PATHOPHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM - PART I

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DYSFUNCTIONAL UTERINE BLEEDING

DEFINITIONS:

Abnormal uterine bleeding
Bleeding not caused by pelvic pathology, medications, systemic disease or pregnancy
Menorrhagia: prolonged or excessive bleeding at regular intervals
Metrorrhagia: irregular, frequent uterine bleeding of varying amounts but not excessive
Menometrorrhagia: prolonged or excessive bleeding ar irregular intervals
Polymenorrhea: regular bleeding at intervals of less than 21 days
Oligomenorrhea: bleeding at intervals greater than every 35 days
Amenorrhea: no uterine bleeding for at least 6 months
Intermenstrual: uterine bleeding between regular cycles

PHYSIOLOGY OF MENSTRUATIONS

MENSTRUAL CYCLE

Cyclical bleeding with shedding of **endometrial lining** during reproductive years
Menarche: first menstrual bleed
Menopause: last menstrual bleed
Anovulatory cycles: bleeding without antecedent ovulation - often results in DUB *
Cycle induces changes in other organs: breasts, uterus, skin, ovaries, sometimes affect

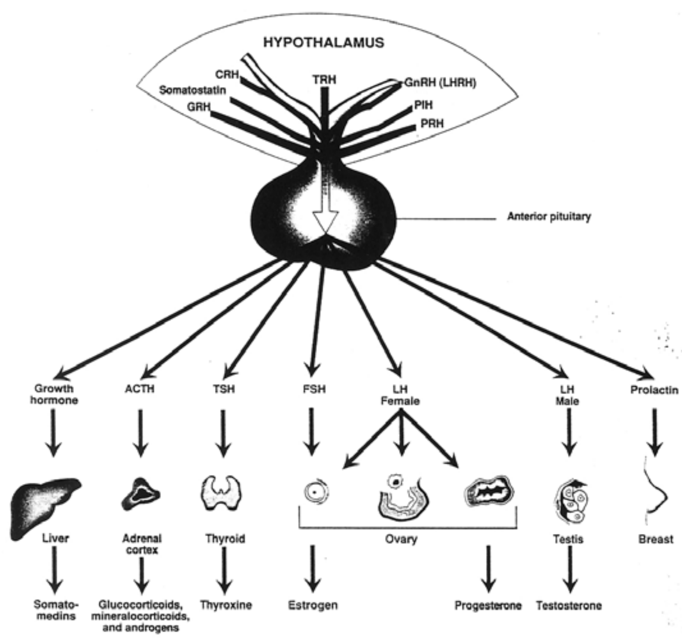
* Dysfunctional uterine bleeding

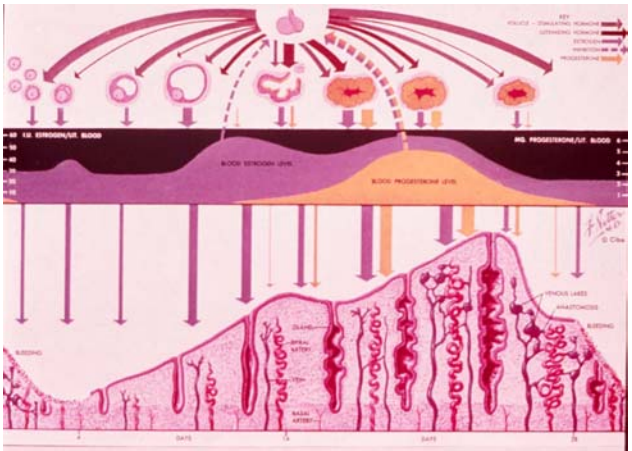
HORMONAL CONTROL

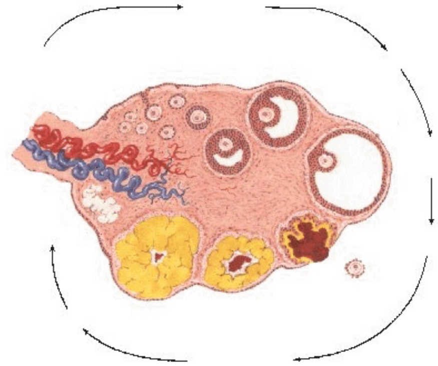
Hypothalamic-Pituitary Hormones

GnRH from **hypothalamus** stimulates anterior pituitary

Anterior pituitary gland secretes **FSH** and **LH** (also secretes **prolactin** stimulates lactation)







FSH stimulates **ovarian follicles** to produce **estrogen**
- Most follicles exist as primary follicles
    - Oocyte and granulosa cells
    - Basement membrane
- 6-12 primary follicles develop into secondary follicles each cycle
    - Oocyte increases in size; granulosa proliferates
    - Zona pellucida develops surrounding oocyte; forming pockets of fluid
    - Remains avascular; blood vessels do not penetrate basement membrane
    - FSH stimulates development of cell layers - theca

One **follicle becomes dominant** - produces high levels of estrogen
- Estrogen is produced by granulosa cells as they mature
- Selection of a <u>dominant follicle</u> occurs with estrogen microenvironment
- Remaining follicles atrophy

Dominant follicle increases in mass
High levels of estrogen exert **negative feedback** on anterior pituitary
- Inhibits multiple follicular development
- Results in **increased LH** levels

Estrogen suppresses FSH which results in **predominance of LH**
LH surge results in **ruptured follicle** i.e. **ovulation** (mature oocyte bursts from follicle)
- Midcycle FSH and LH rise sharpy (gonadotropin surge)
- Estrogen level falls
- Progestin output by follicular cells begins go increase
- Graafian follicle has gradually moved to surface of ovum; thins and ruptures
- Mid-cycle gonadotrophin surge triggers ovulation about 18 hours after peak
- May be associated with **mittelschmerz pains**

Ovum picked up and transported through fallopian tubes
Follicle collapses after ovulation forming **corpus luteum** which secretes **progesterone**
- Granulosa cells invaded by blood vessels and yellow lipochrome-bearing cells
- Leakage of blood into peritoneal surrounding ovary causes mittelschmerz pain

Corpus luteum atrophies if fertilization does not occur forms **corpus albicans**
- White scar tissue
- Hormone support of endometrium is withdrawn - results in **menstruation**
- If **pregnancy** occurs **trophoblastic HCG** prevents luteal regression
- With pregnancy remains functional for 3 months until placenta is fully functional

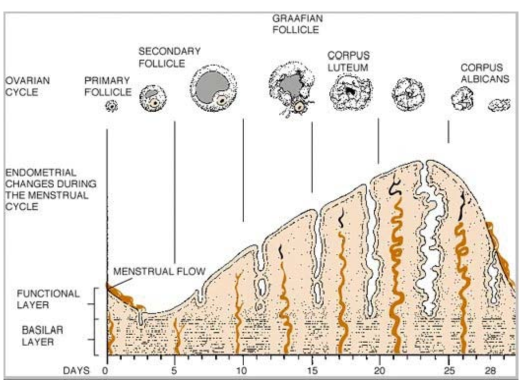
Menstruation - shedding of endometrial lining

PHASES OF MENSTRUAL CYCLE

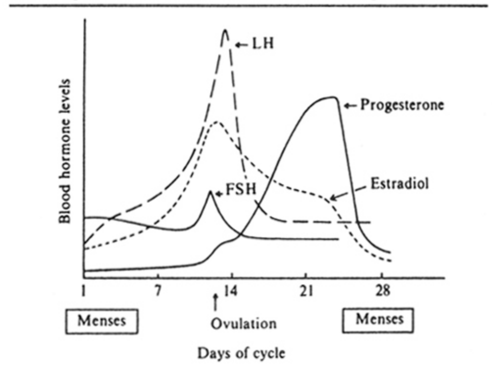
Follicular phase: **proliferative** phase from end of menses to ovulation
- Under the influence of **estrogen** (proliferation)
  - Estrogen halts menstrual flow
  - Promotes **proliferation**
- Glands and stroma grow rapidly
- This phase is more variable making **ovulation timing harder to predict**

Luteal phase: secretary phase from ovulation to menses
- Under influence of **progesterone**
  - Halts endometrial growth
  - Promotes **differentiation**
- Glandular dilation and active mucus secretion
- Endometrium becomes highly vascular and edematous
- This phase is highly predictable in length - 14 days before onset of next menses

Menstrual phase: superficial endometrium degenerates and sloughs off
Response to fall in progesterone from regression of corpus luteum



Blood hormone levels of ovarian hormones and gonadotropins in women during a normal menstrual cycle. LH = luteinizing hormone; FSH = follicle-stimulating hormone.



ENDOMETRIAL CHANGES

Endometrial structure: two distinct layers or zones which respond to hormonal stimulation

Basal layer: adjacent to myometrium - not sloughed during menstruation
Superficial layer (functional layer): arises from basal layer - undergoes proliferation-sloughing
- Thin, superficial and compact layer
- Deeper spongiosa layer - comprises most of secretory, fully- developed endometrium

CAUSES OF DUB

Usually related to one of three hormonal-imbalance conditions

Estrogen breakthrough bleeding

Excess estrogen stimulates endometrium
Proliferates in an undifferentiated manner
Insufficient progesterone to provide structural support
Portions of endometrial lining slough at irregular intervals
Absence of usual progesterone-guided vasoconstriction-platelet plugging
Can result in profuse bleeding

Estrogen withdrawal bleeding

Results from sudden decrease in estrogen levels

- Following bilateral oophorectomy
- Cessation of exogenous estrogen therapy
- Just before ovulation in normal cycle

Usually self-limiting
Tends not to recur of estrogen levels remain low

Progestin breakthrough bleeding

Occurs when progesterone-to-estrogen ration is high
Example: <u>progesterone-only contraceptives</u> or **DepoProvera**
Endometrium becomes atrophic and ulceration due to estrogen deficiency
Prone to frequent, irregular bleeding

APPROACHES TO DYSFUNCTIONAL BLEEDING

PREMENOPAUSAL DUB

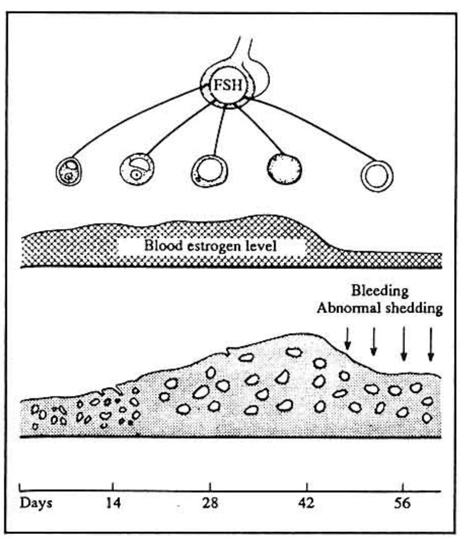
ANOVULATORY BLEEDING

All causes represent a **progesterone-deficient state**
Bleeding usually dysfunctional and can be managed with hormonal therapy
Anovulation is the most common cause in reproductive-aged

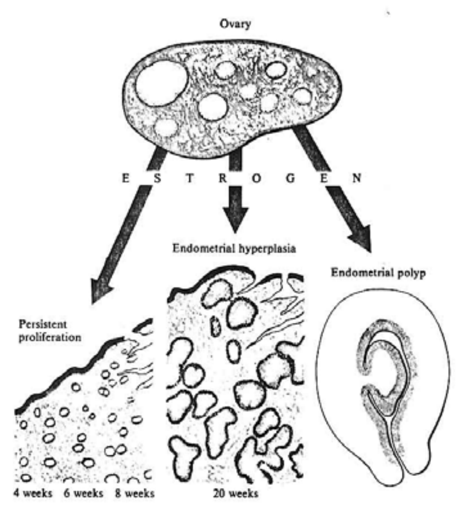
Anovulation due to **immature hypothalamic-pituitary axis** especially common in adolescents
- Up to 80% of cycles are anovulatory in first year after menarche
- Cycles become ovulatory on average of 20 months after menarche
- If not heavy no treatment indicated
- OCs are treatment of choice if bleeding is disturbing

Anovulation secondary to a variety of organic causes
Evaluate anterior pituitary hormones: **TSH** and **prolactin**
Evaluate for hypothalamic anovulation
Weight loss, eating disorders
Stress, chronic illness or excessive exercise
Polycystic ovarian disease: associated with obesity
- Increased circulating androgens (converted to estrogens in peripheral tissue)
- Insulin resistance
- Excessive estrogen results in endometrial hyperplasia and cancer

Idiopathic chronic anovulation



Pathophysiology of the anovulatory cycle.



Mechanism of anovulatory bleeding.

OVULATORY DYSFUNCTIONAL BLEEDING

DUB in women with regular cyclic bleeding or structural lesions

Structural lesion: **uterine leiomyomas, adenomyosis, endometrial polyps**
Bleeding disorder (e.g. Willebrand's disease)
Liver disease with resultant coagulation abnormalities
Chronic **renal failure** results in menorrhagia

Polymenorrhea is usually caused by inadequate luteal phase or shortened follicular phase
Intermenstrual disease: **cervical disease** or **intrauterine device**
Rapid decline in estrogen before ovulation

EVALUATION

Consider endometrial biopsy for certain women
- Prolonged exposure to unopposed estrogen
- Patients who do not respond to initial management
- Women over 35 years

TREATMENT OPTIONS

Oral contraceptives: low-dose monophasic or triphasic
Medroxyprogesterone: 10 mg/d x 10d
Use where contraception is not an issue
Dosing q 3 months will protect vs endometrial hyperplasia
Clomiphene: 50-150 mg/d on days 5-9
Induces ovulation in women desiring pregnancy
Refer if no response in 3-6 months

ANOVULATORY VS OVULATORY CYCLES

Ovulatory Cycles
Regular cycle length
Premenstrual symptoms
Dysmenorrhea
Breast tenderness
Changes in cervical mucus
Mittelschmerz
Biphasic temperature curve
Positive LH predictor kit results

Anovulatory Cycles
Unpredictable cycle length
Unpredictable bleeding pattern
Frequent spotting
Infrequent heavy bleeding
Monophasic temperature curve

PERIMENOPAUSAL DUB

Cycles shorten with intermittent anovulation as menopause approaches
Decline in ovarian follicle numbers
Decrease in estrogen levels

Decline in ovarian follicles results in **lower estradiol levels**
Lower estrogen levels **require higher FSH to stimulate ovulation**
FSH needed to stimulate ovulation increases with decreasing number of follicles

COMMON DIAGNOSTICS

- **HCG** - to rule out pregnancy
- **Endometrial biopsy** most widely studied method to exclude CA (office procedure)

- **Transvaginal u/s** if bleeding persists with treatment - can ID variety of abnormalities
  Atrophic endometrium
  Hypertrophic endometrium (hyperplasia, carcinoma)
  Leiomyomas, endometrial polyps, adenomyosis
  May not distinguish between submucosal fibroid, endometrial polyp or adenomyosis

Sonohysterography (saline infusion into endometrial cavity)
- Enhances detection of fibroids and polyps
- Endometrial biopsy is more convenient and effect

Hysteroscopy with biopsy - considered "gold standard"
Diagnostic hysteroscopy: office procedure without anesthesia or sedation
Operative hysteroscopy
- Uses rigid scope with fluid distending medium
- Useful for diagnosis and treatment

Dilation and curettage used before hysteroscopy was available
- Blind sampling and incomplete
- Less accurate vs hysteroscopy (sampling is blind and incomplete)

TREATMENT OPTIONS

Medroxyprogesterone acetate 10 mg/d x 10 days
Oral contraceptives: Low dose: 20 ug
Can continue till menopause for non-smoker
Switch to HRT at menopause
OCs contraindicated for smoker over 35 yrs
Estrogen dosing in HRT is not sufficient to stop bleeding from atrophic endometrium

WHEN IS A WOMAN CONSIDERED MENOPAUSAL?

- Menopause is technically defined as the last period
- Women generally considered menopausal if no period for 12 months
- Must use contraceptives until no period for at least 12 Months
  Many "change of life" babies result from carelessness with this rule
  - HRT does not protect against pregnancy

- Non-smoking women may use OCs until the menopause

MENOPAUSAL WOMAN

- **Endometrial CA** is most serious concern
  - 5-10% of women with postmenopausal bleeding
  - Must **exclude endometrial carcinoma** in menopausal women

- Uterine pathology: 30% of patients
  Submucosal fibroids
  Endometrial hyperplasia and **polyp**

- Other potential causes
  Cervical CA, cervicitis, other cervical lesions
  Atrophic vaginitis, endometrial atrophy

- Bleeding on HRT therapy - very common

BLEEDING and RISKS WITH HORMONE REPLACEMENT THERAPY

- Bleeding on HRT is very common - 40% or more bleed
- Newer progestins stabilize endometrium better than older products
    - Older agent: medroxyprogesterone acetate (Provera) - bleeding common
        - Prempro, Premphase
    - Newer agents: norethindrone acetate - better stability; less bleeding
        - Femhrt, Activella
- Perimenopausal woman may fair better on low dose OCs
    - Estrogen level still high; progestin in HRT too low to stabilize endometrium
    - Only non-smokers may use OCs during perimenopause
- Since WHI data (2002) - use of HRT has drastically declined
    - HRT associated with increase risks*
    - Recommended for short-term risks to control vasomotor instability only

* Increased incidence of MI, VTE and breast CA

- **Postmenopausal bleeding is never normal** - always requires workup
    - Must evaluate bleeding which occurs 12 months after last period
    - During perimenopause menstrual periods become increasingly infrequent

DYSMENORRHEA

DEFINITIONS:

Dysmenorrhea: cramping pain in lower abdomen occurring just before in during menstruation
Primary dysmenorrhea:
Painful menses occurring in the absences of other disease e.g endometriosis

EPIDEMIOLOGY AND NATURAL HISTORY

Prevalence as high as 90%
Most common gynecologic problem in menstruating women
Initially presentation typically in adolescence
Common cause of absenteeism and reduced quality of life
- 42% report at least one episode of absenteeism or loss of activity
- Absenteeism ranges from 34-50% of subjects
- 600 million lost work hours and $2 billion lost productivity annually

Under-diagnosis and **under-treatment** is common

Conflicting results re role of obesity or ETOH - issue remains controversial
Physical activity not associated with characteristics of pain
Data supporting decreased pain after childbirth are inconsistent (widely held perception)

ETIOLOGY

Increased production of endometrial prostaglandins (esp PGF-2alpha)
Endometrial sloughing and disintegration results in **prostaglandin** release
- Higher levels of prostaglandins result in more severe dysmenorrhea
- Prostaglandin levels highest during first two days of menses when symptoms peak
- Resultant **increased uterine tone**; stronger-more intense **uterine contraction**

NSAIDs
- - Very effective in treating pain
- - Mechanism: inhibit prostaglandins via inhibition of prostaglandin synthetase

DIAGNOSIS

Diagnostic workup usually not necessary for patients with typical presentation
- - Presentation during adolescence within 3 years of menarche (usually within 6 months)
- - Patients with no risk factors for secondary disease

Sharp intermittent spasms of pain, usually centered in suprapubic area
Pain may radiate: back of legs, lower back
Systemic symptoms common:
- Nausea, vomiting, diarrhea, fatigue, fever, headache, lightheadedness

Pattern of pain
- Onset within hours of start of menstruation
- Peaks as flow becomes heaviest (first day or two of cycle

Pain is somewhat different from that associated with PMS
- Breast tenderness and abdominal bloating vs lower abdominal cramping pain
- PMS begins before menses and resolves after flow begins

Differentiating from **endometriosis**
- Progressive dysmenorrhea accompanied by pain during intercourse
- Fertility may be affected
- Family history: 7% of first degree relatives vs overall incidence of 1% in gen population
- **Early diagnosis** during adolescents import step to minimize **long-term sequelae**

Differentiating from **pelvic inflammatory disease** (PID)
- Detailed sexual history: STDs, multiple partners, unprotected sex increase risk
- Bimanual pelvic exam: cervical motion tenderness

Bimanual exam findings with dysmenorrhea
- Performed to rule out secondary etiology (tumors, ovarian cysts, etc.)
- Non-menstrual phase should be negative for pain
- Any reproducible pain should be non-specific and limited to mideline

Therapeutic trial with NSAIDs is diagnostic
- Relief is predictable
- Failure to respond should raise doubts re diagnosis

CAUSES OF SECONDARY DYSMENORRHEA	
Uterine Causes	**Extrauterine Causes**
Adenomyosis	Endometriosis
PID	Adhesions
Cervical stenosis, polyps	Functional ovarian cysts
Fibroids (intracavity, intramural)	Tumors: benign or malignant
IUD	Bowel or bladder
	Ovary or other site
	Inflammatory bowel disease

TREATMENT

NSAIDs mainstay of treatment - 64%-100% effective
- No particular NSAID reliably more effective
- ASA not used: not potent enough in usual dosage
- Response within 30-60 minutes
- Many adolescents not using effective NSAID regimen
- Early initiation of therapy within menses improves efficacy - use at first sign of menses

Oral contraceptives: 90% effective
- Second line unless contraception is needed
- Need for daily medication is too cumbersome for first line vs NSAIDs
- Mechanism: two-fold - no one type is superior to others - all effective
  - Reduction in menstrual fluid volume
  - Suppression of ovulation
- Up to 3 cycles may be needed for noticeable improvement (use NSAIDs in interim)

Norplant and **DepoProvera** are effective

Alternative therapies - much less evidence to support use

Most common reason for failure of traditional therapies is secondary causes esp endometriosis

TENS unit - 42% to 60% had moderate or better relief (4 small studies; total n=126)
Laparoscopic presacral neuroectomy - 33-88% effective (2 small studies; total n=88)
Acupuncture: 91% improvement; 41% decrease in analgesic use (1 study; n=43)
Omega-3 fatty acids: 2 studies (n=181; n=42)
- Low intake correlates with menstrual pain
- Treatment group had significantly lower scores on pain scale

Transdermal nitroglycerine: (1 study; n=65)
- 90% effective but 20% report headache
- 0.1 to 0.2 mg NTG per hour during first few days of cycle

Thiamine (Vit B1): Randomized double blind; n=556
- 100 mg PO qd x 90d
- 87% improved but study in India where preexisting deficiency possible

Magnesium supplements (1 study; n=30) - magnesium pidolate
- Up to 84% decrease in symptoms esp on day 2-3

PREMENSTRUAL SYNDROME - PREMENSTRUAL DYSPHORIC DISORDER

PMS

EPIDEMIOLOGY

- Affects up to 85% of menstruating women
    - Severe symptoms less common
    - Symptoms rarely impair lifestyle
- Incidence: 75% to 80% have noticeable premenstrual changes
    Wide variation in presentation
    Range: Minor and isolated to moderate or severe (30-40% of women)
    PMDD: 5-10% of normally cycling women
    Of patients seeking medical help for PMS: 50-80% meet criteria for PMDD

ETIOLOGY

- Current hypothesis concerns a blunted response to serotonin
    - Reduced whole blood serotonin levels
    - Reduced platelet uptake in luteal phase
    - Heightened sensitivity to 5-HT-1A
- One-half do not respond to SSRIs hence serotonin is only part of overall picture
- Symptoms eliminated of menstrual cycle removed surgically or pharmacologically
- Ratio of estrogen to progesterone may be related to severity of symptoms
    Inferred from research on women whose mood symptoms vary cycle to cycle

DIAGNOSIS

- Symptoms consistent with PMS
- Restriction of symptoms to luteal phase of cycle (assessed prospectively)
- Impairment of some facet of woman's life
- Exclusion of other diagnoses which may better explain symptoms

DIFFERENTIAL DIAGNOSIS

- Menstrual magnification of psychiatric or medical condition
    Depressive disorders, migraines, seizure disorders, IBS, asthma, chronic fatigue syndrome, allergies
- Endocrine abnormalities
- Perimenopause

TREATMENT

Nonpharmacologic Therapy

Supportive therapy (not rigorously studied)
- Reassurance
- Counseling
- Relaxation therapy
- Value of formal psychiatric intervention not demonstrated

Aerobic exercise (limited evidence to support)

- May not specifically benefit PMS but all patients will benefit to some extent
- Overall health benefits support recommending it to all women with PMS

Dietary supplementation (insufficient data base to support)

- Calcium and magnesium (small trials reveal benefit)
- Vitamin E (minimal data)
- Vitamin B (limited clinical benefit)
- Carbohydrate beverages may improve mood *
- Primrose oil may relieve breast tenderness *

* efficacy needs further investigation

Pharmacologic Therapy

Selective serotonin reuptake inhibitors (SSRI)
- Consider as first-line for severe symptoms
- <u>Evidence strongly supports</u> use
- **Fluoxetine (Prozac, Sarafem)** most rigorously studied
- Other SSRI
  sertraline (Zoloft), paroxetine (Paxil)
  Fluvoxamine (Luvox)

- <u>Intermittent SSRI</u> therapy during symptomatic phase
  Efficacious esp for headache, jitteriness, nausea, insomnia

Other anti-depressant agents which have shown benefit

- Nefazodone (Serzone)
- Venlafaxine (Effexor) - serotonin and norepinephrine
- Clomipramine (Anafranil)- TCA with typical high side effect profile

ACOG CRITERIA FOR PREMENSTRUAL SYNDROME

Patient reports at lease one of each of the following affective and somatic symptoms during five days before menses in three (3) consecutive months

Affective

Depression
Angry outbursts
Irritability
Anxiety
Confusion
Social withdrawal

Somatic

Breast tenderness
Abdominal bloating
Headache
Swelling of extremities

Symptoms must also meet the following criteria

- Be relieved within four days of onset of menses, without recurrence until at least cycle day 13
- Be present in the absences of any pharmacologic therapy, hormone ingestion or dug or alcohol use
- Be causing identifiable dysfunction in social or economic performance
- Occur reproducibly during two

OTHER PHARMACOLOGIC APPROACHES

Alprazolam (Xanax) - anxiolytic with mixed results
- Potential for dependency, development of tolerance, problematic sedation
- Use only where other interventions fail and where anxiety is primary symptoms

Diuretic therapy
- Rational: treatment of fluid retention symptoms
- Spirolactone (Aldactone) only agent with proven efficacy (efficacy reports are mixed)

Progesterone: long history of use but benefits have not been shown

HORMONAL SUPPRESSION

Oral contraceptives (few data supports use)
- Most effective when symptoms are primarily physical
- Less effective for mood complaints

Gonadotropin-releasing hormone agonists (efficacy supported by most studies)
- Induce hypoestrogenic state and associated hazards/side-effects
- Side effects: osteoporosis, hot flushes, etc.
- Estrogen add-back therapy should be considered with long-term use
- Costly, use limited to most severe cases unresponsive to other treatments

PMDD

DSM -IV DIAGNOSTIC CRITERIA FOR PMDD :

A. In most menstrual cycles over past year, 5 or mores symptoms present during the last week of luteal phase and remit after onset of follicular phase (absent in week post-menses) - at least one must be symptom 1-4

1. Markedly depressed mood, feelings of hopelessness, self-deprecating thoughts
2. Marked anxiety, tension, feelings of being keyed up or on edge
3. Marked affective lability (feeling suddenly sad, tearful or sensitive to rejection)
4. Persistent marked anger or irritability, increased interpersonal conflicts
5. Decreased interest in usual activities (work, hobbies, school, friends)
6. Subjective sense of difficulty in concentrating
7. Lethargy, easy fatigability or marked lack of energy
8. Marked change in appetite, overeating or specific food cravings
9. Hypersomnia or insomnia
10. Subjective sense of being out of control
11. Other physical symptoms
    Breast tenderness or swelling, headaches, joint/muscle pain, sensation of bloating, weight gain

DIFFERENTIAL DIAGNOSIS FOR PMDD

- Premenstrual exacerbation of a medical disorder
  - Hormones exacerbating another medical disorder
  - Migraine, asthma, allergies, IBS, arthritis, DM, seizure disorder
- Psychiatric disorder other than PMDD
  - Depression, anxiety, eating, personality disorder
  - Psychiatric disorder will be exacerbated
  - Symptoms worse in luteal phase but present to some degree throughout cycle
  - Common presentations
    - Heightened depressive symptoms
    - More frequent and severe panic attacks
    - Increased phobic episodes
- Episodic symptoms not tied to menstrual cycle

  Patient may coincidentally feel worse just before period and mistakenly tie symptoms

ALTERNATIVE THERAPIES

Scant evidence demonstrating benefit of alternative therapies

Vitamins and minerals

B6: open label suggests benefit (PMS); inconsistent for double-blind, placebo-controlled

E: little evidence supports use

Herbals: no benefit demonstrated for primrose oil, herbal supplements, teas

PHARMACOLOGIC THERAPIES

SSRI:

- Sixty percent (60%) of women with PMDD or severe PMS have significant relief
  - Most effective for emotional or behavorial changes
  - Sometimes improve physical symptoms
  - Particularly good for anxiety
- Particular agent chosen does not matter: choice is function of side-effect profile
- **Fluoxetine (Prozac, Sarafem)** most widely studied
- Other SSRI also effective: **sertraline (Zoloft), paroxetine (Paxil) fluvoxamine (Luvox**)
- Avoid under-dosing and use for at least one full cycle to gage efficacy
- Published studies have utilized therapy throughout cycle
- Ongoing studies involve <u>limiting use to luteal phase</u> - effective for some women

  Establish therapeutic dosing for one or two cycles with continuous therapy

  Switch to luteal phase to see if it manages symptoms

  Can also use half-dosing for 2-3 weeks and go to full dosing when symptomatic
- <u>Venlafaxine (Effexor)</u>, SSRI and norepinephrine reuptake inhibitor, can be used

TCA: not indicated unless SSRIs fail and anxiolytic is contraindicated

- Side effects limit use
- Placebo controlled trials of TCA lacking except for clomipramine (Anafranil)

Anxiolytic

- Alprazolam (Xanax) is next choice after SSRI
- Well tolerated and proven effective for PMS when given during luteal phase
- Dosing
  - 0.25 mg tid; increase prn to 1-1.25 mg/d
  - Some may need 2.5 mg/d
  - Some may need 0.50 am and HS with 0.25 midday
  - Some require qid regimen
- Rule out ETOH or drug abuse before prescribing alprazolam
- Patient must be reliable to limit use to luteal
  - Some may need for entire luteal phase
  - Some may need treatment only for 4-5 days before start of menses
- Taper therapy for 2-3 days once period starts; abrupt D/C may produce withdrawal

- Other benzodiazepines not well-studied
- Buspirone (Buspar) tid throughout cycle may be effective

GnRH

- Available formulations
  SQ form as goserelin
  IM for depot suspension as leuprolide
  Intranasal formulation as nafarelin

Produces a medical oophorectomy in patients for whom no other treatment works
Produces symptoms of menopause and risk of osteoporosis
- Limit use to 6 consecutive months; not clear whether HRT can facilitate longer use
- HRT dosing may induce some PMS but not sufficient to cancel GnRH benefits

Danazol (Danocrine) - effective but masculinizing side effects
- Poorly tolerated
- Hirsutism and deepening voice

Oral Contraceptives: effective for approximately 33% of women
Most effective for breast pain and cramps
Affective symptoms may worsen

OTHER MEDICATIONS

Progesterone is not effective vs PMS
- Numerous placebo-controlled studies failed to show effectiveness
- Some studies were large and statistically robust
- Neither natural progesterone (suppository or micronized oral) nor synthetic preps effective
- Use is declining with SSRIs becoming more clearly established choice

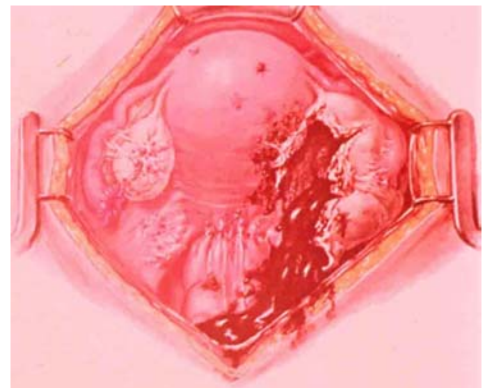
NSAIDS
- No effect on emotional or behavioral problems
- Helpful in treating breast and joint pain, headache, abdominal cramps

Bromocriptine
- No effect on emotional or behavioral symptoms
- May be helpful for premenstrual mastalgia if NSAIDs fail

Diuretics: do not treat any specific symptom - often abused

ENDOMETRIOSIS

- Presence of endometrial glands and stroma outside of uterine cavity
- Common problem in women of child-bearing age
- Affects 2.5%-3.3% of all reproductive-aged women
- Particular prevalent in certain populations
    - 43% of women undergoing tubal sterilization
    - 25%-65% of women undergoing therapeutic laparoscopy for pelvic pain
- Presentation is widely variable
    - Asymptomatic
    - Pelvic pain, **dysmenorrhea**
    - Sexual dysfunction, infertility
- Difficult to manage
    - Heterogeneous symptomatology
    - Lack of effective cure
    - Uncertain etiology



EPIDEMIOLOGY

- Preciously thought to affect upper middle class Caucasians
- Now known to affect all ethnic, racial and socioeconomic groups
- True prevalence is not known
    - Previous estimates generated from surgical candidates
        - Pelvic pain evaluation
        - Sterilization and infertility
    - Estimates at 5 million women
- Health care costs: hundreds of millions $ (includes inpatient and outpatient costs)

GENETICS

- Some evidence suggests genetic influence
    - Relative rate of 7.2 in mothers and sisters of infected women
    - 75% concordance in homozygous twins
    - Often more severe presentation with positive family history
- Mechanisms
    - Dominant gene with low penetrance or multifactorial inheritance pattern
    - No specific markers known

ETIOLOGY

- Single cause has yet to be established
- Two leading theories
    - **Retrograde menstruation**
    - Coelomic metaplasia
- **Direct evidence in support of a single theory is lacking**

RETROGRADE MENSTRUATION

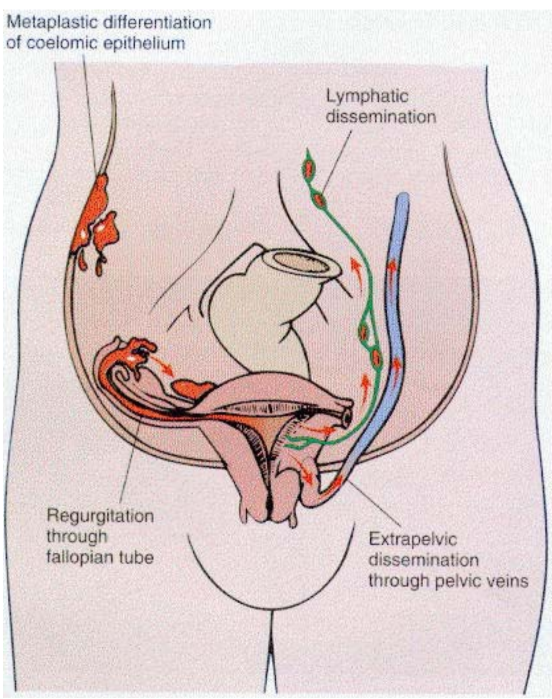
- Retrograde flow occurs during menstruation via fallopian tubes
- Viable fragments of endometrium implant at intraperitoneal sites
- Theory was proposed by Sampson in 1921 (first description of endometriosis)
    - Fragments implant and proliferate within pelvis
    - Respond to hormonal "milieu" during cycle

- Support for theory
    - Laparoscopy during menses: virtually all patients have menstrual fluid in pelvis *
    - Viable endometrial cells from menstrual fluid are transplantable to extrauterine peritoneal sites
- Shortcomings of theory
    - Implants occasionally occur at distant sites outside of pelvis (Pleura, umbilicus, brain)
    - Transport through lymphatics or blood may be explanation

* if tubes are patent

COELOMIC METAPLASIA

- In situ development of endometriosis
- Based on concept of **totipotential coelomic epithelium**
- Inflammatory processor or hormonal alteration triggers transformation of epithelium
- Epithelium transforms into ectopic endometrial tissue
- Immune system may have role in endometriosis
    - Monocyte-macrophage cells and natural-killer cells are known peritoneal scavengers
    - Endometriosis patients have alteration cell numbers and activity levels



CLINICAL PRESENTATION

- Wide variety symptomatology
- Some symptoms highly suggestive of diagnosis
- No symptom is pathognomonic
- Many patients are asymptomatic but have extensive disease at time of surgery

- **Pelvic pain** is most notable and frequent complaint
- Other classic symptoms
    - Secondary dysmenorrhea (acquired)
    - Dyspareunia
    - Low abdominal pain, low back pain

SYMPTOMS OF ENDOMETRIOSIS

- Abdominal pain
- Bowel/bladder problems
- Dysmenorrhea
- Dyspareunia
- Infertility
- Low back pain
- Pelvic pain

- Other possible symptoms
    - Dysuria, hematuria
    - Diarrhea with associated pain and bleeding
    - Painful dysmenorrhea since menarche (non-acquired)

- <u>No direct correlation with extent of disease and intensity of pain</u>
    - Some with minimal disease have intense pain
    - Some with extensive disease have minimal pain

- Generalized and deep pain may be secondary to <u>infiltrating subperitoneal endometriosis</u>.

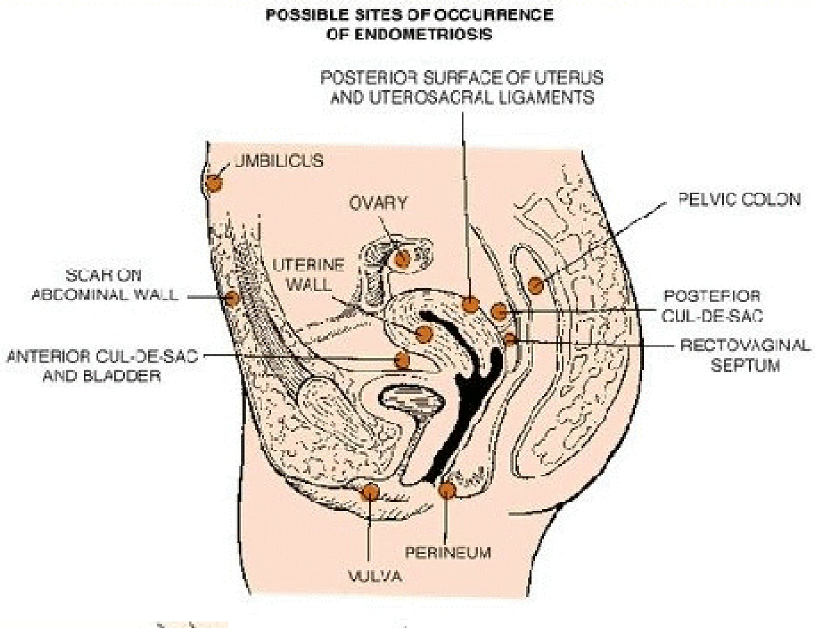
- <u>Possible etiology</u> of pain (leading theory but still <u>speculative</u>)
    - Endometrial peritoneal implants -> bleed and enlarge during menstrual cycle
    - Fibrotic tissue around implants prevents expanding
    - Hemorrhagic fluid unable to escape -> pain from pressure/inflammation
    - Inflammation -> adhesions -> additional pain from physiologic movement of tissues

CHARACTERISTICS OF THE PAIN

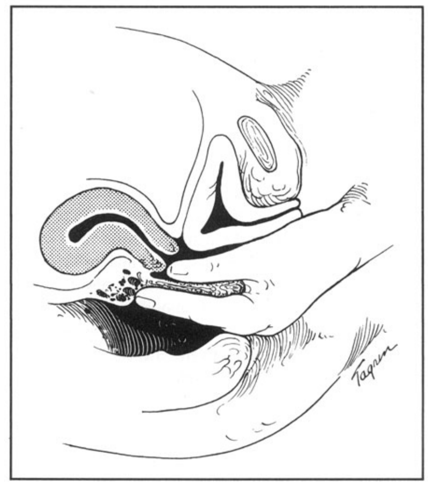
- May precede menses
- Variable intensity
    From mild discomfort to debilitating low abdominal pain
- Localized or diffuse
- May be accompanied by rectal pressure

CLASSIC FINDINGS WITH ENDOMETRIOSIS ON GYNECOLOGIC EXAM

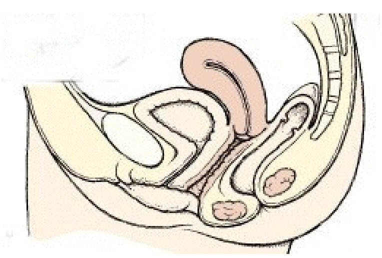
- Localized tenderness at uterosacral ligaments (thickened and nodular)
- Pain with mobilization of uterus
- Tenderness to palpation of adnexa especially if enlarged
- **Retroverted uterus** in severe cases where implants obliterate **posterior cul-de-sac**
- Tenderness on palpation of posterior cul-de-sac on rectal exam



RECTAL EXAM OF PATIENT WITH ENDOMETRIOSIS reveals tender nodularity of uterosacral ligaments and cul-de-sac and fixed retroversion of the uterus which findings are virtually diagnostic of disease.



Anterior Flexed



Normal Anterior

Posterior (Retroverted)

Posterior Flexed (Retroflexed)

Positions of the Uterus

CUTANEOUS MANIFESTATIONS: LESS COMMON

- Perineum, groin, umbilicus, vagina
- Lesions appear black on skin but may appear brown
- Lesions may become large and painful during menses
- Cyclic tenderness is hallmark of cutaneous lesions - question dx if not present
- Exudation of sanguinous fluid especially from umbilical implants
- Lesions common in scar and near previous laparotomy sites

INFERTILITY

- Association of endometriosis with infertility - remains controversial
- Some studies suggest as high as 68% but inherent selection bias of studies
- Causal link not established
- Lower pregnancy rates is lower for women with endometriosis and improves after surgery
- Occasionally link is obvious: pelvic distortion from lesions or blocked tubes, etc.

DIAGNOSIS

- Only true confirmation is via histologic evaluation of laparoscopic biopsy specimens
- Heterogenous disease - appearance may be variable at surgery
- Classic lesions
    - Pigmented "powder burn: type implants - range in color from dark blue to black
    - May appear as red or yellow papules or white opacified areas on pelvic peritoneum
- Fibrosis or adhesions suggests previous sites - may still be harbored below surface
- Evidence suggests that non-pigmented lesions are more symptomatic (more hormonally active)
- "Normal" appearing peritoneum in endometriosis had implants 25% of the time*
    - Visually identified lesions were confirmed 80% of time
    - Demonstrates that virtually impossible to identify all diseased areas visually

* Murphy at al. Unsuspected endometriosis documented by scanning electron microscopy in visually normal peritoneum. *Fertil Steril* 1986; 46:522-24 (used electron scanning microscope

CLASSIFICATION

- American Society for Reproductive Medicine revised classification in 1996
- System uses scalar scoring based on lesion location, size and number; also if adhesions
- Endometriosis is classified as mild, moderate or severe
- Classification system has limitations
    - Not based on symptoms or outcomes
    - Degree of pathology does not correlate with pain severity or infertility

TREATMENT

- Medical and surgical options or combo
- Support groups may be helpful
- Choice of therapy
    - Severity of symptoms
    - Anatomic findings
    - Desire for future childbearing
- **Untreated disease tends to progress**

PATIENT SUPPORT GROUPS

The Endometriosis Association
8585 N 76th Place - Milwaukee WI 53223
800-992-3636
http://www.endometriosisassn.org

Resolve Inc (for infertility)
1310 Broadway, Somerville, MA 02144-1779
617-623-0744 http://www.resolve.org

- Wide range of therapeutic options
    - Hormonal alteration of menstrual cycle: **oral contraceptives**
    - **Danocrine (Danazol)**
    - GnRH analog (agonist): **leuprolide (Lupron), nafarelin (Synarel)**, **goserelin (Zoladex)**
    - Surgical ablation: wide variation of options (ranges from)
        - Laser or surgical removal of implants
        - Complete extirpation of uterus, ovaries, and tubes
    - Debilitating symptoms: specialist referral is warranted
    - Mild symptoms
        - Primary care provider can treat with OCs/NSAIDs for 4-6 months
        - Refer if not improved

MEDICAL THERAPY

- Association between estrogen stimulation and growth of endometriosis
- Goal of medical therapy is to suppress estrogen -> regression and atrophy of implants
    - Impairs proliferation of implants
    - Creates **pseudomenopause (GnRH)** or **chronic anovulation (OCs)**
- **Progestin**: can induce anovulation -> suppress estrogen
    - Provoke marked endometrial decidualization and acyclic status
    - Research evidence available to support use
    - 90% of patients report amelioration or resolution of pain
    - No difference in pain relief as compared with other suppressive therapies
    - Side effects: bloating, edema, hirsutism,* hair loss,* wt gain
    - Advantages of progestin use both with and without estrogen
        - Can prolong treatment: no serious side effects (in contrast to GnRH)
        - Lower cost vs alternative treatments (esp as compared to GnRH)

* less common with second and third generation progestins

- **Danazol:** induces anovulation by reducing mid-cycle surge of LH* and FSH*
    - Does not alter baseline of LH and FSH; reduces mid-cycle surge
    - Estradiol levels reduced in absence of preovulatory surge
    - Used widely in past; now held in lower regard vs other ovulation suppressants
    - Still an option to treat endometriosis-induced infertility - as effective as surgical ablation
    - Dose: 400 mg -800 mg q d
    - Adverse effects:
        - Weight gain, fluid retention, acne, hirsutism, hot flushes, atrophic vaginitis, diminished libido
        - <u>Voice deepening which is potentially non-reversible</u>
        - Liver toxicity (rare): cholestatic hepatitis, jaundice, alteration in lipid profile

* LH = luteinizing hormone; FSH = follicle-stimulating hormone

Gonadotropin-releasing hormone agonists (**GnRH**)
- Suppress release of pituitary gonadotropins
- Clinical trials demonstrate effectiveness in reducing implant size after 4-6 months
- Produce a hypoestrogenic environment -> prevent stimulation implants
    - Prevent stimulation of estrogen-sensitive receptors on implants
    - Cause involution of implants
- Decrease pelvic pain and symptoms of dysmenorrhea and pelvic tenderness
- <u>Reduce symptoms of chronic pelvic pain up to 90%; complete resolution in 60%</u>
- <u>Endometriosis often recurs when treatment stopped</u> (recurrence rate 56%)
- Optimal length of time is unclear: currently used 3-6 months
- Limitations to prolonged use
    - Menopause-like side effects: **hot flush, atrophic vaginitis, mood-swings**
    - <u>Reversible osteoporosis</u>

- Investigation re: “add-back” therapy with low doses of estrogen and progestins
    - Several regiments shown in trials to reduce symptoms and preserve bone
    - May allow use of GnRH for 12 mo with 6 mo “add-back”

- **Oral Contraceptives**
- Frequently used to manage but utility is yet unproven
- Ethinyl estradiol does not significantly suppress endogenous estrogens or GnRH

ADD BACK REGIMENS FOR USE WITH GNRH TREATMENT

Estrogen alone
Estrogen plus progestin
Progestin alone (norethindrone acetate)
Organic **bisphosphates**
Calcitonin

SURGICAL THERAPY

- **Laparoscopy:** conservative surgical ablation
    - Treatment of choice for infertile women with severe endometriosis
    - Laparoscope: confirmation of diagnosis and treatment
    - Goal to remove endometrial implants, restore normal anatomy, preserve uterus
    - Cures 70%-100% in immediate post-op period; 82% cured 1 year later
    - Now considered integral part of investigation for infertility
        - Use was previously controversial
        - Now appears to benefit infertile women with even mild to moderate disease
    - Requires skilled surgeon with experience to recognize and resect lesions

- **Electrosurgery** (**fulguration** and **vaporization** or **laser resection**)
    - Goal to remove all visible lesions -> decrease pain if not cure disease

- **Hysterectomy**
    - Indicated for severe disease in patients who do not desire fertility
    - Hysterectomy with bilateral oophorectomy: eliminates pain in 90%
    - Hysterectomy alone: recurrence rate up to 45% after 5 years