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Ovarian Cysts

Ovarian cysts in neonates

- Ovarian cysts are the most common cause of abdominal cysts in female fetuses and neonates, usually presenting in the third trimester.
- Most are unilateral and simple in nature
- The cause is usually fetal gonadotrophins, maternal oestrogen or placental human chorionic gonadotrophin (hCG).
- Management is often conservative and may involve serial scans, but if the cyst is very large or if torsion is suspected, then surgical management is considered

Ovarian cysts in children and adolescents

Types

Benign (majority)	Malignant (4–16%)
• Simple cyst (60%, risk of malignancy is < 1%) • Complex cyst (mature cystic teratoma, endometrioma, gonadoblastoma, serous cytadneoma, mucinous cystadenoma, cystadenofibroma) • Ovarian torsion • Tubo-ovarian abscess • Paratubal and paraovarian cysts	• Sex cord-stromal tumours: Juvenile granulosa cell tumour (most common), Sertoli–Leydig cell tumour • Germ cell tumours: Dysgerminoma, yolk sac tumour, embryonal carcinoma, polyembryoma, immature teratoma • Epithelial tumours: Serous adenocarcinoma, mucinous adenocarcinoma

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Benign ovarian tumours:

- **Functional cysts:**
  - Most functional cysts resolve spontaneously.
  - Functional haemorrhagic cysts may result in midcycle pain in postmenarchal girls and there may be some free fluid or haemoperitoneum. Most cases resolve spontaneously

- **Paratubal cysts:**

  They can grow and do not tend to resolve. If the cyst is large or causing pain, It should be managed laparoscopically.

- **Mature cystic teratomas (dermoid cysts):**
  - Germ cell tumours are the most common in children and adolescents (55–70% are dermoid cysts)
  - 10% may be bilateral.
  - Usually asymptomatic and discovered incidentally. 15% of dermoid cysts can present with abdominal pain and torsion.
  - Spontaneous rupture occurs in less than 1%
  - Malignant transformation occurs in 1.7%.
  - Rare complications include carcinoid tumours, struma ovarii, haemolytic anaemia and anti-NMDA receptor encephalitis.

- **Gonadoblastoma:**
  - It is a mixed germ cell tumour that develops in girls with gonadal dysgenesis, when there is a Y chromosome
  - It is benign. However, it can evolve into a dysgerminoma with malignant features.

Malignant ovarian tumours

- **Juvenile granulosa cell tumours (JGCTs):**
  - It accounts for almost 50% malignant ovarian tumours in children and adolescents
  - They are the most common sex cord-stromal tumours
  - Usually, solid tumours
  - 50% are diagnosed between the ages of 6 and 13 years, and one-third are diagnosed between the ages of 14 and 19 years.
  - 2–5% of tumours are bilateral

- The most common presenting feature of is pseudoprecocious puberty (breast enlargement, vaginal discharge and pubic hair growth)
- Although JGCTs are mainly oestrogen-secreting tumours, they may present with excessive androgenism (clitoral enlargement, hirsutism, deep voice, irregular periods or amenorrhoea)
- Prognosis is good. Over 95% of tumours are limited to the ovary at diagnosis. Survival rate is greater than 90% with surgical resection alone

- **Malignant ovarian germ cell tumours (MOGCTs):**
  - They account for 1.5% of ovarian cancers
  - Most occur in the first two decades of life
  - One-third of cases are dysgerminomas and one-third are immature teratomas
  - Early diagnosis and multi-agent chemotherapy are associated with high cure rate. Risk of premature ovarian insufficiency is low (3%)

- **Immature teratomas:**
  - Most are unilateral. Mature teratomas may present in the contralateral ovary
  - They may be isolated or within a mixed germ cell tumour

Clinical presentation

- Asymptomatic or incidental
- Pain (30%)
- Abdominal distension or effects of abdominal mass
- Weight loss
- Polymenorrhoea and menorrhagia
- Precocious puberty, hyperandrogenism
- Dysuria, constipation
- Leg pain
- Acute tubo-ovarian torsion (acute unilateral constant or intermittent non-migrating pain associated with vomiting and tachycardia). Pain here has longer duration compared to appendicitis (> 48 hours)
- Non-malignant ascites (Meigs' syndrome) is a rare complication of fibromas, thecomas and granulosa cell tumours

Investigations

- **Ultrasound:**
  - Transabdominal pelvic ultrasound is easy, cost effective and requires full bladder
  - If an adolescent has been sexually active, then she could have a transvaginal ultrasound scan

Sonographic findings of torsion

- Unilateral ovarian enlargement and oedema are the most consistent sonographic findings in ovarian torsion.
- Abnormal Doppler signals in the ovarian vessels are seen in almost all cases, with either absent peripheral blood flow or coiling of ovarian vessels in subacute ovarian torsion.

- **Pelvic MRI:**

  If a complex ovarian cyst is diagnosed on an ultrasound, Pelvic MRI should be requested.

- **CT scan with contrast:**

  If there are any complex features with suspicion of malignancy, CT with contrast is indicated to identify the bowel, and identify metastasis in the chest, abdomen, and pelvis.

- **Tumour markers:**

  Tumour markers are indicated in the presence of complex cysts or large persistent simple cysts

Tumour marker	Ovarian neoplasm
AFP	Immature teratoma, Sertoli–Leydig cell tumour, Yolk sac tumour, Embryonal carcinoma
HCG	Dysgerminoma, Embryonal carcinoma
LDH	Dysgerminoma, Immature teratoma
CA-125	Epithelial tumours
CEA	Epithelial tumours
Oestradiol	Juvenile granulosa cell tumour
Testosterone	Sertoli–Leydig cell tumours

- **Hormonal profile:**
  - It is indicated if there are any signs of precocious puberty
  - A hormone profile (including follicle-stimulating hormone, luteinizing hormone, oestradiol and thyroid function) should also be performed

Sterile pyuria has been observed in the presence of ovarian torsion and often mimics a urinary tract infection

Management

- Multidisciplinary approach is recommended and priority to minimally invasive ovarian preserving surgery whenever possible
- With laparoscopic ovarian cystectomy, the main risk is intraoperative cyst rupture which includes:
  - Risk of dissemination of potential malignancy: to avoid any spill in a potentially malignant tumour, a tissue bag can be used to collect cyst contents, or laparotomy can be considered
  - Chemical peritonitis with dermoid cysts (< 0.2%): pelvic lavage with warm saline is indicated in any intraperitoneal rupture

Laparoscopic surgery in adolescents

- Catheterisation can cause urethral trauma in children < 10 years
- Caution with umbilical incision since the aorta is just beneath the skin
- Smaller scopes (2–5 mm) and smaller trocars should be used
- Pneumoperitoneum should be adjusted to 12–15 mmHg for thin adolescents and 8-10 mmHg for younger children
- Keep the camera in the port when umbilical port is removed
- Keep the port open while removing it

- If adnexal torsion is suspected, immediate intervention is indicated. Detorsion with or without cystectomy should be performed even if the ovary looks necrotic
- Gonadopexy (oophoropexy) after detorsion can be considered, especially with previous oophorectomy and the presence of unilateral torted ovary
- There is no risk of thromboembolism following untwisting of the ovarian pedicle in detorsion

- Recurrence risk must be considered with laparoscopic surgery for mature cystic teratoma (10%). Young age, large cyst size and bilaterality are predictive factors for recurrence

Simple cyst 3-5 cm	Rescan in 3 months for reassurance
Simple cyst 5-7 cm	• If asymptomatic, rescan in 3months. If persistent, tumour markers and MRI should be considered • If symptomatic, consider tumour markers and MRI
Simple cyst > 7 cm	• Laparoscopic ovarian cystectomy OR • Rescan in 3months if asymptomatic
Complex cysts	• If there is no suspicion of cancer, size is > 5cm, symptomatic: perform laparoscopic ovarian cystectomy • If cancer is suspected, a multidisciplinary team should discuss management plan

Ovarian cysts in adult premenopausal women

Epidemiology

- Lifetime incidence of surgery for ovarian mass is 10%
- 10% of suspected ovarian masses are found to be non-ovarian
- Risk of malignancy in the presence of symptomatic premenopausal ovarian cyst is 1:1000. The risk increase to 3:1000 by the age of 50

Diagnosis

- **History:**
  - History of risk factors and protective factors
  - Family history of breast or ovarian cancer
  - Symptoms of endometriosis
  - Symptoms suggestive of malignancy i.e. persistent abdominal distension, change in appetite, abdominal and pelvic pain, urgency, and frequency

- **Physical examination:**

  Physical examination yields poor sensitivity in differentiating benign from malignant ovarian masses (15-51%)

- **Ultrasound:**
  - Pelvic ultrasound is the most effective diagnostic tool
  - Doppler assessment does not increase diagnostic accuracy. However, transvaginal ultrasound in combination with colour flow mapping and 3D imaging may improve sensitivity
  - Assessment of the endometrium is indicated in women with oestrogen secreting tumours
  - Up to 20% of borderline ovarian tumours may appear as simple cysts in ultrasound. However, the majority have suspicious findings

- **Tumour markers:**
  - **Indications:**
    - CA 125 is tested in women with suspected ovarian cysts e.g. complex ovarian cysts
    - Premenopausal women younger than 40 with complex ovarian cyst should be tested for LDH, APF, and hCG
    - Premenstrual women with simple ovarian cyst do not have to be tested for CA 125

  - **Value and interpretation:**
    - Preoperative differentiation between benign and malignant tumours in premenopausal women is challenging with tumour markers. An exception is germ cell tumours which can be suspected by hCG and AFP
    - CA 125 is not reliable particularly in this age group because:
      - It is associated with high false positive results e.g. pelvic inflammatory disease, endometriosis
      - It is confined to epithelial tumours
      - It is only raised in 50% of early cases

    If CA125 is < 200, it may be reasonable to rule out cancer and anticipate other causes However, if CA 125 is high, follow-up may verify diagnosis since rapid rise in CA 125 is suggestive of malignancy compared to a high plateaued level. A level above 200 should be discussed with an oncologist

- HE4 is a new tumour marker that does not increase in endometriosis and is associated with lower false positive results with benign conditions

Risk assessment

- Risk of malignancy index (RMI) I is the most effective tool to identify suspected ovarian cancer
- In addition, since CA 125 has a poor specificity in this age group. An alternative to CA 125 is IOTA group ultrasound rules: B-rules and M-rules (sensitivity 95%, specificity 91%)

B-rules	M-rules
▪ Unilocular cysts ▪ Presence of acoustic shadowing ▪ Solid components with the largest component < 7 mm ▪ No blood flow ▪ Smooth multilocular tumour ▪ Largest diameter < 10 cm	▪ Irregular solid tumour ▪ Ascites ▪ At least 4 papillary structures ▪ Irregular multilocular solid tumour ▪ The largest diameter > 10 cm ▪ Very strong blood flow

If any of M-rule features are present, women should be referred to gynaecologic oncology service

Management

- **Management decision:**

Management of asymptomatic simple ovarian cysts depends on cyst size:

Simple ovarian cyst < 5 cm	There is no need for follow-up (likely physiologic)
Cyst size between 5-7 cm	yearly follow-up is recommended If the cyst persists or increases in size, it is unlikely functional and surgical intervention is recommended. In this case, RMI I or US rules should be considered
Cyst size > 7 cm	MRI or surgical intervention should be considered

Combined oral contraceptives (COCs) do not promote resolution of functional cysts

- **Surgical intervention:**
  - **Approach:**
    - Laparoscopy is the standard approach (cost effective)
    - Laparotomy may be considered for large ovarian masses with solid components. Risk of cyst rupture with laparoscopy is high with cysts larger than 7 cm
  - **Procedure:**
    - Ovarian cystectomy is the standard procedure if possible
    - Laparoscopic or vaginal aspiration of cyst is less effective and is associated with high rate of recurrence (50-85%)
    - Removal of benign cysts should be done through the umbilical port (less pain, quicker retrieval time)
  - **Precautions:**
    - Spillage of cyst contents should be avoided as much as possible specially if preoperative diagnosis is suspicious. However, preoperative and intraoperative assessment cannot preclude malignancy. Tissue retrieval bag is recommended
    - Risk of chemical peritonitis after spillage of dermoid contents is < 0.2%
      In these cases, irrigation with large amount of warm fluid is recommended. Avoid cold irrigation, which may cause hypothermia and solidification of fat-rich contents
    - In the presence of endometriomas larger than 3 cm, histology should be obtained to rule out malignancy
    - Possibility of oophorectomy should be discussed with women prior to surgery

Ovarian cysts in postmenopausal women

Epidemiology

- Incidence of ovarian cysts in postmenopausal women is 5-17%
- Any ovarian cyst that is 1 cm or larger in diameter is considered significant in this age group

Diagnosis

- **History:**
  - **Risk factors of ovarian cancer:**
    Women are at high risk of ovarian cancer there is known history of BRCA 1, BRCA 2 or mismatch repair mutations OR if they are not tested but they are first or second degree relative to individuals with known mutation
  - **Symptoms suggestive of malignancy:**
    Postmenopausal women with symptoms suggestive of irritable bowel syndrome in the last 12 months (especially if older than 50 or in the presence of significant family history of cancer) should be investigated
  - **Family history of ovarian, breast or bowel cancer:**
    Women with significant family history should be referred to a regional cancer genetics service

Acute abdominal pain in postmenopausal women may be caused by ovarian cyst accident (haemorrhage, torsion, rupture)

Significant family history

- 2 or more first degree relatives of each other with ovarian cancer
- 1 member with ovarian cancer (any age) + 1 member with breast cancer < 50 years who are first degree relatives
- 1 member with ovarian cancer (any age) + 2 member with breast cancers < 60 years who are first degree relatives
- 3 members with colon cancer OR 2 with colon cancer + 1 member with ovarian/endometrial/urinary tract/small bowel cancer in 2 generations who are first degree relatives of each other
- 1 member with ovarian and breast cancer

- **Physical examination:**
  - Physical examination includes assessment of body mass index, abdominal examination for ascites, and vaginal/abdominal for palpable pelvic masses
  - Physical examination yields poor sensitivity

- **Investigations:**

  Any postmenopausal women with ovarian cysts should be assessed by CA 125 and transvaginal ultrasound

  - **CA 125:**
    - CA 125 is the only tumour marker used for primary evaluation. CA 125 is not used in isolation (sensitivity and specificity is approximately 80%)
    - Factors that increases CA 125 (false positive results): fibroids, pelvic inflammatory disease, torsion, cyst haemorrhage, endometriosis, cirrhosis, ascites, hepatitis, pancreatitis, peritonitis, pleuritis, breast, pancreatic, lung, colon cancer
    - Factors that may decrease CA 125: caffeine intake, hysterectomy, and smoking

  - **Imaging:**
    - **Transvaginal ultrasound:**

      it is the single most effective evaluation tool. Transabdominal ultrasound may be used in conjugation with transvaginal ultrasound if the cyst is large

Features of simple cysts	Features of complex cysts
• Round or oval shaped • Thin walled • Posterior acoustic enhancement • Anechoic fluid • Absence of septations or nodules Diagnostic accuracy of ultrasound is 95-99%	• Multilocular (malignancy risk is 8%) • Solid nodules (malignancy risk is 36-39%) • Papillary projects

    - **Colour Doppler:**

      It should not be used as a routine. It does not improve diagnostic accuracy of malignancy
    - **3D ultrasound:**

      It should not be used as a routine. It does not improve diagnostic accuracy of malignancy
    - **Magnetic resonance imaging (MRI):**

      MRI is not a primary evaluation tool. It is considered for characterization of indeterminate ovarian cysts when ultrasound is inconclusive

- **Computerized tomography (CT) scan:**
  - CT scan is not recommended during initial evaluation
  - If clinical picture, ultrasound, and CA 125 are suspicious of malignancy, CT abdomen/pelvis should be considered to assess potential disease metastasis and women are referred to a gynaecologic oncology multidisciplinary team

Risk assessment

- RMI I is the most validated and utilized triaging system of suspected ovarian cancer
- If RMI I ≥ 200, CT scan and referral to gynaecologic oncology team should be considered (some authors use a threshold of 250). Sensitivity of RMI I ≥ 200 is 78% and specificity is 87
- Other scoring systems may be less practical. IOTA has a classification based on US expertise that is comparable to RMI I

Management

- **Management decision:**
  - Postmenopausal women with simple unilateral unilocular cyst < 5cm, and normal CA125 can be managed conservatively

    In this case, women are followed up after 4-6 months. If cyst size is the same or less, follow-up can be stopped after 1 year
  - If the cyst is symptomatic or complex, surgical evaluation is indicated

- **Procedure:**
  - **Laparoscopic bilateral salpingo-oophorectomy:**
    - The procedure is indicated if RMI I < 200
    - Bilateral salpingo-oophorectomy is performed. Ovarian cystectomy is not recommended
    - Intraperitoneal spillage should be avoided by using tissue retrieval bag through the umbilical port
    - If malignancy is suspected, full staging will be required, and the patient should be referred to a cancer centre (this scenario should be included in preoperative counselling)
  - **Staging laparotomy:**

    Staging laparotomy is indicated if RMI > 200, preoperative CT or laparoscopy is suspicious

- **Aspiration:**

  Aspiration is contraindicated in postmenopausal women unless the procedure is indicated for symptom relief in advanced cancer stages

- **Manging team:**
  - Ovarian cysts associated with RMI I < 200 are manage by general gynaecology or cancer unit
  - Ovarian cysts associated with RMI I > 200 should be managed by cancer unit

Ovarian Cancer

Epidemiology

- Ovarian cancer is the sixth most common cancer in women. It accounts for 4% of all new cases of cancer in women
- Lifetime cancer risk 1.3%
- It is associated with the highest rate of mortality among all gynaecologic cancer; it accounts for 6% of all cancer deaths in women
- Approximately 70% of all cases are diagnosed at stage 3 or 4. One third of patients are diagnosed in emergency department; 75% of them are not eligible for active treatment

Risk factors

- BRCA1 (risk of ovarian cancer is 40%) and BRCA2 (risk of ovarian cancer is 10-15%) mutations
- Mismatch repair genes (LYNCH syndrome)
- Nulliparity
- First birth after 35 years
- Early menarche
- Late menopause

Protective factors

- Combined oral contraceptives (COCs)
- Pregnancy
- Sterilization and tubal ligation
- Hysterectomy

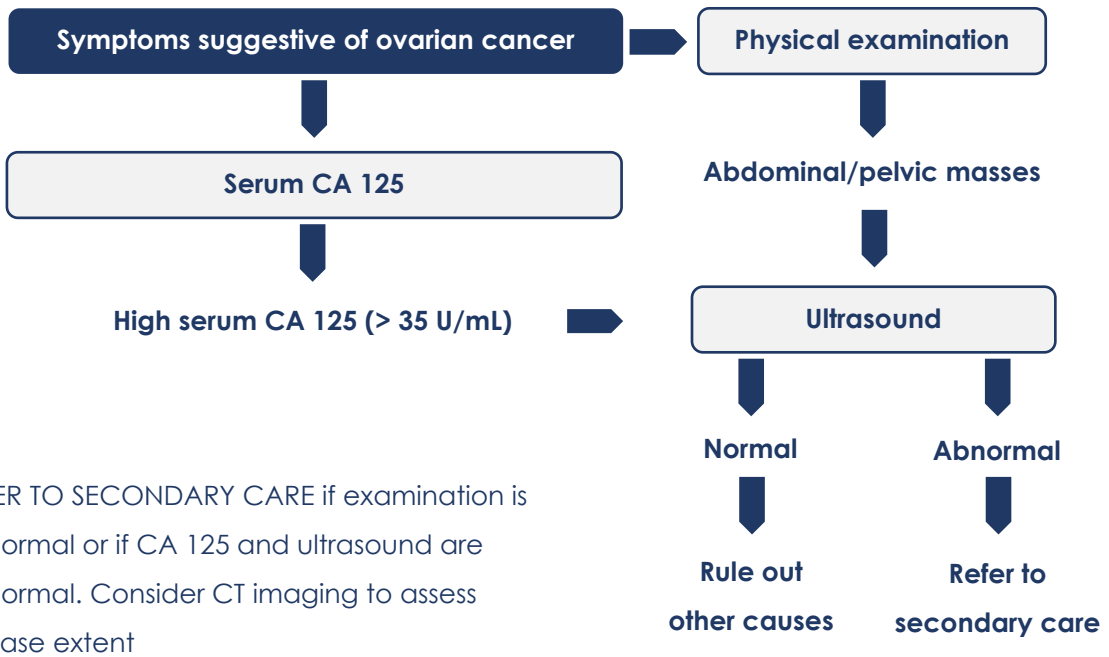
Diagnosis

- **Symptoms:**
  - 12 episodes per month or more than 1 year of persistent abdominal distension, bloating, early satiety, loss of appetite, pelviabdominal pain, and urinary urgency (particularly in women above the age of 50)
  - Unexplained weight loss
  - Fatigue
  - Change in bowel habits
  - Postmenopausal bleeding

- **Physical examination:**
  - Examination is performed to assess pelvic and abdominal masses
  - Examination is always recommended prior to surgery

- **Investigations:**
  - **Ultrasound and CA 125:**

    Postmenopausal women with symptoms or signs of ovarian cancer should be assessed by CA125 and transvaginal ultrasound



REFER TO SECONDARY CARE if examination is abnormal or if CA 125 and ultrasound are abnormal. Consider CT imaging to assess disease extent

If risk of malignancy index (RMI) > 250, consider further investigations and referral to a specialist

- **Other tumour markers:**

AFP, hCG, and inhibin	In women with suspected ovarian cancer who are younger than 40 years, AFP, hCG, and inhibin should be added to CA 125 (tumour markers of germ cell and sex cord-stromal tumours)
CEA and CA 19-9	▪ If CA125 is elevated, CA 125: CEA ratio should be assessed ▪ If this ratio is < 25 specially with elevated CA19-9, peritoneal carcinomatosis with gastrointestinal cancer should be suspected, and bidirectional gastrointestinal endoscopy should be performed prior to primary debulking surgery
HE4	HE4 is promising diagnostic and prognostic marker in younger as it is associated with fewer false positive results compared to CA 125 e.g. not elevated in women with endometriosis or pelvic infection

- **Computerized tomography (CT):**
  - CT scan is performed at referral to assess distant macroscopic disease (liver, lung, and lymph node metastasis) synchronous cancers, and thromboembolic events
  - Ability of CT to predict suboptimal debulking is insufficiently reliable and is not used alone to make the final decision

- **Magnetic resonance imaging (MRI):**
  - MRI is not routinely used
  - MRI is considered in young women with a solitary mass who want to preserve their fertility

- **Histopathology:**
  - Histopathology is crucial to confirm diagnosis, determine pathological type, and grade
  - If primary chemotherapy is considered to manage suspected ovarian cancer, tissue diagnosis should be made before treatment via image guided biopsy or laparoscopy
  - if tissue sampling is not feasible e.g. poor performance status, imaging **OR** CA125: CEA ratio > 25 **PLUS** positive cytology is used as an alternative to allow chemotherapy
  - Negative cytology does not exclude cancer specially in the presence of inflammation
  - Routine use of laparoscopy for assessment or tissue biopsy is not recommended
  - Intraoperative frozen section assessment may be used if it may alter intraoperative management. This technique has many limitation

- **Genetic testing:**

  High grade serous carcinoma and G3 endometroid adenocarcinoma are associated with 18% risk of germline BRCA mutation (45% of these patients have no family history)

Advantages of BRCA testing

- Testing provides prognostic information (longer remission period)
- A positive test promotes counselling of other family members
- BRCA positive women are eligible for PARP inhibitor treatment. Treatment may provide better response and longer remission in some of these patients Therefore, Olaparib can be offered to BRCA carriers, who responded to platinum-based chemotherapy after 3 or more courses.

Risk assessment

- Risk of malignancy index (RMI) = U X M X CA125
- U = 0 (no sonographic features) ,1 (1 feature), or 3 (2-5 features)

  Ultrasound features: multilocular cyst, solid areas, metastasis, ascites, bilateral lesions
- M = 1 (premenopausal), or 3 (if menopausal or older than 50 years with hysterectomy)
- If RMI > 250, women should be referred to a specialist

Prevention

- **Screening:**
  - No screening is recommended for low risk women
  - Ovarian cancer screening for high risk group is not well established

- **Preventive interventions:**
  - When ovarian cancer risk is above 10%, risk reducing salpingo-oophorectomy should be considered. It reduces cancer risk by 98%. However, there is 2% risk of peritoneal cancer
  - If risk-reducing surgery is declined, annual ultrasound and CA125 surveillance should be offered (positive predictive value is 25%, negative predictive factor is 100%)

Management

30% of apparently early ovarian cancer are upstaged in surgery

Treatment

Surgical treatment

Early stage

Surgery should be performed at cancer center by a specialist multidisciplinary team (MDT)

Complete macroscopic resection and adequate surgical staging if fertility sparing surgery is not planned

If disease is unexpectedly malignant by postoperative histopathology, restaging procedure by an oncologist should be performed

Second look surgery is not recommended

Late stage

Primary cytoreductive surgery followed by adjuvant chemotherapy is the standard treatment

Neoadjuvant chemotherapy followed by interval cytoreductive surgery is not inferior to primary debulking and adjuvant chemotherapy and is appropriate if disease burden is extensive or if resectability of the disease is uncertain (yields less morbidity)

Neoadjuvant chemotherapy for 3 cycles followed by interval debulking is superior to no surgery (prolongs progress free interval and improves overall survival)

Bulky lymph nodes should be removed as a part of debulking surgery (prolongs survival)

Systemic treatment

Early stage

Adjuvant platinum-based chemotherapy should be offered to women with ovarian cancers except low grade (1 or 2) stage 1A or 1B disease

Grade 3 or stage 1C should receive 6 cycles of carboplatin

There is no role for targeted therapy in early ovarian cancer

Systemic treatment

Late stage

Intraperitoneal chemotherapy may be offered within clinical trials

Targeted therapy (bevacizumab) PLUS chemotherapy and then alone for 12-15 months as a maintenance therapy. It prolongs progress free survival but not overall survival

Anti-angiogenic therapy increases toxicity, increase progress free interval but not overall survival (e.g. pazopanib)

Adjuvant chemotherapy for all stages consists of carboplatin and paclitaxel every 3 weeks for 6 cycles

If there is allergy or intolerance to paclitaxel, consider protein-bound paclitaxel or pegylated liposomal doxorubicin as an alternative

Recurrence-related symptoms are reviewed, and examination is performed. CA 125 is not mandatory (no survival benefit). Visits are scheduled every 3 months for 2 year then every 6 months for up to 5 years

Surgical staging of ovarian cancer

- Peritoneal washing/ascitic sampling
- Total hysterectomy and bilateral salpingo-oophorectomy
- multiple peritoneal biopsies from paracolic spaces and subdiaphragmatic spaces bilaterally.
- Infracolic omentectomy
- Pelvic and paraaortic lymph node assessment up to level of origin of ovarian vessels in absence of peritoneal dissemination
- Appendectomy if the tumour is mucinous

Systemic retroperitoneal lymphadenectomy in absence of enlarged lymph nodes is not warranted

Recurrent disease

Types of recurrent disease	
Platinum sensitive	Disease progresses after 12 months of completion of treatment
partially platinum sensitive	Disease progresses after 6-12 of completion of treatment
Platinum resistant	Disease progresses after < 6 months of completion of treatment
Platinum refractory	Disease progresses during or within 4 weeks of completion of treatment

- Cytoreductive surgery is indicated if the disease is resectable, platinum sensitive, and the patient is eligible for surgery (good performance status). Surgery improves progress free survival and overall survival
- If chemotherapy is considered, combination therapy is considered if disease free interval is more than 6 months. A single agent is used to managed recurrence if disease free interval is less than 6 months (less toxic and similarly effective)

Type-specific considerations

Low grade serous ovarian cancer	• 5% of serous tumours • Surgery is the most effective treatment • Low grade tumours are less responsive compared to high grade serous cancer. Response to combined regimen is 25%. However, there is no superior regimen
Endometroid ovarian cancer	• The second most common type of epithelial ovarian cancers (10-15%) • 15% of cases are associated with synchronous ovarian cancer • Grade 3 endometrial ovarian cancer management is similar to high grade serous cancer, adenofibromatous pattern and squamous metaplasia
Mucinous tumour	• 3-5% of all ovarian cancers • Primary advanced primary tumour is rare. Secondaries from primary gastrointestinal tumour should be excluded Primary ovarian tumours exhibit CK7+\CK2-\CDX2- immunoprofile
Small cell carcinoma of the ovary	• It includes hypercalcaemic, pulmonary, and large cell variant • Treatment protocol is comparable to serous tumours
Wolffian tumour	• Usually begin • It consists of cysts of different size, solid and spindled areas
Clear cell carcinoma	• It is most frequently associated with pelvic endometriosis, paraneoplastic hypercalcaemia, and venous thromboembolism • This type is characterised by clear (hobnail) cells in papillary, glandular, or solid pattern • Management is similar to high grade serous carcinoma. However, it lacks hormonal receptors and is less responsive to chemotherapy
Carcinosarcoma	• 2% of all ovarian cancers (rare) • Characterised by epithelial and mesenchymal component • It is associated with aberrant p53 expression, occasionally germline mutation BRCA2 • Prognosis is worse than high grade ovarian cancer and 90% of cases are diagnosed at advanced stage

Prognosis

- Average 5-year survival rate of ovarian cancer is 35%
- Disease Stage is the most prognostic factor

Borderline Ovarian Tumours

Epidemiology

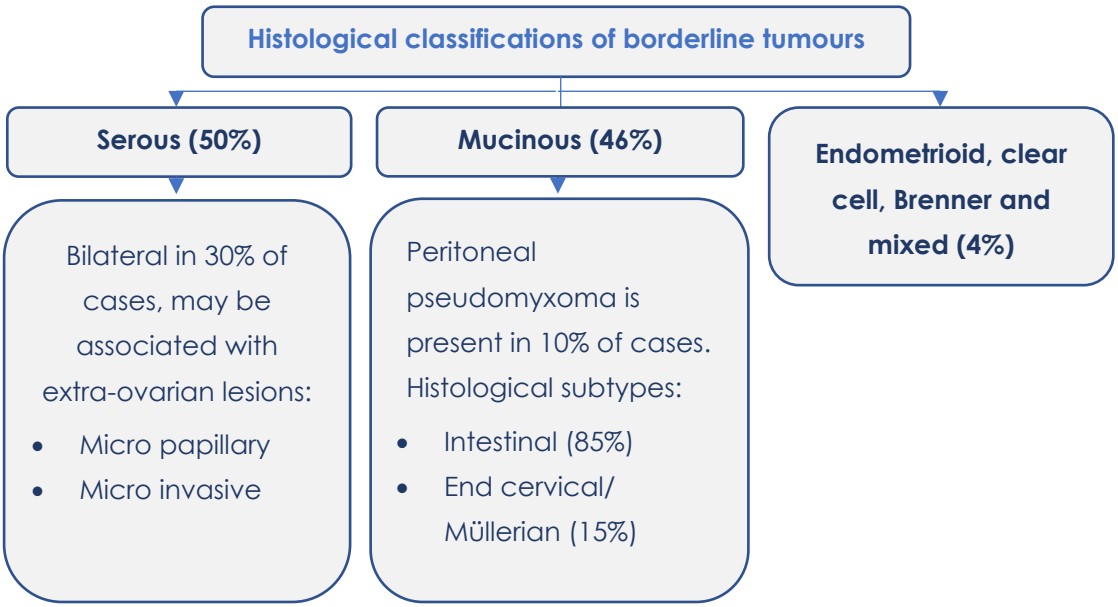
- They account for 10–15% of all epithelial ovarian neoplasms
- Unlike ovarian cancer, borderline tumours are characterized by presence of atypical epithelial proliferation without stromal invasion

Risk factors

- Younger age (40 years vs. 60 years for ovarian cancer)
- Nulliparity (multiparty and breast feeding are protective factors)
- Hormonal contraception is not protective (unlike ovarian cancer)

Classification

- Ovarian cancer is classified to either high grade serous cancer (associated with high rate of P53 mutation) and low-grade cancer including borderline tumours, mutation of BRAF/KRAS pathway
- Because low grade cancer does not progress to high grade cancer, if borderline tumours progress, they will behave as low-grade cancer (which is uncommon)



Diagnosis

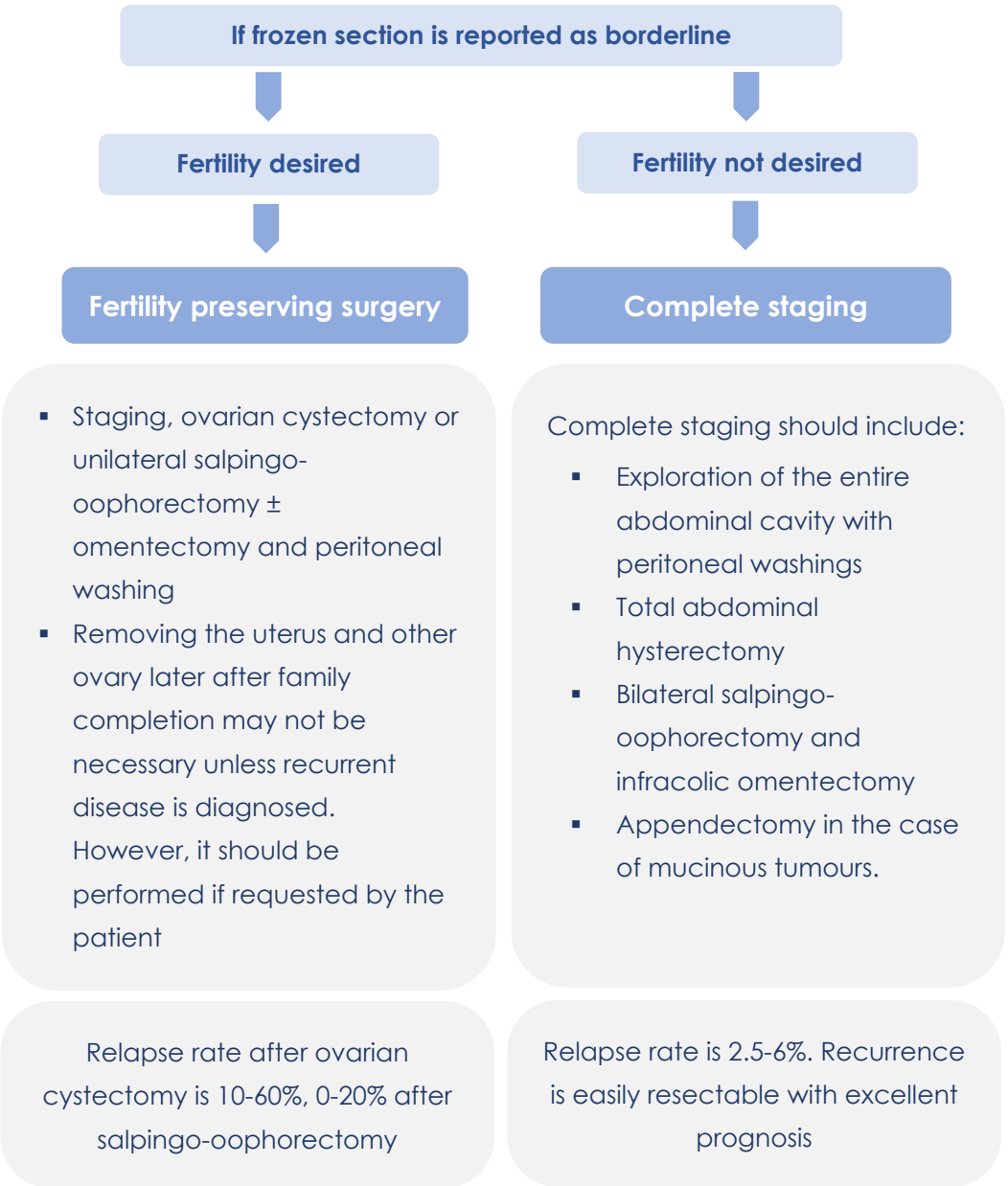
Most patients are asymptomatic. Diagnosis is commonly incidental during physical examination or pelviabdominal imaging for other indications

Symptoms	Investigations
• Pelvic pain • Bloating • Dyspareunia • Menstrual irregularities • Pressure symptoms • Frequency of micturition • constipation	• **CA 125:** ▪ CA 125 is elevated in 75% of serous tumours ▪ CA 125 is elevated in only 30% with mucinous tumours (elevated CA 19-9 is more common with mucinous tumours) • **Transvaginal ultrasound:** ▪ Ultrasound is the standard modality to assess cyst features ▪ Presence of intra-cystic blood flow is a sensitive finding for ovarian cancer

Management

- **Determinants of management:**
  - Patient age
  - Disease stage
  - Desire of fertility preservation
  - Peritoneal implants

- **Standard management:**
  - Standard surgery is accurate staging and cytoreductive surgery via laparotomy
  - If available, frozen section testing should be performed. However, diagnostic accuracy of frozen section to borderline ovarian tumours is low; 33% of cases will be reclassified as invasive cancer on final histopathology



- After fertility preserving management, 50% of women conceive spontaneously. If fertility treatment is indicated, it should be confined to stage I and number of cycles should be limited. Recurrence rate following fertility treatment 13-30%
- Lymphadenectomy has no role in borderline ovarian tumours. However, it may be considered in women with invasive disease
- Chemotherapy has no role unless the disease is recurrent and is irresectable

- **Restaging and completion of surgery:**

Indications of restaging *	• Micropapillary tumours • Invasive implants (5-year risk of recurrence is 31% vs. 21% with non-invasive implants). • Tumour DNA aneuploidy (19-fold increased risk of mortality compared to diploid tumour)
Restaging procedure	• Peritoneal washings • Omentectomy • Complete examination of the peritoneum • Hysterectomy and oophorectomy (only if there is no fertility desire) • No role of lymphadenectomy

* Restaging is unlikely indicated if a woman has undergone full laparotomy with inspection of all surfaces (including contralateral ovary, momentum and peritoneal surfaces) during primary surgery. Therefore, these steps are indicated as a routine during primary surgery

Follow-up

- After treatment, patients should be followed-up every 3 months for 2 years
- After 2 years, follow-up visits are scheduled every 6 months for another 2 years and then annually

Prognosis

- 5-year survival rate of stage I borderline ovarian tumours is excellent (95–97%)
- Women with stage III disease also have a good prognosis; 5-year survival rate is 50–86%
- Overall 10-year survival rates range from 70–80%, due to late recurrence

Ovarian Cancer Prevention

Epidemiology

- Ovarian cancer is the second most common gynaecologic malignancy
- 90% of ovarian tumours are epithelial in origin
- Lifetime risk of ovarian cancer in the general population is 1.4%
- Overall 5-year survival is less than 45%.
- Spread of cancer beyond ovaries at time of diagnosis occurs 75% of cases

Risk factors

Family history of ovarian cancer is the strongest risk factor (10-15% of all cases)

Family history	Risk of ovarian cancer increases even it occurs in sporadically. However, hereditary cancer syndrome is associated with significant increase in cancer risk: • If 1 family member has ovarian cancer: risk is 5% • If 2 family members have ovarian cancer: risk is 7% • Family history consistent with hereditary cancer syndrome: risk is 15-50%

Breast ovarian cancer syndrome	• Women with BRCA gene mutations have significantly increased risk of ovarian and breast cancers
	• BRCA mutations may account for up to 90% of hereditary ovarian cancers
	• The estimated risk of ovarian cancer is:
	  ▪ 35–46% in BRCA1 mutation carriers
	  ▪ 13–23% in BRCA2 mutation carriers
	• BRCA2 carriers have a better cancer prognosis than non-carriers

Other high-risk genetic syndromes	• Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC): ▪ It accounts for 1% of ovarian cancers ▪ Risk of ovarian cancer in women with Lynch syndrome is 4-14% • Peutz-Jeghers syndrome: ▪ Risk of ovarian cancer is 20% ▪ Tumours are likely sex-cord stromal tumours
Non-genetic risk factors	• Endometriosis: ▪ Risk of malignant transformation is 2.5% ▪ Developing cancer is likely well differentiated, low stage carcinoma (good prognosis) • PCOS and obesity: There may be small increase in risk of ovarian cancer in women with PCOS and obesity • Ovulation induction: It does not increase risk of ovarian carcinoma. However, it may be associated with increased risk of borderline ovarian tumours
Protective factors	These factors may reduce the risk of ovarian cancer: • Pregnancy • Breast feeding for more than 12 months (risk reduction is 0.7) • Combined oral contraceptives (COCs) decrease risk by 20% every 5 years, reaching approximately 50% after 15 years. The effect extends for 30 years. Risk reduction is 30% within 10 years of cessation and 15% 30 years after cessation • Tubal ligation decreases risk by 60% among BRCA 1 patients Risk reduction is 72% if COCs are used • Hysterectomy decreases risk by 34%

Screening of ovarian cancer

Screening is not recommended in low risk. Combined screening is associated with anxiety and unnecessary interventions and it does not improve mortality

	High risk women	Low risk women
Risk factors	• Family history suggestive of a hereditary cancer syndrome • BRCA1 carrier • BRCA2 carrier • Lynch syndrome (HNPCC)	• Positive family history, single member affected • not suggestive of a hereditary cancer syndrome • Risk of ovarian cancer: 4–5%
Management	• Offer risk-reducing bilateral salpingo-oophorectomy (BSO) after age 35 when childbearing is complete • If surgery is declined, women can be offered screening with transvaginal ultrasound and CA 125 every 6 months starting at the age of 35 or 5-10 years earlier than the youngest age at diagnosis in the family. COCs should be offered if not given before	• No evidence to support screening in this group • Risk-reducing bilateral salpingo-oophorectomy (BSO) may be considered based on individual considerations after thorough counselling

Prevention of ovarian cancer

- **Chemoprevention:**
  COCs are found to reduce yield long-term reduction in ovarian cancer risk including women who are BRCA carriers

- **Risk-reducing surgery:**

  Patients should be counselled that risk-reducing surgery is not completely protective; risk of cancer is 2% after surgery owing to peritoneal cancer

Time of surgery	▪ BRCA 1 carriers: 55% diagnosed before age of 50 while 2-3% are diagnosed before age of 40. Therefore, surgery should be considered at age 35 ▪ BRCA 2 carriers: Age of cancer diagnosis is later than BRCA 1 carriers (2-3% at age of 50). Therefore, surgery may be delayed to the age of 45. Nevertheless, this delay precludes benefit of reducing breast cancer ▪ If women have not completed their family, embryo cryopreservation or surrogacy may be discussed
Preoperative measures	• Perform Transvaginal ultrasound and CA 125 prior to surgery • Counsel women on possible need for full staging at time of surgery since incidence of occult malignancy is 4-8%, reaching up to 20% above the age of 45
Surgical procedure	• BSO with removal of all ovarian tissues and all ovarian adhesions • Ovarian vessels are clamped at least 2 cm proximal to ovary or ideally at pelvic brim to ensure removal of all ovarian tissue • Tubes should be completely removed. The interstitial part does not have to be removed as it is not associated with cancer development • Concurrent hysterectomy: ▪ It should be considered in women with Lynch syndrome since the risk of endometrial cancer is 40-60% ▪ Some BRCA carrier who receive tamoxifen for chemoprophylaxis may be offered hysterectomy ▪ It may be considered in women who will receive hormone replacement therapy so they can use oestrogen only (which is not associated with significant increase in breast cancer risk in postmenopausal compared to combined therapy)

- Oophorectomy at time of hysterectomy for benign indications decrease risk of breast and ovarian cancer. However, it increases the risk of all-cause mortality and mortality related to coronary heart disease.

Premature menopause

- Surgical menopause is associated with abrupt decrease in sex hormones
- Hormone replacement therapy does not interfere with benefit of risk-reducing surgery in reducing risk of breast cancer
- Hormone replacement therapy is associated with small increase in breast cancer risk. However, if breast cancer develops, it is typically low grade. There is no increase in breast cancer mortality with hormone replacement therapy
- BRCA 1 is typically oestrogen/progesterone receptor negative. BRCA 2 is typically receptor positive. Hormone replacement therapy is contraindicated if there is personal history of breast cancer.

Endometrial Hyperplasia

Risk factors

- High body mass index (peripheral conversion of androgen to oestrogen)
- Perimenopausal anovulation, polycystic ovary syndrome (PCOS)
- Oestrogen secreting ovarian tumours e.g. granulosa cell tumour (up to 40%)
- Long term tamoxifen
- Systemic oestrogen replacement therapy
- Immunosuppression: e.g. renal graft patients with abnormal uterine bleeding (70%)

Assessment

- **Outpatient endometrial sampling:**
  - Endometrial surveillance for endometrial hyperplasia is performed using outpatient endometrial biopsy and the diagnosis is made by histological examination
  - Up to 10% of endometrial pathology may be missed even if inpatient endometrial sampling is performed
- **Hysteroscopy:**
  - If outpatient sampling fails or is non-diagnostic, diagnostic hysteroscopy should be performed
  - Hysteroscopy is also indicated if hyperplasia is diagnosed within a polyp or other discrete focal lesion
- **Transvaginal ultrasound:**
  - It may have a role in diagnosing endometrial hyperplasia in pre- and postmenopausal women

- Endometrial thickness ≤ 4mm is associated with cancer risk < 1%. Endometrial thickness with PCOS is unlikely hyperplasia if < 7mm

- **CT and MRI:**
  They are not routinely recommended

Management

Reversible risk factors should be identified and managed e.g. obesity, hormone replacement therapy (HRT)

- **Endometrial hyperplasia without atypia:**
  - **Indications of treatment:**
    ① In all women, progestin treatment is superior to observation alone in regression rate
    ② Failure of observation
    ③ Symptomatic patients with abnormal uterine bleeding

    Risk of progression to cancer is < 5%. The majority regress spontaneously
  - **Treatment options:**
    - First line treatment is levonorgestrel-releasing intrauterine system (LNG-IUS) since it is the most effective form of progestin therapy, and is associated with fewer side effects
    - If LNG-IUS is declined, continuous progestin (medroxyprogesterone acetate [MPA] 10-20 mg/day or norethisterone 10-15 mg/day) is used
    - Cyclic progestin treatment is not recommended (less effective)
  - **Treatment duration:**
    - A minimum of 6 months is required to allow disease regression
    - Women who are not interested in pregnancy should be counselled on keeping LNG-IUS for 5 years to reduce the risk of relapse
  - **Follow-up:**
    - Endometrial surveillance should be performed every 6 months. At least, two successive negative samples should be obtained prior to discharge
    - Women at higher risk of relapse e.g. BMI ≥ 35 should be followed up every 6 months, till 2 negative results are obtained and then annually
    - If abnormal bleeding recurs after treatment, referral and reassessment should be considered
    - Risk of relapse is maximum in the first 2 years after treatment

- **Hysterectomy:**
  - **Indications of hysterectomy:**
    ① Progression to atypical hyperplasia
    ② Failure of regression after 12 months of treatment
    ③ Relapse after progestin therapy
    ④ Persistence of bleeding symptoms
    ⑤ Patients declining or not compliant to surveillance
  - **Procedure:**
    - Total hysterectomy with bilateral salpingo-oophorectomy is considered in postmenopausal women
    - In premenopausal women, hysterectomy with bilateral salpingectomy should be performed. Decision of oophorectomy should be individualized

- **Atypical hyperplasia:**
  - **Definitive management:**
    - Total hysterectomy is the standard management
    - Intraoperative frozen section or routine lymphadenectomy is not recommended
  - **Fertility sparing management:**
    - Women who wish to retain fertility should be counselled on risk of malignancy progression, rule out invasive cancer or coexisting ovarian cancer
    - Before fertility sparing treatment is discussed, transvaginal ultrasound/MRI and CA125 should be considered (risk of coexisting ovarian cancer is up to 4%)
    - First line of management is LNG-IUS. Second line is oral progestins followed by hysterectomy after completing her family
    - Follow-up after treatment consists of endometrial surveillance every 3 months till 2 consecutive negative biopsies are obtained then every 6-12 months until hysterectomy is performed

Assisted reproductive technology (ART) may be considered since it is associated with higher pregnancy rate. It may prevent relapse compared to attempting natural conception

- At least one sample should show regression before trying to conceive. Women are referred to fertility specialist. Regression of endometrial hyperplasia is associated with higher implantation and clinical pregnancy rate

- **Hyperplastic polyps:**

  In presence of hyperplasia within a polyp, polyps should be removed, and background endometrium should be sampled

- **Hormonal treatment and endometrial hyperplasia:**

Hormone replacement therapy (HRT)	▪ Unscheduled bleeding should be assessed ▪ Women with endometrial hyperplasia on sequential HRT should be switched to combined continuous HRT or start using LNG-IUS ▪ If endometrial hyperplasia develops while using continuous HRT, treatment may continue, progestin treatment (dose is not well defined or LNG-IUS should be considered
Tamoxifen	• Women taking Tamoxifen are at high risk of hyperplasia or cancer • Any abnormal vaginal bleeding or discharge should be assessed promptly • LNG-IUS is not recommended for prophylaxis • If hyperplasia develops on Tamoxifen, management should be discussed with an oncologist
Aromatase inhibitors	• Aromatase inhibitors e.g. letrozole do not increase risk of hyperplasia or cancer

Uterine Cancer

Incidence

- Uterine cancer is the 6th most common cancer worldwide in women and the 14th most common cancer overall
- It accounts for 5% of female cancer cases. Mean age at diagnosis is 60 years
- 2-5% of endometrial cancer cases are genetic

Cancer screening

Screening in low-risk women

- There is **NO** role of screening in low risk asymptomatic women
- Only symptomatic women with postmenopausal bleeding/abnormal uterine bleeding should be assessed by transvaginal ultrasound (TVUS).
- If endometrial thickness (ET) by transvaginal sonography is ≤ 4mm, risk of endometrial carcinoma (EC) is unlikely (<1%)

Screening in high-risk women (selective screening)

- **Lynch syndrome:**
  - Lynch syndrome is an autosomal dominant disorder of mismatch repair genes, that results in colon, endometrial and ovarian cancer. Life-time risk of EC is 40-60%.
  - Women with Lynch Syndrome and their first-degree relatives are offered annual screening with TVUS and endometrial biopsy starting at the age of 35 years or if they are symptomatic
  - Mean age at diagnosis is 47 years
- **Tamoxifen therapy:**
  - Routine screening is not recommended
  - Symptomatic patients should be evaluated by TVUS, hysteroscopy and biopsy

Cancer Prevention

Prevention in the general population

A normal body mass index (BMI) reduces risk of EC. Lifetime risk in obese is women is 9-10% (vs. 3% in general population)

Every 5 kg/m^2 increase body weight is associated with 1.6-fold increase in EC risk

80% of EC are overweight (BMI 25-29.9) and 50% are obese (BMI is 30 or more)

Sustained weight loss decreases risk by 25%.

Loss of wright either by bariatric surgery or lifestyle modification may reduce EC risk

If BMI in later life is less than BMI at age 20, these women are 50% less likely to develop EC compared to other women

Prevention in high-risk group

Prevention in high risk population

- Risk reducing surgery is effective in preventing EC in high risk women
- Prophylactic hysterectomy and bilateral salpingo-oophorectomy when family is completed prevents endometrial and ovarian cancer in high-risk women
- Non-invasive procedures e.g. levonorgestrel-releasing intrauterine system and weight loss may play a role. However, their role has not been established yet

diagnosis

- **Presenting symptoms:**
  - postmenopausal bleeding (PMB). EC represents 5-10% of patient with PMB
  - intermenstrual or prolonged bleeding in premenopausal women

- **Examination:**
  - Women with any of the above symptoms should undergo abdominal, speculum and pelvic examination
  - Endometrial sampling is indicated in women with:
    ① Abnormal uterine bleeding at or above 45 years
    ② Women with irregular bleeding or bleeding unresponsive to treatment in younger age group

- **Diagnostic investigations:**

TVUS

- It is the first investigation in women with PMB
- If endometrial thickness ≤ 4 mm with no other abnormalities, EC is unlikely, and no further management is needed

Endometrial biopsy

- If endometrial thickness is more than 4 mm, outpatient endometrial biopsy is indicated
- Recurrent PMB, regardless of TVUS, warrants endometrial biopsy

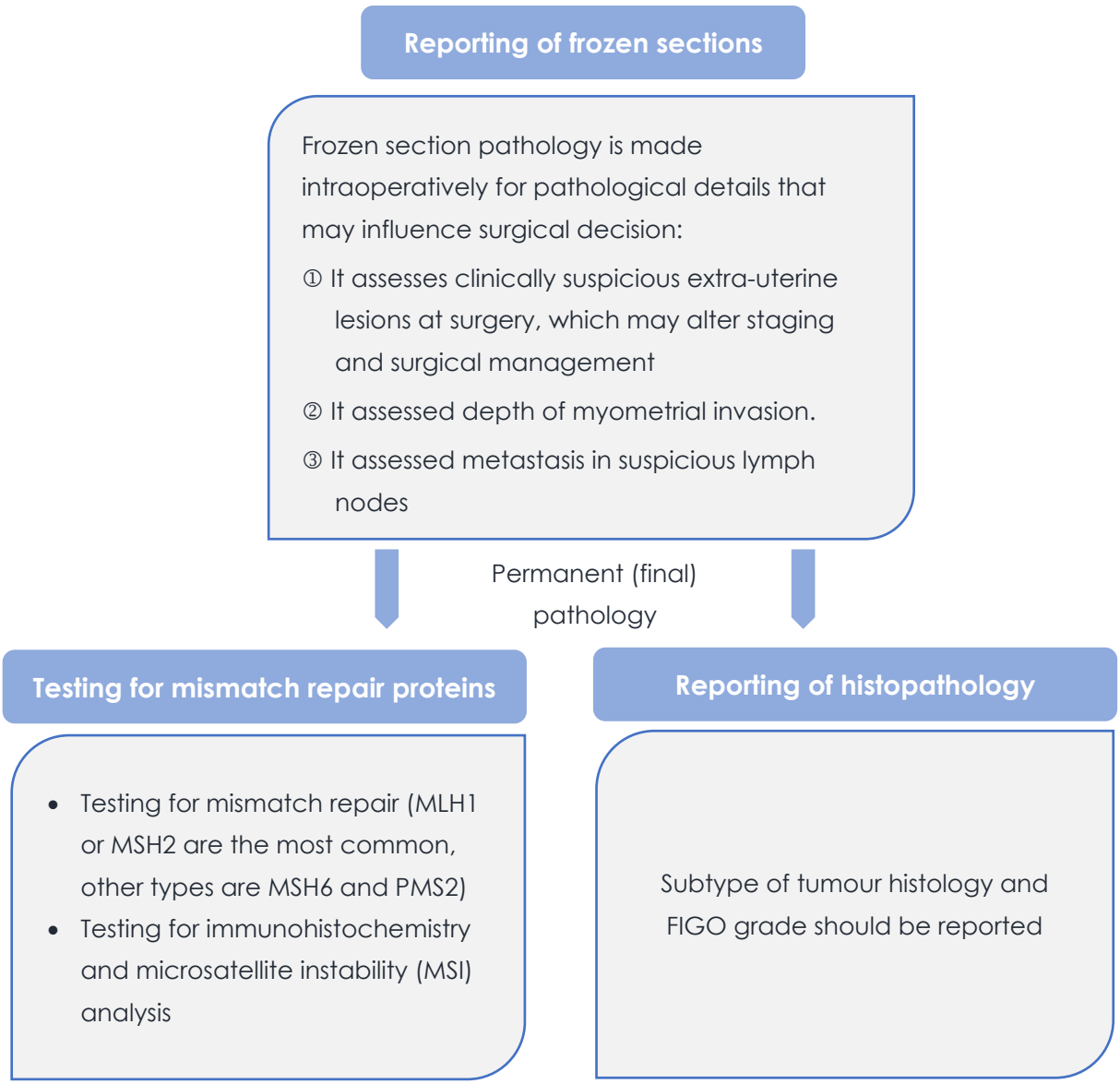
Hysteroscopy

- Outpatient hysteroscopy is performed if office endometrial biopsy is not available, in women at high risk of EC or recurrent PMB
- Suspicious findings are associated with 70% risk of EC
- Negative findings are associated with 0.6% risk of EC

Hysterectomy

- Hysterectomy is indicated in women with hyperplasia specially in the presence of atypia due to risk of coexisting cancer foci and risk of conversion to EC
- Hysterectomy is offered to women with recurrent PMB when no cause is identified

- **Metastatic investigations:**
  - Chest radiology (chest x-ray or CT): should be performed in all women with diagnosis of EC
  - Abdomino-pelvic MRI or CT abdomen and pelvis: in women with high-risk histological subtype (non-endometroid EC). If histological subtype was not known prior to surgery, these tests should be performed postoperatively to determine adjuvant therapy. MRI is superior to CT in assessment of lymph nodes
  - PET scan and CA-125 are not recommended.



- **Clinical information required on the specimen request form:**
  - Patient demographics
  - Clinical presentation
  - Previous biopsies and imaging investigations
  - Surgical procedure in details
  - Family history of cancer
  - Hormonal therapy
  - Careful report of site of origin and orientation of the specimen

Surgical management

Where to treat women with endometrial caner

- Women with stage 1A G1 or 2: surgery can be done in a diagnostic centre by a gynaecologist who is member of specialist gynaecological cancer multidisciplinary team meeting.
- Women with papillary, serous, clear, carcinosarcoma, G3, or 1B: surgery is done in a cancer centre by a specialized surgeon
- Failsafe mechanisms should be applied to ensure reliable direction and management of patients

- **Management of early disease (FIGO Stage I and II):**
  - Women with stage I-II grade 1 or 2 EC are treated with hysterectomy and bilateral salpingo-oophorectomy. In women with stage II disease, simple hysterectomy with radiotherapy is comparable to radical hysterectomy
  - Lymphadenectomy is not indicated. It does not affect survival or recurrence
  - Laparoscopy and robotic surgery are appropriate approaches

Sentinel lymph node

- In low risk and intermediate risk patients,10% and 15% positive lymph nodes with sentinel lymph node assessment. Diagnostic performance is promising but routine use has not yet been adopted
- In high risk patients, sentinel lymph nodes are not recommended because 50% may have metastasis. Lymphadenctomy may be considered

- **Management of stage III and IV:**
  - Surgical resection of all visible disease is performed (it may improve survival)
  - Systematic lymphadenectomy is associated with 4-fold increase in detection rate of metastasis compared to selective sampling of enlarged lymph nodes
  - In the presence of irresectable disease, surgery may be considered if disease responds well to neoadjuvant chemotherapy

Adjuvant therapy

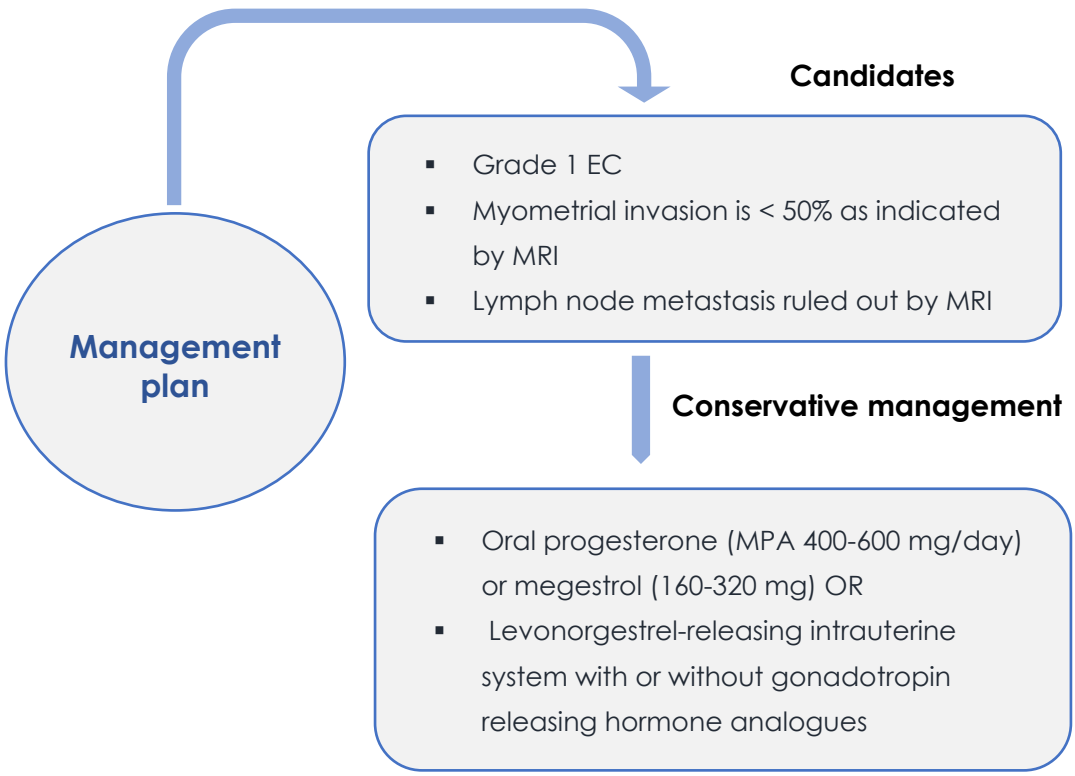
Classification	Definition	Treatment
Low risk	FIGO grade 1, Stage Ia, Ib, no LVSI FIGO grade 2, Stage Ia, no LVSI	• No adjuvant treatment
Intermediate risk	FIGO grade 2, Stage Ib, no LVSI FIGO grade 3, Stage Ia, no LVSI	• Vaginal brachytherapy
High-intermediate risk	FIGO grade 3, Stage 1a, regardless of LVSI FIGO grade 1, grade 2, LVSI unequivocally positive, regardless of depth of invasion	• Consider external beam radiation versus vaginal brachytherapy if nodal status is unknown • Consider adjuvant brachytherapy versus no adjuvant therapy if nodes are negative
High risk	FIGO grade 3, Stage Ib	• Consider external beam radiation versus vaginal brachytherapy. • Consider adjuvant chemotherapy

LVSI: lymphovascular space invasion

Management of unfit patient

Fertility preserving management

- Less than 5% of endometrioid EC occur in young women (< 45 years)



Follow-up

- Telephone follow-up may be an alternative to clinic visits in women with grade 1 EC
- Imaging and labs are not routinely indicated

- **Frequency of visits:**

Low grade endometroid cancer	High grade endometroid cancer
• Infrequent visits in the first 2 years or patient-initiated follow-up	• More frequent visits in the first 2 years and up to 5 years after surgery

Management of relapsed EC

- PET/CT scan should be considered to rule out distant metastasis prior to treatment
- If recurrent disease is an isolated lesion, it should be managed by surgery and adjuvant chemotherapy
- If residual lesions appear after surgery, external beam radiotherapy or brachytherapy may be considered
- If the patient has not received prior radiotherapy, consider radical radiotherapy

Vulval Cancer

Background

- Incidence of vulval cancer is 4:100.000, crude mortality rate is 1:100.000
- 90% of vulval cancers are squamous cell carcinoma (SCC)
- Nodal spread is present in 30% of operable women

Excisions		
Incisional biopsy	**Excisional biopsy**	**Radical excision**
For securing a diagnosis only	No safety margin	Excision with safety margin at least 1 cm after fixation

Screening

- There is no screening strategy for general population
- High grade vulval intraepithelial neoplasia (VIN), high grade VIN with multicentric disease, VIN in immunocompromised women, Paget's disease, and melanoma in situ, needs a specialist multidisciplinary clinic or gynaecologic oncologists for assessment and follow-up
- Women with Paget's disease need prolonged follow-up
- Follow-up of uncomplicated lichen sclerosus does not need to be hospital-based

Diagnosis

- Diagnosis is made by biopsy. Vulvar cytology should not substitute biopsy
- If the lesion is highly suspicious, do not await biopsy results and consider immediate referral
- Diagnostic biopsies of suspected vulval cancer should be incisional biopsies. Removal of the whole lesion (excisional biopsy) should be avoided

Treatment

- **Primary treatment:**
  - Surgery is primary treatment
  - The standard surgery is wide radical local excision of the primary tumour with a minimum margin of 15 mm of disease-free tissue (a margin greater than 8 mm is associated with 0% recurrence compared to 50% if the margin is less than 8 mm)
  - Primary radiotherapy is considered only if surgery is not possible even under regional anaesthesia
  - Long saphenous vein preservation decreases groin wound and lower limb complications
  - Plastic surgeons should be involved if large defects are anticipated and when radiotherapy is used
  - Diverting stoma 1-2 weeks before definitive surgery may be considered

Surgical management of non-squamous vulval cancer

Carcinoma of Bartholin gland (SCC or adenocarcinoma)	Basal cell carcinoma/verrucous carcinoma	Malignant melanoma [Breslow classification is preferred)
Partial resection with reconstruction, defunctioning temporary colostomy and bilateral lymphadenectomy (deeper cancer, likely to metastasize, and close to anal sphincter)	No lymph node dissection needed Basal cell carcinoma can be treated with radiotherapy (if surgery would affect sphincter function)	Wide local excision is preferred. No benefit from block dissection of the groin. Vulval melanomas should be managed by a melanoma multidisciplinary team

- **Lymph node management:**
  - If there is a unifocal tumour < 4 cm with no evidence of lymph node metastasis, sentinel lymph node biopsy should be considered

Eligibility for sentinel lymph node biopsy

① Primary SCC
② Cancer size is less than 4 cm
③ Macroscopic unifocal cancer
④ No clinical or radiological evidence of lymph node metastasis
⑤ No safety issues with use of patent blue dye and/or technetium[99]

If sentinel lymph node biopsy fails, radical lymph-adenectomy is performed

- If there is a lateral tumour, ipsilateral groin node surgery should be considered. If these lymph nodes are positive, contralateral lymphadenectomy should be performed
- Groin lymph node surgery is done through separate incisions (triple incisions) to decrease morbidity (incidence of skin bridge recurrence is low with early stage disease)
- In the presence of a large primary tumour with clinically suspicious lymph nodes, radical vulvectomy with en-bloc groin lymph node dissection should be considered
- If fixed or ulcerated groin nodes, do surgery and/or RT.
- Superficial groin node dissection should not be performed (higher risk of groin recurrence)

Stage IA (lesion < 2 cm, stromal invasion ≤ 1 mm	Stage ≥ IB (depth of invasion > 1mm or size > 2 cm)	Lesion < 4 cm
Wide local excision without groin node dissection	Triple incision technique	Bilateral sentinel lymph nodes

- Groin lymph node dissection is not indicated with:
  - Stage IA SCC
  - Verrucous tumour
  - Basal cell carcinoma
  - Melanoma

- **Reconstructive surgery:**

<table>
<tr><th colspan="4">Reconstructive surgery</th></tr>
<tr><td>Secondary intention</td><td>Split skin grafts (thigh, buttocks)</td><td colspan="2">Flap coverage</td></tr>
<tr><td rowspan="2">Smaller defects can be left to heal if tension-free closure cannot be done</td><td rowspan="2">Only for large areas when no flap options. Less reliable after radiotherapy or with extensive scarring (depends on underlying blood supply)</td><td colspan="2">Thicker, suitable for less vascularized areas and areas that would receive irradiation</td></tr>
<tr><td>Local flaps</td><td>Distant flaps</td></tr>
<tr><td colspan="2"></td><td>Rhomboid flaps, lotus petal flaps, pudendal thigh flaps</td><td>Gracilis, rectus abdominis for larger bulky reconstruction</td></tr>
</table>

- **Radiotherapy:**

Indications of primary radiotherapy

- Advanced vulval cancer
- Preoperative treatment to preserve anal sphincters if risk of damage is high with surgery
  In these cases, radiotherapy may be considered primarily or prior to surgery to decrease the risk of functioning stomas. However, radiotherapy increases risk of surgical complications and morbidity and the decision should be carefully made
- Treatment of histologically proven groin lymph node metastasis (post-radiation lymph node dissection is of unknown role)
  Pathological assessment of lymph nodes (fine needle aspiration) prior to radiotherapy is mandatory to confirm metastasis

- **Chemotherapy:**

  Primary and recurrent vulval cancer respond to chemotherapy. However, response is variable, and treatment is associated with risk of toxicity

Chemotherapy		
Neoadjuvant chemotherapy	**Adjuvant chemotherapy**	**Chemoradiation**
Response of invasive SCC to this approach is variable	May be useful in women with high risk of relapse (cisplatin)	Similar to its use in cervical cancer treatment [Cisplatin (40 mg/m2) alone or with 5-flurouracil

- **Targeted therapy:**

  Erlotinib (after mutation testing) may improve toxicity benefit ratio

Complications

Complications

Risk factors of short-term complications	Risk factors of long-term complications
• Older age • Diabetes • En bloc surgery • Large drain output on last day of drain placement	• Younger age • Lymphocele ✹ Dissection of greater number of nodes is protective against long-term complications

Surgical complications	
• Wound breakdown • Infection • Deep venous thrombosis (DVT), pulmonary embolism (PE) • pressure sores • Introital stenosis • UI, rectocele • Fecal incontinence	• Inguinal lymphocyst • Lymphedema • Hernia • psychosexual complications

Follow-up

After treatment, patients should be followed up every 3 months for 1 year, then every 6 months for 1 year, and then annually

Prognosis

Recurrence

- Recurrence rate is 15-30%.
- Most common sites of recurrence are:
  - The vulva 70%
  - Groin nodes is 25%
  - Distant recurrence 20%
  - Pelvis 15%
- Groin recurrence: poorer prognosis.
  - If primary management was surgery, radiotherapy is recommended and vice versa. If both methods were done, palliative treatment should be considered

Survival

- 5-year survival rate is 45%
- Survival rate is significantly influenced by nodal metastasis:
  - Survival rate is 80% if there is no nodal spread
  - Survival rate is < 50% with inguinal lymph node spread
  - Survival rate is 10-15% if iliac or other lymph nodes are involved

- The following factors are associated with poorer prognosis:
- Infiltrative growth pattern
- Lymphovascular space invasion
  Both factors are associated with high local recurrence and poorer prognosis. However, adjuvant treatment is not recommended
- Prominent fibromyxoid stroma at invasive edge

Staging

FIGO Classification	
Stage I	***Tumour confined to vulva***
Stage Ia	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1 mm. No nodal metastasis
Stage Ib	Lesions > 2 cm in size, or with stromal invasion > 1 mm confined to the vulva or perineum. No nodal metastasis
Stage II	***Tumour of any size with extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus) with negative nodes***
Stage III	***Tumour of any size with or without extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus) with positive inguinofemoral nodes***
Stage IIIa	(i) With 1 lymph node metastasis (≥ 5 mm), or (ii) 1-2 lymph node metastasis(es) (< 5 mm)
Stage IIIb	(i) With 2 or more lymph node metastases (≥ 5 mm), or (ii) 3 or more lymph node metastases (< 5 mm)
Stage IIIc	With positive nodes with extracapsular spread
Stage IV	***Tumour invades other regional (upper 2/3 urethra, 2/3 vagina) or distant structures***
Stage IVa	Tumour invades any of the following (i) Upper urethral &/or vaginal mucosa; bladder mucosa; rectal mucosa or fixed to pelvic bone, or (ii) Fixed or ulcerated inguinofemoral lymph nodes
Stage IVb	Any distant metastasis including pelvic lymph nodes

Gestational Trophoblastic Disease

Definition

Gestational trophoblastic disease (GTD) is a spectrum of conditions that are associated with elevated hCG after molar, non-molar and live pregnancy

Incidence

Overall incidence of GTD is 1:700. Incidence is approximately doubled in Asian population (1:380)

Types

- Hydatidiform mole (complete or partial)
- Invasive mole
- Choriocarcinoma
- Placental-site trophoblastic tumour
- Epithelioid trophoblastic tumour

Complete mole	Partial mole
Paternal origin (sperms only)	Maternal and paternal origin
Diploid chromosomes	Triploid (90%), tetraploid or mosaic (10%)
No foetal tissues	Foetal tissues/blood cells are present
6% eventually receive chemotherapy	0.5% eventually receive chemotherapy

Diagnosis

- **Clinical presentation:**

Common presentation	Uncommon presentation
• Positive pregnancy test • History of hyperemesis in early pregnancy • Uterine enlargement • Irregular uterine bleeding	• Hyperthyroidism • Early onset pre-eclampsia • Acute respiratory symptoms • Neurological symptoms

- **Investigations:**

  - **Initial (pre-evacuation) diagnosis:**
    Initial diagnosis is made by ultrasound:
    - ***Complete mole:*** It is diagnosed by the presence of the characteristic "snowstorm" appearance in absence of gestational sac or foetal parts
    - ***Partial mole:*** diagnosis is more challenging. The following clues facilitate diagnosis:
      ① Presence of cystic spaces in the placenta
      ② Ratio of transverse: anteroposterior diameter of the gestational sac is greater than 1.5

    Diagnostic accuracy depends on gestational age (40% if less than 14 weeks of gestation, 60% if more than 14 weeks of gestation)

  - **Definitive diagnosis:**
    Final diagnosis is made by histopathology. Molar pregnancy may be misdiagnosed with an embryonic or delayed miscarriage

Early detection

GTD may complicate different types of conception. Recommendations to prevent misdiagnosis and delayed diagnosis of GTD include:

- Products of conception from all miscarriages should be tested by histopathology to rule out GTD. Immunohistochemistry stain for P57 and ploidy stains should be used to differentiating between complete and partial mole
- Histopathology examination is not indicated in women who underwent therapeutic termination of pregnancy if ultrasound shows foetal parts
- Pregnancy test should be performed 3 weeks after medical treatment of failed pregnancy with no previous history of GTD to confirm normalization of hCG
- Pregnancy test is indicated if bleeding is persistent after any pregnancy even

The prognosis is worse after non molar pregnancy due to delayed diagnosis

Management

- **Cervical preparation:**

  Prostaglandins may be used only for cervical ripening and for a short duration

- **Surgical evacuation:**
  - **Complete mole:**

    Treatment of complete mole is achieved by suction evacuation. Medical evacuation with mifepristone and misoprostol is avoided whenever possible because of the theoretical increased risk of embolization and dissemination. These agents increase uterine sensitivity to prostaglandin
  - **Partial mole:**
    - If foetal size is small, treatment is achieved by suction evacuation
    - If foetal size is significant, management with medical evacuation is recommended
  - **Control of bleeding:**
    - Oxytocin should not be used prior to complete evacuation
    - If bleeding is significant, evacuation may be expedited. Oxytocin may be considered if extremely necessary

- **Post-evacuation management:**
  - Anti-D prophylaxis is indicated
  - Patients should be monitored for symptoms after evacuation. If symptoms are persistent, patients should be assessed with ultrasound and hCG. If hCG is below 5000 mIU/ml, evacuation may be repeated

Indications of registration to trophoblast screening center

- Complete mole and partial mole
- A twin with complete or partial mole
- Limited molar changes
- Chemotherapy or PSTD
- Atypical placental site nodule

- **hCG Follow-up:**

  hCG is followed-up weekly:
  - If it is negative within 56 days, continue follow-up for 6 months after evacuation
  - If it is negative after 56 days, continue follow-up for 6 months after hCG becomes negative
  - If there is history of GTD, hCG should be followed-up for 6-8 weeks after any future pregnancy

- **Contraception:**
  - Barrier methods are appropriate until HCG is normalised. Combined contraceptive pills should be avoided (because of potential increased risk of neoplasia). Intrauterine devices should be avoided (risk of perforation)
  - Combined contraceptive pills and intrauterine devices can be used after normalisation
  - If combined contraceptive pills started before hCG normalisation, do not stop them (risk is low)

Twin pregnancy with a complete mole

Management

- Prenatal karyotyping to rule out partial mole or suspected mesenchymal hyperplasia
- Referral to foetal medicine

Outcomes

- Incidence of live birth is 25%
- Risk of early pregnancy loss is 40%
- Risk of preterm labour is 36%
- Risk of pre-eclampsia is 4-20%
- Risk of GTN or chemotherapy is not increased compared to singleton molar

Gestational trophoblastic neoplasia

- **Definition:**

Gestational trophoblastic neoplasia (GTN) refers to the subtypes of GTD that have invasion potential e.g. invasive mole, choriocarcinoma, placental site trophoblastic tumour, and epithelioid trophoblastic tumour

- **Modified WHO Prognostic Scoring System (adopted by FIGO):**

Scores	0	1	2	4
Age	< 40	≥ 40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval from antecedent pregnancy (in months)	<4	4–6	7–12	≥ 13
Pretreatment serum β-hCG (mIU/mL)	< 1000	1000-10000	10000-100000	≥ 100000
Largest tumor size	—	3–5 cm	≥ 5 cm	—
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	—	1–4	5–8	> 8
Previous failed chemotherapy	—	—	1	≥ 2
Blood type		O or A	AB or B	

- If the score is 0-6, patients are classified as low risk, and are eligible for a single agent chemotherapy treatment with 100% cure rate
- If the score is 0-6, patients are classified as high risk, and are eligible for a multiagent chemotherapy treatment with 95% cure rate

- **Management:**
  - Single agent treatment: Methotrexate and folic acid are given. Each cycle is 1 week followed by a 6-day off period
  - Multiagent treatment: it consists of methotrexate plus dactinomycin and vincristine, etoposide, cyclophosphamide. Treatment should continue for 6 weeks after normalisation of hCG. Pregnancy should be avoided for 1 year thereafter

Long term complications of chemotherapy	
Methotrexate	It may induce earlier menopause (by 1 year when used as a single agent and 3 years when used as a part of a multiagent protocol)
Etoposide	There is increased risk of secondary cancers in women who receive combination treatment for longer than 6 months e.g. • Colon cancer (4 times) • Acute myeloid leukemia (16 times) • Melanoma (3 times) • Breast cancer (5 times)

  - Surgery (hysterectomy): it is the first choice for women with placental site trophoblastic tumour because this histologic subtype is chemo-resistant

Recurrence

- Recurrence rate of molar pregnancy is 1/80 (less than 2%)
- Same histologic type is found in approximately 75% of cases of recurrence of GTD

Cervical Cancer Screening

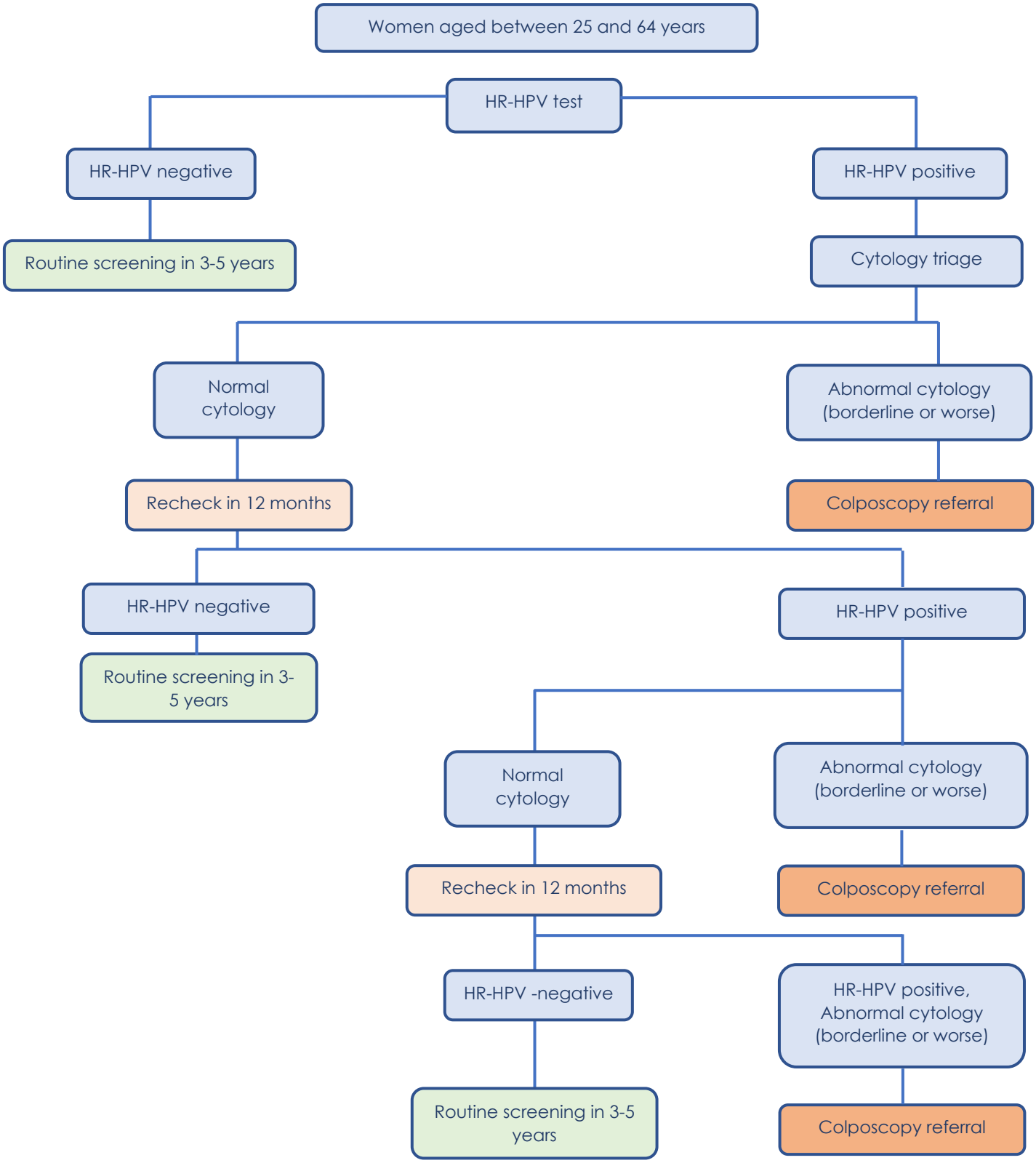
Screening schedule

Screening initiation	Screening frequency	Screening termination
All women should be screened starting at the age of 25	• Age 25-49 years: screening every 3 years • Age 50-64 years: screening every 5 years	Screening should stop after the age of 64 except if: • No cervical screening is done after the age of 50 • A recent cervical cytology is abnormal.

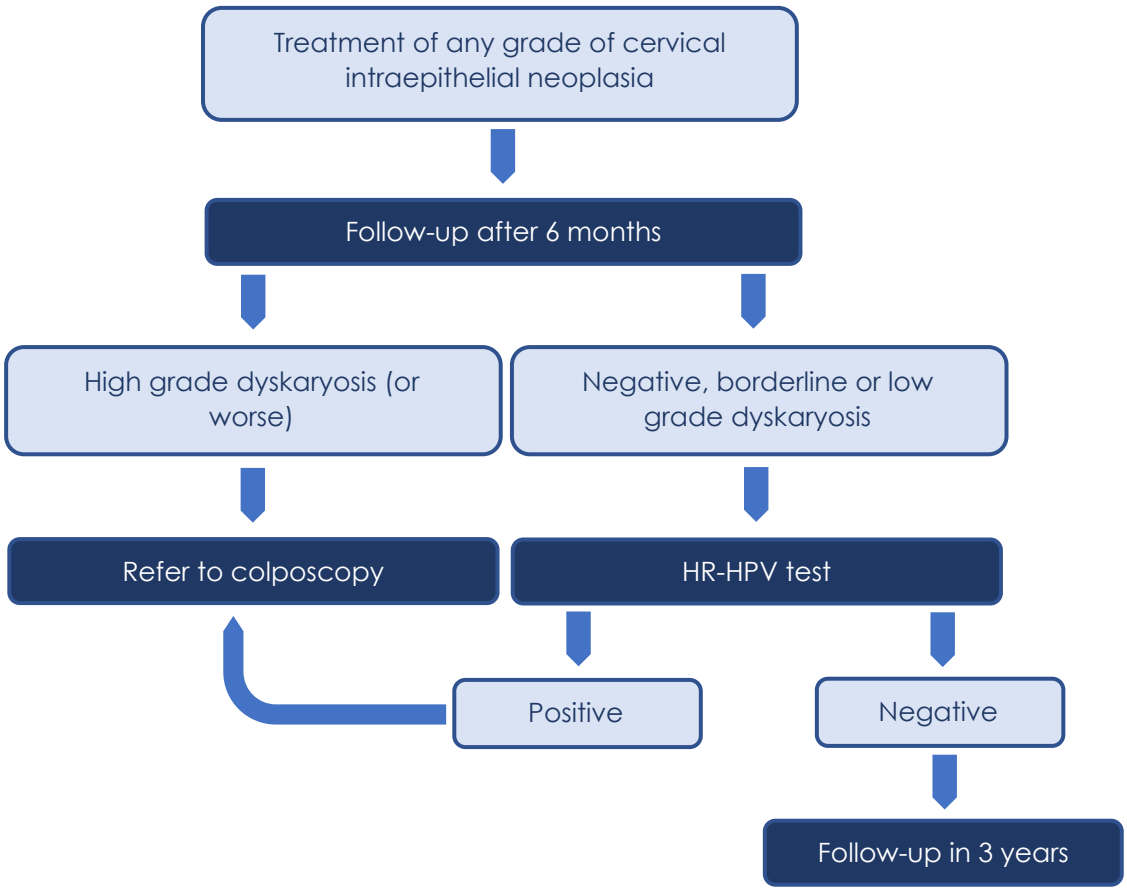
Screening method

- HR-HPV testing has replaced traditional cervical cytology as an initial screening test for cervical neoplasia cytology as the primary test.
- Cervical cytology is performed on samples obtained from women if their HR-HPV testing is positive

Management of screening results



Follow-up after treatment



Cervical Cancer

Risk factors

- **Age:** the most common age is between 35 and 44 years.
- **Socioeconomic status:** it is more common among low socioeconomic levels
- **Inadequate cervical cancer screening:** including non-compliance to Pap testing
- **Early coitarche:** due to increased risk of acquiring HPV infection at young age
- **Multiple sexual partners:** due to increased risk of acquiring oncogenic human papillomavirus (HPV) infection
- **Tobacco smoking:** it increases the risk among HPV-positive women
- **Cervical high-risk HPV infection:**
  HPV 16 is most associated with squamous cell cervical cancer. HPV 18 is most associated with adenocarcinoma
- **High parity:** This may be due to the action of hormonal status, and impaired immunity during pregnancy
- **Combined oral contraceptives (COCs):** The risk is related to duration of use

Diagnosis

- **Symptoms:**
  - **Asymptomatic:**
    Early stages of invasive carcinoma may be asymptomatic

  - **Early symptoms of cervical carcinoma:**
    - Vaginal bleeding: usually starts as postcoital bleeding. Then, bleeding may become spontaneous, irregular, and variable in amount.

- Vaginal discharge
- Dyspareunia
- Vaginal mass

- **Late symptoms of cervical carcinoma:**
  - **Pain:**
    - Deep pelvic pain (parametrial invasion)
    - Flank pain (ureteric obstruction)
    - Dysuria (bladder invasion)
    - Pain with defecation (uterosacral ligaments or rectal invasion)
    - Suprapubic colicky pain (pyometra and cervical obstruction)
    - Sciatic pain or obturator pain (nerve compression)
    - Low back pain (uterosacral ligament infiltration or spinal metastasis)
  - **Urinary/faecal incontinence**
  - **Leg swelling**

- **Physical examination:**
  - Cervical cancer appears as a nodule, cauliflower mass, or an ulcer. Cervix may appear normal or barrel-shaped with infiltrative cancer
  - Parametrium may be indurated due to malignant spread or infection
  - Uterosacral ligaments, and rectal involvement should be assessed with rectal examination

- **Investigations:**
  - Diagnosis is made by biopsy
  - Computerized tomography (CT) scan is essential once the diagnosis is made to assess disease extent, lymph node and organ metastasis
  - Cystoscopy and Sigmoidoscopy: may be performed to rule out bladder and rectal spread, respectively

Management

- **Fertility sparing surgery:**

Stage IA1	Conization (cone biopsy) can be considered: • **If margins are negative:** no further treatment is indicated • **If the margins are positive:** repeat conization versus radical trachelectomy should be performed
Stage IA2	Two options can be performed: • Conization with pelvic lymph node dissection • Radical trachelectomy with pelvic lymph node dissection
Stage IB1	Radical trachelectomy with pelvic lymph node dissection

- **Radical surgery:**

Management is determined by disease stage:

Stage		Treatment
Stage I	Stage IA1 Tumour confined to the cervix (≤ 3 mm in depth and ≤ 7 mm in width)	• Simple hysterectomy (if there is no lymphovascular invasion) • Radical hysterectomy with pelvic lymphadenectomy (if there is lymphovascular invasion)
	Stage IA2 Tumour confined to the cervix, stromal invasion 3-5 mm, and ≤ 7 mm in width	• External beam radiation therapy (EBRT) to the pelvis + brachytherapy OR • Radical hysterectomy with pelvic lymph node dissection and sampling of para-aortic lymph nodes
	Stage IB1 clinical lesions ≤ 4 cm in size	• Same as stage IA2 • Chemotherapy may be given with radiation (concurrent chemoradiation).

	Stage IB2 clinical lesions greater than 4 cm in size	• Chemoradiation (primary treatment): ▪ Chemotherapy: cisplatin or cisplatin plus fluorouracil. ▪ Radiation: both external beam radiation and brachytherapy. • Radical hysterectomy with pelvic lymph node dissection and para-aortic lymph node sampling in addition to concurrent chemoradiation if lymph nodes are positive, or in the presence of positive margins
Stage II	Stage IIA Involvement of the lower third of the vagina	Same as stage IB1
	Stage IIB parametrial involvement not reaching the pelvic side wall	Chemoradiation
Stage III IIIA: no extension to the pelvic wall, but involvement of the lower third of vagina IIIB: extension to the pelvic wall, or hydronephrosis or nonfunctioning kidney due to the tumor		Chemoradiation
Stage IV	Stage IVA spread of growth to adjacent pelvic organs	Chemoradiation
	Stage IVB spread to distant organs	Palliative treatment

Hormonal Therapy After Gynecologic Cancer Treatment

Hormone replacement therapy

Hormone replacement therapy (HRT) may be indicated in menopausal women with history of gynaecologic cancer treatment either those who undergo natural menopause or surgical menopause secondary to cancer surgery. The following summarizes safety of HRT in these women:

Malignancy	Type	Stage	HRT recommendation
Ovarian	Epithelial	Any	Limited data
	Germ cell		Avoid
	Sex cord stromal		Avoid
	Borderline		Avoid/use cautiously
Endometrial	Type 1 (Endometrioid)	I and II	Estrogen only if no concerns of possible occult foci (adequately staged); otherwise, continuous combined regimen is used
		III and IV	Avoid
	Type 2		Avoid
Cervical	Squamous cell	I and II	Estrogen only if previous hysterectomy; otherwise, continuous combined regimen is used
		III	Avoid/use cautiously
		IV	Avoid/use cautiously
	Adenocarcinoma	Any	Avoid/use cautiously

Vaginal	Squamous cell	Any	Estrogen only if previous hysterectomy; otherwise, continuous combined regimen is used
	Non-squamous cell		Avoid
Vulval	Squamous cell	Any	Oestrogen only if she had previous hysterectomy; otherwise, continuous combined regimen is used
	Non-squamous cell		Avoid

Alternatives to hormonal therapy

Women who experience vasomotor symptoms and in whom HRT should be avoided can be offered other options, which are generally similar to options offered when HRT is contraidicated. These options include:

- Lifestyle modifications
- Non-hormonal medications including venlafaxine, fluoxetine, paroxetine, citalopram, clonidine or gabapentin.
- Complementary medicines such as isoflavones, black cohosh or St John's wort should NOT be recommended.
- Acupuncture is generally of poor quality.
- Cognitive behavioural therapy (CBT) can be used to treat low mood or anxiety as a consequence of the menopause.

Gynaecologic oncology

Abstract

Despite all ongoing clinical and research efforts, cancer remains the most challenging disease in all medical specialties. Although modern medicine has managed to control some types of cancers such as cervical cancer though effective screening strategies, other types, such as ovarian cancer,

remain frustrating since there is no efficient way to screen or diagnose them early. In this chapter, we will discuss screening, diagnosis, and management of common gynaecologic cancers.

Keywords

Ovarian cancer, endometrial cancer, cervical cancer, cervical screening

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