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Epidemiological Risk Factors for Primary Ovarian Malignancy in Indian Population- A Case Control Study from a Tertiary Care Centre in Kerala

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ABSTRACT

Background: *Ovarian malignancy accounts for almost 25 % of all gynaecological malignancies. Despite advances in molecular biology, surgery and chemotherapy long term survival of primary ovarian malignancy have hardly changed. Hence it is important to identify the risk factors. Though India comes under low incidence population for ovarian malignancy, age adjusted incidence rates are steadily increasing. A few studies only is reported from India and hence the need for this study.*

Methods: *This is a case control study done at SAT Hospital, Government Medical College Thiruvananthapuram, Kerala over a period of one year. 50 women with a histological diagnosis of primary ovarian malignancy were studied. 50 age matched controls were taken. Data were collected by face to face interview. The data was coded and analysed using SPSS package. Case control analysis was done to find out the strength of association of individual risk factors. Odds ratio and corresponding 95% confidence interval were calculated.*

Results: *Cases and controls were similar in socio-demographic variables. The significant risk factors were, age at menarche 13 or less, period of ovulation in postmenopausal woman more than 33 years and not underwent tubal ligation. Parity one or less, BMI more than 25 were not found as risk factors in our study.*

Conclusion: *Ovarian carcinoma is hormone dependant with consistent association between ovulatory events or ovulation associated with ovarian inflammation. The importance of tubal ligation as a protective factor in ovarian carcinoma has to be highlighted.*

Keywords: *ovarian malignancy, risk factors, ovulation, Indian population.*

INTRODUCTION

Ovarian malignancy accounts for almost 25 % of all gynaecological malignancies and present greatest challenge to gynaecologic oncologist. It is one among the six major causes of cancer in women. It constitute about 2% of all cancer cases in UK and the incidence is on the increasing trend since 1970. Despite advances in molecular biology, surgery and chemotherapy ovarian cancer remains a challenging disease to manage and long

term survival have hardly changed in the last three decades[1]and hence it is important to identify the risk factors of the occurrence of this disease.

There are considerable variation in the incidence of ovarian cancer across the countries[2]with the highest rates in industrialised western nations and lowest rate in developing countries[3]. In India, in spite of the low incidence, there is a steady increase in age standardised prevalence of ovarian cancer by 3% per year in different state registries over a period of time[4]. In most of the population based cancer registries in India, ovarian cancer remains the third leading cause of cancer among women. The age adjusted incidence rates of ovarian cancer varies between 5.4 and 8.0 per one lakh in different parts of country[4].

Several epidemiologic and clinical risk factors were known to influence a life time risk for ovarian cancer. Reproductive behaviours of a woman, like age at menarche[5], period of ovulation,age of menopause were found to be significant risk factors. Studies have shown that increase in parity is protective against ovarian cancer[6]. The relationship with fertility treatment and hormone replacement therapy has been inconsistent with conflicting results[7]. The association with epidemiological risk factors like BMI and perineal application of talc have been controversial in many studies. Other risk factors like, family history of ovarian or breast cancers is a major risk factor in many studies.

Many epidemiological studies have been conducted on ovarian cancers, but majority being in Europe and North America. A few studies came from Indian sub-continent. Indian population being different in genetic, environmental, socio cultural factors, there is a need for studies from India. Hence a case control study was undertaken from a tertiary centre in Kerala, a southern state in India.

METHODS

A case control study was undertaken to find out the strength of association of known risk factors of primary ovarian malignancy in Sree Avitom Thirunal Hospital, Government Medical College, Thiruvananthapuram Kerala over a period of one year after getting approval from institutional review board.

Women referred to SAT Hospital with a provisional diagnosis of ovarian tumour was interviewed after getting informed consent. Details regarding demographic, reproductive and other epidemiologic risk factors were collected at the first visit by face to face interview by a structured questionnaire, which took 15 minutes. The patients were investigated including staging laparotomy and a histological diagnosis was made.Women with a histological diagnosis of primary ovarian malignancy were taken as cases. Age matched women who came as caretakers of antenatal women were taken as controls.

Study variables were demographic data, reproductive history (age at menarche, age of menopause, period of ovulation), use of ovulation induction drugs for more than one year, hormone replacement therapy for more than 6 months, perineal use of talc powder, tubal ligation etc.

All data were reviewed for completeness at the end of each interview. The data was coded and analysed using SPSS package. Comparison of socio demographic and other study variables were done. Case control analysis was done to find out the strength of association of individual risk factors. Odds ratio and corresponding 95% confidence interval were calculated. P value of ≤ 0.05 was taken as significant.

RESULTS

87 women with provisional diagnosis of ovarian malignancy were taken up for study. One women died before staging laparotomy hence excluded. Histological diagnosis was benign in 19 cases, borderline neoplasm in11 patients and secondary malignancy in 6 patients. 50 patients with a histological diagnosis of primary ovarian malignancy were studied.

Demographic data: Age distribution of cases ranged from 13 to 76 years. 56% of cases were above the age of 45 years; of which 93 % were in

the age group 45 to 64 years. 82% of primary ovarian malignancy were surface epithelial tumours. Socio demographic characteristics like religion, place of residence, educational status and income of cases, when analysed were similar to controls. (Table1)

Table 1: Demographic and socio economic characteristics of cases and controls

Characteristics	Cases n=50	Controls n=50	p value
Religion			0.84
Hindu	37	36	
Christian	8	10	
Muslim	5	4	
Place of residence			0.65
Rural	37	35	
urban	13	15	
Income			0.64
BPL	38	36	
APL	12	14	
Educational status			0.54
No formal education	3	5	
Primary education	23	18	
Secondary education	21	24	
Degree or above	3	3	

Comparison of risk factors in cases and controls showed mean age at menarche was earlier in cases (13.4 years) than controls (14.45 years). There was significant difference in the mean age of menopause in cases (47.7 years) than controls (44.6 years). There was a significant difference in the period of ovulation in postmenopausal women (p-0.01) but not in premenopausal (p- 0.64). Parity status in cases and controls were similar. Tubal ligation was done only in 28 % of cases whereas 70% of controls had undergone tubal ligation (p-0.0005).Family history of ovarian, breast or any other malignancy in the first or second degree relatives were not found in any of the cases or controls. The comparison of prevalence of the risk factors in cases and controls are shown in Table.2

Table 2: Comparison of reproductive risk factors between cases and controls

Characteristics	Cases n=50	Controls n=50	P value
Age at menarche			0.002
Not attained	1	2	
10-12	10	2	
13-14	32	24	
15 & above	7	22	
Parity			0.36
0	3	2	
1-2	30	32	
3-4	11	10	
5 or more	2	3	
Unmarried	4	3	
Tubal ligation not done	36	15	<0.005
BMI			0.52
Less than 18.5	3	0	
18.5 – 25	43	43	
25 – 30	4	6	
Above 30	0	1	

Case control analysis of the risk factors is presented in Table.3 The risk factors found significant were. age at menarche 13 or less (OR: 3.77, 95% CI: 1.63, 8.72), period of ovulation in postmenopausal woman more than 33 years (OR: 6.75, 95% CI: 1.6, 27.5)and not underwent tubal ligation (OR:6.0, 95% CI 2.5,14.2). Parity one or less, BMI more than 25 were not found as risk factors in our study.

Table 3: Case control analysis of risk factors

Risk factors		OR	95% CI	p value
Age at menarche	13 or less	3.77	1.63, 8.72	0.002
	14 or above			
Age of menopause	Above 48	2.13	0.56, 8.19	0.265
	Below 48			
Period of ovulation in post-menopausal women	>33 years	6.75	1.66, 27.5	0.03
	≤33 years			
Tubal ligation	Not done	6.0	2.53,14.24	0.00005
	done			
parity	1 or less	1.23	0.38,3.97	0.36
	2 or more			
BMI	More than 25	0.53	0.15,1.95	0.57
	18.5 - 25			

DISCUSSION

This case control study was undertaken in a tertiary care centre in Kerala, a southern state in India to find out risk factors of ovarian cancer in Indian population. The baseline demographic characteristics like age, religion, place of residence, educational and socioeconomic status, when analysed were similar in cases and controls.

Analysis of risk factors showed a significant association between hormonal factors and ovarian malignancy. Age at menarche less than 13 years and period of ovulation more than 33 years in post-menopausal women were found to be significant risk factors for ovarian cancer in our study.This finding is consistent with incessant ovulation hypothesiswhich postulates that the rupture and subsequent rapid proliferation of the ovarian surface epithelium with ovulation may lead to malignant transformation of ovarian epithelium[8,9].Various studies found an increase of 1year worth of ovulationwas associated with a 2 to 6% increase in risk of ovarian malignancy[10, 11]. In this study themean age of menopause was significantly delayed in cases (47.7 years vs44.6years) than controls (p- 0.05). Earlier studies were inconclusive regarding late age of menopause as a risk factor, but recent studies has foundit to bea risk factor[12] and includedin the prediction modelfor the screening of ovarian cancer [13.]

Another important observation in this study was that Tubal ligation not done was found as a significant risk factor (OR:6.0, 95% CI 2.5, 14.2) for ovarian malignancy. Tubal ligation could possibly have aprotective effect via a reduction in utero ovarian blood flow resulting in local hormonal and growth factor levels, or via its protection against the ascent of infection. Various studies have shown that tubal ligation, use of oral contraceptives and other contraceptive devices reduce ovarian cancer risk [12,13,14].

Compared to nulliparous women, parous women are at reduced risk of ovarian cancer with a significant risk reduction by one birth event[8, 11]. This is because, exposure to high progestin levels, whether through pregnancy or exogenous hormones, reduces ovarian cancer risk. Experim-ental studies in animals or human cell lines have shown that administration of progestins up-regulates expression of the p53 tumour suppressor gene and induces apoptosis. These data suggest that apoptosis resulting from high progesterone levels during pregnancy or from exogenous hormones could “clear” transformed cells in the ovarian epithelium.

The reduced risk with increase in parity was not observed in our study which is similar to other studies done in Indian population[15]. Several reasons can be accounted for this observation in Indian population. Firstly several studies have reported, late age at last child birth, long interval between first and last live birth were more important than the total number of pregnancies [16]. But the general customs in the Indian population is women getting married at very early age and hence early first and last child birth with no long intervals between the births. According to Harlow and Ephross (1995), menstrual cycles occurring between ages 25 and 39 are most likely to be ovulatory and pregnancies occurring between these ages have a greater potential to interrupt ovulatory cycles. Moreover gonadotrophin levels increases with increasing age and are particularly high during menopause. Due to the prevailing customs women from the study population end up their full term pregnancies or live childbirth before they reach their ovulatory age and excessive gonadotrophin exposure during ovulatory age without parity increases oestrogenic stimulation of the ovarian surface epithelium leading to malignant transformation [17].

This study could not find any increase in risk of ovarian cancer with increase in BMI. Results on the association between body size and ovarian cancer risk, are inconsistent. Ovarian cancer is associated with height and, among never-users of hormone therapy with body mass index.[18]In high-income countries, both height and body mass index have been increasing in birth cohorts now developing thedisease. If all other relevant factors

had remained constant, then these increases in height and weight would be associatedwith a 3% increase in ovarian cancer incidence per decade. But studies done in Asian cohorts failed to show this association, which is similar to our observations[11].

Prevalence of other epidemiological risk factors described in literature like hormone replacement therapy, treatment for infertility for more than a year, oral contraceptive use more than one year, perineal application of talc were very low to make any comment. Family history of ovarian or breast cancer were also not seen in any of the cases or controls.

CONCLUSION

In this study, significant risk factors for primary ovarian malignancy were, early menarche and period of ovulation in post-menopausal women. This shows that ovarian carcinomais hormone dependantwith consistent association between ovulatory eventsor ovulation associated with ovarian inflammation. The importance of tubal ligation as a protective factor in ovarian carcinoma has to be highlighted because it is one of the best accepted permanent method of sterilisation in developing countries. Unlike developed countries prevalence of other epidemiological risk factors described in literature like BMI, parity, family history,hormone replacement therapy, treatment for infertility, oral contraceptive use were very low in the study population to make any conclusions. Larger studies are needed in Indian population find out the role of these risk factors.

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