

MANAGEMENT OF OVARIAN CYSTS

Associate Professor Russell Hogg

Ovarian cysts are a common finding. While the majority of cysts in premenopausal women are functional cysts, a significant number of women have malignant or borderline malignant lesions. Any persistent cyst should be considered as potentially malignant, particularly in the post-menopausal woman. Discrimination of these lesions requires careful assessment. Inappropriate surgery can change a stage 1 ovarian tumour into a stage 3 cancer, with obvious sequelae. Collection of a careful history, including family history and performance of a speculum and pelvic examination is essential.

FURTHER TESTS

Investigational tools include tumour markers, ultrasound and computed tomography (CT). CA125 is a relatively poor indicator of malignancy, as it is normal in 50% of stage 1 malignant tumours and raised in non-malignant conditions (especially pelvic inflammatory disease or endometriosis). CA125 levels over 100-200 U/ml may reflect malignant disease. HE4 is a relatively new marker. While it is being promoted as improving specificity in deciding whether the cyst is likely to be benign or malignant, the main value of HE4 is in discriminating between endometriosis and malignancy in a woman with a mildly raised CA125 level.¹ CEA is commonly mildly elevated in mucinous ovarian tumours of gastrointestinal type or colon tumours. Other tumour markers (eg. CA19.9 or CASA) add little value in assessing a cyst.

Routine measurement of CA125 (or transvaginal ultrasound) as "screening" is contraindicated as large randomised trials have shown no improvement in mortality but significantly increased morbidity when employed in asymptomatic women.²

IMAGING

Ultrasound (preferably both trans-abdominal and trans-vaginal), performed in a high-quality service provides the most information. CT scans usually contribute little extra information in the absence of ascites (which will be detected with ultrasound) or pelvic/paraortic lymphadenopathy (which is uncommon in the absence of markedly abnormal pelvic ultrasound findings).

Liver metastases are very uncommon in primary ovarian cancer.

Characteristic ultrasound findings include:

Simple single cysts – which have NO solid areas and may resolve or, if a benign serous or mucinous cystadenoma, increase slowly over time.

Haemorrhagic cysts – mixed solid and cystic masses of <8cm in premenopausal women, which reduce in size or resolve when rescanned 6 weeks later.

Endometriomas – cysts with "ground glass" appearance, which change slowly over time and may be associated with mild-moderately elevated CA125 levels.

Borderline tumours may have nodular tissue or thickening of the walls of otherwise simple appearing cysts on high quality images. These tumours can only be confidently diagnosed at intraoperative frozen section and should be removed intact (Figure 1). There is a higher risk of cyst rupture and spillage with laparoscopic cystectomies. The developing evidence suggests that these tumours develop from benign adenomas, progressing to borderline tumours and then low grade carcinomas over some years. Surgical staging is important in detecting extra-ovarian implants which, if histologically invasive, require treatment with chemotherapy.



Figure 1

The more common high grade serous tumours progress rapidly, with apparently normal ovary on imaging not uncommonly being found to coexist with disseminated carcinoma. Removal of potential borderline or malignant cysts should be via laparotomy or laparoscopic oophorectomy with collection of pelvic washings. Laparoscopic cystectomy carries a significant risk of rupture of the cyst intraabdominally with increased risk of recurrence. A laparotomy for a cystectomy or a laparoscopic unilateral oophorectomy does not impair subsequent fertility providing the contralateral ovary is normal. Women with borderline tumours require prolonged follow up

as recurrences have been documented 10-20 years after apparently complete resection.

Complex cysts (mixture of solid and cystic areas) are highly suspicious for malignancy in postmenopausal women. A complex cyst in a post-menopausal woman, or a non-resolving complex cyst in a premenopausal woman requires evaluation by a Gynaecological Oncologist. A complex cyst of <8cm diameter in a pre-menopausal woman may be a functional cyst but should have at least partially resolved when rescanned in 6 weeks.

Ascites suggests possible malignancy. A small amount of free fluid (<50mls) seen at ultrasound may be physiological.

Ovarian cysts in pregnancy require careful assessment and management by a Specialist Obstetrician/Gynaecologist, with consultation with a Gynaecological Oncologist if there is suspicion of malignancy. Most cysts in pregnancy are benign. However, germ cell tumours should be considered in this age group. The risk of antenatal rupture, torsion or intrapartum complications requires careful assessment and consideration of surgery in the early second trimester.

In summary, most ovarian cysts are functional and will resolve with "watchful waiting", usually requiring a repeat ultrasound in 6 weeks. Low risk masses (e.g. simple cysts or likely endometriomas which do not resolve when rescanned in 6-8 weeks) require assessment by a Specialist Gynaecologist. Moderate or high-risk ovarian masses should be referred to a Gynaecological Oncologist. Evidence suggests that women with ovarian malignancy have a better prognosis when managed within a Multidisciplinary Team, which includes input from the patient's General Practitioner, Gynaecological Oncologist, Medical Oncologist, Radiation Oncologist, Gynaecological Pathologist, Familial Cancer Specialist, Social Worker and Psychologist.

References available on request.



A/PROF RUSSELL HOGG

BSc (Hons) MBBS PhD
FRANZCOG CGO

A/Prof Russell Hogg is a Gynaecological Oncologist. His additional training includes radical pelvic surgery and advanced laparoscopic surgery. He is a member of the Skilled Cancer Professional Group at the Cancer Institute of NSW and the Gynaecological Oncology Co-Chair at the NSW Agency for Clinical Innovation.

Contact 9687 2940

SIGNIFICANT ADVANCES IN BREAST IMPLANTATION

By Dr John Kippen

Silicone-containing breast implants have been used since 1964. The first polyurethane covered breast implants (PCBI) have been used since 1969 to reduce one of the commonest problems associated with breast implants namely capsular contracture. Silimed have been manufacturing PCBI in Brazil since 1983. These dates give an idea of the reliability associated with PCBI.

PCBI are TGA approved in Australia, which is the Australian Government regulating body. Polyurethane is also used in other medical devices such as pacemakers and blood vessel grafts.

These implants address the two most common concerns associated with implants, which are capsular contracture and displacement or rotation. An added benefit of this is a more rapid recovery. When coupled with newer operating techniques this may be as little as 24 hours, without the use of drains, bras, binding or strapping.

Capsule formation is the body's response to a foreign material. It is a normal process and problems only arise when the tissue shortens. Scar tissue develops around the implants or other medical device. Over time this may contract. Fibrous scar tissue aligns longitudinally and is therefore able to overlap and shorten.

With implants the first sign is a firmness or hardness followed by an obvious visual change and distortion. Finally the implants may become uncomfortable and even painful. The longer the implants have been in the body the more likely this is to occur. Studies of the incidence of capsule contracture, with conventional implants, vary from about 8% at 3 years to 16% at 8 years and possibly higher. This is the most common reason that implants need to be exchanged. The incidence of contraction for PCBI is quoted as 1% at 15 years.

Polyurethane foam is a 3 dimensional lattice and mesh structure covering a moderately textured breast implant. This structure does not allow the formation of and breaks up the longitudinal scar

tissue orientation, therefore preventing contraction. The layer of polyurethane foam is bonded to the implant by a process of vulcanization. This limits delamination and separation.

Implant rotation may occur and this is especially problematic with tear-drop shaped implants. Implants moving sideways, laterally or rotating have been described. The PCBI have a softer foam surface which has a "Velcro" type effect on the interface with tissue. This adhesive effect limits this rotation of implants and allows a more rapid recovery with less need for strapping or supportive bras. Once the implants are sited, they remain in that position. Downward displacement or "bottoming-out" and lateral displacement are also unlikely to occur.

Issues initially quoted as being associated with PCBI have been extensively studied and been shown to be not valid. There are 60 scientific papers attesting to their safety. The incidence of infection, implant removal difficulty, seroma or fluid collection, rupture and late contracture formation have not been shown to be any different to currently used silicone filled, cohesive gel implants. As mentioned the commonest problem of capsule contracture is significantly less, 16% at 8 years vs 1% at 15 years.

A temporary, localized, itchy rash that occurs in less than 3% of cases is reported. This is most common in the second week and lasts about a week. Resolution of the rash occurs with no long term issues. Symptomatic treatment of the itch is all that is required.

These implants were initially recommended for problematic cases such as repeat or early capsule formation, implant rotation and downward or lateral displacement. A growing number of surgeons recognize the distinct advantage of these implants and are using them first up as their implant of choice. Why wait for a problem to occur and then treat it when it may be possible to reduce the incidence of problem from the start?

The advantages include a capsule contracture rate 10 times less than conventional implants, the higher

POLYURETHANE COVERED BREAST IMPLANTS

Massive reduction in common complications

TEBBETTS SURGICAL TECHNIQUES

Significant reduction in recovery – down to 24 hours

co-efficient of friction or "Velcro" effect that limits rotation and downward or lateral displacement.

The cohesive gel is also slightly softer giving a more natural feel. There is a long safety record over many decades.

SURGICAL TECHNIQUE

A very important addition is PCBI combined with advances in surgical techniques and instrumentation, 90% of women return to normal activities within 24 hours of surgery. The techniques are based on a method popularised by Tebbetts. Ninety percent of women can go shopping, return to non-physical work, drive a car, perform light domestic duties without restrictive binding, bandaging or drains within 24 hours of surgery.

The methods minimize tissue trauma and prospectively control bleeding. Tebbetts reports blood loss of less than a few milliliters per side. Monopolar forcep coagulation is extensively used to achieve this. Accurate pocket dissection and general anaesthesia is required in addition to short acting muscle relaxation. Procedures are performed in a Day Surgery Centre.



DR JOHN KIPPEN

BSc MBBCh FRACS

Dr John Kippen graduated in medicine in 1989 in South Africa. In Australia he studied further in Surgery at RNSH before specialising and obtaining the RACS Fellowship in Plastic and Reconstructive Surgery. He has fellowships in Cosmetic Surgery, Hand Surgery and Reconstructive Surgery. Contact 1300 547 736.

PATHOLOGY UPDATE: COELIAC DISEASE TESTING

Dr Michelle Keir, Nola Hitchcock and Dr Bevan Hokin

INTRODUCTION

The first clinical description of Coeliac Disease (CD) by Samuel Gee in 1888 was that of an irritable child with chronic diarrhoea who 'failed to thrive'.

CD is a systemic inflammatory illness caused by a diet containing the protein gluten (contained in wheat, oats, rye and barley) also referred to as gluten sensitive enteropathy. In order to be susceptible to the disease, CD sufferers must have the HLA-DQ2 and /or HLA-DQ8 genotype. However, only 30% of people with this genotype will develop the disease.

Small bowel biopsy is the gold standard for CD diagnosis. Small bowel villous atrophy and lymphocytic infiltration is characteristic of the disease and results in nutrient malabsorption.

PATHOGENESIS

The initial immune response in CD is increased gut permeability, thought to be a result of Environmental Factors (EF) such as infection, injury, gastroenteritis, sepsis, trauma, stress, medication or other inflammatory responses.

Summary of the pathogenesis of Coeliac disease:

1. Gluten and/or Gliadin (digested gluten protein), the trigger protein, is deamidated in the Lamina propria (LP) by tissue transglutaminase.
Relevant tests: Coeliac serology.
2. Deamidated gliadin protein has a high affinity for MHC class II molecules (HLA-DQ2/DQ8) and when bound is presented to T cells lymphocytes and initiates an immune response.
Relevant test: Genetic testing
3. The immune response causes lymphocytic infiltration and auto-antibody production. These combined immune responses result in intestinal mucosal inflammation and damage as seen in CD's characteristic histology.
Relevant test: small bowel biopsy.

WHY DIAGNOSE COELIAC DISEASE?

Serious health consequences can result if there is a delay in diagnosis and treatment of CD.

These include:

Increased risk of certain forms of cancer such as enteropathy-associated T-cell lymphoma of the small bowel, squamous cell carcinoma of oropharynx and oesophagus, adenocarcinoma of the small intestine.

Malabsorption of nutrients can lead to significant medical complications such as chronic poor health, chronic fatigue malnutrition, liver failure, osteoporosis infertility, miscarriage, depression and dental enamel defects.

In children, undiagnosed CD can cause delayed development, short stature, behavioural problems and reduced educational performance.

PREVALENCE OF COELIAC DISEASE

The prevalence of CD has increased, to approximately 1% of the Australian and New Zealand population, due to improvements in diagnostics and increased medical awareness through the broadening of CD's clinical spectrum. Despite this about 80% of Australians with CD remain undiagnosed. 1% prevalence equals about 210,000 Australians with CD.

Classical CD: Initially CD was considered only as a classical presentation. It was thought to occur only in children who were underweight, were 'failing to thrive', and had diarrhoea and significant GI symptoms. These GI symptoms are common in the clinically overt cases and are absent in the majority of CD patients.

Silent CD: are patients who have positive serology and positive small bowel biopsy (SBB) in the absence of symptoms. These patients represent a large proportion of the CD population, being 7-15 times more common than classical CD.

Latent/Potential CD: These patients have positive serology but have a normal SBB. These patients must be monitored for the development of GI involvement. There is insufficient evidence as to whether these patients eventually develop clinical CD.

SYMPTOMS OF CD

Classical symptoms commonly seen in children:

- Delayed growth, 'Failure to thrive'

- Abdominal cramping and distension, bloating, flatulence
- Nausea, vomiting is common
- Weight loss and malnutrition due to malabsorption
- Muscle wasting
- Diarrhoea and steatorrhoea
- Delayed puberty in children
- Developmental delay

Classical symptoms commonly seen in adults:

CD can now be associated with a diverse range of clinical presentations. Consequently, CD is now being diagnosed in adults with at least 20% of CD patients being over the age of 60. Adults sometimes present in a similar fashion to children with diarrhoea and weight loss, but they rarely have nausea and vomiting. About half of adult CD patients do not have diarrhoea, and therefore presentation of CD in adults varies. Awareness of the more atypical features of CD is important, as they might be the only clues on presentation. These include:

- Diarrhoea, constipation or both
- Gastrointestinal symptoms, ill-defined abdominal symptoms, abdominal pain, indigestion, bloating or flatulence similar to Irritable Bowel Syndrome
- Dermatitis herpetiformis, skin rashes
- Deficiencies of Iron, zinc, folate, vitamin D or B12 deficiency
- Fatigue, lack of energy and tiredness most common
- Recurrent mouth ulcers
- Easy bruising of skin
- Bone and joint pain
- Low blood calcium levels with muscle spasms and stiffness
- Recurrent headaches
- Peripheral neuropathy
- Altered mental alertness and irritability

A number of other indicators may be suggestive of CD:

- A CD patient is likely to have other autoimmune diseases, such as thyroid and liver disease or diabetes type 1.
- 1 in 20 people with Type 1 diabetes also have CD.
- 2 – 5% of CD patients are IgA deficient.
- 1 in 20 people with Down Syndrome have CD.
- CD is present in 1 in 15 people with Turner syndrome.
- Osteoporosis and osteopenia have been associated with CD infertility.
- 6 – 10% of people with untreated CD experience neurological problems, peripheral neuropathy and ataxia most common.
- Up to 50% of women with untreated CD experience miscarriage and therefore CD should be considered in cases of unexplained infertility.

DIFFERENTIAL DIAGNOSIS

CD has ubiquitous symptoms that are present in other diseases. Therefore, a differential diagnosis is achieved by a systematic assessment of the clinical findings. Other conditions that share non-specific gastrointestinal symptoms with CD:

- Irritable bowel syndrome
- Chronic giardiasis
- Crohn's disease
- Lactose intolerance
- Pancreatic insufficiency
- Milk protein intolerance (children)
- Cystic fibrosis (children)

These patients often have symptoms suggesting these other conditions and therefore can be misdiagnosed. Consequently, CD patients may have had a previous diagnosis of IBS. Therefore, this contributes to the delayed diagnosis and treatment of CD. Furthermore, antibodies to tissue transglutaminase (tTG) are not only found in CD patients, but in several other conditions, including juvenile diabetes, inflammatory bowel disease and various forms of arthritis.

DIAGNOSIS

The first important step Clinicians should undertake is to determine the pretest probability of CD. Coeliac serology should be ordered when high risk symptoms are observed.

Serology tests detect >90% of untreated CD if

gluten has been eaten regularly. If gluten has not been regularly consumed prior to testing, a Gluten challenge should be considered. This consists of the consumption of at least 2 – 4 slices of bread (children-adults) or equivalent of 10 – 20g gluten consumed daily for a minimum of six weeks. This is to allow accurate diagnosis.

WHEN TO ORDER COELIAC SEROLOGY TESTS (AND WHICH TEST?)

Serological tests have been developed as useful screening tools that are cost effective and less invasive than small bowel biopsy (SBB).

- Anti-gliadin antibodies (AGA) to the native form of gliadin, are produced in response to gluten consumption. AGA was one of the first recognised serological markers for CD. The AGA test is now superseded because of its low sensitivity and specificity and it often does not correlate with SBB results (Table 1).

- The anti-endomysial antibody (EMA) test has been one of the most reliable serology tests for some time, due to its high specificity and sensitivity, Table 1. However, there are limitations such as:

- subjective operator assessment and interpretation of results,
- expense,
- it is a qualitative assay which limits its use in follow-up testing, and only available in IgA form.

- it has been discovered that the EMA antibodies contains a form of transglutaminase called "tissue transglutaminase" (tTG). Therefore EMA and tTG detect the same autoantigen.

- Tissue transglutaminase antibody (tTG) is an autoantibody against the transglutaminase protein with very high specificity and sensitivity. tTG was discovered to be the autoantigen responsible for EMA. Consequently, the EMA test has been superseded by the current tTG IgA assay which has similar if not better sensitivity and specificity. Table 1. Advantages of tTG are:

- it is less expensive and cost effective
- it can be standardised between labs because it is technically more efficient not operator dependent.
- ELISA based testing means that it can give quantitative results (U/ml) and,
- tTG has been used for monitoring dietary compliance to a GFD.

However, tTG and EMA results are not informative in the setting of IgA deficiency.

- Deamidated Gliadin Protein (DGP) is the most recently developed assay. DGP IgG is used to complement tTG IgA to detect CD patients that may be IgA deficient and children of <2yrs. Gliadin peptides which are synthesized as the deamidated form have much higher sensitivity and specificity, as shown in Table 1.

The panel for San Pathology Coeliac Serology will be, DGP IgG and tTG IgA.

WHEN TO ORDER HLA GENE TEST?

- The gene test [HLA DQ2/HLA DQ8] is not diagnostic; it can only exclude a CD diagnosis, but is used to determine the risk factor of CD.
- In addition the gene test is not dependent on the inclusion of gluten in the diet.
- Therefore a HLA gene test may be ordered when a patient has been on a gluten free diet (GFD) for more than 1 month and not prepared to undertake a gluten challenge.
- Immunosuppressive drugs.
- Family history of CD.

Therefore, if someone has a positive gene test, this means that they are at greater risk of CD, it does not mean the diagnosis is CD. A negative gene test means that a person is not at risk of CD.

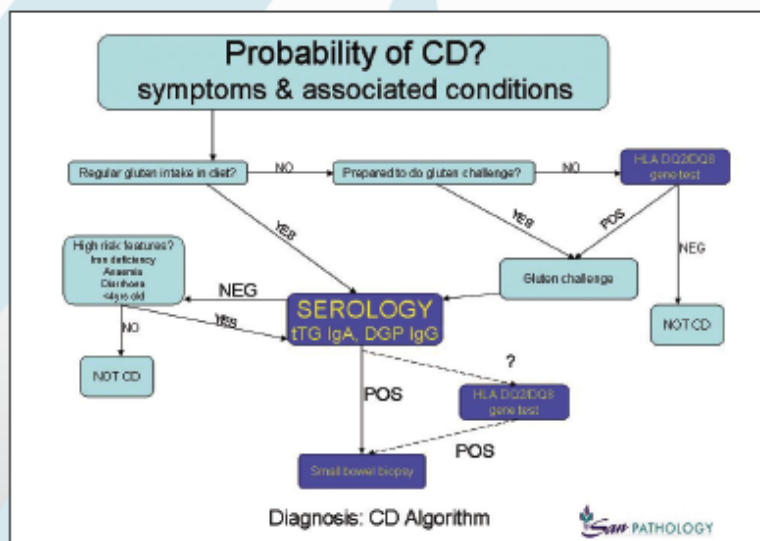


Table 1: Coeliac Serology Test

TEST	SENSITIVITY %	SPECIFICITY %	PPV %	NPV %
AGA ¹ IgG	57-100	42-98	20-95	41-88
AGA ¹ IgA	53-100	65-100	28-100	65-100
EMA ¹ IgA	75-98	96-100	98-100	80-95
tTG ² IgA	90-98	95-97	95-99	79-85
tTG ² IgG	68-81	84-94	93-97	49-62
DGP IgG	91	98	-	-
DGP ⁴ IgA	86-90	93-96	-	-

DR MICHELLE KEIR
BSc (Hons), Grad Dip LS, PhD

Dr Michelle Keir is a Senior Scientist in San Pathology. Her interests include Molecular diagnostics and implementation and validation of new test methods. Contact San Pathology on 9487 9500.

WHEN TO ORDER SMALL BOWEL BIOPSY (SBB)?

In 1969 the SBB was introduced as the gold standard for the diagnosis of CD. Despite the introduction of serological screening small bowel histology is still the gold standard for a definitive diagnosis of CD. In addition, Coeliac serology appears normal in 10% of untreated CD, even with CD positive histology.

A SBB should be performed:

- in all cases of positive Coeliac serology as confirmation of disease,
- with negative serology and if there is a strong family history or suggestive symptoms,
- to assess bowel recovery EMA and tTG disappearance is only an indicator on how successful gluten exclusion has been and not indicative of bowel recovery.

If the patient has positive blood tests and biopsy-proven dermatitis herpetiformis, a small bowel biopsy is not required.

CONCLUSION

The range and severity of symptoms can vary widely between individuals with CD and therefore there is no 'common' presentation of CD. Health professionals play a critical role in the diagnosis and management of those with CD. Knowledge of the varying presentations of untreated CD and current diagnostic procedures is therefore critical.

NEWS FROM THE SAN

A NEW CAR PARK will be operational at the San from early November providing space for more than 400 cars. It will provide an alternative parking area while a new multi-storey car park is being built. After the completion of the SAH Redevelopment there will be parking for over 2000 cars on site – an increase of over 700 from current spaces. Visitors to the SAH site are asked to take particular care and follow signage and traffic controllers' directions during the construction.

THE SAN'S FREE ANNUAL COMMUNITY CAROLS BY CANDLELIGHT WILL BE HELD ON SUNDAY 11TH DECEMBER. Celebrating 'Christmas from the Heart' performers include **Gina Jeffreys** and **Becky Cole**. **Laura Jane**, **Dave Martin & The Carols Band** and the **Wahroonga Adventist Primary School Choir**. The Sanitarium Weet-Bix Kids' Concert will feature the popular 'Smurf, Smurfette & Pappa Smurf' from the **Very Smurfy Christmas Show**. Food stalls and family activities start at 4pm before the Kids Concert at 7pm and the main program starts at 8pm.

NOV / DEC DIARY DATES

NOVEMBER

Month MOverber Changing the Face of Men's Health

Month Lung Awareness Month

1st Nov Melbourne Cup Day

DECEMBER

11th Dec San Free Carols by Candlelight

25th Dec Christmas Day **26th Dec** Boxing Day