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Clinical outcome of high-grade cervical intraepithelial neoplasia during pregnancy: A 10-year experience

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ABSTRACT

Objective: To investigate the clinical outcome of high-grade cervical intraepithelial neoplasia (CIN) diagnosed by colposcopy-directed biopsy during pregnancy and to evaluate the risk factors for persistent disease.

Study Design: This retrospective study included pregnant women who were diagnosed with CIN2+ by colposcopy-directed biopsy from January 2005 to December 2014. The clinical characteristics, histopathologic results, and human papillomavirus (HPV) test results were reviewed. The final histopathologic result after delivery was compared with the initial diagnosis to determine disease progression, persistence, or regression.

Results: During the 10-year period, 215 pregnant women were diagnosed with high-grade CIN (75 CIN2, 140 CIN3) by colposcopy-directed biopsy. The mean age of the patients was 30.4 years. A total of 187 patients (87.0%) had high-risk HPV infections, with 76 (35.3%) infections identified as HPV genotype 16 or 18. Excisional procedures for diagnosis and treatment were not performed during pregnancy. The histopathologic results of 160 patients (normal in 43, CIN1 in 10, CIN2 in 15, CIN3 in 89, and invasive cancer in 3) were evaluated during the postpartum period. Multivariate logistic regression analysis was performed, and postpartum high-risk HPV infection (OR 5.09; 95% CI 2.15–12.05; P < 0.001) was identified as a significant independent predictor of CIN2+ persistence.

Conclusions: Conservative management of CIN2-3 during pregnancy is acceptable. However, persistent high-risk HPV infection is a major risk factor for CIN2+ persistence. Close follow-up with HPV testing, and postpartum colposcopy evaluation are necessary.

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Introduction

Cervical cancer is the most common gynecologic cancer diagnosed during pregnancy [1,2]. Fortunately, cervical cancer has precancerous lesions and remains at the cervical intra-epithelial neoplasia (CIN) grade for an extended period of time. The incidence of CIN peaks when women are in their thirties, which corresponds to the period of maximum childbearing activity [3]. The incidence of CIN in pregnancy is estimated to be 2000–8000 per 100,000 pregnancies [4]. Pregnancy is immunosuppressive and causes a variety of hormonal changes, which make women more vulnerable to human papillomavirus (HPV) infection [5]. In addition, the diagnosis of cervical cancer during pregnancy can be delayed because the symptoms, such as abnormal vaginal bleeding, discharge, and pelvic pain, are similar to those that can occur during a normal pregnancy [6,7]. Therefore, screening for cervical cancer in pregnant women is essential, and a cervical cytology test at the first prenatal care visit is recommended.

Abnormal cervical cytology is found in approximately 5% of pregnant women [8]. If the abnormal cytology is suspected to be CIN2+, a colposcopy-directed biopsy should be performed to

histologically confirm the CIN lesion [9]. Pregnant women infected with a high-risk HPV genotype, such as 16 or 18, may require a colposcopy-directed biopsy for monitoring purposes during their pregnancy and postpartum periods [10]. If the results of colposcopy-directed biopsy do not indicate a high-grade CIN (CIN2+) lesion, follow-up is recommended after delivery [11]. The aims of this study were to investigate the clinical outcome of high-grade CIN (CIN2+) that was diagnosed by a colposcopy-directed biopsy during pregnancy, and to evaluate the risk factors for persistent disease.

Materials and methods

This study included 215 pregnant women who were diagnosed with CIN2+ by colposcopy-directed biopsy from January 2005 to December 2014 at Cheil General Hospital, Dankook University College of Medicine (Fig. 1). After obtaining institutional review board (IRB) approval (No. CGH-IRB-2017-35), the following data pertaining to the patients were retrospectively reviewed: clinical characteristics, HPV test results, cervical cytology, and prenatal and postnatal histopathologic results. The final histopathologic result after delivery was compared with the initial diagnosis to determine disease progression, persistence, or regression. Data analyses were performed using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA). Categorical variables were presented as numbers and percentages. Associations were shown as odds ratios (OR) with 95% confidence intervals (CI), and a $P < 0.05$ was considered statistically significant.

Results

During the 10-year period, 215 pregnant women were diagnosed (75 CIN2, 140 CIN3) by colposcopy-directed biopsy (Table 1). The mean age of the patients was 30.4 years (range, 19–42 years). A total of 187 patients (87.0%) had high-risk HPV infections, with 76 (35.3%) infections identified as HPV genotype 16 or 18. Excisional procedures for diagnosis and treatment were not performed during pregnancy. All patients had abnormal antepartum cervical cytology: 25.1% had atypical squamous cells of undetermined significance (ASC-US), 14.4% had low-grade squamous intraepithelial lesion (LSIL), 37.7% had high-grade squamous intraepithelial lesion (HSIL), and 22.8% had atypical squamous
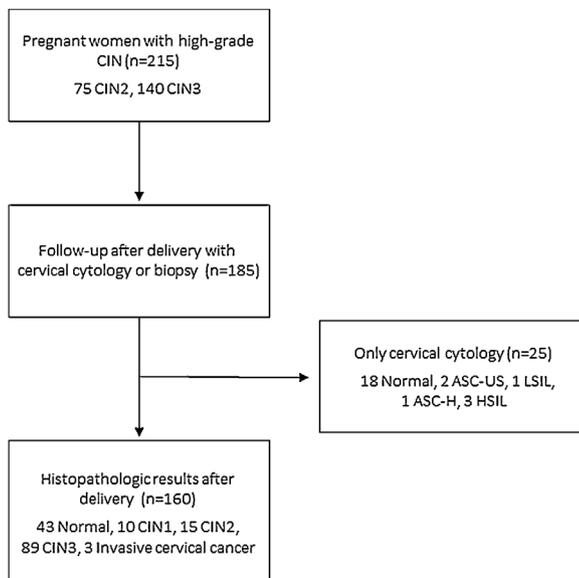
Table 1
Clinical characteristics of pregnant women with CIN2+ (N = 215).

Characteristics	Number (%)
Age, mean ± SD (years, range)	30.4 ± 3.8 (19—42)
Parity	
0	193 (89.8)
1	16 (7.4)
≥2	6 (2.8)
Tobacco use (current or past)	
No	198 (92.1)
Yes	17 (7.9)
Previous treatment for CIN	
Cold-knife conization/LEEP	2 (0.9)
Laser vaporization	1 (0.5)
Cervical cytology	
ASC-US	54 (25.1)
LSIL	31 (14.4)
ASC-H	49 (22.8)
HSIL	81 (37.7)
HPV infection	203
High-risk infection	187 (92.1)
HPV 16 or 18	76 (40.6)
Other high-risk type	111 (59.4)
Negative or only low-risk infection	16 (7.9)
Gestational age of antepartum colposcopy-directed biopsy	
1st trimester	104 (48.4)
2nd trimester	107 (49.8)
3rd trimester	4 (1.9)
Histopathologic result of antepartum colposcopy-directed biopsy	
CIN2	75 (34.9)
CIN3	140 (65.1)
Mode of delivery	
Vaginal delivery	126 (58.6)
Cesarean section	67 (31.2)
Unknown	22 (10.2)

CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; ASCUS, atypical squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude HSIL; HSIL, high-grade squamous intraepithelial lesion; HPV, Human papillomavirus.

cells, cannot exclude HSIL (ASC-H). The majority of colposcopy-directed biopsies were performed in the first (48.4%) and second (49.8%) trimester. Three patients had been treated for CIN before their pregnancy. One patient was diagnosed with carcinoma in situ of the cervix by cold-knife conization, and another patient was found to have CIN2 after a loop electrosurgical excision procedure

Table 2
Postpartum results of pregnant women with CIN2+ (N = 185).

Results	Number (%)
Cervical cytology	175 (94.6)
Normal	40 (22.9)
ASC-US	30 (17.1)
LSIL	6 (3.4)
ASC-H	38 (21.7)
HSIL	61 (34.9)
HPV infection	141 (76.2)
High-risk	101 (71.6)
HPV 16 or 18	45 (44.6)
Other high-risk type	56 (55.4)
Negative or only low-risk infection	40 (28.4)
Colposcopy-directed biopsy at postpartum	146 (78.9)
Type of cervical excision	85 (45.9)
LEEP	17 (20.0)
Cold-knife conization	68 (80.0)
Final histopathology at postpartum	160 (86.5)
Normal	43 (26.9)
CIN1	10 (6.2)
CIN2	15 (9.4)
CIN3	89 (55.6)
Invasive cancer	3 (1.9)

ASC-US, atypical squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, Human papillomavirus; LEEP, loop electrosurgical excision procedure.

Fig. 1. Algorithm for study population.

(LEEP). Finally, one patient had laser treatment for CIN1 and vaginal condyloma.

As follow-up after delivery, 185 patients underwent cervical cytology testing or a biopsy (Table 2). Cervical cytology test was performed in 175 patients at approximately 10 weeks postpartum. Ten patients underwent LEEP after their postpartum colposcopy examination. Although the results of cervical cytology tests were normal in 40 (22.9%) patients, ASC-H or HSIL was still seen in 99 (56.6%) patients. High-risk HPV infections were found in 101 patients, and 45 of these infections were HPV genotype 16 or 18. A total of 146 women underwent a postpartum colposcopy-directed biopsy, and 85 women underwent a postpartum cervical excision. The final histopathologic results were normal in 43 (26.9%) women and indicated CIN1 in 10 (6.2%) women, CIN2 in 15 (9.4%) women, CIN3 in 89 (55.6%) women, and invasive cancer in 3 (1.9%) women. Cervical cytology test results in 25 patients who did not undergo cervical biopsy were normal in 18 patients and indicated ASC-US in 2 patients, LSIL in 1 patient, ASC-H in 1 patient, and HSIL in 3 patients.

The histopathologic results of 160 patients (normal in 43, CIN1 in 10, CIN2 in 15, CIN3 in 89, and invasive cancer in 3) were evaluated during the postpartum period (Table 3). A total of 43 (26.9%) patients showed spontaneous conversion to normal cervical cytology. However, the final postpartum results of 20 (12.5%) patients showed disease progression (CIN2 to CIN3/ invasive cancer, or CIN3 to invasive cancer) compared with their antenatal histopathology. The rates of regression to normal/CIN1 or persistent HSIL (same grade) were 33.1% and 50.6%, respectively. Only 3 patients were diagnosed with invasive cervical cancer after delivery; these 3 patients had HPV 16 infection and had carcinoma in situ of the cervix identified by colposcopy-directed biopsy during pregnancy. All patients underwent cold-knife conization after delivery, and the histopathologic results were stage IB1 in 1 patient and IA1 in 2 patients. A laparoscopic radical hysterectomy was performed in 2 patients who had no additional pregnancy plan, and 1 patient was lost to follow-up.

Logistic regression analysis was used to evaluate the risk factors for high-grade CIN persistence after delivery (Table 4). Multiparity and postpartum high-risk HPV infection was associated with disease persistence. Multivariate logistic regression analysis was performed, and postpartum high-risk HPV infection (OR 5.09; 95% CI 2.15–12.05; $P < 0.001$) was identified as a significant independent predictor of CIN2+ persistence. Age, cigarette smoking, parity, and mode of delivery were not significantly associated with a high risk for disease progression.

Discussion

Pregnancy gives women who have not been tested in the past an opportunity to undergo tests for cervical cancer. Although pregnancy itself is not a risk factor for worsening cervical lesions, the cervical changes that occur during pregnancy, such as changes in the shape or size of the cervix, increased vascularity, and changes in squamous and glandular epithelial cells, can complicate the interpretation of cervical cytology and colposcopy [5,12]. Pregnant women with CIN require colposcopic surveillance to monitor for malignancy [13] because CIN can sometimes progress to invasive cervical cancer (approximately 1%) [8,14]. If cervical biopsies show a normal histology, re-evaluation can be deferred until 6–12 weeks postpartum [15]. However, suspicious microinvasive lesions should be treated by an excisional procedure no later than the 20th–24th week of pregnancy [16].

There have been several studies on the prognosis of CIN during pregnancy, but the regression and persistence rates of disease are inconsistent. Palle C et al. [8] compared initial and postpartum histology of 142 women to analyze changes in the severity of CIN and reported that 25% of the women showed spontaneous regression, 28% showed progression, and 47% showed persistence; in addition, 2 patients were diagnosed with microinvasive carcinoma in the postpartum period. In a study by Vlahos G et al. [16] of 78 pregnant women with CIN2+, disease persisted in 30 (38.4%) patients and regressed to CIN1 in 48 (61.6%) patients in the postpartum period; no patient developed invasive carcinoma. Siddiqui G et al. [10] reported that most cervical dysplasia lesions are associated with a high rate of regression (approximately 64%) and a very low rate of progression (approximately 3%). In another study of 30 pregnant women by Coppolillo EF et al. [17], a high CIN2-3 persistence rate of 70% was reported with a postpartum invasive carcinoma rate of 13.3%. In our study, a total of 160 patients with CIN2+ underwent a postpartum biopsy, and 53 (33.1%) patients showed spontaneously reversion to a normal/CIN1 status. Our regression rate may be underestimated because we did not include the 18 patients who had a normal cytology with no biopsy. However postpartum CIN2/3 was diagnosed in 104 (65%) patients and invasive cervical cancer was diagnosed in 3 (1.9%) patients. In addition the progression rate was 12.5%. This result

Table 3
Histologic prognosis in pregnant women with CIN2+ (N = 160).

| | Antepartum | | |
	CIN2	CIN3	Total
Postpartum			
Normal	13	30	43
CIN1	8	2	10
CIN2	9	6	15
CIN3	17	72	89
Invasive cancer	0	3	3
Total	47	113	160

CIN, cervical intraepithelial neoplasia.

Table 4
Logistic regression analysis for disease prognosis after delivery.

Category		CIN2+ No. (%)	≤CIN1 No. (%)	Univariate		Multivariate	
				Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age (year)	≥35	20 (18.7)	8 (15.1)	1.29 (0.53–3.12)	0.662		
	<35	87 (81.3)	45 (84.9)	1			
Cigarette smoking	Yes	10 (9.3)	3 (5.8)	1.68 (0.44–6.40)	0.549		
	No	97 (90.7)	49 (94.2)	1			
Parity	≥1	18 (16.8)	1 (1.9)	10.52 (1.36–81.01)	0.004	8.01 (0.97–66.20)	0.054
	0	89 (83.2)	52 (89.1)	1		1	
Postpartum high-risk HPV	Positive	75 (86.2)	25 (54.3)	5.25 (2.26–12.18)	<0.001	5.09 (2.15–12.05)	<0.001
	Negative	12 (13.8)	21 (45.7)	1		1	
Mode of delivery	C/sec	38 (35.5)	16 (30.2)	1.27 (0.53–3.17)	0.662		
	Vaginal delivery	69 (64.5)	37 (69.8)	1			

HPV, Human papillomavirus.

suggests that all pregnant women diagnosed with CIN2+ need a postpartum follow-up colposcopy and, if necessary, appropriate treatment.

The results of our study indicated that persistence of high-grade CIN after delivery is associated with persistent high-risk HPV infection. Persistent infection with high-risk HPV is a risk factor for cervical carcinogenesis. Pregnancy may promote HPV infection by reducing the immune activity [18]. In addition, high levels of sex hormones appear to be involved in cervical carcinogenesis; oestrogen has been linked to the stimulation of HPV gene expression, which can influence the cervical immune response and stimulate cell proliferation in the transformation zone [19,20]. Infection with high-risk HPV genotypes (types 16, 18, 31, 35, 45, 51, 52, and 56) is more prevalent in pregnant women than in non-pregnant women [21].

The management of CIN during pregnancy has changed from aggressive treatments like conization to a more conservative approach due to the low progression rate of CIN and the concerns for surgical complications during pregnancy [18,22]. Historically, women with high-grade CIN were treated by conization [23]. However, conization in pregnant women can affect perinatal outcomes of both the mother and fetus, because it can cause cervical stenosis (1–17%), preterm labor, and infertility (approximately 4%) by reducing the length of the cervix as a result of local immunologic reactions and fibrotic tissue changes [24]. In addition, immediate or delayed bleeding and spontaneous abortion have been reported up to 14% and 15–33% of women, respectively [25]. Therefore, conization during pregnancy should only be performed if there is a definite suspicion of malignancy [3,26]. Close observation without treatment is the widely accepted protocol for CIN management during pregnancy. Excisional procedures for persistent lesions may be recommended after 3 months postpartum [27]. Based on the high persistence rate (65%) of CIN 2+ and risk of invasive cancer observed during pregnancy in this study, adequate follow-up and proper management are recommended during both the pregnancy and postpartum periods. Because persistent high-risk HPV infection is a major risk factor for persistent high-grade CIN, HPV testing is advantageous to predict prognosis. Conservative management of CIN2–3 during pregnancy is acceptable, but close follow-up with HPV testing, and postpartum colposcopy evaluation are necessary.

Conflict of interest

The authors declare that they have no conflict of interest.

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