Original article:

Association of Oral Contraceptives and Female Reproductive Tract Carcinomas

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Abstract:

Introduction: Cervical cancer is the 5th most common cancer in humans, third most common cause of deaths due to cancer in women worldwide and the second most common cancer and cancer related deaths in developing countries like India. Relation between cancer risk and OCP use is complicated by a number of other factors; peak incidence of majority of cancers in old age, use of multiple hormonal formulations, existence of many confounding factors like number of pregnancies, age at first pregnancy, number of sexual partners, etc.

Material and methods: This was an Analytical cross section-case control study,conducted in the Oncology department of Pravara Rural Hospital, Loni in a 2 months duration. IEC approval was received for this study from our IEC. This study project was approved by Indian Council for Medical Research (ICMR), Delhi. Type of sampling was simple random and number of subjects were, 50 as cases and 100as controls, both being same in all regards except OCP use.

Results: 2 out of 40 cases and the same number out of 98 controls used OCPs for long term (5-10 years). A risk of 2.38 times was calculated for cervical cancer in individuals who had used OCPs for 5-10 years and is significant. It is seen that on long term OCP use cancer was induced earlier than short term use. Time relationship of around 20-25years was observed with long term use while 31-39 year with short term.100% of the subjects were unaware about any association, only 40% subjects knew about contraceptives.

Conclusion: Protection was seen in case of endometrial and ovarian cancer. Long term OCP users are at a risk of developing cervical cancer earlier than short term. They develop cancer after a period of about 20-25 years whereas short term users develop cancer after 31-39 years.

INTRODUCTION:

Cervical cancer is the 5th most common cancer in humans, third most common cause of deaths due to cancer in women worldwide and the second most common cancer and cancer related deaths in developing countries like India. It is well documented that hormonal factors significantly modulate risk of certain cancers of the reproductive tract. In the past few decades use of oral contraceptives has increased to a commendable level especially in urban areas. Clinical observations and various researchers have suggested a strong association between endocrine influence and the induction and progression of female reproductive tract carcinomas in association with other etiologic factors too. There is a wealth of data on OC use and the development of certain cancers, although results of these studies have not always been consistent.

Relation between cancer risk and OCP use is complicated by a number of other factors; peak incidence of majority of cancers in old age, use of multiple hormonal formulations, existence of many confounding factors like number of pregnancies,

age at first pregnancy, number of sexual partners, etc. Each cancer has different etiologic and confounding factors. Cervical cancer is probably a venereal disease due to HPV infection and multiple sexual partners. Multiple pregnancies, increasing age and obesity also play a role. Ovarian cancers on the other hand decrease due to high parity due to decreased ovulation trauma. Endometrial cancer is due to high oestrogenic stimulation which causes hyperplasia and finally anaplasia. Genetic basis and racial factors play a major role too. In fact even socioeconomic status and immunosuppression have their effects. Race and nationality do not have direct effect but reflect social practices. Duration of use of these pills and the age when pill was started also plays an important role in analysing the risk. Although these pills have social and economic risks, they have protective effects. The reason that these pills are still in use maybe due to no clear evidence of any association or maybe benefit overpowers the risk. But is it safe for women to use these pills? Is it right to mislead the community into believing that what they're using is good for them?

An attempt is made to analyse the association. Do they lead to precipitation of carcinomas, do they protect from carcinomas, and is it safe to use OCPs for birth control? Or invention of new safer OCPs should be done to reduce the risk. A brief retrospective analytical case control study of the mentioned association is done with the help of a questionnaire. Case control tables and graphs were made and odds ratio was calculated for cervical, endometrial and ovarian cancer taking into consideration the duration of pill usage and other high risk etiological factors. With this view present work was planned to study the association of use of oral contraceptives and female reproductive tract carcinomas and to find out time relationship between use of OCPs and female reproductive tract carcinomas with find out the awareness regarding association of the two in rural population.

MATERIAL AND METHODS:

This was an Analytical cross section-case control study, conducted in the Oncology department of Pravara Rural Hospital, Loni in 2 months duration. IEC approval was received for this study from our IEC. This study project was approved by Indian Council for Medical Research (ICMR), Delhi. Type of sampling was simple random and number of subjects were, 50 as cases and 100 as controls, both being same in all regards except OCP use.

INCLUSION CRITERIA:

1. Histologically proven female reproductive tract carcinomas.
2. Age more than 18 years.
3. Age less than 70 years.

EXCLUSION CRITERIA:

1. Patients with genetic predisposition.
2. Patients with menarche below age of 11.
3. Patients with menopause above age of 55.
4. Patients with previous history of malignancy.
5. Patients with previous history of exposure to radiation therapy.

Written informed consent was enclosed with every questionnaire.

All eligible candidates were interviewed by the examiner with help of the same and information was pooled and tabulated in MS. Excel sheet and statistical analysis was done.

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QUESSTIONNAIRE:

1. Do you know what contraceptives are?
   Yes No Not sure
2. Have you ever used them?
   Yes No
3. Which contraceptive have you used?
   Oral Others
4. If oral, what type?
   Combined Progesterone only pills Emergency pill
5. When did you start using them?
   15-20 years 21-25 years 26-30 years 31-35 years above 35 years
6. Duration of pill taken?
   less than 5 years5-10 years more than 10 years
7. Number of pregnancies?
8. Age at first pregnancy?
9. Number of abortions/still born/dead born?
10. What age was cancer detected?
    before 35 years 35-40 years 41-45 years 46-50 years 51-55 years 56-60 years 60-65 years 65-70 years
11. Menarche age?
    before 11 years of age 11-15 years of age after 15 years of age
12. Menopause age?
    before 45 years of age 45-55 years of age after 55 years of age
13. Any prior radiations?
    Yes no
14. Does anybody in your family have female reproductive tract carcinoma?
    Yes no
15. If yes, who?
    1st degree relative 2nd degree relative Distant relatives.
16. Are you aware of the association between long term OCP use and female reproductive cancer?
    Yes no

OBSERVATIONS AND RESULTS:

Total 50 subjects were studied out of which 43 were cervical carcinoma patients, six were endometrial and one was an ovarian carcinoma patient. Out of the 50, three cervical carcinoma patients had used OCP, a combined pill marketed as Mala-D. Amongst them one subject used it for less than 5 years i.e. for short term while the other two for 5-10 years. In controls, 5 subjects used the same pill, three used it for less than 5 years while two for 5-10 years. None of the subjects used these pills for more than 10 years.

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1. **Details of cases.**

TABLE 1

CANCER	CERVICAL	ENDOMETRIAL	OVARIAN	TOTAL
No. of patients	43	6	1	50
OCP USERS(SHORT TERM)	1	0	0	1
OCP USERS(LONG TERM)	2	0	0	2

2. **Details of controls.**

TABLE 2

SHORT TERM OCP USER	LONG TERM OCP USER	NON OCP USER	TOTAL
3	2	95	100

3. **Cervical carcinoma (less than 5 years user)**

TABLE 3

	CASES	CONTROLS	TOTAL
OCP USERS	1	3	4
OCP NONUSERS	40	95	135
TOTAL	41	98	139

EXPOSURE RATE (CASES) = 2.43%

EXPOSURE RATE (CONTROLS) = 3.06%

ODDS RATIO=0.79

1 out of 40 cases used OCPs for a short duration (3 years), since the other 2 subjects used OCPs for longer term they were not included in the total and 3 out of 98 controls used and similarly the 2 controls who used for long term were not included in the total.

A 0.79 times benefit is seen in individuals who have used OCPs for less than 5 years.

4. **Cervical carcinoma (5-10 years user)**

TABLE 4

	CASES	CONTROL	TOTAL
OCP USERS	2	2	4
OCP NONUSERS	40	95	135
TOTAL	42	97	139

EXPOSURE RATE(CASES)=4.76%

EXPOSURE RATE(CONTROLS)= 2.06%

ODDS RATIO=2.38

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2 out of 40 cases used OCPs for long term (5-10 years) and 2 out of 98 controls used. A risk of 2.38 times for cervical cancer was seen in individuals who used OCPs for 5-10 years and is significant.

5. **Endometrial carcinoma**

TABLE 5

	CASES	CONTROL	TOTAL
OCP USERS	**0**	**5**	**5**
OCP NONUSERS	**6**	**95**	**101**
TOTAL	**6**	**100**	**106**

EXPOSURE RATE(CASES)=0%

EXPOSURE RATE(CONTROLS) =5%

ODDS RATIO=0

No risk seen as none of the patients had a history of OCP usage. It looks protective.

6. **Ovarian carcinoma**

TABLE 6

	CASES	CONTROL	TOTAL
OCP USERS	**0**	**5**	**5**
OCP NONUSERS	**1**	**95**	**96**
TOTAL	**1**	**100**	**101**

EXPOSURE RATE(CASES)=0%

EXPOSURE RATE(CONTROLS) =5%

ODDS RATIO=0

No risk seen as none of the patients had a history of OCP usage. It looks protective.

7. Obstetric profile of OCP users:

TABLE 7

Sr. No.	NUMBER OF PREGNANCIES	AGE AT FIRST PREGNANCY	ABORTIONS, STILL OR DEAD BORN
1(short term use)	5	19	1
2(long term use)	3	19	0
3(long term use)	5	17	0

Lower age at first pregnancy is seen in both long term users plus in one of them higher number of pregnancies is also seen both of which contribute by increasing the risk of cervical carcinoma. Lower age and higher number of pregnancies is also seen in the short term user.

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8. Time relationship between OCP use and age of cancer.

TABLE 8

Sr. No.	AGE AT WHICH OCP WAS STARTED.	AGE AT WHICH CANCER WAS DETECTED	DURATION
1.(short term)	21-25 years	56-60 years	31-39 years
2.(long term)	21-25 years	41-45 years	16-24 years
3.(long term)	21-25 years	46-50 years	21-29 years

It is seen that on long term OCP use cancer was induced earlier than short term use. Time relationship of around 20-25years was observed with long term use while 31-39 year with short term.

100% of the subjects were unaware about any association, only 40% subjects knew about contraceptives. All subjects used the combined pill of Ethinylestradiol30µg with Norgestrel0.3mg. (Mala-D)

DISCUSSION

Cervical carcinoma is the most common cancer of the reproductive tract and is mainly caused by Human Papillomavirus type 16 and 18. Other risk factors include genetic predisposition, multiple pregnancies and multiple sexual partners therefore more common in female sex workers. Women with low socioeconomic status have higher risk of developing invasive cervical carcinoma as commonly defined by income and education therefore very common in rural population.

No confirmed evidence of OCP association is found yet. A 2003 analysis by the International Agency for Research on Cancer found an increased risk of cervical cancer with longer use of OCs. However, in another long-term study published in 2002, researchers concluded that OC use did not increase the risk of cervical cancer in a well-screened population. [24] This could be because none of the studies adjusted for all of the confounding factors simultaneously and it would be necessary to analyse individual subject data from these studies, with and without adjustment for each factor in turn, to investigate fully the role of these potential confounding factors. [25]

In our study, short term use i.e. less than 5 years did not increase risk of cervical cancer. An odds ratio 0.79 is protective. Therefore they can be used safely without concern about cervical cancer since they offer various benefits too, like reduction in hirsutism, acne, regulation of menstrual cycles, prevention of osteoporosis, anemia, fibroids and fibroadenoma, but only the probability of risks and benefits can be known in advance.

Long term use i.e. 5-10 years however increased the risk of cervical cancer by approximately 2.38 times according to this study which means longer the duration of OCP use higher is the risk. Other confounding factors like genetic predisposition and age are excluded in this study.

As with multiparity, long term use is thought to increase risk for cervical carcinoma through elevated levels of circulating hormones in the woman's body. The OCPs may bind to HPV DNA to either increase or suppress transcription of certain genes.[20]Other studies show that OCPs (and other factors such as smoking) may accelerate the cervical maturation process, representing increased cell proliferation and thus a possible greater vulnerability to HPV.[21] Still other studies show that long-term use of OCPs may lead to a more frequent persistence of HPV.[22]Another possibility could be

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that OCP users do not use condoms(barrier methods), therefore have an increased risk of HPV transmission.

A population-based cohort study of over 10,000 women showed positive correlation of HPV prevalence with older age and current use of OCPs. This study occurred in South Africa where cervical cancer rates are among the highest in the world.[23]

An important limitation of our study was the lack of means to know about HPV infection, we could not diagnose it in our university. Also, since the study was conducted in a rural setup the numbers of OCP users were only a few.

Endometrial carcinoma is of two types. Type I is associated with endometrial hyperplasia and II with atrophy. Major factor causing type I endometrial carcinoma is estrogenic stimulation leading to endometrial hyperplasia. According to this study there is a protective benefit.

According to previous studies, a protective effect is seen too. Had it been onlyestrogenic stimulation the risk would have been higher but due to the progestinic component of the pill a protective effect is seen. “Incessant ovulation” largely equates with “incessant menstruation” involving repeated disruption and re-growth of the uterine lining. A greater number of cycles of endometrial regeneration may increase the likelihood of random genetic mutations because DNA replication errors occur during cell division, and thus are more likely to occur in tissues undergoing many cell divisions.[18]

The protective effect starts within 5 years of use increases with duration of use, reaches 75% reduced risk after 10 years and persists for more than 10 years after cessation of OC according to Heinemann et al., 2003 in their study” Benign gynaecological tumours: estimated incidence”

Ovarian carcinomas are divided into surface epithelial tumours, germ cell tumours and sex cord stromal tumours. Confounding factors include parity and breast feeding. Risk factors include cysts, mutations in BRCA1 and 2, excess gonadotropin hormone and low parity. Repeated microtrauma during ovulation to ovarian surface epithelial cells, DNA damage during ovulation and dysfunction of its recognition and repair and excess gonadotropin levels are important causes of ovarian tumours.

Anovulatory cycles due to OCPs lead to reduction in trauma to the epithelium and are therefore protective. Also they decrease gonadotropin levels by feedback inhibition and could be protective by this mechanism.

According to this study a protective benefit is seen.

In a 1992 analysis of 20 studies of OC use and ovarian cancer, researchers from Harvard Medical School found that the risk of ovarian cancer decreased with increasing duration of OC use. Results showed a 10- to 12-percent decrease in risk after 1 year of use, and approximately a 50-percent decrease after 5 years of use. This association between OC use and decreased risk of ovarian cancer has also been observed among women who have certain genetic changes in the BRCA1 or BRCA2 gene that increase their risk of ovarian cancer.[24] According to Tworoger et al., 2007 a reduction of relative risk for ovarian cancer by 48, 38 and 31% respectively in women who used OCP for 5-9 years, 10-19 years or 20-29 years previously and is seen with both high and low doses oestrogen component.

These pills need not be contraindicated as benefits of protection against endometrial and ovarian cancer overpower the slight risk against cervical cancer which is significant only with long term use and possibly only when an underlying predisposing condition or any other etiological factor like multi-parity or HPV infection or multiple sexual partners, etc. is present. They should however be cautiously

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used for long term especially in women with predisposing factors or a positive family history. Cervical cytology/Pap smear screening must be done in all patients using OCPs as early detection of an in-situ lesion can lead to prevention of cancer. In case of cervical cancer, long term users got cancer at an earlier age than short term users. In long term users cancer appeared approximately 20-25 years later while in short term users there was a gap of about 31-39 years. Risk increases as duration of use increases. No significant time relation could be found with endometrial and ovarian cancer due to lack of OCP users in rural area. As per previous and this study, and consideration of biological plausibility they appear to prolong the age at which cancer would have occurred otherwise. There is no awareness regarding the two in the rural population, in fact about 60% individuals were unaware of contraceptives.

CONCLUSION

From this study we may conclude, short term OCP users had a protective benefit of 0.79 times for cervical cancer whereas long term OCP use increased risk of cervical cancer to 2.38 times. They offer protection for endometrial and ovarian cancer. Also long term OCP users are at a risk of developing cervical cancer earlier than short term. They developed cancer after a period of about 20-25 years whereas short term users developed cancer after 31-39 years. It was also observed, there is no awareness regarding OCP and cancer in rural population.

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