GY Gynecology

Sarah Freeman, Vanessa Rojas Luengas, and **Ryan Ramos,** chapter editors
Danielle Jeong and **Nivethan Vela,** associate editors
Khizar Karim and **Ryan Wang,** EBM editors
Dr. Sari Kives, Dr. Danielle Vicus, and **Dr. Fay Weisberg,** staff editors

Acronyms

β-hCG	beta-human chorionic gonadotropin
ACEI	angiotensin converting enzyme inhibitors
AFP	alpha-fetoprotein
AIS	androgen insensitivity syndrome
ARB	angiotensin II receptor blockers
ASCUS	atypical squamous cells of undetermined significance
AUB	abnormal uterine bleeding
BMD	Bone mineral density
BMI	body mass index
BSO	bilateral salpingo-oophorectomy
BV	bacterial vaginosis
CAH	congenital adrenal hyperplasia
CHC	combined hormonal contraception
CMV	cytomegalovirus
D&C	dilatation and curettage
DES	diethylstilbestrol
DHEA	dehydroepiandrosterone
DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetate or Depo-Provera®
DUB	dysfunctional uterine bleeding
DVT	deep venous thrombosis
EPC	emergency postcoital contraception
FSH	follicle stimulating hormone
GA	gestational age
GIFT	gamete intrafallopian transfer
GnRH	gonadotropin-releasing hormone
GTD	gestational trophoblastic disease
GTN	gestational trophoblastic neoplasia
HERS	heart and estrogen/progestin replacement study
HMG	human menopausal gonadotropin
HPO	hypothalamic-pituitary-ovarian
HPV	human papillomavirus
HRT	hormone replacement therapy
HSG	hysterosalpingography
HSIL	high grade squamous intraepithelial lesion
HSV	herpes simplex virus
IBD	inflammatory bowel disease
ICSI	intracytoplasmic sperm injection
ITP	immune thrombocytopenic purpura
IUD	intrauterine device
IUI	intrauterine insemination
IUS	interauterine system
IVDU	intravenous drug use
IVF	*in vitro* fertilization
IVM	*in vitro* maturation
JRA	juvenile rheumatoid arthritis
LDH	lactate dehydrogenase
LEEP	loop electrosurgical excision procedure
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LMP	last menstrual period
LN	lymph node
LNMP	last normal menstrual period
LSIL	low grade squamous intraepithelial lesion
LVSI	lymphovascular space involvement
MRKH	Mayer-Rokitansky-Küster-Hauser
NK	natural killer
N/V	nausea/vomiting
OCP	oral contraceptive pill
OGTT	oral glucose tolerance test
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PG	prostaglandin
PID	pelvic inflammatory disease
PMB	postmenopausal bleeding
PMDD	premenstrual dysphoric disorder
PMN	polymorphonuclear neutrophils
PMS	premenstrual syndrome
RPR	rapid plasma reagin
SCC	squamous cell carcinoma
SERMs	selective estrogen receptor modulator
SHBG	sex hormone binding globulin
SHG	sonohysterography
SPERM	selective progesterone receptor modulator
SSRIs	selective serotonin reuptake inhibitors
STI	sexually transmitted infections
TAH	total abdominal hysterectomy
TET	tubal embryo transfer
TH	total hysterectomy
TOT	tension-free transobturator tape
TSH	thyroid-stimulating hormone
TVT	tension-free vaginal tape
TZ	transformation zone
UAE	uterine artery embolization
U/S	ultrasound
UTI	urinary tract infection
VDRL	venereal disease research laboratory
VIN	vulvar intraepithelial neoplasia
VTE	venous thromboembolism
vWD	von Willebrand disease
W/D	withdrawal
WHI	Women's Health Initiative
ZIFT	zygote intrafallopian transfer

Basic Anatomy Review

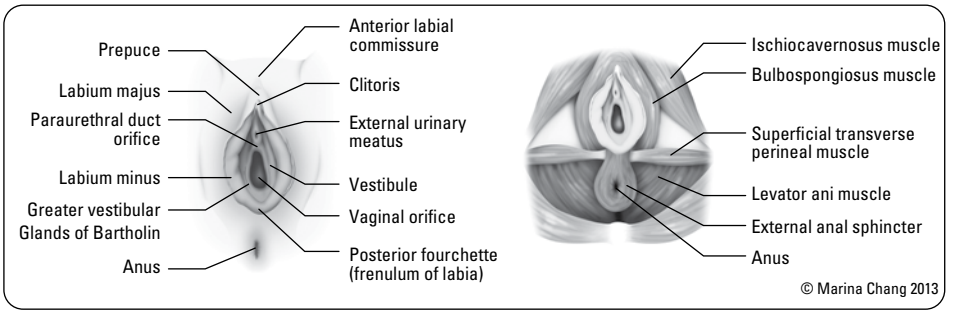


Figure 1. Vulva and perineum

A. EXTERNAL GENITALIA

- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

B. VAGINA

- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- lined by rugated, stratified squamous epithelium
- upper vagina separated by cervix into anterior, posterior, and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastamoses from uterine, inferior vesical, and middle rectal arteries

C. UTERUS

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus
    - blood supply: uterine artery (branch of the internal iliac artery, anterior division)
  - cervix
    - blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs, and 4 paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals then terminate in the labia majora
    - function: anteversion
    - blood supply: Sampson's artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - function: mechanical support for uterus, prevent prolapse and contain autonomic nerve fibres
  - cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
    - function: mechanical support, prevent prolapse
  - broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics

- infundibulopelvic ligament (suspensory ligament of the ovary): continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
- position of the uterus
  - anteverted (majority), retroverted, neutral

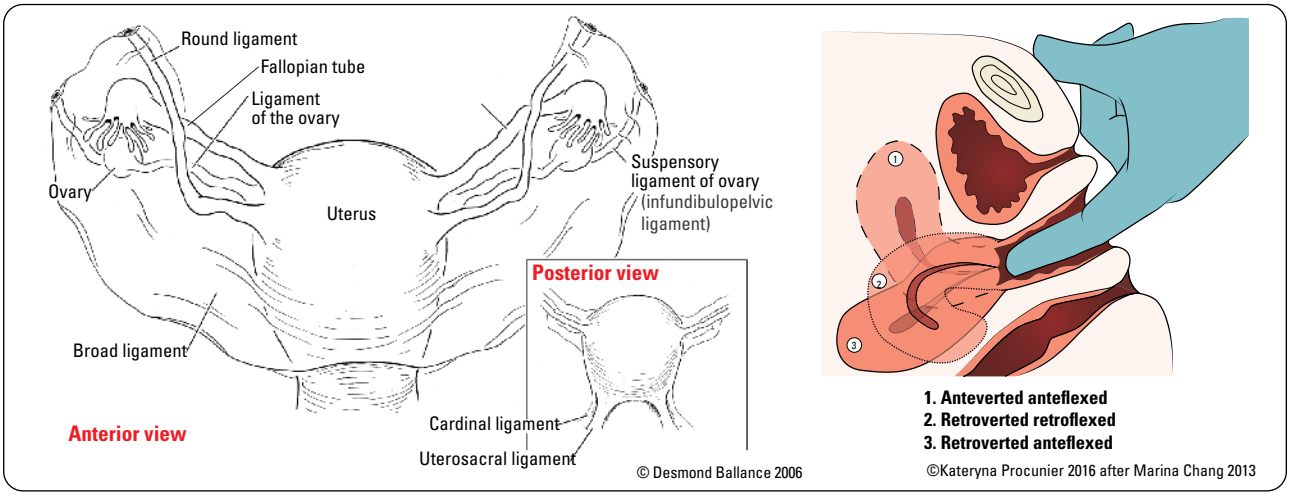


Figure 2. Genital organs and positioning of the uterus

D. FALLOPIAN TUBES

- 8-14 cm muscular tubes extending laterally from the uterus to the ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. OVARIES

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off of aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

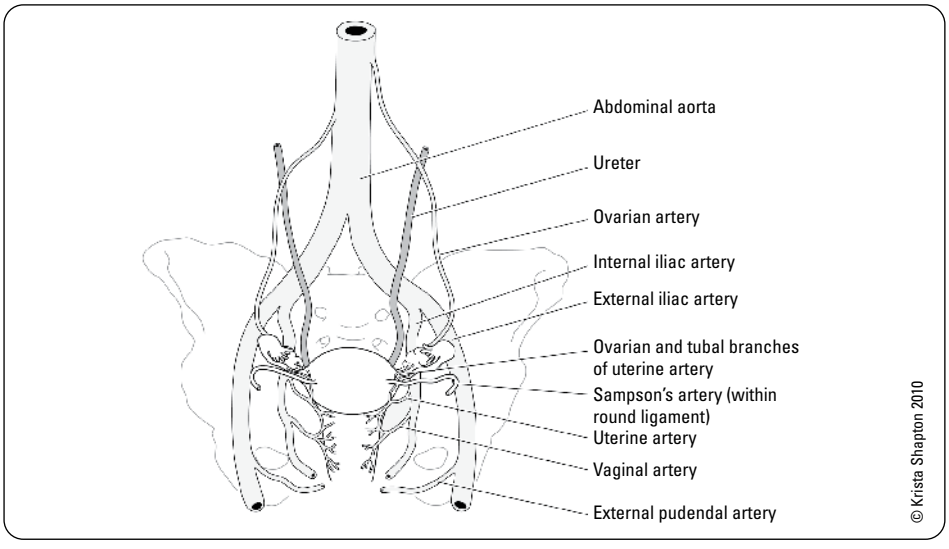


Figure 3. Vascular supply

Determination of Uterine Position by Clinical Exam

- If cervix faces anteriorly (under the urethra and less easily accessible), i.e. toward vaginal orifice, more likely RETROVERTED UTERUS
- If cervix faces posteriorly (easily accessible), i.e. toward sacrum or rectum, more likely ANTEVERTED UTERUS
- If uterus palpable on bimanual exam, more likely ANTEVERTED UTERUS

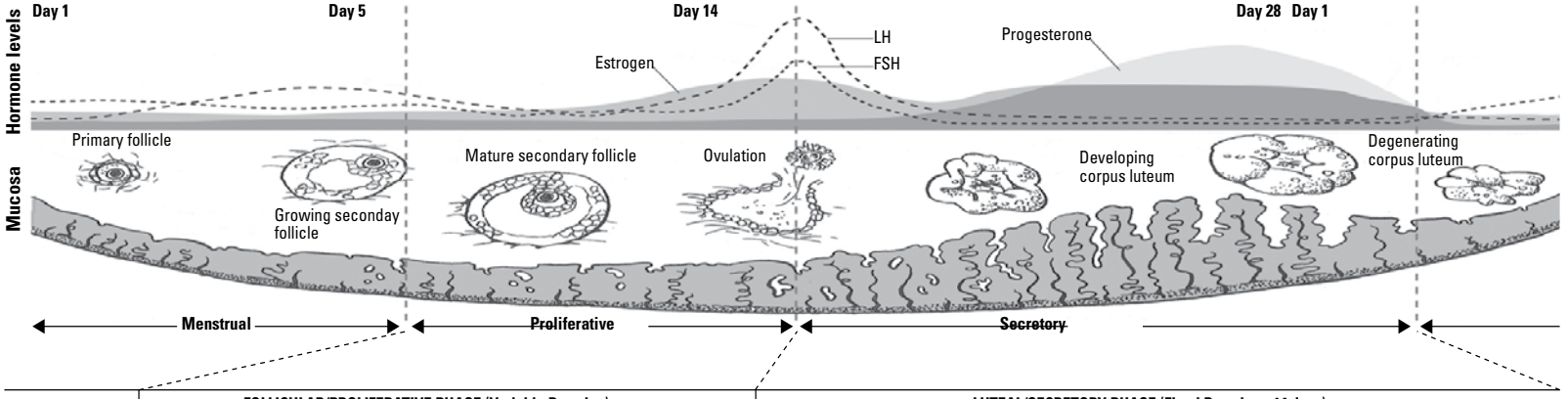
"Water Under the Bridge"
The ureters run posterior to the uterine arteries

Common Anatomy Questions in the OR

- **What is the origin of the left and right ovarian arteries?**
  Descending aorta
- **What are the drainage sites for the left and right ovarian veins?**
  Left to left renal vein, right to inferior vena cava
- **What is the most common place to locate the ureter?**
  Pelvic brim, medial leaf of the broad ligament as it passes under the uterine artery
- **Which artery runs under the round ligament?**
  Sampson's artery

Menstruation

Menstrual Cycle



	FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)			LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)		
	Early	**Mid**	**Late**	**OVULATION**	**Early-Mid**	**Late**
Initiating Events	↓ E and ↓ P (from end of previous cycle)	↑ FSH acts on ovarian granulosa cells	Growing follicles continue to secrete E	Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH)	Switch back to negative feedback	No fertilized oocyte
HPO Axis	↑ GnRH pulse frequency ↑ FSH ↑ LH pulse frequency	↑ E from follicles (ovary)		↑↑ LH pulse amplitude (LH surge)	↓ LH	
Hormones			↑ E from follicles, especially from dominant follicle	E peaks → LH surge → ovulation	↑ P from corpus luteum	↓ P secondary to degeneration of corpus luteum
Feedback on HPO Axis		Negative feedback E → ↓ FSH, ↓ LH		Positive feedback: E and P → ↑ FSH, ↑ LH	Negative feedback P → ↓ FSH, ↓ LH	
Ovaries	↑ FSH → follicular growth in 3-30 follicles	↑ follicular growth (by reducing atresia) → ↑ E	Dominant follicle persists, remainder undergo atresia Granulosa cells luteinize → produce P	~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P		Cessation of P from corpus luteum
Endometrium	Menses from P withdrawal (from end of previous cycle)		E builds up endometrium		P stabilizes endometrium	Withdrawal of P → menses
Cervical Mucus		Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy				Cervical mucus: Opaque, scant amount, Spinnbarkeit 1-2 cm

E = estrogen; FSH = follicle-stimulating hormone; GnRH = gondatropin-releasing hormone; HPO = hypothalamic pituitary-ovarian; LH = lutenizing hormone; P = progesterone

Figure 4. Events of the normal menstrual cycle

CHARACTERISTICS
- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

ESTROGEN
ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle

Estrogen effects
- On the follicles in the ovaries
  - Reduces atresia
- On the endometrium
  - Proliferation of glandular and stromal tissue
- On all target tissues
  - Decreases E receptors

PROGESTERONE
PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle)

Progesterone effects
- On the endometrium
  - Cessation of mitoses (stops building endometrium up)
  - "Organization" of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues
  - Decrease E receptors (the "anti-estrogen" effect)
  - Decrease P receptors

Stages of Puberty

- see Pediatrics, P31
- adrenarche: increased secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8 yr
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding

Stages of Puberty

"Boobs, Pubes, Grow, Flow"
Thelarche, Pubarche, Growth spurt, Menarche

Tanner Stage

Thelarche
1. None
2. Breast bud
3. Further enlargement of areolae and breasts with no separation of contours
4. 2º mound of areolae and papilla
5. Areolae recessed to general contour of breast – adult

Pubarche
1. None
2. Downy hair along labia only
3. Darker/coarse hair extends over pubis
4. Adult-type hair with no thigh involvement
5. Adult hair in distribution and type; extends over thighs. Not all patients achieve Tanner Stage 5. For image see Pediatrics, P32

Premenstrual Syndrome

- synonyms: "ovarian cycle syndrome," "menstrual molimina" (moodiness)

Etiology
- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter (serotonin, dopamine, GABA) interactions with sex steroids (P, E, and T)
- serotonergic dysregulation – currently most plausible theory

Diagnostic Criteria for Premenstrual Syndrome
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness or swelling, abdominal bloating, headache, swelling of extremities, joint or muscle pain, or weight gain
- symptoms relieved within 4 d of onset of menses and do not recur until at least day 13 of cycle
- symptoms present in the absence of any pharmacologic therapy, hormone ingestion, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or occupational performance

Premenstrual Syndrome
Physiological and emotional disturbances that occur 1-2 wk prior to menses and last until a few days after onset of menses; common symptoms include depression, irritability, tearfulness, and mood swings

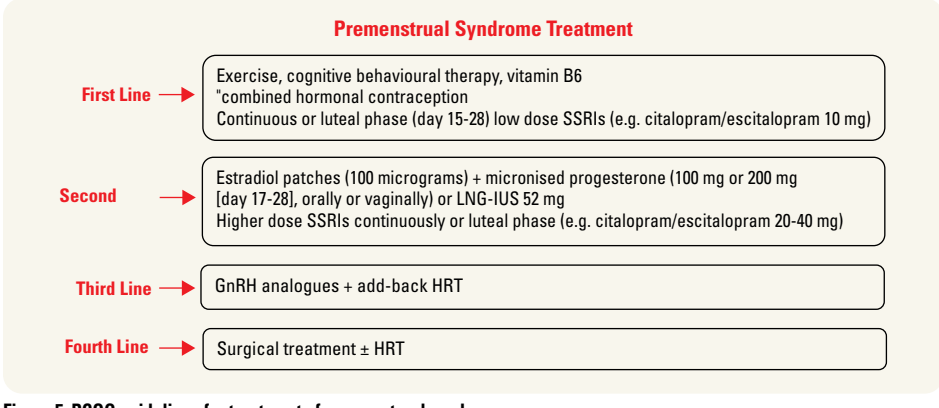


Figure 5. RCOG guidelines for treatment of premenstrual syndrome
Adapted from source: https://www.rcog.org.uk/globalassets/documents/guidelines/gt48managementpremensturalsyndrome.pdf

Premenstrual Dysphoric Disorder

Clinical Feature
- irritability, depressed mood
- breast pain and bloating

Diagnostic Criteria for Premenstrual Dysphoric Disorder
- at least 5 of the following 11 symptoms during most menstrual cycles of the last year (with at least 1 of the first 4)
  - depressed mood or hopelessness
  - anxiety or tension
  - affective instability
  - anger or irritability
  - decreased interest in activities
  - difficulty concentrating
  - lethargy
  - change in appetite
  - hypersomnia or insomnia
  - feeling overwhelmed
  - physical symptoms: breast tenderness/swelling, headaches, joint/muscle pain, bloating, or weight gain
- symptoms cause significant distress and/or interfere with social or occupational functioning
- symptoms must be present during the week prior to menses and resolve within a few days after onset of menses
- may be superimposed on other psychiatric disorders, provided it is not merely an exacerbation of another disorder

Common Investigations and Procedures

Imaging

Ultrasound (U/S)

- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1500 (β-hCG must be ≥6500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, and ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec®) is optional
- more invasive procedure (i.e. D&C) may be done in the office or operating room ± hysteroscopy. This may be required if endometrial biopsy is not possible in the office setting or if there is suspicion for an endometrial polyp
- indications
  - AUB/PMB
    - age >40
    - risk factors for or history of endometrial cancer
    - failure of medical treatment
    - significant intermenstrual bleeding
    - consider in women with infrequent menses suggesting anovulatory cycles

Hysterectomy

Indications

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

Approaches

1. Open (abdominal approach): uterus removed via transverse (Pfannenstiel) or midline laparotomy
2. Minimally invasive approaches
   - vaginal hysterectomy: entire procedure performed through the vagina. No abdominal incisions
   - laparoscopic-assisted vaginal hysterectomy: vascular pedicles are divided by a combination of laparoscopic and vaginal approaches
   - total laparoscopic hysterectomy: all vascular pedicles including the colpotomy approached laparoscopically and removed through the vagina
   - robotic: a type of laparoscopic approach. May be advantageous in high BMI patients. More costly

No. 377 – Hysterectomy for Benign Gynaecological Indications
J Obstet Gynaecol Can 2019;41(4):543-557
Summary:

1. Hysterectomy should be approached by either vaginal, laparoscopic, or open routes
2. Correction of preoperative anemia (hemoglobin <120 g/L), preoperative antibiotic prophylaxis, and measures to decrease risk of venous thromboembolism are recommended
3. In patients with endometriosis, full excision of local endometriosis should be performed concurrently
4. Opportunistic salpingectomy can be considered at the time of hysterectomy, but the planned surgical approach should not be changed for this sole purpose
5. Urinary tract injury is a known complication of hysterectomy and there should be a low threshold for further investigation in cases where injury is suspected- consider routine cystoscopy

Women should be counselled about the benefits and risks of removing the ovaries, the risk of ovarian cancer versus the long-term health implications of earlier menopause

Table 1. Classification of Hysterectomy

Classification	Tissues Removed	Indications
Subtotal Hysterectomy	Uterus	Inaccessible cervix (e.g. adhesions) Patient choice/preference Severe endometriosis
Total Hysterectomy (extrafascial simple hysterectomy/type 1)	Uterus, cervix, uterine artery ligated at uterus	Uterine fibroids Endometriosis Adenomyosis Heavy menstrual bleeding DUB
Total Hysterectomy (extrafasical simple hysterectomy/type 1) + Bilateral Salpingo-Oophorectomy	Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries	Endometrial cancer Malignant adnexal masses Consider for endometriosis
Modified Radical Hysterectomy (type 2)	Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments, and upper 1-2 cm vagina	Cervical cancer (up to stage 1B1)
Radical Hysterectomy (type 3)	Uterus, cervix, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum), and upper 1/3-1/2 vagina	Cervical cancer

Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

With Secondary Sexual Development		Without Secondary Sexual Development	
Normal breast and pelvic development	**Normal breast, abnormal uterine development**	**High FSH (hypergonadotropic hypogonadism)**	**Low FSH (hypogonadotropic hypogonadism)**
Hypothyroidism Hyperprolactinemia PCOS Hypothalamic dysfunction	Androgen insensitivity Anatomic abnormalities Müllerian agenesis, uterovaginal septum, imperforate hymen	Gonadal dysgenesis Abnormal sex chromosome (Turner's XO) Normal sex chromosome (46XX, 46XY)	Constitutional delay (rare in girls) Congenital abnormalities Isolated GnRH deficiency Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.) Acquired endocrine disorders (type 1 DM) Pituitary tumours Systemic disorders (IBD, JRA, chronic infections, etc.) Functional hypothalamic amenorrhea

Most Common Causes of Primary Amenorrhea
1. Müllerian agenesis
2. Abnormal sex chromosomes (Turner's syndrome)
3. Functional hypothalamic amenorrhea

Table 3. Differential Diagnosis of Secondary Amenorrhea

With Hyperandrogenism	Without Hyperandrogenism
PCOS Autonomous hyperandrogenism (androgen secretion independent of the HPO axis) Ovarian: tumour, hyperthecosis Adrenal androgen-secreting tumour Late onset or mild congenital adrenal hyperplasia (rare)	Hypergonadotropic hypogonadism (i.e. primary ovarian insufficiency: high FSH, low estradiol) Idiopathic Autoimmune: type 1 DM, autoimmune thyroid disease, Addison's disease Iatrogenic: cyclophosphamide drugs, radiation Hyperprolactinemia Endocrinopathies: most commonly hyper or hypothyroidism Hypogonadotropic hypogonadism (low FSH): Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan's syndrome Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)

Functional hypothalamic amenorrhea is the most common cause of secondary amenorrhea

Investigations

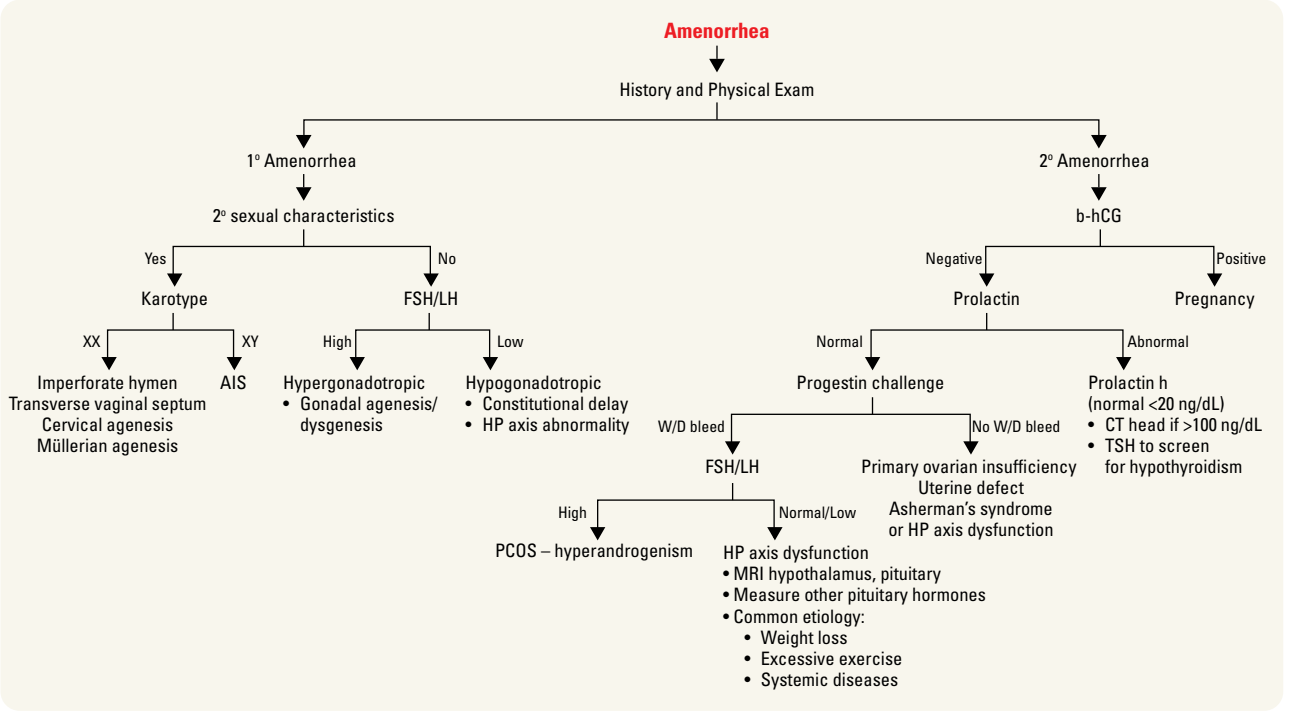


Figure 6. Diagnostic approach to amenorrhea

- β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/ withdrawal bleed
    - withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
    - if no bleeding occurs, this may be secondary to inadequate estrogen (hypoestrogenism), excessive androgens, or progesterones (decidualization) or pregnancy
- karyotype: indicated if primary ovarian insufficiency or absent puberty
- U/S to confirm normal anatomy, identify PCOS

Prolactinoma Symptoms
Galactorrhea, visual changes, headache

Treatment

Table 4. Management of Amenorrhea

Etiology	Management
1° AMENORRHEA	
Androgen insensitivity syndrome	Gonadal resection after puberty
	Psychological counselling
	Creation of neo-vagina with dilation
Anatomical	
Imperforate hymen	Surgical management
Transverse vaginal septum	Surgical management
Cervical agenesis	Suppression and ultimately hysterectomy
Müllerian dysgenesis (MRKH syndrome)	Psychological counselling
	Creation of neo-vagina with dilation
	Diagnostic study to confirm normal urinary system and spine

Primary Amenorrhea
No menses by age 13 in absence of 2° sexual characteristics, or no menses by age 15 with 2° sexual characteristics, or no menses 2 yr after thelarche

Secondary Amenorrhea
No menses for >6 mo or 3 cycles after documented menarche

Table 4. Management of Amenorrhea (continued)

Etiology	Management
2° AMENORRHEA	
HP-axis dysfunction	**Identify modifiable underlying cause** Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work)
Hyperprolactinemia	MRI/CT head to rule out lesion If no demonstrable lesions by MRI Bromocriptine, cabergoline if fertility desired Combined OCPs if no fertility desired Demonstrable lesions by MRI: surgical management
Polycystic ovarian syndrome	See *Polycystic Ovarian Syndrome*, GY23
Premature ovarian failure	Screen for DM, hypothyroidism, hypoparathyroidism, hypocorticolism Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis; can use OCP after induction of puberty
Uterine defect	Evaluation with hysterosalpingography or sonohysterography
Asherman's syndrome	Hysteroscopy: excision of synechiae

2° amenorrhea is pregnancy until proven otherwise

Abnormal Uterine Bleeding

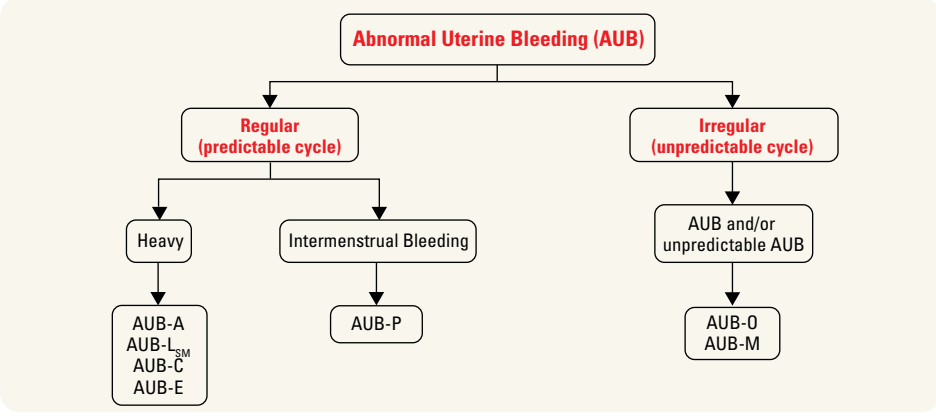


Figure 7. Diagnostic approach to abnormal uterine bleeding

Approach

- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, impact on quality of life, and timing (inter or premenstrual or breakthrough)
- is it regular?
  - regular: cycle to cycle variability of <20 d – "Can you predict your menses within 20 days?"
  - irregular: cycle to cycle variability of ≥20 d
- is it heavy?
  - ≥80 cc of blood loss per cycle or
  - ≥8 d of bleeding per cycle or
  - bleeding that significantly affects quality of life
- is it structural?
  - PALM
- is it non-structural?
  - COEIN

Postmenopausal bleeding is endometrial cancer until proven otherwise

Abnormal Uterine Bleeding
Change in frequency, duration, or amount of menstrual flow that affects quality of life

Table 5. AUB – Etiologies, Investigations, and Management

Etiology	Investigations	Management
	STRUCTURAL	
Polyps (AUB-P)	Transvaginal sonography Saline infusion sonohysterography	Polypectomy (triage based on symptoms,polyp size, histopathology and patient age)
Adenomyosis (AUB-A)	Transvaginal sonography MRI	See *Adenomyosis*, GY13
Leiomyoma (AUB-L) **Submucosal (AUB-Lsm)** **Other (AUB-Lo)**	Transvaginal sonography Saline infusion sonohysterography Diagnostic hysteroscopy	See *Fibroids (Leiomyomata)*, GY13
Malignancy and Hyperplasia (AUB-M)	Transvaginal sonography Endometrial biopsy for all women >40 yr with AUB, for women <40 yr with persistent AUB or endometrial cancer risk factors	Dependent on diagnosis
	NON-STRUCTURAL	
Coagulopathy (AUB-C)	CBC, coagulation profile (especially in adolescents), vWF, Ristocetin cofactor, factor VIII	Dependent on diagnosis (hormonal modulation (e.g. OCP), Mirena IUS, endometrial ablation)
Ovulatory dysfunction (AUB-O)	Bloodwork: β-hCG, ferritin, prolactin, FSH, LH, serum androgens (free testosterone, DHEA), progesterone, 17-hydroxy progesterone, TSH, free T4 pelvic ultrasound	See *Infertility*, GY22
Endometrial (AUB-E)	Endometrial biopsy	Tranexamic acid Hormonal modulation (e.g. OCP) Mirena IUS Endometrial ablation
Iatrogenic (AUB-I)	Transvaginal sonography (rule out forgotten IUD) Review OCP/HRT use Review meds (especially neuroleptic use)	Remove offending agent
Not yet classified (AUB-N)	—	—

Treatment

- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider AUB
- medical
  - mild AUB
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - combined hormonal contraceptive
    - progestins (Provera®) on first 10-14 d of each month or every 3 mo if AUB-O
    - Mirena® IUD
    - correct anemia - iron
  - acute, severe AUB
    - replace fluid losses, consider admission

    a) estrogen (Premarin®) 25 mg IV q4h x 24 h with Gravol® 50 mg IV/PO q4h or anti-fibrinolytic (e.g. Cyklokapron®) 10 mg/kg IV q8h (rarely used)

    b) tapering OCP regimen, 35 μg pill tid x7d then taper to 1 pill/d for 3wk with Gravol® 50 mg IV/PO q4h
      - or taper to 1 tab tid x 2 d → bid x 2 d → OD (more commonly used)
    - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
      - medical (can also consider):
        - high dose progestins
        - danazol (Danocrine®)
        - GnRH agonsits (e.g. Lupron ®) with add-back if taken for >6 mo
        - ulipristal acetate
- surgical
  - endometrial ablation
    - if finished childbearing
    - repeat procedure may be required if symptom recur, especially if <40 yr
  - hysterectomy: definitive treatment

Dysmenorrhea

Etiology
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease
  - IUD (copper)
  - foreign body

Primary Dysmenorrhea
Recurrent crampy lower abdominal pain during menses in the absence of demonstrable disease

Secondary Dysmenorrhea
Pain during menses that can be attributed to an underlying disorder (endometriosis, adenomyosis, fibroids)

Table 6. Comparison of Primary and Secondary Dysmenorrhea

	Primary Dysmenorrhea	Secondary Dysmenorrhea
Features	Recurrent, crampy lower abdominal pain that occurs during menses in the absence of demonstrable disease	Similar features as primary dysmenorrhea but with an underlying disorder that can account for the symptoms, such as endometriosis, adenomyosis or uterine fibroids
Signs and Symptoms	Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)	Associated dyspareunia, abnormal bleeding, infertility
Diagnosis	Assess for associated dyspareunia, abnormal bleeding, infertility (signs of 2° dysmenorrhea) Rule out underlying pelvic pathology and confirm cyclic nature of pain Pelvic examination not required; indicated for patients not responding to therapy or with signs of organic pathology	Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women <20 yr) U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis Vaginal and cervical cultures may be required
Treatment	Regular exercise, local heat NSAIDs: should be started before onset of pain Combined hormonal contraceptives with continuous or extended use: suppress ovulation/ reduce menstrual flow	Treat underlying cause

Endometriosis

Definition
- the presence of endometrial tissue (glands and stroma) outside of the uterine cavity
- chronic condition, resolving only with menopause

Etiology
- not fully understood; proposed mechanisms include (combination likely involved):
  - retrograde menstruation (Sampson's theory)
  - immunologic: decreased NK cell activity limiting clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Differential Diagnoses
- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy

Classic Triad of Endometriosis
- Dysmenorrhea
- Dyspareunia (cul-de-sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)

Epidemiology
- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

Risk Factors
- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolves with treatment of anomaly
- nulliparity
- age >25 yr

Sites of Occurrence

- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

Clinical Features

- may be asymptomatic and can occur with one of 3 presentations

1. pain

- menstrual symptoms
  - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
  - secondary dysmenorrhea
  - sacral backache with menses
  - pain may eventually become chronic, worsening perimenstrually
  - deep dyspareunia
- bowel and bladder symptoms
  - frequency, dysuria, hematuria
  - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)

2. infertility

- 30-40% of patients with endometriosis will be infertile
- 15-30% of those who are infertile will have endometriosis

3. mass (endometrioma)

- ovarian mass can present with any of above symptoms or be asymptomatic
- physical examination:
  - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
  - fixed retroversion of uterus
  - firm, fixed adnexal mass (endometrioma: an endometriotic cyst encompassing ovary)

Investigations

- definitive diagnosis can be made based on:
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125 (cancer antigen 125)
  - may be elevated in patients with endometriosis but should NOT be used as a diagnostic test

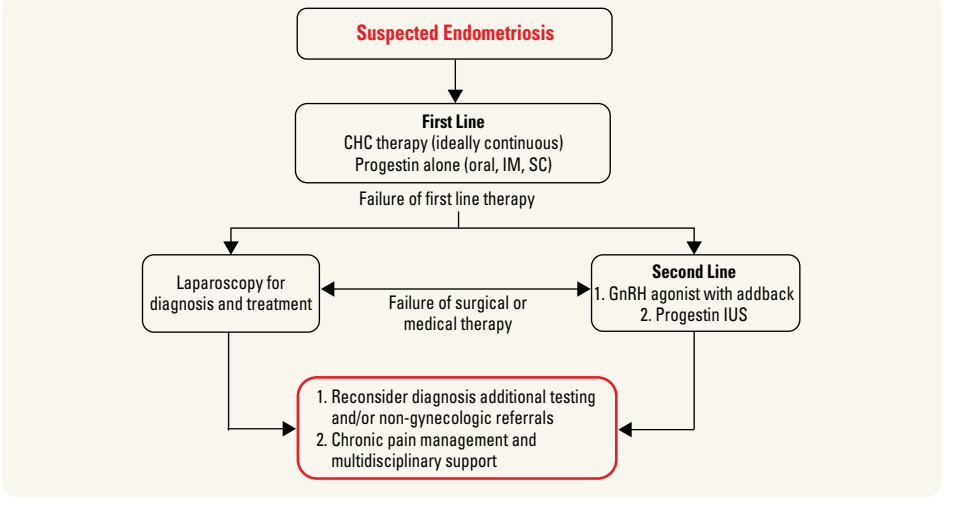


Figure 8. SOGC guidelines for treatment of endometriosis

Endometriosis – Take Home Points

- Suggestive history even with a negative exam should be considered adequate for a presumptive diagnosis
- Pelvic pain that is not primary dysmenorrhea should be considered endometriosis until proven otherwise
- Medical management is the mainstay of endometriosis

Treatment

- surgical confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)

- medical
  - NSAIDs (e.g. naproxen sodium – Anaprox®)
  - 1st line
    - cyclic/continuous estrogen-progestin (OCP)
    - progestin (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®))
    - Mirena® IUS
  - 2nd line
    - GnRH-agonist (e.g. leuprolide (Lupron®)): suppresses pituitary
      - side effects: hot flashes, vaginal dryness, reduced libido
      - use >6 mo: include add-back progestin or estrogen to prevent decreased BMD, reduce vasomotor side-effects
    - danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change
- surgical
  - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: bilateral salpingo-oophorectomy ± hysterectomy
  - best time to become pregnant is immediately after conservative surgery
  - if patient is not planning to become pregnant post-op, suppress ovulation medically to prevent recurrence

Adenomyosis

- synonym: "endometriosis interna" (uterine wall may be diffusely involved)

Adenomyosis
Extension of areas of endometrial glands and stroma into the myometrium

Epidemiology
- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features
- often asymptomatic
- heavy menstrual bleeding, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm
- Halban sign: tender, softened uterus on premenstrual bimanual exam

Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI

Investigations
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Treatment
- medical
  - iron supplements for anemia
  - analgesics, NSAIDs
  - Mirena® IUS
  - CHC, medroxyprogesterone (Depo-Provera®) – limited evidence for efficacy
  - GnRH agonists (e.g. leuprolide (Lupron ®))
  - low dose danazol 100-200 mg PO OD (trial x 4 mo)
- surgical
  - definitive: hysterectomy – treatment of choice in women who have completed childbearing

Fibroids

Leiomyomata/Fibroids
Benign smooth muscle tumour of the uterus (most common gynecological tumour)

Epidemiology
- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1000)
- typically regress after menopause

Submucosal leiomyomata are most symptomatic (bleeding, infertility)

Pathogenesis
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - fibroids can degenerate, become calcified, develop sarcomatous component, or obtain parasitic blood supply

The effect of pregnancy on fibroid size is variable

Clinical Features

- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, heavy menstrual bleeding
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - constipation, bloating (rare)
  - acute urinary retention (extremely rare, but surgical emergency!)
- acute pelvic pain
  - fibroid degeneration
  - fibroid torsion (if pedunculated subserosal)
- infertility, recurrent pregnancy loss
- pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

Investigations

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or for assessing intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
- occasionally MRI is used for pre-operative planning (e.g. before myomectomy)

Treatment

- only if symptomatic (heavy menstrual bleeding, menometrorrhagia, bulk symptoms), rapidly enlarging or intracavitary
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - CHC, IUS or Depo-Provera®
  - GnRH agonist: leuprolide (Lupron®)
    - often used for 3 mo preoperatively to increase Hb and reduce fibroid size
    - reduces bleeding, shrinks fibroids, and corrects anemia
    - can be used long-term to bridge to menopause in combination with add-back progestin or estrogen
  - ulipristal acetate (Fibristal ®): a selective progesterone receptor agonist
    - 5 mg daily for 3 mo
    - reduces bleeding, shrinks fibroids
    - repeat courses only if patient not eligible for surgery; patients must menstruate between courses
    - associated with benign, non-physiological endometrial changes (selective progesterone receptor modulator-associated endometrial changes (PAEC)) which are reversible with discontinuation of therapy
    - note: rare side effect of liver failure. Screen for liver disease prior to prescribing, and monitor liver function before, during, and after treatment courses. Do not prescribe in patients with underlying liver disorder
- interventional radiology approach
  - uterine artery embolization (UAE) occludes both uterine arteries, shrinks fibroids by 50% at 6 mo; improves heavy bleeding in 90% of patients within 1-2 mo; not an option in women considering childbearing
    - higher risk of surgical re-intervention than with surgical approaches
- surgical approach
  - myomectomy (hysteroscopic, transabdominal, or laparoscopic)
  - hysteroscopic resection of fibroid and endometrial ablation for AUB-Lsm
  - hysterectomy (see *Hysterectomy*, GY6)
  - note: avoid operating on fibroids during pregnancy (due to vascularity and potential pregnancy loss); expectant management usually best

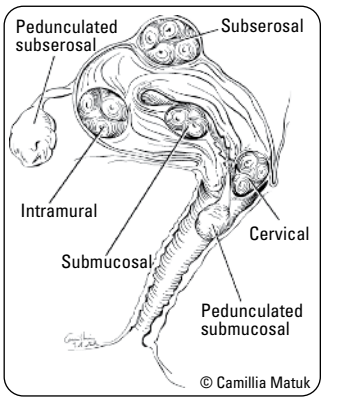


Figure 9. Possible anatomic locations of uterine leiomyomata

Ulipristal Acetate vs. Leuprolide Acetate for Uterine Fibroids
NEJM 2012;366:421-432
Study: Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.
Outcomes: Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.
Patients: 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.
Results: Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 11% (5 mg) and 10% (10 mg) of the ulipristal groups did.
Conclusions: Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids and has a better side-effect profile.

Uterine artery embolization for symptomatic uterine fibroids
Cochrane Database Syst Rev. 2014, 12: CD005073
Purpose: To compare outcomes of uterine artery embolization (UAE) to other medical or surgical therapies for symptomatic uterine fibroids. Primary outcomes were patient satisfaction and live birth rate.
Results: Seven RCTs with 793 women were included. There was no evidence of a difference in the primary outcomes or risk of major complications between the interventions. UAE was associated with a higher risk of minor complications and the need for additional surgical intervention within two years.
Conclusions: No significant differences in patient satisfaction or major complications in UAE compared to surgical intervention. UAE is associated with an increased risk of surgical re-intervention.

Contraception

• see Family Medicine, FM20

Table 7. Classification of Contraceptive Methods

Type	Effectiveness (Perfect Use, Typical Use*)
Physiological	
Withdrawal/coitus interruptus	96%, 77%
Rhythm method/calendar/mucus/symptothermal	76%
Lactational amenorrhea	98% (first 6 mo postpartum)
Chance – no method used	15%
Abstinence of all sexual activity	100%
Barrier Methods	
Condom alone	98%, 82%
Spermicide alone	82%, 72%
Sponge – Parous	80%, 76%
– Nulliparous	91%, 88%
Diaphragm with spermicide	94%, 88%
Female condom	95%, 79%
Cervical cap – Parous	74%, 68%
– Nulliparous	91%, 84%
Hormonal	
OCP	99.7%, 92%
Nuva Ring®	99.7%, 92%
Transdermal (Ortho Evra®)	99.7%, 92%
Depo-Provera®	99.7%, 97%
Progestin-only pill (Micronor®)	90-99%
Mirena® IUS	99.9%
Jaydess® IUS	99.9%
Copper IUD	99.3%
Surgical	
Tubal ligation	99.65%
Vasectomy	99.9%
Emergency Postcoital Contraception (EPC)	
Yuzpe® method	98% (within 24 h), decreases by 30% at 72 h
"Plan B" levonorgestrel only	98% (within 24 h), decreases by 70% at 72 h
Postcoital IUD	99.9%
Ella	98% (within 120 h)

*Effectiveness: percentage of women reporting no pregnancy after 1 yr of use

Counselling the Adolescent about Contraception
More than 90% of adolescent pregnancies are unintended, and ~50% of all pregnancies occur within the first 6 mo of initiating sexual activity; in addition, 85% of sexually active women become pregnant within 1 yr if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy

New Oral Contraceptive Preparations and the Risk of Venous Thromboembolism vs. Second Generation Drugs
BMJ 2015;350:h2135
Summary: Risks of thromboembolism associated with combined OCPs were higher for drug preparations with newer progesterone types than for second generation drugs (levonorgestrel and noresthisterone) and norgestimate.
Methods: Two nested case-control studies were performed on UK population through two large databases containing total of 1340 practices. Women aged 15-49 years with a first diagnosis of VTE in 2001-13 were matched with five controls by age, practice, and calendar year. OR for VTE incidence and use of combined OCPs were adjusted for smoking status, alcohol consumption, ethnic group, BMI, comorbidities, and other contraceptive drugs.
Results: Current exposure to OCP was associated with adjusted OR of 2.97 (95% CI 2.78-3.17) compared to no exposure in previous year. Risks associated with current exposure to new progesterone drug preparations (desogestrel, gestodene, drospirenone, cyproterone) were significantly higher than those for second generation contraceptives (levonorgestrel, noresthisterone) and norgestimate.

Hormonal Methods

Combined Oral Contraceptive Pills

- progestin: prevents LH surge, suppresses ovulation, thickens cervical mucus, decreases tubal motility, decidualizes endometrium
- estrogen: suppresses FSH and follicular development, causes endometrial proliferation
- most contain low dose ethinyl estradiol (20-35 μg) plus progestin (norethinedrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

Transdermal (Ortho Evra®)

- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

Contraceptive Ring (Nuva Ring®)

- thin flexible plastic ring; releases etonogestrel 120 μg/d and estradiol 15 μg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

Starting Hormonal Contraceptives

- thorough history and physical exam, including blood pressure and breast exam
- can start at any time during cycle but ideal if within 5 d of LMP
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam not required as STI screening can be done by urine and pap smear screening does not start until >21 yr

Table 8. Combined Estrogen and Progestin Contraceptive Methods

Advantages	Side Effects	Contraindications
Highly effective Reversible Cycle regulation Decreased dysmenorrhea and heavy menstrual bleeding (less anemia) Decreased benign breast disease and ovarian cyst development Decreased risk of ovarian and endometrial cancer Increased cervical mucus which may lower risk of STIs Decreased PMS symptoms Improved acne Osteoporosis protection (possibly)	**Estrogen-related** Nausea Breast changes (tenderness, enlargement) Fluid retention/bloating/edema Weight gain (rare) Migraine, headaches Thromboembolic events Liver adenoma (rare) Breakthrough bleeding (low estradiol levels) **Progestin-related** Amenorrhea/breakthrough bleeding Headaches Breast tenderness Increased appetite Decreased libido Mood changes HTN Acne/oily skin* Hirsutism* * Androgenic side effects may be minimized by prescribing formulations containing desogestrel, norgestimate, drospirenone, or cyproterone acetate	**Absolute** Known/suspected pregnancy Undiagnosed abnormal vaginal bleeding Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis Cerebrovascular or coronary artery disease Estrogen-dependent tumours (breast, uterus) Impaired liver function associated with acute liver disease Congenital hypertriglyceridemia Smoker age >35 yr Migraines with focal neurological symptoms (excluding aura) Uncontrolled HTN **Relative** Migraines (non-focal with aura <1 h) DM complicated by vascular disease SLE Controlled HTN Hyperlipidemia Sickle cell anemia Gallbladder disease **Drug Interactions/Risks** Rifampin, phenobarbital, phenytoin, griseofulvin, primidone, and St. John's wort can decrease efficacy, requiring use of back-up method No evidence of fetal abnormalities if conceived on OCP No evidence that OCP is harmful to nursing infant but may decrease milk production; not recommended until 6 wk postpartum in breastfeeding and non-breastfeeding moms, ideally ≥3 mo postpartum if BF

Table 9. Selected Examples of OCPs

Type	Active Compounds (estriol and progestin derivative)	Advantages	Disadvantages
Alesse®	20 µg ethinyl estradiol and 0.5 mg levonorgestrel	Low dose (20 µg) OCP Less estrogen side effects	Low-dose pills can often result in breakthrough bleeding If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content
Tri-cyclen®	35 µg ethinyl estradiol and 0.180/0.215/0.250 mg norgestimate Triphasic oral contraceptive (graduated levels of progesterone)	Low androgenic activity can help with acne	Triphasic OCPs not ideal for continuous use >3 wk in a row (unlike monophasic formulation)
Yasmin® and Yaz®	Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin) Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-d pill (4 d pill free interval) Drospirenone has antimineralocorticoid activity and antiandrogenic effects	Decreased perception of cyclic weight gain/bloating Fewer PMS symptoms Improved acne	Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency) Check potassium if patient also on ACEI, ARB, K⁺-sparing diuretic, heparin Continue use of spironolactone

Irregular breakthrough bleeding often occurs in the first few months after starting OCP; usually resolves after three cycles

Progestin only contraceptives must be taken at the same time every day

Missed Combined OCPs

Miss 1 pill in <24 h
- Take 1 pill ASAP, and the next pill at the usual time

Miss ≥1 pill in a row in 1st wk
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Use back-up contraception for 7 d; EPC may be necessary

Miss <3 pills in 2nd or 3rd wk of cycle
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- No need for back-up contraception

Miss ≥3 pills during the 2nd or 3rd wk
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Do ot take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- Use back-up contraception for 7 d; EPC may be necessary

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations. *JOGC* 2008;30:1050-1062. http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

PROGESTIN-ONLY METHOD

Table 10. Progestin Only Contraceptive Methods

Indications	Mechanism of Action	Side Effects	Contraindications
Suitable for postpartum women (does not affect breast milk supply) Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease) Women intolerant of estrogenic side effects of combined OCPs	Progestin prevents LH surge Thickening of cervical mucus Decrease tubal motility Endometrial decidualization Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs	Irregular menstrual bleeding Weight gain Headache Breast tenderness Mood changes Functional ovarian cysts Acne/oily skin Hirsutism	**Absolute** None

SELECTED EXAMPLES OF PROGESTIN-ONLY METHODS

Progestin-Only Pill ("minipill")

- Micronor® 0.35 mg norethindrone
- must be taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited only in 60% of women; most have regular cycles (but may cause oligo/amenorrhea)
- highly effective if also post-partum breastfeeding, or if >35 yr
- relies on the progestin effects on the cervical mucous and endometrial lining

Depo-Provera®

- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate ideally within 5 d of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women. Can consider quick start
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- suppresses ovulation very effectively
- side effect: decreased bone density (may be reversible) and weight gain
- disadvantage: restoration of fertility may take up to 9 mo

Missed Progestin-Only Pills >3 h
Use back-up contraceptive method for at least 48 h; continue to take remainder of pills as prescribed

Missed Depo-Provera

- If last injection given 13-14 wk prior: give next injection immediately
- If >14 wk prior, do β-hCG
  - If β-hCG is positive, give EPC and no injection
  - If β-hCG is negative, give next injection right away and:
    - Intercourse occurred in last 5 d: give EPC, use back-up contraception for 7 d ; repeat β-hCG in 3 wk
    - Intercourse occurred >5 d ago but within the last 14 d: use back-up contraception for 7 d; repeat β-hCG in 3 wk
    - Intercourse occurred >14 d ago: use back-up contraception for 7 d
  - No evidence of fetal abnormalities if conceived on DMPA

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations.
JOGC 2008;30:1050-62. http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

Intrauterine Device

Table 11. IUS/IUD Contraceptive Methods

Mechanism of Action	Side Effects	Contraindications
Copper-Containing IUD (Nova-T®): mild foreign body reaction in endometrium; toxic to sperm and alters sperm motility **Progesterone-Releasing IUS (MirenaV, Kyleena®, Jaydess®):** decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation Highly effective (95-99%); failure rate 0-1.2% Contraceptive effects last 5 yr Reversible, private, convenient May be used in women with contraindications to OCPs or wanting long-term contraception	**Both Copper and Progesterone IUD** Breakthrough bleeding Expulsion (5% in the 1st yr, greatest in 1st mo and in nulliparous women) Uterine wall perforation (1/1000) on insertion If pregnancy occurs with an IUD, increased risk of ectopic Increased risk of PID (within first 10 d of insertion only) **Copper IUD:** increased blood loss and duration of menses, dysmenorrhea **Progesterone IUD:** bloating, headache	**Absolute** **Both Copper and Progesterone IUD** Known or suspected pregnancy Undiagnosed genital tract bleeding Acute or chronic PID Lifestyle risk for STIs* **Copper IUD** Known allergy to copper Wilson's disease **Relative** **Both Copper and Progesterone IUD** Valvular heart disease Past history of PID or ectopic pregnancy Presence of prosthesis Abnormalities of uterine cavity, intracavitary fibroids Cervical stenosis Immunosuppressed individuals (e.g. HIV) **Copper IUD** Severe dysmenorrhea or heavy menstrual bleeding

*Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

Continuous or Extended Cycle vs. Cyclic Use of Combined Hormonal Contraceptives for Contraception
Cochrane DB Syst Rev 2014:7
Purpose: Systematic review of RCTs assessing the efficacy and side effects of cyclic administration vs. extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combination oral contraceptives (COC).
Results: The initial review published in 2012 identified 12 RCTs that ultimately showed no difference between groups with regards to efficacy (pregnancy rates), safety, and compliance rates. Continuous or extended CHCs were shown to reduce menstrual symptoms (headaches, tiredness, bloating, and menstrual pain). In addition, 11 of 12 studies reported similar or improved bleeding patterns with continuous or extended cycles.
Conclusions: This recently published updated systematic review identified a further 4 RCTs, however, results did not change.

Committee Opinion No. 602: Depot Medroxyprogresterone Acetate and Bone Effects
Obstet Gynecol 2014(6):1298-402

- The effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive yr.
- BMD loss due to DMPA appears to be substantially or fully reversible.
- Contraceptive implants and intrauterine devices that do not affect BMD should be considered as first-line for adolescents.
- Inform patients about benefits and the potential risks of DMPA, and encourage daily exercise, calcium and vitamin D intake.
- Routine BMD monitoring is not recommended for DMPA users.

Emergency Postcoital Contraception

Table 12. Emergency Contraceptive Methods

Method	Mechanism of Action	Side Effects	Contraindications
HORMONAL			
Yuzpe Method Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/ levonorgestrel 500 µg) Can substitute with any OCP as long as same dose of estrogen used 2% overall risk of pregnancy Efficacy decreased with time (e.g. less effective at 72 h than 24 h)	Unknown; theories include: Suppresses ovulation or causes deficient luteal phase Alters endometrium to prevent implantation Affects sperm/ova transport	Nausea (due to estrogen; treat with Gravol®) Irregular spotting	Pre-existing pregnancy (although not teratogenic) Caution in women with contraindications to OCP (although NO absolute contraindications)
"Plan B" Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse. Can be taken up to 5 d Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if >24 h No estrogen thus very few contraindications/side effects (less nausea) Less effective in overweight individuals (>75 kg less effective, >80 kg not recommended)	Same as above	Same as above	Same as above but no caution in women with contraindications to OCP
Ulipristal 30 mg PO within 5 d	Selective Progesterone Receptor Modulator (SPERM) with primarily antiprogestin activity: may delay ovulation by up to 5 d	Headache, hot flashes, constipation, vertigo, endometrial thickening	Same as above but no caution in women with contraindications to OCP
NON-HORMONAL			
Postcoital IUD (Copper) Insert up to 7 d postcoitus Prevents implantation 1% failure rate Can use for short duration in higher risk individuals Mirena® IUS cannot be used as EPC	See Table 11	See Table 11	See Table 11

Follow-up

- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counselling

Termination of Pregnancy

There is no association between termination of pregnancy and either future breast cancer or future development of psychiatric disease

Indications

- patient desires an end to pregnancy
- may be for medical reasons (mother or fetus unhealthy) or social reasons, including patient request

Legal Issues

- no current law in Canada concerning abortion therefore considered legal at any gestational age
- CPSO: a physician must refer for abortion services regardless of personal beliefs, but not compelled to perform procedure

Rates

- 13.1 abortions/1000 women aged 15-44 in Canada (2017 CIHI data)
- worldwide: 42 million induced abortions per year; half are unsafe (WHO data)
- maternal mortality almost zero where induced abortion is safe and legal; rises to 100 maternal deaths/100,000 live births in sub-Saharan Africa and other countries where abortion is illegal and unsafe
- in Canada, 91% of induced abortions occur <12 wk GA; very rare after 24 wk (usually only for maternal/fetal reasons)

Methods of induced abortion

- medical
  - gold standard up to 9 wk GA: mifepristone and misprostol : 95-98% effective
  - mifepristone blocks the progesterone receptor (progesterone required in early pregnancy)
  - misoprostol induces uterine contractions
  - can also use misoprostol alone or methotrexate and misoprostol (with lower success rates of 90-95%)
  - side effects: bleeding (self-limited) and pain (while tissue passes) are expected side effects

- surgical
  - <14 wk:
    - manual vacuum aspiration – up to about 8-9 wk with hand held aspiration device
    - suction dilatation + aspiration ± curettage – may involve pre-surgical preparation of cervix with laminaria tents and/or misoprostol
  - 14-24 wk: dilatation and evacuation; pre- surgical preparation of cervix required with laminaria tents
  - pain or discomfort during procedure mitigated by use of appropriate analgesia/sedation/anesthesia (including paracervical blocks)
  - rare complications (1-5%): laceration of cervix, infection/endometritis, retained products of conception, ongoing pregnancy
  - very rare complications: (0.1-2%) : hemorrhage, perforation of uterus, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), future preterm birth (controversial and likely only with repeated abortion)
- counselling
  - options counselling always provided; always offer possibility of carrying pregnancy with/without adoption
  - offer future contraception and family planning services
  - ensure follow-up

Pregnancy-Related Complications

First and Second Trimester Bleeding

Approach to the Patient with Bleeding in T1/T2

History
- risk factors for ectopic pregnancy (see *Ectopic Pregnancy*, GY20)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

Physical
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness, cervical motion tenderness)

Investigations
- β-hCG (may be lower than expected for GA in spontaneous abortion, can be used to diagnose viable pregnancy vs. ectopic pregnancy vs. abortion)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Bleeding in Pregnancy Definitions
- First trimester bleeding: vaginal bleeding within the first 12 wk
- Second trimester bleeding: 12-20 wk

Differential Diagnosis
- Physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial β-hCGs
- Abortion (threatened, inevitable, incomplete, complete)
- Abnormal pregnancy (ectopic, molar) (see *Hydatidiform Mole*, GY49)
- Trauma (post-coital or after pelvic exam)
- Genital lesion (e.g. cervical polyp, neoplasms)
- Subchorionic hematoma

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

Spontaneous Abortions

- see *Termination of Pregnancy* for therapeutic abortions, GY18

Table 13. Classification of Spontaneous Abortions

Type	History	Clinical	Management (± Rhogam®)
Threatened	Vaginal bleeding ± cramping	Cervix closed and soft	Watch and wait <5% go on to abort
Inevitable	Increasing bleeding and cramps ± rupture of membranes	Cervix closed until products start to expel, then external os opens	a) Watch and wait b) Mifepristone 200 mg PO followed by Misoprostol 800 µg PV 24 h later c) D&C
Incomplete	Extremely heavy bleeding and cramps ± passage of tissue noticed	Cervix open	a) Watch and wait b) Mifepristone 200 mg PO followed by Misoprostol 800 µg PV 24 h later c) D&C
Complete	Bleeding and complete passage of sac and placenta	Cervix closed, bleeding stopped	No D&C – expectant management
Missed	No bleeding (fetal death in utero)	Cervix closed	a) Watch and wait b) Mifepristone 200 mg PO followed by Misoprostol 800 µg PV 24 h later c) D&C
Recurrent	≥3 consecutive spontaneous abortions		Evaluate mechanical, genetic, environmental, and other risk factors
Septic	Contents of uterus infected – infrequent		IV broad spectrum antibiotics and prompt uterine evacuation

Embryonic demise can be diagnosed by ultrasound based on an intrauterine gestational sac, embryonic crown-rump length ≥7 mm, and no cardiac activity

Ectopic Pregnancy

Definition

- embryo implants outside of the endometrial cavity

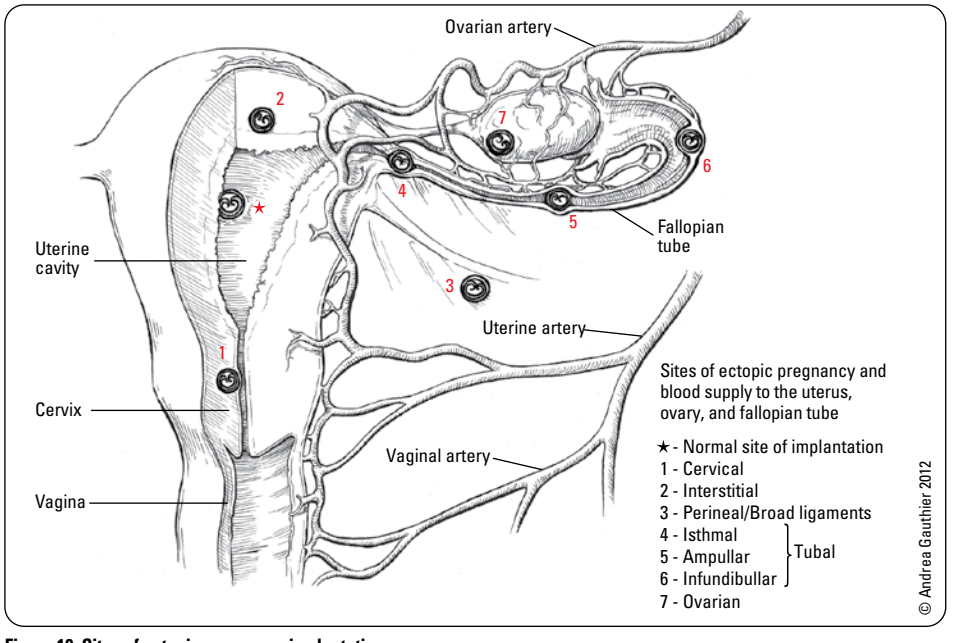


Figure 10. Sites of ectopic pregnancy implantation
ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of maternal death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

Etiology

- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

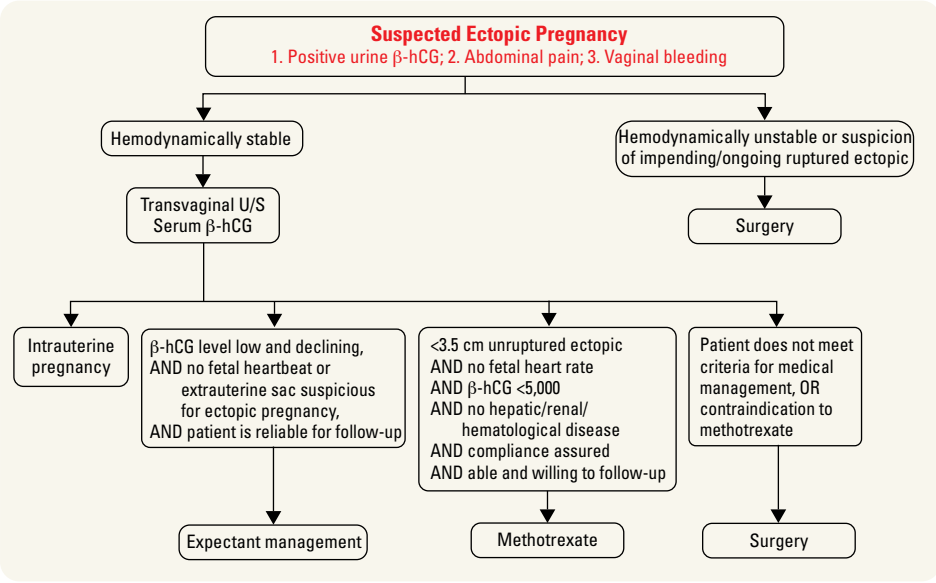


Figure 11. Algorithm for suspected ectopic pregnancy

Risk Factors

- previous ectopic pregnancy
- gynecologic
  - current IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with *C. trachomatis*), salpingitis
  - infertility
- infertility treatment (IVF pregnancies following ovulation induction (7% ectopic rate))
- previous procedures
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

Investigations

- serial β-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
  - rise of <20% of β-hCG (1.6-2.4 d) is 100% predictive of a non-viable pregnancy
  - prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - specific finding on transvaginal U/S is a tubal ring
- suspect ectopic in case of empty uterus by TVUS with β-hCG >2000-3000 mIU/ml
- laparoscopy (sometimes used for definitive diagnosis)

Treatment

- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable, however, patient must be reliable to follow-up with weekly β-hCG
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
  - 15% risk of persistent trophoblast if salpingectomy; must monitor β-hCG titres weekly until they reach non-detectable levels
  - consider Rhogam® if Rh negative
  - patient may require laparotomy if unstable, extensive abdominal surgical history, etc.
- medical = methotrexate
  - use 50 mg/m^2 body surface area; given in a single IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
  - follow β-hCG levels weekly until β-hCG is non-detectable
    - plateaued or rising levels suggest persistent trophoblastic tissue requiring further treatment

Contraindications to Methotrexate Therapy for Ectopic Pregnancy

- Abnormalities in hematologic, hepatic or renal function
- Immunodeficiency
- Active pulmonary disease
- Peptic ulcer disease
- Hypersensitivity to methotrexate
- Heterotopic pregnancy with coexisting viable intrauterine pregnancy
- Breastfeeding
- Unwilling or unable to adhere to methotrexate protocol

DDx of Lower Abdominal Pain

- Urinary tract: UTI, kidney stones
- GI: diverticulitis, appendicitis
- Gyne: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

Any woman presenting with abdominal pain, vaginal bleeding and amenorrhea is an ectopic pregnancy until proven otherwise

More than half of patients with ectopic pregnancy have no risk factors

Presentation of Ectopic Pregnancy Ruptures

- Acute abdomen with increasing pain
- Abdominal distention
- Shock

Management of Abortions

- Always rule out an ectopic
- Always check Rh; if negative, give Rhogam®
- Always ensure patient is hemodynamically stable

  - 82-95% success rate, but up to 25% will require a second dose
    - administer a second dose if β-hCG does not decrease by at least 15% between days 4 and 7
  - tubal patency following methotrexate treatment approaches 80%
- expectant management is an option for patients who are clinically stable, reliable for follow-up, and have β-hCG levels that are low and declining

Prognosis
- 9% of maternal deaths during pregnancy attributed to ectopic pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

Infertility

Epidemiology
- 10-15% of couples, must investigate both members of the couple

Female Factors

Etiology
- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
    - stress, poor nutrition, excessive exercise (even with presence of menstruation), history of eating disorders
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - primary ovarian insufficiency
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure), diabetes
  - congenital (Turner's syndrome, gonadal dysgenesis, or gonadotropin deficiency)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligation/occlusion (e.g. previous ectopic pregnancy)
  - uterine factors (<5%)
    - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure, intrauterine adhesions (e.g. Asherman's syndrome), fibroids/polyps (particularly intrauterine)
    - infection (endometritis, pelvic tuberculosis)
    - endometrial ablation
  - cervical factors (5%)
    - hostile or acidic cervical mucus, anti-sperm antibodies
    - structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

Investigations
- ovulatory
  - day 3: FSH, LH, TSH, prolactin ± DHEA, free testosterone (if hirsute) add estradiol for proper FSH interpretation
  - day 21-23: serum progesterone to confirm ovulation
  - initiate basal body temperature monitoring (biphasic pattern)
  - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
- tubal factors
  - HSG (can be therapeutic – opens fallopian tube)
  - SHG (can be therapeutic; likely less – opens fallopian tube)
  - laparoscopy with dye insufflation (or tubal dye test) rarely done as diagnostic
- peritoneal/uterine factors
  - HSG/SHG, hysteroscopy
- other
  - karyotype

Infertility: inability to conceive or carry to term a pregnancy after one year of regular, unprotected intercourse
Primary infertility: infertility in the context of no prior pregnancies
Secondary infertility: infertility in the context of a prior conception
Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr

When Should Investigations Begin?
- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo
- >40 yr: immediately
- Earlier if
  - History of PID
  - History of infertility in previous relationship
  - Prior pelvic surgery
  - Chemotherapy/radiation in either partner
  - Recurrent pregnancy loss
- Moderate-severe endometriosis

Ethical Considerations in Infertility Treatment
- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
- If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

Treatment
- education: timing intercourse relative to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
- medical
  - ovulation induction
    - clomiphene citrate (Clomid®): estrogen antagonist causing a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; which increases FSH and LH and induces ovulation (better results if anovulatory)
    - followed by β-hCG for stimulation of ovum release
    - Letrozole: aromatase inhibitor. May be associated with a higher rate of live births in patients with PCOS
  - may add:
    - bromocriptine (dopamine agonist) if elevated prolactin
    - dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    - metformin (for PCOS)
    - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
    - anticoagulation and ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
    - thyroid replacement to keep TSH <2.5
- surgical/procedural
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  - sperm washing
  - IVF (fertilization)
  - IFT (intrafallopian transfer)
  - GIFT* (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
  - ZIFT* (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
  - TET* (tubal embryo transfer): transfer after >24 h culture
  - ICSI (intracytoplasmic sperm injection)
  - IVM (in vitro maturation)
  - ± oocyte or sperm donors
  - ± pre-genetic screening for single gene defects in karyotype of zygote

*not performed in Canada

Male Factors

- see Urology, U36

Etiology
- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

Investigations
- semen analysis and culture
- postcoital (Huhner) test: rarely done

Normal Semen Analysis (WHO lower reference limits)
- Must be obtained after 2-7 d of abstinence
  - Volume 1.5 cc
  - Count 15 million/cc
  - Vitality 58% live
  - Motility 32% progressive, 40% total (progressive + non-progressive)
- Morphology 4.0% normal

Polycystic Ovarian Syndrome

- also called chronic ovarian androgenism

Etiology

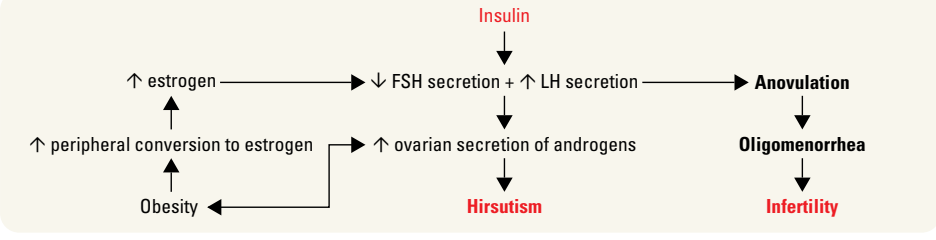


Figure 12. Pathophysiology of polycystic ovarian syndrome

Polycystic Ovarian Syndrome – HAIR-AN
Hirsutism, **H**yper**A**ndrogenism, **I**nfertility, **I**nsulin **R**esistance, **A**canthosis **N**igricans

Diagnosis

- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence - hirsutism or acne
    - biochemical evidence - raised free testosterone
  - polycystic ovaries on U/S (not appropriate in adolescents)

Clinical Features

- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis as adolescence resembles PCOS
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- acanthosis nigricans: browning of skin folds in intertriginous zones (indicative of insulin resistance)
- insulin resistance occurs in both lean and obese patients
- family history of DM

Investigations

- goal: identify hyperandrogenism or chronic anovulation and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T4, androstenedione, SHBG
  - LH:FSH >2:1; LH is chronically high with FSH mid-range or low (low sensitivity and specificity)
  - increased DHEA-S, androstenedione and free testosterone (most sensitive), decreased SHBG
- transvaginal or transabdominal U/S: polycystic-appearing ovaries ("string of pearls" – 12 or more small follicles 2-9 mm, or increased ovarian volume)
- tests for insulin resistance or glucose tolerance
  - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
  - 75 g OGTT yearly (particularly if obese)
- laparoscopy
  - not required for diagnosis
  - most common to see white, smooth, sclerotic ovaries with a thick capsule; multiple follicular cysts in various stages of atresia; and hyperplastic theca and stroma
- rule out other causes of abnormal bleeding

Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - OCP monthly or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if type 2 diabetic or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- infertility
  - medical induction of ovulation: letrozole, clomiphene citrate (no longer available in Canada), human menopausal gonadotropins (HMG [Pergonal®]), LHRH, recombinant FSH, and metformin
    - metformin may be used alone or in conjuction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary
  - bromocriptine (if hyperprolactinemia)
- hirsutism
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-α reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone: androgen receptor inhibitor

PCOS May be Confused with

- Late onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

Clinical Signs of Endocrine Imbalance

- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- DM (10%)

Long-Term Health Consequences

- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Infertility
- Obesity
- Sleep apnea

Insulin-Sensitising Drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for Women with Polycystic Ovary Syndrome, Oligo Amenorrhoea and Subfertility

Cochrane Database Syst Rev 2012; (5):CD003053

Purpose: To evaluate efficacy of insulin-sensitising drugs in improving reproductive outcomes of women with PCOS.

Methods: 42 RCTs (n=3992) were included.

Conclusions: Metformin was associated with improved clinical pregnancy rates whether used alone or in combination with clomiphene. However, this did not translate into live birth rates.

Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies

JOGC 2008;8:671-679

At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multi-factorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.

Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Pruritus

- can be caused by physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features: irritation, pruritus, discharge, vulvar erythema, vaginal bleeding (specifically due to Group A Streptococci and Shigella)
- etiology
  - poor hygiene (proximity of anus to vagina)
  - foreign bodies (most commonly tissue paper)
  - irritation by perfumed soaps, chemicals, and tight clothing
  - localized skin disorders: lichen sclerosis, condyloma acuminata
  - trauma: accidental straddle injury, sexual abuse
  - infectious
    - pinworms
    - Candida (if using diapers or chronic antibiotics)
    - Group A streptococcus, *S. aureus* and *Shigella*
    - discovery of STI should raise suspicion of sexual abuse
  - other
    - polyps, tumour (ovarian malignancy)
    - psychosomatic vaginal complaints (specific to vaginal discharge)
    - endocrine abnormalities (specific to vaginal bleeding)
    - blood dyscrasia (specific to vaginal bleeding)
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
  - pH, wet-mount, and KOH smear in prepubertal adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls

	Pinworms	Lichen Sclerosis	Foreign Body
Diagnosis	Cellophane tape test	Area of white patches and thinning of skin (figure of 8)	
Treatment	Empirical treatment with mebendazole	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

Vulvovaginitis
Vulvar and vaginal inflammation

Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality
- Clinicians who treat adolescents must be aware of federal, state, and provincial laws related to adolescent consent and confidentiality
- Cllinicians must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice

There is no high quality evidence showing a link between vulvovaginal candidiasis and hygienic habits or wearing tight or synthetic clothing

Most common gynecological problem in prepubertal girls is non-specific vulvovaginitis, not yeast

INFECTIOUS VULVOVAGINITIS

Table 15. Infectious Vulvovaginitis

	Candidasis	Bacterial Vaginosis (BV)	Trichomoniasis
Organisms	*Candida albicans* (90%) *Candida glabrata* (<5%) *Candida tropicalis* (<5%)	*Gardnerella vaginalis* *Mycoplasma hominis* Anaerobes: *Prevotella, Mobiluncus, Bacteroides*	*Trichomonas vaginalis* (flagellated protozoan)
Pathophysiology or Transmission	Predisposing factors include: Immunosuppressed host (DM, AIDS, etc.) Recent antibiotic use Increased estrogen levels (e.g. pregnancy, OCP)	Replacement of vaginal *Lactobacillus* with organisms above	Sexual transmission
Discharge	Whitish, "cottage cheese," minimal	Grey, thin, diffuse	Yellow-green, malodourous, diffuse, frothy
Other	20% asymptomatic	50-75% asymptomatic	25% asymptomatic
Signs/Symptoms	Intense pruritus Swollen, inflamed genitals Vulvar burning, dysuria, dyspareunia	Fishy odour, especially after coitus Absence of vulvar/vaginal irritation	Petechiae on vagina and cervix Occasionally irritated, tender vulva Dysuria, frequency
pH	≤4.5	≥4.5	≥4.5
Saline Wetmount	KOH wetmount reveals hyphae and spores	>20% clue cells = squamous epithelial cells dotted with coccobacilli (*Gardnerella*) Paucity of WBC Paucity of *Lactobacilli* Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)	Motile flagellated organisms Many WBC Inflammatory cells (PMNs) Can have positive whiff test
Treatment	Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments Treatment in pregnancy is usually topical Fluconazole 150 mg PO in single dose (can be used in pregnancy)	No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure **Oral** Metronidazole 500 mg PO bid x 7 d **Topical** Metronidazole gel 0.75% x 5 d OD (may be used in pregnancy) Clindamycin 2% 5 g intravaginally at bedtime for 7 d Probiotics (*Lactobacillus* sp.): oral or topical alone or as adjuvant	Treat even if asymptomatic Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative) Symptomatic pregnant women should be treated with 2 g metronidazole once
Other	Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole Routine treatment of partner(s) not recommended (not sexually transmitted)	Associated with recurrent preterm labour, preterm birth, and postpartum endometritis Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action) Routine treatment of partner(s) not recommended (not sexually transmitted)	Warnings accompanying metronidazole use Treat partner(s) (sexually transmitted)

Sexually Transmitted Infections

• see Family Medicine, FM42

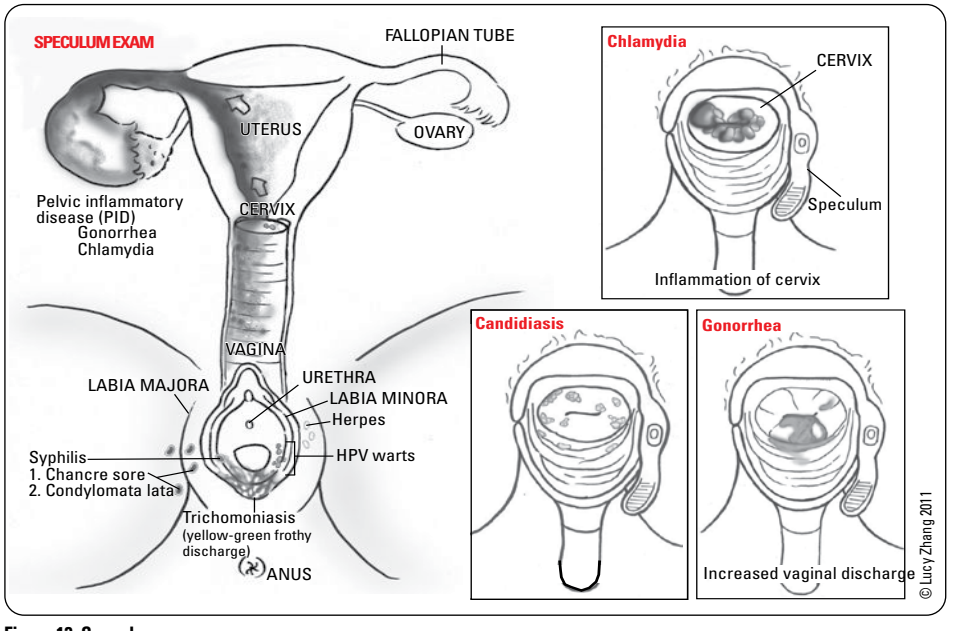


Figure 13. Speculum exam

CDC Notifiable Diseases
- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

Risk Factors for STIs
- History of previous STI
- Contact with infected person
- Sexually active individual <25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Street involvement (homelessness, drug use)

TRICHOMONIASIS
- see *Infectious Vulvovaginitis*

CHLAMYDIA

Etiology
- Chlamydia trachomatis

Epidemiology
- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae*

Clinical Features
- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

Investigations
- cervical culture or nucleic acid amplification test (can present in pharynx, rectum)
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and self vaginal tests now available, which are equally or more effective than cervical culture

STI Testing
- Vaginal swab
  - Tests for bacterial vaginosis, trichomoniasis, candida
- Cervical swab
  - Tests for gonorrhea and chlamydia

Treatment
- doxycycline 100 mg PO bid for 7 d or azithromycin 1 g PO in a single dose. Doxycycline is contra-indictated in the 2nd and 3rd trimesters of pregnancy
- also treat gonorrhea because of high rate of co-infection
- reportable disease, partners should also be referred for treatment
- test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

Screening
- high-risk groups
- during pregnancy
- when initiating OCP if sexually active (independent risk factor)

Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated
Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant

Complications
- PID: low-grade salpingitis and adhesions resulting in tubal obstruction
- infertility
- ectopic pregnancy
- chronic pelvic pain
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
- Neisseria gonorrhoeae
- symptoms and risk factors same as chlamydia

Investigations
- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

Treatment
- single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
  - if pregnant: above regimen or 2 g spectinomycin IM plus azithromycin 1 g PO (avoid quinolones)
  - also treat chlamydia, due to high rate of co-infection
- treat partners
  - reportable disease
  - screening as with chlamydia

HUMAN PAPILLOMAVIRUS

Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification (check pharynx too)
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cytology
- koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- patient administered
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
- provider administered
  - cryotherapy with liquid nitrogen: repeat q1-2wk
  - podophyllin resin in tincture of benzoin: weekly
  - trichloroacetic acid (TCA) (80-90%) or bichloroacetic acid weekly x 4-6 wk; safe in pregnancy
  - surgical removal/laser
  - intralesional interferon

Prevention
- vaccination: Gardasil®9, Gardasil®, Cervarix® (see Table 28, GY45)
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d after contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent, and shorter in duration (usually only HSV-2)

Investigations
- viral culture preferred in patients with ulcer present; however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear) shows multinucleated giant cells, acidophilic intranuclear inclusion bodies
- HSV DNA PCR
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)

Genital Warts During Pregnancy
- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- C-section only if obstructing birth canal or risk of extensive bleeding
- Do not use imiquimod, podophyllin, or podofilox

Human Rights in Health Equity: Cervical Cancer and HPV Vaccines
Am J Law Med 2009;35:365-87
- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries cervical cancer rates have risen or remained unchanged.
- Must recognize that cervical cancer disparities between race groups, urban and rural residence, and high and low socioeconomic status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited health care settings, sexual health stigma, and related [illegible] concerns.

A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women
NEJM 2015;372:711-23
Purpose: To determine the efficacy and immunogenicity of the qHPV (types 6, 11, 16, 18) vs. 9vHPV (five additional types 31, 33, 45, 52, 58) vaccines.
Method: International randomized, double-blinded phase 2B-3 study of 9vHPV vaccine in 14,215 women between ages of 16-26. Participants were randomized to the 9vHPV vaccine group or the qHPV vaccine group and each received a series of three IM injections (day 1, 2, and 6 mo). Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue was obtained and used for HPV DNA testing/Pap smear.
Results: Rate of high-grade cervical, vulvar, or vaginal disease was 14.0 per 1000 person-years in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1000 person-years in the 9vHPV group and 1.6 per 1000 person-years in the qHPV group (95% CI = 80.9-99.8). Antibody responses to HPV-6, 11, 16, and 18 were not significantly different between the two vaccine groups although adverse events related to injection sites were more common in the 9vHPV group.
Conclusions: The 9vHPV vaccine was non-inferior to qHPV vaccine in preventing infection and disease related to HPV-6, 11, 16, and 18 and also covered additional oncogenic types HPV-31, 33, 45, 52, and 58 in a susceptible population.

Treatment
- first episode: acyclovir 200 mg PO five times daily x 7-10 d, or famciclovir 250 mg PO tid x 7-10 d or valacyclovir 1 g PO bid x 7-10 d
- recurrent episode: acyclovir 400 mg PO tid x 5 d, valacylovir 1 g PO OD x 5 d or famciclovir 250 mg PO BID x 5 d
- daily suppressive therapy
  - consider for >6 recurrences per yr or recurrence every 2 mo
  - acyclovir 400 mg PO bid or valacyclovir 500 mg PO OD or valacyclovir 1 g PO OD or famciclovir 250 mg PO bid
- severe disease: IV acyclovir 5-10 mg/kg IV q8h x 2-7 d or until clinical improvement observed followed by oral antiviral therapy to complete 10 d of therapy total
- education regarding transmission: avoid sexual contact from onset of prodrome until lesions have cleared, use barrier contraception

SYPHILIS

Etiology
- Treponema pallidum

Epidemiology of Genital Ulcers

HSV	70-80%
1° Syphilis	5%
Chancroid (*Haemophilus ducreyi*)	<1%

Classifications
- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based, fleshy, grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate, and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

Investigations
- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis): look for spirochetes
- non-treponemal screening tests (VDRL, RPR); non-reactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
- reportable disease, partners should be referred for treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high-risk groups
  - in pregnancy (see Obstetrics, *Infections During Pregnancy*, OB29)

Complications
- if untreated, 1/3 will experience late complications

HIV
- see Infectious Diseases, ID25

Bartholin Gland Abscess

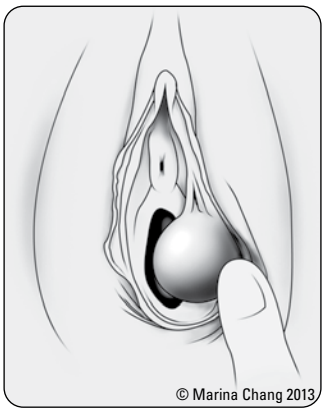


Figure 14. Bartholin gland abscess

Etiology
- often anaerobic and polymicrobial
- *U. urealyticum, N. gonorrhoeae, C. trachomatis, E. coli, P. mirabilis, Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

Clinical Features
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

Treatment
- sitz baths, warm compresses
- antibiotics: cephalexin x 1 wk
- incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk (or as long as stays in situ)
- marsupialization under general anesthetic: more definitive treatment
- rarely treated by removing gland

Pelvic Inflammatory Disease

PID accounts for up to 20% of all gynecological hospital admissions

- up to 20% of all gynecology-related hospital admissions
- inflammation of the upper genital tract (above the cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum ± contiguous structures

Etiology
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
    - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - *E. coli, Staphylococcus, Streptococcus, Enterococcus, Bacteroides, Peptostreptococcus, H. influenzae, G. vaginalis*
    - cause of recurrent PID
    - associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non-acid-fast anaerobe)
    - 1-4% of PID cases associated with IUDs
  - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

Risk Factors
- age <30 yr
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 d after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)

Clinical Feature
- up to 2/3 asymptomatic: many subtle or mild symptoms
- common: fever >38.3°C, lower abdominal pain and tenderness, abnormal discharge (cervical or vaginal)
- uncommon: N/V, dysuria, AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

PID Diagnosis
Must have
- Lower abdominal pain

Plus one of
- Cervical motion tenderness
- Adnexal tenderness

Plus one or more of
- High risk partner
- Temperature >38°C
- Mucopurulent cervical discharge
- Positive culture for *N. gonorrhoeae, C. trachomatis, E. coli,* or other vaginal flora
- Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
- Leukocytosis
- Elevated ESR or CRP (not commonly used)

Investigations
- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoeae, C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

Treatment

- must treat with polymicrobial coverage

Table 16. Inpatient and Outpatient Management Options for Pelvic Inflammatory Disease

	Inpatient	Outpatient
Indications	Moderate to severe illness Atypical infection Adnexal mass, tubo-ovarian mass, or pelvic abscess Unable to tolerate oral antibiotics or failed oral therapy Immunocompromised Pregnant Adolescent (first episode) Surgical emergency cannot be excluded (e.g. ovarian torsion) PID is secondary to instrumentation	Typical findings Mild to moderate illness Oral antibiotics tolerated Compliance ensured Follow-up within 48-72 h (to ensure symptoms not worsening)
Antibiotic Regimen	Cefoxitin 2 g IV q6h + doxycycline 100 mg PO/IV q12h or Clindamycin 900 mg IV q8h + gentamycin 2 mg/kg IV/IM loading dose then gentamycin 1.5 mg/kg q8h maintenance dose Continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d Percutaneous drainage of abscess under U/S guidance When no response to treatment, laparoscopic drainage If failure, treatment is surgical (salpingectomy, TAH/BSO)	1st line: ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14 d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycycline 100 mg PO bid ± metronidazole 500 mg PO bid x 14 d 2nd line: ofloxacin 400 mg PO bid x14 d or levofloxacin 500 mg PO OD x 14 d ± metronidazole 500 mg PO bid x 14 d Consider removing IUD after a minimum of 24 h of treatment Reportable disease Treat partners Consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection

Complications of Untreated PID

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID: 13% infertility
  - 2 episodes of PID: 36% infertility
- bacteremia
- septic arthritis, endocarditis

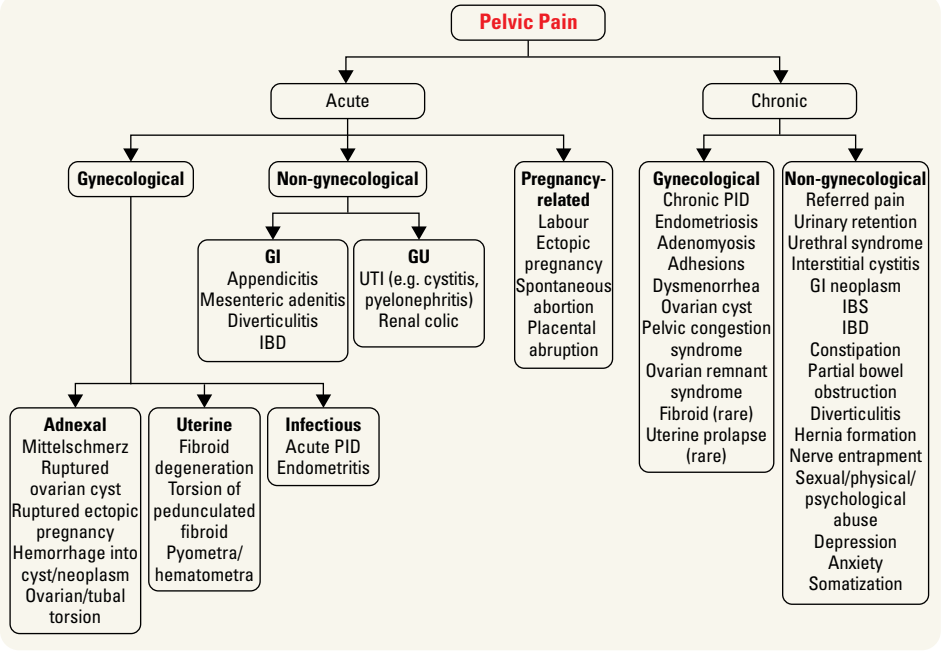


Figure 15. Approach to pelvic pain

Toxic Shock Syndrome

- see Infectious Diseases, ID21

Risk Factors
- tampon use
- diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

Toxic Shock Syndrome
Multiple organ system failure due to *S. aureus* exotoxin (rare condition)

Clinical Feature
- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

Treatment
- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics (e.g. cloxacillin)
- steroid use controversial, but, if started within 72 h, may reduce severity of symptoms and duration of fever

Surgical Infections

Post-Operative Infections in Gynecological Surgery
- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, discharge involving vaginal cuff
  - treat if fever and leukocytosis with broad-spectrum antibiotics (i.e. clindamycin and gentamicin)
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General Surgery, *Post-Operative Fever*, GS7

Sexual Abuse

- see Family Medicine, FM26, Emergency Medicine, ER27

Sexuality and Sexual Dysfunction

SEXUAL RESPONSE
1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

SEXUAL DYSFUNCTION

Etiology
- psychological or emotional: depression, abuse
- hormonal: menopause
- neurologic dysfunction: spinal cord injury
- vascular insufficiency: DM
- drug side effects: β-blockers
- trauma: episiotomy

Classification
- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to

- dyspareunia (3-6%): painful intercourse, superficial or deep
  - vaginismus (15%)
  - vulvodynia
  - vaginal atrophy
  - vulvar vestibulitis: associated with history of frequent yeast infections
  - PID

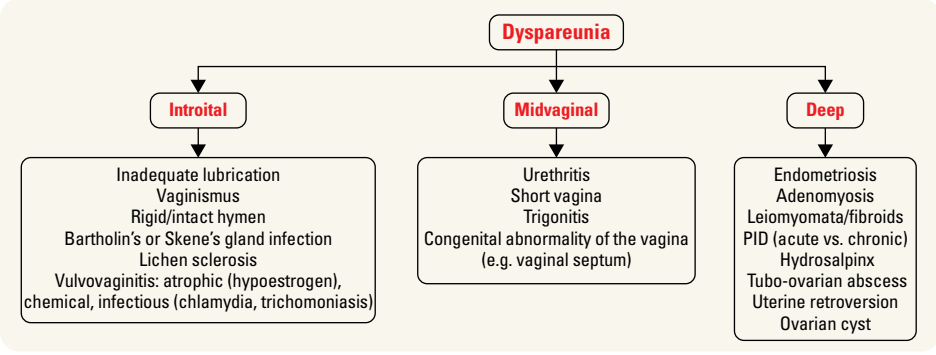


Figure 16. Approach to dyspareunia

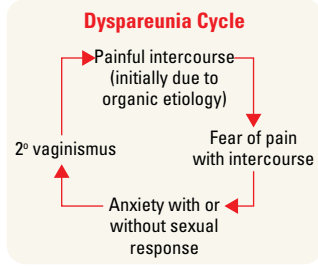


Figure 17. Dyspareunia cycle

Treatment
- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioural techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, dietary changes (increased citrate, decreased oxalate), and vestibulectomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve-blocking therapy (amitriptyline, gabapentin) orally or topically, topical anesthetics, estrogen cream
  - pain clinic
  - removal of environmental factors: bubble baths, soaps, perfumes, sanitary pads with plastic lining

Kegel Exercises
Regular contraction and relaxation to strengthen pelvic floor muscles

Reverse Kegel Exercises
1 s contraction then 5 s of relaxation

Menopause

- see Family Medicine, FM40

Definitions
- lack of menses for 1 yr
- types of menopause
  - physiological; average age 51 yr (follicular atresia)
  - primary ovarian insufficiency; before age 40 (autoimmune disorder, infection, Turner's syndrome)
  - iatrogenic (surgical/radiation/chemotherapy)

Menopause
Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins)

"Being in menopause"
Lack of menses for 1 yr

Perimenopause
Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset

Clinical Features
- associated with estrogen deficiency
  - vasomotor instability (tends to dissipate with time)
    - hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  - urogenital atrophy involving vagina, urethra, bladder
    - dyspareunia, pruritus, vaginal dryness, bleeding, post-coital bleeding, urinary frequency, urgency, incontinence
    - inspection may reveal: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - skeletal
    - osteoporosis, joint and muscle pain, back pain
  - skin and soft tissue
    - decreased breast size, skin thinning/loss of elasticity
  - psychological
    - increased anxiety, depression, irritability, fatigue, decreased libido, memory loss

- 85% of women experience hot flashes
- 20-30% seek medical attention
- 10% are unable to work

Investigations
- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
- FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
- decreased levels of estradiol (later)

Treatment

Table 17. Treatment of Menopause

Goal is for individual symptom management						
Vasomotor Instability	**Vaginal Atrophy**	**Urogenital Health**	**Osteoporosis**	**Decreased Libido**	**CVD***	**Mood And Memory**
HRT (first line) SSRI venlafaxine gabapentin propranaolol clonidine acupuncture	Local estrogen: cream (Premarin®), vaginal suppository (VagiFem®), ring (Estring®), lubricants (Replens®), oral or transdermal hormone replacement therapy, intravaginal laser	Lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery	1000-1500 mg calcium OD, 800-1000 IU vitamin D, weight-bearing exercise, smoking cessation, bisphosphonates (e.g. alendronate), selective estrogen receptor modifiers (SERMs) (e.g.raloxifene [Evista®]), HRT (second-line treatment)	Vaginal lubrications, counselling, androgen-replacement testoterone cream or the oral form (Andriol®)	Manage CVD risk factors	Anti-depressants (first line), HRT (augments effect)

*CVD (cardiovascular disease)

Menopause Pathophysiology

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)
↓
Less estrogen is produced
↓
Decreased negative feedback on hypothalamic-pituitary-adrenal axis
↓
Increased FSH and LH
↓
Stromal cells continue to produce androgens as a result of increased LH stimulation

Figure 18. Menopause pathophysiology

- Osteoporosis is the single most important health hazard associated with menopause
- Cardiovascular disease is the leading cause of death post-menopause

- Increased risk of breast cancer (RR 1.3) is associated with estrogen+progesterone HRT, but not with estrogen-only HRT
- All women taking HRT should have periodic surveillance and counselling regarding its benefits and risks

Hormone Replacement Therapy

- see Family Medicine, FM40
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

HRT Components

- estrogen
- oral or transdermal (e.g. patch, gel)
- transdermal preferred for women overall, especially with hypertriglyceridemia or impaired hepatic function, smokers, and women who suffer from headaches associated with oral HRT
- low-dose (preferred dose: 0.3 mg Premarin®/25 µg Estradot® patch, can increase if necessary)
- progestin
- given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

Table 18. Examples of HRT Regimens

HRT Regimen	Estrogen Dose	Progestin Dose	Notes
Unopposed Estrogen	CEE 0.625 mg PO OD	None	If no intact uterus
Standard-Dose	CEE 0.625 mg PO OD	MPA 2.5 mg PO OD, or micronized progesterone 100 mg PO OD	Withdrawal bleeding may occur in a spotty, unpredictable manner Usually abates after 6-8 mo due to endometrial atrophy Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)
Standard-Dose Cyclic	CEE 0.625 mg PO OD	MPA 5-10 mg PO days 1-14 only, or micronized progesterone 200 mg PO OD days 1-14 only	Bleeding occurs monthly after day 14 of progestin (can continue for years) PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT
Pulsatile	CEE 0.625 mg PO OD	MPA low-dose	3 d on, 3 d off
Transdermal	Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d Estalis®-Estradiol 140 µg/d or 250 µg/d	Estroderm®-MPA 2.5 mg PO OD Estalis®-NEA 50 µg/d	Use patch twice weekly Can use oral progestins (Estroderm®) Combined patches available (Estalis®)
Topical	Estrace® 2-4 g/d x 1-2 wk, 1 g/d maintenance Premarin® 0.5-2 g/d for 21 d then off 7 d for vaginal atrophy, 0.5 g/d for 21 d then off 7 d or twice/wk for dyspareunia Estragyn® 2-4 g/d	Crinone® 4% or 8% (45 or 90 mg applicator)	If simultaneously taking oral estrogen tablet, may need to adjust dosing If intact uterus, also take progesterone

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimens, PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg); Estrace® (topical 17β-estradiol) = 0.1 mg active ingredient/g; Premarin® (topical CEE) = 0.625 mg active ingredient/g; Estragyn® (topical estrone) = 1 mg active ingredient/g

Side Effects of HRT

- abnormal uterine bleeding
- mastodynia: breast tenderness and swelling
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

Contraindications to HRT

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - history of breast cancer
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

Absolute Contraindications to HRT

ABCD
Acute liver disease
Undiagnosed vaginal **B**leeding
Cancer (breast/uterine), **C**ardiovascular disease
DVT (thromboembolic disease)

WOMEN'S HEALTH INITIATIVE (launched in 1991)

- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
  - continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
  - estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE, and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
- the apparent increase in CHD was in disagreement with results of previous observational trial
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
- benefits and risks reported as number of cases per 10,000 women each year

Table 19. HRT Benefits vs. Risks

Benefits	Risks
Vasomotor Symptoms: less frequent and severe with use of either combined or estrogen alone HRT	**Stroke**: 8 additional cases with combined HRT and 12 additional cases for estrogen alone (WHI)
Osteoporosis: 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT; 6 fewer cases of hip fractures with estrogen alone	**DVT/PE**: 18 additional cases with combined HRT and 9 additional cases for estrogen-alone (WHI)
Colon Cancer: 6 fewer cases with combined HRT (WHI); one additional case with estrogen alone	**CHD**: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged >70 yr and for women who start HRT >10 yr post-menopause
	Breast Cancer: 8 additional cases with combined HRT (WHI); risk only increased after >5 yr of combined HRT use; no increased risk for estrogen alone
	Dementia and Mild Cognitive Impairment: 50% greater risk of developing dementia in women taking estrogen alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65

Long-Term Hormone Therapy for Perimenopausal and Postmenopausal Women
Cochrane DB Syst Rev 2012;7:CD004143
Purpose: To determine the effect of long-term HRT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition, and QOL in perimenopausal and postmenopausal women, during HRT use, and after cessation of HRT.
Results: 23 studies with 42,380 women included. 70% of the data from the WHI (1998) and HERS (1998). None of the studies focused on perimenopausal women. Combined continuous HRT: increased risk of coronary event after 1 yr (absolute risk 18/1000, 95% CI 3-7), venous thromboembolism after 1 yr (AR 7/1000, 95% CI 4-11), stroke after 3 yr (AR 18/1000, 95% CI 14-23), breast cancer after 5.6 yr (AR 23/1000, 95% CI 19-29), gallbladder disease after 5.6 yr (AR 27/1000, 95% CI 21-34), and death from lung cancer after 5.6 yr use (AR 9/1000, 95% CI 6-13). Estrogen only HRT: increased risk of venous thromboembolism after 1-2 yr use (AR 5/1000, 95% CI 2-10; after 7 yr AR 21/1000, 95% CI 16-28), stroke after 7 yr (AR 32/1000, 95% CI 25-40), and gallbladder disease after 7 yr use (AR 45/1000, 95% CI 36-57) and did not significantly affect the risk of breast cancer. Women >65 yr of age taking combined HRT had a statistically significant increase in the incidence of dementia after 4 yr use (AR 18/1000, 95% CI 11-30). Women taking HRT had a decreased risk of fractures with combined HRT after 5.6 yr (AR 86/1000, 95% CI 79-84) and 7.1 yr of estrogen only HRT (AR 102/1000, 95% CI 91-112).
Conclusions: HRT is not indicated for primary or secondary prevention of cardiovascular disease or dementia. Although HRT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable.

Urogynecology

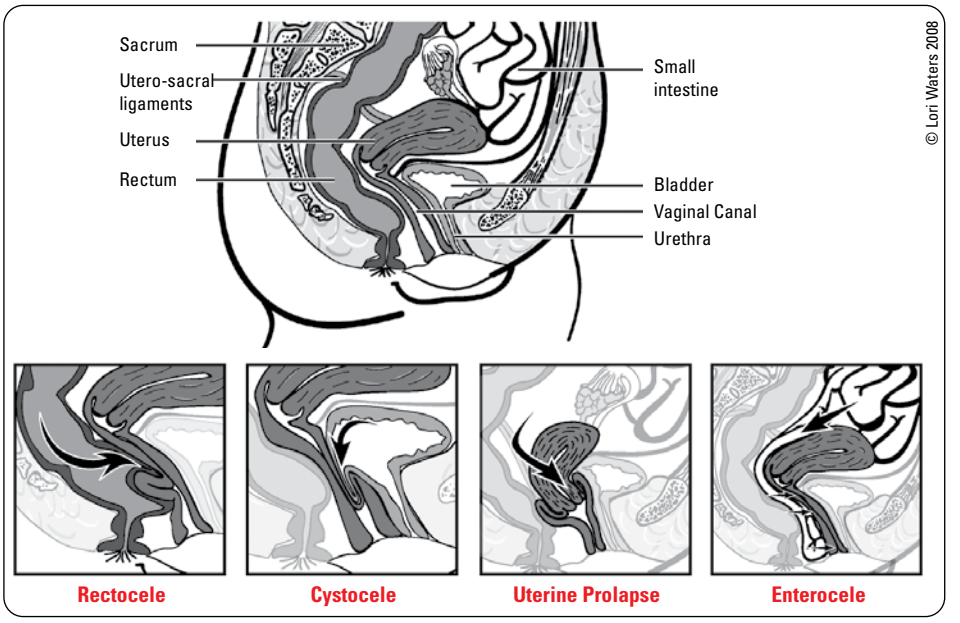


Figure 19. Pelvic anatomy

Prolapse

Etiology

- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
- related to:
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - following pelvic surgery
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - congenital (rarely)
  - ethnicity (Caucasian women > Asian or African women)
  - collagen disorders

GENERAL CONSERVATIVE TREATMENT

(for pelvic relaxation/prolapse and urinary incontinence)

- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary (intravaginal suspension disc)

Grading of Pelvic Organ Prolapse

- 0 = no descent during straining
- 1 = distal portion of prolapse >1 cm above level of hymen
- 2 = distal portion of prolapse ≤1 cm above or below level of hymen
- 3 = distal portion of prolapse >1 cm below level of hymen but without complete vaginal eversion
- 4 = complete eversion of total length of lower genital tract
- Procidentia: failure of genital supports and complete protrusion of uterus through the vagina

Pelvic Relaxation/Prolapse

Protrusion of pelvic organs into or out of the vagina

Table 20. Pelvic Prolapse

Type	Clinical Features	Treatment
Cystocele (protrusion of bladder into the anterior vaginal wall)	Frequency, urgency, nocturia Stress incontinence Incomplete bladder emptying ± associated increased incidence of UTIs (may lead to renal impairment)	See above Anterior colporrhaphy ("anterior repair") Consider additional/alternative surgical procedure if documented urinary stress incontinence
Enterocele (prolapse of small bowel in upper posterior vaginal wall)		Similar to hernia repair Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated
Rectocele (protrusion of rectum into posterior vaginal wall)	Straining/digitation to evacuate stool Constipation	See above Also laxatives and stool softeners Posterior colporrhaphy ("posterior repair"), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)
Uterine Prolapse (protrusion of cervix and uterus into vagina)	Groin/back pain (stretching of uterosacral ligaments) Feeling of heaviness/pressure in the pelvis Worse with standing, lifting Worse at the end of the day Relieved by lying down Ulceration/bleeding (particularly if hypoestrogenic) ± urinary incontinence	See above Vaginal hysterectomy ± surgical prevention of vault prolapse Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present
Vault Prolapse (protrusion of apex of vaginal vault into vagina, post-hysterectomy)		See above Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension

The only **true** hernia of the pelvis is an ENTEROCELE because peritoneum herniates with the small bowel

Urinary Incontinence

• see Urology, U6

STRESS INCONTINENCE

Definition
• involuntary loss of urine with increased intra-abdominal pressure (cough, laugh, sneeze, walk, run)

RISK FACTORS FOR STRESS INCONTINENCE IN WOMEN
• age
• obesity
• parity
• vaginal delivery
• pelvic prolapse
• pelvic surgery
• hypoestrogenic state (post-menopause)
• smoking
• neurological/pulmonary disease

Treatment
• see *Prolapse*, GY36
• surgical
  ▪ tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

URGE INCONTINENCE

Definition
• urine loss associated with an abrupt, sudden urge to void
• "overactive bladder"
• diagnosed based on symptoms

Urge Incontinence
Urine loss associated with an abrupt, sudden urge to void

Etiology
• idiopathic (90%)
• detrusor muscle overactivity ("detrusor instability")

Associated Symptoms
• frequency, urgency, nocturia, leakage

Rule Out Neurological Causes of Urge Incontinence
• MS
• Herniated disc
• DM

Treatment
• behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
• Kegel exercises
• medications
  ▪ anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  ▪ tricyclic antidepressants: imipramine

Gynecological Oncology

Pelvic Mass

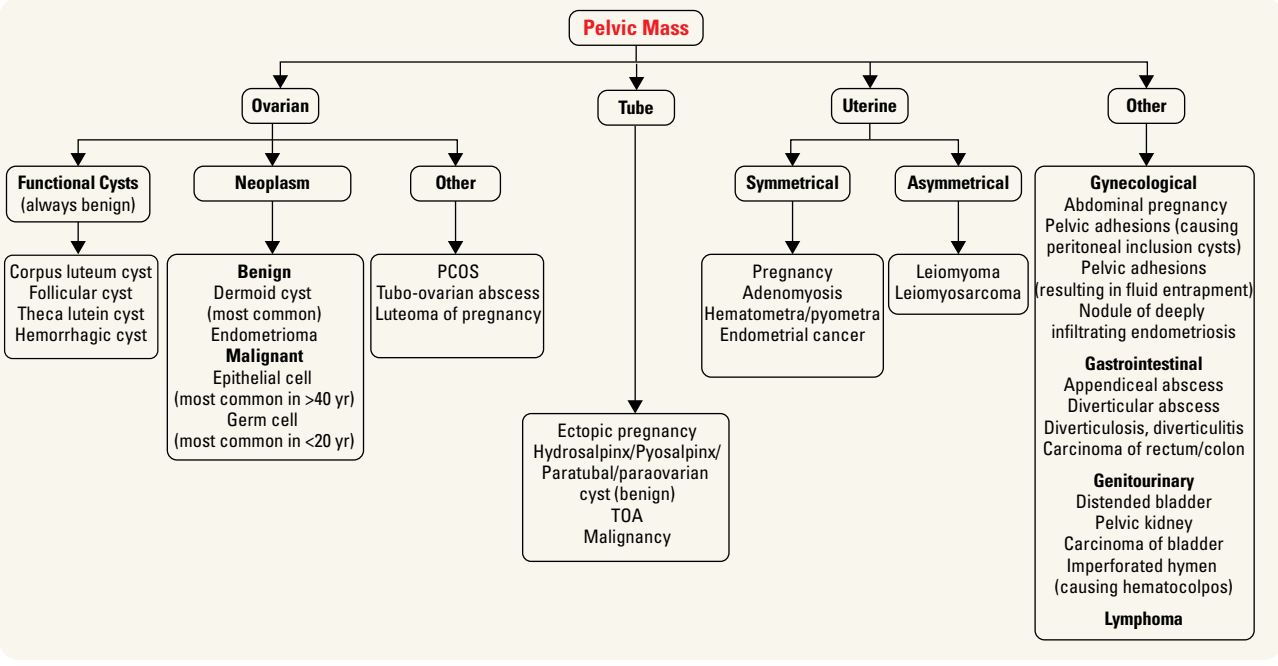


Figure 20. Differential diagnosis of pelvic mass

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology

- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% 5 yr survival for all stages

Table 21. Features of Type I and Type II Endometrial Cancer

	Type I	Type II
Description (Both types related to estrogen, but Type II to a lesser degree)	Characterized as estrogen-related (i.e. excess/unopposed estrogen): Endometrioid Includes well-differentiated endometrioid adenocarcinoma	Characterized as non-estrogen related: Non-endometrioid Includes serous, clear cell, grade 4 endometrioid and undifferentiated carcinomas, as well as carcinosarcoma More aggressive histologic subtypes; prognosis typically worse than type I, with a poorer 5 yr survival
Risk Factors (Increasing age and family history are risk factors for both types)	PCOS Diabetes mellitus Unbalanced HRT (balanced HRT is protective) Nulliparity Late menopause (>55 yr), early menarche Estrogen-producing ovarian tumours (e.g. granulosa cell tumours) HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome Tamoxifen	Parous women Increasing age of menarche and number of children not significantly associated with reduced risk in clear-cell endometrial carcinoma Has been associated with p53 mutations
Clinical Features	~80% of cases Postmenopausal bleeding in majority Abnormal uterine bleeding in majority of affected pre-menopausal women (menorrhagia, intermenstrual bleeding)	~15% of cases Post-menstrual bleeding Abnormal uterine bleeding

Incidence of Malignant Gynecological Lesions in North America
endometrium > ovary > cervix > vulva > vagina > fallopian tube

Risk Factors for Endometrial Cancer

COLD NUT
Cancer (ovarian, breast, colon)
Obesity
Late menopause
Diabetes mellitus
Nulliparity
Unopposed estrogen: PCOS, anovulation, HRT
Tamoxifen: chronic use

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding

Screening
- no known benefit for mass screening
- annual endometrial sampling starting at age 30-35 only for women at high risk (HNPCC [Hereditary Non-Polyposis Colorectal Cancer]/ Lynch II syndrome)
- routine pelvic ultrasound should not be used as screening test (high false positives)

Investigations
- endometrial sampling
  - office endometrial biopsy
  - D&C ± hysteroscopy
- ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  - not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

Table 22. FIGO Staging of Endometrial Cancer (2009)

Stage	Description	Stage	Description
I	Confined to corpus uteri including endocervical glandular involvement	**IIIC**	Metastasis to pelvic ± para-aortic LNs
IA	No or less than half myometrial invasion	**IIIC1**	Positive pelvic LN
IB	Invades through ≥½ of myometrium	**IIIC2**	Positive para-aortic LN ± positive pelvic LNs
II	Tumour invades cervical stroma, but does not extend beyond uterus*	IV	Invasion of bladder ± bowel mucosa ± distant metastases (note: omental disease is stage IV)
III	Tumour involving serosa, adnexa, vagina, or parametrium	**IVA**	Invasion of bladder ± bowel mucosa
IIIA	Invasion of serosa ± adnexae	**IVB**	Distant mets, including intra-abdominal and intraperitoneal mets ± inguinal LNs
IIIB	Vaginal ± parametrial involvement		

FIGO: International Federation of Gynecology and Obstetrics *Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Treatment
- surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
  - goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
  - laparoscopic approach associated with improved quality of life (optimal for most patients)
- adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
- chemotherapy: often used for recurrent disease (if high grade or aggressive histology)
- hormonal therapy: progestins can be used for recurrent disease (especially if low-grade)

Prognostic Factors
Most important is FIGO stage
Other Prognostic Factors:
- Age
- Grade
- Histologic subtype
- Depth of myometrial invasion
- Presence of lymphovascular space involvement (LVSI)

Complications of Therapy

Surgical Complications
- Surgical site infection
- Lymphedema

Radiation Complications
- Radiation fibrosis
- Cystitis
- Proctois

Uterine Sarcoma – Symptoms
BAD-P
Bleeding
Abdominal distention
Foul-smelling vaginal **D**ischarge
Pelvic pressure

A rapidly enlarging uterus, especially in a postmenopausal woman, should prompt consideration of leiomyosarcoma. Nevertheless, all postmenopausal patients with an enlarging uterus should have an endometrial biopsy

UTERINE SARCOMA
- rare; 3-9% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
- behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5 yr survival is 35%
- vaginal bleeding is most common presenting symptom

Table 23. Summary of Uterine Sarcoma Subtypes and Features

Type	Epidemiology	Features	Diagnosis	Treatment
PURE TYPE				
1. Leiomyosarcoma	Most common type of uterine sarcoma Average age of presentation is 55 yr, but may present in pre-menopausal women Often coexists with benign leiomyomata (fibroids)	Histologic distinction from leiomyoma 1. Increased mitotic count (>10 mitoses/10 high-power fields) 2. Tumour necrosis 3. Cellular atypia Rapidly enlarging fibroids in a pre-menopausal woman Enlarging fibroids in a postmenopausal woman	Often post-operatively after uterus removed for presumed fibroids Stage using FIGO 2009 staging for leiomyosarcomas and ECC	Hysterectomy/BSO usually No routine pelvic lymphadenectomy Chemotherapy is used in cases of metastatic disease Radiation therapy does not improve local control or survival Poor outcomes overall, even for early-stage disease
2. Endometrial Stromal Sarcoma (ESS)	Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding	Abnormal uterine bleeding Good prognosis	Diagnosed by histology of endometrial biopsy or D&C Stage using FIGO 2009 staging for leiomyosarcomas and ECC	Hysterectomy & BSO (remove ovaries as ovarian hormones may stimulate growth) No routine pelvic lymphadenectomy Adjuvant therapy based on stage and histologic features (hormones and/or radiation) Hormonal therapy (progestins) may be used for metastatic disease
3. Undifferentiated Sarcoma	Rare; less common than leiomyosarcoma, endometrial stromal sarcoma	Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack smooth muscle or endometrial stromal differentiation Poor prognosis	Often found incidentally post-operatively for abnormal bleeding	Treatment primarily surgical Radiation and/or chemotherapy for advanced diseased or unresectable disease
MIXED TYPE				
4. Adenosarcoma	The rarest of the uterine sarcoma Mixed tumour of low malignancy potential	Present with abnormal vaginal bleeding Polypoid mass in uterine cavity	Mixture of benign epithelium with malignant low-grade sarcoma Often found incidentally at time of hysterectomy for PMB Stage using FIGO 2009 staging for adenosarcoma	Treatment is surgical with hysterectomy and BSO

Table 24. FIGO Staging of Uterine Sarcoma (2009)

Stage	Description	Stage	Description
I	**Tumour limited to uterus**	**III**	
IA	<5 cm	IIIA	Tumour invades abdominal tissues, one site
IB	>5 cm	IIIB	Metastasis to pelvic and/or para-aortic lymph nodes
		IIIC	Tumour invades bladder and/or rectum
II	**Tumour extends beyond uterus**	**IV**	
IIA	To the pelvis, adnexal involvement	IVA	Tumour invades bladder and/or rectum
IIB	To extra-uterine pelvic tissue	IVB	Distant metastasis

Ovary

BENIGN OVARIAN TUMOURS

- see Table 25
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour (rare)

MALIGNANT OVARIAN TUMOURS

- see Table 25

Epidemiology

- lifetime risk 1.4%
- in women >50 yr, more than 50% of ovarian tumours are malignant
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 85% epithelial; 15% non-epithelial
- 10-15% of epithelial ovarian cancers are related to hereditary predisposition

Risk Factors (for epithelial ovarian cancers)

- early menarche and/or late menopause
- personal history of breast, colon, endometrial cancer
- family history of breast, colon, endometrial, ovarian cancer
- Lynch syndrome and BRCA mutations
- use of fertility drugs

Protective Factors (for epithelial ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
- pregnancy/breastfeeding

Prophylactic Measures

- salpingectomy (prophylactic)
- BSO (prophylactic hysterectomy or tubal ligation performed for this reason in high-risk women [i.e. BRCA mutation carriers])

Screening

- no effective method of mass screening
- routine CA-125 level measurements or U/S not recommended
  - high false positive rates
- controversial in high-risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  - familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  - other cancers (e.g. endometrial, breast, colon)
  - BRCA-1 or BRCA-2 mutation: recommendation is prophylactic bilateral oophorectomy after age 35 or when childbearing is completed

Clinical Features

- most women with epithelial ovarian cancer present with advanced stage disease as patients often asymptomatic until disseminated (symptoms with early-stage disease are vague and non-specific)
- when present, symptoms may include:
  - abdominal symptoms (nausea, bloating, pain, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
    - increased abdominal girth (from ascites or tumour itself)
    - urinary urgency and frequency
    - constipation

Ovaries are like GEMS
Germ-cell
Epithelial
Metastatic
Sex cord stromal

Most (70%) epithelial ovarian cancers present at stage III disease

Ovarian Tumour Markers
- Epithelial cell: CA-125
- Stromal
- Granulosa cell: inhibin
- Sertoli-Leydig: androgens
- Germ cell
- Dysgerminoma: LDH
- Yolk sac: AFP
- Choriocarcinoma: β-hCG
- Immature teratoma: none
- Embryonal cell: AFP + β-hCG

Diagnosis of ovarian tumours requires surgical pathology

Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise

Omental Cake: a term for ascites plus a fixed upper abdominal and pelvic mass; almost always signifies ovarian cancer

Malignant Ovarian Tumour Prognosis
5 Year Survival

Stage I	75-95%
Stage II	60-75%
Stage III	23-41%
Stage IV	11%

Screening for Ovarian Cancer Updated Evidence Report and Systematic Review for the US Preventive Services Task Force
JAMA 2018; 319(6):595-606
Objective: To systematically review evidence on benefits and harms of ovarian cancer screening among average-risk, asymptomatic women.
Methods: Systematic review of RCTs of ovarian cancer screening in average-risk women that reported mortality or quality-of-life outcomes. Interventions included transvaginal ultrasound and/or CA-125 testing. Comparators were usual care or no screening.
Results: Four trials (N = 293 587) were included. No trial found a significant difference in ovarian cancer mortality with screening. In 2 trials, screening led to surgery for suspected ovarian cancer in 1% of women without cancer and in 3% for transvaginal ultrasound with or without CA-125 screening, with major complications occurring in 3% to 15% of surgeries. Evidence of psychological harms was found in cases of repeat follow-up scans and tests.
Conclusions: Ovarian cancer mortality did not significantly differ between screened women and those with no screening or in usual care.

Low Malignant Potential (also called "Borderline") Tumours

- a subcategory of epithelial ovarian cancer (~15% of all epithelial ovarian tumours)
- pregnancy, OCP, and breastfeeding are protective factors
- tumour cells with histologically malignant characteristics arise from the ovarian surface, but do not invade ovarian stroma
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  - chemotherapy has limited benefit: can be treated with hormonal manipulation (letrozole)
- generally slow growing, excellent prognosis
  - 5 yr survival >99%
  - recurrences tend to occur late, may be associated with low-grade serous carcinoma

Table 25. Ovarian Tumours

Type	Description	Presentation	Ultrasound/Cytology	Treatment
FUNCTIONAL TUMOURS (all benign)				
Follicular Cyst	Follicle fails to rupture during ovulation	Usually asymptomatic May rupture, bleed, tort, infarct causing pain ± signs of peritoneal irritation	4-8 cm mass, unilocular, lined with granulosa cells	Symptomatic or suspicious masses warrant surgical exploration Otherwise if <6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression): will prevent development of new cysts Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)
Corpus Luteum Cyst	Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic	More likely to cause pain than follicular cyst May delay onset of next period	Larger (10-15 cm) and firmer than follicular cysts	Same as for follicular cysts
Theca-Lutein Cyst	Due to atretic follicles stimulated by abnormal β-hCG levels	Associated with molar pregnancy, ovulation induction with clomiphene		Conservative Cyst will regress as β-hCG levels fall
Endometrioma	See *Endometriosis*, GY11			
Polycystic Ovaries	See *Polycystic Ovarian Syndrome*, GY23			
BENIGN GERM-CELL TUMOURS				
Benign Cystic Teratoma (dermoid)	Single most common ovarian germ cell neoplasm Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)	May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive yr	Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic	Treatment usually laparoscopic cystectomy; may recur
MALIGNANT GERM-CELL TUMOURS				
General Information	Rapidly growing, 2-3% of all ovarian cancers	Usually children and young women (<30 yr)		Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy
Dysgerminoma	Produces LDH	10% bilateral		When diagnosed at stage IA, no adjuvant treatment is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Immature Teratoma	No tumour marker identified	Almost always unilateral		When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated When diagnosed at Grade 2-3, either adjuvant chemotherapy or surgical staging If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Yolk Sac Tumour	Produces AFP	Abdominal pain and pelvic mass		When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
Ovarian Choriocarcinoma	Produces hCG	Precocious puberty and irregular vaginal bleeding		When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure
EPITHELIAL OVARIAN TUMOURS (malignant or borderline)				
General Information	Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (includes malignant)		Varies depending on subtype	**Borderline** Cystectomy vs. unilateral salpingo-oophorectomy **Malignant** 1. Early stage (stage I): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy) 2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatic/paclitaxel vs. intraperitoneal chemotherapy (stage III) neoadjuvant chemotherapy with IV carboplatin/paclitaxel, followed by delayed debulking with further adjuvant IV chemotherapy
Serous	Most common ovarian tumour 50% of all ovarian cancers 75% of epithelial tumours 70% benign	20-30% bilateral	Lining similar to fallopian tube epithelium Often multilocular Histologically contain Psamomma bodies (calcified concentric concretions)	

Table 25. Ovarian Tumours (continued)

Type	Description	Presentation	Ultrasound/Cytology	Treatment
EPITHELIAL OVARIAN TUMOURS (malignant or borderline)				
Mucinous	20% of epithelial tumours	Rarely complicated by Pseudomyxoma peritoneii: implants seed abdominal cavity and produce large quantities of mucin	Resembles endocervical epithelium Often multilocular May reach enormous size	Poor response to chemotherapy If mucinous, remove appendix as well to rule out possible source of primary disease
SEX CORD STROMAL OVARIAN TUMOURS				
General Information				Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
Fibroma/Thecoma (benign)	From mature fibroblasts in ovarian stroma	Non-functioning Occasionally associated with Meig's syndrome (benign ovarian tumour and ascites and pleural effusion)	Firm, smooth rounded tumour with interlacing fibrocytes	
Granulosa-Theca Cell Tumours (benign or malignant)	Can be associated with endometrial cancer Inhibin is tumour marker	Estrogen-producing: feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)	Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies	
Sertoli-Leydig Cell Tumour (benign or malignant)	Can measure elevated androgens as tumour markers	Androgen-producing: virilizing effects (hirsutism, deep voice, recession of front hairline)		
METASTATIC OVARIAN TUMOURS				
From GI Tract, Breast, Endometrium, Lymphoma	4-8% of ovarian malignancies Krukenberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast) with "signet-ring" cells			

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
    - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar)
- physical exam findings largely dependent on stage of disease
- blood work: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
- radiology
  - transvaginal ultrasound best to visualize ovaries
  - CT abdomen and pelvis to look for metastatic disease
  - bone scan or PET scan not indicated
- try to rule out other primary source if suspected, based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms: gastroscopy ± upper GI series
  - abnormal vaginal bleeding: endometrial biopsy to rule out concurrent endometrial cancer; abnormal cervix: need to biopsy cervix (not Pap smear); breast lesion identified or risk factors present: mammogram

A Risk of Malignancy Incorporating CA-125, Ultrasound, and Menopausal Status for the Accurate Pre-Operative Diagnosis of Ovarian Cancer
BJOG 1990;97:922-29
RMI = U x M x CA-125
Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 1 (for U/S scores of 0 or 1)
U = 4 (for U/S scores of 2-5)
Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI>200: gynecologic oncology referral is recommended

Table 26. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2014)

Stage	Description
I	**Growth limited to the ovaries**
IA	1 ovary, no ascites, no tumour on external surface, capsule intact, negative washings
IB	2 ovaries, no ascites, no tumour on external surface, capsule intact
IC	1 or 2 ovaries with any of the following: surgical spill (IC1), capsule ruptured (IC2), tumour on ovarian surface (IC2), or malignant cells in ascites (IC3)
II	**Growth involving one or both ovaries with pelvic extension or primary peritoneal cancer**
IIA	Extension ± implants to uterus/tubes
IIB	Extension to other pelvic structures
III	**Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal nodes**
IIIA	Positive retroperitoneal LNs and/or microscopic metastasis beyond pelvis
IIIA1	Positive retroperitoneal LNs
IIIA2	Microscopic, extrapelvic peritoneal involvement ± positive retroperitoneal LNs
IIIB	Macroscopic peritoneal metastasis beyond pelvis ≤2 cm, ± positive retroperitoneal LNs. Includes extension to capsule of liver/spleen
IIIC	Same as above but peritoneal metastasis >2 cm
IV	**Distant metastasis beyond peritoneal cavity**
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis or metastasis to extra-abdominal organs (inguinal LNs and LNs outside of abdominal cavity included)

FIGO = International Federation of Gynecology and Obstetrics

Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually serous epithelial carcinoma
- new evidence shows that some serous ovarian cancers originate in the fallopian tube
- more common in fifth and sixth decade

Clinical Features
- classic triad present in minority of cases, but very specific
  - watery discharge (most specific): "hydrops tubae profluens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
  - most patients present with a pelvic mass (see *Ovarian Tumours*, GY41 for guidelines regarding diagnosis/investigation)

Treatment
- as for malignant epithelial ovarian tumours

Effectiveness, Safety, and Cost-Effectiveness of Primary Cytoreductive Surgery
Cochrane Database Syst *Rev* 2011;(8):CD007565
Summary: During primary surgery for stage III or IV epithelial ovarian cancer, all attempts should be made to achieve complete cytoreduction. When this is not achievable, optimal (<1cm) residual disease should be the goal.
Methods: Identified 11 retrospective studies consisting of 4735 women using comprehensive search strategy.
Results:
1. When suboptimal (margins >1cm) was compared with optimal (<1cm) cytoreduction, the survival estimates were reduced but remained statistically in favour of the lower volume disease group
2. No significant difference in overall survival between suboptimal and optimal cytoreduction
3. Borderline difference in progression-free survival when residual disease >2 cm and <2 cm were compared (p=0.05)

Cervix

BENIGN CERVICAL LESIONS
- Nabothian cyst/inclusion cyst: no treatment required
- endocervical polyps: treatment is polypectomy (office procedure)

MALIGNANT CERVICAL LESIONS

Epidemiology
- majority are SCC (95%); adenocarcinomas increasing (5%); rare subtypes include small cell, adenosquamous
- 8000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

Etiology
- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from columnar to squamous)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia progresses to carcinoma in situ (CIS), which further progresses to invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors
- HPV infection
  - see *Sexually Transmitted Infections*, GY26
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high-risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high-risk male partner
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
  - immigrant Canadians
  - First Nations Canadians
  - geographically-isolated Canadians
  - sex-trade workers
  - low socioeconomic status Canadians

Cervical Cancer Screening Guidelines (Pap Test)
- see Family Medicine, FM5

Causes of Elevated CA-125
- Age influences reliability of test as a tumour marker
- 50% sensitivity in early-stage ovarian cancer (poor), therefore not good for screening

Malignant
- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

Non-Malignant
- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure

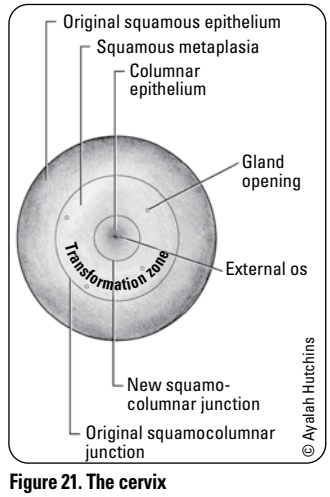


Figure 21. The cervix

Cervical cancer is most prevalent in developing countries and, therefore, is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies, such as CT and MRI

Clinical Features

- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix

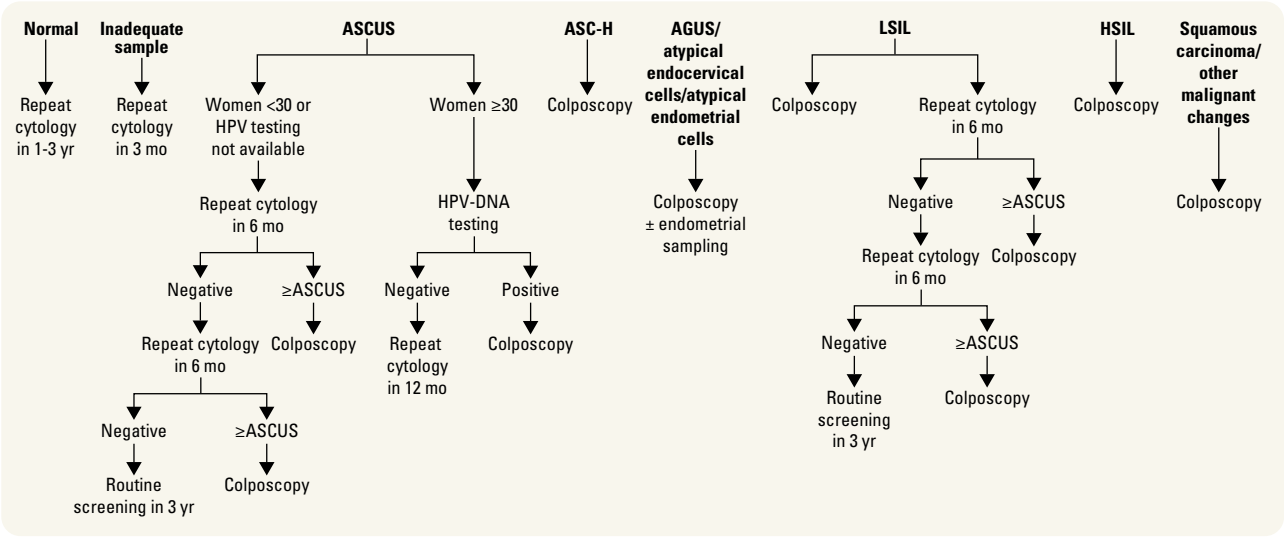


Figure 22. Decision making chart for Pap test (not applicable for adolescents)
Adapted from: Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province

Diagnosis

- colposcopy is a clinical procedure that facilitates identification and biopsy of suspicious cells
- in colposcopy:
  - apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
  - endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
  - diagnostic excision (LEEP) if:
    - unsatisfactory colposcopy (poor visualization/access to transformation zone)
    - discrepancy between cytology, colposcopy, and histological findings
    - positive findings/glandular abnormalities in endocervical curettage
    - suspicious for adenocarcinoma in situ (consider cold-knife conization)
    - recurrence of lesion post-ablation or excision
    - inability to rule out invasive disease, i.e. large lesions (lesions extending into endocervical canal, extending widely on cervix, or onto vaginal epithelium)
- consider cold-knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including examination under anesthesia), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, intravenous pyelogram, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. Cervical intraepithelial neoplasia (CIN) or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

CA-125 is indicated for monitoring response to treatment

Table 27. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2018)

Stage	Description
I	**Confined to cervix**
IA	Microinvasive (diagnosed only by microscopy)
IA1	Stromal invasion not >3 mm deep, not >7 mm wide
IA2	3-5 mm deep; not >7 mm wide
IB	Clinically visible lesion confined to cervix, or microscopic lesion >IA
IB1	Clinically visible lesion ≤4 mm in greatest dimension
IB2	Clinically visible lesion >4 mm in greatest dimension
II	**Beyond uterus but not to the pelvic wall or lower 1/3 of vagina**
IIA	No obvious parametrial involvement
IIA1	Clinically visible lesion ≤4 mm in greatest dimension
IIA2	Clinically visible lesion >4 mm in greatest dimension
IIB	Obvious parametrial involvement
III	**Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney**
IIIA	Involves lower 1/3 vagina but no extension into pelvic side wall
IIIB	Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney
IV	**Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum**
IVA	Spread of the growth to adjacent organs (bladder or rectum)
IVB	Distant metastases

Treatment: Prevention and Management

Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

Table 28. Comparison of Two Vaccines against Human Papillomavirus (HPV)

	Gardasil®*	Cervarix®
Viral Strains Covered	6, 11, 16, 18	16, 18
Route of Administration	IM	IM
Schedule of Dosing	0, 2, 6 mo	0, 1, 6 mo
Side Effects	Local: redness, pain, swelling General: headache, low grade fever, GI upset	Local: redness, pain, swelling General: headache, low grade fever, GI upset
Approved Age	Females age 9-45, males age 9-26	Females age 10-25
Contraindications	Pregnant women and women who are nursing (limited data)	

*Gardasil-9 also covers types 31, 33, 45, 52, and 58; also used to prevent genital wards

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination

Causes of Elevated CA-125

- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) – therefore not good for screening

Malignant

- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

Non-Malignant

- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure

Cervical Cancer Prognosis 5 yr Survival

Stage 0	99%
Stage I	75%
Stage II	55%
Stage III	30%
Stage IV	7%
Overall	50-60%

Efficacy of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine Against Cervical Infection and Precancer Caused by Oncogenic HPV Types (PATRICIA): Final Analysis of a Double-Blind, Randomized Study in Young Women

Lancet 2009;374:301-14

Study: Phase III double-blind, controlled RCT.

Patients: 18,644 women aged 15-25.

Selected Outcomes: Development of HPV-16/18 associated CIN II+ was the primary outcome. Secondary to this were persistence of infections with HPV-16, HPV-18, or other oncogenic HPV types.

Selected Results: Efficacy against development of HPV-16/18 associated CIN II+ was 98.1% ($p<0.0001$). High levels of cross-protection were observed for persistent infection with HPV-31 and HPV-45 and HPV-31 or HPV-45 associated CIN II+.

Conclusions: The HPV-16/18 AS04-adjuvanted vaccine protected against HPV-16/18 associated CIN II+ lesions and lesions associated with HPV-31, HPV-33, and HPV-45.

Table 29. Management of Abnormal Cervical Histology and Cervical Cancer

	Management
CIN I	Preferred option for biopsy-proven CIN I is observation Repeat assessment and cytology in 12 mo Management according to cytology results If after HSIL or AGC: Cytology and histology should be reviewed If discrepancy remains, excisional biopsy may be considered
CIN II and CIN III	Women ≥25 yr CIN II or III should be treated Excisional procedures preferred for CIN III Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage Women <25 yr Same treatment for CN II and CN III: observe with colposcopy at 6-mo intervals for up to 24 mo before treatment considered During pregnancy CIN II or III suspected or diagnosed during pregnancy: repeat colposcopy and treatment delayed until 8-12 wk after delivery
Stage IA1 (no LVSI)	LEEP if future fertility desired (and lesion ≤2 cm) Simple hysterectomy if future fertility is not desired
Stage IA2, IB1	Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study) If high chance of adjuvant radiation then consider primary chemoradiation as more morbidity occurs from double-modality treatment (surgery and radiation) Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy Advantage is that ovaries can be spared if pre-menopausal For fertility preservation (if tumour <2 cm), may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease Chemoradiation therapy if adverse high-risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins or adverse cervical factors (2 or more): deep stromal invasion, size >4 cm, LVSI
Stages IB2 (>4 cm), II, III, IV	Primary chemoradiation therapy CT assess extent of disease: evaluate pelvic and para-aortic nodes For positive nodes on PET: primary chemoradiation with extended field RT Hysterectomy generally not suggested following primary treatment with curative intent

Abnormal Pap Tests in Pregnancy

- incidence: 1/2200
- Pap test at all initial prenatal visits
  - if abnormal Pap or suspicious lesion, refer to colposcopy
  - if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
  - if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
  - if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
    - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
    - recommendations in T2/T3: delay of therapy until viable fetus and C-sectionfor delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium

- biopsy is necessary to make diagnosis and/or rule out malignancy:

1) Hyperplastic dystrophy (squamous cell hyperplasia)
   - surface thickened and hyperkeratotic
   - pruritus most common symptom
   - typically postmenopausal women
   - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
2) Lichen sclerosis
   - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
   - pruritus, dyspareunia, burning
   - 'figure of 8' distribution
   - most common in postmenopausal women but can occur at any age
   - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down, can consider long-term suppression twice a week
3) Mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
   - hyperkeratotic areas with areas of thin, shiny epithelium
   - treatment: fluorinated corticosteroid ointment

Tumours
- papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - more likely in younger women
    - 90% of vulvar intraepithelial neoplasia (VIN) contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - usually postmenopausal women

Risk Factors
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)
- history of cervical cancer
- cigarette smoking
- immunodeficiency

Clinical Features
- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal, then spreading to pelvic nodes)
  - hematogenous

Investigations
- ± vulvar biopsy
- always biopsy any suspicious lesion
  - do not remove entire lesion (allows for site identification through sentinel LN injection if malignant)

Any suspicious lesion of the vulva should be biopsied

Prognosis
- depends on stage: particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

Treatment
- T1 lesions (tumour confined to vulva; no extension to adjacent perineal structures): radical local excision
- T2 lesions (tumour of any size with extension to adjacent perineal structures): modified radical vulvectomy
- T3 lesions (extension to any of: proximal 2/3 of urethra, proximal 2/3 of the vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone): chemoradiation followed by selective resection of residual primary
- node positive disease: adjuvant chemoradiation or radiation therapy

Vagina

BENIGN VAGINAL LESIONS

- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS

Epidemiology

- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr old

Risk Factors

- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations

- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are metastatic from one of these sites)
- staging

Clinical Features

Table 30. Clinical Features of Malignant Vaginal Lesions

Type	Clinical Features
Vaginal Intra-Epithelial Neoplasia (VAIN)	Grades: analogous to cervical dysplasia
Squamous Cell Carcinoma (SCC)	Most common site is upper 1/3 of posterior wall of vagina Asymptomatic Painless discharge and bleeding Vaginal discharge (often foul-smelling) Vaginal bleeding especially during/post-coitus Urinary and/or rectal symptom 2° to compression
Adenocarcinoma	Most are metastatic, usually from cervix, endometrium, ovary, or colon Most primaries are clear-cell adenocarcinomas 2 types: non-DES and DES syndrome

Treatment

- Stage I
  - radiation therapy: for tumours >2 cm diameter or tumour involvement of the mid- to low-grade vagina
  - surgical excision: radical hysterectomy, upper vaginectomy, and bilateral pelvic lymphadenectomy
- Stage II-IV: chemoradiation

Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast

Epidemiology
- 1/1000 pregnancies
- marked geographic variation (as high as 1/125 in Taiwan)
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (Benign GTD)

Complete Mole
- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues or membranes present
- 46XX or 46XY, chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors
  - geographic (South East Asia most common)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency not proven)
- clinical features often present during apparent pregnancy with abnormal symptoms/findings
  - vaginal bleeding (97%)
  - hyperemesis gravidarum (26%)
  - excessive uterine size for LMP (51%)
  - hyperthyroidism (7%)
  - theca-lutein cysts >6 cm (50%)
  - β-hCG >100,000 IU/L
  - preeclampsia (27%)
  - no fetal heartbeat detected

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

Partial (or Incomplete) Mole
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

Investigations
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- U/S findings
  - if complete: no fetus (classic "snow storm" due to swelling of villi)
  - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

Treatment
- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

Follow-up
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN: patient needs chemotherapy

GTN (MALIGNANT GTD)

Invasive Mole or Persistent GTN
- diagnosis made by rising or plateau in β-hCG, development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

Placental-Site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

CLASSIFICATION of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% of patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma, which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
  - highly vascular tumour, which is more likely to bleed and result in anemia
  - all have rising or plateau of β-hCG
  - classification of metastatic GTN
    - divided into good prognosis and bad prognosis
    - features of bad prognosis
      - long duration (>4 mo from antecedent pregnancy)
      - high pre-treatment β-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
      - brain or liver metastases
      - prior chemotherapy
      - metastatic disease following term pregnancy
    - good prognosis characterized by the absence of each of these features

Lungs are the primary site for malignant GTN metastases; when pelvic exam and chest x-ray are negative, metastases are uncommon

Investigations (for Staging)
- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis only
- if CXR shows lung metastasis then CT abdo/pelvis, MRI brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
- ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

Table 31. FIGO Staging and Management of Malignant GTN

Stage	Findings	Management
I	Disease confined to uterine corpus	Single agent chemotherapy for low risk disease (WHO score ≤6) 1st line: pulsed actinomycin D (Act-D) IV q2wk Alternatives: MTX-based regimen 20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single-agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour
II	Metastatic disease to genital structures	As above
III	Metastatic disease to lungs with or without genital tract involvement	As above
IV	Distant metastatic sites including brain, liver, kidney, GI tract	Usually high risk (EMA-CO) with surgical resection of sites of disease Persistence/resistance to chemotherapy Consider radiation for brain mets

Table 32. WHO Prognostic Score for GTD (2011)

	Score			
Prognostic Factor	**0**	**1**	**2**	**4**
Maternal Age	>40	40		
Antecedent Pregnancy	Mole	Abortion	Term	
Interval (End of Antecedent Pregnancy to Chemotherapy in Months)	<4	4-6	7-13	>13
HCG IU/1	<103	103-104	104-105	>105
Number of Metastases	0	1-4	5-8	>8
Site of Metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Largest Tumour Mass		3-5 cm	>5 cm	
Prior Chemotherapy			Single drug	Two drug

Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

GTN Diagnosis

- β-hCG plateau: <10% drop in β-hCG over four values in 3 wk (e.g. days 1, 7, 14, and 21) OR
- β-hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- β-hCG persistently elevated >6 mo OR
- metastases on work-up

Common Medications

Table 33. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
acyclovir (Zovirax®)	Antiviral; inhibits DNA synthesis and viral replication	**First Episode**: 400 mg PO tid x 7-10 d **Recurrence**: 400 mg PO tid x 5 d	Genital herpes	**S/E**: headache, GI upset **D/I**: zidovudine, probenecid
bromocriptine (Parlodel®)	Dopaminomimetic, agonist at D2R and antagonist at D1R; acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin	**Initial**: 1.25-2.5 mg PO qhs with food Then: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response **Usual Range**: 1.5-15 mg OD For IVF: **Initial**: 1.25 mg/d PO between days 4-6 of follicular phase **Then**: 2.5 mg/d until 3 d after onset menstruation	Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF	**S/E**: N/V, headache, postural hypotension, somnolence **C/I**: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding **D/I**: domperidone, macrolides, octreotide
clomiphene citrate (Clomid®)	Increases output of pituitary gonadotropins to induce ovulation	50 mg OD x 5 d Try 100 mg or 160 mg OD If ineffective 3 courses: adequate trial	Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy	**S/E**: Common: hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare: ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects **C/I**: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding
clotrimazole (Canesten®)	Antifungal; disrupt fungal cell membrane	**Tablet**: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose **Cream** (1 or 2%): 1 applicator intravaginally qhs x 3-7 d **Topical**: apply bid x 7 d	Vulvovaginal candidiasis	**S/E**: vulvar/vaginal burning
danazol (Cyclomen® [CAN]) (Danocrine® [US])	Synthetic steroid: inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties	200-800 mg in 2-3 divided doses Use for 3-6 mo Biannual hepatic U/S required if >6 mo use	Endometriosis 1° menorrhagia/DUB	**S/E**: weight gain, acne, mild hirsutism, hepatic dysfunction **C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease **D/I**: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives

Table 33. Common Medications (continued)

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
doxycycline	Tetracycline derivative; inhibit protein synthesis	100 mg PO bid x ≥7 d	Chlamydia, gonococcal infection, syphilis	**S/E**: GI upset, hepatotoxicity **C/I**: pregnancy, severe hepatic dysfunction **D/I**: warfarin, digoxin
fluconazole (Diflucan®)	Antifungal; disrupt fungal cell membrane	150 mg PO x 1 dose	Vulvovaginal candidiasis unresponsive to clotrimazole	**S/E**: headache, rash, N/V, abdominal pain, diarrhea **D/I**: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin
leuprolide (Lupron®)	Synthetic GnRH analog; induces reversible hypoestrogenic state	3.75 mg IM q1mo or 11.25 mg IM q3mo Usually ≤6 mo, check bone density if >6 mo Retreatment with Lupron® alone not recommended because of effects on bone density	Endometriosis Leiomyomata DUB Precocious puberty	**S/E**: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset **C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding
menotropin (Pergonal®)	Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development	75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U HCG 1 d after last dose	Infertility	**S/E**: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding
metronidazole (Flagyl®)	Bactericidal; forms toxic metabolites which damage bacterial DNA	2 g PO x 1 dose or 500 mg PO bid x 7 d	Bacterial vaginosis, trichomonas vaginitis	**S/E**: headache, dizziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V) **C/I**: pregnancy (1st trimester) **D/I**: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine
oxybutinin (Ditropan®)	Anticholinergic; relaxes bladder smooth muscle, inhibits involuntary detrusor contraction	5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d	Overactive bladder (urge incontinence)	**S/E**: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache **C/I**: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function
tolterodine (Detrol®)	Anticholinergic	1-2 mg PO bid	Overactive bladder (urge incontinence)	**S/E**: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain **C/I**: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function
tranexamic acid (Cyklokapron®)	Anti-fibrinolytic; reversibly inhibits plasminogen activation	1-1.5 g tid-qid for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk	Menorrhagia	**S/E**: N/V, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain **C/I**: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yr
ulipristal acetate (Fibristal®)	Selective progesterone receptor modulator (SPRM)	5 mg PO OD for max 3 mo; first tablet taken anytime during first 7 d of menstruation	Leiomyoma (pre-operative)	**S/E**: headache, hot flushes, constipation, vertigo, endometrial thickening **C/I**: pregnancy, undiagnosed vaginal bleeding, any gynecological cancer
urofollitropin (Metrodin®)	FSH	75 U/d SC x 7-12 d	Ovulation induction in PCOS	**S/E**: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding
combined oral contraceptive pill (OCP)	Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration		Contraception Disorders of menstruation	See Table 8-12
intrauterine device (IUD) **copper IUD (Nova-T®)** **progesterone-releasing IUD (Mirena®, Jaydess®)**	**Copper IUD**: mild foreign body reaction in endometrium, which is toxic to sperm and alters sperm motility **Progesterone-releasing IUD**: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last 3 yr (Jaydess®); up to 5 yr (Copper IUD, Mirena®)	Same as above	See Table 8-12

References

Agency for Healthcare Research and Quality, Rockville, MD. Available from: http://www.ahrq.gov/clinic/utersumm.htm.
American College of Obstetricians and Gynecologists. Hormone therapy in primary ovarian insufficiency. Committee Opinion No. 698. Obstet Gynecol 2017;129:e134-41.
American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed). Washington DC: American Psychiatric Association; 2013.
Anderson GL, Limacher M, Assaf AR, et al. (WHI Steering Committee). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy – Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-1712.
ARHP Quick Reference Guide for Clinicians. Managing premenstrual symptoms. June 2008.
Bélisle S, Blake J, Basson R, et al. Canadian consensus conference on menopause, 2006 update. JOGC 2006;28(2 Suppl 1):S1-S94.
Bentley J, Bertrand M, Brydon L, et al. SOGC Joint Clinical Practice Guidelines. Colposcopic management of abnormal cervical cytology and histology, 2012. JOGC 2012;284;1188-1202.
Berek JS, Hacker NF. Gynecologic oncology, 5th ed. Lippincott Williams & Wilkins, 2010.
Brännström M, Johannesson L, et al. Livebirth after uterus transplantation. Lancet 2015;385:607-16.
Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. NEJM 2011;365:2473-2483.
Burnett M, Lemyre M. No. 345-Primary Dysmenorrhea Consensus Guideline. J Obstet Gynecol Canada 2017;39(7):585-595.
Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized control trial. JAMA 2011;305:2295-2303.
Canadian Consensus Conference on Menopause, 2006 Update. JOGC 2006;171.
Centres for Disease Control and Prevention (CDC). Recommendations on the use of quadrivalent human papillomavirus vaccine in males – Advisory Committee on Immunization Practices (ACIP), 2011. MMWR 2011;60:1705-1708.
Cunningham FG, McDonald PC, Gant NF. Williams obstetrics, 14th ed. Appleton and Lange, 1993.
Davey E, Barratt A, Irwig L, et al. Effect of study design and quality of unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. Lancet 2006;367:122-132.
Davis V, Dunn S. Emergency postcoital contraception. SOGC Clinical Practice Guidelines July 2000;82.
Del Priore G, Goff B, Falk S. Endometrial Sampling Procedures. UpToDate. 2019.
Dickey RP. Managing contraceptive pill patients, 9th ed. Fort Collins, CO: EMIS, Inc. Medical Publishers, 1998.
Donnez J, Tomaszewski J, Vasquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. NEJM 2012;366(5):421-432.
Duffy JM, Arambage K, Correa FJ, et al. Laparoscopic surgery for endometriosis. Cochrane DB Syst Rev 2014;4:CD011031.
Elson CJ, Salim R, Potdar N, Chetty M, Ross JA, Kirk EJ on behalf of the Royal College of Obstetricians and Gynaecologists. Diagnosis and management of ectopic pregnancy BJOG 2016;123:e15–e55.
Erdman JN. Human rights in health equity: Cervical cancer and HPV vaccines. Am J Law & Medicine 2009;35:365-387.
Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative memory study. JAMA 2004;291:2959-2968.
Esyma (ulipristal acetate) - MHRA safety alert. RCOG. 2018. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/esmya-ulipristal-acetate---mhra-safety-alert/
Guilbert E, Boroditsky R, Black A, et al. Canadian consensus guideline on continuous and extended hormonal contraception. J Obstet Gyn Canada 2007;29:S1-S32.
Hacker NF, Moore JG. Essentials of obstetrics and gynecology, 2nd ed. WB Saunders, 1992.
Health Canada safety review finds possible link between Fibristal and risk of liver injury. Government of Canada. 2019. Available from: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/68806a-eng.php
Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. Am Fam Physician 2016;94(3):236-240. Available from: https://www.aafp.org/afp/2016/0801/p236.html
Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613.
Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. BJOG 1990;97:922-929.
Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ 2011;342:d2151.
Joura EA, Giuliano AR, Iversen OE et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. NEJM 2015;372:711-723.
Klipping C, Duijkers I, Trummer D, et al. Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. Contraception 2008;78:16-25.
Lidegaard O, Lokkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. NEJM 2012;366:2257-2266.
Lipscomb GH, McCord ML, Stovall TG, et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. NEJM 2001;341:1974-1978.
Lopez LM, Chen M, Mullins S, et al. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane DB Syst Rev 2012;8:CD009849.
Luciano AA, Solima RG. Ectopic pregnancy: from surgical emergency to medical management. Ann NY Acad Sci 2001;943:235-254.
Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. JOGC 2008;30:671-9.
Maclennan AH, Broadbent JL, Lester S, et al. Oral oestrogen and combined oestrogen/progetogen therapy versus placebo for hot flushes. Cochrane DB Syst Rev 2004;18.
Management of uterine fibroids. Summary, Evidence Report/Technology Assessment: Number 34. AHRQ Publication No. 01-E051, January 2001.
Manson JE, Martin KA. Postmenopausal hormone replacement therapy. NEJM 2001;345:34-40.
Mantha S, Karp R, Raghavan V, et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ 2012; 345:e4944.
Marchbanks PA, Aneger JF, Coulman CB, et al. Risk factors for ectopic pregnancy: a population based study. JAMA 1998;259:1823-1827.
Martin JL, Williams KS, Abrams KR, et al. Systematic review and evaluation of methods of assessing urinary incontinence. Health Technol Assess 2006;10:1-132,iii-iv.
Marjoribanks J, Farquhar C, Roberts H et al. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2017; 1:CD004143.
National guideline for the treatment of bacterial vaginosis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). Sex Transm Infect 1999;75:S1 6-8.
Ontario Cervical Screening Practice Guidelines. June 2005. Available from: http://www.cancercare.on.ca/index – cervical screening.htm.
Ouellet-Hellstram R, Graham DJ, Staffa JA, et al. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. CHC-CVD final report 111022v2.
Paley PJ. Screening for the major malignancies affecting women: current guidelines. Am J Obstet Gynecol 2001;184:1021-1030.
Public Health Agency of Canada, 2010. Canadian guidelines on sexually transmitted infections. (Updated January 2010). Available from: http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php.
Public Health Agency of Canada, 2011. Public health information update on the treatment of gonococcal infection. Available from: http://www.phac-aspc.gc.ca/std-mts/sti-its/alert/2011/alert-gono-eng.php.
PHAC National Advisory Committee on Immunization (NACI). Update on human papillomavirus (HPV) vaccines. Canada Communicable Disease Report 2012;38:ACS-1.
Rambout L, Hopkins L, Hutton B, et al. Prophylactic vaccination against human papillomavirus infection in women: a systematic review of randomized controlled trials. CMAJ 2007;177(5):469-479.
Ratner S, Ofri D. Menopause and hormone replacement therapy. West J Med 2001;175:32-34.
Reade CJ, McVey RM, Tone AA et al. The fallopian tube as the origin of high grade serous ovarian cancer: review of a paradigm shift. J Obstet Gynaceol Can 2014;36:133-140.
Reid R. Oral contraceptives and the risk of venous thromboembolism: an update. SOGC Clinical Practice Guideline. JOGC 2010;32:1192-1197.
Rimsza ME. Counselling the adolescent about contraception. Pediatr Rev 2003;24:162-170.
Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risks of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-1477.
Seeger JD, Loughlin J, Eng PM, et al. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol 2007;110:587-593.
Setiawan VW, Yang HP, Pike MC, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol 2013;31(20):2607-2618. doi:10.1200/JCO.2012.48.2596.
Sexuality and U. Society of Obstetricians and Gynaecologists of Canada. Available from: http://www.sexualityandu.ca.
Shapter AP. Gestational trophoblastic disease. Obs Gynecol Clin North Am 2001;28:805-817.
Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative memory study. JAMA 2004; 291:2947-2958.
Singh S, Best C, Dunn S, Leyland N, Wolfman W. No. 292-Abnormal uterine bleeding in pre-menopausal women. J Obstet Gyn Canada 2018;40(5):e391-e415.
SOGC Clinical Practice Guidelines: Abnormal Uterine Bleeding in Pre-Menopausal Women. JOGC May 2013;35(5 eSupple):S1-S28.
SOGC Clinical Practice Guidelines: Emergency Contraception. JOGC Sep 2012;34(9):870-878. Available from: http://www.sogc.org/guidelines/documents/gui280CPG1209E_000.pdf
SOGC Committee Opinion on Missed Hormonal Contraceptives: New recommendations. JOGC 2008;30:1050-1062. Available from: http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf.
SOGC News Release. New recommendations from national ob/gyn society address Depo-Provera, bone loss. May 2006. Available from: http://www.sogc.org/media/pdf/advisories/dmpa-may2006_e.pdf.
Tang T, Lord JM, Norman RJ et al. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev 2012; (5):CD003053.
Tingulstad S, Hagen B, Skjeldestad FE, et al. The risk of malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol 1999;93:448-452.
Wooltorton E. The Evra (ethanyl estradiol/norelgestromin) contraceptive patch: estrogen exposure concerns. CMAJ 2006;174:164-165.
Wooltorton E. Medroxyprogesterone acetate (Depo-Provera) and bone mineral density loss. JAMA 2005;172:746.
Yudin M, Money H, Deborah M, et al. Screening and management of bacterial vaginosis in pregnancy. Obstet Gynecol Can 2017;39;184-191.