19th Annual Women's Imaging Conference
University of Toronto - 2016

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Sunnybrook Health Science Centre
University of Toronto, Dept Medical Imaging, Obstetrics & Gynecology

Disclosures : None

If an adnexal mass is indeterminate on ultrasound the most appropriate next step is:

1. Serial follow-up ultrasound
2. Referral to an ultrasound expert
3. Referral for MRI
4. Utilization of a risk-referral model such as IOTA or LR2
5. Correlation with serum biomarkers.
6. Referral to a gynecological-oncology surgeon.

The key contribution of MRI in adnexal mass evaluation is in:

1. Identifying benign features.
2. Identifying malignant features.

Do simple or unilocular cysts increase the risk of ovarian cancer?

1. Yes
2. No

Talk is to share…..

- AIUM convened a multi-disciplinary / international consensus panel to address the diagnosis and management of asymptomatic women with pelvic masses November 2014
  - Chairs: Drs. Glanc, Goldstein

Panel Members	Academic Affiliation	Society Affiliation	Country	Specialty
S. Goldstein, Chair	Professor, NYU	American Institute of Ultrasound in Medicine (AIUM)	USA	Gynecology
P. Glanc, Chair	Associate Professor, UToronto	Canadian Association of Radiologists	Can	Radiology
B Benacerraf MD	Professor, Harvard	AIUM	USA	Radiology
T Bourne MD PhD	Adjunct Professor, Imperial College, London	International Society of Ultrasound in Obstetrics and Gynecology	Europe	Gynecology
D Brown, MD	Professor Mayo Clinic	Society Radiologists in Ultrasound	USA	Radiology
B Coleman MD	Professor U of Penn; CHOP	American College of Radiology	USA	Radiology
C Crum MD	Professor, Harvard	Support AIUM	USA	Pathology
J Dodge MD	Assistant Professor UToronto	Society of Gynecologic Oncology of Canada	USA	Gynecologic Oncology
D Levine MD	Professor, Harvard	Society Radiologists in Ultrasound	USA	Radiology
E Pavlik MD, PhD	Associate Professor, University of Kentucky	Society of Gynecology Oncology	USA	Gynecologic Oncology
D Timmerman MD,PhD	Professor, U Hospitals Leuven	IOTA, Flanders Ultrasound Society	Europe	Gynecology
F Ueland MD	Professor ,U Kentucky	American College of Obstetrics & Gynecology	USA	Gynecologic Oncology
W Wolfman MD	Professor, U Toronto	Society of Obstetrics & Gynecology Canada	Can	Gynecology

2015: Group Acknowledged

√ Agreed that the consensus statement published by SRU in 2009/10 entitled "Management of Asymptomatic Ovarian and Adnexal Cysts Imaged at Ultrasound" remains relevant and appropriate in 2015

*Levine D, Brown DL, Andreotti RF, Benacerraf B, Benson CB, Brewster WR, et al. Management of Asymptomatic Ovarian and Other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement Radiology. **2010**;256(3):943-54.*

2015: Group Acknowledged

√ Pelvic US is still the primary imaging modality to evaluate adnexal masses

√ Sonomorphologic features in combination with Doppler evaluation of vascularity by an expert sonographer can correctly characterize most adnexal masses, especially if their appearance is classic for that entity

√ Ovarian lesions common, majority benign

***So why did we need another consensus statement? ***

*Levine D, Brown DL, Andreotti RF, Benacerraf B, Benson CB, Brewster WR, et al. Management of Asymptomatic Ovarian and Other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement Radiology. **2010**;256(3):943-54.*

Why Another Consensus Conference?

Panelists all Agreed 2 main premises

1, Excess surgery for clearly benign masses

- ~ 200,000 USA women undergo surgery for pelvic mass to find 22,000 women with ovarian cancer (0.1%)

2, Too many women do not benefit from a gynecologic oncologic evaluation prior to surgical intervention

- Abundant data demonstrates women with ovarian malignancies have better long-term outcomes when treated by specialists in gynecologic malignancy

Premise #2

Role Referral Gynecologic Oncology Consult

- Most important factor for survival is stage at diagnosis.
- **After stage**, appropriate referral to a center **specialized in gynecological malignancy** is the important prognostic factor in improving patient survival
  - Gynecologic Oncologist for optimal surgery/therapy
  - Pathologist with specialized expertise
    - less risk over and underdiagnoses of ovarian malignancies, in particular of borderline ovarian tumors on frozen section

Background

Ovarian Cancer (OC): Not a Monolithic Entity

- **Epithelial OC 2 types** : Morphology & genetics
  - **Type 1**: Slow growth, good prognosis
    - low grade serous, mucinous, endometriod, clear cell, Brenner, borderline
  - **Type 2**: 75% all OC and 90% deaths
    - p53 mutation in 80%
    - Precursor in situ lesion "serous intraepithelial tubal carcinoma" which resembles high grade ovarian serous carcinoma
    - Majority arise in fimbriated end fallopian tube

The 3 Buckets

Category	Management
Almost certainly benign	Variable but conservative
Indeterminate*	Second stage testing
Suspicious for malignancy	Proceed to surgical evaluation involving gynecology-oncology

*Defined unable to unambiguously place into either the benign or malignant category after US

Mass Characterization
Bucket 1: Almost certainly benign

- Simple or unilocular cyst
- Classic hemorrhagic cyst, including hemorrhagic corpora lutea
- Classic endometriomas
- Classic dermoids
- Classic Ovarian fibromas

Levine D, Brown DL, Andreotti RF, Benacerraf B, Benson CB, Brewster WR, et al. Management of Asymptomatic Ovarian and Other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement 1. Radiology. 2010;256(3):943-54.

Discussion Points & Background
Malignant Potential Simple Cysts

Review some larger trials ovarian cancer screening
Help define natural history of adnexal lesions

Risk Malignancy Unilocular Cystic Tumors <10cm
University of Kentucky Ovarian Screen Trial:

- 15,106 women > 50yr underwent annual TV
  - If positive repeat in 4-6 wks
  - 18% (2,763) unilocular* cysts
    - ~70% resolved spontaneous (2/3 within 3 months)
    - Thus role for serial US

**Defined no septae, papillae or solid components, anechoic*

Modesitt SC, Pavlik EJ, Ueland FR, et al. Risk of malignancy in unilocular ovarian cystic tumors <10 cm in diameter. O&G. 2003;102(3):6.;

Discussion Points - Trials
Risk Malignancy Unilocular Cystic Tumors <10cm
University of Kentucky Ovarian Screen Trial:

No malignant or borderline in unilocular cysts < 10 cm

- 133 surgically excised unilocular cystic masses
  - 52% serous cystadenomas versus 12% serous cystadenofibromas, 8% mucinous cystadenoma
    - *10 women diagnosed with invasive cancer*
      - *7 demonstrated morphological change (solid/papillary)*
      - *2 after cyst had resolved, 1 in other ovary*
- Overall risk < 0.1%

Modesitt SC, Pavlik EJ, Ueland FR, et al. Risk of malignancy in unilocular ovarian cystic tumors < 10 cm diameter. O&G. 2003;102(3):6.

Malignant Potential Simple Cysts
Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO)

- 4 year RCT 78,216 age 55-74
  - Annual TV-US & Ca125
- Single trigger to recommend surgery thus generated large # FP
  - Although did not improve cancer mortality there was increase in adverse health effects primarily due increase surgery
  - Concluded simple cyst(s) did not increase risk subsequent invasive OC

Greenlee et al. Prevalence, incidence, and natural history of simple ovarian cysts among women >55 years old in a large cancer screening trial. AJOG. 2010;202(4):9.(American)

Malignant Potential Simple Cysts

United Kingdom Collaborative Trial of ovarian cancer screening by US in PMW

- RCT cohort study 48,053 PMW detected adnexal lesions 9.1%
- 2,531 unilocular cysts (IOTA def)
  - Absolute risk malignancy 0.4% (4 /1,000) in subgroup with unilocular or multilocular cyst with no solid elements at initial scan
    - Thus simple or unilocular cysts no rush to surgery but some interval F/U appropriate

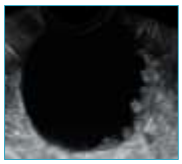
Sharma et al. ***Risk of epithelial ovarian cancer in asymptomatic women with US-detected ovarian masses: a prospective cohort study UK collaborative trial of ovarian cancer screening (UKCTOCS)***. *UOG. 2012;40(3):7*

Malignant Potential "Simple" Cysts

- No documented relationship between serous cystadenomas & high grade serous carcinoma
  - The long-term risk of malignancy following the diagnosis of a serous cystadenoma is similar to that of the general population.
    - All published linkages have been on retrospective data.
    - Statement is supported by the literature on mutation analysis in ovarian cancer

Discussion Points
Papillary Projection in unilocular cyst

- IOTA defined papillary projection as solid element protruding into cyst ≥ 3mm
- Data demonstrated > risk malignancy if ≥ 4 in number or any size involving > half inner wall
- < risk avascular



Timmerman et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. UOG. 2008;31(6):681-90 Hassen, et al. Characterization of papillary projections in benign versus borderline and malignant ovarian masses on conventional and color Doppler US. AJR. 2011;196(6):1444-9.

Malignant Potential
Septations- No solid Elements

- *2870 septated cystic tumors repeat TVS US @ 4 to 6-month for an average of 77 months
- No cancer regardless septal number/width
- Majority serous or mucinous cystadenomas

**Ueland FR, et al. Risk of malignancy in sonographically confirmed septated cystic ovarian tumors. Gynecol Oncol. 2010;118(3):278-82. Timmerman et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol. 2008;31(6):681-90.*

Malignant Potential: Mature Cystic Teratomas

- Risk related to size > 10cm, solid component (may enhance), *rapid growth, cyst wall penetration, peritoneal spread*
  - *Malignant* component in 0.17**- 0.8%

Park J-Y et al Malignant transformation of mature cystic teratoma of the ovary: experience at a single institution. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2008;141(2):173-8. ** Comerci et al. Mature cystic teratoma: a clinicopathologic evaluation of 517 cases and review of the literature. Obstetrics & Gynecology. 1994;84(1):22-8.

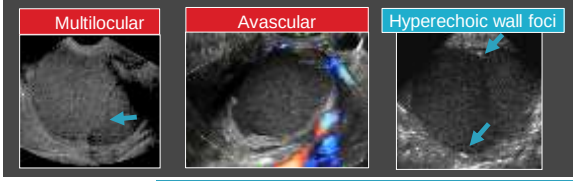
Malignant Potential Endometriomas

- Prevalence with cancer ~ 0.3- 0.8%
- Risk related to > 9cm, > 45 years, rapidly enlarging solid vascular regions

Kobayashi et al. International J of Gynecological Cancer 2007. Johnson et al Human Reproduction. Van Holsbeke et al. UOG 2010

Characteristic Features ;**Endometrioma**
Homogenous LLE, multilocular +/- hyperechogenic wall foci

Caution not all adnexal masses with LLE are endometriomas thus important to ensure septations smooth and no solid elements



LLE + Multilocular + Hyperechoic wall Foci - LR

The 3 Buckets

Category	Management
Almost certainly benign	Variable but conservative
Indeterminate*	Second stage testing
Suspicious for malignancy	Proceed to surgical evaluation involving gynecology-oncology

*Defined unable to unambiguously place into either the benign or malignant category after US

Bucket 2: Indeterminate: 10-25%

Category	Management
Almost certainly benign	Variable but conservative
Indeterminate*	**Second stage testing**
Suspicious for malignancy	Proceed to surgical evaluation involving gynecology-oncology

*Defined unable to unambiguously place into either the benign or malignant category after US

Next Steps: Referral to Expert

- Despite extensive research into various risk prediction models, subjective assessment in the hands of an expert remains as accurate as any technique
  - Sensitivity as high as 96.7% with FN 1/30
- BUT, Expertise is not easily transferred

Should we improve the general expertise in the US community or go to the model of expert referral - well accepted in obstetric US

Next Steps: Serial US

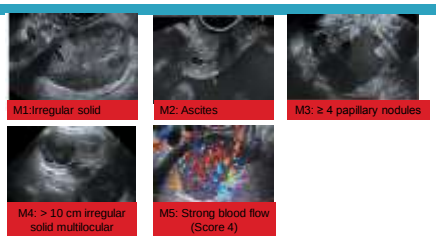
- Majority resolve on follow-up
- Provide opportunity monitor growth or change in morphology

Next Step: Risk Prediction Models
International Ovarian Tumor Analysis (IOTA)

- IOTA > 20 centers, multiple countries, academic/non-academic, > 10,000 patients
  - Consistent results suggest data is robust/generalizable
- Results:
  - **Pattern recognition in experienced hands is best**
  - IOTA **Simple Rules** classify 75% benign or malignant.
    - Simple to use therefore simple to implement
    - Triage point: to experienced imager for 25% inconclusive

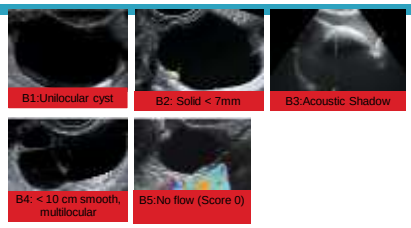
Improving strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. UOG. Volume 41, Issue 1 p8–20, 2013

IOTA Simple Rules
Five Malignant Features



Simple ultrasound-based rules for diagnosis ovarian cancer. Timmerman et al. UOG, 2008 681-690

IOTA Simple Rules
Five benign features



Simple ultrasound-based rules for the diagnosis of ovarian cancer. Timmerman et al. UOG, 2008 (31) 681-690

IOTA "SIMPLE RULES"

- If ≥ 1 M-rules apply in the absence of a B-rule, the mass is classified as malignant.
- If ≥ 1 B-rules apply in the absence of an M-rule, the mass is classified as benign.
- If both M-rules and B-rules apply or if no rules apply then the mass cannot be classified.

Next Steps:
Risk Prediction Models: IOTA, LR1/2

- A significant limitation ~25% do not have features clearly predictive of benign or malignancy
- To date surgical experience
- Thus role for expert referral
  - The rules work best for classic benign/malignant ie easily classifiable

https://itunes.apple.com/us/app/iotamodels/id637567054;
http://www.iotagroup.org

Next Steps: Referral for MRI

- MRI with contrast enhancement provides the highest post-test probability of ovarian cancer detection
- The key contribution of MRI is its specificity because it provides confident diagnosis of many benign adnexal lesions
  - Tissue characterization (blood, fat, fibrous)
  - Enhancement pattern, big picture..

Kaijser J, Sayasneh A, Van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, et al. *Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems: a systematic review and meta-analysis* Human Reproduction Update. 2013;0(0):14.

Next Steps: Referral Biomarkers

- OVA1 and the Risk of Malignancy Algorithm (ROMA) are only FDA-cleared tests for preoperative evaluation ovarian tumor
- ROMA and OVA1: No RCT or direct comparisons
  - OVA1 may be >sensitive (early-stage malignancy & premenopausal
- Neither HE4 nor CA125 should be used as individual diagnostic tests in the preoperative evaluation of an adnexal mass.
- Role best if indeterminate malignant risk
  - Help decide if refer to a gynecologic oncologist

Next Steps: Referral Gynecologic-Oncologist

- If mass indeterminate" referral to a gyne-oncologist
  - Not necessarily for prompt surgical exploration, but for utilization of their expertise, will be an appropriate "next step".

Mass Characterization
Bucket 3:Suspicious for Malignancy

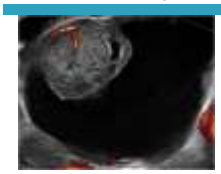
- No ultrasound is perfect at discriminating benign from malignant, nor is any algorithm a replacement for sound clinical judgement
- Nonetheless there are some features which should trigger concern for potential malignancy within an adnexal mass.

Feature	Comment
Solid component	Solid component worrisome for malignancy with following exceptions: - classic hyperechoic lesion with acoustic shadowing fat (mature cystic dermoids) - classic hypoechoic lesion with strong acoustic shadowing (fibromas)
Blood Flow	Central vascularity > peripheral. Higher degrees of vascularity
Septations	Multiple, irregular or vascular (> 3mm?)

Feature	Comment
Papillary Projections	≥ 4 papillary projections > ½ wall involved with papillary projections
Ascites	Complex pelvic fluid extends beyond the pelvis is > worrisome than simple fluid not extend beyond
Interim growth	No convincing data to determine amount of growth which is worrisome.
Change in Morphology	In particular the development of solid or vascular features is concerning.

Feature	Comment
Hemorrhagic mass in a PMW	If clearly post-menopausal then no physiological etiology for HOC/CL *(Endometriomas can persist into PM state)*
Bilateral Ovarian Masses	Query if primary tumor with metastases to the contralateral ovary or both represent metastatic deposits.
Ovarian Mass with Known Malignancy	Requires the same detailed evaluation as in the absence of known malignancy would receive - in order to determine whether this if is a benign, indeterminate or suspicious mass.

Suspicious for Malignancy



Solid Nodule
Central Vascularity
Diagnosis: Sertoli Leydig
(Masculinization due androgen)

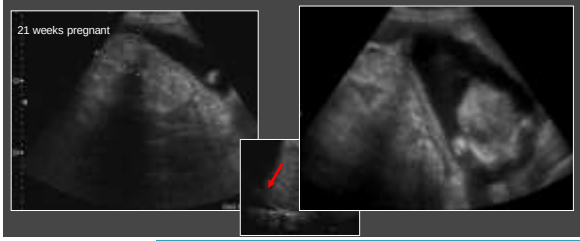
Irregular Septations
Papillary Projections
Diagnosis: Serous cystadenocarcinoma

Suspicious for Malignancy


Interim growth 8 months from 3 to 5.5 cm

GCT

LOOK SPECIFIC FEATURE: FAT



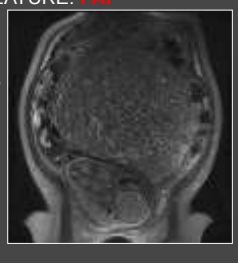
Pitfall

Tip Iceberg – Difficult Diagnosis

: LOOK FOR SPECIFIC FEATURE: FAT

Clinical:

- Non specific pain
- 18 week " normal fetus & fibroid ~ 25 cm"
- 22 weeks referred pain
- US heterogenous mass vascular, ascites, effusions
- Surgical resection revealed malignant high grade immature teratoma, umbilical implant
- PTL 5 days later live 22.3 wk

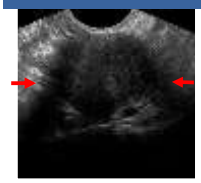


Pitfall

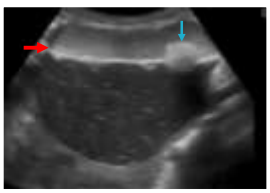
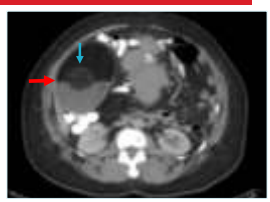
Tip Iceberg can be difficult appearance
Clue rapid growth

Dermoid: Echogenic mass with strong acoustic shadowing which may obscure the back wall of a large mass which gives rise to the descriptor "tip of the iceberg" sign

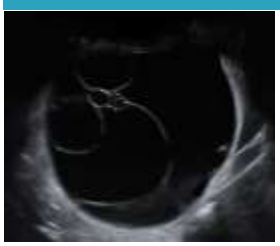
Fibroma: Hypoechoic mass with strong acoustic shadowing



Classic Fat-Fluid Level
Classic Dermoid Ball

Size & number locules (< 10/10)



Thickened irregular & nodules

Mucinous Cystadenocarcinoma: Size , complexity

Mucinous BOT:
Typically > 10 locules , > 10 cm, no solid elements

Mosaic or Stained Glass versus LLE

Wall Nodule > 1 cm or vascular

Endometrioma with wall nodule

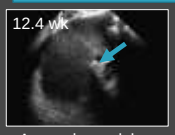
- Adherent clot
- Fibrotic nodule
- Decidualization
  - *Pregnancy*
- Malignant transformation

Role CDS (MRI) : Blood, fibrous, vascular

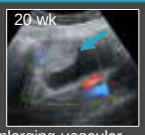
Pitfa

Wall Nodule > 1 cm or vascular

Malignant Degeneration Endometrioma in Pregnancy
Clear Cell Carcinoma removed at C-section



Avascular nodule
< 1cm on
background LLE

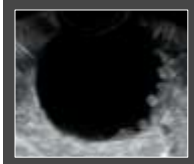


Enlarging vascular
MRI (no add info)
Declined surgery
intrapartum

Progressive
enlargement vascular
solid component

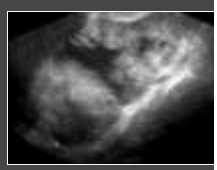
Pitfall

Endometrioma and Nodule



Multiple papillations

Irregular Cystic Solid



Irregular Mostly Solid

Malignant

Referral Gyne-Oncologist

Consensus Achieved following statements

- Real-time pattern recognition US the most accurate method of characterizing an ovarian mass *in hands of an expert*

Consensus Recommendations

- Simple ovarian cysts are not precursor lesions to malignant ovarian cancer
  - There is very low risk that these simple or even unilocular cysts can progress to malignancy thus some degree of follow-up may be prudent.
- Majority of ovarian lesions are benign
  - IF US suggests benign patient may be followed rather than having urgent surgical removal.

Consensus Recommendations

- If an ovarian lesion is indeterminate on initial scan (appropriate clinical evaluation) then "second-step" (in no particular order).
  - *Serial ultrasound or referral to a specialized ultrasound consultant*
  - *Application of established risk-prediction models*
  - *Correlation with MRI imaging*
  - *Correlation with serum biomarkers.*
  - *Referral to a gynecologic oncologist for further evaluation*

Consensus Recommendations

- The group did not come to consensus on length or timing of follow-up
  - Not enough data
- Group recognized less surgical intervention may well result in an increase in ultrasound surveillance

Summary

- Panel mandate was to ***address*** the gap between current knowledge and the translation of this knowledge into practice
  - Aim to further decrease unnecessary surgery
    - 90% surgery is on benign masses
  - Aim to improve referral rates to gynecology-oncologist when suspicious of malignancy
    - Only 1/3 patients refer such referrals in malignant OC
  - Aim to provide alternate next steps for indeterminate masses

Thank you for the opportunity to present results of this consensus conference

My Place
Sunnybrook Health Sciences Center