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## Prevalence of occult gynecological cancer in women undergoing surgeries for benign indications in a tertiary healthcare center of Chhattisgarh

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### ABSTRACT

**Background:** Hysterectomy, the surgical removal of uterus, is 2<sup>nd</sup> most frequently performed major surgical procedures on women, with 90% of hysterectomies are performed for benign indications. However, there may be cases in which malignancy or premalignant lesions which are only confirmed on histopathology are defined as occult malignancy.

**Methods:** We conducted a prospective observational study on a cohort of women undergoing various gynaecological surgeries for benign indications in a time period of January 2019 to January 2020 in the Department of obstetrics and gynaecology, Dr. BRAM hospital and Pt. J. N. M. medical college, Raipur (C.G) to find out the prevalence of occult pre malignant and malignant lesions.

**Results:** Of 132 women who underwent surgeries for benign gynecological indications, based on final histopathological report, prevalence of occult premalignant lesion was 11.36% (95% CI 5.7-16.3%) and prevalence of occult malignancy was 2.27% (95% CI 0.2 -4.8%). Prevalence of occult premalignant lesion of corpus uteri and cervix uteri was 2.3 and 9.1% respectively. No occult premalignant lesion of ovary was found. Prevalence of occult malignant lesion of corpus uteri and ovary was 1.5 and 0.75% respectively.

**Conclusions:** We observed that even after complete preoperative workup only 72.7% of the preoperative clinical diagnoses were correlated with their histopathological diagnosis. Thus, while making the diagnosis, risk factors along with standard preoperative approach should be strongly adhered to prevent misdiagnosis and to prevent missing of any pre malignant or malignant findings.

**Keywords:** Benign indications, Hysterectomy, Myomectomy, Occult malignancies, Risk factors

### INTRODUCTION

Hysterectomy, the surgical removal of uterus, is 2<sup>nd</sup> most frequently performed major surgical procedures on women all over the world, next only to cesarean.<sup>1</sup> Hysterectomy and myomectomy are common gynecological procedures with more than 600,000 and 43000 surgeries performed yearly in U.S respectively.<sup>2</sup>

Nearly 90% of hysterectomies are performed for benign indications, whereas myomectomies are performed only for benign indications (like uterine fibroid).<sup>2</sup> Common

indications of hysterectomy are benign gynecological conditions like uterine leiomyoma (40.7%), endometriosis (17.7%), uterine prolapse (14.5%), endometrial hyperplasia (2.7%), rest all other benign conditions (15.2%); and cancer (9.2%).<sup>1</sup>

However, there may be cases in which uterine, cervical or tubo-ovarian malignancy or premalignant lesions which are confirmed on surgical histopathology but did not have clinical preoperative suspicion of malignancy. Such cases can be defined as occult malignancy.<sup>3</sup> Current evidence on the risk of occult uterine malignancy remains highly

variable with estimated prevalence ranging from 0 to 3.17% across studies and through present study we want to emphasize that though occult malignancy is rare but not nonexistent.<sup>2,3,6,12</sup>

The present study is aimed to estimate the prevalence of preoperatively undiagnosed occult malignancy and pre malignant lesions of corpus uteri, cervix uteri, and ovaries in women undergoing gynecological surgeries for benign indications.

Aims and objectives of the study were to find the prevalence of occult malignant and premalignant gynecological lesions among the women who underwent surgeries for benign indications and had a normal preoperative workup, in a tertiary healthcare setup of Chhattisgarh.

## METHODS

We conducted a prospective observational study on a cohort of women undergoing various gynecological surgeries for benign indications in a time period of January 2019 to January 2020 in the department of obstetrics and gynecology of Dr. Bhim Rao Ambedkar memorial hospital and Pt. J. N. M. medical college, Raipur (C.G) after approval from institutional scientific and ethical committee.

Our primary outcome measure was the prevalence of occult malignancy and pre malignant lesions of the corpus uteri, cervix uteri, and ovary. Woman's socio-demographic profile and clinical characteristics were analyzed for the risk assessment.

### *Inclusion criteria*

All the women of age more than 30 years getting admitted in gynecology wards of Dr. B. R. Ambedkar memorial hospital Raipur for gynecological surgeries of benign indications.

### *Exclusion criteria*

The patient with diagnosed or suspected malignancy before beginning of surgery.

Standard preoperative workup included laboratory tests such as complete blood count, liver and renal function test, random blood sugar, coagulation profile, urine routine-microscopy, lipid profile; detailed physical examination of abdomen and pelvis; complete gynecologic examination including pap smear, vaginal culture; bimanual and rectovaginal examination in case of genital organ prolapse; ultrasonography of abdomen and pelvis and MRI or CT scan of abdomen and pelvis was done to help in making diagnosis in cases of suspected malignancy. Tumor markers such as CA<sub>125</sub>, CA<sub>19.9</sub>, human chorionic gonadotropin, LDH, alpha fetoprotein was sent and histopathological examination of

endometrial sampling and biopsy of selected cases was done. Chest x ray and ECG was done and medical and anesthesia fitness was taken for proposed procedure.

The postoperative surgical specimens were sent for histopathological examination and diseases reclassified in benign, pre malignant and malignant based on final histopathology report.

We studied clinico-pathological correlation between the pre-operative clinical diagnosis and post-operative diagnosis based on final histopathology report to find out the sensitivity of standard preoperative workup and to find the positive predictive values of standard pre-operative tests in predicting risk of occult premalignant and malignant lesion.

### *Statistical analysis*

We have estimated the 95% confidence intervals based on binomial distribution and calculated the odds ratios to find the association between available patient characteristics and the presence of occult pre malignant and malignant lesion. The significant association was defined by the p value of less than 0.05 (p value<0.05).

## RESULTS

Among 26,179 women who attended the gyne OPD of Dr. B. R. A. M. hospital, Raipur (C.G) from January 2019 to January 2020, total 132 women met our eligibility criteria.

In our study, the most common surgery performed during study period was hysterectomy (78.8%). Among hysterectomies, most common hysterectomy performed was total abdominal hysterectomy (37.1%) followed by non-descent vaginal hysterectomy (12.8%), vaginal hysterectomy (11.4%) and vaginal hysterectomy with pelvic floor repair (6.06%). 2.2% women had laparoscopy assisted vaginal hysterectomy and 0.75% had subtotal hysterectomy. Total 9.1% women had undergone TAH with BSO and 2.3% had TAH with unilateral salpingo-oophorectomy in our study, as per our institutional norms to preserve ovaries in accordance to ACOG criteria of ovarian preservation till the age of 65 year.

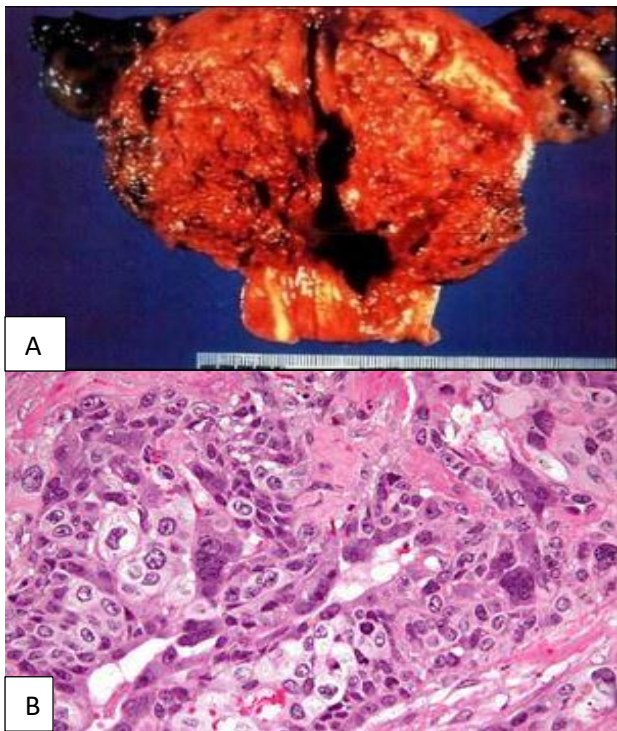
Second most common surgery was myomectomy performed for fibroid uterus (6.8%) followed by ovarian cystectomy (4.5%) and hysteroscopic polypectomy (4.5%). Salpingectomy alone was done in 3% women and salpingo-oophorectomy was performed in 1.5% women. Unilateral salpingectomy with cystectomy was performed in 0.75% women.

We have observed that only 72.7% of preoperative clinical diagnosis was correlated with histopathological diagnosis. Most common missed diagnosis was adenomyosis (it was missed in 6.06% women) followed

by endometrial hyperplasia (in 3.0%) and leiomyoma (in 2.27%) (Table 1).

Out of all the surgery performed, 86.36% women had benign lesion on histopathological examination. 3.9% of the women with leiomyoma, 22.2% of the women with adenomyosis, 3.3% of the women with endometrial hyperplasia, 29.4% of the women with genital organ prolapse and 11.1% of the women with endometrial polyp had occult pre malignant lesion in their histopathological examination report. Most common occult premalignant lesion was HSIL (80%) followed by endometrial hyperplasia with atypia (20%) (Table 2).

6.7% of women with endometrial hyperplasia, 33.3% of women with benign tubo-ovarian mass and 33.3% of the women with gestational trophoblastic disease had occult malignant lesion in their histopathological examination report i.e., carcinoma endometrium IIIb, dysgerminoma of ovary and choriocarcinoma respectively (Table 3). Figure 1, 2 and 3 depict gross and microscopic view of occult malignant lesions of our study.

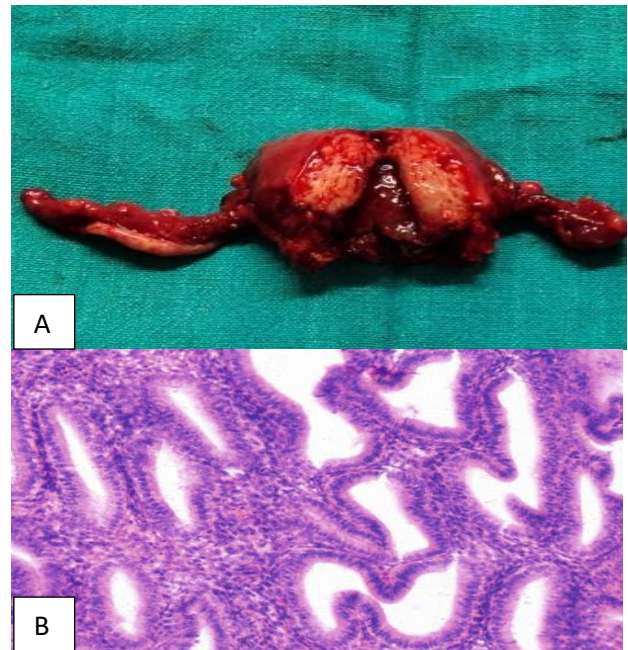


**Figure 1: Choriocarcinoma.**

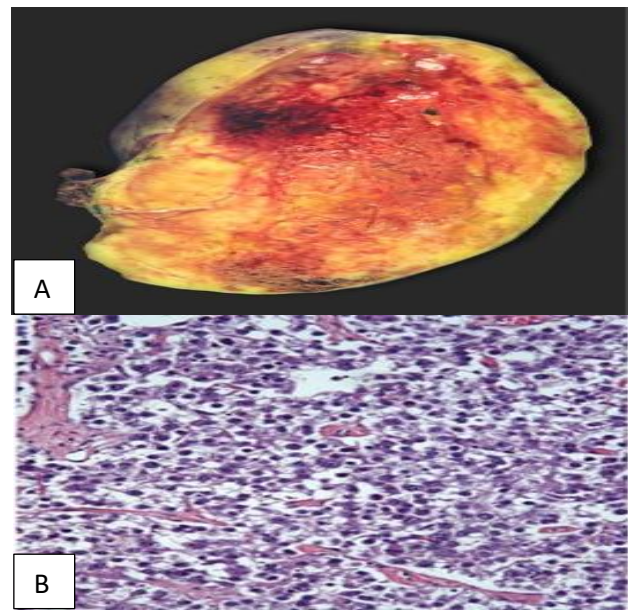
86.7% women with occult pre malignant lesion had some risk factors associated for that lesion whereas 100% women with occult malignant lesion had some risk factors associated.

In our study protocol, the sensitivity of bio-physical investigation (Table 4 and 5) (which included, PAP smear, colposcopy, hysteroscopy, laparoscopy, endometrial aspiration) was highest (92.8%) followed by

physical-radiological investigations (83.3%) and then bio-chemical investigations (75.0%).



**Figure 2: Endometrial carcinoma.**



**Figure 3: Ovarian dysgerminoma.**

Of all women who underwent surgeries for benign gynecological indications, based on final histopathological report, prevalence of occult premalignant lesion was 11.36% (95% CI 5.7-16.3%) and prevalence of occult malignancy was 2.27% (95% CI 0.2-4.8%). Prevalence of occult premalignant lesion of corpus uteri and cervix uteri was 2.3 and 9.1% respectively. No occult premalignant lesion of ovary was found. Prevalence of occult malignant lesion of corpus uteri and ovary was 1.5 and 0.75% respectively.



**Table 1: Distribution of women according to type of histopathological finding.**

Pre-operative diagnosis	Total number	Benign histopathological findings (n=114) (86.4%)	Pre malignant histopathological finding (n=15) (11.36%)	Malignant histopathological finding (n=3) (2.27%)
Leiomyoma	51	49 (96.0)	02 (3.9)	None
Adenomyosis	09	07 (77.8)	02 (22.2)	None
Endometrial hyperplasia	15	09 (60.0)	05 (33.3)	01 (6.7)
Genital organ prolapse	17	12 (70.6)	05 (29.4)	None
Endometrial polyp	09	08 (88.9)	01 (11.1)	None
Endometriosis	05	05 (100)	None	None
Benign ovarian cyst	13	13 (100)	None	None
Tubo-ovarian mass	03	02 (66.7)	None	01 (33.3)
Gestational trophoblastic disease	03	02 (66.7)	None	01 (33.3)
Chronic PID	02	02 (100)	None	None

**Table 2: Women with occult premalignant lesions on histopathological examination (n=15).**

Clinical diagnosis	Surgery	Premalignant finding on HPE
Third degree uterine prolapse-5 cases	VH	HSIL (CIN II) of cervix
AUB-M	NDVH	Endometrial hyperplasia with atypia
AUB-M	NDVH	Cervix- HSIL (CIN II)
AUB-M with right ovarian dermoid cyst	TAH with BSO	Cervix- HSIL (CIN II)
AUB- A, M	TAH	Endometrial hyperplasia with mild atypia
Fibroid uterus	TAH	Cervix- HSIL (CIN II) with squamous metaplasia
Adenomyosis	NDVH	Cervix- HSIL (CIN III)
AUB-A with right ovarian cyst	TAH with salpingectomy	Cervix- HSIL with chronic cervicitis
Fibroid uterus	TAH	Endometrial hyperplasia with mild atypia
AUB-M with cystocele with rectocele	TAH	Cervix-HSIL (CIN II) with chronic cervicitis
AUB-P, L	TAH	Cervix- HSIL (CIN II)

**Table 3: Women with malignant lesion on histopathological examination (n=3).**

Clinical diagnosis	Surgery	Histopathological finding	Final diagnosis
Persistent gestational trophoblastic disease	TAH	Evacuation s/o invasive mole Hysterectomy specimen-s/o features of choriocarcinoma	choriocarcinoma
Endometrial hyperplasia	TAH with BSO	Endometrium- well differentiated hyperplasia with nuclear atypia with areas of necrosis and lymphocytic infiltration Myometrium- myometrial invasion of endometrial gland present s/o malignancy Cervix- hyperplasia, cervicitis	Carcinoma endometrium stage IIIB
Benign tubo-ovarian mass	TAH with right salpingo-oophorectomy	Right ovary- mixed germ cell tumor s/o dysgerminoma	Dysgerminoma

**Table 4: Distribution of women according to standard pre-operative workup and correlation of clinical diagnosis with final histopathological diagnosis.**

Pre-operative clinical diagnosis	Bio-chemical (CA <sub>125</sub> , CA <sub>19.9</sub> , LDH, AFP, Beta-hcg)	Physical-radiological (physical examination, USG, MRI/CT)	Biophysical (PAP smear, colposcopy, hysteroscopy, laparoscopy, endometrial aspiration)	Total no. of cases	Correct diagnosis by standard preoperative workup (%)	Incorrectly diagnosed on standard preoperative workup (%)	Standard preoperative workup missed the diagnosis (n) (%)	Occult premalignant or malignant lesion (%)
<b>Leiomyoma</b>	yes	yes		51	44 (86.3)	07 (13.7)	03 (2.27)	02 (1.5)
<b>Adenomyosis</b>		yes		09	07 (77.8)	02 (22.2)	08 (6.06)	02 (1.5)
<b>Benign endometrial hyperplasia</b>	yes	yes	yes	18	12 (66.7)	06 (33.3)	04 (3.0)	06 (4.5)
<b>Genital organ prolapse</b>		yes	yes	17	17 (100.0)	-	-	05 (3.8)
<b>Endometrial polyp</b>		yes	yes	09	07 (77.7)	2 (22.2)	-	01 (0.75)
<b>Endometriosis</b>	yes	yes	yes	05	05 (100)	-	-	-
<b>Benign ovarian cyst</b>	yes	yes		13	13 (100)	-	-	-
<b>Tubo-ovarian mass</b>	yes	yes	yes	03	02 (66.7)	01 (33.3)	-	01 (0.75)
<b>Gestational trophoblastic disease</b>	yes	yes	yes	03	02 (66.7)	1 (33.3)	-	01 (0.75)
<b>Chronic PID</b>		yes	yes	08	08 (100)	-	-	-

**Table 5: Sensitivity and positive predictive value of standard pre-operative workup.**

Standard pre-operative workup	Sensitivity of the test (%)	PPV for predicting risk of pre malignant or malignant lesion (%)
<b>Biochemical (CA<sub>125</sub>, CA<sub>19.9</sub>, LDH, AFP, Beta-hcg)</b>	75	11.1
<b>Physical-radiological (physical examination, USG, MRI/CT)</b>	83.3	12.8
<b>Biophysical (PAP smear, colposcopy, hysteroscopy, laparoscopy, endometrial aspiration)</b>	92.8	27

**Table 6: Statistical association between characteristics of women and the risk of having occult gynecological cancer in surgical specimen and its significance.**

Characteristic	N (prevalence)	Odds ratio <sup>^</sup> (OR)	95% confidence interval	P value	Statistical significance <sup>+</sup>
<b>Age (year)</b>					
45 or less	83 (10)	0.70	0.25-1.91	0.49	Not significant
More than 45	49 (08)	1.42	0.52-3.80		
<b>Locality</b>					
Rural	59 (13)	3.8	1.28-11.51	0.016	Significant <sup>+</sup>
Urban	73 (05)	0.26	0.08-0.77		
<b>Education</b>					
Up to primary school	60 (14)	5.17	1.60-16.70	0.006	Significant <sup>+</sup>
Middle school and above	72 (04)	0.19	0.05-0.62		
<b>Socio economic status</b>					
Class I/II	22 (01)	0.26	0.03-2.06	0.20	Not significant
Class III/IV/V	110 (17)	3.83	0.48-3.04		
<b>Parity</b>					
P <sub>0/1/2</sub>	66 (05)	0.23	0.07-0.77	0.016	Significant <sup>+</sup>
P <sub>&gt;=3</sub>	66 (13)	4.17	1.29-13.45		
<b>Hormonal status</b>					
Pre-menopausal	100 (14)	1.13	0.34-3.74	0.82	Not significant
Post-menopausal	32 (04)	0.87	0.26-2.88		
<b>Route of surgery</b>					
Abdominal	91 (10)	0.50	0.18-1.40	0.19	Not significant
Vaginal	41 (08)	1.96	0.71-5.41		
<b>Weight of uterus (hysterectomy specimen) (gm)</b>					
150 or less	63 (11)	1.35	0.48-3.80	0.55	Not significant
More than 150	40 (07)	0.73	0.26-2.05		
<b>Medical condition</b>					
Hypertension	15 (02)	0.97	0.20-4.71	0.97	Not significant
Hypothyroidism	04 (01)	2.17	0.21-22.1	0.51	Not significant
PID	09 (02)	3.61	0.81-15.9	0.09	Not Significant
Tobacco addiction	32 (05)	1.23	0.40-3.79	0.70	Not significant

## DISCUSSION

In our study, prevalence of occult premalignant lesion of corpus uteri and cervix uteri was 2.3 and 9.1% respectively, and prevalence of occult malignant lesion of corpus uteri and ovary was 1.5 and 0.75% respectively which is comparable to similar studies in past.<sup>2,4,5</sup> But the prevalence is slightly lower in some other studies.<sup>6,7</sup>

We observed a particular higher risk of occult premalignant and occult malignant lesions in women with older age group. ie 16.32% of women aged more than 45 year had occult pre malignant and malignant lesion as compared with 12.04% in those aged 45 year or less and more risk was associated with lower socioeconomic status. This is consistent with the prior studies by Desai, Mahnert, Sawke, Singh and Singh et al.<sup>2,8-11</sup>

In present study vaginal route was more strongly associated with findings of occult pre malignant lesion on

histopathology. But abdominal route has been shown to have higher risk of occult malignant changes. Kho Kimberly, Frick, and Wright et al also found similar results.<sup>3,6,12</sup> This difference may reflect firstly, the differences in the underlying cause of the surgery. For instance, women with prolapse often treated with vaginal hysterectomy and they have higher risk of premalignant changes but lower risk of occult malignancy. Secondly, the surgeon may prefer one route over the other based on their expertise and they may systematically select the patient for different types of surgeries based on their risk profile.<sup>13,14</sup>

Among patients with occult premalignant and malignant lesions only 11.1% (2 women) had TAH with bilateral salpingo-oophorectomy and 5.5% (1 woman) women had TAH with right salpingo-oophorectomy and these women had associated ovarian pathology or belonged to high-risk group. There is a decreasing trend of bilateral salpingo-oophorectomy all over the world which was mainly done in order to decrease risk of ovarian cancer and the age

limit was 45 year.<sup>15,16</sup> But the current scientific evidence suggest that elective oophorectomy is not advisable in majority of the women, as it may lead to higher risk of death from cardiovascular disease and hip fracture and higher incidence of dementia and Parkinson's disease.<sup>16-18</sup>

In present study, clinico-pathological correlation was only 72.7%, consistent to prior studies.<sup>4,7,19,20</sup> This suggests that the standard preoperative workup made for routine gynecological surgeries are not sufficient in predicting the cancerous lesions and they need standardized modifications.<sup>21,22</sup> Ultimate final diagnosis is always made on histopathological examination which always has more sensitivity and specificity.

### Limitations

As our study was time bound, conducted for a period of 1 year so our sample size was small and it was a single institution-based study. This limits the generalization of results of our study because for this large sample size and multicentric study is required.

### CONCLUSION

We have seen that in most of the women with occult pre malignant or malignant lesions, risk factors were present but even then, prevalence of occult pre malignant lesion was 11.4% and prevalence of occult malignant lesion was 2.27%. We have also seen that even after complete pre-operative workup only 72.7% of the pre-operative clinical diagnoses were correlated with their histopathological diagnosis. Thus, while making the diagnosis, standard pre-operative approach should be strongly adhered to prevent any misdiagnosis and to prevent missing of any pre malignant or malignant after findings.

Hence more research is required in this field to develop more sensitive and cost-effective screening methods for better prevention of unknown malignancies and to identify them during their early stage for better patient care and management.

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