CASE 4

Short case number: 3_18_4
Category: Endocrine & Reproductive Symptoms
Discipline: Obstetrics & Gynaecology
Setting: General Practice
Topic: Chronic Pelvic Pain-Endometriosis

Case
Juliette Forster, is 18 years old and presents with a history of pelvic pain, over the last 6 months she has experienced increasing pain in the week before her periods, sometimes it is so bad that she needs to take time off work. She has experienced period pain in the past, but this pain is different and worse that her 'usual' period pain. **Ponstan and naprogesic are not helping and she is concerned about having to take medication with every menstrual cycle.**

Questions

1. What are the key features of history and examination that will assist in differentiating the key cause of chronic pelvic pain?
2. What features of history and examination would support a diagnosis of endometriosis?
3. You think that Juliette may have endometriosis, how would you explain the aetiology of endometriosis and the clinical symptoms she may experience?
4. What investigations would you undertake in your assessment of Juliette and why?
5. Juliette undergoes a laparoscopy, outline the use of laparoscopy in the assessment of chronic pelvic pain and summarise the frequency of the findings.
6. Juliette is diagnosed with endometriosis, outline the complications of endometriosis.
7. In your management of Juliette, outline the aims of treatment and the use of hormonal and surgical treatments that assist in the achievement of these aims.
8. What are the indications, contraindications and side effects of danazol and GnRH agonists in the treatment of endometriosis?

Suggested reading:

1. Abbott, J., Bowyer, L., & Finn, M. (2014). *Obstetrics and Gynaecology: an evidence-based guide (2nd ed).* Australia, Elsevier.
2. Stones, W.R.(2007). Chronic pelvic pain. In K. Edmonds (Ed.), *Dewhurst's Textbook of Obstetrics & Gynaecology* (Chapter 43) Blackwell Publishing.
3. Kennedy, S., & Koninckx, P. (2007). Endometriosis. In K. Edmonds (Ed)., *Dewhurst's Textbook of Obstetrics & Gynaecology* (Chapter 44) Blackwell Publishing.
4. Australian Medicines Handbook 2015.

ANSWERS

1. **What are the key features of history and examination that will assist in differentiating the key cause of chronic pelvic pain?**
   HISTORY

   Pain Nature, site, radiation, severity, onset
   Frequency and duration
   Relationship to menstrual cycle / sexual intercourse
   Aggravating/ relieving factors
   Assess impact on lifestyle e.g. Days off work
   Menstrual history
   Gynae/ surgical/ obstetric history
   Social history including relationship and sexual partners.
   History mental/physical abuse including domestic violence
   Pyschiatric and orthopedic history including postural problems
   Previous therapy and effectiveness, allergies

   Gynae cause more likely where related to specific phases of menstrual cycle/ sexual intercourse. Otherwise urinary gastro and musculoskeletal symptoms should be elicited.

   EXAMINATION
   General and Gynae examination (if never been sexually active nil vaginal examination)

2. **What features of history and examination would support a diagnosis of endometriosis?**
   Clinical presentations:
   Asymptomatic endometriosis: Factors assoc with reduced risk of endometriosis are an irregular cycle, >2 births, >1 TOP. May present with an adnexal mass.

   Pain: Progressively increasing dysmenorrhoea, deep dyspareunia and chronic pelvic pain. There is often a poor correlation between symptoms and extent of disease. May have dyschezia or cyclical changes in bowel movements.

   Infertility: Mechanisms; interference with ovum transport, mechanical disruption of normal tubo-ovarian anatomy, impaired oocyte quality, (cytokines released from ectopic endometriotic deposits adversely affecting oocyte and embryo quality), Iatrogenic (suppressive hormone therapy and destructive surgery), relative endometrial progesterone resistance.

   Cyclic bleeding: In any organ system may be due to endometriosis

   Examination:
   Normal
   Fixed retroversion of the uterus
   Tender nodularity of uterosacral ligaments
   Ovarian endometriomas

3. **You think that Juliette may have endometriosis, how would you explain the aetiology of endometriosis and the clinical symptoms she may experience?**
   Theories of Pathogenesis:
   Retrograde menstruation – described in up to 80% of menstrual cycles
   Immunological theory – interplay of enhancing/suppressing genes + environment
   Abnormal proliferation – Angiogenesis, release of cytokines and inflammatory mediators appear to be part of disease process
   Direct spread – Via surgical transplantation, blood vessels, lymphatics. Explains remote locations and presence in episiotomy/abdominal wounds
   Metaplasia – constant irritation by retrograde menstruation may cause metaplasia of similarly derived embryonic tissue such as the pelvic peritoneum.

   PERITONEAL ENDOMETIROSIS
   Superficial lesions scattered over the peritoneal, serosal and ovarian surfaces.
   - Menstrual effluent containing viable cells is transported into the peritoneal cavity in a retrograde direction along the fallopian tubes, and implants on exposed tissue. Increased risk where this is increased menstrual exposure (short cycles, prolonged bleeding, obstructed outflow)
   - Expression of cell adhesion molecules, proteolytic enzymes and cytokines affecting the implantation and proliferation of tissue may differ between women.
   - Changes in systemic humoral immunity have been implicated (higher rates of endometriosis in women with autoimmune diseases)

   OVARIAN ENDOMETROSIS
   Ovarian endometriomas
   - Superficial lesions on the ovarian cortex become inverted and invaginated, and that endometriomas are derived from functional ovarian cysts or metaplasia of the coelomic epithelium covering the ovary.
   - Endometriomas have features in common with neoplasia such as clonal proliferation, and are associated with subtypes of ovarian malignancy (e.g. endometrioid and clear cell carcinoma)

   DEEPLY INFILTRATING DISEASE
   DIE nodules extend >5mm beneath the peritoneum and may involve the uterosacral ligaments, vagina, bowel, bladder and uterus.

4. **What investigations would you undertake in your assessment of Juliette and why?**
   Endometriosis can only be accurately diagnosed by laparoscopy (and confirmed by histology of biopsy). Ultrasound may detect small endometriomas within the ovary, presence of pelvic adhesions by a lack of mobility of the bowel and "fixation" of the ovaries.

5. **Juliette undergoes a laparoscopy, outline the use of laparoscopy in the assessment of chronic pelvic pain and summarise the frequency of the findings.**
   Laparoscopy is the gold standard for diagnostic purposes, unless disease is visible in the vagina or elsewhere. Histological confirmation of at least one peritoneal lesion is ideal (and

mandatory if DIE or >3cm). The entire pelvis, appendix and upper abdomen should be examined.

	Number of studies	% with disease
Pelvic pain	15	4.5 – 62%
Infertility	32	2.1 – 78%
Sterilisation	13	0.7 – 43%

6. Juliette is diagnosed with endometriosis, outline the complication of endometriosis.

Pain – dysmenorrhoea, dyspareunia, chronic pelvic pain, ovulation pain
Chronic Fatigue
Subfertility

7. In your management of Juliette, outline the aims of treatment, and the use of hormonal and surgical treatment that assist in the achievement of these aims.

Treatment aims may be:

Improve natural fertility
Enhance chances of success at assisted reproduction
Pain relief

Hormonal treatment (COCP, progestagens, danazol, gestrinone, GnRH agonists)

- All appear to induce atrophy and decidualization of peritoneal deposits by suppressing ovarian function.
- Peritoneal and DIE lesions decrease in size, during therapy but reappear rapidly after treatment. Endometriomas rarely decrease in size and adhesions will be unaffected
- All reduce the total amount of pain, but the effects on non-menstrual pain is variable
- Hormonal treatment for subfertility does not improve the chances of natural conception.

Surgical Treatment

- The goal of surgery is to eliminate all visible peritoneal lesions, endometriomas, DIE and assoc adhesions and to restore normal anatomy.
- Ablation of lesions + LUNA (laparoscopic uterine nerve ablation) in mild-mod disease reduces pain at 6 months compared to diagnostic laparoscopy. LUNA is not common in practice, excision of lesions rather than ablation (diathermy / laser) where possible.
- Ablation of lesions + adhesiolysis in min-mild endometriosis enhances fertility. No RCT have been conducted for mod-severe disease.
- Ovarian endometriomas should be removed via laparopscopic cystectomy
- If there is clinical evidence of DIE, the possibility if ureteric, bladder and bowel involvement should be considered pre-op.

8. What are the indications, contraindications and side effects of danazol and GnRH agonists in the treatment of endometriosis.

Rationale for drug use

Relieve pain (dysmenorrhoea, dyspareunia, other pelvic pain) and other symptoms.
Induce atrophy within ectopic endometrium (hormonal treatment)

Drug choice

Treatment should be individualised according to age, symptoms, extent of disease and pregnancy plans.

Hormonal treatments include COCs, progestogens, danazol, gestrinone and GnRH agonists. They induce atrophy within ectopic endometrium either by suppressing oestrogen activity or by suppressing ovarian oestrogen production. All are equally effective in reducing pain but they differ in terms of adverse effects and cost.

NSAIDs

May be adequate for symptom relief in some women and can be used with other treatments. They are effective in relieving dysmenorrhoea, however, evidence is inconclusive regarding their effect on pain due to endometriosis.

Combined oral contraceptives

Can be taken long term and are usually well tolerated. Both cyclical and continuous regimens are used but there is no evidence that one regimen is more effective than the other. However, 'tricycling' (having a pill-free interval once every 3 months) may be useful in women with dysmenorrhoea.

Progestogens

Norethisterone, dydrogesterone and IM or oral medroxyprogesterone can all be used long term. Adverse effects include irregular bleeding and weight gain. Continuous oral progestogens and IM medroxyprogesterone also provide contraception if no doses are missed. Limited evidence suggests the levonorgestrel IUD may also be effective in reducing pain associated with endometriosis.

Danazol, gestrinone

Danazol and gestrinone both have androgenic adverse effects that limit their use: duration of treatment is 6–9 months with danazol and 6 months with gestrinone. An effective non-hormonal method of contraception must be used during treatment.

Gonadotrophin-releasing hormone agonists

The GnRH agonists are associated with hypo-oestrogenic adverse effects such as hot flushes, vaginal dryness and decreased BMD. Duration of treatment is limited to 6 months due to loss of BMD. Adding combined HRT allows treatment for up to 2 years (reduces these adverse effects and protects against BMD loss while maintaining efficacy). An effective non-hormonal method of contraception must be used during treatment (to avoid pregnancy in the event of missed doses).

	Danazol	GnRH agonists
Contraindications	• History of thromboembolic disorder • Androgen-dependent tumour • Severe hepatic impairment • Unexplained vaginal bleeding—(investigate first) • Pregnancy and breastfeeding (If taken by the mother at or after 8 weeks post conception, danazol can cause virilisation of the female foetus)	• Unexplained vaginal bleeding • Women at risk of low BMD, e.g. weight-related amenorrhoea, immobilisation, corticosteroid use, family history of osteoporosis • Polycystic ovarian disease—risk of cystic enlargement at the beginning of the treatment. • Pituitary adenoma—risk of pituitary apoplexy; avoid use. • Pregnancy and Breastfeeding
Precautions	• Cardiac disease, epilepsy, migraine—may be worsened due to fluid retention. • Diabetes—glucose tolerance may be impaired. • Renal - risk of oedema • Contraception - may not inhibit ovulation in all women	
Side effects	Weight gain Bloating Increased body hair Acne and oily skin Deep voice (irreversible) Decreased breast size Muscle cramps Headaches Hot flushes Limb tingling Decreased libido Menstrual spotting	Hot flushes Night sweats Headaches Vaginal dryness Irritability Insomnia Decreased libido Palpitations Joint stiffness
Complications	Liver tumours Adverse effects on lipids	Bone loss 'Flare' effect