

## Prevalence of human papilloma virus genotypes 16, 18 in women with abnormal cervical cytology smears (abnormal Pap smear) attending Erbil Maternity Teaching Hospital

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### Abstract

**Background and objective:** Cervical cancer is the fourth most common cancer among women. Carcinogenic Human Papilloma Virus (HPV) infection is the major etiological agent for cervical cancer, of which 70% are caused by HPV-16 and HPV-18 genotype infection. This study aimed to detect high risk HPV (16,18) in women with different abnormalities in pap smear to allow subsequent more accurate management of the cases and provide information that assists in future development of guidelines in our hospital.

**Methods:** We performed a cross-sectional study on 100 ladies with an abnormal pap smear. Subjects were interviewed and underwent cervical testing with broom using liquid based samples to confirm the cytological abnormality and test for HPV genotypes 16 and 18 using Polymerase Chain Reaction (PCR). Then, colposcopy referral was done according to local protocols.

**Results:** The median age of the subjects was 34. The prevalence of HPV genotypes 16,18 in the whole studied sample was 36%. Various studied risk factors showed significant association with abnormal pap smear and positive HPV genotypes 16,18, including the number of partners, increasing parity, age at first pregnancy, and smoking. Data were analyzed by the statistical package for the social sciences (version 23).

**Conclusion:** The prevalence of HPV 16,18 was 36% in the sample, with the highest proportion being among those with high-grade lesions. Those using natural methods of contraception had higher rates of infection in comparison with other methods.

**Keywords:** Human Papillomavirus; Abnormal pap smear; Atypical squamous cell of undetermined significance; Low grade squamous intraepithelial lesion; High grade squamous intraepithelial lesion.

### Introduction

Cervical cancer is the fourth most common cancer among women, after breast, colorectal, and lung cancer.<sup>1</sup> About 80% of new cases of cervical cancer occur in developing countries.<sup>2</sup> Oncogenic HPV infection is the major etiological agent of cervical cancer, of which 70% are caused by HPV-16 and HPV-18 type.<sup>2,3</sup> It may take up to 5-10 years for the infection to progress to the precancerous lesion.<sup>3</sup> HPV genotype distribution varies with the severity of the cervical disease, patient demographics such as age, as well as geographical location.<sup>4,5</sup> There has been a large decline in cervical cancer incidence

and death rate in countries with regular cervical screening program during the past few decades. Unfortunately, there is no such decline in countries without such a screening program. The disproportionate burden of cervical cancer in developing countries with poor health systems is mainly due to a lack of effective screening program.<sup>2</sup> In developing countries, limited access to effective screening means that the disease is often not identified until it is further advanced and symptoms develop. In addition, prospects for the treatment of such late-stage disease may be poor, resulting in a higher rate of death from cervical cancer in these countries.<sup>6</sup>

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The high mortality rate from cervical cancer globally (52%) could be reduced by effective screening and treatment programs.<sup>6</sup> Despite increased research into HPV, and the introduction of HPV vaccines to prevent infection and subsequent cervical cancer development, the screening will remain important.<sup>7-9</sup> However, improved screening methods have also introduced some confusion, even controversy.<sup>8</sup> HPV testing is more sensitive than the Pap test for detecting precancerous lesions.<sup>10</sup> The HPV test identifies viruses that can cause cancer. On the other hand, some gynecologists still in use of Pap smear (plus HPV testing) as they believe that unknown cancer causing viruses can be missed by HPV test only. However, reports of rare HPV-negative, Pap-test-positive cancers are motivating ongoing use of both tests (co-testing) despite the high costs.<sup>5</sup> The accumulated evidence supports the inclusion of HPV testing in screening; thus, the main choice moving forward is between cotesting and primary HPV testing only.<sup>10</sup> To the best knowledge of the researchers of this article, this is the first time to test for HPV in a sample of Kurdish women. Therefore, this study aimed to detect high risk HPV types(16,18) in women presenting with different abnormalities in the pap smear to allow subsequent more accurate management of the cases. The study provides information that may help in the future development of guidelines in our community in light of the lack of regular cervical screening programs in our community.

## Methods

### Design and setting of the study

This cross-sectional study was carried out in a group of women attending the Maternity Teaching Hospital in Erbil city, Kurdistan region of Iraq, from June 2017 to September 2018.

### Sampling method and sample size:

A sample size of 94 women was calculated based on having a 10% accepted margin of

error around an estimated prevalence of HPV type 16 of 41.9% in women with cervical cytological abnormality with a 95% confidence interval,<sup>12</sup> and the sample size had been increased to 100. The women who underwent Pap smear examination in Maternity teaching hospital and had cervical cytological abnormality were selected to participate in the study until the required sample size gained. The inclusion criteria included all married women between 21-65 years of age, including those who had a history of chronic medical illnesses like diabetes and hypertension. This age group was included according to the guidelines of cervical screening, which includes this age group. The exclusion criteria included women who had hysterectomy for causes other than cervical cytological abnormalities, women younger than 21, and women older than 65. Unmarried women were also not included in the study for social and cultural reasons and those who refused to give consent.

### Data collection

The sample collection was carried out from September 2017 to September 2018. It was preceded at the time of sample collection by an interview using a structured epidemiological questionnaire that included information on sociodemographic characteristics, habits, and sexual and reproductive history. The patients who have been classified as being in the inclusion group were educated about the precautions that are recommended before taking the cervical smear (liquid based sample collection), including not being in menstrual period and avoiding sexual intercourse, douching, and using spermicidal products the day before the test. The patient was asked to lie supine, in a dorsal lithotomy position to correctly perform a pap smear. The coccyx of the patient was at the edge of the examination table to provide adequate visualization of the cervix once the speculum is inserted. After adequate positioning, careful clinical examination of

the external genitalia, and the perianal region was done. Then, the speculum was inserted, and an adequate sample was obtained from the cervix using a broom like device. The central bristles of the broom was inserted into the endocervix deep enough to allow the shorter bristles to fully contact the ectocervix, then pushing and rotating the broom in a clockwise direction five times. The broom was then rinsed as quickly as possible into alcohol based liquid container (the thinprep pap test container) by pushing the broom into the bottom of the container 10 times. The cap of the container was tightened, and the patient's name and ID number were recorded on the container then patient information and medical history were recorded on the cytology requisition form. The sample container and the requisition form were transported to the laboratory.

#### **Cytological examination and HPV analysis**

Cytological smears consisted of collected cells from the transformational zone (squamo-columnar junction) using the broom. After appropriate collection of the samples, results for both the pap smear and HPV detection were reported using the same samples at the cytological and histopathological department of the laboratory in Maternity teaching hospital. The results of the samples and the degree of cervical abnormalities were interpreted according to the Bethesda System revised in 2001. The extraction of the genomic DNA from the samples was performed using PCR. The PCR results were reported as positive for HPV16, positive for HPV18, positive for HPV 16,18 or negative for HPV 16,18.

#### **Ethical approval**

Ethical approval to conduct this study was obtained from the Scientific Council of Obstetrics and Gynecology/Kurdistan Board for Medical Specialties. All interviews performed were in accordance with the ethical standards of the institutional research committee. Informed consent was obtained from each woman

who agreed to participate in the study. Participants were assured that confidentiality would be maintained and that their information would only be used for research purposes.

#### **Statistical analysis**

Data were analyzed by the statistical package for the social sciences (SPSS, version 23). Means and proportions were displayed. The student's t-test was used to compare means, and the Chi-square test or Fisher's Exact test was used for the comparison of categorical variables as appropriate. A *P* value of  $\leq 0.05$  was considered significant.

#### **Results**

Hundred ladies with abnormal Pap smear results had been included in the study. Their mean age  $\pm$  SD was  $36.5 \pm 8.5$  years, with a median of 34 years. The age range was 24 to 53 years. The results showed that 7% of the sample aged 35-39 years, 12% aged 40-44 years, while the rest of the age group represents 27%. The outcome shows that the majority (84%) of the women started their sexual activity at 17 years or over, and (88%) had only one sexual partner throughout their life. The majority (84%) of the studied sample used some sorts of contraception throughout their life, and 19% were smokers (Table 1), 36% of the women had five children or more, and only 8% became pregnant before the age of 17 years.

**Table 1:** Basic characteristics of the studied sample.

| Characteristic                               | No.        | (%)           |
|--|------------|---------------|
| <b>Age (years)</b>                           |            |               |
| < 30   | 27         | (27.00)       |
| 30-34  | 27         | (27.00)       |
| 35-39  | 7          | 7.00          |
| 40-44  | 12         | 12.00         |
| ≥ 45   | 27         | 27.00         |
| <b>Initiation of sexual activity (years)</b> |            |               |
| < 17   | 16         | 16.00         |
| ≥ 17   | 84         | 84.00         |
| <b>Number of sexual partners in lifetime</b> |            |               |
| One  | 88         | 88.00         |
| Two  | 12         | 12.00         |
| <b>Number of children born</b>               |            |               |
| 0  | 4          | 4.00          |
| 1-4  | 60         | 60.00         |
| ≥ 5  | 36         | 36.00         |
| <b>Age of first pregnancy (years)</b>        |            |               |
| < 17   | 8          | 8.00          |
| ≥ 17   | 92         | 92.00         |
| <b>Ever use of contraception</b>             |            |               |
| Yes  | 84         | 84.00         |
| No   | 16         | 16.00         |
| <b>Smoking</b>                               |            |               |
| Yes  | 19         | 19.00         |
| No   | 81         | 81.00         |
| <b>Total</b>                                 | <b>100</b> | <b>100.00</b> |

Table 2 shows that the prevalence of HPV in the whole sample was 36%. No significant association was detected between the prevalence of HPV and the Pap smear results ( $P = 0.140$ ). However, it is worth mentioning that the highest rates were among those with high grade squamous intraepithelial lesion (HSIL) (50%) and those with the atypical squamous cell of undetermined significance (ASCUS) (44%). The prevalence of HPV was highest among women using the natural methods of

contraception (62.5%), while none of those using condoms tested positive for HPV ( $P < 0.001$ ). Half of those with a history of gonococcal infection tested positive for HPV, and none of those with a trichomonas infection history tested positive. The highest prevalence (62.5%) was among those with unknown history for STIs ( $P < 0.001$ ). The prevalence of HPV was 100% among those with a family history of breast cancer, compared with 36.8% among those with no cancer history ( $P < 0.001$ ).

**Table 2:** Prevalence of HPV by some risk factors.

|                             | Prevalence of HPV |                |           |                | Total      |                 | P value  |
|-----------------------------|-------------------|----------------|-----------|----------------|------------|-----------------|----------|
|                             | Positive          |                | Negative  |                | No.        | (%)             |          |
|                             | No.               | (%)            | No.       | (%)            | No.        | (%)             |          |
| <b>Pap smear</b>            |                   |                |           |                |            |                 |          |
| ASCUS                       | 16                | (44.40)        | 20        | (55.60)        | 36         | (100.00)        |          |
| LSIL                        | 8                 | (22.20)        | 28        | (77.80)        | 36         | (100.00)        |          |
| HSIL                        | 8                 | (50.00)        | 8         | (50.00)        | 16         | (100.00)        |          |
| Severe cervicitis           | 4                 | (33.30)        | 8         | (66.70)        | 12         | (100.00)        | 0.140    |
| <b>Contraception</b>        |                   |                |           |                |            |                 |          |
| OCP                         | 8                 | (28.60)        | 20        | (71.40)        | 28         | (100.00)        |          |
| Condom                      | 0                 | (0.00)         | 16        | (100.00)       | 16         | (100.00)        |          |
| Natural                     | 20                | (62.50)        | 12        | (37.50)        | 32         | (100.00)        |          |
| Implants                    | 4                 | (50.00)        | 4         | (50.00)        | 8          | (100.00)        |          |
| None                        | 4                 | (25.00)        | 12        | (75.00)        | 16         | (100.00)        | < 0.001  |
| <b>History of STIs</b>      |                   |                |           |                |            |                 |          |
| Gonococcal infection        | 4                 | (50.00)        | 4         | (50.00)        | 8          | (100.00)        |          |
| Trichomonus                 | 0                 | (0.00)         | 4         | (100.00)       | 4          | (100.00)        |          |
| None                        | 12                | (21.40)        | 44        | (78.60)        | 56         | (100.00)        |          |
| Unknown                     | 20                | (62.50)        | 12        | (37.50)        | 32         | (100.00)        | < 0.001* |
| <b>Family history of CA</b> |                   |                |           |                |            |                 |          |
| Cervical CA                 | 0                 | (0.00)         | 4         | (100.00)       | 4          | (100.00)        |          |
| Endometrial CA              | 0                 | (0.00)         | 8         | (100.00)       | 8          | (100.00)        |          |
| Breast CA                   | 8                 | (100.00)       | 0         | (0.00)         | 8          | (100.00)        |          |
| Others                      | 0                 | (0.00)         | 4         | (100.00)       | 4          | (100.00)        |          |
| None                        | 28                | (36.80)        | 48        | (63.20)        | 76         | (100.00)        | <0.001*  |
| <b>Total</b>                | <b>36</b>         | <b>(36.00)</b> | <b>64</b> | <b>(64.00)</b> | <b>100</b> | <b>(100.00)</b> |          |

\*By Fisher's exact test.

Abbreviations: ASCUS = Atypical squamous cell of undetermined significance. LSIL = Low grade intraepithelial lesion. HSIL = High grade intraepithelial lesion. STIs = Sexually transmitted infections.

Table 3 shows no significant association between age and prevalence of HPV ( $P = 0.745$ ). The table shows that 100% of women whose first pregnancy was before 17 tested positive for HPV ( $P < 0.001$ ). The prevalence of HPV was significantly ( $P = 0.026$ ) higher among those with two partners (66.7%) than among those with one partner (31.8%). No significant

association was detected between the prevalence and the age of marriage ( $P = 0.317$ ). The highest prevalence (100%) was among the nulliparous women ( $P = 0.036$ ), but it is evident that only four women were nulliparous. The prevalence among smokers (63.2%) was significantly higher than the prevalence (29.6%) among the non-smokers ( $P = 0.006$ ).

**Table 3:** Prevalence of HPV by age and some social behaviors.

|                               | Positive |          | negative |         | Total |          | P value  |
|-------------------------------|----------|----------|----------|---------|-------|----------|----------|
|                               | No.      | (%)      | No.      | (%)     | No.   | (%)      |          |
| <b>Age (years)</b>            |          |          |          |         |       |          |          |
| < 30                          | 11       | (40.70)  | 16       | (59.30) | 27    | (100.00) | 0.745*   |
| 30-34                         | 7        | (25.90)  | 20       | (74.10) | 27    | (100.00) |          |
| 35-39                         | 3        | (42.90)  | 4        | (57.10) | 7     | (100.00) |          |
| 40-44                         | 4        | (33.30)  | 8        | (66.70) | 12    | (100.00) |          |
| ≥ 45                          | 11       | (40.70)  | 16       | (59.30) | 27    | (100.00) |          |
| <b>Age at first pregnancy</b> |          |          |          |         |       |          |          |
| < 17                          | 8        | (100.00) | 0        | (0.00)  | 8     | (100.00) | < 0.001* |
| ≥ 17                          | 28       | (30.40)  | 64       | (69.60) | 92    | (100.00) |          |
| <b>Number of partners</b>     |          |          |          |         |       |          |          |
| One                           | 28       | (31.80)  | 60       | (68.20) | 88    | (100.00) | 0.026*   |
| Two                           | 8        | (66.70)  | 4        | (33.30) | 12    | (100.00) |          |
| <b>Age of marriage</b>        |          |          |          |         |       |          |          |
| < 17                          | 4        | (25.00)  | 12       | (75.00) | 16    | (100.00) | 0.317    |
| ≥ 17                          | 32       | (38.10)  | 52       | (61.90) | 84    | (100.00) |          |
| <b>Parity</b>                 |          |          |          |         |       |          |          |
| 0                             | 4        | (100.00) | 0        | (0.00)  | 4     | (100.00) | 0.036*   |
| 1-4                           | 20       | (33.30)  | 40       | (66.70) | 60    | (100.00) |          |
| ≥ 5                           | 12       | (33.30)  | 24       | (66.70) | 36    | (100.00) |          |
| <b>Smoking</b>                |          |          |          |         |       |          |          |
| No                            | 24       | (29.60)  | 57       | (70.40) | 81    | (100.00) | 0.006    |
| Yes                           | 12       | (63.20)  | 7        | (36.80) | 19    | (100.00) |          |
| <b>Total</b>                  | 36       | (36.00)  | 64       | (64.00) | 100   | (100.00) |          |

\*By Fisher's exact test.

It is evident in Table 4 that all the patients aged  $\geq 45$  years had HPV 16, and all of the patients aged 35-44 years were positive for HPV 16 and 18 ( $P < 0.001$ ). All those with severe cervicitis were positive for HPV 16.

There was a significant association between Pap smear results and type of HPV ( $P = 0.010$ ). No significant association was detected between the HSIL diagnosis with the type of HPV ( $P = 0.227$ ).

**Table 4:** Prevalence of HPV subtypes by age, Pap smear results and HSIL.

|                   | HPV16     |                | HPV18    |                | HPV 16 & 18 |                | Total     |                 | P value  |
|-------------------|-----------|----------------|----------|----------------|-------------|----------------|-----------|-----------------|----------|
|                   | No.       | (%)            | No.      | (%)            | No.         | (%)            | No.       | (%)             |          |
| <b>Age</b>        |           |                |          |                |             |                |           |                 |          |
| < 30              | 1         | (9.10)         | 8        | (72.70)        | 2           | (18.20)        | 11        | (100.00)        |          |
| 30-34             | 4         | (57.10)        | 0        | (0.00)         | 3           | (42.90)        | 7         | (100.00)        |          |
| 35-39             | 0         | (0.00)         | 0        | (0.00)         | 3           | (100.00)       | 3         | (100.00)        | < 0.001* |
| 40-44             | 0         | (0.00)         | 0        | (0.00)         | 4           | (100.00)       | 4         | (100.00)        |          |
| $\geq 45$         | 11        | (100.00)       | 0        | (0.00)         | 0           | (0.00)         | 11        | (100.00)        |          |
| <b>Pap smear</b>  |           |                |          |                |             |                |           |                 |          |
| ASCUS             | 4         | (25.00)        | 4        | (25.00)        | 8           | (50.00)        | 16        | (100.00)        |          |
| LSIL              | 4         | (50.00)        | 4        | (50.00)        | 0           | (0.00)         | 8         | (100.00)        |          |
| HSIL              | 4         | (50.00)        | 0        | (0.00)         | 4           | (50.00)        | 8         | (100.00)        | 0.010*   |
| Severe cervicitis | 4         | (100.00)       | 0        | (0.00)         | 0           | (0.00)         | 4         | (100.00)        |          |
| <b>HSIL</b>       |           |                |          |                |             |                |           |                 |          |
| No                | 12        | (42.90)        | 8        | (28.60)        | 8           | (28.60)        | 28        | (100.00)        |          |
| Yes               | 4         | (50.00)        | 0        | (0.00)         | 4           | (50.00)        | 8         | (100.00)        | 0.227*   |
| <b>Total</b>      | <b>16</b> | <b>(44.40)</b> | <b>8</b> | <b>(22.20)</b> | <b>12</b>   | <b>(33.30)</b> | <b>36</b> | <b>(100.00)</b> |          |

\*P calculated by Fisher's exact test.

## Discussion

Our prospective study concluded that the prevalence of HPV 16,18 was 36% in the whole population, and the highest proportion was among those with high grade lesions (HSIL). Those using natural contraception methods also had higher rates of infection compared with other methods, and cases with a history of gonococcal infection were positive for HPV 16 or 18 in half of them. A higher prevalence has been found in a study that had been carried out in Australia, Melbourne in 2009 which showed that overall 83.9% of women with an abnormal pap smear, had one of the high risk HPV infections.<sup>5</sup> On the other hand, another study which was done in Turkey showed that overall prevalence of HPV in women with abnormal pap smear was 36% and HPV 16 infection being the commonest.<sup>13</sup> The prevalence of HPV was highest among those younger than 35 years old, although it was statistically not significant. A study done in the UK showed that women below 30 years were more likely to have HPV infection.<sup>14</sup> Such difference in the two results may be due to earlier diagnosis and intervention in the second population group (UK). Despite the nonsignificant association, HSIL was associated with the highest positivity rate for either subtype 16 or 18 HPV infection. The association may be limited by the sample size, and bigger sample size may solve this problem. These findings were in conformity with the data given by the University of Pittsburg (Infectious Diseases and Microbiology Graduate School of Public Health). According to them, high risk HPV was positive in 79 – 90% cases of HSIL.<sup>13</sup> Condom use appears to offer relatively good protection from HPV infections and associated cervical neoplasia.<sup>16</sup> This was obvious in our study as none of those using condoms had been tested positive for HPV 16 or 18. The current study findings were comparable with a systemic review performed on condom use in the prevention of HPV infection and cervical

neoplasia by Department of Public Health, University of Copenhagen.<sup>15</sup> Although HPV infection is the commonest type of sexually transmitted infections (STI) in many parts of the world, there is an association of HPV infection with other STIs.<sup>16</sup> In our study, 50% of those with gonococcal infection tested positive for either HPV 16 or 18. However, the lack of specialized STI clinics in our area makes reporting the prevalence of STIs and their association with HPV infection very difficult. According to a longitudinal cohort study of American female college students, initiation of sexual intercourse at an early age makes the possibility of being infected with HPV more likely than later sexual initiation in part because of certain behavioral factors and partner characteristics.<sup>17</sup> This study found a significant association between the age of first pregnancy and HPV infection in the studied population. Those with the age of first pregnancy less than 17 have 100% rate of being positive for either HPV 16 or 18. In light of these findings, it is suggested that providers encourage adolescents who have not yet had sexual intercourse to postpone sexual initiation. It is also recommended that youth who had their first sexual experience at early age should benefit from counseling that stresses on the importance of safe sex practices including barriers such as condoms and dental dams.<sup>17</sup> To our knowledge, this is the first cross-sectional study on the prevalence of HPV (16,18) in women with abnormal pap smear in Erbil city. The study was conducted in Erbil Maternity Teaching Hospital, the only governmental hospital in Erbil city serving obstetric and gynecologic cases. Even patients who have been seen in private clinics would be referred to the cervical pathology unit of this hospital for further assessments. This makes the population that has been studied a good representative sample of those with an abnormal pap smear. These points make the study unique in this area of research at the moment. As a limitation in this study, we did not correlate the

cytological changes and HPV results with the colposcopy appearance of the cervix and histological changes. Such limitation is because HPV triage has become a new way for follow up of patients with some confusing borderline changes in the pap smear, so colposcopy has not necessarily been done for all patients. Future studies should address this issue to provide further information and classification of the cervical pathology to help reform local protocols in our hospital. HPV vaccine for the prevention of some HPV genotypes has been approved by US Food and Drug Administration for women between 9-26 years of age in 2006.<sup>18</sup> In the background of our research result, vaccination is recommended for women in our community in the hope of preventing HPV infection.

### Conclusion

The prevalence of HPV 16,18 was 36% in the sample, with the highest proportion being among those with high grade lesions (HGSIL). Those using natural methods of contraception had higher rates of infection in comparison with other methods.

### Competing interests

The authors declare no competing interests.

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