Endometriosis & Cancer Association

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Disclosures

- None

Learning objectives

- Identify the epidemiology and classification of endometriosis
- State the impact of atypical endometriosis on malignant gynecologic tumours
- Discuss potential ways to prevent future ovarian cancer in women with endometriosis

Learning objectives

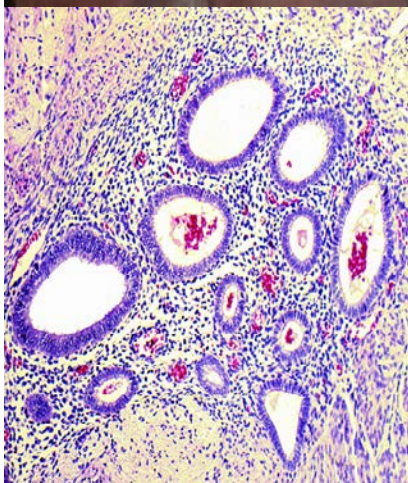
- **Identify the epidemiology and classification of endometriosis**

- State the impact of atypical endometriosis on malignant gynecologic tumours

- Discuss potential ways to prevent future ovarian cancer in women with endometriosis

Endometriosis

- 1 in 10 reproductive-aged women (~1 million in Canada)
- ~$2 billion and ~$50 billion in annual costs in Canada and the United States

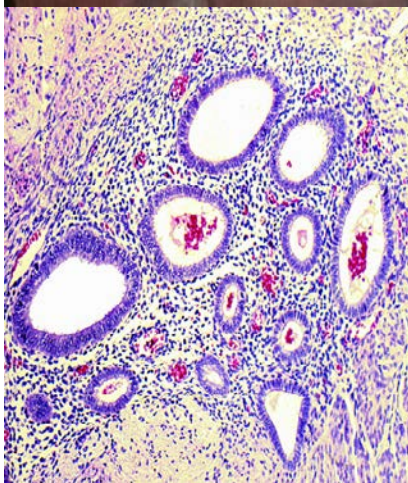


Levy et al. JOGC 2011;33:830-7
Simoens et al. Hum Reprod Update 2012;27:1292-9

Endometriosis

- Definition:
  - Uterine endometrial tissue, present ectopically elsewhere in the pelvis (or elsewhere)

- Etiology
  - Retrograde menstruation/Immune
  - Metaplasia
  - Blood/lymphatic dissemination



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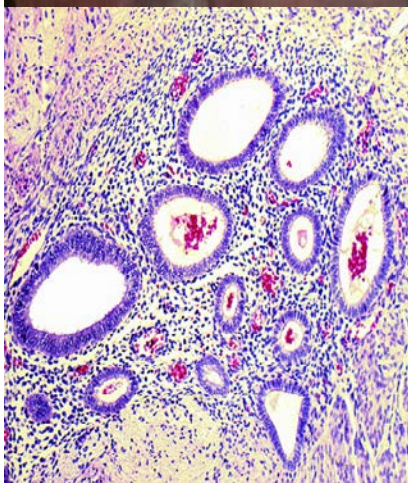
Endometriosis

- Pathophysiology
  - Lesions
    - Estrogen-dependent (systemic and local)
    - Inflammation (prostaglandins)
    - Genetics (inherited and somatic)
  - Uterus
    - Similar changes as in ectopic lesions
  - Comorbidities
    - Myofascial, Urologic, Gastrointestinal
    - Central sensitization



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Symptoms

- Pelvic pain
  - Menstrual cramps
  - Painful intercourse (deep)
  - Painful bowel movements
  - Cyclical or chronic pelvic pain
- Infertility
- Asymptomatic

Classification

- Anatomic subtype:
  - Superficial
  - Ovarian
  - Deep

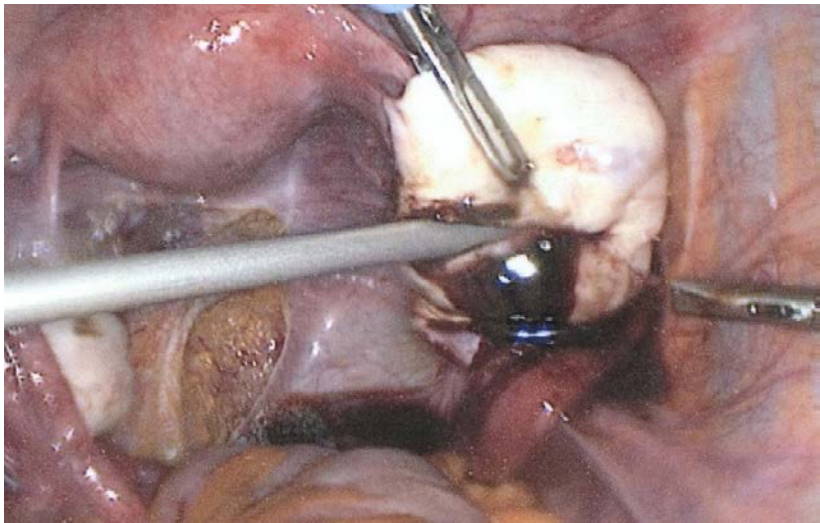
- Stage
  - I/II: minimal-mild
  - III/IV: moderate-severe

Superficial endometriosis

- Superficially attached to peritoneum
- Classically pigmented
- Can have other appearances
  - Red
  - White
  - Increased vascularity

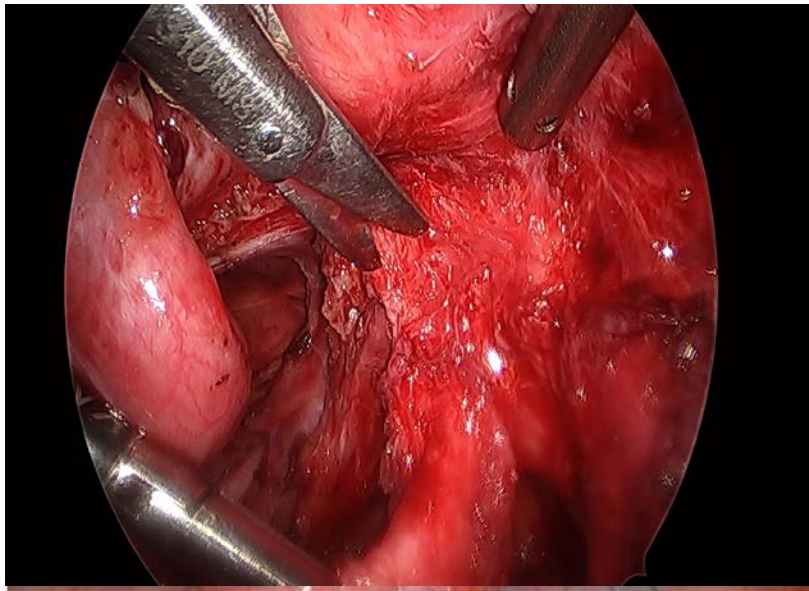
Ovarian endometriomas

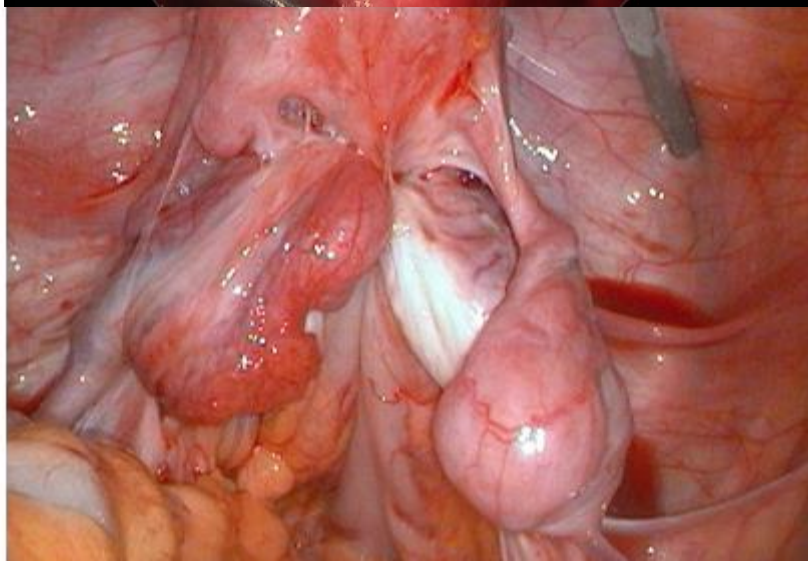
- Chocolate cysts
- Virtually pathognomonic at ultrasound and surgery



Deep endometriosis

- Invasive > 5mm
- Forms “nodules”
- Can “obliterate” the pouch of Douglas





American Society of Reproductive Medicine: Surgical staging of endometriosis

ENDOMETRIOSIS		<1 cm	1-3 cm	>3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	Right Superficial	1	2	4
	Deep	4	16	20
	Left superficial	1	2	4
	Deep	4	16	20
POSTERIOR CUL-DE-SAC OBLITERATION		Partial	Complete	
		4	40	
ADHESIONS		<1/3 Enclosure	1/3 - 2/3 Enclosure	>2/3 Enclosure
Ovary	R Filmy	1	2	4
	Dense	4	8	16
	L filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4[1]	8[1]	16
	L Filmy	1	2	4
	Dense	4[1]	8[1]	16

[1] If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16. Staging: Stage I (minimal): 1-5; stage II (mild): 6-15; stage III (moderate): 16-40; stage IV (severe): >40. Revised ASRM Classification. *Fertil Steril* 1997; 67: 819.

American Society of Reproductive Medicine: Surgical staging of endometriosis

Scoring system for Stages:

Stage	Description	Scoring Range
Stage I	minimal	1-5
Stage II	mild	6-15
Stage III	moderate	16-40
Stage IV	severe	>40

Poorly correlated to symptoms (and malignancy?)

Diagnosis

- Can be suspected based on history and exam
  - Symptoms and/or infertility
  - Tenderness on pelvic exam
- Diagnosis made by surgery and pathology; or
  - Nodularity on pelvic examination
  - Routine or specialized ultrasound
  - MRI
- CA-125 can be elevated; but not a diagnostic or screening tool

Treatment

- Hormonal
  - NSAID
  - Estrogen-progestin contraceptive
  - Progestin (dienogest, norethindrone)
  - Progestin IUD (treatment efficacy can be < 5 yrs)
  - GnRH agonists
- Surgical (laparoscopic)
  - Conservative: ablation or excision
  - Definitive: hysterectomy +/- BSO

Learning objectives

- Identify the epidemiology and classification of endometriosis
- **State the impact of atypical endometriosis on malignant gynecologic tumours**
- Discuss potential ways to prevent future ovarian cancer in women with endometriosis

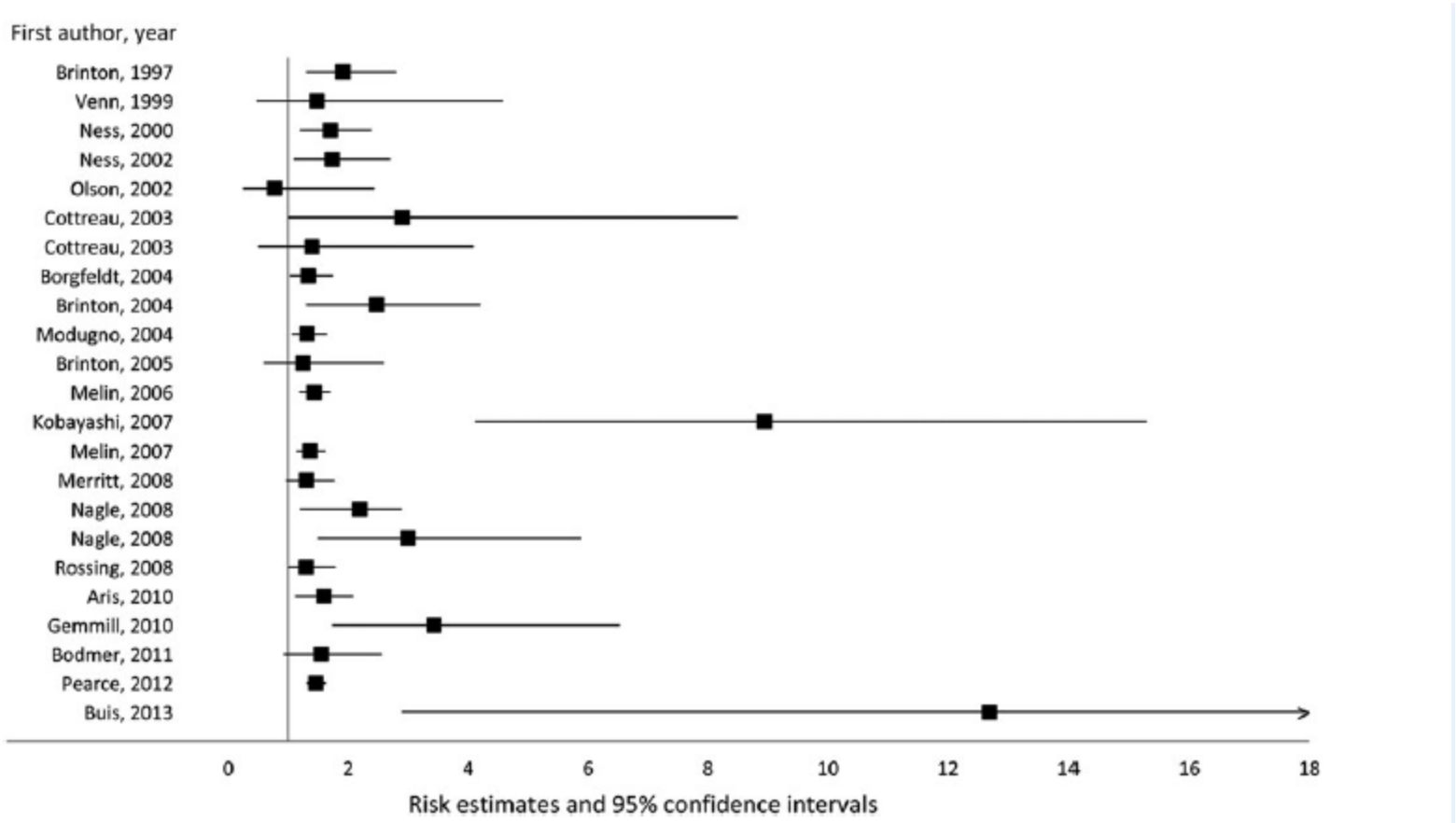
Other clinical implications

- Extra-pelvic endometriosis (e.g. thoracic)
- Pregnancy complications (e.g. placenta related)
- Autoimmune disease (e.g. MS)
- Coronary heart disease
- Cancer
  - Ovarian: higher
  - Endometrial and breast: equivocal
  - Cervical: lower

Human Reproduction Update, Vol.21, No.4 pp. 500–516, 2015

What's the risk of ovarian CA?

- Risk estimates for endometriosis and ovarian CA



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Ovarian CA subtypes

- Endometriosis is a risk factor for clear cell and endometrioid (and low-grade serous?)

	Crude		Stratified only		Stratified and adjusted	
	OR (95% CI)	p value	OR (95% CI)*	p value	OR (95% CI)†	p value
Invasive	1·49 (1·34–1·65)	<0·0001	1·53 (1·37–1·70)	<0·0001	1·46 (1·31–1·63)	<0·0001
Clear-cell	3·73 (3·04–4·58)	<0·0001	3·44 (2·78–4·27)	<0·0001	3·05 (2·43–3·84)	<0·0001
Endometrioid	2·32 (1·94–2·78)	<0·0001	2·20 (1·82–2·66)	<0·0001	2·04 (1·67–2·48)	<0·0001
Mucinous	1·09 (0·76–1·58)	0·63	1·04 (0·71–1·51)	0·86	1·02 (0·69–1·50)	0·93
High-grade serous	1·11 (0·96–1·29)	0·16	1·16 (1·00–1·35)	0·056	1·13 (0·97–1·32)	0·13
Low-grade serous	2·02 (1·38–2·97)	<0·0001	2·22 (1·48–3·31)	<0·0001	2·11 (1·39–3·20)	<0·0001
Borderline	1·26 (1·05–1·50)	0·012	1·19 (0·99–1·43)	0·062	1·12 (0·93–1·35)	0·24
Mucinous	1·27 (0·97–1·67)	0·078	1·19 (0·90–1·57)	0·23	1·12 (0·84–1·48)	0·45
Serous	1·31 (1·05–1·63)	0·015	1·28 (1·02–1·61)	0·034	1·20 (0·95–1·52)	0·12

OR=odds ratio. *Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other). †Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other), and adjusted for duration of oral contraceptive use (never, <2 years, 2–4·99 years, 5–9·99 years, ≥10 years), and parity (0, 1, 2, 3, ≥4 children).

Table 3: **Association between history of endometriosis and the histological subtypes of ovarian cancer**

Lancet Oncol 2012; 13: 385–94

Atypical endometriosis

- Observation of histologically atypical endometriosis contiguous with ovarian CA
  - Crowding of cells
  - Increase of nuclear/cytoplasmic ratio

- NOTE: Other meanings of "atypical" endometriosis
  - "Atypical" ovarian endometriomas on ultrasound
  - "Atypical" appearance at laparoscopy

Anglesio and Yong, Clin Obstet Gynecol, in press

Atypical endometriosis

- Genomic evidence that atypical endometriosis is the ***precursor*** to endometrioid/clear cell ovarian CA:
  - Shared regions of loss-of-heterozygosity
  - Shared *ARID1A* mutations (Weigand et al., NEJM)
  - Shared up to 98% of somatic mutations (Anglesio et al., J Path)
- **Suggests that endometriosis can accumulate somatic mutations and become atypical, and eventually transform to ovarian CA**

Anglesio and Yong, Clin Obstet Gynecol, in press

However…

- Deep endometriosis can also harbour somatic mutations (Anglesio et al., NEJM)
- But extremely rare for deep endometriosis to become atypical and undergo malignant transformation
- Thus, there must be role of ovarian micro-environment

Anglesio and Yong, Clin Obstet Gynecol, in press

Learning objectives

- Identify the epidemiology and classification of endometriosis
- State the impact of atypical endometriosis on malignant gynecologic tumours
- **Discuss potential ways to prevent future ovarian cancer in women with endometriosis**

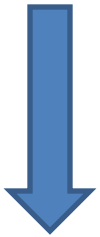
What's the risk of ovarian CA?

- Endometriosis: approx 2 fold increase in risk
  - May be higher with tissue confirmed ovarian endometriosis compared to self-reported history
- However, this is average risk and likely to be heterogeneous – e.g. estrogen exposure
- **Goal**: ***Identifying the endometriosis patient who is at higher risk for ovarian CA.***

Journal of Minimally Invasive Gynecology (2014) 21, 55–63

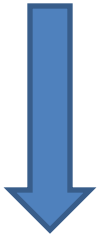
Crux of the problem

- **Endometriosis** ***Common***



Time?

- **Atypical endometriosis** ***Uncommon***



Time?

- **Clear cell or endometrioid ovarian CA**

Gyne oncologist

- **What the gyne oncologist is likely to see**
  - Concurrent endometriosis found in 30-40% of clear cell ovarian cancer
  - Atypical endometriosis can be seen in this context
  - Sometimes a continuum is seen consisting of endometriosis, atypical endometriosis, and frank carcinoma

General gynecologist or family physician

- **What we're more likely to see**
  - Patient with benign ovarian endometrioma

    1) What's the risk of ovarian CA?

    2) How can we prevent and who's at higher risk?

  - Atypical endometriosis found on pathology, in what looked like a benign endometrioma

    1) How frequent is this finding?

    2) How to manage?

General gynecologist or family physician

- **What we're trying to avoid**
  - Published case report
  - Age 24: MIS left ovarian cystectomy → ***endometrioma***
  - Age 29: MIS right ovarian cystectomy → ***endometrioma with atypical endometriosis***
  - Age 33: MIS bilateral ovarian cystectomies → ***right endometrioid ovarian CA***

Case Rep Oncol 2013;6:480–484

General gynecologist or family physician

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How can we prevent ovarian CA?

- **Factors that may reduce risk**:
  - Hormonal therapy
    - Combined oral contraceptives (dose response)
    - Progestin
    - Progestin IUD
  - Parity (vs. nulliparity or infertility)
  - Tubal ligation (salpingectomy); Hysterectomy
  - Oophorectomy and complete surgical removal of endometriosis

Acta Obstetricia et Gynecologica Scandinavica **92** (2013) 546–554

Human Reproduction Update, Vol.21, No.5 pp. 640–651, 2015

Who's at higher risk of ovarian CA?

- Examples of women with endometriosis who may be at higher risk for ovarian CA:

OCP use	Parity	Tubal ligation	Endometriosis	Family history *	Genetic risk quintile	Lifetime risk
Never	None	No	Yes	No	5	6.47%
Never	1 birth	No	Yes	Yes	4	7.99%

- Problem: we don't know which of our patients are at genetic risk quintile 4-5

Cancer Epidemiol Biomarkers Prev; 24(4)671–6.

Case 1

- 50 year old perimenopausal G0 with symptomatic left sided 5 cm endometrioma
  - Hypertension, Smoker
  - BMI 40
  - Previous laparotomy, left ovarian cystectomy
  - No previous tubal ligation
- CA-125: 100
- Exam: evidence of Stage IV endometriosis

Case 1

- **Management**:
- Surveillance until menopause?
- Try hormonal therapy, and surveillance?
- Surgery (oophorectomy)?

Case 1

- **Surveillance until menopause?**
  - Advantages
    - Avoid surgical risk
  - Disadvantages
    - Will endometrioma resolve, and if so, how long will it take?
    - If endometrioma no longer apparent on ultrasound, is it truly resolved or is there still endometriosis in the ovary that could become atypical?

Case 1

- **Hormonal therapy, with surveillance?**
  - Advantages
    - Improvement in symptoms and reduce size of cyst
    - Chemoprevention
  - Disadvantages
    - Clot risk (if combined estrogen-progestin)
    - If endometrioma no longer apparent on ultrasound, is it truly resolved or is there still endometriosis in the ovary that could become atypical?

Case 1

- **Surgery? (oophorectomy, removal of endometriosis, +/- hysterectomy and bilateral salpingectomy)**
  - Advantages
    - Tissue diagnosis
    - Prevention of future ovarian CA?
  - Disadvantages
    - Surgical risk (Stage IV endometriosis)

Case 1

- Patient opts for surgery: hysterectomy, BSO, complete removal of endometriosis

- 6 week post-op visit: Patient presents with significant hot flushes. What type of HRT?
  - Estrogen and Progesterone

Hum Reprod Update 23(4):481-500

General gynecologist or family physician

- **What we're more likely to see**
  - Patient with benign ovarian endometrioma

    1) What's the risk of ovarian CA?

    2) How can we prevent and who's at higher risk?

  - Atypical endometriosis found on pathology, in what looked like a benign endometrioma

    1) How frequent is this finding?

    2) How to manage?

Atypical endometriosis in (benign) endometrioma

- **How frequent?**
  - Risk of atypical endometriosis in ovarian endometriosis approx 1-2% (4/255)

- **How to manage?**
  - No guidelines
  - Possibilities: Surveillance? Hormonal therapy? Repeat surgery?

Histopathology 1997;30:249-55

Case 2

- 30 year old, G0, with infertility
  - History/physical suspicious for endometriosis
  - AMH = 2.0 ng/mL
  - Workup shows 5cm right endometrioma
  - Patient opts for laparoscopy, cystectomy done
- Pathology: right endometrioma with evidence of atypical endometriosis, no malignancy
- Post-operative U/S: 1cm “follicle” in right ovary

Case 2

- **Management?**

- Expectant and try for pregnancy, re-evaluate postpartum?
- Hormonal therapy and proceed to ART, then re-evaluate postpartum?
- Oophorectomy, then try for pregnancy?

Case 2

- **Expectant and try for pregnancy, re-evaluate postpartum?**
  - Advantages
    - Preserve fertility, spontaneous conception
  - Disadvantages
    - Residual atypical endometriosis present?

Case 2

- **Hormonal therapy and proceed to ART, then reevaluate post-partum?**
  - Advantages
    - Chemoprevention
    - Preserve fertility
  - Disadvantages
    - Residual atypical endometriosis present?
    - ART required (e.g. cost)

Case 2

- **Oophorectomy, then try for pregnancy?**
  - Advantages
    - Prevention of ovarian CA?
  - Disadvantages
    - Loss of ovary – but AMH reasonable and could conceive from other ovary

Case 2

- Patient opts for oophorectomy, conceives spontaneously from remaining ovary

- 6 week post-partum visit: Patient asks about spacing next pregnancy. What type of family planning?
  - Hormonal (estrogen-progestin or progestin)

Take home points

- Identify the epidemiology and classification of endometriosis

Endometriosis is common, and the ovarian subtype appears to be at risk for malignant transformation

Take home points

- State the impact of atypical endometriosis on malignant gynecologic tumours

Genomic evidence that endometriosis can become atypical, which is a <u>precursor</u> to ovarian CA (clear cell or endometrioid)

Take home points

- Discuss potential ways to prevent future ovarian cancer in women with endometriosis

Possibilities: Hormonal therapy, Parity, Tubal ligation (Salpingectomy), Hysterectomy, Oophorectomy, Complete surgical removal of endometriosis

Questions?

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BC Women's Centre for Pelvic Pain and Endometriosis:

Http://www.womenspelvicpainendo.com