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# AOGD BULLETIN


***AOGD Theme 2017-18***

'Optimizing Women's Health Through Enhanced Skills and Best Practices'

***Issue:***

**Gynecologic Oncology**

**AOGD SECRETARIAT**

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**Volume 17-5, September 2017**


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# President's Message

Dear Friends

Greetings from the AOGD office! The countdown for the much-awaited Annual conference of AOGD to be held from 17th to 19th November 2017 has begun. The conference website is now live at www.aogdconference2017.com and registrations open. I urge all of you to participate actively, submit abstracts, update yourselves, interact with International and National authorities on wide ranging topics and enjoy a once a year academic bonanza! See you all in large numbers.

August saw AOGD partnering with FOGSI and DGES in what I may call a truly intellectual and skilling experience! Dr Ranjana Khanna, VP FOGSI NZ and Dr. Malvika Sabharwal, President DGES need commendations for the hard work that went into making both conferences a success. Dr. Nalini Mahajan, Chairperson, AOGD Reproductive and Endocrinology Committee had two back to back CME's and another organised by Dr. Kaberi Banerjee and Dr. Anita Sabharwal with Independence day celebrations were thought provoking. I'm happy that the AOGD monthly clinical meetings are running full-house. Dr. Pratima Mittal and her team at Safdarjang hospital presented near miss cases managed successfully by the Obstetric ICU team.

This issue is dedicated to 'Gynecologic Malignancy' and gives an update on all genital cancers. In the ever-increasing scenario of malignancies occurring in younger women, quality of life issues especially fertility preserving strategies become important. This issue carries a comprehensive article on this aspect. In the past, when cancer struck, treatment was 'radical' but is no longer true and individualised treatment tailored to age, histopathology, stage etc is now the standard of care. R zero clearance in ovarian cancer has prolonged survival and targeted therapy with anti-angiogenic agents, PARP inhibitors etc have prolonged life for long periods. Genetic testing has also become important and gynaecologists must start using these tests to identify those at risk and institute preventive measures. Enjoy this issue and post your comments.

Until next time Adieu!

**Shalini Rajaram**
President, AOGD (2017-18)

# Vice President's Message

Dear Friends

I take this opportunity to personally thank all my AOGD fellows and friends from Delhi-NCR for coming in huge numbers and making 'BOH-The Triology' a roaring success. I also wish to congratulate the proud AOGDians for winning many awards in this conference. As we embark upon the festive season amidst the menace of Dengue and swine flu, we need to gear up for the next mega event of AOGD- Annual Conference. Our website is active and vibrant. Please visit and register in large numbers.

Our editorial team is bringing out yet another important issue on Gynaecologic-oncology. Ovarian and cervical cancers are the most common gynaecological cancers affecting women worldwide and in India. Cervical cancer is on a declining trend, but remains the second most common cancer in women after breast cancer. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from this disease. Of all the cancers, only cervical cancer has a screening test when treatment can be most effective. Since there is no simple and reliable way to screen for other cancers, it is important to recognize early symptoms and learn to reduce the risk by early diagnosis. There is a need to organize National gynecologic cancer awareness campaign to raise awareness of gynecologic cancers, including cervical cancer, also develop national cancer registry, promote and support research and outreach programmes. The HPV vaccine coverage is a huge challenge in India and program needs a real push and political will. The current issue deals with these issues and many more.

Thank you once again. Cheers!!

**Kiran Guleria**
Vice President AOGD (2017-18)

# From the Secretary's Desk.....

Greetings From AOGD!!

Hope you are keeping well & enjoying great weather of our city.

It has been the endeavor of our editors to provide you with latest and relevant information about a particular subject in each issue. Continuing the same we have come up with the oncology issue. Pertinent SOPs like how to manage hyperplasia endometrium will be a handy guide for general gynecologist. Fertility preserving techniques in oncology will be of help in managing young patients with malignancy. I wish to thank you for encouraging feedbacks, it inspires the team to better themselves.

We are getting great response to skills workshop on **"CTG & Instrumental Delivery"** on 21st September in GTB Hospital. Register early as there are only few seats left. Registration is free.

I am enthused by your response to our conference website www.aogdconference2017.com & am thankful to *early birds* who have already registered through it. It is the easiest way to register with online payment gateway. I urge you to register early to get choice of workshop.

Keep well! Enjoy life.

Be seeing you in November!!

**Abha Sharma**
Secretary AOGD (2017-18)

## Monthly Clinical Meet

Monthly Clinical Meet will be held at Hindu Rao Hospital, New Delhi
on **Friday, 29th September, 2017** from 4:00-5:00pm.

# From the Editorial Board

Respected Seniors & Dear Friends,

We feel encouraged and humbled by the overwhelming response to the bulletins and kind words of appreciation. After two consecutive issues on surgery, we are bringing out this issue on Gynecologic Oncology. In the month of September when there is a chill in the air and festive season begins, this issue discussing various recent advances is a message of hope for the grave diagnosis.

Recent years have seen tremendous advancements in the field of Gynecologic Oncology. It is not only about going radical for improving survival, the quality of life issues, the desires for fertility preservation are also given due considerations while planning therapy. The advances in our understanding of the disease progression have given the option of being conservative in early stage disease as discussed in the chapter of carcinoma cervix and endometrial cancer. For malignancy, nothing is more important than screening at the pre malignant stage and early detection. Also the management issues of all important and common gynecological cancers are discussed.

It is important for all of us to be aware about genetic predispositions for cancers and hereditary cancer syndromes in our patients. BRCA1 and 2 mutations can be tested & knowing susceptibility in individuals and their family members for hereditary cancers, gives a unique opportunity for risk reduction by different approaches like enhanced screening, prophylactic surgeries and chemoprevention. That's why we have included an article on BRCA1/2 in Female malignancies. Another upcoming area in the field of oncology is about understanding the cellular pathways in the biology of cancers. Development of various targeted therapies acting on these pathways have shown some positive results especially as maintenance therapies for long period of time. "Targeted Therapy in Gynecological Cancers" will add to the armamentarium of various therapies for treating cancers. Along with advanced therapies, the basics like proper diet and exercise are equally important for managing the cancers. Another important topic of Endometrial Hyperplasia is dealt with in a simplified manner in the form of SOP.

Hope you all will find this issue informative and helpful in clinical practice. Do attempt the quiz in the end. Your feedbacks are always welcome.

**The Editorial Team**
AOGD (2017-18)

# Management of Carcinoma Cervix: An Update

**Seema Singhal**
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## Disease Burden

Carcinoma cervix is the fourth most common cancer among women worldwide with an estimated 5,28,000 new cases and 2,66,000 deaths per year. India contributes to 23% of global burden with incidence varying from 13-24/100,000 women per year and 67,477 women die every year because of this disease. In last few decades, important advances have taken place in the management of cervical malignancy. This review will address current controversies and advances in the management of cervical malignancy.

## Pre- Treatment Evaluation and Staging

Carcinoma cervix is a clinically staged disease. The International Federation of Gynaecology and Obstetrics (FIGO) staging system takes into account the results of the physical examination, colposcopy, histopathology (cervical biopsy or conisation), radiography (chest radiograph, intravenous pyelography, barium enema) and endoscopy (cystoscopy or sigmoidoscopy).

Despite efficacy of imaging and surgery to accurately stage the disease, these are not yet incorporated into the FIGO staging system. This is because of lack of consensus about best modality and yet unproven role of surgical staging. Therefore considering higher prevalence of disease in resource constraint areas and in order to standardize the staging internationally, clinical staging remain as standard of care.

## Role of Imaging and Lymph Node Assessment

Imaging (CT/MRI/PET-CT) has been utilized to define the local extent of disease and also to define lymph node status. Although Some studies have shown that MRI correlated more closely with surgico pathologic findings than CT or physical examination, its superiority over clinical examination alone to assess tumor size and local spread remain controversial.

Lymph node evaluation is critical for further treatment planning and is done either with imaging or surgery. PET/CT has been found to be more sensitive than PET alone for detection of nodal metastases.

Surgical staging includes pelvic and para aortic lymphadenectomy done either at the time of radical hysterectomy or before primary chemoradiation prior to treatment planning to individualize the radiation field. The evaluation procedure can be performed via laparotomy or laparoscopy through a transperitoneal or extraperitoneal approach. Although this modality has been utilized to define the extent of radiation and some studies have shown excellent results after surgical staging but one RCT found no survival advantage of surgical staging over clinical staging. Laparoscopic extraperitoneal lymphadenectomy has an advantage of both laparoscopy and retroperitoneal dissection and improved the accuracy of diagnosis in 24% of stage IB tumours, 52% of stage II tumors, and 45% of stage III B tumours.

**Role of Sentinel lymph node (SLN) biopsy:** SLN biopsy in management of carcinoma cervix is investigational. SLN biopsy is promising because of its high negative predictive value (NPV:98%) and sensitivity (89-90%). It is important to perform complete lymphadenectomy if the mapping procedure fails to detect a sentinel node in one hemipelvis because of increased risk of false negativity. SLN mapping has best detection rates in tumors < 2 cm although it can be used in tumors upto 4 cm. Pathology evaluation with ultrastaging is typically used for sentinel nodes, and this may result in increased identification of metastatic lymph nodes. However the importance of micrometastatic disease or isolated tumor cells in sentinel nodes remains to be established.

## Role of Tumour Markers

Role of various tumour markers including serum squamous cell carcinoma (SCC) antigen, tissue polypeptide antigen, carcinoembryonic antigen (CEA), CA-125, and CYFRA 21-2 has been investigated for assessing prognosis, monitoring response to therapy and detecting recurrence. Some studies have suggested the role of elevated pre- operative serum SCC antigen(>1.9ng/ml) for predicting the need for post op radiation therapy.

## Types of Hysterectomy

The Querleu-Morrow classification is based on the lateral extent of resection. Four types of radical hysterectomy are described, including a limited number of subtypes. Two major objectives remain constant: excision of central tumor with clear margins and removal of any potential sites of nodal metastasis. The extent of dissection in all subtypes is shown in Table 1.

**Table 1: Types of Radical Hysterectomy**

| Type of radical hysterectomy | Extent of Dissection | | |
|---|---|---|---|
| | **Lateral parametrium** | **Ventral parametrium** | **Dorsal parametrium** |
| **A** | Halfway between the cervix and ureter (medial to the ureter–ureter identified but not mobilized) | Minimal excision | Minimal excision |
| **B1** | At the ureter (at the level of the ureteral bed–ureter mobilized from the cervix and lateral parametrium) | Partial excision of the vesicouterine ligament | Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold |
| **B2** | Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structures | Partial excision of the vesicouterine ligament | Partial resection of the rectouterine-rectovaginal ligament and uterosacral fold |
| **C1 (Nerve sparing)** | At the iliac vessels transversally, caudal part is preserved | Excision of the vesicouterine ligament at the bladder. Proximal part of the vesicovaginal ligament (bladder nerves are dissected and spared) | At the rectum (hypogastric nerve is dissected and spared) |
| **C2** | At the level of the medial aspect of iliac vessels completely (including the caudal part) | At the bladder (bladder nerves are sacrificed) | At the sacrum (hypogastric nerve is sacrificed) |
| **D** | At the pelvic wall, including resection of the internal iliac vessels and/or components of the pelvic sidewall | At the bladder. Not applicable if part of exenteration | At the sacrum. Not applicable if part of exenteration |

## Managing Early Stage Disease

Early stage disease comprises of stage IA to IB1 disease. Treatment options for these patients include definitive surgery (Modified radical hysterectomy for stage IA2, Radical hysterectomy for IB1), fertility sparing surgery and primary radiation therapy with or without chemotherapy.

### *Definitive Surgery*

The benefits of Primary surgery over RT was analysed in 4885 women with early cervical cancer from SEER database and it was observed that surgery resulted in significant survival benefit compared with RT alone (hazard ratio [HR] 0.41, 95% CI 0.350.50). None of the studies have prospectively compared the survival benefits of surgery over chemoradiation in this group of patients.

Patients with stage I A2 are preferably treated by modified radical hysterectomy (class II) with pelvic lymphadenectomy which is usually definitive treatment and is associated with better survival and QOL. Para aortic lymphadenectomy should be done if pelvic nodes are suspicious of disease. Patients with stage IB are treated by Class III radical hysterectomy. Both surgery and chemoradiation are thought to be equally effective for the management of stage IB1 disease. Surgical management has potential advantages in younger women by preserving ovarian function and avoiding radiotherapy related delayed complications especially vaginal stenosis. Careful preoperative selection of patients for radical surgery avoids subjecting them to double therapy and related morbidities. Recently it has been suggested that for stage 1B1 it may be advisable to avoid parametrectomy if tumour size is<2cm and depth of invasion is <10mm because of lower incidence of LVSI (0.4-0.6%) and lower risk of lymph node metastasis.

### *Fertility Preservation Surgeries*

- Women with FIGO stage I A1 with no evidence of intermediate or high risk features (Table 2) may be treated with conization or extra fascial hysterectomy (EFH) depending on the desire to preserve future fertility. Risk of lymph node metastasis and recurrence is very low in these cases.
- Ovarian preservation is done in young women with squamous histopathology because of very small risk (0.8%) of ovarian metastasis with squamous variants than adenocarcinoma (5%). Transposition of ovaries beyond the field of radiation is done to protect ovarian function.
- Fertility preserving surgery can be done for those who desire future pregnancy and size of growth is <2cm with no lymph node involvement. LVSI is the most important prognostic factor as the risk of lymph node involvement is <1% if there is no lymphovascular space invasion (LVSI). Conization with negative margins or trachelectomy is the treatment of choice for women who wish to conserve their fertility (Table 2).

### *Primary Radiotherapy*

Primary RT can be given to those with poor surgical risk. There is no data to confirm the benefits of primary chemo-radiation in early stage disease.

## Role of Adjuvant Therapy

After surgical management patient can be planned for either observation or adjuvant treatment depending on the presence of risk factors as mentioned in Table 3.

**Table 2: Choice of treatment for carcinoma cervix**

| Stage | Choice of treatment |
|---|---|
| IA1 | Cone biopsy/Simple Trachelectomy / Simple hysterectomy<br>LND not required |
| IA2 | Cone biopsy/Simple Trachelectomy / Simple hysterectomy, LND may be done as per institutional practice |
| l A1/ l A2 +LVSI | Cone biopsy/Simple Trachelectomy / Simple hysterectomy+LND |
| l B1 | Low volume disease (<500mm3): Simple Trachelectomy / Simple Hysterectomy+LND<br><2 cm: Radical Trachelectomy/ Radical Hysterectomy +LND<br>2-4cm: Radical Hysterectomy +LND |
| lB2/IIA | Chemoradiation/ radical Hysterectomy+LND |
| llB-lVA | Chemoradiation |
| IVB | Chemotherapy+ Palliative RT |

LND : Lymph node dissection

### *Role of Minimally Invasive Surgery*

Extensive data is now available to confirm safety, feasibility, efficacy and optimum oncological outcomes of minimally invasive approach (both laparoscopic and robotic) for radical hysterectomy. Reduced blood loss and shorter hospital stay are added advantages with no difference in risk of recurrence.

## Management of Locally Advanced Cervical Cancer

This includes stage IB2 to IVA and these patients have a higher rate of recurrence and worse survival than those with early stage disease. Lymph node assessment is critical for further treatment planning. Although it does not alter the FIGO staging but changes TNM staging by American Joint Committee on Cancer (AJCC). If para aortic involvement is suspected on imaging further evaluation either with CT guided biopsy or lymphadenectomy may be done depending on protocols. Urinary tract obstruction if present should be corrected before definitive treatment as it improves progression-free survival (PFS) and median overall survival (OS).

For Stage IB2 cervical cancer surgical management comprising of Type C radical hysterectomy or chemoradiation are available. However the rate of lymph node involvement is approximately 44% in these patients. Therefore although primary surgery is feasible and has its own advantages including removal of tumour bulk , removal of bulky lymph nodes and proper assessment of tumour extension , requirement of double treatment with post op chemoradiation remain high. For stage IIA surgery or chemoradiation are thought to be equally effective.

Primary chemoradiation remains the main modality of treatment for these patients with stage IIB-IVA. Surgical management for advanced stages is associated with increased morbidity and is also not curative. Chemoradiation is associated with significant survival benefit, reduced risk of recurrence over RT but is associated with higher rates of adverse events including gastrointestinal toxicity.

**Table 3 : Planning of Adjuvant Therapy after Surgery**

| | **Intermediate risk disease** | **High risk disease** |
|---|---|---|
| Risk factors in final histology report | Sedlis' criteria<br>1.LVSI* +, deep 1/3rd of cervical stromal invasion and tumor of any size,<br>2.LVSI+, middle 1/3rd stromal invasion with tumor size ≥2 cm<br>3.LVSI +, superficial 1/3rd of stromal invasion and tumor size ≥5 cm<br>4.No LVSI but deep or middle 1/3rd stromal invasion and tumour size ≥4cm | Peter's criteria<br>1.Pathological node involvement<br>2.Parametrial invasion<br>3.Positive surgical margins |
| Risk of recurrence following surgery alone | 30% | 40% |
| Treatment of choice | Adjuvant RT# | Chemoradiation |

*LVSI: Lymphovascular space invasion, RT# Radiotherapy,

## Role of Radiotherapy

Radiation is delivered to pelvis using external beam RT (radiotherapy) and brachytherapy with or without chemotherapy.

**Brachytherapy:** Brachytherapy delivers higher dose of radiation to cervix and at the same time also spares normal tissues. Brachytherapy is usually initiated during EBRT once optimal tumour reduction is achieved that occurs between 2-5 weeks. It can be delivered either with Low dose rate (LDR: 0.4-2 Gy per hour), Pulse dose rate (PDR: using HDR source but treating only 10-30 min at a time), high dose rate ( HDR: >12 Gy per hour). The dose delivered per brachytherapy procedure is adjusted to account for the total number of insertions. The following techniques can be used for application

1. Intracavitary application includes placement of intrauterine tandem with vaginal ovoids, vaginal cylinders, or a vaginal ring. The dose to bladder and rectum is reduced with shielded ovoids or vigorous packing.
2. Interstitial brachytherapy consist of placement of needles especially in cases with extensive vaginal involvement.
3. PDR brachytherapy uses a single Iridium-192 source that is programmed to move through various dwell positions in placed applicators using remote after loading technology.

The prescribed brachytherapy dose depends on tumor stage, initial disease bulk and response to pelvic radiation, ability to displace bladder and rectum, and use of LDR, HDR, or PDR technique. The total prescription dose to point A is 80 to 90 Gy LDR equivalent, depending on tumor stage

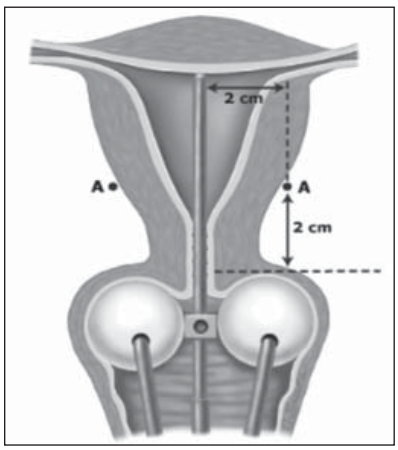


**Fig 1 : Brachytherapy reference points**

### *Recent Advances in Brachytherapy*

IMRT (Intensity modulated RT) use preliminary data has shown similar survival outcomes and improved toxicity profiles. The treatment of locally advanced disease has undergone paradigm change during the last two decades. In 1999 concomitant chemoradiation became the standard of care with a 6% improvement in OS. Studies showed that clinical factors such as FIGO stage, response to EBRT, treatment time, tumor width at diagnosis interfere with the dose – response relationships. A trend thus emerged, towards tailored approach of treatment, with adaptation of planning aims according to tumour width, response, stage, treatment time and development of individualized applicators. The introduction of image guided adapted brachytherapy (IGABT) has been another advancement in the management of locally advanced disease. IGABT provides high local control rates and low morbidity as compare to classical radiographs based brachytherapy modality. Image-guidance modalities are developed with a better use of MRI or even the use of more easily available modalities including transrectal ultrasound. Moreover geometrically constructed points that have been used since decades for treatment planning and organs at risk dose evaluation are replaced by use of target delineation and dose volume histograms.

**Treatment of para aortic nodes**: Para-aortic lymph node involvement occurs in 11-50% cases of locally advanced cervical cancer Para aortic involvement is a poor prognostic factor with 5 year survival rates of 40%. These patients require extended field RT with superior border of the field to the level of T12 to L1. Extended field RT improves survivial but is associated with a high rate of acute and late toxicities. There is not enough evidence to suggest the prophylactic extended field radiotherapy without evidence of paraaortic node involvement and therefore usually extension of the upper border of the field by 5 cm above the last gross nodal disease detected, is often advised.

## Integrating Chemotherapy in the Management of Cervical Cancer

Concurrent chemoradiation (CCRT) (with cisplatin alone or in combination) is currently the standard treatment approach. CCRT results in a 5-year overall survival rate of 66% and a disease-free survival of 58%. About 30–40% of patients with locally advanced cervical cancer fail to achieve complete response to CCRT; alternative approaches are needed to improve the outcome for such patients (Table 4).

**Time of Completion of Chemoradiation** : Chemoradiation should be completed within 8 weeks time. Time to completion of brachytherapy >8 weeks is associated with a higher rate of disease progession within the pelvis, though there is no effect on distant disease progression or disease-specific mortality.

## Role of Targeted Therapy

Recently, a number of molecular pathways that are involved in cellular proliferation, interaction with angiogenesis, extracellular matrix adhesion/ invasion, apoptosis, cell cycle pathways and DNA repair mechanisms have been identified as potential therapeutic targets (Table 5). Bevacizumab is associated with improved survival in patients with recurrent/ metastatic cervical cancer. Whether Bevacizumab and other similar novel agents targeting molecular pathways could be used in front-line treatment along with cytotoxic chemotherapy is likely to be an area of research in future studies.

**Table 4: Overview of Chemotherapy Regimen**

| *Chemotherapy regimen* | *Drug used* | *Mechanism of benefit* | *Impact on survival* |
|---|---|---|---|
| CCRT (Concurrent chemoradiation) | Cisplatin either alone or with 5- FU/ Gemcitabine | Cytotoxic and anti-proliferative effects<br>Also targets microscopic systemic foci thus reduces local and distal recurrence<br>Inhibits the repair of sublethal damage from radiation<br>Radiosensitizer<br>Hypoxia sensitizer | Benefit of 6% in OS at 5 years with CCRT as compare to RT(HR = 0.81, p < 0.001)<br>**Cisplatin + RT versus cisplatin-based doublet chemotherapy + RT**<br>cisplatin-based doublet chemotherapy along with RT was associated with improved OS and PFS and a reduced rate of locoregional relapse for patients (FIGO stage IB–IVA). |
| NACT Prior to RT | Cisplatin based combinations | May shrink primary tumor, making malignant cells sensitive to subsequent RT<br>Higher concentration at tumour site in radiation naïve patients, Targets micro-metastatic disease. | After 2-3 cycles response rates vary from 40-80% with CR in <10%. No improvement in PFS and OS as compared to radiation alone. Rather outcome was inferior to RT in few studies. |
| NACT Prior to surgery | VBP<br>BOMP | Reduced the need for adjuvant RT by decreasing tumor size and lymph node and distant metastasis | 5-year OS NACT arm = 70%;Sx arm = 74.4% (p=0.85). |
| NACT for fertility preserving surgery (Done for stage IB1 | CHF | A tumor size of >2 cm and a stromal invasion depth of >50% are risk factors for recurrence | Following 2–3 cycles of NACT, more than 50% of patients achieve pathological CR and have a good reproductive outcome. |
| Dose dense NACT prior to CCRT | Weekly Paclitaxel (60–80 mg/m$^2$) and Carboplatin (AUC 2) for 6 weeks | This combination maximizes potential additive/synergistic interactions with different mechanism of actions. | Following dose dense NACT, a response rate of 67.5–70% was achieved, mostly being partial responses. After CCRT, 85–100% of eligible patients achieved CR. |
| Adjuvant chemo After surgery or RT | | | May improve survival in early stage disease. Insufficient data for its role in advanced disease. |
| Palliative chemo | Ifosfamide, Bleomycin, 5-FU, Mitomycin C, Paclitaxel, Gemcitabine, Topotecan, combination | Recurrent disease | Combination regimen could achieve complete response in 10-20% pts and a median duration of response of 7-12 months. |

NACT: Neoadjuvant chemotherapy, CR: complete remission, RT: Radiotherapy, VBP = vincristine, bleomycin and cisplatin, BOMP = Bleomycin, Vincristine, Mitomycin-C and Cisplatin, CHF: Cisplatin, Hydroxyurea, 5 FU

**Table 5: Pathways and Agents for Targeted Therapy in Management of Carcinoma Cervix**

| *Pathway* | *Therapeutic agent* | *Comments* |
|---|---|---|
| Epidermal growth factor receptor (EGFR) | Monoclonal antibody: Cetuximab-chimeric Matuzumab-humanized<br>Tyrosine kinase inhibitor: Gefitinib Erlotinib | EGFR is a transmembrane protein critical for cell survival. If overexpressed can lead to resistance to chemo and radiation. Minimal benefit on PFS, OS when used for Tt of both recurrent and persistent cervical cancer. |
| Human epidermal growth factor receptor-2 (Her-2-neu) | Lapatinib | 5% Objective response rates. |
| Angiogenesis | Bevacizumab, Pazopanib, Sunitinib<br>Helps To normalize the abnormal tumor vasculature, increase tumor oxygenation, and reduce interstitial fluid pressure | In a GOG study of 452 pts with recurrent, persistent or metastatic cervical cancer the addition of bevacizumab to chemotherapy was associated with increased OS and higher response rates, but with increased incidence of hypertension, thromboembolic events and gastrointestinal fistulas. |

**Prognosis of disease:** Table 6 depicts 5 year survival for FIGO stage.

**Table 6: Stage wise survival rates for Cervical Malignancy**

| FIGO stage | 5 year survival |
|---|---|
| IB | 80% |
| IIA | 63% |
| IIB | 58% |
| III | 30% |
| IV A | 16% |

## Quality of life (QOL) issues

Cancer treatment is known to be associated with negative impact on quality of life. In a survey conducted on 121 cervical cancer survivors it was observed that patients treated with surgery followed by adjuvant RT had the poorest QOL scores compared with women treated with either surgery alone or surgery followed by adjuvant chemotherapy. A higher degree of sexual dysfunction is seen in these women. Survivors did not

have issues related to achieving orgasm after one year of treatment but lack of lubrication was the most frequent complaint especially among those treated with RT.

HRT does not increase the risk of replication of HPV or recurrence. There is no difference in survival or cancer recurrence between HRT users and non users.

## Summary

The management of cervical cancer currently requires a multidisciplinary team approach. Over the past few years, women with cervical cancer have benefited from improved imaging techniques, better treatments (including chemoradiotherapy), and more conservative surgical approaches. A careful review of clinical findings, imaging, pathology and availability of surgical skills can aid clinicians in making decisions about individual treatment modality.

## Suggested Reading


- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): cervical cancer. Version 1.2016.
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# Fertility Preservation in Endometrial Cancer

**Monisha Gupta**
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## Introduction

Endometrial carcinoma (EC) is primarily a disease of post-menopausal women, and is relatively uncommon in younger women of childbearing age group (2-14%).[1] Due to current trend of delayed childbearing, a significant number of premenopausal nulliparous women will be diagnosed with EC. In this age group, EC may be familial, associated with Lynch syndrome, or sporadic, associated with obesity, PCOS, anovulatory cycles or other hyper estrogenic conditions.

EC in young age group is often well-differentiated endometrioid adenocarcinoma with infrequent myometrial invasion and lymph node metastasis. Thus, the standard surgical treatment (Total hysterectomy with bilateral salpingo-oophorectomy and assessment of retroperitoneal lymph nodes) poses a challenging dilemma to oncologists. Therefore, the possibility of fertility preserving management with no survival compromise for young women with EC using hormonal agents is an emerging issue for both women and oncologists.

The important issues a treating oncologist has to consider before offering conservative approach to women with EC:

1. Tumor's clinicopathological features: histological type, grade, presence of myometrial invasion and LVSI.
2. Optimal type, dose and duration of hormonal treatment and proper follow up.

## Selection of Right Patient

Only women with stage IA (with no myometrial invasion) grade 1 endometrioid EC should be offered conservative management, if desired. These women have excellent prognosis with chances of retro-peritoneal lymph node involvement less than 1% and 5 year overall survival (OS) exceeding 95%.[2] Also, they have a greater chance of responding to treatment with progestins. However, to establish correct grade and stage of tumor without performing hysterectomy is not an easy task.

### Grade: Dilatation and Curettage (D&C) Vs Pipelle Biopsy

The differentiation or grade of EC is the most important predictor of stage and response to treatment with progestins. Duska et al[3] demonstrated that only grade 1 EC could predict stage 1 disease among young women with EC. In addition, Thigpen et al showed that in advanced disease the response rate to MPA was 37% for grade 1 tumors compared with only 9% for grade 3 tumors.

Endometrial biopsy is gold standard to diagnose EC. Both D&C and Pipelle biopsy can be used for histological diagnosis. When both the techniques were compared, D&C correlates better with final histology. Specifically for grade1 EC, Leitao et al[4] showed that the rate of up gradation on final histology was 8.7% with D&C and 17.4% with Pipelle biopsy, a statistically significant difference ($p = 0.007$). Also, D&C removes the tumor completely, thus, theoretically, reducing the tumor burden and enhancing the response to progestins.[4]

***Recommendation: D&C is recommended by European Society of Gynecological Oncology Task Force (ESGOTF) and ESMO-ESGO-ESTRO consensus.***

### Histological Difficulties in Grading Type 1 EC

In a Japanese study among 47 patients, 7 discrepancies in histological diagnosis between its centre and the central review were identified. Specifically, 5 cases were downgraded from grade1 EC to atypical hyperplasia, whereas 2 cases were upgraded from grade 1 to grade 2. In a study by Kaku et al[5], only 19 of 39 cases of either endometrial hyperplasia or EC were confirmed correctly after a thorough histological review performed by 3 different pathologists. Therefore, some presumed cases of EC were included in the analysis showing excellent response rates, which could have been only cases of atypical hyperplasia where higher response rates are expected. This highlights the need for review of initial pathology from more than one experienced histopathologist.

***Recommendation: All specimens should be examined by 2 pathologists (ESGOTF) or a specialised gynaecopathologist (ESMO-ESGO-ESTRO Consensus)***

### Stage: Myometrial Invasion (MI) According to Imaging

Myometrial invasion is second most important factor for advanced disease in patients with EC. The 5-year OS of women with superficial MI is 80-90%, that drops down to 60% when deep MI is identified. Thus, it is crucial to identify MI correctly when managing women with EC conservatively.

Transvaginal ultrasound scan (TVUS), Computed tomographic scan (CT-Scan), and magnetic resonance imaging (MRI) scan have all been studied quite thoroughly with various sensitivities and specificities. According to a meta-analysis, the authors reported a post-MRI probability of MI of less than1% in grade1 tumors if the MRI scan was negative.

TVUS has also yielded promising results in identifying degrees of MI when performed by experienced radiologists. In a prospective study, TVUS showed comparable efficiency to MRI scan and could be used in centres with difficult access to MRI.[13] However, we have to emphasize that a method for predicting MI with an accuracy of 100% does not exist.

***Recommendation: Enhanced MRI scan is the option for establishing the depth of MI (ESGOTF AND ESMO-ESGO-ESTRO Consensus). Expert Ultrasound can be considered as an alternative option***

## Selection of Medication and Dose

### MPA or MA and the Role of LNG-IUD

Various hormonal agents have been described in literature for conservative management of EC in young women: MPA (Medroxy Progesteroce Acetate) and MA (Megestrol Acetate) being the most common. Other medications like GnRH analogs, letrozole, tamoxifen and LNG-IUD are being evaluated. However, there is no RCT so far comparing the efficacy of all the regimens.

Conflicting data exists in literature regarding comparison between MPA and MA. According to a meta-analysis[6], the use of other medical therapies (including MPA) was associated with a higher risk of recurrence when compared with MA. In contrast, the so far largest series, which had not been included in the previously mentioned meta-analysis, revealed - although the complete response rate was similar- MPA was associated with reduced risk of recurrence[7]. In several studies, different doses have been used of either MPA (100 -1200mg/d) or MA (40 to 600 mg/d). However, most of the series were small and retrospective and due to their inherent heterogeneity, definitive conclusions cannot be drawn

LNG-IUD is as effective as oral progestins in terms of response rates in patients with EC. In a prospective study, LNG-IUD and GnRH analog were used for young women with EC and comparable results (using either MPA or MA) with complete remission rate of 57% and recurrence rate of 25% were shown.

***Recommendation: Either MPA (400-600mg/d) or MA (160-320mg/d) should be used (ESGOTF and ESMO-ESGO-ESTRO Consensus). However, treatment with LNG-IUD with or without GnRH analogues can also be considered (ESMO-ESGO-ESTRO Consensus).***

## Duration of Treatment, Response and Follow –up

So far, the optimal duration of treatment with hormonal agents has not been determined.

In the Korean study, the mean duration of treatment with progestins was 8 months (2-31 months) and the median time to achieve complete response was 18 weeks (8-55 weeks).[7] Koskas et al[6] showed that most of the patients will respond within 6 months of treatment (72.4%) with only a small additional benefit for prolongation of treatment after that (78% at 12 months).

In the largest retrospective as well as prospective cohort, complete response was defined as absence of any form of hyperplasia.[7] According to the study detailing the histopathologic changes associated with progestin therapy (including LNG-IUD), only persistent architectural abnormalities and/or cytologic atypia in the 7- to 9-month biopsies are predictive of treatment failure. Response rate associated with conservative management of EC is ~75%.[8] To prove complete response, histological assessment with either D&C or Pipelle biopsy should be done. In this respect, a small prospective observational study has demonstrated that Pipelle biopsy is less reliable as compared to D&C.

In case of complete response, it is advisable to pursue pregnancy as early as possible (as chances of recurrence is as high as 40%[8]), even during the first month after achieving complete response. Thus, women should be referred to fertility clinic for assisted reproductive treatment (ART) to reduce the time to conception, thus reducing the time at risk for recurrence. For patients not willing to conceive immediately, maintenance treatment with low-dose cyclic progestin or a progestin-containing IUD (better treatment compliance) should be offered as it has been shown to be associated with lower chances of recurrence in a Korean study.[15]

After completion of childbearing, definitive surgical treatment should be offered to women as chances of recurrence is high and also, because the predisposing factors of unopposed estrogens leading to EC have not been corrected.[5]

### *Recommendation*

- **Initial assessment with D&C and imaging at 6 months should be done.**
- **In case of complete response, conception must be encouraged and referral to fertility clinic is recommended.**
- **Maintenance therapy should be considered in responders who wish to delay pregnancy.**
- **Patients not undergoing hysterectomy should be clinically re-evaluated every 6 months.**
- **After completion of child bearing, standard surgical treatment is recommended. Preservation**

**of bilateral ovaries can be considered depending upon age and genetic risk factors**.

## Role of Progesterone Receptors (PgR)

Duska et al[3] showed that estrogen and PgR positivity or negativity was comparable between responders and non responders. However, other studies suggested that response to progesterone was significantly associated with the presence or absence of PgRs.

***Recommendation: Although PgR status is a reliable predictive factor for disease remission, a routine check is not recommended as significant number of PgR negative women will also respond to progestin therapy (ESGOTF and ESMO-ESGO-ESTRO Consensus)***

## Non-responders or Partial Responders

Women with EC on conservative management are likely to respond within the first 6 months of treatment with either MPA or MA.

### *Recommendation:*

- **If no response at 6 months, standard surgical treatment should be done.**
- **In case of partial response (complex atypical hyperplasia), women could be offered continuation of treatment with MPA for another 3 to 6 months.**

## Recurrence

The recurrence rate of EC after conservative management is consistently reported between 30% and 40%, while the median time to recurrence is 15 months (4 - 66 months).[7,8] In addition, Koska et al[6] meta-analysis showed that the probability of recurrence was increasing in relation to time for at least 5years.

There is literature for re-treatment with progestins for recurrent EC. In a study of 27 patients by Perri et al[9], 15 of 24 complete responders experienced a recurrence after initial treatment with progestins. Eleven of them were retreated with progestins and all of them responded again with 3 subsequent pregnancies. Park et al[10] showed that among 33 patients that were re-treated with progestins after initial complete response, five patients delivered six healthy babies. After a follow-up of 51 months, none of the patient had died of disease.

***Recommendation: In case of recurrent disease in initial complete responders, re-treatment with progestins seems to be efficient and hence can be offered.***

## Success Rates and Pregnancy Outcomes

All the meta-analysis and review studies on conservative management of EC with progestins have shown the complete response rate of 75%. Gallos et al's meta-analysis showed a pooled regression rate of 76.2%.[8] These numbers are comparable with the Korean series reporting a response rate of 77.7%.[7]

Gallos et al[8] showed that among 325 women treated with progestins, 75 managed to achieve at least one live birth, resulting in a pooled live birth rate of 28%. Furthermore, the live birth rate among women trying to conceive reached 39.4% when ART was used compared to only 14.9% with spontaneous conception.

Regarding the question whether ART is safe, in conservatively treated EC patients, Park et al[10] reported comparable 5-year disease-free survival rates between women receiving fertility drugs and women trying to conceive spontaneously. Also, the disease-free survival was improved significantly among patients who achieved at least one pregnancy compared with those who did not. Moreover, this difference remained irrespective of whether ovulation drugs had been used or not.

### *Recommendation*

- **Complete response rates are up to 75%.**
- **Women with complete response with progestins should be promptly referred and encouraged regarding the use of ART.**

## Risk of Synchronous and Metastatic Ovarian Tumors

A multicenter retrospective study found that among 102 young women with EC, a synchronous or metastatic ovarian carcinoma was identified in 25%. However, this percentage accounts for all stages and grades of EC. In 26 women who were treated conservatively (presumed grade 1 and no myometrial invasion), only 1 (3.8%) synchronous ovarian carcinoma was identified after treatment failure.

Signorelli et al[11] reported performing staging laparoscopy routinely in all cases of conservative management in EC to exclude the presence of synchronous ovarian tumors. Among the 21 patients, despite intensive screening with MRI scan, U/S scan and diagnostic laparoscopy, 2 (9.5%) patients with intraparenchymal ovarian carcinomas (15 and 12 mm) were identified soon after failure of conservative management. Yamazawa et al, reported that 2 patients who developed recurrent EC after complete initial response with MPA were found to have a synchronous ovarian cancer at the time of hysterectomy.

***Recommendation: Excluding suspicious ovarian lesions with imaging modalities like MRI scan or TVUS is mandatory. The possibility of a diagnostic laparoscopy should be discussed with the patient; however, no strong evidence exists to support its routine use***.

## Recent Advances

Recently, translation studies have shown that metformin has an anti-proliferative effect in women with EC and insulin resistance and thus, suppresses the EC cell growth[12], suggesting future role of metformin in combination with progesterone and active weight management for the treatment of early stage EC in the future.

Young women with EC should also be counselled regarding a genetic test for detection of women with Lynch syndrome[27] who will need a very close monitoring about their further follow up and management. However, it is debatable whether a patient with Lynch Syndrome should be offered conservative management for EC.

## To Conclude

The incidence of young women with EC asking for fertility preserving management is going to increase in the future, thus it's a high time that oncologists should formulate standard guidelines on how to manage these women conservatively without compromising survival outcome. The use of progestins seems to offer very good results in terms of response rate and fertility outcomes. Also, despite high recurrence rate, the mortality associated with conservative management of EC is extremely low.

Extensive counselling of the patient with detailed information about all aspects and risks associated with conservative management is mandatory and informed written consent should be obtained.

The above mentioned recommendations should be interpreted with caution as they are based upon mainly retrospective low quality evidence and thus, individualisation of treatment for every woman is still a norm as every woman has different characteristics as well needs and expectations.

## Suggested Reading


1. Lekhi A, Manchanda R et al. Emdometrial carcinoma in young women management options and its review. *Int J Reprod Contracept Obstet Gynecol. 2016; 5(4): 944-47.*
2. MorrowPC, BundyBN et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynaecologic Oncology Group study*. Gynecol Oncol. 1991; 40: 55-65.*
3. Duska LR, Garrett A, Rueda BR, et al. EC in women 40 years old or younger. *Gynecol Oncol. 2001; 83: 388-93.*
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8. Gallos ID, Yap J et al. Regression, relapse, and live birth rates with fertility-sparing therapy for EC and atypical complex endometrial hyperplasia: a systematic review and meta-analysis. *Am J Obstet Gynecol.2012; 207:266.e1-266.*
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10. Park JY, Seong SJ, Kim TJ, et al. Pregnancy outcomes after fertility-sparing management in young women with early EC. *Obstet Gynecol. 2013; 121:136-42.*
11. Signorelli M, Caspani G, Bonazzi C, et al. Fertility-sparing treatment in young women with EC or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. *BJOG. 2009; 116:114-18.*
12. Takahashi A, Kimura F, Yamanaka A, et al. Metformin impairs growth of EC cells via cell cycle arrest and concomitant autophagy and apoptosis. *Cancer Cell Int. 2014; 14:53.*


## Calendar of Monthly Clinical Meetings 2017-2018

| Months | Name of the Institute |
|---|---|
| 29th September 2017 | Hindu Rao Hospital |
| 27th October 2017 | ESI Hospital, Basaidarapur |
| 24th November 2017 | MAMC & LN Hospital |
| 29th December 2017 | Sir Ganga Ram Hospital |
| 19th January 2018 | Dr RML Hospital |
| 23rd February 2018 | Lady Hardinge Medical College |
| 23rd March 2018 | UCMS & GTB Hospital |
| 27th April 2018 | Apollo Hospital, Sarita Vihar |

# SOP: Endometrial Hyperplasia

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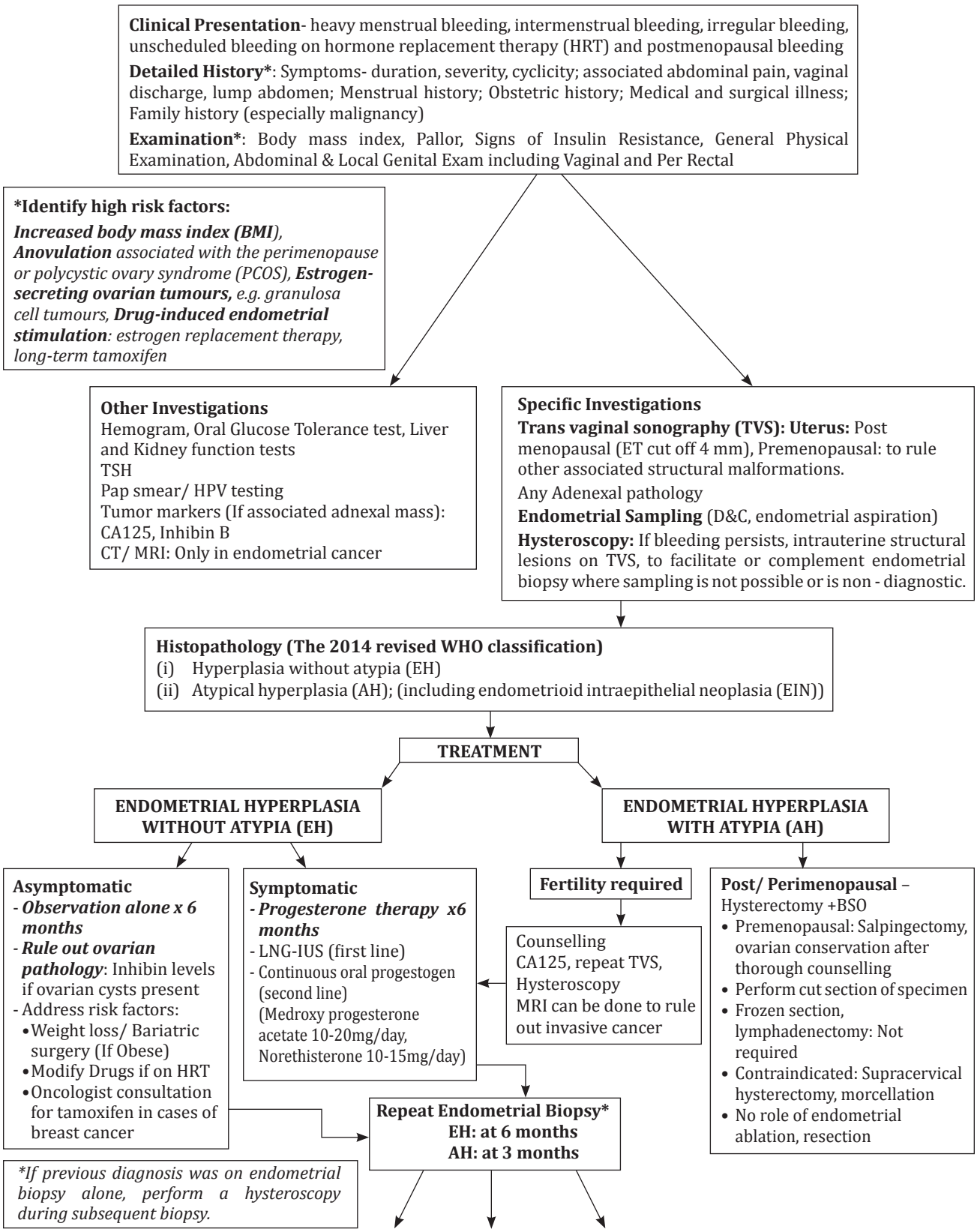

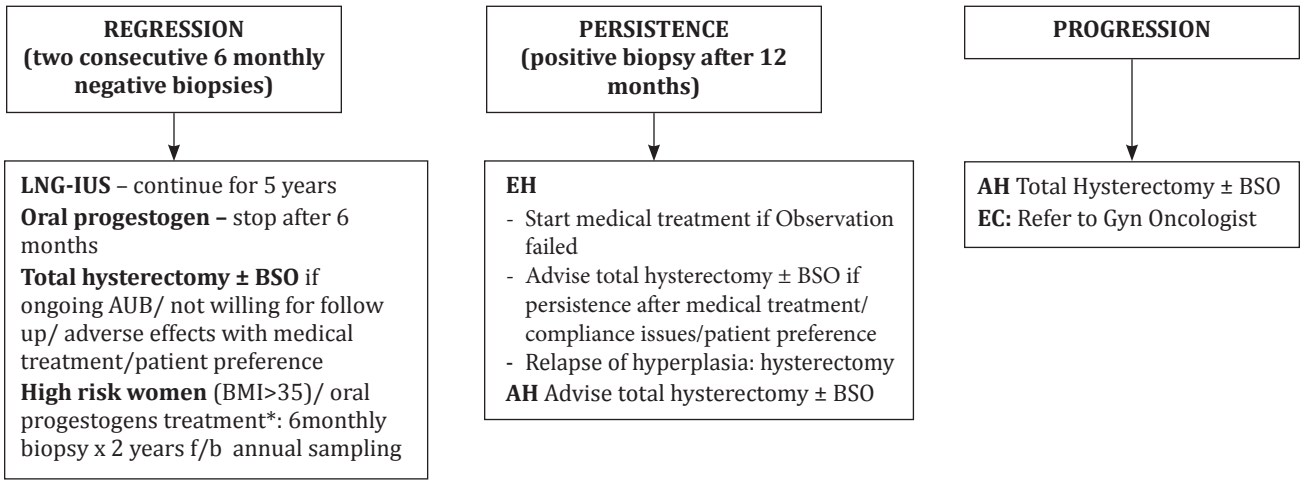


**Notes**

1. Post menopausal woman: Hysterectomy with BSO
2. Perimenopausal woman: Hysterctomy with salpingectomy. Ovarian conservation in hyperplasia without atypia after through counselling
3. Premenopausal: Ovarian conservation after counselling

**Notes**

EH: Risk of progression to cancer: <5% in 20 years; 75-81% spontaneous regression, 85-96%regression after progestogen

AH:25-30% progession to cancer in 20 years; 35-40% may have concurrent endometrial cancer

## References

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2. Management of Endometrial Precancers 2012. Avaialble at: https://sgo.org/wp-content/ uploads/2012/11/Management-of-Endometrial-Precancers.pdf. Accessed on 19th August 2017
3. Management of endometrial hyperplasia. Available at: http://www.uptodate.com/ contents/management-of-endometrial-hyperplasia. Accessed on 20th August 2017.

## Forthcoming Events

- CME on **"Induction of Labour"** by FOGsd under aegis of AOGD on 22nd September, 2017 at 01:30pm, Madhuban GK- 1. For participation contact : Dr Anita Sabharwal (9810366459).
- Gynae Endocrine Society of India in association with AOGD is organizing Symposium under theme of **"Ovary: Unfolding the secrets in management"** in case-discussion format, to be held on 24th September, 2017 at J L N Auditorium, AIIMS, New Delhi.
- Skill Workshop of AOGD on **"Obstetrics Skills"** on 28th September, 2017 at 7th Floor, MCH Block, GTB Hospital. Registration Free. Contact: AOGD Office (011-22692505)
- Next **AOGD Clinical Meeting** on 29th September, 2017 at Hindu Rao Hospital.
- **39th AOGD Annual Conference** on 18th and 19th November, 2017 at Indian Habitat Centre; Pre-conference workshops on 17th November, 2017. Visit website: www.aogdconference.com.

# Screening of Common Gynaecological Cancers in A Nutshell

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Gynaecological cancers are a group of different malignancies of the female reproductive system. The most common types are endometrial, ovarian and cervical cancer. The other less common gynaecological malignancies are of the vagina, vulva, fallopian tube and gestational trophoblastic tumours. Though cervical cancer incidence has seen a decline but it still remains the second most common cancer in women after breast cancer.

This chapter focuses on screening protocols for the more common gynaecological cancers and also touches upon the screening guidelines for breast cancer as it is the most common cancer affecting women in India.

**Screening** is defined as the process of subjecting an "at risk asymptomatic" population to tests which help to detect the disease at a stage when it is curable. Theoretically a disease benefits from screening if it has a preclinical stage.

## Endometrial Cancer

Endometrial cancer is the most common gynaecological cancer in the developed countries, with an increasing incidence seen in postmenopausal women. In lesser developed countries like India, it is less prevalent. Its main risk factors are obesity and unopposed estrogen stimulation of the endometrium. 5% of endometrial cancers are associated with Lynch syndrome type II. Abnormal uterine bleeding is the most common symptom in 90% of the patients. This cancer has a good prognosis if detected early with five year survival rate of about 80%.

## Screening Guidelines

**Screening for endometrial cancer for asymptomatic women is not recommended by any major organization.**

International guidelines including British Gynecological Cancer Society (BGCS) and The National Cancer Institute's (NCI) don't recommend screening for endometrial cancer based on the following facts:

- No evidence suggests that transvaginal sonography reduces mortality from endometrial cancer.
- There is inadequate evidence that endometrial sampling (biopsy) reduces mortality.
- The early clinical presentation and high early detection rate of endometrial cancer (85%) makes it unlikely that screening will have a successful impact on earlier detection and increased survival rate.

The American Cancer Society (ACS) recommends that at the time of menopause, all women should be made aware of the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physician.

***Transvaginal sonography (TVS)*** as a diagnostic tool for endometrial cancer has been widely investigated. An endometrial thickness of ≤ 4 mm reduces the probability of endometrial cancer to < 1%. However, in asymptomatic women i.e. without abnormal bleeding this cut off has high false positive and poor sensitivity.

***Endometrial sampling with Pipelle's aspirator*** is indicated in symptomatic women with thickened endometrium, but in asymptomatic women its role has limited acceptability. It may yield insufficient tissue in up to 25% cases and in addition may cause discomfort, bleeding, increased risk of infection and perforation.

## Postmenopausal Women Receiving Tamoxifen Therapy

Tamoxifen increases the risk of endometrial cancer two- to threefold. Its effect on the endometrial lining is not seen before 2 years of use. However, the absolute risk of developing endometrial cancer while taking tamoxifen is 1.2/1,000 per year or only 6/1,000 after 5 years.

The NCI's PDQ cancer information summary, ACOG and ACS agree that there is no indication that routine screening would improve early detection or survival rates for women at increased risk for endometrial cancer due to a history of receiving either estrogen therapy or tamoxifen therapy. BGCS recommends routine questioning of these women at breast cancer follow up visits about symptoms of vaginal bleeding / discharge. The women must be made aware of the risks. Symptoms if any should be investigated with ultrasound and hysteroscopic directed biopsy.

## Lynch Syndrome

Women with Lynch syndrome (Hereditary NonPolyposis Colorectal Cancer) have a 60% increased risk for endometrial cancer and an 80% increased risk for colorectal cancer.

Joint guidelines issued the European Society for Medical Oncology, the European Society of Gynaecological Oncology, and the European Society of Radiotherapy

and Oncology (ESMO/ESGO/ESTRO) recommends annual surveillance by transvaginal ultrasound and biopsy starting from the age of 35 until hysterectomy for all Lynch syndrome mutation carriers. In addition, for management of women with Lynch syndrome recommendations include:

- Annual screening beginning at age 35
- Regular hysteroscopy and endometrial biopsies
- The application of local progesterone using the levonorgestrel intrauterine device
- Treatment of premalignant disease (i.e, atypical endometrial hyperplasia or endometrial intraepithelial neoplasia).

The National Comprehensive Cancer Network (NCCN) guidelines endorse universal immunohistochemistry (IHC) or microsatellite instability (MSI) testing to diagnose Lynch syndrome in :

- All individuals diagnosed with colorectal or endometrial cancers
- All women diagnosed with endometrial cancer before age 50
- Family members of patients with Lynch syndrome.

The NCCN guidelines include the following recommendations for surveillance and risk reduction in women with Lynch syndrome:

- Hysterectomy and bilateral salpingo-oophorectomy should be offered to women who have completed child bearing and carry *MLH1, MSH2,* or *MSH6* mutations
- Annual endometrial sampling for carriers of *MLH1* or*MSH2*
- Annual colonoscopy (to decrease risk of colorectal cancer).

Routine transvaginal ultrasound and serum CA-125 testing are not recommended.

In 2014, joint guidelines published by the American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) recommend that all women who are diagnosed with endometrial cancer should be screened for Lynch syndrome. Genetic testing is preferred when resources are available, but clinical screening that includes focused family history is acceptable. Asymptomatic women with a first-degree relative diagnosed with either endometrial or colorectal cancer before age 60 should also be tested.

# Ovarian Cancer

It is the 7th most common cancer diagnosed in women worldwide. Early stage ovarian cancer has a high cure rate ( a 5 year survival rate of 92%) but usually at the time of diagnosis only 15% of the patients have disease confined to the ovary. Therefore there is a need to formulate screening guideline to detect ovarian cancer in the early stages.

At present there are no screening programmes for ovarian cancer as there are no reliable screening tests available for detection of ovarian cancer in the early stages. NICE Guidelines recommend protocols utilizing CA 125 and then transvaginal sonography in evaluating women with suspected ovarian cancer.

The following are the recommendations of various societies in the United States.

## *Asymptomatic Population*

- US Preventive Services Task Force (USPSTF ) in 2016 has concluded that annual screening of asymptomatic women with transvaginal ultrasonography and testing for a tumour marker , CA-125 does not decrease the ovarian cancer deaths, but can lead to major surgical interventions in women who do not suffer from cancer. Therefore, with evidence suggesting that harms of screening outweigh the benefits, **USPSTF recommends against screening for ovarian cancer in asymptomatic women.**
- ACOG, ACS, SGO, and Memorial Sloan Kettering Cancer Center also recommend against screening in aysmptomatic women.
- At present there are no validated tests which can screen for ovarian cancer in general public.

## *At Risk Population*

These include women with

1. BRCA1 and BRCA2 genetic mutation
2. Lynch Syndrome
3. Family history of ovarian cancer. History of 2 or more 1st or 2nd degree relative with a history of ovarian cancer or a combination of both.
4. Ashenazi Jewish descent having 1st or 2nd degree relative on the same side of the family with breast or ovarian cancer.

The lifetime risk of ovarian cancer in this population ranges from 5%- 46%. Annual screening with a combination of a thorough pelvic examination, measurement of serum levels of CA-125 and transvaginal Sonography(TVS) may be offered in high risk population.

## Surgical Intervention for Ovarian Cancer Prevention

The recommended surgery *is* ***Risk Reducing bilateral salpingo-oophorectomy (RRSO)*** at 35-40 years and upon completion of family or at least 5-10 years prior to age of detection of ovarian cancer in family member. RRSO also reduces the risk of breast cancer by 30-75% in these women. Women who do not wish to undergo RRSO due to the health risks associated may be offered

the option of salpingectomy after childbearing is completed, followed by oophorectomy in the future.

### Risk of Ovarian Cancer Algorithm (ROCA)

The ROCA was designed to improve the sensitivity of CA 125 in detecting ovarian cancer. It is based on the hypothesis that CA 125 levels would steadily increase over time in a women who is likely to develop ovarian cancer whereas the levels of CA 125 would remain stable or even decrease in a non cancerous condition like endometriosis. The CA 125 levels and age of a women are incorporated in a mathematical model to infer the ROCA score. It aims to intercept the increase in the levels before it starts to spread.

In US and UK ( UK Collaborate Trial of Ovarian Cancer Screening ) ROCA trials conducted have reported to have results consistent with each other. Both the trials showed specificity of 99.8% and positive predictive value of 37.5%. However survival data are not mature enough to allow us to determine whether ROCA can reduce the mortality levels for ovarian cancer.

### UK Familial Ovarian Cancer Screening Study (UKFOCSS)

This is an ongoing study for high risk population for ovarian cancer. It includes those females with BRCA 1/2 mutation or >10% lifetime risk for ovarian cancer, who refused risk reducing bilateral salpingo oophorectomy. Phase I of the trial concluded that transvaginal sonography and CA 125 screening in high risk women lacks sensitivity for early stage disease. In its phase II trial it included CA-125 level measurement every 4 months and incorporated ROCA. TVS was performed if ROCA results were normal or earlier at 2 months if abnormal. Phase II trials have concluded that ROCA based screening is an option for women at high risk who defer or decline RRSO. However it remains unknown whether this strategy would improve survival in screened high risk women.

### Newer Developments

#### *Human Epididymis Protein 4 (HE-4)*

HE-4 is a protein first discovered in the distal epithelium of the epididymis. Its levels are found to be elevated in ovarian cancer being higher in serous and endometrioid type than in other types. HE-4 as a marker for ovarian cancer has a sensitivity of 90% and a specificity of 77.6%. When combined with CA-125 the sensitivity is increased to 94%. At present this marker has the FDA approval for monitoring of ovarian tumors where CA-125 levels are normal.

#### *Surface - enhanced laser desorption ionization time-of -flight mass spectrometry (SELDI-TOF MS)*

SELDI-TOF MS technique was first introduced in 1993. This technique is a highly sensitive protein analysis tool capable of detecting minute protein profile differences between biological samples. In studies to diagnose ovarian cancer it has shown sensitivity, specificity and accuracy of 99%.It can prove to be a promising tool in diagnosis of early and advanced stage ovarian cancer.

## Cervical Cancer

India accounts for 17% of world population & 26.2% of global incidence of cervical cancer. It is leading cause of cancer related deaths in women in developing countries. One out of every four deaths due to cervical cancer is of an Indian woman.

Screening is effective for cancer of the cervix because of its easy access to examination & sampling, the presence of well defined pre-cancerous lesions, a long latent period, a well defined viral aetiology and availability of effective treatment for pre-cancerous lesions.

**Important screening tests** are

- **Paps Smear:** Papanicolau smear is a test involving examination of the surface epithelial cells of the cervix for any precancerous changes. It forms the basis of cytology based screening protocols. It has the disadvantage of having a low sensitivity of 47-65% and also being observer dependent.
- **Visual inspection by Acetic Acid/ Lugol's iodine:** Acetic acid and/ or Lugols iodine are used to highlight precancerous lesions which can be visualized by naked eye. This obviates the need for laboratories, need to transport the specimen, and specialized equipment. Its sensitivity of 45-79%, is similar to cytology. This test is ideal for low resourced settings but has the disadvantage of requiring adequate training and supervision and also it is observer dependent.
- **High risk HPV DNA testing:** These tests detect the presence of HPV types in the cervical or vaginal cells. Presence of high risk HPV strains help predict those women who are at risk of developing invasive lesions and require colposcopy. It has a sensitivity of 66-95%. It has the advantage of not being observer dependent.

**The National Program for Cancer, Diabetes, Cardiovascular disease and Stroke** (NPCDCS), India, 2016 recommends opportunistic screening for cancer of the cervix by Visual Inspection of cervix with Acetic Acid (VIA). NPCDS recommends opportunistic screening for all women between 30-65 years by VIA. The test is to be repeated at 5year interval till the age of 65.

In 2012, three organizations, American Society of Colposcopy and Cervical Pathology (ASCCP), American Cancer Society(ACS) and American Society of Clinical Pathology (ASCP) created six working groups and formulated the **ASCCP** screening guidelines for cancer of the cervix.

1. Cervical cancer screening to begin at 21 years of age.
2. Screening with cytology every 3 years for women in the age group of 21-30 years
3. Screening for women in the age group 30-65 years by
   - Cytology with HPV co-testing every 5 years (preferred) or
   - Cytology alone every 3 years (acceptable)
4. Screening can be stopped at 65 years of age provided she did not have >CIN2+ in the last 10 years
5. In women who have been vaccinated against HPV, the recommended screening practices should not change.
6. In HIV positive women the screening should begin at the initiation of sexual activity irrespective of the mode of transmission but not later than 21 years. Cytological screening is done annually without HPV testing. If 3 consecutive annual cytology is negative then screening can be done every 3 years.

# Breast Cancer

As per the GLOBOCON 2012 statistics, United States, China and India account for almost one third the burden of breast cancer globally. The decline in the death rates in spite of increase in new cases in the United States has been made possible by early detection and treatment.

In India, breast cancer is the commonest cancer in females with an age adjusted rate as high as 25.8 per 100,000 women with a mortality of 12.7 per 100,000 women.

## Screening Modalities for breast cancer

***Breast Awareness:*** Breast Awareness implies familiarity with one's own breast. A self examination can be done monthly during bath, best time being just at the end of menses. This helps to keep in notice any irregularity, any lumps, the skin, the nipple etc. Also, breast awareness also includes a knowledge of breast cancer. A woman should be aware of what possible changes could occur in a breast when a cancer develops in the breast.

***Clinical Breast Examination:*** Clinical Breast Examination (CBE) implies a visit to a doctor, where the doctor makes a detailed evaluation of the patient's history and performs breast examination with an aim to detect any suspicious abnormality.

***Mammography*:** It is the most common screening test for breast cancer using low dose x-ray imaging to create detailed images of the breast. There are two types of mammography - screening mammography which is

**Table 1: Screening Recommendations for Cancer Cervix**

| | **American Society of Colposcopy and Cervical Pathology (ASCCP), American Cancer Society(ACS) and American Society of Clinical Pathology (ASCP) 2012** | **American College Of Obstetrics and Gynaecology (2009)** |
|---|---|---|
| **When to start Screening** | Age 21, regardless of the onset of sexual activity (strong recommendation) | Age 21, regardless of the onset of sexual activity |
| **Statement about annual screening** | Women at any age should not be screened with any screening method (strong recommendation) | Physicians should inform their patients that annual gynaecological examination may be appropriate (level C recommendations) |
| **Screening Methods and Interval** Cytology (Conventional & LBC<br>**i) 21-29 yrs**<br>**ii) 30-65 yrs**<br>**HPV co- test (cytology +HPV)**<br>**i) 21-29 yrs**<br>**ii) 30-65 yrs**<br>**Primary HPV testing** | <br>Every 3 yrs<br>Every 3 yrs<br>Not recommended in < 30 yrs<br>Every 5 yrs<br>For women aged 30-65 yrs screening by HPV testing alone is not recommended in most clinical settings | <br>Every 2 yrs<br>May screen every 3yrs, with previous 3 negative reports<br>Not recommended in < 30 yrs<br>Every 3 yrs if cytology and HPV are negative<br>Not addressed |
| **When to stop Screening** | Age > 65 yrs with previous negative screening history<br>Age > 65 yrs with previous CIN 2, CIN 3, or ASCUS should continue screen till 20 yrs after spontaneous regression or management. | Between 65- 70 yrs with 3 consecutive normal cytology tests and no abnormal test in the past 10 yrs. An older women who is sexually active or has multiple sexual partners should continue routine screening. |
| **Screening post Hysterectomy** | No screening unless hysterectomy done for precancer or cancer of the cervix. Supra cervical hysterectomy women should continue screening as per guidelines | No screening unless high grade CIN or worse. Continue screening in post hysterectomy if no documented negative reports. |
| **Need for bimanual examination** | Not addressed | Annual Gynaecological examination appropriate |
| **Screening among those immunised against HPV 16/18** | Continue screening as per Guidelines | Continue screening as per Guidelines |

performed on asymptomatic women and diagnostic mammography, which is performed on symptomatic women. Symptomatic women include those who have a breast lump or nipple discharge or any abnormality found during self examination or screening mammography. It has a sensitivity of 67.8% and specificity of 75%. Combined with CBE, its sensitivity increases to 77.4%.

***Ultrasonography:*** It is generally used to assist the clinical examination of a suspicious lesion detected on physical examination or mammography. Its use is limited by the fact that it cannot pick up microcalcifications and has a poor specificity of 34%.

***Magnetic Resonance Imaging (MRI)****:* MRI breast has limited role as a screening modality due to a ten times more cost than mammography and a lower specificity. MRI along with mammography is recommended only for screening of women with high risk factors such as BRCA mutation, first degree relative of BRCA carrier but untested, chest radiation in age group 10-30 years and women with Li- Fraumeni syndrome and her first degree relatives.

The most commonly accepted and followed are the **NCCN Guidelines**

***Normal risk woman, 20 to 40 years of age*:**

- Clinical breast examination: to be done every 1-3 years
- Breast Awareness.

***Normal risk woman, more than 40 years of age:***

- Annual Clinical Breast Examination: yearly examination by a qualified and trained medical personnel is a must.
- Annual Mammography: From 40 to 50 years of age, recommended yearly. After 50 years of age, mammography may be done every 2 years.
- Breast Awareness

***Women with increased risk of breast cancer***

a) These include women who have positive family history: One or more family member (blood relation) has a history of breast or ovarian cancer

b) Genetic Predisposition: One or more family member (blood relation) is known to harbor a 'genetic' abnormality causing breast cancer. This significantly increases the risk of developing a breast cancer

c) Previous Radiation therapy to chest wall for any cause, she stands an increased risk of developing breast cancer

*In these women, screening (Clinical examination 6-12 months and annual Mammography/ MRI) is to start 10 years before the age of occurrence of cancer in family member ( but not < 30 yrs)/ 8-10 rs after radiation exposure ( not < 25 years)*

**US Preventive Task Force 2016** recommendations for Breast cancer screening are:

- Biennial screening mammography for women aged 50-70 years
- No requirement for routine screening mammography in women aged 40-49 years
- Insufficient current evidence to assess the additional benefits and harms of screening mammography in women aged 75 years or more
- Insufficient current evidence to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging instead of mammography as screening modality
- No requirement for clinicians to teach women to perform Self Breast Examination (SBE) as studies have not shown any benefit in reducing mortality rates.
- Insufficient current evidence to assess the additional benefits and harms of Clinical breast examination (CBE) beyond mammography in women aged 40 years or older.

**ACOG** differs in its recommendations from USPTF by recommending Breast Self Awareness. It also recommends

- Screening mammography every 1-2 years for women 40-49 years
- Screening mammography every year for women aged 50 years or older.

Government of Indian has launched **the National Program for Cancer, Diabetes, Cardiovascular diseases and Stroke in 2016.**

It recommends

- Evaluation of all women for breast cancer between 30-65 years with Clinical Breast Examination by grass level health workers.
- Rescreen once in 5years.
- Women with suspected abnormalities are referred to a surgeon at CHC/District Hospital(DH) for confirmation using a breast ultrasound sound probe followed by biopsy in appropriate cases.
- In case of a benign lump on USG, the woman is subjected to more frequent follow up as per the discretion of the surgeon.
- In case of a suspicious or malignant lump /suspected nipple discharge, excisional biopsy of the lump/nipple is performed. If cytology at DH is confirmatory for breast cancer ,refer to medical college or Regional Cancer Centre for staging and treatment as per standard protocol.

## Conclusion

Breast and cervical cancer which are the leading cause of death in women, are easily accessible to

screening modalities. National screening guidelines if implemented all over with standardization and proper quality controls can reduce the mortality associated with these cancers. Further advancement in detecting ovarian cancer at an early stage is still under research. Awareness regarding screening guidelines is important but must be carried out under supervision of expert to avoid undue interventions and anxiety.

## Suggested Reading


- Barton M B, Lin k. Screening for Ovarian Cancer, Evidence Update for the US Preventive Task Force. Reaffirmation Recommendation statement AHRQ publication number 12-05165-EF3. Rockville, MD: agency of Healthcare research and quality; April 2012. Accessed at www. uspreventiveservices taskforce. org/ uspstf12/ ovarian:htm on 30 Aug 2012
- https://www.mskcc.org/cancer-care/types/ovarian/screening/screening-guidelines-ovarian
- Cancer Screening Guidelines- Detecting Cancer early- American Cancer Society, https://www. cancer. org>
- Endometrial (uterine) cancer guidelines - emedicine. medscape.com> article>250, updated Sep 2016. author Jori S carter
- Screening for Endometrial Cancer- NCBI, https://www.ncbi.nlm.gov>pubmed by G. Robertson 203
- Endometrial Cancer- Prevention- screening- Best practice- Oct 2016
- National Guidelines for Cervical Cancer Screening. The IARC Screening Group, Screening,iarc.fr>doc>SAcervical cancer
- ASCCP Guidelines- ASCCP, www.asccp.org>asccp-guidelines
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Breast Cancer Version 2.2017-April 6, 2017. Available at https://www.nccn.org/professionals/physician_gls/PDF/breast.pdf
- Operational Guidelines for Common Gynaecological Cancers By National Health Mission


### *Riding the Storm*

The winds howled and the sky grew dark.
The storm hit and we were the mark.
The winds blew with exceeding force.
The storm would set our lives off course.

I begged this storm to not strike us, please.
For this storm was truly a terrible disease.
It hits with sudden force and there is no protection.
It is not choosy in making its selection.

Once chosen by this storm, there is no going back.
Your life will continually follow the treatment track.
Treatment is a battle with more than one side-effect.
And there is no guarantee of which plan will be correct.

The storm will ravage psyches of kids and spouses.
And lives will forever be changed inside those houses.
Hospitals, doctors, and prescriptions become a way of life.
And you will need to learn to handle emotional strife.

As the storm passes, rays of hope will appear.
But the threat of ensuing storms remain with those that are dear.
The sun will shine and life will be good.
Yet, the fear of wind and rain is always understood.

Living with cancer is like riding the storm.
Fear of recurrence is ever the norm.
One feels blessed with each day of life.
Now truly knowing the importance of being a mother and a wife.

Only God knows if the skies will remain blue.
Faith in Him must always shine through.
Life must be lived with joy in mind.
And pray that your body's cells will always remain kind.

*Written by Michael McHugh – A Cancer Survivor*

# Events Held in August 2017

- CME on **"Postnatal Services-Continuum of Care"** under aegis of AOGD on **4th August, 2017** by Department of Obstetrics & Gynaecology at UCMS & GTB Hospital.

CME on Postnatal Services-Continuum of Care

- **FOGsd** with Advance Fertility & Gynecological Centre under aegis of AOGD organized a **CME** on **"Recurrent Miscarriages".** It was organized by Dr Kaberi Banerjee and Dr Anita Sabharwal at Hotel Park Inn, Lajpat Nagar on **10th August, 2017**. Independence Day was also celebrated

CME on "Recurrent Miscarriages"

- "AUB UPDATE" under aegis of AOGD on **11th August, 2017** at GTB Hospital, **Speaker:** Dr Sruthi Bhaskaran


AUB Update on 11th August, 2017

- CME under aegis of AOGD on **11th August, 2017** at Hotel City Park, Pitampura organized by the **Reproductive Endocrinology Committee AOGD** under leadership of Dr Nalini Mahajan. GI disorders & Cholestasis of Pregnancy were discussed.




CME on 11th August, 2017

- CME on **"Reproductive Health Dilemma's - Adolescence to Menopause"** under aegis of AOGD on **12th August, 2017** at India Habitat Centre organized by the Reproductive Endocrinology Committee AOGD under leadership of Dr Nalini Mahajan




CME on Reproductive Health Dilemma's - Adolescence to Menopause on 12th August, 2017

- **FOGSI BOH Triology** Conference on **19th - 20th August, 2017** at The Leela Ambience Gurugram under the leadership of Dr Rishma Pai & excellent organization by Dr Ranjana Khanna, Dr Shakuntla Kumar and Dr Kiran Guleria


FOGSI BOH Triology Conference at Leela Ambience Gurugram on 19th & 20th August, 2017

- **FOGsd** organized a CME on **"Breast Cancer"** under aegis of Breast Cancer Awareness Sub-committee of AOGD on **22nd August, 2017** at Madhuban Hotel GK – 1, by Dr Anita Sabharwal.

CME on "Breast Cancer" on 22nd August, 2017

- AOGD Monthly Clinical Meeting at Safdarjung Hospital, organized by Dr Pratima Mittal & Team on **24th August, 2017** with the theme of journey in critical care obstetrics

AOGD Monthly Clinical Meeting at Safdarjung Hospital

- Annual Conference of DGES (Delhi Gynecological Endoscopists Society) & IAGE (NZ) was held in association with AOGD on 25th -27th August, 2017 at Indian Habitat Centre, Lodhi Road. Organizing Chairperson was Dr Malvika Sabharwal


Annual Conference of DGES & IAGE (NZ)

# 39th Annual Conference of AOGD 2017

## Scientific Programme

### Day 1: Saturday, 18th November 2017

| | | |
|---|---|---|
| 07:30am onwards | **Registration** | |
| 08:00am - 05:00pm | **Hall C (Free communications/Posters/Quiz Theory)** | |
| **Session 1** | **Hall A** | **Hall B** |
| 09:00am - 10:00am | **Understanding Preeclampsia** | **Resurrection of the Contraceptive Basket** |
| | Predictors of Preeclampsia: From bench to bedside | Antara and Chaya: Old wine in a new bottle |
| | Late onset Preeclampsia: Is the pathogenesis different? | Emergency Contraception: Expanding indications |
| | Management of Acute onset Severe Pre-eclampsia | Progesterone Vaginal Ring and Sino Implant II |
| | Drug Therapy for Control of Hypertension in Pregnancy: An update | Menstrual Moksha |
| | Discussion | Discussion |
| 10:00am - 10:30am | **Tea & Exhibition** | |
| **Session 2** | **Main Hall** | |
| 10:30am - 11:00am | **AOGD President's Oration:** Unfurling the Facts of Assisted Reproduction: Dr Sudha Prasad | |
| 11:00am - 11.20am | **Key Note Address:** ABC of Breast Health: What to do & What not to Do! Dr P Raghuram, President, Association of Breast Surgeons of India | |
| 11:20am - 11.40pm | **Expert Opinion:** Proritizing Surgical Safety and Minimising Surgical Infections | |
| 11.40am - 12.20pm | **Panel Discussion:** Addressing and Rationalising Rising Cesarean section rates | |
| 12.20pm - 01.00pm | **Inauguration & Role Play 'Violence against Doctors'** | |
| 01:00pm - 02:00pm | **Lunch, Exhibition & Poster Viewing** | |
| **Session 3** | **Hall A** | **Hall B** |
| 02:00pm - 02.40pm | **Panel Discussion:** Minimally Invasive Surgery in Gynecologic Malignancy: Safe and Best Practice | |
| 02.40pm - 03.40pm | **High Risk Obstetrics: Time to gear up!** | **Infertilty: Technical update** |
| | Pregnancy after Bariatric Surgery | Biomarkers for ovarian reserve: What is best? |
| | Jaundice in Pregnancy: Minimising morbidity & mortality | Pre-implantation Genetic Screening: Should the practice continue? |
| | Unexplained Recurrent Miscarriage | Ovarian Aging: Can it be stopped? |
| | An Approach to a Case with Oligoamnios | Luteal Support: What, when and for how long? |
| | Establishing a High Dependency Unit/Obstetric ICU | Maximising Succesful Implantaton: Advances in endometrial receptivity |
| | Discussion | Discussion |
| 03.40pm - 04.00pm | **Sponsored symposium (Educational grant)** | **Sponsored Symposium (Educational grant)** |
| **Session 4** | **Hall A** | **Hall B** |
| 04.00pm - 05.00pm | **Video Session: Obstetrics** | **Video Session: Gynecology** |
| | Retrograde Hysterectomy for Placenta Praevia/ Accreta | Endoscopic Sentinel Node Dissection |
| | Laser Ablation in TTTS | Le Fort's Procedure: Simplicity personified! |
| | 12 week Scan: NT, Nasal Bone, Anomalies | Mini Sling for SUI |
| | Innovation in PPH Management: Bakri & Chhattisgarh balloon | Clitoroplasty |
| | Laparoscopic Encerclage | Specimen Retrieval Techniques in Laparoscopy |
| | Step wise Devascularisation of Uterus & Internal Iliac Artery Ligation made Easy | Robotic Management of Deep Endometriosis |
| 05:00pm - 05:30pm | **Tea & Exhibition** | |

# 39th Annual Conference of AOGD 2017

## Scientific Programme

### Day 2: Sunday, 19th November 2017

| | | |
|---|---|---|
| 07:30am onwards | **Registration** | |
| 08:00am - 05:00pm | **Hall C (Free communications/Posters/Quiz Oral)** | |
| **Session 5** | **Hall A** | **Hall B** |
| 09:00am - 10:00am | **Fetal Medicine: Expert's speak** | **Rational Use of Hormones: Which, when, how much and how long?** |
| | Rh Isoimmunisation/Fetal Anemia: When to refer, what to do? | Early Pregnancy Bleeding |
| | Options beyond Laser in complicated Twin Pregnancy | Ovarian Insufficiency |
| | Growth Problems, Monitoring and Timing Delivery in Multiples | Adolescent Endometriosis |
| | Ultrasound in Delivery Decisions | Menopausal HT |
| | Discussion | Discussion |
| 10:00am - 10:30am | **Tea & Exhibition** | |
| **Session 6** | **Main Hall** | |
| 10:30am - 11:00am | **Brigadier Khanna Oration:** Management of Endometrial Cancer: MSKCC Practice Dr Mario Leitao, Director, Robotic surgery, Memorial Sloan Kettering Hospital, New York | |
| 11:00am - 11.20am | **Key Note Address:** Abnormal Uterine Bleeding: Evidence Based Management: Alka Kriplani | |
| **Session 7** | **Hall A** | **Hall B** |
| | **Genetic Testing in Prenatal Diagnosis** | **Cancer Genetics** |
| 11.20am - 11.40am | Genetic Tests & Prenatal Diagnosis: Changing practice: Case studies | Understanding Genetic Tests in Breast & Gyn Cancers: Case studies |
| **Session 8** | **Hall A** | **Hall B** |
| | **Contemporary Practice** | **Smart Science** |
| 11.40am - 11.55am | Role of Atosiban & Magnesium Sulfate in Preterm Labor | The FIGO Smart phone application for management of Gynecological Cancers |
| 11.55am - 12.10pm | Fetomaternal Risks and Monitoring in GDM | Dilemmas in management of Ectopic pregnancy |
| 12:10pm - 01:40pm | **Competition Papers** | **Round Table Discussions** |
| 01.40pm - 02.30pm | **Lunch, Exhibition & Poster Viewing** | |
| **Session 9** | **Hall A** | **Hall B** |
| 02:30pm - 03:45pm | **Best of 2017: Evidence Based Practice in Pregnancy** | **Best of 2017: Evidence Based Practice in Gynecology** |
| | Exercise Training and Weight Gain in Obese Pregnant Women | Uterine Artery Embolization vs. Hysterectomy in the Treatment of Symptomatic Uterine Fibroids: EMMY trial |
| | Thyroid Disorders in Pregnancy: 2017 Guidelines | Treatment Strategies for WHO Type II Anovulation: Systematic review and metaanalysis |
| | Preterm Birth Prevention in Singleton & Twin Pregnancy | Risk Reducing Salpingectomy/Salpingo-Oophorectomy: Current Guidelines |
| | Elective Delivery versus Expectant Management for Pre-eclampsia: Meta analysis of RCT's | Morcellation in Fibroids: Risks and Current Practice |
| | Antiretroviral Therapy in Pregnancy: An Update | Selective Progesterone Receptor Modulator: Latest Recommendations |
| **Session 10** | **Hall A** | **Hall B** |
| 03:45pm - 04:45pm | **Razor-sharp Debates** | **Confronting Controversies** |
| | Cesarean on Demand is the Right of a Pregnant Mother | Management of Adenomyosis in Women under 35 |
| | Soil and Seed are Ripe for Uterine Transplantation in India | IVF vs Reversal of Sterilisation after Tubal Ligation |
| | All Fibroids seen during Cesarean Section must be Removed | Hydrosalpinx: Tubal Surgery or in vitro fertilisation: An everlasting dilemma |
| | Egg Freezing before 30: Sure shot way of achieving future pregnancy | Vaginal versus Laparoscopic Hysterectomy: The better route! |
| 04:45pm - 05:15pm | **Valedictory** | |
| 05:15pm | **Tea & Exhibition** | |

# 39th Annual Conference of Association of Obstetricians and Gynecologists of Delhi

**18th - 19th November, 2017**

**Pre-conference Workshops: 17th November 2017**

*Venue:* **India Habitat Centre, Lodhi Road, New Delhi**

## REGISTRATION FORM

Name ..... Institution.....

Department ..... Designation .....

Category: (Tick any) Delegate ( ) PG Student ( ) Faculty ( ) AOGD Membership No.....

Address ..... City ..... Pin Code .....

Mobile No ..... Landline No ..... Email .....

**PRE CONGRESS WORKSHOPS**

1. Gynae Oncology ( )
2. Gynae Endoscopy ( )
3. Basic Infertility ( )
4. Fetal Medicine ( )
5. Intrapartum Skills ( )
6. Urogynaecology ( )

**THEME TOPICS FOR ABSTRACT SUBMISSION**

1. Improvising Surgical Techniques: Old & New ( )
2. High Dependency Obstetrics ( )
3. Gynecological Emergencies ( )
4. Rational use of Hormones in Obstetrics & Gynecology ( )
5. Miscellaneous ( )

❖ **Guidelines for Abstract Submission are available on conference website**

All DD/Cheque payable at New Delhi & should be made in favour of **"AOGD CONFERENCE 2017"**

- Write your Name and Contact No. at the back of DD/Cheque

❖ **Registration for the conference is mandatory in order to register for the pre conference workshops.**

❖ **Online payment through payment gateway can be made only if Registration form is filled online.**

❖ **AOGDIANS above the age of 70 years are exempted from registration fees. Age proof required**

❖ **Online registration form & payment gateway facility available at www.aogdconference2017.com**

**PAYMENT DETAILS**

Please find enclosed herewith Cash/DD/Cheque No ..... Dated .....

Drawn on (Name of the Bank) ..... Branch .....

For Rs. ..... (In words) .....

**REGISTRATION FEES**

| | Conference | | | Workshop | | |
|---|---|---|---|---|---|---|
| **Registration Category** | **Upto 30th Sept '17** | **Upto 30th Oct '17** | **Spot Registration** | **Upto to 30th Sept '17** | **Upto to 30th Oct '17** | **Spot Registration** |
| AOGD Member | Rs. 4500 | Rs. 4800 | Rs. 5000 | Rs. 2000 | Rs. 2200 | Rs. 2500 |
| PG Student | Rs. 4000 | Rs. 4200 | Rs. 4500 | Rs. 1500 | Rs. 1800 | Rs. 2000 |
| Non- AOGD Member | Rs. 5000 | Rs. 5500 | Rs. 6000 | Rs. 2000 | Rs. 2500 | Rs. 2700 |
| Accompanying Person | Rs. 4300 | Rs. 4500 | Rs. 4800 | - | - | - |

**AOGD OFFICE**

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Dilshad Garden New Delhi 110095. Mr. Ashish – 9136708721, 011- 22692505
www.aogd.org. Email: secretaryaogd2017@gmail.com, info@aogd.org

# CTG & Instrumental Delivery

**28th September, 2017**

**Registration 11.00am-11.30am**

| Time | Topic | Speaker | Chairpersons |
|---|---|---|---|
| 11.30am - 12.30pm | CTG: Interpretation and application in clinical practice | Renu Mishra | Roopam Arora<br>Y. Mala<br>Rinku Sengupta |
| 12.30pm - 01.30pm | Case Scenarios & Discussion | | |
| 01.30pm - 02.00pm | Lunch | | |
| 02.00pm - 03.00pm | Instrumental delivery :<br>Forceps and Ventouse | Neerja Goel | Jyoti Bhaskar<br>Kalpana<br>Jyoti Agarwal |
| 03.00pm - 05.00pm | **Hands on training**<br>**Resource faculty** Ritu Katuja, Shelly Agararwal, Rachna Agarwal, Himsweta Srivastava, Rashmi Malik, Seema Prakash, Alpana Singh, Bindiya Gupta, Richa Agarwal, Sruthi Bhaskar, Shweta Prasad, Archana Chaudhary, Vishnu Bhartiya | | |

***Venue***

7th Floor, Seminar Room, Department of Obstetrics & Gynaecology
MCH Block, GTB Hospital, Delhi

**Fee details** (only 30 spots available)

***Free Contacts***

Ashish - 09136708721, Richa Sharma - 9868399747, A. G. Radhika - 9868399726

# SOCIETY OF FETAL MEDICINE (SFM)

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# BRCA1 & 2: Role in Female Malignancies

**Achint Kaur**
Genetic Counselor, Centogene India Pvt. Ltd.

Hereditary cancers of the breast, ovaries and the endometrium comprise a large proportion of cancers affecting women worldwide. In the consensus document for management of breast cancer published by Indian Council of Medical Research (ICMR) in 2016, breast cancer topped the list of the most common cancers in India with over 144,000 cases being reported every year, followed by lung and cervical cancer[1].

## Genetic Predisposition for Cancers

5-10% of the breast cancers have an underlying genetic predisposition. Women with genetic susceptibility have a much higher risk of developing cancers as compared to the general population, and therefore screening by the clinicians has become extremely important. Obstetricians/ Gynecologists play an integral role in the care of women with hereditary cancer syndromes. Rapid advancements in genetic technology have improved our understanding of these cancer syndromes. The increased speed and lower cost associated with Next Generation Sequencing (NGS) platforms has resulted in enhanced clinical availability of multi-gene panels, thereby facilitating risk assessment and further management of these patients. Thus, awareness of these new genes and availability of genetic tests among the primary healthcare providers is critical.

**Hereditary Breast and Ovarian Cancer Syndrome (HBOC)** accounts for 60-75% of inherited cases of breast cancer. *BRCA1*- and *BRCA2*- associated HBOC is characterized by increased risk of female and male breast cancers, ovarian cancers and other malignancies including fallopian tube cancer, primary peritoneal cancer, prostate cancer, pancreatic cancer and melanomas.

## BRCA 1 & 2 Mutations

*BRCA1* and ***2*** are tumor suppressor genes. *BRCA1* is located on chromosome 17 and is involved in both DNA repair and regulation of cell-cycle checkpoints. The exact molecular mechanism is unclear. *BRCA2* is located on chromosome 13 and is involved in repair of replication-mediated double-strand DNA breaks.

*BRCA1* and *BRCA2* mutations are inherited in an autosomal dominant manner. Majority of the patients inherit the mutated copy from either of their parent, this is referred to as the germline mutation, i.e. either the egg or the sperm harbors the mutated copy and that may be passed on to the offspring. As a result, all the cells of the body carry the variation in the gene. Although mutations in these genes are highly penetrant, not all individuals who harbor the mutation (unaffected parents of carrier individuals) develop the cancers- this could be due to incomplete penetrance, variable age of onset of the cancer or early death. Offspring and siblings of carrier individuals are at a 50% risk of inheriting the mutation (if their parent had the same mutation). Once a cancer-predisposing *BRCA1* or *BRCA2* germline pathogenic variant has been identified in a family, testing of at-risk relatives can be performed to identify mutation carriers, thereby warranting increased surveillance and early intervention when a cancer is identified.

Germline *BRCA1* or *BRCA2* mutations account for approximately 10% of all ovarian cancers, 20-40% of breast cancers that runs in families and about 5-10% of all breast cancer patients. *BRCA1* mutation carriers are at a high risk of early-onset breast cancer. Identifying pathogenic variants in the women in these two genes, allows for timely genetic counseling to help them understand their lifetime risks for breast and ovarian cancers and helps them make an informed decision regarding management of cancer risks and to make subsequent lifestyle decisions such as child bearing. Risk of malignancies for *BRCA1* and *BRCA2* as compared to the general population is given in table 1 (2, 3, 4). Mutations in *BRCA2* (also known as *FANCD1*), if inherited from both the parents, can cause a subtype of Fanconi Anemia (FA-D1), a syndrome associated with childhood solid tumors and acute myeloid leukemia. Similarly, mutations in *BRCA1* (also known as *FANCS*) when inherited from both the parents results in another subtype of Fanconi anemia.

**Table 1: Malignancy Risk in women with BRCA1/BRCA2 mutations**

| Cancer Type | General Population Risk (by age 70 years) | Risk for Malignancy | |
|---|---|---|---|
| | | ***BRCA1*** | ***BRCA2*** |
| Primary Breast | 8-12% | 46-87% | 38-84% |
| Contralateral Breast | 2% within 5 years | 21.1% within 10 years<br>83% by age 70 | 10.8% within 10 years<br>62% by age 70 |
| Ovarian | 1-2% | 39-63% | 16.5-27% |
| Male Breast | 0.1% | 1.2% | Up to 8.9% |
| Prostate | 6% | 8.6% by age 65 | 15% by age 65<br>20% lifetime |
| Pancreatic | 0.5% | 1-3% | 2-7% |
| Melanoma | 1.6% | | Elevated risk |
| Uterus | 1.5% | 2.47% | |
| Cervix | 0.6% | 2.16% by age 50<br>3.57% by age 70 | |

*BRCA1*- and *BRCA2*- associated HBOC should be suspected in individuals with the following features:

- Previously identified pathogenic *BRCA1/2* variant in the family
- Personal history of breast cancer diagnosed at or before 50 years of age
- Personal/ family history of ovarian cancer
- Multiple primary breast cancers (ipsilateral/ contralateral)
- Triple-negative (estrogen receptor-negative, progesterone receptor-negative, and HER2/neu [human epidermal growth factor receptor 2]-negative) breast cancer (particularly when diagnosed before age 60 years)
- Combination of pancreatic and/or prostate cancer with breast and/or ovarian cancer
- Two or more blood relatives with breast cancer diagnosed before the age of 50 years
- Three or more relatives with breast cancer at any age
- Family history of male breast cancer.

## Genetic Testing

Several genetic tests are available to detect mutations in *BRCA1* and *BRCA2*. These include targeted mutation analysis when there is a known deleterious mutation in the family. For individuals from a family without a known *BRCA1/2* mutation (and who meet the testing criteria), genetic testing should be comprehensive, including full gene sequencing of *BRCA1/2* and testing for large genomic rearrangements (deletion duplication testing). In families where more than one gene can explain an inherited cancer syndrome, multi-gene panels may be considered. Next generation sequencing now allows for multiple genes to be sequenced simultaneously. These panels include both high- and moderate- penetrance genes responsible for causing HBOC, thus being more efficient and/or cost effective. For example, ovarian cancer is mainly associated with *BRCA1/2* mutations, but it also may be associated with mutations in *BARD1*, *BRIP1*, *CHEK2*, *MRE11A*, *MSH6*, *NBN*, *PALB2*, *RAD50*, *RAD51C* and *TP53*[5]. Similarly, in addition to *BRCA1/2*, hereditary breast cancers may also be caused due to pathogenic variants in *PALB2*, *TP53*, *PTEN*, *STK11* and *CDH1*[5]. Genetic counselling is recommended before and after the genetic test for any inherited cancer.

### *When to Test*

Whenever possible, the genetic testing should be performed in the affected members in the family to determine the underlying cause of the cancer. If more than one family member is affected, members with the youngest age of onset/ multiple primaries/ having other associated cancers/ most closely related to the individual seeking consultation, should be considered. Testing unaffected individuals should only be considered when the affected family member is not available for testing (deceased).

### *Test Interpretation*

A positive test result indicates that a person has inherited a known harmful mutation in *BRCA1* or *BRCA2* and therefore has an increased risk of developing certain cancers. However, it cannot tell whether or when an individual will develop the cancer. Additionally, a positive test result has implications for the family members and future generations too. On the other hand, a negative test result may either mean that the person does not carry the harmful mutation and has population risk of developing the cancer (as in the case of targeted mutation testing- when the familial mutation is known) or the proband has a mutation in a gene other than *BRCA1* or *BRCA2* which was not tested.

### *Risk reduction in Test Positives*

Once tested positive for a mutation in *BRCA1/2*, there are several options available for managing cancer risks in these individuals. These include enhanced screening, prophylactic surgery, and chemoprevention. The National Comprehensive Cancer Network (NCCN) guidelines for HBOC surveillance in women who test positive for *BRCA1/2* include the following[5]:

- Monthly breast self-exam (BSE) starting at the age of 18 years
- Semi-annual clinical breast exam (CBE) starting as the age 25 years
- Annual mammograms and breast MRI screening with contrast starting 25-30 years or individualized based on earliest age of cancer onset in the family
- Discuss options of risk reducing mastectomy (RRM)- Retrospective analysis with median follow up period of 13-14 years have indicated that bilateral RRM decreased the risk of developing breast cancer by at least 90%. It is important to address the psychosocial effects related to RRM.
- Recommend risk-reducing salpingo-oophorectomy (RRSO) between 35-40 years and upon completion of child bearing- RRSO reduces the risk of ovarian cancer by ~75-96%. Screening for ovarian cancers using transvaginal ultrasounds and blood tests for CA-125 antigen may not be effective in early detection.
- Option of prenatal diagnosis and Pre-Implantation Genetic Diagnosis (PGD) may also be discussed.

Use of selective estrogen receptor modulator (i.e. Tamoxifen and Raloxifene) has been shown to reduce the risk of invasive breast cancer in *BRCA1/2* positive post-menopausal women. Additionally, long-term use oral contraceptives have shown to reduce the risk of ovarian cancer by approximately 50% in *BRCA1/2*

mutation carriers[5]. However, their role in breast cancer reduction is not very well established.

There are several studies underway that are looking at novel approaches for the treatment of *BRCA*-associated cancers. These include studies on the use of Poly (ADP-ribose) Polymerases (PARP) inhibitors in treatment of recurrent ovarian cancers, breast cancers and more recently its role in pancreatic cancer. Several PARP inhibitors are currently in trials in the adjuvant, neoadjuvant and metastatic treatments of *BRCA*- related cancers[6]. Role of short term Hormone Replacement Therapy in *BRCA1/2* carriers is also being investigated[2].

## Conclusions

In summary, rapidly advancing technology is expanding our ability to identify new genes and mutations associated with familial cancers, and to offer predictive testing for at-risk members. Gynecologists along with Clinical Geneticists and Genetic Counselors can help address the issues involving early detection, appropriate surveillance and management, to reduce the genetic burden of these deadly female malignancies.

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# Thermocoagulation: New kid on the block

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The treatment of cervical precancerous lesions is carried out by a variety of methods leading to destruction or excision of the entire transformation zone harboring the Cervical Intraepithelial Neoplasia (CIN) and potentially at risk for cervical neoplasia. This involves treatment of the entire transformation zone and not limited to the abnormal area of the cervix. The main aim of treatment should be to achieve a depth of at least 7mm. Currently available ablative methods for treatment of CIN include thermocoagulation (cold coagulation), cryotherapy, laser ablation, and electrocoagulation which can be performed on an out-patient basis.

Two low-cost and simple treatment methods are represented by cryotherapy and thermocoagulation. Cryotherapy is a highly effective intervention with a good cure rate, but the limited availability of refrigerant gas makes its use challenging in resource constraint settings.[1] In such situations, thermocoagulation may represent an attractive alternative for the treatment of cervical precancerous lesions. Thermocoagulation or cold coagulation has been available for several decades in Western countries. A meta-analysis has shown that the use of thermocoagulation for the treatment of CIN is as effective as other methods, such as cryotherapy, with the advantage of being rapid and associated with fewer side effects.[2]

## Indications for Thermocoagulation

Treatment by thermocoagulation can be done if the following criteria are satisfied:

- Type 1 transformation zone
- Lesion involving <75% of transformation zone
- Lesion is entirely located in the ectocervix
- No endocervical canal or vaginal involvement by the lesion
- No evidence of invasive cancer
- Non Pregnant
- No menstrual bleeding

**Fig 1a: Thermocoagulator**

**Fig 1b:Metallic probe**

## Equipment and consumables necessary for Thermocoagulation

- Thermocoagulator unit (Figure 1a,)
- Metallic probe (Fig 1b)
- Wire for electrical connection
- A good white light source
- Instrument tray containing
  - o Self-retaining bivalve speculum
  - o Freshly prepared acetic acid (5%) solution
  - o Disposable gloves
  - o Sterile cotton swabs and cotton tipped swabs

## Thermocoagulation procedure

- Woman should be in lithotomy position
- Expose the cervix using the self-retaining speculum
- Focus light source for clear visualization of cervix
- Delineation of the lesion using 5% acetic acid and Lugol's iodine
- Set the Thermocoagulator at 100°C
- Apply the heated thermocoagulator probe on the area to be treated on the ectocervix and heat for 45 seconds at 100°C
- Multiple overlapping applications of 45 seconds each can be used to cover the entire lesion

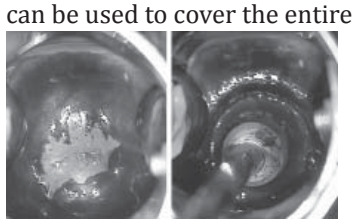

**Fig 2: Treatment by thermocoagulation**

## Advise on post-treatment care and follow up

- The woman should be told that she may experience excessive watery discharge for upto 4 weeks. She should not get worried about it.
- The woman should be asked to abstain from intercourse for 4 weeks.
- Avoid douching or use of tampon for 4 weeks
- Inform her of possible complications and ask her to return immediately if she notes:
  - o Fever with temperature higher than 38 °C lasting for more than 48 hrs

- o Severe lower abdominal pain
- o Foul-smelling or pus-like discharge
- o Bleeding for more than two days or bleeding with clots

## Side effects and complications

Thermocoagulation is well tolerated. However following symptoms may be experienced rarely:

- Mild pain
- Watery discharge
- Vasovagal reactions (fainting, giddiness, mild cramps etc)
- Vaginal burns (in case of careless application)
- Bleeding (extremely rare)
- Pelvic inflammatory disease
- Cervical stenosis (very rare)

## Advantages and limitations

There are certain advantages of thermocoagulation over other ablative methods which make this procedure more acceptable. These include shorter time of treatment, less side effects, multiple applications and does not require refilling of gas. However it has limitations with respect to its high cost and requirement of electricity which is not available in remote rural places.

## Efficacy of the procedure

Cure rates of cervical intraepithelial neoplasia (CIN) following thermocoagulation reportedly vary from 93-99%, depending upon the size of the lesions, histological grade and number of treatment applications.[3] A cure rate of 95% following a single application was reported in a large group comprising of 1628 women with CIN 3 lesions in Scotland.[4] The largest experience for the efficacy of cold coagulation has been evaluated in a setting of 'see and treat' following colposcopy and directed biopsies, where the cure rates exceeded 95%.[5]

## Pregnancy outcome following treatment

The most important determinant of unimpaired cervical function is fertility and pregnancy outcome following treatment. Of women treated with thermocoagulation, 94% have reportedly conceived within 2 years of treatment.[6] In another study, 226 pregnancies in a large group of 1628 women with CIN 3 treated with cold coagulation, 40 women had a legal abortion (18%), nine (4%) had a first trimester miscarriage, three (1%) had ectopic pregnancies, and 174 resulted in deliveries. Pregnancies in women treated by thermocoagulation for CIN3 and their outcome was as good as in untreated women.

To conclude, thermocoagulation is an effective gasless ablative procedure, with low running costs and high cure rates in CIN.

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"Body, Mind and Soul"

# Role of Diet in Cancer


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Eating the right kinds of foods is an important part of cancer treatment, as it can help one feel better and keep up the strength. Cancer treatments including surgery, chemotherapy and/or radiation cause side effects, such as loss of appetite, vomiting, and fatigue.

Nutrition during cancer treatment may take on a whole new form, as cancer treatment can affect the way body tolerates food and uses nutrients. This will vary for each person. In general, cancer patients need a variety of foods to meet their nutritional needs, with a focus on protein, carbohydrates, fat, water, minerals, and vitamins.

## Nutrients in diet

### Protein

Protein deficiency can lead to a reduced resistance to infections and a longer recovery time from illnesses. During cancer treatment, requirement of protein is increased to help heal tissues and fight infections. Fish, lean red meat, and eggs are some good sources of protein.

American Cancer Society (ACS) has issued some guidelines for consuming meats. Studies have shown that eating large amounts of red meat and processed meats (hot dogs, deli meats, bacon) can increase the risk of certain types of cancers like colon cancers. Research has also shown that grilling, frying, or broiling meats at very high temperatures creates chemicals that might increase the risk of some types of cancer. Therefore, the ACS recommends that one should limit intake of processed and red meats and avoid cooking these at high temperatures.

### Fat

Fat is used by the body to insulate body tissues, transport vitamins through the blood, and store energy. Monounsaturated and polyunsaturated fats should be consumed more often than saturated fats or trans fats.

Some studies have been done on whether different types of fat might affect cancer risk and survival. However, this research has produced mixed results. Evidence has shown that certain types of fat, including saturated fats, may increase the risk of cancer. In fact, one study showed that a low-fat diet may lower the chance of recurrence in women who had cancers that were estrogen-receptor negative.

In general, those who are going through (or have gone through) cancer treatment should try to minimize trans fats, such as margarine, baked goods, and snack foods that contain partially hydrogenated oils, as they have harmful effects.

### Carbohydrates

Carbohydrates are a major source of energy for the body. Some of the best sources of carbohydrates are whole grains which contain fibre both soluble and insoluble. These include oats, barley, spelt, rye, brown rice and whole wheat which have the maximum benefit. Besides carbohydrates and dietary fibre, whole grains also provide an array of vitamins, minerals and other nutrients, such as **antioxidants and phytochemicals**. These facilitate DNA repair, control cell growth and provide DNA protection. According to Oregon State University, phytochemicals are associated with reduced ovarian cancer risk.

### Minerals and Vitamins, Fibre rich food

In general, it is often recommended that one should eat good sources of fibre, such as beans, whole grains, nuts, fruits, and vegetables, during cancer treatment. These can also reduce risk of heart disease and improve bowel function. Some studies have shown that a high intake of vegetables may reduce recurrence and improve survival. However, more research is needed. It is usually recommended for those undergoing cancer treatments and cancer survivors should eat at least 2 to 3 cups of vegetables and 1½ to 2 cups of fruit each day.

Besides fibre, fruits and vegetables are a rich source of minerals and vitamins. In general, fresh fruits and vegetables are believed to have the most nutritional value. Canned fruits and vegetables may have lost some nutrients due to the high temperatures used in the canning process. Some canned products may also contain heavy syrup and high sodium levels. In some cases, cooking vegetables and fruits can help body absorb certain nutrients (such as carotenoids) more effectively. Steaming is the best way to preserve the nutrients; boiling, especially for long periods of time, can remove many water-soluble vitamins.

### Water

Water is crucial to enhance cell repair and tissue healing. Decreased consumption may lead to serious imbalances

in important minerals in the body. One needs at least eight 8-ounce glasses of liquid each day; however, if experiencing vomiting or diarrhea, water intake has to be more.

## Specific food items with Anti - Cancer Properties

### Flax seed

Research has shown that flaxseed may slow down cancer cell growth and make certain types of cancer treatment more effective. Although flaxseed is a good source of vitamins, minerals, fibre, and omega-3 fatty acids, more research is needed to determine the effects of flaxseed on cancer treatment outcomes.

### Carotenoids and Lycopene

Micronutrients like carotenoids and lycopene are found in several fruits and vegetables and can reduce the risk of cancer. Carotenoids are red, yellow and orange pigments found in vegetables and fruits and therefore spinach, corn, broccoli, yams, oranges, cantaloupe, carrots and collard greens are good cancer prevention foods to eat as a part of daily diet. These are some of the best foods for ovarian cancer prevention and treatment as they contain important antioxidants which prevent DNA damage in the body.

Lycopene is another strong antioxidant which can be found in tomatoes and tomato products like marinara sauce. Some studies on tomato intake, lycopene levels, and disease risk suggest that lycopene intake may have significant benefit in cervical cancer. However, others have found conflicting results. More research is needed before further conclusions can be made. Lycopene and lycopene-rich foods have been studied as a potential therapy for breast cancer. Early studies on breast cancer recurrence and prevention have looked for a possible link between disease risk and fruit or vegetable intake, tomato consumption, or lycopene levels, with mixed results. There is a lack of studies on lycopene supplementation in breast cancer prevention. More research is needed in this area.

### Others

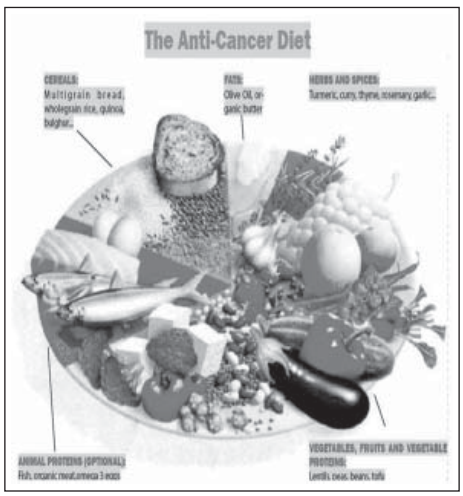
Other good examples of foods that fight cancers are tea, kale and broccoli. Tea contains potent chemicals which are helpful in fighting ovarian and breast cancers. Green tea contains antioxidant compounds called polyphenols which lower the risk of ovarian cancer and is also beneficial to those already suffering from this disease. Kale and broccoli contain vital cancer fighting flavonoids and must be included in an ovarian cancer diet.

Red wine includes a plant flavonoid known as apigenin which destroys free radical that are responsible for causing cancer. However, it is advisable to limit consumption to just one glass a day. Fresh parsley and celery are always better options than the dried versions as they have a higher antioxidant content. Ginger root is another good example of foods with anti-cancer properties. Ginger root causes apoptosis and autophagic death of cancerous cells and can help treat ovarian cancer.

Soy foods are created from soy beans. Foods rich in soy include soy beans, soy milk, soy yogurt, tofu, soy burgers, soy-based protein powders and soy nuts. Soy foods offer valuable amounts of protein, dietary fibre, B vitamins and omega-3 fatty acids - essential fats the body cannot produce on its own. However, diets rich in soy have been associated with increased risk for breast cancer, and should be avoided in breast and endometrial cancers

## Conclusion

An anti- cancer diet should be a balanced diet and should include more of plant foods. Vegetables, fruits and whole grains provide phytochemicals and antioxidants which help in fighting cancer.




# Surgery for Ovarian Cancer

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## Introduction

Malignant ovarian tumors present with varying clinical and biological behavior. Fatality due to ovarian malignancies is high due to advance stage at the time of presentation. It is one of the leading cause of mortality among all cancers of the female genital tract. In India, during the period 2001-2006, age standardized incidence rates for ovarian cancer varied from 0.9 to 8.4/100,000 person years among various registries.[1] Incidence increases with age, with maximal cases reported in 6th-7th decades of life.

Thorough surgical staging with optimal cytoreduction, along with chemotherapy, is the standard of care. The amount of residual tumor is one of the most important prognostic factor for survival.[2]

## General Principles of Surgery for Ovarian Cancer

- A vertical midline incision should be used for laparotomy, when malignant ovarian mass is suspected, and for interval debulking surgery.
- Minimal invasive procedures like laparoscopy or robotic surgery may be used in select cases.
- A comprehensive operative report should be given, which describes the extent of disease in the abdominal cavity (from pelvic brim to ribs) before debulking, and the amount of residual disease after cytoreduction.[3]
- Aspiration of ascites or peritoneal wash should be done for cytologic evaluation.
- The ovarian mass should be removed intact to avoid abdominal cavity spillage (Figure 1).
- Frozen section of the mass should be done where ever available as it will guide the extent of surgery.

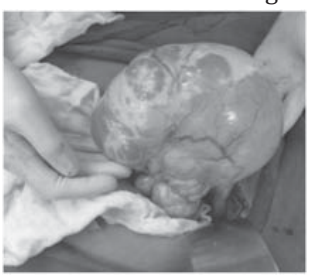

**Figure 1: Ovarian mass removed intact at laparotomy.**

## Epithelial Ovarian Cancer

Epithelial ovarian cancer (EOC) is the most common type of ovarian malignancy. It has four main histology types namely serous, mucinous, endometroid, and clear cell. Serous tumors constitute 70% of all EOC's.

Early stage cancers have traditionally included both stage I and stage II tumors. However, because of high recurrence rates for stage II cancers, these have been included with advanced stage cancers in GOG (Gynecologic Oncology Group) trials since 2009.

A detailed pre-operative workup includes tumor markers and imaging studies like ultrasound of whole abdomen, abdominal contrast-enhanced computed tomographic scan (CECT), magnetic resonance imaging (MRI), and positron emission tomography (PET)- CT scans, to define the extent of disease.

Comprehensive surgical staging is the preferred primary treatment in all cases except patients with stage III and IV who are unfit for surgery, where neo-adjuvant chemotherapy is given followed by interval debulking surgery.

1) **Primary surgery**

The main goal at time of primary surgery is to achieve maximum cytoreduction of all abdominal, pelvic and retroperitoneal disease. Residual disease < 1cm defines optimal cytoreduction. However, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.[4]

- On entering abdomen, aspiration of ascites or peritoneal lavage should be performed for cytologic examination.
- Entire abdominal cavity should be examined, including upper abdomen and under the surface of diaphragm. All visible suspicious areas and adhesions should be removed. In the absence of gross disease, random peritoneal biopsies should be taken from pelvis, para-colic gutters, and under surface of diaphragm.
- Total hysterectomy and bilateral salpingo-oopherectomy should be performed, with effort to remove the encapsulated mass intact. In certain advanced cases where total hysterectomy is not possible, subtotal hysterectomy may be done.
- Omentectomy should be performed. All involved omentum, preferably also including the supra-colic omentum should be removed (Figures 2 and 3).

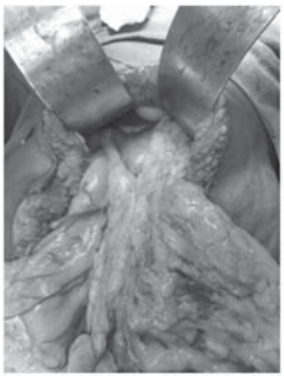

**Figure 2: Metastatic deposits on omentum.**

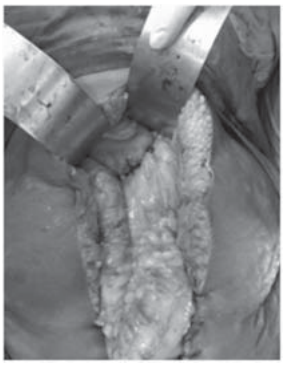

**Figure 3: Complete omentectomy done; stomach and transverse colon are seen in the image.**

- Bilateral pelvic lymphadenectomy should be performed with removal of lymph nodes overlying common iliac and external iliac vessels, overlying and medial to hypogastric vessels, and from the obturator fossa anterior to obturator nerve.
- Para-aortic lymph node dissection should be performed by removing nodal tissue overlying vena cava and aorta, preferably to the level of renal vessels.
- Patients with advanced ovarian cancer in whom complete intra-abdominal resection has been done, and who had no enlarged lymph-nodes both on radiological evaluation and during surgery, are deemed to have been operated adequately. This group of patients need not undergo systematic pelvic and para-aortic lymphadenectomy, as this does not improve the progression free survival or overall survival.[5]
- In advanced cases, procedures like bowel resection, with or without colostomy, appendectomy, peritonectomy, diaphragmatic stripping, splenectomy, partial cystectomy, partial hepatectomy, cholecystectomy, partial gastrectomy or distal pancreatectomy, may be done to achieve optimal cytoreduction (Figure 4).
- Appendectomy should be performed in all mucinous tumors, either early, advanced, or borderline.

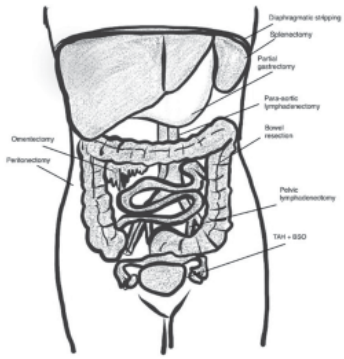


**Figure 4: Various procedures to be done for complete cytoreduction.**

While primary cytoreductive surgery may not fully compensate for aggressive tumor biology, evidence indicates that the volume of disease left at the completion of primary surgery is inversely related to patient survival. Hence, extensive cytoreduction leads to improvement of patient outcomes.[6]

2) **Interval debulking**

As with primary surgery, every effort should be made to achieve maximum cytoreduction at the time of interval debulking surgery. All gross disease in pelvis, abdomen, and retroperitoneum should be removed.

Interval surgery is usually performed after 3 cycles of neo-adjuvant chemotherapy, if there is a good or partial response to chemotherapy. Otherwise, timing of surgery may be individualized based on patient's response to treatment.

- All peritoneal surfaces should be visualized, and suspicious areas and areas of adhesions should be excised.
- Total hysterectomy, bilateral salpingo-oopherectomy, and omentectomy should be done.
- All enlarged and suspicious lymph nodes, and those nodes which were involved at the time of initial diagnosis should be resected.
- Procedures like bowel resection with or without colostomy, appendectomy, peritonectomy, diaphragmatic stripping, splenectomy, partial cystectomy, partial hepatectomy, cholecystectomy, partial gastrectomy, or distal pancreatectomy may be done to achieve optimal cytoreduction.

## Non-Epithelial Ovarian Cancer

In contrast to epithelial tumors, other ovarian malignancies like germ-cell or sex-cord stromal tumors usually present at an early stage. As many of these patients may be of younger age, fertility sparing surgery can be done in these patients. However, if disease is advanced or if the patient does not desire fertility, then

they should undergo comprehensive surgical staging just like epithelial tumors.

Node dissection should be carried out in cases with suspicion of nodal involvement.

An endometrial curettage must be carried out to rule out concomitant uterine cancer in patients with granulosa-cell tumor.

## Fertility Sparing Surgery

Patients desiring fertility, with apparent early stage disease, and low-risk tumors like early stage invasive epithelial tumors, borderline tumors, malignant germ cell tumors, malignant sex-cord stromal tumors, are candidates for fertility sparing procedures. These patients can undergo unilateral salpingo-oopherectomy with preservation of uterus and contralateral ovary. However, comprehensive surgical staging, which includes peritoneal lavage, omentectomy, peritoneal biopsies and removal of all suspicious areas, should be performed to rule out occult higher stage disease.

Ovarian biopsy of the contralateral ovary is not required if it is grossly normal.

## Risk Reducing Surgery

Risk reducing salpingo-oopherectomy is recommended for patients at risk for Hereditary Breast Ovarian Cancer syndrome. The pathologic processing of the removed specimen should include micro-sectioning of the ovaries and tubes, with special attention to the fimbriae.[7]

- The procedure may be done laparoscopically.
- Examine the upper abdomen, bowel surfaces, omentum, appendix, and all pelvic organs.
- Biopsy any abnormal areas, and take peritoneal washings.
- Perform total bilateral salpingo-oopherectomy, removing 2cm of proximal infundibulo-pelvic ligament, all tube upto the cornua and all peritoneum surrounding the tubes and ovaries.

## Role of Minimal Invasive Surgery

Minimal-invasive surgery is performed currently to stage and treat ovarian cancer at different stages of disease. Major concerns of minimal-invasive surgery are related to minimizing tumor disruption and dissemination, removing the adnexal mass intact, and adequate retro-peritoneal staging.

Minimal-invasive surgery may be used in ovarian malignancy in the following situations:

- Ovarian masses with low risk for cancer, i.e. mass less than 10 cm in size on radiology, with distinct border and no solid areas, no ascites, and normal CA 125 levels.
- As part of initial treatment of early stage ovarian cancer when there is no disease outside the ovaries.
- In advanced cases, laparoscopic assessment may be done to assess if complete cytoreduction is possible.
- Minimal invasive surgical methods may also be used to resect localized recurrences.

## Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)

HIPEC is an additional procedure which may be done at the time of surgery in cases of recurrent epithelial ovarian cancers. After the completion of cytoreductive surgery, which may include bowel resection or peritonectomy, chemotherapy is directly instilled into the peritoneal cavity at high flow rate, high temperature, and high concentrations through a closed circuit system using the HIPEC machine. HIPEC takes care of the residual microscopic disease that have been left behind after the cytoreductive surgery.

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# Targeted Therapy in Gynecological Cancers

**Satinder Kaur[1], Randeep Singh[2]**

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## Introduction

We are facing a growing burden of cancers in females with 6.7 million new cancer cases and 3.5 million deaths recorded among females worldwide in 2012. These numbers are expected to increase with increasing geriatric population[1]. Despite advances in surgical techniques and chemotherapy regimens, there has been a marginal improvement in survival rates for advanced gynecological cancers. Our understanding of the biology of cancers with respect to cellular pathways like angiogenesis, molecular alterations and metastasis has led to the development of various targeted therapies which have shown some promising results. Use of Trastuzumab in HER2 positive breast cancer and Geftinib in EGFR positive lung cancer is one of the examples of the success story of targeted therapy in modern oncology. Targeted agents do not induce direct cell kill but prolong time to progression by acting on complex genetic pathways responsible for tumor cell growth and survival, therefore their responses are low if assessed radiologically. In addition, since targeted therapies affect disease-specific alterations and not normal tissues, they can be used as maintenance therapy for a long period of time.

## Ovarian Cancer

With better understanding of molecular pathways involved in carcinogenesis and tumor microenvironment, various new treatment options for ovarian cancer are emerging like anti Vascular endothelial growth factor (VEGF/VEGFR) inhibitors, non-VEGF angiogenic inhibitors, folate receptor inhibitors and IGFR inhibitors.

### *Anti Angiogenetic Inhibitors*

Angiogenesis implicates the growth of new blood vessels, the change in their permeability and vasodilatation, the loss of endothelial cell adhesions and the incorporation of progenitor cells into the new blood vessels[2]. In epithelial ovarian cancer, angiogenesis plays a vital role in tumor growth, formation of ascites and metastasis. The VEGF family of growth factors and its receptors are the most important signaling pathways in tumor angiogenesis[3]. VEGF-A is the best-characterized VEGF ligand and appears to play a dominant role in angiogenesis by binding to VEGF receptor tyrosine kinases (VEGFR). Thus the targeted agents acting against this pathway can be divided into monoclonal antibody (Bevacizumab) and Small molecule TKI (Tyrosine kinase inhibitors).

### Bevacizumab

Bevacizumab is an intravenously administered humanized monoclonal antibody directed against VEGFA that acts by binding and neutralizing VEGFA[4]. ICON7[5] and GOG 218[6] are the two key studies investigating the addition of bevacizumab to conventional chemotherapy in upfront high-risk metastatic ovarian cancer with maintenance bevacizumab following chemotherapy. In ICON7, patients were randomized to standard 6 cycles of three-weekly carboplatin and paclitaxel with or without intravenous bevacizumab 7.5mg/kg every three weeks followed by maintenance bevacizumab for up to 12 months. The median progression free survival (PFS) was 17.5 months with standard therapy alone versus 19.9 months in the bevacizumab arm (HR 0.87; p=0.04). The benefit from bevacizumab was greater in women at higher risk of progression due to incomplete cyto-reductive surgery (≥1 cm residual disease) or FIGO stage IV disease. In this group the PFS was 14.5 compared to 18.1months in women receiving bevacizumab. No difference was seen in the median overall survival (OS), which was 58 months. However, in the higher risk subgroup there was a 9.5 month difference in the median OS, 30.2 vs. 39.7 months (p=0.03) in women receiving bevacizumab[5]. GOG 218 was a US-led 3-arm randomized placebo-controlled study. Each arm received 6 cycles of standard three-weekly carboplatin and paclitaxel with placebo maintenance in arm 1; arm 2, chemotherapy plus bevacizumab (15mg/kg) from cycle 2-6 then switching to placebo maintenance and arm 3 received chemotherapy plus bevacizumab from cycle 2-6 followed by bevacizumab maintenance. Compared to the control (arm 1) a significant improvement in PFS was seen only in women receiving bevacizumab with chemotherapy and as maintenance. The difference in median PFS in this group compared to placebo was 3.9 months and there was no difference in OS[6].

The use of bevacizumab in platinum-sensitive recurrent ovarian cancer was approved based on the OCEANS trial[7], which showed doubling of the progression-free survival. In addition, FDA also approved the use of bevacizumab in patients with recurrent, platinum-resistant ovarian cancer based on the phase III AURELIA trial[8], which demonstrated that bevacizumab with chemotherapy reduced the risk of disease progression by 52% compared with chemotherapy alone.

Toxicities of VEGF-Inhibitors include hypertension, impaired wound healing, proteinuria, increase risk

of thromboembolism and gastrointestinal toxicities. This includes the rare but serious complications of perforation and fistulae and thus a decision to use bevacizumab is to be weighed against the volume of serosa disease, particularly thickening of the sigmoid colon due to tumor, as the risk of perforation is greater in patients with large amounts of serosa disease.

Despite evidence of activity in different phases of the treatment pathway, there is no international consensus about when the value of bevacizumab therapy is greatest.

### Small Molecule TKI

TKIs are multi-targeted, low-molecular weight drugs, which bind to the ATP-binding catalytic site of the tyrosine kinase domains of VEGF-R and other tyrosine kinases. These oral agents often target more than one receptor tyrosine kinase. Various drugs such as cediranib, pazopanib and nintedinib, have shown improvement in PFS in advanced ovarian cancer but none of these has been approved to be used in clinics[9].

### PARP Inhibitors

PARP inhibitors rely on the sensitivity of cells containing a defect in homologous recombination pathways to PARP inhibition (e.g. those with BRCA mutations), which results in the death of target tumor cells while sparing normal cells. BRCA mutations are the first predictive markers for response to PARP inhibitors in ovarian cancer. Olaparib is the first-in-class drug to be licensed for the treatment of ovarian cancer as maintenance therapy in platinum-sensitive ovarian cancer with a BRCA mutation. Study 19, which randomly assigned patients to Olaparib capsules (400mg BD) or placebo within 8 weeks of completing platinum-based therapy showed a significant difference in PFS (8.4 vs. 4.8 months)[10]. In USA the drug is licensed as a single agent, in patients with a BRCA mutation who have received ≥3 lines of chemotherapy. This indication is based on Study 12 that compared Olaparib with Liposomal Doxorubucin in women with a BRCA mutant recurrent ovarian cancer[11]. Encouraging results emerging from studies with other PARP inhibitors (Nirapirib and Rucapirib) are likely to widen the use of this class of drugs in ovarian cancer.

## Cervical Cancer

HPV oncoproteins are the primary viral factors responsible for initiation and progression of cervical cancer. E6, E7 and to a lesser extent E5 play key roles in up-regulating angiogenesis through the VEGF pathway through their effects on p53 degradation, HIF-1α and inactivation of retinoblastoma protein (pRb).

In GOG 240 study bevacizumab was used in combination with paclitaxel plus either Cisplatin or Topotecan in patients with persistent, recurrent, or first line metastatic cervical cancer[12]. GOG 240 showed a significant improvement in OS (12.9 to 16.8 months), PFS and ORR, without a concomitant deterioration of HRQoL. It also demonstrated a proof of concept concerning integration of anti-angiogenesis therapy for advanced cervical cancer patients, and represents a practice-changing clinical trial when compared with prior clinical trials in this setting.

Moving beyond bevacizumab, exploration of small molecule TKI are being undertaken and considered in women with cervical cancer. Single agent, orally administered, multi-TKIs, pazopanib (VEGFR 1, 2, and 3; PDGFR-α and β; and c-KIT inhibitor) and sunitinib (VEGFR 1, 2 and 3; PDGFR, c-KIT, and FLT3 inhibitor) have been investigated and shown modest but clinical insignificant activity[13]. Non-VEGF-dependent therapeutic approaches, including angiopoietin inhibitors and PI3K/AKT/ mTOR pathway may also offer a unique treatment opportunity in cervical cancer.

## Endometrial Cancer

The role of targeted agents in endometrial cancer is less well developed as compared to cervical and ovarian cancer. Except hormone therapy (the sole approved targeted therapy), numerous targeted agents have been investigated with variable disappointing results in recurrent and metastatic endometrial cancer. These include Bevacizumab, Anti-VEGF monoclonal antibody; Aflibercept (VEGF Trap) with a high-affinity binding to VEGF-A, VEGF-B; gefitinib and erlotinib, two tyrosine kinase inhibitors; trastuzumab and lapatinib, both EGFR type 2 (HER2)-related inhibitors that affect signal transduction and temsirolimus and ridaforolimus, which block the phosphoinositide 3- kinase/AKT/mTOR pathway[14]. Other drugs target epigenetic regulation of various cancer genes may be particularly important in type I endometrial cancer. The generally lower response rates of various targeted agents as compared with standard chemotherapy may be due to the multiplicity of carcinogenetic pathways and associated genes.

## Conclusion

The role of targeted therapy in gynecological cancers, like in many remains elusive. Inhibition of tumor angiogenesis and epidermal growth factor receptor directed therapies have focused the most recent clinical research efforts. A thorough molecular characterization of gynecological cancers remains crucial for a rationale implementation of targeted agents and companion biomarkers. Alternative clinical trial designs may also be necessary to optimize the clinical development of new drugs. Hopefully, gynecological cancer management will shift from empirical cytotoxic therapies to an

individualized approach based on the specific features of each tumor in an individual patient.

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# Congratulations

## Young Gynaecologists of AOGD Won Laurels at FOGSI BOH – Triology Conference 2017

❖ **Theme Paper**
- 1st Prize - Dr Anukriti Kumari (GTBH)
- 2nd Prize - Dr Priyanka Aggarwal (SJH)
- 3rd Prize - Dr Anubhuti (SJH)

❖ **Miscellaneous Paper Category**
- 1st Prize - Dr Kavita Aggarwal (SJH)
- 2nd Prize - Dr Supriya Gupta (SJH)

❖ **Posters**
- 1st Prize - Dr Richa Sharma (GTBH)
- 2nd Prize - Dr Shweta Singh (ESI, Basaidarapur)
- 3rd Prize - Dr Divya (SJH)

# Journal Scan

**Rashmi**
Assistant Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences and GTB Hospital, Delhi

1. Lancet Oncol. 2017 Jul 25. pii: S1470-2045(17)30469-2.

## Olaparib Tablets as Maintenance Therapy in Patients with Platinum-Sensitive, Relapsed Ovarian Cancer and a BRCA1/2 Mutation (SOLO2/ENGOT-Ov21): A Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial

**Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, et al.**

### Background

OLAPARIB, a poly(ADP-ribose) polymerase (PARP) inhibitor, has previously shown efficacy in a phase 2 study when given in capsule formulation to all-comer patients with platinum-sensitive, relapsed high-grade serous ovarian cancer. We aimed to confirm these findings in patients with a BRCA1 or BRCA2 (BRCA1/2) mutation using a tablet formulation of olaparib.

### Methods

This international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial evaluated olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with a BRCA1/2 mutation who had received at least two lines of previous chemotherapy. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status at baseline of 0-1 and histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancer. Patients were randomly assigned 2:1 to olaparib (300 mg in two 150 mg tablets, twice daily) or matching placebo tablets using an interactive voice and web response system. Randomisation was stratified by response to previous platinum chemotherapy (complete vs partial) and length of platinum-free interval (6-12 months vs ≥12 months) and treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers. The primary endpoint was investigator-assessed progression-free survival and we report the primary analysis from this ongoing study. The efficacy analyses were done on the intention-to-treat population; safety analyses included patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT01874353, and is ongoing and no longer recruiting patients.

### Findings

Between Sept 3, 2013, and Nov 21, 2014, we enrolled 295 eligible patients who were randomly assigned to receive olaparib (n=196) or placebo (n=99). One patient in the olaparib group was randomised in error and did not receive study treatment. Investigator-assessed median progression-free survival was significantly longer with olaparib (19·1 months [95% CI 16·3-25·7]) than with placebo (5·5 months [5·2-5·8]; hazard ratio [HR] 0·30 [95% CI 0·22-0·41], p<0·0001). The most common adverse events of grade 3 or worse severity were anaemia (38 [19%] of 195 patients in the olaparib group vs two [2%] of 99 patients in the placebo group), fatigue or asthenia (eight [4%] vs two [2%]), and neutropenia (ten [5%] vs four [4%]). Serious adverse events were experienced by 35 (18%) patients in the olaparib group and eight (8%) patients in the placebo group. The most common in the olaparib group were anaemia (seven [4%] patients), abdominal pain (three [2%] patients), and intestinal obstruction (three [2%] patients). The most common in the placebo group were constipation (two [2%] patients) and intestinal obstruction (two [2%] patients). One (1%) patient in the olaparib group had a treatment-related adverse event (acute myeloid leukaemia) with an outcome of death.

### Interpretation

OLAPARIB tablet maintenance treatment provided a significant progression-free survival improvement with no detrimental effect on quality of life in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation. Apart from anaemia, toxicities with olaparib were low grade and manageable.

### *Editor's Comments*

*Lynparza (Olaparib) was first approved under the FDA's Accelerated Approval program in December 2014, as a capsule formulation, making it the first poly ADP-ribose polymerase (PARP) inhibitor approved for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Since then, more than 3,000 advanced ovarian cancer patients have been treated with this. Based on the findings of SOLO2 trial & Study 19 (NCT00753545) (both randomized, placebo-controlled, double-blind, multicenter trials) the U.S. Food and Drug Administration granted regular approval in Aug 2017 to olaparib tablets (Lynparza) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. The dosage is 400 mg tablet twice a day. This improves the progression free survival in relapsed epithelial ovarian cancers.*

2. Int J Gynecol Cancer 2017;27 (6): 1247-55.

## Expression of Estrogen and Progesterone Receptor in Tumor Stroma Predicts Favorable Prognosis of Cervical Squamous Cell Carcinoma

**Mun-Kun Hong, Jen-Hung Wang, Cheng-Chuan Su, Ming-Hsun Li, Yung-Hsiang Hsu, MS, Tang-Yuan Chu**

### Objectives

The aim of this study was to investigate the expression of estrogen receptorα (ERα) and progesterone receptor B (PRB) in the stroma and carcinoma tissues of cervical cancer and their relationship to clinical characteristics and the status of human papillomavirus (HPV) infection.

### Methods

Expressional levels of ERα and PRB in tissue blocks of 95 cervical carcinomas were independently scored by 2 pathologists. Human papillomavirus DNA, viral load, and genotypes were determined by polymerase chain reaction. Clinical characteristics were reviewed from chart and cancer registry.

### Results

Estrogen receptor α and PRB were mainly expressed in the stroma but not in the carcinoma tissues of the cervical cancer, and their expressions were highly correlated. More stromal ERα's were found in early-stage tumors than in advanced-stage tumors. Greater stromal expressions of ERα and PRB were associated with a more favorable prognosis (P = 0.018 and P=0.004, respectively). The expressions were not related to the differentiation of cancer, the status of HPV infection, the HPV load, or the genotype. In multivariate analysis, stromal ERα and PRB expressions were independently associated with a lower risk of mortality. The adjusted hazard ratios of mortality for low and high expressions of ERα were 0.19 (95% confidential interval [95% CI], 0.04 - 0.87) and 0.15 (95% CI, 0.03 - 0.81), respectively, whereas for low and high expressions of PRB hazard ratios were 0.46 (95% CI, 0.19 - 1.16) and 0.24 (95% CI, 0.06 - 0.96), respectively.

### Conclusions

This study showed that stromal ER> and PRB expressions are independent prognostic indicators of cervical squamous cell carcinoma.

### *Editor's Comments*

*Human cervix expresses both estrogen and progesterone receptors and epidemiological studies have shown that long term exposure to endogenous and exogenous hormones is an independent risk factor for cervical cancer. The present study found that these sex hormone receptors were mainly expressed in the stroma and their expressions were significantly associated with favorable survival, indicating that these sex hormones in the cervical stroma may play a role in invasion and/or metastasis of SCC. Besides FIGO stage ERα and PRB expressions were independent prognostic factors for SCC and high expressions were associated with superior 5-year survival. The stromal ERα and PRB expressions may be used to predict clinical outcome and stratify disease for investigating hormone therapy in cervical cancer, like breast and endometrial cancers. However, the mechanisms of stromal ERα and/or PRB in invasion or metastasis of SCC are poorly understood.*

3. Am J Obstet Gynecol. 2017; 216(6):580.e1-580.e9.

## Lifetime Cancer Risk and Combined Oral Contraceptives: The Royal College of General Practitioners' Oral Contraception Study

**Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC**

### Background

Oral contraceptives have been used by hundreds of millions of women around the world. Important questions remain regarding the very long-term cancer risks that are associated with oral contraception. Despite previous research, important questions remain about the safety of these contraceptives: (1) How long do endometrial, ovarian, and colorectal cancer benefits persist? (2) Does combined oral contraceptive use during the reproductive years produce new cancer risks later in life? (3) What is the overall balance of cancer among past users as they enter the later stages of their lives?

### Objectives

The purpose of this study was to examine the very long-term cancer risks or benefits associated with the use of combined oral contraceptives, including the estimated overall life-time balance.

### Study Design

The 46,022 women who were recruited to the UK Royal College of General Practitioners' Oral Contraception Study in 1968 and 1969 were observed for up to 44 years. Directly standardized rates of specific and any cancer were calculated for "ever" and "never" users of combined oral contraceptives; data were standardized for age, parity, social class, and smoking. Attributable risk and preventive fraction percentages were calculated. Poisson regression that adjusted for the same variables was used to estimate incidence rate ratios between ever

and never users and to examine effects by time since last oral contraceptive use.

## Results

There were 4661 ever users with at least 1 cancer during 884,895 woman-years of observation and 2341 never users with at least 1 cancer during 388,505 woman-years of observation. Ever use of oral contraceptives was associated with reduced colorectal (incidence rate ratio, 0.81; 99% confidence interval, 0.66-0.99), endometrial (incidence rate ratio, 0.66; 99% confidence interval, 0.48-0.89), ovarian (incidence rate ratio, 0.67; 99% confidence interval, 0.50-0.89), and lymphatic and hematopoietic cancer (incidence rate ratio, 0.74; 99% confidence interval, 0.58-0.94). An increased risk of lung cancer was seen only among ever users who smoked at recruitment. An increased risk of breast and cervical cancer that was seen in current and recent users appeared to be lost within approximately 5 years of stopping oral contraception, with no evidence of either cancer recurring at increased risk in ever users with time. There was no evidence of new cancer risks appearing later in life among women who had used oral contraceptives. Thus, the overall balance of cancer risk among past users of oral contraceptives was neutral with the increased risks counterbalanced by the endometrial, ovarian, and colorectal cancer benefits that persist at least 30 years.

## Conclusion

Most women who choose to use oral contraceptives do not expose themselves to long-term cancer harms; instead, with some cancers, many women benefit from important reductions of risk that persist for many years after stopping.

## *Editor's Comments*

*Combined oral contraceptives are the most commonly used temporary contraceptive method in the world. But concerns were expressed early on about the method's carcinogenic potentials. Though evidence from various studies mainly case control has shown beneficial effects on ovarian, endometrial and colorectal cancers but increased risk of breast and cervical cancer and liver cancer in some regions have raised concerns and doubts in the minds of users. In this regard, present study provides evidence from the longest running study of health effects of the oral contraceptives in the world. Long term protection from ovarian, endometrial and colorectal cancer lasting > 35 years and loss of increased risk for cervical and breast cancer after 5 years of stopping oral contraceptives, shifts the balance in favor of oral contraceptive providing overall protection in the long run. These results are reassuring.*

# Proceedings of AOGD Monthly Clinical Meet

**AOGD Monthly Clinical Meeting was held at VMMC and Safdarjung Hospital, New Delhi on 24 August 2017**

## Pregnancy related Acute Kidney Injury- Prevention is better than cure

***Archana Kumari, Kanika Gulati, Jagrati Gupta, Sunita Malik, H P Anand, Jyotsna Suri, Pratima Mittal***

**Introduction**: Pregnancy related AKI is challenging for obstetricians because of the complexity of diagnosis due to the renal and cardiovascular adaptations in pregnancy, its association withmultiorgan involvement and its rapid progression, if left untreated. Identification and prevention of AKI at prerenal phase and early involvement of nephrologist for patients not responding to initial management and maintenance of electrolytes, acid base balance & nutritional support plays vital role in improving maternal and fetal outcome.

**Case presentation**: A 22 year old, unbooked, Primigravida at 35 weeks POG presented with 16-18 episodes of rice watery diarrhoea and vomiting over 1 day.There was no h/o feveror any any antenatal complications like hypertension, diabetes or anemia. On examination ,the patient was dehydrated, afebrile. Her PR=124/mt, low volume, BP=80/50mmHg and RR=28/mt. On Abdominal exam, single dead fetus corresponding to the period of gestation was present in cephalic presentation. Uterus was relaxed, non tense and non tender. Intrauterine fetal demise was confirmed by ultrasound. A provisional diagnosis of primigravida at 35 weeks POG with IUFD with acute gastroenteritis (? Cholera) in shock was made. Patient was admitted in obstetric critical care unit. Baseline investigations were sent. On catheterization, minimal high coloured urine drained. ABG showed metabolic acidosis (pH- 7.2; HCO3-6). Her investigations revealedHb-15.2, TLC-16100, PLT-1.76 lakh, S.bil-0.45, AST-273, ALT-109, ALP-497, INR-0.95, RBS-96 and SE-134/5.6. Kidney function tests were highly deranged (BU-72,S.Cr-6.09). Urine routine and microscopy was normal.Fluid resuscitation (1lt over 15 min (RL & NS) followed by 1 lt over next 45 minutes) followed by maintenance fluids was given. Antibioticslike ciprofloxacin, metronidazole and doxycycline were started. Correction of metabolic acidosis was done sodium bicarbonate. Nephrology opinion taken. Serum Electrolytes and ABG monitored 12 hrly. Loose stools subsided after 3 days. However, in view of refractory metabolic acidosis and raised creatininelevels, decision for dialysis was taken by nephrologists. 4 rounds of dialysis was done over a duration of 1 week with daily KFT monitoring. Varying episodes of hypokalemia developed for which K supplementation was given. Pt went into spontaneous labour and delivered a macerated stillborn girl baby of 2.2 Kg on 1.8.17. Pts condition improved and shifted to the ward where her KFT was monitored daily. Her KFT normalized to BU-18 and S.cr-0.6 after 1 week.USG kidneys was normal. Pt was discharged in good condition. Early identification of AKI and critical care involving multidisciplinary team resulted in good outcome.

## Hypertensive Disorders in Pregnancy – Commonest cause of obstetric critical care admissions

***Priyanka Arya, Suruchi, Jyotsna Suri, Vijay Zutshi, Rekha Bharti, Renu Arora, Pratima Mittal***

A 25 year old $G_2P_1L_0$ with 8 months of pregnancy came to gynae emergency with recurrent seizures, refractory to $MgSo_4$ therapy and intractable hypertension. She had history of antepartum eclampsia in her previous pregnancy for which preterm LSCS was done 1 year back and she had early neonatal death. Emergency LSCS was done i/v/o uncontrolled BP and convulsions. A girl baby with 1.3 kg birth weight was born with low APGAR score. This was the case of refractory hypertension as BP remained uncontrolled in post op period despite giving high dose of NTG, lasix and maximum dose of I/v labetalol. BP came under control after 24hrs on multiple anti-hypertensives. As she remained drowsy and disoriented in post op period, NCCT head was done which revealed PRES syndrome. Injmannitol was started after ruling out papilloedema on fundus examination. She gradually improved after 48 hrs and was discharged after 1 week with proper counselling for her reproductive future and BP monitoring. Calcium supplementation in all, low dose aspirin in high risk patients, timely referral from referral point with basic life support management at referral point only (full loading dose of $Mgso_4$, anti-hypertensives), termination of pregnancy and aggressive management are the key points to decrease the fetomaternal morbidity and mortality associated with antepartum eclampsia.

## Peripartum cardiomyopathy- Early diagnosis crucial for good outcome

***Banashreenath, Monu Singh, Achla Batra, Manjula Sharma, Harsha S Gaikwad, Jyotsna Suri, Pratima Mittal***

Incidence of peripartum cardiomyopathy varies with diverse demographic factors. It varies from 1 in 968 in

USA to 1 in 6000 in Japan. Clinicians should have a high degree of suspicion for diagnosis of PPCM in pregnant mothers with one or more risk factors and symptoms of heart failure.

A 20 years old young Primigravida presented with chief complaints of difficulty in breathing for 1 week and absent fetal movement for 24 hrs. On examination, her PR-120, BP-140/105mmHg, RR-35/mt, SpO2- 85% on room air. She was severely anemic. Her urine albumin was 2+. Patient was put on oxygen support (6lit/min) and transferred to critical care unit. All baseline investigations were sent and two units of packed cells were transfused. After 1 hour of admission, condition of the patient deteriorated and Spo2 dropped to 80% despite high flow oxygen. She was put on non-invasive mechanical ventilation. However, her condition continued to deteriorate and she was intubated and put on ventilator (VCV mode). Concurrently, termination of pregnancy was done with dinoprostone gel and she delivered a macerated baby boy of 2.8 Kg. Her condition improved after delivery but chest crepitations still persisted. Echocardiography was done which revealed global hypokinesia, dilated left ventricle and ejection fraction 25-30%. Hence, diagnosis of peripartum cardiomyopathy was made. Patient was started on diuretics, ACE inhibitors, beta blockers and anticoagulant. She responded well to treatmentand discharged on postnatal day 12. This case illustrates the devastating effects of PPCM. It highlights the importance of early diagnosis and treatment to preserve the myocardial function for chances of full recovery.

# Gynecological Cancer Awareness Month

Foundation for Women's Cancer
*Celebrating 25 years of excellence*

September is **Gynecologic Cancer Awareness Month**, established by the Foundation for Women's Cancer in 1999. Gynecological Cancer Awareness Month provides an opportunity to draw attention to this important women's health issue and offer vital information on cancer risks, warning signs, prevention and early detection strategies for gynecologic cancers overall.

Despite the alarming statistics, gynaecological cancer remains a taboo subject among the public. The associated stigma, embarrassment and a lack of knowledge about the disease are key barriers for women to talk openly about gynaecological cancer and seek medical help. The campaign aims to encourage more women to be aware of the signs and symptoms of the disease, and to feel comfortable speaking about them without shame or embarrassment.

A new survey by The Eve Appeal in UK revealed a shocking number of women know little about their own anatomy; with nearly half of those surveyed unable to identify the vagina on an anatomical diagram, and 45% of women couldn't point out the cervix. Awareness of female cancers was also low; the survey found that 14% of women could not name a single gynaecological cancer. This survey highlights a growing need for better sex education. If women are better informed about what is normal or not when it comes to their gynaecological health, there is a higher chance they will seek help. This knowledge will equip young women for the future, and work to remove the stigma associated with gynaecological cancer.

This year, the special focus is on clinical trial awareness. Unfortunately, enrollment in stage three clinical trials has decreased for gynecologic cancers. Throughout the month, the Foundation for Women's Cancer will share facts about clinical trials and bring attention to the crisis.

**What can we do to help end women's cancer?**

- Use hashtags #End Womens Cancer, #share the purple love and #GCAM in related social media posts focused on bringing awareness about gynecologic cancers.
- Write or share social media posts about clinical trial awareness. Share social media posts and use the hashtag #Trials 4GynCancerNOW.
- Read more about clinical trials on website.
- #Sharethepurplelove by donating to the Foundation for Women's Cancer in honor of GCAM. Each dollar goes toward research, awareness and education for gynecologic cancers.
- Write or share social media posts about recognizing the symptoms of gynecologic cancers and the importance of being treated by a gynecologic oncologist if diagnosed. The shareable photos are available on GCAM fast sheets document.
- Share photos of #EndWomensCancer fundraising events or photos of advocates and survivors wearing purple, the designated color of gynecologic cancer awareness.
- Share stories of cancer survivors and advocates!
- Print outGCAM posters for your office.
- Follow FWC's Facebook, Twitter and Instagram pages as the Foundation shares inspiration, information and fun throughout the month.

# Quiz Time: *Tick it, Fill it, Click it, Whatsapp/ Email it*

**Rashmi**

Assistant Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi

Q1. *BRCA1* - and *BRCA2* - associated HBOC should be suspected in individuals with the following features except:

a. Previously identified pathogenic *BRCA1/2* variant in the family
b. Personal/ family history of ovarian cancer
c. Combination of pancreatic and/or prostate cancer with breast and/or ovarian cancer
d. Estrogen and progesterone receptor positive breast cancer (particularly when diagnosed before age 60 years)

Q2. Complete the following:

a. Underlying genetic predisposition is seen in _____% of breast cancers
b. BRCA1 is located on chromosome_____ & BRCA2 on chromosome _____
c. NGS stands for _____
d. HBOC stands for_____
e. RRM stands for_____
f. RRSO stands for _____

Q3. Which mutation can cause Fanconi anemia?

_____

_____

Q4. The National Comprehensive Cancer Network (NCCN) guidelines for cancer surveillance in women who test positive for *BRCA1/2* include the following except

a. Salpingo oophorectomy between 35-40 years and upon completion of child bearing
b. Monthly breast self-exam (BSE) starting at the age of 25 years
c. Semi-annual clinical breast exam (CBE) starting at the age 25 years
d. Annual mammograms and breast MRI screening with contrast starting 25-30 yrs

Q5. In *BRCA1/2* mutation carriers breast cancer risk can be reduced by

a. Selective estrogen receptor modulator (i.e. Tamoxifen and Raloxifene)
b. Long-term use oral contraceptives
c. Risk reducing salpingo oophorectomy

Q6. Ca Cx all are correct except:

a. MRI correlated more closely with surgico pathologic findings than CT
b. PET/CT has been found to be more sensitive than PET alone for detection of nodal metastases.
c. **Sentinel lymph node (SLN) biopsy has** high negative predictive value (NPV:98%) and sensitivity (89-90%).
d. No need for lymphadenectomy if the mapping procedure fails to detect a sentinel node in one hemipelvis.

Q7. In Querleu-Morrow classification of Radical Hysterectomy, which one is nerve Sparing?

a. A
b. B1
c. C1
d. D

Q8. Fertility preserving surgery can be done for those Cases with Ca Cx, who desire future pregnancy and

a. Size of growth is <4cm
b. Minimal lymphovascular space invasion
c. Clinical Stage 1A1

Q9. Match the followings awareness ribbons with the cancer they depict

| **Color of Ribbon** | **Type of Cancer** |
|---|---|
| 1. Purple | a. Ovarian |
| 2. Pink | b. Endometrial |
| 3. Teal | c. All Gynecological |
| 4. Peach | d. Vaginal |
| 5. Blue | e. Breast |

Q10. In premenopausal nulliparous women familial Endometrial carcinoma may be associated with which syndrome?

Ans. _____

Q11. In Endometrial carcinoma conservative management can be offered if:

Ans. Stage_____ Grade_____ Type_____

Q12. For Fertility preservation, following treatments can be given in Endometrial Ca except:

a. Medroxyprogesterone Acetate
b. Norethisterone
c. Megesterol Acetate
d. LNG-IUS

Q13. Considering all stages and grades, in endometrial carcinoma, a synchronous or metastatic ovarian carcinoma can be found in

a. 10%
b. 25%
c. 40%
d. 50%

Q14. Identify


Ans. _____

Q15. Match these targeted therapy with the corresponding cancers

| | |
|---|---|
| 1. Bevacizumab | a. Cervical Cancer |
| 2. Olaparib | b. Endometrial Cancer |
| 3. Pazopanib | c. Ovarian & Cervical |
| 4. Hormone Therapy | d. Ovarian |

Q 16. Fill in the blanks about Endometrial Hyperplasia

a) In EH, risk of progression to cancer _____ in 20 years
b) In EH, spontaneous regression occurs in _____ % and regression after progestins _____ %
c) In AH, risk of progression to cancer _____ in 20 years.
d) Repeat biopsy after progestogen therapy is done in _____ Months in EH & _____ months in AH.

Q 17. Two tests endorsed by NCCN to diagnose Lynch syndrome are?

_____

_____

Q 18. FDA recently approved which drug for maintenance therapy for patients with recurrent epithelial ovarian cancers?

_____

Q 19. What is HIPEC?

_____

Q 20. Interval debulking in Ovarian cancers is performed after how many cycles of chemotherapy?

_____

**Tick the MCQs and fill in the blanks.**
**Click a pic and whatsapp or email to us**
Whatsapp Nos.: 9810645212, 9810719002
Email: info@aogd.org

## Congratulations to the winners of Aug Quiz:

**Dr Monisha** **Dr Monika Sharma**

## Key to Aug Issue Quiz

**1.** For MAP, 3 steps: (1) preoperative placental localization (2) preoperative placement of intraarterial balloon catheters with inflation after delivery or ligation of the uterine arteries (3) no attempt to remove the placenta with en bloc myometrial excision and uterine repair. **2.** 10-15%, **3.** No bladder dissection, **4.** Enblock excision and repair, Conservative management, **5.** D, **6.** A, **7.** B, **8.** A, **9.** Flexion point, **10.** Wurm's cerclage, **11.** A F, b T, c F, d T, e F, f T, **12.** A Post fontanelle, Saggital suture, b contraction, c ghost application, d 0.8

# Royal College of Obstetricians & Gynaecologists - AICC- Northern Zone India

Website: **www.aiccrcognzindia.com**

**Chairperson:** Dr Nirmala Agarwal: (n.menoky@gmail.com / 9811888732)

**Vice Chairperson**
Dr Anita Kaul

**Hon. Secretary**
Dr Arbinder Dang

ANNOUNCING NEXT COURSES / CONFERENCE

## RCOG UK Franchise MRCOG Final Preparation: Part II Written Course

**Saturday 30th - Sunday 31st December 2017 & Monday 1st January 2018 (Total 3 Days)**

**Limited to 25 candidates only (First Come First Serve basis)**

**Course Fee:** Rs 30,000
*Certificate of attendance for this course will be provided by the RCOG UK*

**Venue:** RCOG North Zone Academic Centre, B-235, C R Park, New Delhi-110019, INDIA

UK Course Organizer & Convener - Dr Sanjeev Sharma

India Conveners and Contacts for details - Dr Saritha Shamsunder (shamsundersaritha@gmail.com/9313826748)
Dr Sweta Gupta (swetagupta06@yahoo.com/8130140007)
Dr Mamta Sahu (mamta2sahu@yahoo.co.in/ 9810106470)

**Online payment available on website. www.aiccrcognzindia.com**

## RCOG North Zone India Announces Bi-Annual Colposcopy Courses

**Under Aegis of ISCCP & AOGIN**

(Approved by the International Federation of Colposcopy & Cervical Pathology)

**Venue:** RCOG North Zone Academic Centre, B235, CR Park, New Delhi

**Course Convenors:** Dr Saritha Shamsunder (shamsundersaritha@gmail.com /Contact no. 9313826748)
Dr Mamta Dagar (mamtadagar2004@yahoo.co.in/ Contact no. 9811437782)

**BASIC COLPOSCOPY COURSE** on Monday 18th December, 2017

**ADVANCED COLPOSCOPY COURSE** on Tuesday 19th December, 2017

**Course Fee:** Rs 2000/- for Basic Colposcopy Course & Rs 2500/- for Advanced Course

Number of Delegates Limited to 25 only for each course

Last Date to Apply: 18th November 2017 Spot Registration subject to availability of seats.

**Registration Guidelines**
**Online payment available on website.** *There will be no refunds on cancellation.*
**Offline Payment**

Download Registration form from website www.aiccrcognzindia.com and send by Bank Transfer or Demand Draft made in favour of "**RCOG NZ 2012 Plus**" payable at New Delhi. (Cheques not accepted). Registration request along with Demand Draft to be posted to the Secretariat mailing addresses as given below.

## Kindly Block Dates

**Saturday 16th & Sunday 17th December 2017 RCOG North Zone Annual Conference**

***Mailing Address:*** **RCOG North Zone Secretariat**
**Sant Parmanand Hospital, 18 Alipur Road, Civil Lines Delhi 110054**
Tel No - 91-11-23981260 Ext. 314, 9560069925 / 9716801190 **Email: rcog_nz2012@yahoo.com**

# CENTRE OF EXCELLENCE GYNAE LAPAROSCOPY

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- All Hysteroscopic Procedures like Hysterescopic Myomectomy, Polypectomy, Septal Resection etc,
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