PATHOPHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM - PART II

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LEIOMYOMA

OVERVIEW:

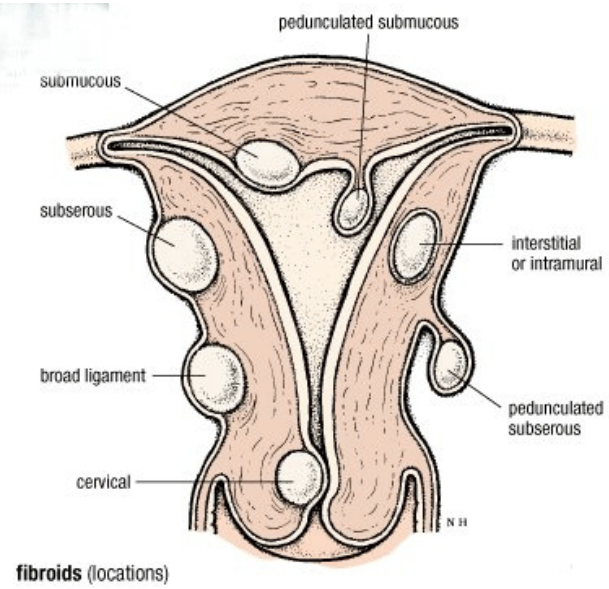
Commonly called **fibroids**
Well-circumscribed benign tumors arising from smooth muscle of myometrium
Composed of smooth muscle and extracellular matrix
- Collagen, proteoglycan
- Fibronectin

Pathogenesis of leiomyoma
- Traditional view is that estrogen/progesterone is modulator
- Now apparent that growth factors and somatic mutations of genes have a role

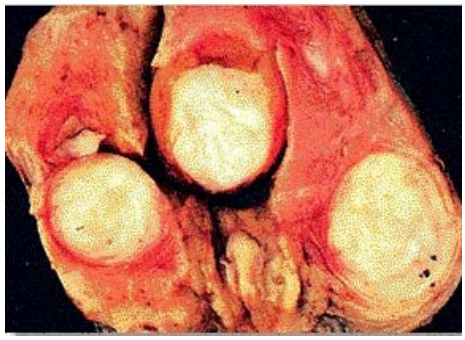
Leiomyomas are clonal in origin
Characterized by location in uterus
- **Sub-serosal**:
  - Located just under uterine serosa
  - May be attached to corpus by narrow band or broad base
- **Intramural**: predominantly within thick myometrium
  - May distort cavity
  - May cause irregular external uterine contour
- **Submucosal**: located just under uterine mucosa (endometrium)
  - May be attached to uterine corpus by narrow or broad base

Few leiomyomas are actually of a single "pure" type
Most hybrids that span more than one anatomic location
- Example: intramural leiomyoma with submucous component

Sarcomatous transformation does not occur - differentiation requires histology



fibroids (locations)



INCIDENCE AND ETIOLOGY

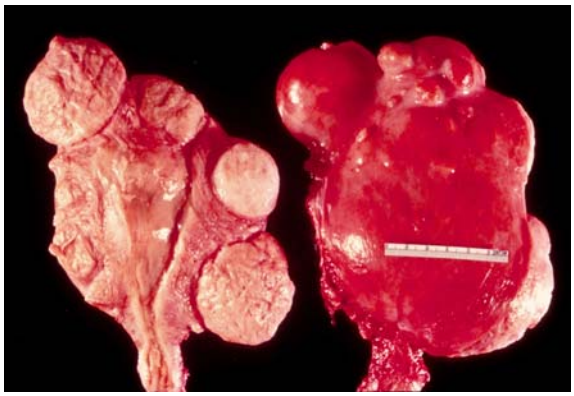
Most common solid pelvic tumor in women
Clinically apparent in 20-25% of women during reproductive years
Pathology reveals that they are present in more than 80% of women
Increased incidence in women of color (RR 1.82-3.25)
Risk increased incidence in women with greater body mass
Decreased risk in women who smoke or have given birth
OCs decrease risk

SYMPTOMS

Tumor-related symptoms in 20%-50% of women
Most common symptoms
Abnormal uterine bleeding esp menorrhagia
- Menorrhagia can occur with any leiomyoma
- Submucosal leiomyoma particularly prone to menorrhagia

Pelvic pressure
Can result from increase in uterine size
Secondary to pressure of myomas on adjacent structures
Colon or bladder: constipation or urinary frequency
Ureters: hydronephrosis (rare)

Reproductive dysfunction
Miscarriage, infertility, premature labor
Fetal malpresentation, complications of labor
Possibly most common with tumors distorting uterine cavity
Resection may be advised for large tumors prior to pregnancy



DIAGNOSIS

Usually diagnosed by **bimanual examination**
- Uterus is enlarged, mobile, often irregular
- May be palpated abdominally above symphysis pubis

Ultrasonography most common method for confirming diagnosis

MRI may prove most useful:
- Distinguishes leiomyoma from adenomyomas or leiomyosarcomas
- Submucosal fibroid can be missed on traditional ultrasonography

Assessment of cavity after it is distended may be indicated
- Important for menorrhagia or recurrent pregnancy loss
- Submucosal fibroid can be missed on traditional ultrasonography
- **Hysterosalpingogram**, **sonohysterogram**, **office hysteroscopy** can supply info

TREATMENT

SURGERY is primary therapy for large or symptomatic leiomyomas

Hysterectomy is most frequent surgical approach
- 175,000 (1987) hysterectomies annually for leiomyomas
- 700,000 (1993) decreasing to 400,000 (1999) with newer therapies
  - Laparoscopic procedures: myolysis, cryomyolysis, myomectomy
  - Uterine artery embolization
- Only true "cure" where future pregnancy is not an issue

Myomectomy performed where need to preserve childbearing potential
- 18,000 performed annually
- Diminishes menorrhagia in 80% of patients
- Significant risk for recurrence: 25%-50% (10% require 2nd surgery)

MEDICAL TREATMENT

GnRH agonist
- Induces **hypoestrogenic, pseudomenopausal** state
- Fibroids are estrogen-dependent for development and growth
- Hypoestrogenic state causes **shrinkage of tumors** and myometrial mass
- Uterine volume decreases 40%-60%b after 3 months therapy
- Induces **amenorrhea** - beneficial for menorrhagia-induced anemia
- Cessation of treatment results in rapid return to pretreatment status
  - Rapid regrowth of leiomyoma
  - Return to pretreatment uterine volume
- Used primarily as presurgical treatment not long-term treatment option
- Estrogen-deprivation side-effects: **osteoporosis**, **hot flushes**
- Vaginal hemorrhage precipitated in small proportion of women

GnRH agonists and low dose hormonal therapy (HRT) - "Add-Back" Regimens
- Extends maximal duration of GnRH agonist therapy safely
- Low dose protects vs hot-flushes and bone loss; does not sacrifice efficacy
- One of the most frequently studied medical regimens
- Optimal steroid and monitoring regiment has yet to be determined
- Newer approach: GnRH with **tibolone** add-back (see below)

GnRH agonist and Tibolone - "Add-Back Therapy"

- Synthetic steroid exhibits estrogenic, progestational, androgenic activity
- Widely used outside US for treatment menopausal symptoms
- Prevents osteoporosis and hot flushes without endometrial-breast stimulation
- Decreased incidence of bleeding at start of therapy
- More likely to become amenorrheic vs HRT
- No inhibition to GnRH-induced leiomyoma shrinkage
- Improved lipid profiles vs GnRH alone
- Appears to provide option for long-term non-surgical treatment

EFFECT OF TIBOLONE ON VARIOUS BODY TISSUE

Brain
Decrease vasomotor instability
Increase libido
Increase energy

Breast
Antiestrogenic
Tamoxifen-like effect

Bone
Prevents bone loss

Vagina
Prevents dryness, atrophy

Heart
Lowers triglycerides
Decreases total cholesterol
Decreases HDL
No effect on LDL

Uterus
Increase progesterone
Causes endometrial atrophy

Pirfenidone - anti-fibrotic agent

Investigational use with fibroids has proved very promising
Other clinical uses
Post-surgical adhesions, myocardial fibrosis, MS, septic shock, endometriosis, BPH, renal fibrosis, liver cirrhosis, atherosclerosis, other fibrotic disorders
Estrogen and progestin promote growth of leiomyoma (production of growth factors)
Pirfenidone inhibits leiomyometrial cells without cytotoxic sequelae
Inhibits new fibrotic lesions and arrests progression of existing lesions
Can reverse existing fibrotic lesions via enhancing fibroblast collagenase
Provides effective nonsteroidal treatment which can be safely used long-term
Currently in phase II trial stage

Androgenic Agents and Progestins

- Agents do not decrease uterine or fibroid volume
- Mechanism of these agents is induction of endometrial atrophy
- May not control menorrhagia

Androgenic agents

Danazol (Danocrine)
Gestrinone

Progestins

Medroxyprogesterone acetate (Provera)
Depo-medroxyprogesterone acetate
(DepoProvera)

POLYCYSTIC OVARIAN SYNDROME

OVERVIEW

Polycystic ovarian syndrome (PCOS) also known as **Stein-Leventhal syndrome**
Complex endocrine disorder - characterized
- **Long term anovulation**
- **Excess circulating androgens**

Characterized by formation of **cysts in ovaries** secondary to **failure to release ovum**
Ovaries enlarged in 67% of cases - reported cases exceed size of uterus
Only 10% of cases become develop symptomatic disease - disease is not uncommon
PCOS is leading cause of premenopausal pathologic amenorrhea

ETIOLOGY AND EPIDEMIOLOGY

Ultrasonic evidence of amenorrhea

- Random study of healthy women:	22%
- Women with amenorrhea	30%
- Oligomenorrhea	75%
- Hirsutism	87%

Results from prolonged period of **anovulation**
Causes relate to etiology of anovulation
- Inability of ovary to respond to gonadotrophic stimulation
- Hypothalamic or pituitary suppression
- Disharmonious gonadotropin and estrogen production

ASSOCIATED CHARACTERISTICS

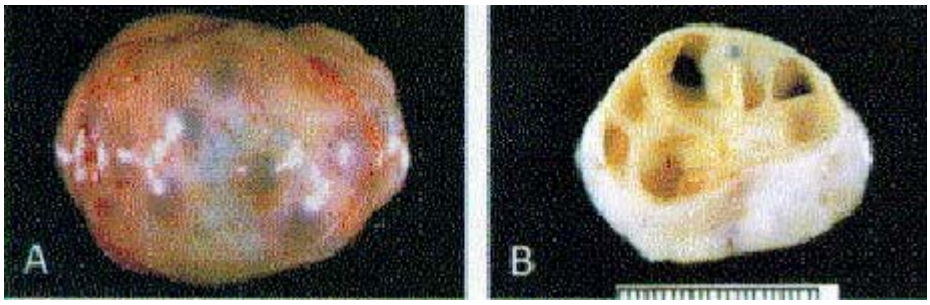
Hyperestrogenemia
Adrenal androgen excess
Ovarian abnormalities
Hyperprolactinemia
Hyperinsulinemia

Other causes - **androgen excess**
- Adrenal enzyme dysfunction
- Adrenal androgen hyperresponsiveness to ACTH
- Androgen therapy for endometriosis and fibrocystic breast disease
- Excess androgen from adrenals or ovaries
- Long-term increased stress has been implicated

Onset is variable
- Onset of menses as heterogenous disorder related to H-P-O axis abnormality
- Months or years after menarche due to other pathologic conditions
  - Congenital adrenal hyperplasia (CAH)
  - **Obesity**
  - **Insulin resistance**

PATHOPHYSIOLOGY

Imbalance of LH to FSH which leads to **thecal hyperplasia**
Relative abundance of LH and deficiency of FSH
Result of imbalance is hyperstimulation of thecal cells
Alteration leads to **thecal call hyperplasia** - stops follicular development
Halted follicular development leads to impaired estradiol production
Follicular development is unpredictable without LH-FSH during cycle
No dominant follicle results in multiple ovarian cysts over months to years
Hyperandrogenemia also results from thecal call hyperplasia



POSSIBLE ETIOLOGY (various theories)

Functional Abnormalities

Evidence suggests functional abnormalities: **hypothalamus**, pituitary and ovary
Observed increase in ratio of LH to FSH implicates hypothalamus and pituitary
Increased amplitude and pulse frequency of LH supports hypothalamic involvement
Ovarian theca cells is the site of androgen steroidogenesis
Hyperstimulation results in excess androgen production
Comorbid inadequate follicle maturation

Merits-weakness of theory
Strength: explains abnormalities
Androgen excess
Menstrual irregularity
Infertility
Weakness: theory does not offer mechanism for altered gonadotropin pulsatility

Obesity-Mediated Changes

Obesity (40% of PCOS) can contribute to gonadotropin secretion abnormalities
Adipose tissue can aromatize **androstenedione** to **estrone** (weak estrogen)
- Occurs even in absence of ovarian function
- Acyclic estrogen stimulation interferes with mid-cycle LH surge (positive estradiol-mediated)
- Result is anovulation (LH surge precipitates ovulation)
High estrone interferes with cyclic menstruation
- Predisposes to **endometrial hyperplasia**
- Intermittent and irregular break-through bleeding

Excess Adrenal Androgen

Primary adrenal abnormality may underlie disease development
Adrenals normally contribute 25% of circulating androgens
Excess androgens from any source can promote PCOS
Treatments which control androgens restore ovarian function
Any defect which causes adrenal androgen overproduction simulates PCOS

Insulin-Mediated Hyperandrogenism

Insulin resistance with hyperinsulinemia
- Reported with lean and obese women with PCOS
- Obese women are more insulin resistant

Greater than additive effect of insulin on LH-stimulated ovarian secretion
Interventions which lower insulin cause decrease in androgen
Weight loss in obese women
Insulin-sensitizing agents

Genetics

PCOS tends to run in families
Genetic basis remains unknown

CLINICAL PRESENTATION

Premenarchal onset
Menstrual dysfunction
Infertility
Hyperestrogenemia
Adrenal androgen excess
Hyperandrogenism
Hirsutism
Seborrhea
Acne
Alopecia
Hyperestrogenemia
Obesity
Hyperinsulinemia
Acanthosis nigricans

DIFFERENTIAL DIAGNOSIS OF EXCESS ANDROGEN IN WOMEN

Adrenal disorders

Late onset congenital adrenal hyperplasia
21-Hydroxylase deficiency
118 Hydroxylase deficiency
38-Hydroxysteroid dehydrogenase deficiency
Adrenal adenoma
Adrenal carcinoma

Ovarian disorders

Polycystic ovary syndrome
Hyperthecosis
Neoplasms
Sertoli/Leydig cell tumors
Granulosa/theca cell tumors

Other endocrinopathies

Hyperprolactinemia
Cushing syndrome
Acromegaly

Idiopathic hirsutism

Medications associated with hirsutism or irregular menses

Danazol
Androgenic oral contraceptives
Steroids
Anticonvulsants

INITIAL PRESENTATION

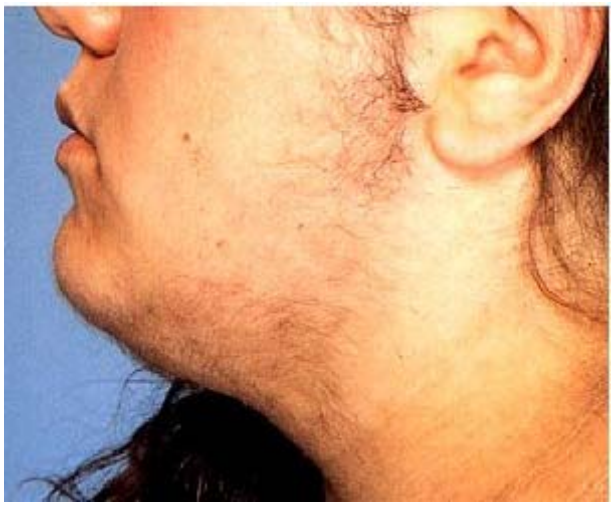
C/O **amenorrhea** or **irregular menstrual cycle**
Some present initially with complaints of infertility
Only 10%-20% of patients are symptomatic
Signs of hyperandrogenism may be subtle or extreme

CLINICAL FEATURES

Hyperandrogenism
Acne
Alopecia

Hirsutism

Excess, thick pigmented body hair (terminal hair)
Androgen-dependent areas
Assess the severity using quantitative scoring system (Ferriman-Gallwey system)
No clear-cut distinction between physiologic and pathologic hirsutism
Consider ethnic background and degree of hirsutism in female family members
Caucasian woman of Mediterranean ancestry have more body hair than Asian women or those of northern European background



Findings which suggest ovarian or adrenal tumor (emergent evaluation)
Voice deepening
Clitoromegaly
Increased muscle mass

Infertility

Infrequent ovulation
Frequent reason for seeking medical attention
Increased rate of spontaneous abortion (etiology unknown)

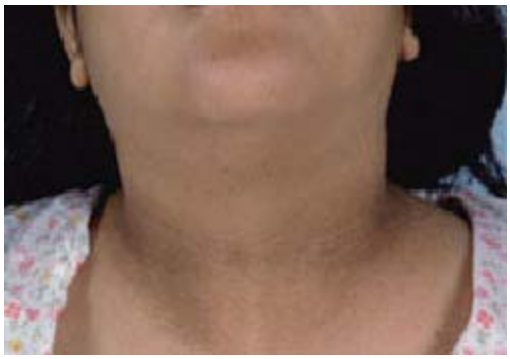
Obesity

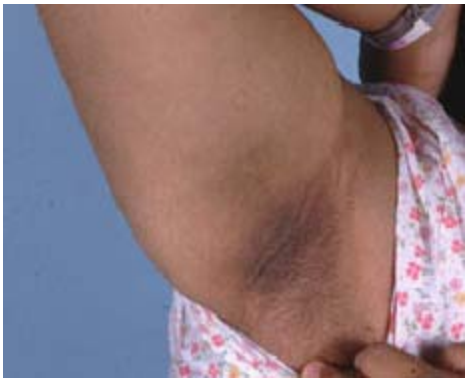
PCOS women tend to accumulate fat in upper body and abdominal regions
Characteristic apple shape
Measurements of central obesity
- Waist-to-hip ratio 0.85
- Waist circumference greater than 35 inch

Upper body obesity is an independent risk factor for CHD and abnormal GTT
Reported in 20% of women with PCOS

Acanthosis nigricans

Velvety smooth hyperpigmentation at nape of neck, axillae, inguinal area
Suggests hyperinsulinemia
Can serve as clinical marker indicating severity of underlying insulin resistance





TREATMENT

Therapeutic goals

- Reversing symptoms of androgen excess
- Instituting cyclic menstruation
- Restoring fertility
- Ameliorating associated metabolic defects

NON-PHARMACOLOGIC

Cosmetic

Hirsutism improvement may take up to six months after antiandrogen therapy
Adjuvant therapy: electrolysis, laser hair removal

Weight Loss

Very effective; often overlooked
Caloric restriction and exercise
Obesity exacerbates insulin resistence and hyperinsulinemia
Effects change in hormone levels: reduces free testosterone
Ovulation may resume as supported by research

Decrease in fasting insulin (lesser extent than testosterone)
Life-long follow-up for weight loss and maintenance recommended

PHARMACOLOGIC

Oral Combined Contraceptives

- **Decrease** adrenal and ovarian **androgen**
- **Increase SHBG**
- Normalize gonadotropin ratios (FSH/LH)
- Reduce circulating concentration testosterone and androstenedione
- Restores regular menses
- Confers contraception
- **Prevents endometrial hyperplasia**

- Favor low dose 2nd and 3rd generation progestins with low to moderate androgenicity
    - Preferred: norethindrone, ethynodiol diacetate, norgestimate, desogestrel
    - Avoid high androgenic: norgestrel, levonorgestrel

Antiandrogens

Spirolactone (Aldactone), flutamide, finasteride (Proscar)
Spirolactone used most frequently: used most frequently - 100 mg qd or bid
Mechanism
    Spirolactone and flutamide inhibit block peripheral androgen receptor
    Finasteride inhibits 5 alpha reductase in peripheral tissues
        Converts testosterone to more potent androgen dihydrotestosterone
Antiandrogens contraindicated in pregnancy - adverse effects on male fetus
Improve hirsutism and acne (OCs are synergics with this effect)
Other side effects
    Menstrual irregularity (avoided if combine with OCs)
    Hyperkalemia
    Transient polyuria, dizziness and GI side effects (nausea)

GnRH analogs

Gonadotropin-releasing hormone (GnRH)
Leuprolide and **nafarelin:** initial increase in gonadotropins followed by decline
Exogenous hormone production by ovaries is reduced
Slowing of hair growth but benefit is offset by estrogen-deficit side-effects
    Osteoporosis
    Hot-flushes
Side-effects warrant reserving use for treatment failures from conservative therapies

Clomiphene Citrate (Clomid)

Treatment to induce ovulation - restore fertility
Estrogen agonist and antagonist properties
Binds to estrogen receptors of hypothalamus
Additional research needed prior to routine use for PCOS

Insulin sensitizing agents

Metformin (Glucophage) - Off Label Use

Reduces fasting and meal-stimulated hyperinsulinemia
Limit ovarian cytochrome p450 activity with associated hormone decreases
- Decreased ovarian 17 hydroxyprogesterone
- Decreased free testosterone

Increased SHBG levels
Restore regular menses
Increase ovulatory menstruation
Reverse infertility
Increase rate of spontaneous pregnancy

Possible benefit to women with high waist-to-hip ratio, elevated BS, dyslipidemia
Some studies dispute benefit to androgen or SHBG
Risk of lactic acidosis if impaired renal function (creatinine > 1.4)

Thiazolidinediones - off-label, experimental usage

Improve insulin action
Decrease circulating androgen in PCOS
Known to resume ovulation in peri-menopausal women
Agents
Troglitazone (Rezulin) withdrawn due to hematoxicity
Rosiglitazone (Avandia)
Pioglitazone (Actos)

Progestins

Restore menses (avoid endometrial hyperplasia) but do not treat hirsutism or infertility
Medroxyprogesterone acetate (Provera) 10 mg/d x 10 d q 1-2 months
Occasionally no withdrawal bleeding
Endometrial atrophy from prolonged exposure to excess androgen

SURGICAL OPTIONS

Wedge Resection

Rarely performed
Rational for previous use
Reduce circulating androgens
Increase rate of ovulation and pregnancy

Out of favor due to high rate of post-op adhesions (70%)

Laser/Electrocautery

Preferred surgical option
Decreases number of ovarian theca cells
May help women achieve ovulation and pregnancy
Used only where ovulation-inducing agents have failed