Editorial

Ovarian Cancer Screening & early Diagnosis

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If it were done when 'tis done, then 'twere well it were done quickly ...
Macbeth (I, VII)
William Shakespeare (1564-1616)

Ovarian Cancer is the silent prowler. It is called the killer that whispers. That subtlety is why it is so deadly.

Ovarian cancer is not a disease that gets lots of attention from the media or TV ads or the "get-yourself-tested" campaigns. Few women know that it is the most lethal type of reproductive cancer. Fewer even can name the symptoms, so insidious, that women may pass off the problem as indigestion until it is too late. While women can get mammograms to spot early breast cancer or PAP smears to catch cervical cancer, there is no screening test in most protocols for the early detection of ovarian cancer.

Yes, it is the lack of awareness that fuels the deadly ovarian cancer. But there are ways women can protect themselves and new discoveries are giving cancer researchers and doctors fresh hope of finding better treatments, or even a test that might catch budding tumours.

Epidemiology:

The lifetime risk of developing ovarian cancer (1.4%) is higher than that for either cancer of the cervix (1.25%) or the endometrium (1.1%) but lower than that for cancer of the breast (7.1%). Deaths from ovarian cancer outnumber those from carcinoma of the cervix and body of the uterus combined.

Incidence of epithelial tumours peaks at 50-70 years. Most epithelial tumours are advanced at diagnosis and less than 25% of women with ovarian cancer are alive at 5 years. 80-85% of women with ovarian cancer will die from their disease. 3% of ovarian cancers are seen in women younger than 35 years. There is no Pre-Malignant Phase.

Aetiology:

Incessant Ovulation Theory

The factors which lead to the development of ovarian carcinoma are not known. Epithelial tumours are most frequently associated with nulliparity, an early menarche, a late age at menopause and a long estimated number of years of ovulation. The infrequent occurance of carcinoma of the ovary in women of high parity is thought to be due to the suppression of continuous ovulation and there is now good evidence that oral contraceptives play a protective role. However, case-control studies which confirm the protective effect of parity also show that the risk of ovarian cancer decreasing with parity and increasing age at first birth in a population in which use of oral contraceptives was very limited. This and other anomalies cast doubt upon the 'incessant ovulation' theory.

Infertility Treatment

There is association between infertility and both ovarian and endometrial cancer. This link appears to be strongest in women with unexplained infertility. However, a pooled analysis of several case control studies showed a small

increased risk for ovarian cancer in infertile women treated with 'fertility drugs' and 12 cases of granulosa cell tumours were reported after ovarian stimulation. The use of clomiphene for more than a year was associated with an increased risk of borderline or invasive ovarian tumours. Subsequently, women who underwent IVF (in-vitro fertilization) showed no increased risk in upto 15 years after ovarian stimulation. Overall, these various studies do suggest the possibility of a link between ovulation induction, but only after prolonged treatment.

Genetic Factors for Ovarian Cancer

Enormous progress has been made in understanding the molecular basis of disease during the last decade, and this has transformed our understanding of the process of carcinogenesis. In recent years, these developments have begun to have an impact in gynaecological cancer.

Gynaecological cancers provide examples of a number of contrasting mechanisms of carcinogenesis. Ovarian and endometrial cancer can occur as components of familial cancer syndromes owing to germiline inheritance of predisposing genetic abnormalities. However, most ovarian cancers result from somatic mutations occuring in ovarian cells with an initially normal genome. There is probably a multistep process requiring an accumulation of genetic lesions in a number of different gene classes, such as AKT2, Ki-RAS. These are activated, with putative oncogene - containing chromosomal regions showing imbalances and DNA amplifications.

Inheritance plays a significant role in about 5% of epithelial ovarian cancers. These tumours are usually serous adenocarcinomas. The lifetime risk for a woman with one affected close relative is twice the risk in the general population. If there are two affected close relatives, the lifetime risk increases to 30-40%. A particular feature of familial cancers is the relatively early age at which they occur. It is unusual to find families with multiple cases of only ovarian cancer. More commonly, there are cases of breast or colorectal cancer in the family. The Lynch syndrome consists of families with colorectal cancer, endometrial cancer and ovarian cancer.

Clinical aspects of the Genetics of Gynaecological Cancer:

Clinical Risk Assessment

Obtain a detailed family history, extending if possible to at least the second degree relatives of the individual seeking advice. The assessment of risk is based largely on the recognition of certain patterns of cancer in the family. The association of breast/ovarian syndrome caused by mutations in BRCAI or BRCA2. Confirmation of the precise site of cancers in relatives is therefore important.

In general, risk assessment has three stages:

1. an estimate of the probability that family history reflects the presence of a predisposing gene;
2. an estimate of the probability that a given individual has inherited the genes, supposing it is present;
3. an estimate of the risks of ovarian cancer and other cancers (e.g. Breast cancer) confered by the gene at a given age (gene penetrance)

Predictions:

The daughter of an affected woman has a 50:50 chance of inheriting the predisposing gene from her mother. In such a family the risks of either breast or ovarian cancer in someone who has the gene is about 80% by age 70, averaged over the 40 year period from age 30. So a 35 year old woman who has a 50:50 chance of having inherited the gene because her mother was affected, has a roughly 10% chance of developing breast or ovarian cancer by age 45, and a roughly 40% chance by age 70.

Penetrance analysis of BRCAI/BRCA2 Genes:

Inherited breast cancer is assessed by linkage and mutation analysis. The disease is linked to BRCA1 in an estimated 52% of families to BRCA2 in 32% of families. 81% of the breast and ovarian cancer families are due to BRCA1.

Cumulative risk of breast cancer reached 28% by age 50 years and 84% by age 70 years. Corresponding ovarian cancer risks were 0.4% by age 50 years and 27% by age 70 years. The lifetime risk of breast cancer appears

similar to the risk in BRCA1 carriers, but there was some suggestion of a lower risk in BRCA2 carriers<50 years of age.

Recent Searches:

HER-2/neu, oncogene is over expressed in 30% of ovarian cancer and indicates poor prognosis. Mutations in P53 are seen in more than 50% of women with advanced diseases. Over expression of C-fms encoding gene for CSF-1, causing persistent and autocrine stimulation of growth factors (Epidermal Growth Factor, Tumour Necrosis Factor, Epidermal Growth Factor Receptor).

Rationale-Efforts for Screening:

Despite advances in molecular biology, surgical oncology and chemotherapy the prognosis for ovarian cancer remains poor due to late diagnosis. Excellent survival rates are seen for Stage I disease. Because carcinoma of the ovary tends to be asymptomatic in the early stages and most patients present with advanced disease, efforts have been made to define a tumour marker which could be used for screening purposes. So far, none has become available which is truly specific and which is suitable for the early detection of epithelial carcinoma.

Tumour Markers:

The only marker assessed in a prospective trial of screening is CA125 tumour marker - CA125 values more than 35u/ml are seen in 85% of women with ovarian cancer. However, high values may be seen in conditions other than ovarian cancer. Normalization of CA125 values is a condition but not a guarantee for regression of the disease. Rise in levels is always associated with progression of the disease.

CA125 is not a valid screening test if used alone. Case-controlled differences of borderline significances were found in CA125 before diagnosis of ovarian cancer, but not large enough to provide a sufficient detection rate.

CA125 values, are not superior to scans in monitoring the response to therapy and confirming relapse. CA125 levels were 7.5 fold higher at the time of re-evaluation by CT. Transvaginal Sonography lagged behind CA125 levels in detecting disease recurrence. CA125 is useful for detection of recurrence of disease.

Color Flow Imaging for Screening Modalities:

EVCD of ovaries should be an integral part of the screening protocol as a part of multiphasic screening or in selective screening. Specific attention is to be paid to Angiogenesis, Neovascularization & Intratumoral flow studies. EVCD imaging and intratumoural blood flow analysis to target population, recruited on the basis of risk factors (pedigree analysis) picked up the lesions. A Resistance Index of <0.30 in the Intra-tumoural vessels should raise suspicion of neo-vascularization and possible malignancy.

Conclusion:

To catch ovarian cancer early, an annual checkup including a internal pelvic examination for ovarian enlargement, a transvaginal sonography combined with an endovaginal colour doppler of the intra-ovarian vessles, tumour marker tests, i.e. CA 125, and if available BRCAI& BRCA2 should be undertaken. Increased awareness of these tests on a routine annual basis is the only available current method of bringing the "Silent prowler" (ie Ovarian Cancer) out in the open before it spreads.

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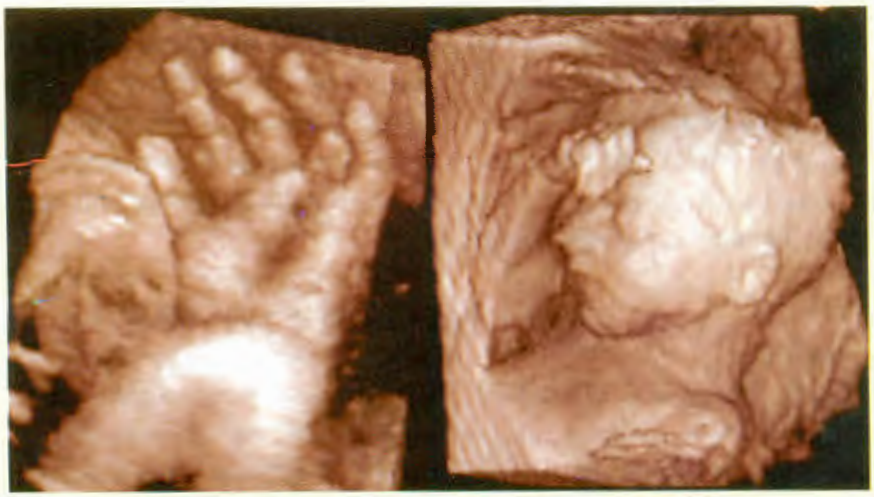

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