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Risk of decreased ovarian reserve in women with HPV infection and cervical lesions

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Abstract

Background: Human papillomavirus (HPV) infection has been considered an important involved factor for infertility. Since one of the causes of decreased ovarian reserve is oophoritis due to viral infections, this study aimed to evaluated the association between HPV infection and ovarian reserve.

Methods: This case-control study was performed on 219 women aged 25–35 years who were referred to the gynecologic oncology clinic during 2019–2020. The positive or negative HPV infection was confirmed by cervical biopsy and polymerase chain reaction (PCR) test. Cervical lesions or abnormalities in the cervix were assessed by colposcopy and histopathological analysis. Serum anti-Mullerian hormone (AMH) levels were measured for all participants to assess ovarian reserve.

Results: The results of this study showed that in patients who were HPV positive, decreased ovarian reserve was more common than in the HPV negative group ($p = 0.0001$). Also, there was a significant difference between Cervical intraepithelial neoplasia (CIN) I and CIN III sub-groups in AMH level ($p = 0.0001$).

Conclusions: Traces of HPV have been observed in various aspects of infertility, but no study has been performed on its association with ovarian reserve. According to the results of this study, decreased ovarian reserve was more common in patients who were HPV positive.

KEYWORDS

AMH, cervical lesions, decreased ovarian reserve, HPV infection, infertility

1 | INTRODUCTION

Human papillomavirus (HPV) is a group of double-stranded DNA viruses that belong to the papillomavirus family. HPV infection is the most common sexually transmitted infection that affects both males and females.[1] Out of 100 types of HPV, 13 types are high-risk which are responsible for some human cancers.[2] HPV infection accounts for almost 2% and 7% of all tumor cases in developed and developing countries, respectively.[3] It has been found that a positive high-risk HPV test is the best predictor of future cervical high-grade lesions.[4] HPV disrupts cell cycle regulation and causes the accumulation of genetic damage in infected cells which may be one of the carcinogenic mechanisms.

It has been demonstrated that HPV infection may affect reproductive function and pregnancy results, including miscarriage and preterm delivery.[5] HPV infection is a likely reason for male and couple infertility by detrimental effects on sperm quality, and adverse effects on the early developing embryo, respectively,[6] Hpv also impacts sperm quality and male fertility.[7,8] A few lectures have investigated the prevalence of cervical HPV in patients who go through fertility treatment, and the studies presented no difference in HPV prevalence of these women compared with the general population.[9,10] Nøhr et al.[11] by a patients-based cohort study found no relationship between a high-risk HPV infection and risk of female factor infertility. However, it has been reported that high-risk HPV infection is not an independent cause of female infertility, but is a potential risk factor.[10] HPV infection has been reported in a meta-analysis in association with an increased risk of spontaneous abortion and spontaneous preterm birth.[12] A large cohort study found HPV infection as a probable risk factor of subsequent female infertility.[13] However, the possible role of HPV infection in female reproductive health has not been completely understood.

Diminished ovarian reserve (DOR) is defined by reductions in oocyte quantity and quality with advanced age which is a normal physiologic event.[14] However, there is no unique definition of DOR,[15] reduction of fecundity related to decreased ovarian function based on clinical assessment (FSH > 10 mLU/mL or AMH < 1.0 ng/mL) is observed in patients with DOR. Among the tests to assess ovarian reserve AMH measurement and antral follicle count (AFC) are sensitive markers for monitoring ovarian reserve. Although each ovarian reserve assessment test provides useful predictive information, AMH is recognized as a good diagnostic test for ovarian reserve because its level is constant throughout the menstrual cycle and has a high specifcity for detecting the ovarian reserve

> AMH is a glycoprotein produced from granulosa cells in 5–8 mm ovarian follicles. AMH is hardly detectable in the serum at birth, reaches a higher level after puberty, and then decreases with age until it disappears at menopause.

> In pathologic DOR women experience DOR much earlier and become prematurely infertile.[14] DOR is a major challenge in reproductive medicine and its underlying pathophysiology is challenging. It has been demonstrated human immunodeficiency virus (HIV) infection is related to decreased ovarian reserve.[15,16]

HPVs have been found in ovarian lesions,[17] and persistent HPV infection has been related to chronic inflammatory process.[18] So, it may link to female infertility through ovarian dysfunction. Viral and bacterial infections are detected in epithelial ovarian cancer (EOC) tissues, and it has been reported that cytomegalovirus (CMV) and HPV infections can be probable risks for EOC progress.[17] These pieces of evidence suggest that the HPV virus also affects the ovaries that one of which may be the effect on ovarian reserve. To the best of our understanding, the present study is the first study evaluating the relationship between HPV infection and cervical lesions with diminished ovarian reserve. So, we conducted a prospective cross-sectional study to examine the effect of HPV infection on ovarian reserve to provide insight for managing HPV infection in infertility treatment.

2 | PATIENTS AND METHODS

2.1 | Study population

Our study is a prospective cross-sectional study that was conducted between September 2019 and November 2020 in Al-Zahra Hospital, Rasht, Iran. The study population consisted of 219 women (25–35 years of age) with clinical presentation including postcoital bleeding (PCB), chronic cervicitis, abnormal Pap smear test, and abnormal vaginal discharge who were a candidate for colposcopy. Exclusion criteria were endocrinological disorder, fertility preservation candidates, polycystic ovary syndrome (PCOS), surgical history of the ovary, chemotherapy, radiotherapy, genetic disorders, consumption of oral contraceptive pill, patients who received HPV vaccine.

2.2 | HPV detection and cervical lesions assessment

For all women, cervical swabs were collected and HPV infection in clinical samples was detected by the HPV PCR with the HPV Direct Flow CHIP System (Master Diagnóstica). Nucleic acid (DNA) testing by PCR reaction was prepared according to the manufactures instruction for detecting the presence of a cervical HPV infection. They were divided into two HPV-positive and negative groups. Patients were named HPV positive if they tested positive for one or more of the high-risk HPV types. We did not include patients with low-risk HPV

CIN or premalignant condition of the cervix was evaluated in HPV positive group by colposcopy. Colposcopic assessment of CIN was based on the observation of well-demarcated, dense, and opaque areas in the transformation zone of the cervix. Colposcopic-directed biopsy for histopathological analysis was obtained from each patient and analyzed by the same pathologist. According to how much epithelial tissue is affected, CIN is classified into three grades: CIN I, CIN II, and CIN III. CIN I is the low-grade

neoplasia and CIN III is the most severe form that affects more than two-thirds of the cervical epithelium.

2.3 | AMH assessment

Serum AMH was assessed by Immunotech Beckman Coulter ELISA kit (cat no: B13127) by one-step sandwich assay according to the manufacturer's instructions. Blood samples were collected by observing standard precautions for venipuncture. AMH level and HPV infection were checked at the same time and the medical laboratory.

2.4 | Statistical analysis

The data were analyzed using IBM SPSS (v 21.0). Quantitative data were reported as mean ± SD, and qualitative data was reported in terms of number and percentage. The relationship between grouped variables was examined using the Chi-square test, and if the necessary condition is not met, Fisher's exact test was used. The statistical significance level was considered $p < 0.05$.

2.5 | Ethical consideration

Ethical approval was gotten from the Research Deputy and Ethics Committee of Guilan University of Medical Sciences (Approval ID: IR.GUMS.REC.1400.003). All the participants signed a written informed consent before enrollment in the study.

3 | RESULTS

In this prospective cross-sectional study, of the 219 women (age 18–35) included, 110 women were high-risk HPV positive, and 109 women were high-risk HPV negative based on PCR results. The mean age in HPV-positive patients was 28.19 ± 3.48, and in HPV negative was 29.90 ± 3.69, respectively. AMH levels in HPV-positive and HPV-negative women were 3.11 ± 2.13 and 4.88 ± 2.14, respectively. As shown in Figure 1, in patients who were HPV positive, AMH levels were significantly lower ($p = 0.0001$). AMH levels in HPV positive sub-group based on colposcopy results are shown in Table 1. There was a significant difference between normal and CIN III sub-groups in AMH level ($p = 0.0001$). The histopathology of CIN grades is presented in Figure 2.

Our study, we investigated the relationship between high-risk HPV infection and AMH level as the ovarian reserve marker. In patients who were HPV positive, AMH levels were significantly lower ($p = 0.0001$), and there was a significant difference between normal and CIN III sub-groups in AMH level ($p = 0.0001$). Our study presented that HPVs infection found in females may have a significant impact on their ovarian reserve.

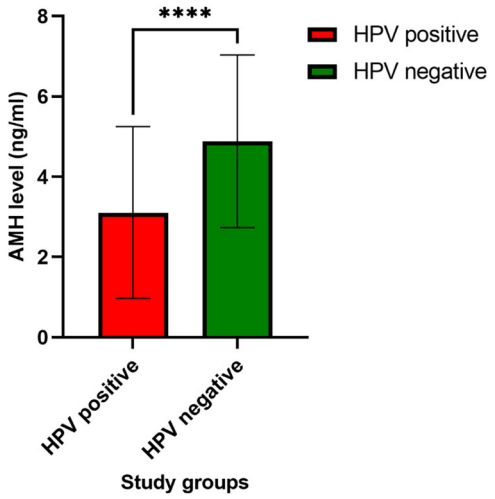

FIGURE 1 AMH levels in two groups of study (HPV positive and HPV negative). As indicated in this figure, in patients who were HPV positive, AMH levels were significantly lower. ****$p = 0.0001$, Mann–Whitney test. AMH, anti-Mullerian hormone; HPV, Human papillomavirus.

4 | DISCUSSION

Many factors determine the fertility potential of females. However, it has been found no association between a high-risk HPV infection and the risk of female infertility,[9] our results showed an association between HPV infection and high-grade cervical lesions and ovarian reserve. Also, a previous study showed the prevalence of high-grade cervical lesions is higher in infertile women compared with the general population.[19] HPV infection affects reproductive function and pregnancy result including abortion and preterm labor, male factor infertility, and embryo development failure.[5,6] It has been reported that high-risk HPV infection is a potential risk factor for female infertility.[10,20] In vitro fertilization (IVF) outcomes, pregnancy rate, and intrauterine insemination (IUI) outcomes have been demonstrated to be lower in HPV-positive patients.[21,22] Hsu et al. reported a higher risk of female infertility in women with HPV infection, specifically those aged 26–35 years.[13] However, the possible role of HPV infection in female reproductive health has not been completely understood.[23,24]

In the present study, as well to evaluating the association between HPV infection and ovarian reserve, we also assessed the relationship between cervical lesion grade and ovarian reserve. As indicated in Table 1, CIN III, or the high-grade neoplasia sub-group, had the lowest AMH level. HPV is one of the most common sexually transmitted infections. Chronic inflammation due to infection may disturb the balance of the immune system required for ideal fertility.[25] Although there is not enough evidence, it is possible that HPVs infection can have a detrimental effect on the ovaries by disturbing the balance of the immune system and inflammation. Inflammation caused by HPVs infection may have a detrimental effect on the function of granulosa cells, thereby reducing the level of AMH observed in our study.

TABLE 1 AMH levels in patients based on colposcopy results.

	No of cases	Mean	Std. deviation	95% confidence interval for mean		Minimum	Maximum
				Lower bound	Upper bound		
Normal	129	4.5393	2.07746	4.1774	4.9012	0.60	9.50
CIN I	59	3.4908	2.60025	2.8132	4.1685	0.04	10.20
CIN II	19	3.5368	2.19297	2.4799	4.5938	0.60	8.00
CIN III	12	1.5983	1.07095	0.9179	2.2788	0.10	3.50
Total	219	4.0087	2.31653	3.7002	4.3172	0.04	10.20

Abbreviations: AMH, anti-Mullerian hormone; CIN, cervical intraepithelial neoplasia.

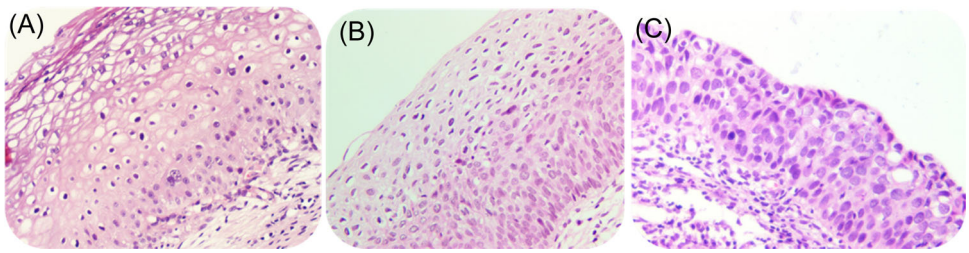

FIGURE 2 Histopathology of the CIN grades. (A) CIN I with mild dysplasia and nuclear angulation and vacuolization. Nuclear enlargement, pleomorphism, and irregular nuclear contour are observed with distributed coarse chromatin. (B) CIN II is more severe and variation in the size of cells, and nuclei, and Suprabasal mitotic activity is observed. (C) CIN III involves changes in cell and nuclear size, as well as abnormal mitoses, in all layers of the epithelium. Epithelial cell crowding, pleomorphism, and suprabasal mitotic activity are also observed. Hematoxylin & Eosin stain, X40. CIN, cervical intraepithelial neoplasia.

Oophoritis or inflammation of the ovaries, is a cause of POI that develops due to a variety of infections (viral and bacterial).[26] Biological mechanisms for an association between HPVs infection and female infertility caused by ovarian dysfunction have not yet been established. It has been suggested that chronic pelvic inflammation may decrease ovarian reserve.[27] Persistent high-risk HPV infections cause changes in the release of pro-inflammatory cytokines and subsequently chronic inflammation. However, as this pilot study is the first study investigating the relationship between HPVs infection and ovarian reserve, our results must be confirmed in further large trials. and in ovarian tissue to confirm this hypothesis.

5 | CONCLUSIONS

The role of HPVs infection has been observed in various aspects of infertility, such as endometriosis, and male factor infertility, but no study has been performed on its association with ovarian reserve. According to the results of the present study, decreased ovarian reserve was more common in patients who were high-risk HPV positive. This may be due to inflammation caused by infection with the HPV virus.

AUTHOR CONTRIBUTIONS

Fereshteh Fakor: Conceptualization; writing—review & editing. **Nasrin Ghanami Gashti**: Writing—original draft; writing—review & editing. **Amirhossein Hajizadeh Fallah**: Data curation; methodology; writing—review & editing. **Roya Kabodmehri**: Data curation; methodology; supervision; writing—review & editing. **Zahra Rafiei Sorouri**: Conceptualization; data curation; writing—review & editing. **Aida Hasanzadi**: Data curation; writing—review & editing. **Zahra Pourhabibi**: Formal analysis; methodology; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Related data of this project are available on request.

TRANSPARENCY STATEMENT

The lead author Roya Kabodmehri affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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