Chapter 3

Female Reproductive Disorders
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This chapter provides brief information about major female reproductive disorders. This will include the following disorders

1. Endometriosis
2. Uterine Fibroids
3. Amenorrhoea
4. Abnormal Uterine Bleeding
5. Dysmenorrhoea
6. Premenstrual Syndrome
7. Pelvic Inflammatory Disease
8. Polycystic Ovarian Syndrome (PCOS)
9. Mullerian agenesis

Endometriosis

Endometriosis is characterized by the presence of ectopic endometrial-like tissue outside the uterine cavity. Some associated symptoms include dysmenorrhoea (pelvic pain with menstruation), dyspareunia (pain with intercourse), chronic pelvic pain and infertility. Meta-analysis studies on endometriosis patients showed about 50% reduction in the pregnancy rates than healthy women, poor ovarian reserve in advance stages of endometriosis, low oocyte and embryo quality and poor implantation (Barnhart et al. 2002, Olivennes et al. 2003). The frequency of endometriosis ranges 6-10% in general female population. The disorder is generally diagnosed by laparoscopy or laparotomy. The etio-pathology of
endometriosis is not exactly known but two common theories are prevalent. First, the possibility of retrograde menstruation may allow viable menstruation debris to attach and implant into pelvic organs and peritoneum. This theory is further supported by the higher volume of refluxed menstrual blood and endometrial-tissue fragments in women with endometriosis than women without the disorder (Halme et al. 1984). These affected women have more frequent subendometrial myometrial contractile waves than healthy controls with an antegrade pattern (Salamanca et al. 1995). Second theory suggests the probable occurrence of coelomic metaplasia in the pelvic peritoneum may result in endometriosis.

Several genetic studies have been carried out for endometriosis for around 25 years. The genetic dissection of the disorder is challenging due to its complex trait nature, different disease stages and surgery based diagnosis. Genetic linkage analysis and affected sibling pairs based genetic studies revealed several candidate genes. These candidate genes include detoxifying enzymes and tumor suppressor genes (Bischoff et al. 2004). The high frequency of loss of heterozygosity and somatic mutations of tumor suppressor genes in endometrial cysts sets women with endometriosis at high risk of ovarian cancers (Giudice et al. 2002).

**Uterine Fibroids**

Uterine fibroids or leiomyomas are benign myometrial neoplasms enriched in extracellular matrix. The prevalence rates of this disorder are reported in a range of 20-50% among various populations (Bajekal et al. 2000). The advance stages of the disorder are major cause of hysterectomy.
Obesity and early menarche are major risk factors for leiomyomas due to increased exposure of estrogen. Leiomyomas are morphologically similar with parturient myometrium including increased production of extracellular matrix (ECM), the expression of receptors for peptides and steroid hormones and expression of connexin 43 (required for cell-cell communication). Unlike parturient myometrium, leiomyomas fail to regress by apoptosis (Cesen-Cummings et al. 2000). Fibroids can be classified as submucous, intramural and subserosal. Submucous fibroids cause the distortion of the uterine cavity. Intramural fibroids do not cause distortion of uterine and the protrusion is <50% into the serosal surface of uterus whereas subserosal fibroids cause >50% protrusion into the serosal surface of uterus. Submucous and intramural fibroids can impair uterine contractility, sperm migration, ovum transport or nidation (Vollenhoven et al. 1990). Leiomyomas can also cause implantation failure, gestation discontinuation due to vascular perturbation of endometrium, inflammation and secretion of vasoactive substances. After completing the families, women with this disorder generally opt for hysterectomy to avoid recurrence of fibroids and other menstrual disturbances.

**Amenorrhoea**

Amenorrhea is defined as the absence or cessation of menstruation in a woman of reproductive age. Amenorrhea can be classified basically as primary and secondary amenorrhoea.

Primary amenorrhea is defined as the complete absence of menstruation or spontaneous vaginal flow with or without development of
secondary sexual characteristics. The causes for amenorrhea could be either anatomical or endocrinal. Anatomical factors include either complete absence or defect in uterus or vagina (Baird et al. 1997). Other major factors are Gonadal dysgenesis, Turner's syndrome, Mullerian agenesis, Androgen insensitivity syndrome etc. Primary amenorrhoea cases are evaluated by the presence or absence of secondary sexual characteristics (eg, breast development, pubic hair etc) hormonal levels such as FSH and LH, ultrasonography of the uterus and karyotype analysis (Master-hunter and Heiman 2006).

Secondary amenorrhea is defined as absence of menstruation for a period of three months in a woman with previous normal cycles or for a period of six months in a woman with previous irregular cycles. This type is more common than the primary amenorrhea. The major causes for this could be pregnancy, anovulation, menopause, hypothalamic-pituitary dysfunction, etc. In this pregnancy, lactation and menopause are considered absolutely physiological and hence not pathological. The secondary amenorrhea is evaluated on the basis of negative pregnancy test, levels of different hormones such as TSH and prolactin, progesterone challenge test, MRI to evaluate for prolactinoma (Master-hunter and Heiman 2006).

Management or treatment of the amenorrhoea cases depends on the presenting symptoms or of the underlying problems of the individual patients such as hypothyroidism, hyperprolactenemia, Hypergonadotropic hypogonadism etc. If PCOS is the underlying factor then weight loss will be the immediate remedy. Secondary amenorrhea responds mostly to gonadotropins which induces ovulation (Mclver et al. 1997).
Abnormal Uterine Bleeding

Excessive bleeding during menstrual cycles is defined as abnormal uterine bleeding (AUB). Normal menstrual cycle flow lasts 3-7 days with the majority of blood loss occurring within first three days. Normal menstrual blood flow amounts to 35ml consisting of effluent debris and blood. The excess blood flow amounting 80-100ml is clinical indication of AUB. AUB can be classified as either anovulatory bleeding or ovulatory dysfunctional bleeding. Anovulatory bleeding is generally due to failure of corpus luteum to sustain developing endometrium. Anovulatory bleeding can be continuous or episodic. AUB patients have high levels of plasminogen activators than normal female. Anovulatory bleeding is generally associated with puberty and perimenopausal years. Ovulatory dysfunctional bleeding occurs when ovulatory cycles coexist with intracavitary lesions including fibroids, polyps, hyperplasia, endometrial cancer, which cause excessive bleeding. Such patients also have associated symptoms like premenstrual cramping, breast discomfort, elevated mucoid vaginal discharge midcycle, bloating, mood and appetite changes. AUB can be due to pregnancy related etiologic factors like abortion, retention of conception debris, endomyometritis, ectopic and trophoblastic disease. AUB becomes a serious threat when there is any family history of blood diathesis (coagulation abnormality) or epistaxis. AUB can result in anemic condition, sexual compromise and embarrassment.
Dysmenorrhoea

Dysmenorrhoea is chronic, cyclic pelvic pain associated with menstruation. Typically it is cramping, lower abdominal pain occurring just before and/or during menstruation, usually commencing soon after menarche once regular ovulation is established. Dysmenorrhoea affects nearly 90% of menstruating women. The common associated symptoms include nausea, vomiting, diarrhea and fatigue. Dysmenorrhoea is common in women with premenstrual syndrome. Dysmenorrhoea is not a serious problem but may affect person's daily life, social disabilities. Psychological problems such as anxiety, depression, family and marital disharmony, drug and alcohol abuse, physical and sexual abuse and sexual dysfunction may manifest as physical pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid and naproxen can be very effective in relieving dysmenorrhoea. Continuous ignorance of dysmenorrhoea may lead to more severe symptomatic stage called secondary dysmenorrhoea. Secondary dysmenorrhoea may be any of these disorders like adenomyosis, menorrhagia, fibroids, miscarriages, endometriosis, ovarian carcinomas etc (French et al. 2005).

Premenstrual Syndrome

Premenstrual syndrome (PMS) is characterized by emotional and physical symptoms consistently occurring during the menstrual cycle's luteal phase (the phase that begins with ovulation and ends with the onset of menses) (Campagne et al. 2007). The common symptoms of PMS are
depression, irritability, angry outburst, tension and dysphoria. Somatic symptoms include breast tenderness, abdominal bloating, headache and extremity swelling. The etiology of PMS is still unknown but the changes at neurotransmitters and neurohormonal levels by ovulation may possibly account for this. Around 3-5% of menstruating women get affected by more severe form of PMS, known as premenstrual dysphoric disorder (PMDD). PMS or PMDD patients should maintain a symptoms calendar which accurately measures a daily rating of the symptoms and their severity. The physical examinations including weight, blood, thyroid, abdominal and pelvic examinations should be performed for diagnosis.

**Pelvic Inflammatory Disease**

Pelvic inflammatory disease (PID) is defined as inflammation of the upper genital tract including the endometrium, fallopian tubes, and/or contiguous structures that follows infection from micro-organisms that ascend from the cervix and/or vagina (Westrom et al. 1984). The associated symptoms are abdominal pain, dyspareunia, fever, back pain, vomiting, abnormal vaginal discharge or bleeding, itching or odor. Severe infection may cause infertility or ectopic pregnancy. The common infectious agents are *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium* and aerobic and anaerobic vaginal flora. Sexually transmitted infections (STIs) such as gonorrhoeae and Chlamydia account for 33-50% of PID infections. Some procedures like Intrauterine device (IUD) insertion, dilatation, curettage and operative termination of pregnancy (TOP) may also introduce infections and PID. Other risk factors include young age, high
frequency of partner change, lack of barrier contraception, low socio-economic group and smoking. Laparoscopy is highly useful for the diagnosis of PID but is invasive, costly and impractical. Vaginal/urinal/cervical swabs can be tested to detect the Chlamydia by PCR, gonorrhoeae and other organisms by bacterial cervical culture. Antibiotics can be used for the treatment of such infections in cases of PID.

Polycystic Ovarian Syndrome (PCOS)

Polycystic Ovarian Syndrome, also known clinically as Stein-Levinthal Syndrome is an endocrine disorder that affects about 4-8% of women of reproductive age. There are numerous definitions available to diagnose PCOS. However, according to a consensus workshop held in 2003, PCOS can be diagnosed if two of the following three criteria are met: 1) Oligoovulation and/or Anovulation 2) excess androgen activity 3) Polycystic ovaries.

Three major hypotheses exist to explain the pathology underlying PCOS. They are, (Matalliotakis et al 2006)

(1) LH Hypothesis: This is a primary neuroendocrinal defect resulting in LH excess leading to ovarian hyderandrogenism and anovulation.

(2) Insulin Hypothesis: A defect in insulin metabolism leads to hyperinsulinaemia which results in excess androgen secretion and anovulation.

(3) Ovarian Hypothesis: A primary defect in sex steroid synthesis or metabolism which leads to exaggerated ovarian androgen synthesis and anovulation.
A fourth hypothesis includes the presence of polycystic ovary which is confirmed by histological method or by pelvic ultrasound.

The common signs and symptoms of PCOS include Amenorrhea, Oligomenorrhea, Infertility, Chronic pelvic pain, Obesity (Centered around the lower part of the tarso), Acne etc. Other symptoms include multiple cysts on the ovaries (looks like a string of pearl), enlarged ovaries, ratio of LH: FSH > 2 or 3 etc.

PCOS has a familial inheritance in that it is commonly found in the family members than in the general population (Legro RS and Strauss JF 2002). It appears to be inherited as a complex genetic trait. Mainly the steroid synthesis gene CYP11α and the regulatory polymorphism in the insulin gene VNTR are found to be associated. This could account for the variation in the androgen production and insulin resistance found in these patients (Matalliotakis et al 2006). The main candidate genes studied are related to steroidal biosynthesis and action, gonadotropic action, weight and energy regulation and insulin action (Goodarzi MO and Azziz R 2006).

The treatment for PCOS is focused towards decreasing androgen levels to improve hirsutism, protecting the endometrium and rectifying insulin resistance (King J 2006) Simple measures for obese patients would include weight reduction by calorie restriction and exercise.

**Mullerian agenesis**

Mullerian agenesis is a congenital malformation of the genital tract and a common cause of primary amenorrhea. Three dimensional ultrasonography and magnetic resonance imaging can be used for diagnosis
of primary amenorrhoea/Mullerian agenesis. These patients have undeveloped or absent uterus/vagina. The mullerian tissues are rudimentary, located over the pelvic brim on both sides. The incidence rate is estimated around 1 in 4000-5000 female births. The etiology of the disorder is largely unknown but hypothetically activating mutations in AMH gene (Anti Mullerian Hormone) or its receptor may cause such abnormalities. The AMH is responsible for the regression of mullerian duct during fetus development. This hormone plays very important role in differentiating the development of testis from undifferentiated gonads in male during fetus development. The expression of this hormone is repressed in female fetus hence development of mullerian ducts and other major reproductive parts take place. In case of activating mutations in AMH or its receptor may induce regression of mullerian ducts as well as other reproductive parts. The non-surgical treatment includes progressive use of dilators and surgical treatment is Abbe McIndoe technique to correct vagina. This surgical method involves the construction of vaginal cavity at the site of vaginal dimple by making an H-shaped incision in the space between the urethral opening and the posterior fourchette (Folch et al. 2000).