SUMMARY & CONCLUSION
7.0 Summary and Conclusion

The significant risk factors for the development of ovarian carcinoma in this study population was found to be full time employment which increased the risk 3 times on comparison with non-employed women, early age at menarche which increased the risk 6 times on comparison with women with late menarche and post menopausal status which increased the risk 3 times on comparison with pre and peri menopausal women.

The study showed the ovarian carcinoma of the study population to be hormone dependant with consistent association between ovulatory events or ovulation associated with ovarian inflammation.

Of all the ovarian carcinoma cases analysed, 18 (25%) of the cases were found to contain one or more of p53 variations.

One of the p53 variations was found to be polymorphism thus leaving 17 alterations detected in ovarian carcinoma.

Nine of the p53 mutations were found to be frameshift, 7 deletions and 2 were insertions.

All the p53 mutations reported in the present study were confined to the DNA binding domain with deleterious functional defects including loss of transactivation of RGC, BAX, PIG3, PCNA, MDM2, Waf1.

As a result of mutations at codon 139 and 138, there is a upregulation of MRP1 and CDDP resistance, which contribute to the drug resistance of the ovarian carcinoma patients and in failure of the first line chemotherapy.

No significant differences were found in p53 mutation in regard to histological types of tumour.

The correlation between p53 mutation and history of narcotics use showed that the narcotics users are at a reduced risk of acquiring p53 mutation compared with women without a history of narcotics use.

The study on the I655V polymorphism in HER2 gene showed that 27.7% of the case patients and 40.3% of the control subjects were heterozygous for
Valine allele and 69.4% of the case patients and 10.7% of the control subjects were homozygous for this allele.

Compared with Ile/Ile genotype women with Val/Val or Val/Ile genotype of the HER2 gene had an elevated risk of ovarian cancer.

The genotype distributions in this study population were consistent with the Hardy-Weinberg equilibrium with Valine allele frequency as 0.30 which is similar to that of the German Caucasian subjects.

There was no statistically significant difference between the groups of patients with different genotypes (AA, AG, GG) regarding the histological types.

A joint effect of HER2 polymorphism and factors related to endogenous estrogen exposure such as age at menarche and late menopause has been demonstrated.

The immunohistochemistry analysis showed HER2 protein to be strongly expressed in 38.5% of the patients.

The relationship between HER2 polymorphism and protein overexpression showed a statistically significant association.

In total 8 (11.1%) of the 72 ovarian carcinoma patients were found to be positive for BRCA mutation.

None of the cases were found to be positive for founder mutations, 5382insC in BRCA1 and 6174delT in BRCA2.

The mutation frequency for BRCA1 was found to be 6.9% and for BRCA2 it was 4.2%.

One mutation 1750delA has been identified in three BRCA1 carriers thus this mutation alone contribute to a mutation frequency of 4.2%. Thus this particular mutation can be considered as a founder mutation in case of the study population.

Mean age at diagnosis of ovarian cancer patients with BRCA1 mutation was 55.6 and for BRCA2 it was 36. BRCA2 carriers were found to be significantly younger when compared to BRCA1 carriers.
BRCA1 mutated cases were found to be of serous adenocarcinoma and BRCA2 carriers as serous cystadenoma.

From the results of the mutation studies it can be concluded that I655V polymorphism plays an important and major role in the development of ovarian carcinoma among this study population followed by p53 mutation and BRCA. Thus the neoplasm is hormone dependent, and “ovulation” mechanism determine the level of risk. If the clinical history of a suspected women favours hormone dependant risk then they can be screened for HER2 polymorphism and overexpression. The treatment regimen in a such can be the use of Herceptin (anti-HER2 antibody) coupled with chemotherapy drugs that enhances the survival rate of the patients. The screening program for mutations can include the afore mentioned mutations in the exons of BRCA1, BRCA2 and p53.

The other aetiologies for ovarian carcinoma are

- Nearly 21 actinomycetes isolates have been obtained from the endocervical swabs of the women categorized into five groups.
- In the present study out of the 9 ovarian carcinoma cases who had a history of IUD usage, 4 were found to be positive for actinomycetes infection.
- Of these four cases, 3 were reported clinically to have previous history of PID.
Through this we propose a hypothesis of simulation of ovarian carcinoma by actinomycetes species that have colonized the IUD. The use of IUDs facilitates the colonization of actinomycetes which in turn leads to PID and pelvic actinomycosis. Further pelvic actinomycosis simulates pelvic malignancies.

Out of the 21 actinomycetes isolates, three showed (A4, C15, C17) showed high biofilm forming ability. These three isolates were characterized as *Nocardia* sp. strain C15, *Nocardia* sp. strain C17 and *Streptomyces* sp. strain A4. *Nocardia* sp. strain C17 showed high biofilm forming ability on the copper sheets resisting copper ions. The biofilm formed by these isolates were found to be susceptible to the polyene antibiotic nystatin at a concentration of 0.16mg/ml. The probable mechanism of biofilm inhibition by nystatin is by the inhibition of the twitching motility of the isolates.

38.5% of the ovarian carcinoma cases were found to have HPV infection. The results showed HPV 6 to be the probable infecting HPV genotype. The positive amplification for the E6 and E& genes of HPV showed the integration of the HPV genome into the host genome resulting in consequence of neoplastic transformation of ovarian epithelium.

At baseline 80% of the ovarian carcinoma cases were found to be positive for *Chlamydia* infection. Approximately 50% of the cases showed detectable CMV DNA.

Thus in conclusion if the case patients have a previous history of PID or IUD usage then they can be screened for actinomycetes infection followed by treatment with linezolid and gentamycin antibiotics. As a prophylactic measure nystatin coated IUDs can be commercialized. Since 80% of the ovarian carcinoma cases are affected by *Chlamydia* infection, the use of antibiotics including amoxicillin, azithromycin, doxycyclin, erythromycin, tetracycline and ofloxacin can be used to augment chemotherapy regimen.