

Teratogen: An agent or factor that causes the production of physical defects in the developing embryo.

Thecoma: Functioning ovarian tumor composed of theca cells.

Trimester: A period of three months. The period of gestation is divided into three units of three calendar months each. Some important obstetrical events may be conveniently categorized by trimesters.

Trophoblast: The epithelium of the chorion, including the covering of the placental villi. It comprises a cellular layer (cytotrophoblast) and syncytiurn (syncytiotrophoblast).

Tubercles, Montgomery’s: The enlarged sebaceous glands of the areolae of the mammary glands during late pregnancy and lactation.

Varicocele: Abnormal testicular vascular configuration associated with decreased sperm quality.

Vasectomy: Surgical interruption of the ductus (vas) deferens for permanent contraception.

Viability: The condition of a fetus weighing 500 grams or more.

Virilization: The development of masculine traits in the female.

Withdrawal bleeding: Uterine bleeding after the interruption of hormonal support of the endometrium.