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

Nearly 90% of hysterectomies are performed for benign indications, whereas myomectomies are performed only for benign indications (like uterine fibroid).² 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%).³

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.¹ 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.2,3,6,12

The present study is aimed to estimate the prevalence of preoperatively undiagnosed occult malignancy and pre malignant lesions of corpus uterus, 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 CA125, CA19-9, 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 gynecology 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 subtotal 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 and0.75% 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.

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 1: Choriocarcinoma.

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 proplaspe      | 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                    | choriocarcinoma                                       |
|                                           |               | Hysterectomy specimen- s/o features of choriocarcinoma |                                                      |
|                                           |               | 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                 |                                                      |
| Endometrial hyperplasia                   | TAH with BSO  | Carcinoma endometrium stage IIIB                |                                                      |
|                                           |               | Right ovary- mixed germ cell tumor s/o dysgerminoma |                                                      |
|                                           |               | Dysgerminoma                                     |                                                      |
| Benign tubo-ovarian mass                  | TAH with right salpingo-oophorectomy            |                                                      |                                                      |
Table 4: Distribution of women according to standard pre-operative workup and correlation of clinical diagnosis with final histopathological diagnosis.

| Pre-operative clinical diagnosis | Biochemical (CA_{125}, CA_{19.9}, 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 (%) |
|---------------------------------|-------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------|---------------------------------|
| Leiomyoma                       | yes                                                   | yes                                                     |                                                                                        | 51                | 44 (86.3)                                             | 07 (13.7)                                                | 03 (2.27)                                                              | 02 (1.5)                                      |
| Adenomyosis                     | yes                                                   |                                                          |                                                                                        | 09                | 07 (77.8)                                             | 02 (22.2)                                                | 08 (6.06)                                                              | 02 (1.5)                                      |
| Benign endometrial hyperplasia   | yes                                                   | yes                                                     |                                                                                        | 18                | 12 (66.7)                                             | 06 (33.3)                                                | 04 (3.0)                                                              | 06 (4.5)                                      |
| Genital organ prolapse          | yes                                                   | yes                                                     |                                                                                        | 17                | 17 (100.0)                                            | -                                                        | -                                                                     | 05 (3.8)                                      |
| Endometrial polyp               | yes                                                   | yes                                                     |                                                                                        | 09                | 07 (77.7)                                             | 2 (22.2)                                                 | -                                                                     | 01 (0.75)                                      |
| Endometriosis                   | yes                                                   | yes                                                     |                                                                                        | 05                | 05 (100)                                              | -                                                        | -                                                                     | -                                             |
| Benign ovarian cyst             | yes                                                   | yes                                                     |                                                                                        | 13                | 13 (100)                                              | -                                                        | -                                                                     | -                                             |
| Tubo-ovarian mass               | yes                                                   | yes                                                     |                                                                                        | 03                | 02 (66.7)                                             | 01 (33.3)                                                | -                                                                     | 01 (0.75)                                      |
| Gestational trophoblastic disease | yes                                                  | yes                                                     |                                                                                        | 03                | 02 (66.7)                                             | 1 (33.3)                                                 | -                                                                     | 01 (0.75)                                      |
| Chronic PID                     | 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 (%) |
|-----------------------------------------|-------------------------------|---------------------------------------------------------------|
| Biochemical (CA_{125}, CA_{19.9}, LDH, AFP, Beta-hcg) | 75                            | 11.1                                                          |
| Physical-radiological (physical examination, USG, MRI/CT) | 83.3                          | 12.8                                                          |
| Biophysical (PAP smear, colposcopy, hysteroscopy, laparoscopy, endometrial aspiration) | 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 (OR) | 95% confidence interval | P value | Statistical significance* |
|----------------|----------------|-----------------|-------------------------|---------|--------------------------|
| **Age (year)** |                |                 |                         |         |                          |
| 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               |         |                          |
| **Locality**   |                |                 |                         |         |                          |
| Rural          | 59 (13)        | 3.8             | 1.28-11.51              | 0.016   | Significant*              |
| Urban          | 73 (05)        | 0.26            | 0.08-0.77               |         |                          |
| **Education**  |                |                 |                         |         |                          |
| Up to primary school | 60 (14)     | 5.17            | 1.60-16.70              | 0.006   | Significant*              |
| Middle school and above | 72 (04) | 0.19            | 0.05-0.62               |         |                          |
| **Socio economic status** | |                 |                         |         |                          |
| 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               |         |                          |
| **Parity**     |                |                 |                         |         |                          |
| P<0/1/2        | 66 (05)        | 0.23            | 0.07-0.77               | 0.016   | Significant*              |
| P>0/3          | 66 (13)        | 4.17            | 1.29-13.45              |         |                          |
| **Hormonal status** |             |                 |                         |         |                          |
| Pre-menopausal | 100 (14)       | 1.13            | 0.34-3.74               | 0.82    | Not significant           |
| Post-menopausal| 32 (04)        | 0.87            | 0.26-2.88               |         |                          |
| **Route of surgery** |            |                 |                         |         |                          |
| Abdominal      | 91 (10)        | 0.50            | 0.18-1.40               | 0.19    | Not significant           |
| Vaginal        | 41 (08)        | 1.96            | 0.71-5.41               |         |                          |
| **Weight of uterus (hysterectomy specimen) (gm)** | |                 |                         |         |                          |
| 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               |         |                          |
| **Medical condition** |        |                 |                         |         |                          |
| 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.2,4,5 But the prevalence is slightly lower in some other studies.6,7

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.2,8-11

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.3,6,12 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.13,14

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
In present study, clinico-pathological correlation was only 72.7%, consistent to prior studies. 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. 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 preoperative 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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