UROGENITAL SYSTEM

PATHOLOGY OF THE FEMALE GENITAL TRACT

Learning Objectives:

- Know the common tumour or tumour-like lesions in the vulva, vagina, cervix, uterine corpus, Fallopian tubes and ovaries
- Understand the principles of cervical cancer screening
- Understand the risk factors of cervical cancer

VULVA AND VAGINA

The vulva is prone to many of the non-neoplastic and neoplastic skin conditions seen elsewhere in the body. The vagina may also be affected. May present with pruritus vulva, leukoplakia or mass.

I. Inflammation (refer to “Pathology of Male Genital Tract”)

II. Non-neoplastic epithelial disorders of the vulvar skin and mucosa

A. Lichen Sclerosis
   • Skin and mucosa become atrophic and friable with fissures, adhesions and introital stenosis.
   • Hyperkeratosis with thinning of the epidermis and flattening of the dermo-epidermal junction.
   • Hyalination of upper dermal collagen with subjacent band of cheonic inflammatory cells.

B. Squamous hyperplasia
   • Hyperplasia of the stratified squamous epithelium with no specific dermatological diagnosis.

III. Neoplasia

A. Vulvar intra-epithelial neoplasia (VIN) and Vaginal intra-epithelial neoplasia (VAIN)
   • Associated with HPV infection. The average age of patients is decreasing.
   • VIN I to III, depending on the thickness of the vulval epithelium involved by dysplastic squamous cells. (Refer to “Cervix”)
   • May progress to invasive carcinoma.

B. Invasive squamous cell carcinoma (SCC)
   • VIN or VAIN is present in the adjacent mucosa or skin in about 70% of cases.
   • Extends locally and by lymphatic spread to inguinal then later to pelvic lymph nodes.
   • May be associated with a second malignancy, usually cervical (CIN/invasive).

C. Adenocarcinoma
   • In the vagina, secondary tumours are much more common than primary tumours.
   • Primary adenocarcinoma in young girls is associated with vaginal adenosis and intrauterine Diethylstilboestrol (DES) exposure.
   • Extramammary Paget’s disease (in-situ adenocarcinoma) may also occur in the vulva.
UTERUS - CERVIX

I. Inflammation (refer to “Pathology of Male Genital Tract”)

II. Endocervical Polyp
- Common lesion. Most are single and less than 1 cm in diameter.
- Usually asymptomatic but may result in vaginal bleeding or discharge.

III. Cervical Neoplasia

A. Cervical Intra-epithelial Neoplasia (CIN)
- Arise from transformation zone of cervix
- The dysplastic cells show increase in nucleus / cytoplasmic ratio, nuclear pleomorphism, increased and abnormal mitotic figures, i.e. features associated with malignant cells.
- CIN is graded into 3 grades: I-III, reflecting the degree of involvement.
- Whilst a significant portion of CIN, especially that of CIN I may spontaneously regress, it is not possible to judge which individual case of CIN will progress, regress, or remain stationary.
- May progress to SCC of cervix over years (form the basis of cervical cancer screening).

B. Invasive squamous cell carcinoma

Incidence:
- 7th commonest cancer in HK females.
- It can occur at any age from the 2nd decade onwards, with a peak at the 4th to 5th decades.

Gross:
- Early lesions may produce focal induration, shallow ulceration or slight granularity
- The more advanced lesion may be either exophytic or endophytic.

Microscopy:
- Keratinising,
- Large cell non-keratinising (Majority)
• Small cell non-keratinising
• Microinvasive carcinoma of cervix - a subgroup of SCC which has only invaded the cervical stroma superficially, with relatively small chance of lymph node metastasis and thus can be treated conservatively (cone biopsy or simple hysterectomy).

**Dissemination:**
• Spreads locally to invade contiguous pelvic structures. Ureteric involvement may cause obstruction and subsequent renal failure.
• Regional and distant LN may also be involved early.

C. **Adenocarcinoma**
• Adenocarcinoma is the commonest of the remaining 10-25% of cervical malignancies.
• It usually arises from the endocervical epithelium and may have an intra-epithelial phase, glandular dysplasia and adenocarcinoma in situ.

**Aetiology of carcinoma of the cervix**
• Risk factors reported for SCC: early marriage, early pregnancy, increased parity, sexual promiscuity, sexually transmitted disease, smoking, low socio-economic status and immunocompromised state.
• Human Papilloma Virus: (>70 types HPV found)
  ✓ Low risk HPV: associated with low grade CIN and condyloma accuminatum or planum e.g. HPV types 6 and 11
  ✓ High risk HPV: associated with high grade CIN, invasive carcinoma of the cervix (SCC & adenocarcinoma), vulva and vagina (e.g. HPV types 16, 18, 31, 33, 35, 45, 56, 68).
• Interaction with tumour suppressor genes, such as p53, is involved.
• Relationship between men with penile warts and the presence of CIN in their partners.

**Detection of carcinoma of cervix:**
1. Exfoliative cytology “Pap smear”:
• Microscopic examination of the cells obtained from scraping the squamo-columnar junction is a convenient and inexpensive method to detect cervical neoplasia.

<table>
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<th>Cytology (Bethesda System)</th>
<th>Biopsy</th>
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<td>Low grade squamous intraepithelial lesion</td>
<td>CIN I, HPV changes (koilocytosis)</td>
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<tr>
<td>High grade squamous intraepithelial lesion</td>
<td>CIN II, CIN III</td>
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2. Colposcopy and biopsy:
• Colposcopy is used by the gynaecologist to identify cervical neoplasia by observing changes in the surface epithelium and the vascular pattern and make directed biopsies.
• It can also assess the extent of the disease.

**ENDOMETRIUM (UTERINE CORPUS)**

A. **Inflammation**
• Acute and chronic (plasma cell infiltrate)
• Related to abortion, parturition, retained products of gestation, pelvic inflammatory disease, IUD users, tuberculosis

B. **Endometrial polyp**
• Consists of a local overgrowth of endometrium. May cause abnormal bleeding.
• Malignant change is rare.
C. **Endometrial Hyperplasia**
- Related to hyper-estrogen stimulation: ovarian tumours (such as a functioning theca cell and granulosa cell tumour), repeated anovulatory cycles, or prolonged exogenous oestrogen use.
- Risk factors: obesity, diabetes, hypertension, infertility.
- The endometrium may be focally or diffusely involved.
- Histological types: Simple hyperplasia, Complex hyperplasia and Atypical Hyperplasia
- Atypical hyperplasia carries significant risk (≈ 30%) of progressing into endometrial adenocarcinoma.

D. **Carcinoma of the endometrium**
- The majority are endometrioid adenocarcinomas which resemble endometrium.
- Risk factors are similar to those related to endometrial hyperplasia.
- May be localized polypoid masses or they can diffusely involve the endometrial surface.
- It may spread locally to the myometrium, parametrium, fallopian tubes, ovaries and pelvis. Para-aortic LN involvement occurs early.

E. **Tumour of the endometrial stroma**
- Tumours with pure endometrial stromal features eg. Stromal Sarcoma.
- Tumours with a combination of stromal (sarcoma) and epithelial (carcinoma) elements (e.g. mixed mullerian tumours)

F. **Gestational Trophoblastic Disease (GTD)**
- GTD encompasses a heterogeneous group of diseases that arise from the placental trophoblasts.
- It includes complete and partial hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumour.
- Choriocarcinoma and PSTT are frank malignant tumours while hydatidiform mole may just be abnormal placentas that are prone to malignant transformation.

**MYOMETRIUM**

A. **Adenomyosis**
- Presence of nests of endometrial glands and stroma within the myometrium.
- Uterus is enlarged with a faintly whorled look on cut surface. Small blood containing cystic spaces may be present.
- Patients often have menorrhagia or dysmenorrhoea.

B. **Smooth muscle tumours**
1. **Leiomyoma**
    - One of the most common tumours in women.
    - Usually multiple and may be found in subserosal, submucosal, or intramural sites.
    - May have effect on fertility and pregnancy.
    - Tend to increase in size during pregnancy and undergo atrophy after the menopause.
    - Well-circumscribed spherical nodules with a white whorled appearance.
    - Composed of bundles of smooth muscle with some fibrous tissue.

2. **Leiomyosarcoma**
    - Less well-demarcated than the benign lesion
    - Often show areas of necrosis and haemorrhage.
    - Increase in cellularity, cytological atypia and mitotic figures.

**FALLOPIAN TUBE**

A. **Inflammation**
- Significance: May impair fertility and predispose to ectopic pregnancy.
• Acute (usually ascending infection via uterine cavity), chronic, and granulomatous (Tuberculous salpingitis due to haematogenous spread).

B. **Ectopic Pregnancy**
• Implantation in any site other than normal uterine location.
• Approximately 90% in the tube.
• Rupture of tubal pregnancy is a medical emergency.

C. **Endometriosis**
• Refers to abnormal foci of endometrial glands and stroma in the tubes.

D. **Tumours**
• Primary carcinoma of the Fallopian tube is rare. Metastasis from genital or extragenital sites has to be excluded. Often the diagnosis is made only at laparotomy.
• Histologically, it is usually a papillary adenocarcinoma.

**OVARY**

A. **Inflammation**

B. **Non-neoplastic cysts**
• Non-neoplastic cysts are the commonest causes of ovarian enlargement.
• Include germinal inclusion cysts, follicular cysts, corpus luteum cysts and theca lutein cysts and are lined by simple epithelium, granulosa cells or theca cells with or without luteinization.
• Often asymptomatic. Torsion may occur producing haemorrhagic infarction and pain while rupture may cause hemoperitoneum. Hormonal effect may be produced related to abnormal production of oestrogen and gonadotrophic hormones.

C. **Ovarian neoplasia** (Simplified classification)
1. **Surface Epithelial Tumours**
   - Histological type
     - a) Serous tumour
     - b) Mucinous tumour
     - c) Endometrioid
     - d) Brenner tumour
     - e) Clear cell
     - f) Undifferentiated
   - Degree of malignancy
     - a) Benign
     - b) Borderline
     - (Low Malignant Potential)
     - c) malignant
     - (invasive carcinoma)

2. **Germ Cell Tumours**
   - a) Teratoma - Mature, Immature, Malignant Transformation
   - b) Dysgerminoma
   - c) Endodermal sinus tumour
   - d) Choriocarcinoma
   - e) Embryonal carcinoma
   - f) Mixed

3. **Sex Cord Stromal Tumours**
   - a) Granulosa cell tumour
   - b) Thecoma - Fibroma
   - c) Sertoli - Leydig cell tumour

4. **Miscellaneous** - e.g. Lymphoma, tumours of mesenchymal origin.

5. **Metastatic tumours**
1. **Surface Epithelial Tumours**
   - "Borderline tumour" or "tumour of low malignant potential"
   - Different from the benign tumour by presence of epithelial budding, increased mitotic activity, nuclear stratification and atypia.
   - Different from malignant tumours by the absence of destructive stromal invasion.
   - Good prognosis

   - Incidence:
     - 60% of all ovarian tumours and about 80% of primary ovarian malignancies.
     - In young patients, most are benign or borderline tumours. Frankly invasive epithelial tumours are uncommon under 40 years of age.

   - Risk factors:
     - Genetic: inheritance of genetic mutation conferring a predisposition to cancer e.g. the breast and ovarian cancer syndrome and the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome.
     - Tumour suppressor genes are involved in these syndromes.
     - Environmental: ? infertility drugs, obesity

   - Clinical presentation:
     - Usually present with symptoms and signs of pelvic mass. Early detected by screening is difficult.
     - Staging depends on the presence of capsular or contralateral ovary involvement, malignant ascites and nodal, pelvic, intreperitoneal or distant metastases.

   a) Serous tumours
      - Neoplastic epithelium resembles that of fallopian tube +/- Psammoma bodies (calcified spherules)
      - May be bilateral, +/- peritoneal lesions.

   b) Mucinous tumours
      - Neoplastic epithelium resembles endocervical glandular epithelium.
      - Occasionally associated with pseudomyxoma peritoneii +/- co-existing appendiceal lesion.

   c) Endometrioid tumours
      - Neoplastic epithelium resembles endometrium.
      - +/- co-existing endometriosis or concurrent endometrioid carcinoma of endometrium

   d) Brenner Tumours
      - Benign form (commonest type) shows round masses of transitional epithelium surrounded by ovarian stroma.

   e) Clear cell tumours
      - Most commonly in form of clear cell carcinoma.
      - Considered to be of poorer prognosis.

2. **Germ Cell Tumours**
   - General Features:
     - Second largest group of ovarian neoplasms (20%)
     - In children and adolescents, > 60% of ovarian neoplasms are of germ cell origin and 1/3 of them are malignant.
     - In adults, the great majority of germ cell tumours are benign: mature cystic teratoma

   a) Teratoma
      (i) Mature Cystic teratoma
      - Complications include torsion, rupture, and malignant change (about 2% and usually a squamous carcinoma).
      (ii) Immature teratoma
(iii) Teratoma with malignant transformation eg. SCC

b) Dysgerminoma (≈ seminoma of testis)
- Occurs in young women.

c) Yolk Sac Tumour / Endodermal sinus tumour (≈ counterpart of testis)
- Occurs in the young female.

d) Choriocarcinoma & e) Embryonal carcinoma
- Usually combined with other germ cell tumours of the ovary.

3. **Sex Cord – stromal tumours**

   ![Diagram of sex cords, granulosa cells, sertoli cells, theca cells, and leydig cells]
   - Granulosa cells (graffin follicle)
   - Sertoli cells (seminiferous tubules)
   - Theca cells
   - Leydig cells

   a) **granulosa Cell Tumours**
   - A low grade indolent malignancy which occurs at all ages, most commonly after menopause.
   - Solid and/or cystic tumour composed of granulosa cells arranged in follicles or trabeculae
   - Excessive estrogen secretion ⇒ precocious puberty in young girls, or abnormal uterine bleeding, endometrial hyperplasia and endometrial adenocarcinoma in adults.

   b) **Thecoma-Fibroma**
   - Benign tumour arising from ovarian stromal cells.
   - Spindle cells resembling fibroblasts to polygonal cells resembling theca cells.

   c) **Sertoli-Leydig Cell Tumours**
   - Likely to be malignant.
   - Often secrete androgens and cause virilism, breast atrophy, hirsutism and amenorrhea.

4. **Miscellaneous**
   - Malignant lymphomas, or rarely soft tissue tumours (leiomyoma, leiomyosarcoma etc)

5. **Metastatic tumours**
   - Most commonly from carcinoma of breast, lower genital tract and gastrointestinal tract.

**REFERENCES:**