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Role of cervical cancer screening during prenatal checkups for infectious diseases: A retrospective, descriptive study

Yasuyo Maruyama[1], Akiko Sukegawa[1,2], Hiromi Yoshida[3], Yukiha Iwaizumi[1], Sayako Nakagawa[1], Tamina Kino[1], Yukio Suzuki[2,4], Kazumi Kubota[5], Tomoo Hirabuki[1], Taichi Mizushima[2] and Etsuko Miyagi[2]

Abstract

Objective: This study was conducted to evaluate the status and role of cervical cytology affected by human papillomavirus infection and other infectious diseases screened during routine prenatal checkups.

Methods: We retrospectively examined medical records containing the screening results for infectious diseases and cervical cancer in women who delivered neonates in our hospital from 2014 to 2017.

Results: Among 3393 deliveries, 18.8% of women underwent a regular cervical cancer screening within 1 year of becoming pregnant, and 2641 women underwent a cervical cytology screening during this pregnancy. The cytological diagnostic results showed that 2562 women (97.0%) were negative for intraepithelial lesions or malignancy, whereas 79 (3.0%) had abnormal results. Of those with abnormal cytology results, 70 had abnormal cytology that was newly detected in this

[1]Obstetrics and Gynecology, Odawara Municipal Hospital, Odawara, Kanagawa, Japan
[2]Department of Obstetrics and Gynecology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan
[3]Nursing Department, Odawara Municipal Hospital, 46 Kuno, Odawara, Kanagawa, Japan
[4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA
[5]Department of Biostatistics, Yokohama City University, Yokohama, Kanagawa, Japan

Corresponding author:
Etsuko Miyagi, Department of Obstetrics and Gynecology, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.
E-mail: emiyagi@yokohama-cu.ac.jp

pregnancy, and 42 had grade ≥1 cervical intraepithelial neoplasia lesions. Spatulas were the most frequently used cytological sampling instruments, followed by cotton swabs. Cervical cytology revealed no major adverse reactions during these pregnancies.

Conclusions: Our results confirm the importance of screening for infectious diseases during pregnancy. Only 20% of the women underwent a regular pre-pregnancy cervical cytology screening. Cervical cytology screening during pregnancy may currently be playing a crucial role in preventing cervical cancer in Japan.

Keywords

Pregnant women, cervical cytology, infectious disease, human papillomavirus, sampling instrument, screening, cervical cancer

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Introduction

Morbidity due to cervical cancer is expected to decrease through early detection by cervical cancer screening, and the human papillomavirus (HPV) vaccine should prevent HPV infection. In Japan, the HPV vaccine was included as a routine vaccination in 2013, and girls aged 11 to 16 years (sixth-year elementary school students through first-year high school students) can currently be vaccinated free of charge. However, the HPV vaccination has not been actively recommended since June 2013; thus, vaccination for HPV is uncommon. A cervical cancer screening program has been implemented in Japan since 1983 in accordance with the Geriatric Health Law. This screening involves a medical consultation, visual examination, cervical cytology, and pelvic examination once every 2 years for women aged ≥20 years.[1] In Japan, the current guideline for countermeasure-type cervical cancer screening is cervical cytology alone; HPV testing is performed only in a few municipalities and voluntary screening programs. The rate of cervical cancer screening consultation is low at approximately 40%.[2] Women often visit a gynecologist for the first time when they become pregnant. The directors of the Equal Employment Opportunity Division and the Maternal and Child Health Division of the Ministry of Health, Labour and Welfare issued a notification indicating that cervical cancer screening is "one of the standard tests in early pregnancy."[3]

Odawara Municipal Hospital is a regional perinatal maternal and child medical center in a residential area in the suburbs of a prefecture adjacent to Tokyo, Japan. Our hospital handles 700 to 800 deliveries yearly and accepts obstetric emergencies and women with high-risk pregnancies. This study was conducted to clarify the incidence of infectious diseases and the status of abnormal cervical cytology (ACC) detected during prenatal examinations in this hospital. We also aimed to determine the subsequent follow-up status, differences based on sampling instruments used for cervical cytology screening in pregnant women, and necessity of cervical cytology as part of prenatal examinations.

Patients and methods

The medical records of pregnant women who delivered neonates in Odawara Municipal Hospital from 1 January 2014 to 31 December 2017 were retrospectively examined. Women who had multiple

deliveries during this period were included. Among them, pregnant women who underwent cervical cytology examinations during their pregnancy were included. We do not perform cervical cytology screening during early pregnancy in women who underwent cervical cytology within 1 year prior to pregnancy. This time frame of $\leq$1 year before pregnancy is used because in Japan, where cervical cancer screening is recommended once every 2 years, if the cervical cytology screening is not performed within 1 year, approximately 1 year will pass after delivery. This will result in an interval of more than 2 years before the next cervical cytology examination. The cytology procedure is performed in the first trimester of pregnancy at our hospital or at a referral source clinic or hospital. The cytological diagnosis is determined based on the Bethesda system by a pathologist at a licensed laboratory affiliated with the office gynecologist or by a pathologist belonging to the hospital. In our hospital, spatulas are mainly used for collection instruments, whereas at referring medical institutions, cotton swabs are more common, although the instrument used is at the discretion of the collecting physician. Additionally, in our hospital, positivity above atypical squamous cells of undetermined significance (ASC-US) is defined as ACC. HPV testing is immediately performed in patients with positivity for ASC-US, and if the patient is HPV-positive (and thus deemed at high risk), colposcopy biopsy is performed. Colposcopy biopsy is also immediately performed in patients with positivity above a low-grade squamous intraepithelial lesion (LSIL).

In the present study, we surveyed the women's ages, number of deliveries, delivery outcomes, results of tests conducted during pregnancy, cervical cytology results, and sampling instruments. We traced the medical records of women with ACC until March 2020. Tests included those for hepatitis B virus, hepatitis C virus, syphilis, human T-cell leukemia virus type 1, toxoplasmosis, genitourinary *Chlamydia trachomatis*, gonorrhea, group B *Streptococcus*, and *Candida albicans*.

In the analysis of matches between the cytological results and histological diagnoses for each cytological sampling instrument, "matched" for cytology and histology was defined as cervical intraepithelial neoplasia grade 1 (CIN1) or lower for ASC-US, CIN1 for an LSIL, CIN2 or higher for a high-grade squamous intraepithelial lesion (HSIL), CIN2–3 for atypical squamous cells not excluding HSIL (ASC-H), and squamous cell carcinoma (SCC) for SCC. Other results were defined as "unmatched."

The chi-square test was used to analyze comparisons between two groups without unknown cases, including differences based on sampling instruments. IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) was used for the analysis. A P value of <0.05 for a two-tailed test was considered statistically significant. The ethics review board of Odawara Municipal Hospital approved this study (Approval No. 2018-1). After approval, an opt-out form was provided to all pregnant women, but none declined to participate. All patient information has been de-identified. This study complies with the STROBE guidelines.[4]

Results

There were 3393 deliveries among 3393 women during the study period. Of the 3393 women, 2641 (77.8%) underwent cervical cytology screening during pregnancy. We excluded 113 (3.3%) women with unknown cytological results (women in whom cervical cytology was not performed because of failure to receive antenatal checkups and women whose cervical cytology results could not be confirmed in the medical records) and 639 (18.8%) women who underwent cervical cytology examination

within 1 year prior to pregnancy (Figure 1). Of the 2641 women who underwent cervical cytology, 2562 (97%) were diagnosed as being negative for intraepithelial lesions or malignancy (NILM), and 79 (3.0%) had ACC results. Of these 79 women, 9 had abnormal pre-pregnancy cytology results: 4 had ASC-US, 3 had ASC-H, 1 had LSIL, and 1 had HSIL. Seventy patients had cytological abnormalities noted for the first time during this pregnancy, including 35 with ASC-US, 5 with ASC-H, 15 with LSIL, 14 with HSIL, and 1 with SCC.

Table 1 shows the characteristics of all women included in the study and their characteristics after being classified by their cervical cytological results. The median age of the 2641 women was 31 years (range, 15–47 years). We compared the backgrounds of the women in the NILM group (n = 2562, 97.0%) and ACC group (n = 79, 3.0%). The rate of induced artificial abortions was significantly higher in the ACC group than in the NILM group ($P < 0.001$).

Table 2 shows the overall results of the infectious disease tests that were recommended during pregnancy. The women were classified into the NILM and ACC groups. The overall frequencies of positive

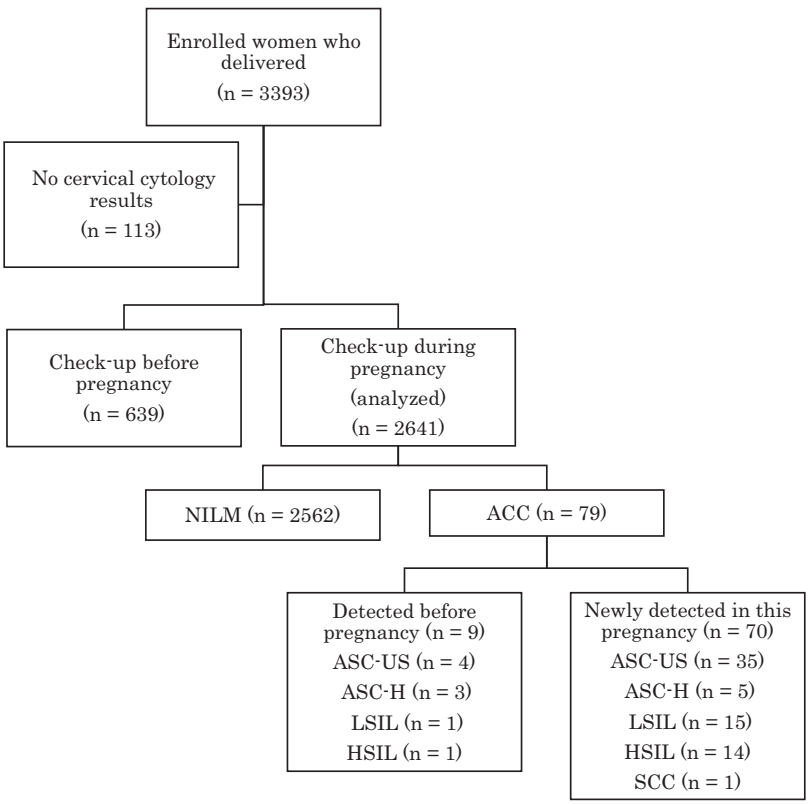

Figure 1. Study participants.
NILM, negative for intraepithelial lesions or malignancy; ACC, abnormal cervical cytology; ASC-US, atypical squamous cells of undetermined significance; LISL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells not excluding HSIL; SCC, squamous cell carcinoma.

Table 1. Participants' demographics.

Test item			Cervical cytology results				
	Overall (n) 2641	%	NILM group (n) 2562	% 97.0%	ACC group (n) 79	% 3.0%	P value
Age group, years							
15–19	58	2.2%	55	94.8%	3	5.2%	
20–24	285	10.8%	269	94.4%	16	5.6%	
25–29	649	24.6%	626	96.5%	23	3.5%	
30–34	888	33.6%	865	97.4%	23	2.6%	
35–39	588	22.3%	577	98.1%	11	1.9%	
40–44	167	6.3%	164	98.2%	3	1.8%	
45–49	6	0.2%	6	100.0%	0	0.0%	
Reproductive history							
Primiparous	1260	47.7%	1222	97.0%	38	3.0%	0.993
Multiparous	1381	52.3%	1340	97.0%	41	3.0%	
Smoking							
Yes	211	8.0%	202	95.7%	9	4.3%	0.232
No	2205	83.5%	2143	97.2%	62	2.8%	
Unknown	225	8.5%	217	96.4%	8	3.6%	
Body mass index*, kg/m^2							
<18	264	10.0%	253	95.8%	11	4.2%	
18–25	2001	75.8%	1944	97.2%	57	2.8%	
>25	374	14.2%	364	97.3%	10	2.7%	0.851
Unknown	2	0.1%	1	50.0%	1	50.0%	
Artificial abortion history							
Yes	385	14.6%	362	94.0%	23	6.0%	<0.001
No	1199	45.4%	1172	97.7%	27	2.3%	
Unknown	1057	40.0%	1028	97.3%	29	2.7%	

The chi-square test was used for all cases other than those with unknown survey items.
*Body mass index was compared based on being underweight or obese.
NILM, negative for intraepithelial lesions or malignancy; ACC, abnormal cervical cytology.

results for the other tests were as follows: 15 (0.6%) women had hepatitis B virus, 11 (0.4%) had hepatitis C virus, 6 (0.2%) had syphilis, 4 (0.2%) had human T-cell leukemia virus type 1, 45 (1.7%) had toxoplasmosis, 55 (2.0%) had *Chlamydia trachomatis*, 2 (0.1%) had gonorrhea, 403 (15.3%) had group B *Streptococcus*, and 424 (16.1%) had *Candida albicans*. The positive rate for *Chlamydia trachomatis* was significantly higher in the ACC group (n = 50, 6.3%) than in the NILM group (n = 5, 2.0%; P = 0.007).

Table 3 shows the outcomes of the 70 women diagnosed with newly detected ACC during pregnancy; 42 women (1.6%) had lesions classified as CIN1 or higher on histopathological examination. Two women were diagnosed with SCC and underwent cervical conization during pregnancy, followed by hysterectomies after delivery. Five women (7.2%) with CIN1 or higher discontinued hospital visits of their own accord from delivery to 6 months post-delivery. Two patients who were not diagnosed with CIN during

Table 2. Test results of infectious disease screening and cervical cytology during pregnancy.

	Overall		Cervical cytology results				
	n	%	NILM group (n)	%	ACC group (n)	%	P value
	2641		2562	97.0%	79	3.0%	
HBV							0.495
Negative	2626	99.4%	2547	97.0%	79	3.0%	
Positive	15	0.6%	15	100.0%	0	0.0%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
HCV‡							0.234
Negative	2630	99.6%	2552	97.0%	78	3.0%	
Positive	11	0.4%	10	90.9%	1	9.1%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
Syphilis							0.667
Negative	2635	99.8%	2556	97.0%	79	3.0%	
Positive	6	0.2%	6	100.0%	0	0.0%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
HTLV-1							0.725
Negative	2636	99.8%	2557	97.0%	79	3.0%	
Positive	4	0.2%	4	100.0%	0	0.0%	
Unknown	1	0.04%	1	100.0%	0	0.0%	
Toxoplasmosis							0.766
Negative	2548	96.5%	2472	97.0%	76	3.0%	
Positive	45	1.7%	44	97.8%	1	2.2%	
Unknown	48	1.8%	46	95.8%	2	4.2%	
Chlamydia							0.007
Negative	2572	97.4%	2499	97.2%	73	2.8%	
Positive	55	2.1%	50	90.9%	5	9.1%	
Unknown	14	0.5%	13	92.9%	1	7.1%	
Gonorrhea							0.799
Negative	2228	84.4%	2158	96.9%	70	3.1%	
Positive	2	0.1%	2	100.0%	0	0.0%	
Unknown	411	15.6%	402	97.8%	9	2.2%	
GBS							0.071
Negative	2180	82.5%	2112	96.9%	68	3.1%	
Positive	403	15.3%	397	98.5%	6	1.5%	
Unknown	58	2.2%	53	91.4%	5	8.6%	
Candida							0.556
Negative	2158	81.7%	2098	97.2%	60	2.8%	
Positive	424	16.1%	410	96.7%	14	3.3%	
Unknown	59	2.2%	54	91.5%	5	8.5%	

The chi-square test was used for all cases other than those with unknown results for cervical cytology and infectious diseases.

NILM, negative for intraepithelial lesions or malignancy; ACC, abnormal cervical cytology; HBV, hepatitis B virus; HCV, hepatitis C virus, HTLV-1, human T-cell leukemia virus type 1; GBS, group B *Streptococcus*.

Table 3. Outcomes of 70 women diagnosed with newly detected abnormal cervical cytology during pregnancy.

Cervical cytology results	n	HPV testing	n	Pathology results during pregnancy	n	Conization during pregnancy (n)	Discontinued hospital visits from delivery to 6 months postdelivery (n)	Developed dysplasia after delivery (n)	Operation after delivery
ASC-US	35	HPV-positive	16	Cervicitis	2		1		
				CIN1	8				
				CIN2	3			2 (CIN3, 3 months each)	2 (conization)
				No biopsy	3		1		
		HPV-negative	16	No biopsy	15			1 (CIN1, 16 months)	
				Cervicitis	1			1 (CIN3, 6 months)	1 (conization)
		HPV not tested	3	No colposcopy findings	1				
				Postpartum follow-up	2		2		
ASC-H	5			Cervicitis	1				1 (conization)
				CIN1	3				
				CIN3	1				
LSIL	15			Cervicitis	1				
				CIN1	8			1 (CIN2, 9 months)	
				CIN2	3				
				Cervicitis in early pregnancy SCC at 28 weeks' gestation	1	1			1 (hysterectomy)
				No biopsy	2		1		
HSIL	14			CIN1	4				
				CIN2	6			4 (CIN3, 4, 16, 21, and 31 months, respectively)	4 (conization)
				CIN3	4				3 (conization)
SCC	1			CIN3 in early pregnancy, SCC at 22 weeks' gestation	1	1			1 (hysterectomy)

Histological diagnosis: CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; SCC, squamous cell carcinoma.
Cytological diagnosis: ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells not excluding HSIL; SCC, squamous cell carcinoma.

pregnancy were diagnosed with CIN after delivery. For seven patients who were diagnosed with CIN during pregnancy, the CIN grade escalated after delivery. Thirteen patients required surgery after delivery. Of five patients diagnosed with CIN3 or carcinoma in situ during pregnancy, four underwent postpartum conization; the remaining patient did not because the dysplastic lesion disappeared after delivery. Eight patients who did not have CIN3 or higher during pregnancy were diagnosed with CIN3 at the postpartum follow-up and underwent cervical conization.

We investigated the sampling instruments used for cervical cytology. The most commonly used instrument was a spatula (n = 1775, 67.2%), followed by cotton swabs (n = 436, 16.5%). The instrument was unknown in 427 cases (16.2%). Other collection instruments included brushes (two cases) and a sponge (one case). No women required treatment for adverse events such as excessive bleeding. In the comparison of the frequencies of ACC results by sampling instrument, the ACC positivity rate was 3.4% for spatulas, 2.8% for cotton swabs, and 0.0% for brushes and sponges. The positivity rates did not significantly differ between spatulas and other sampling instruments.

We further assessed the 47 women with newly detected histological diagnoses during pregnancy and examined the concordance rate of cervical cytology and histological diagnosis based on the sampling instrument (Table 4). The concordance rate of cervical cytology and histological diagnosis was 67% for samples collected using a spatula and 60% for samples collected using a cotton swab. The concordance rate of cervical cytology and histological diagnosis by sampling instrument was higher for the spatula, but not significantly.

Discussion

In this study, we focused on the current status of cervical cancer screening for pregnant women who delivered neonates at Odawara Municipal Hospital. Although nearly all of the women should have undergone cervical cancer screening, only 18.8% underwent screening within 1 year before becoming pregnant. Consequently, almost 90% of the pregnant women in whom ACC was detected were newly diagnosed at their prenatal check-ups. Thirteen of the pregnant women with ACC required treatment before delivery and the postpartum period. Two women with histological

Table 4. Concordance rate between cervical cytology and histological diagnosis based on sampling instrument.

	Matched n (%)	Unmatched n (%)	Total	P value
Spatula	28 (66.7%)	14 (33.3%)	42	0.766
Cotton swab	3 (60.0%)	2 (40.0%)	5	
Total	31 (66.0%)	16 (34.0%)	47	

The participants included 47 women with an abnormal cytodiagnosis found during pregnancy. They were classified according to whether a cotton swab or spatula was used as the sampling instrument, and histological diagnosis was performed.

"Matched" for cytology and histology was defined as CIN1 or lower for ASC-US, CIN1 for LSIL, CIN2–3 for ASC-H, CIN2 or higher for HSIL, and SCC for SCC. All other findings were defined as "Unmatched."

CIN, cervical intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells not excluding HSIL; SCC, squamous cell carcinoma.

SCC underwent cervical conization during pregnancy. One was diagnosed with stage IB1 cervical cancer and underwent elective cesarean section at 32 weeks' gestation, followed by total hysterectomy 1 month later. The other woman was diagnosed with CIN3 based on a surgical specimen; the pregnancy was continued until the third trimester, and total hysterectomy was performed after vaginal delivery. The 11 women who underwent cervical conization after delivery comprised 3 women with a diagnosis of CIN3 during pregnancy and 8 women whose lesions had progressed to CIN3 at the postpartum follow-up. Our data showed the outcomes and clinical course during and after pregnancy in a population mostly comprising women who had not undergone pre-pregnancy cervical cancer screening.

Reports from various countries have shown that gynecological examinations during pregnancy present a good opportunity for cervical cancer screening. Countries such as Thailand,[5] Turkey,[6] the United Arab Emirates,[7] and India[8] lack screening programs for social or religious reasons and offer few opportunities for women to undergo cervical cytology screenings before pregnancy. However, countries with screening programs that offer high coverage tend not to conduct screenings during pregnancy. The National Health Service Cervical Screening Program in the United Kingdom of Great Britain and Northern Ireland does not recommend conducting Pap tests during pregnancy. This is because appropriate cervical cytological sampling is difficult during pregnancy and is associated with bleeding, and cervical cancer is not treated during pregnancy.[9] Thus, sampling during pregnancy is recommended in regions that lack screening programs and for women who have not undergone previous cervical cytology screening. For women with ACC results during pregnancy, some guidelines indicate that follow-up cervical cytology and a colposcopy examination after delivery are sufficient unless the findings suggest invasive cancer.[10,11] A national survey in Japan showed that 227 pregnant women had complications of malignant tumors[12]; 162 (71.4%) of these women had cervical cancer, and 92.0% were diagnosed via cervical cytology in early pregnancy. Two cases of pediatric lung cancer resulting from mother-to-infant transmission of uterine cervical cancer were recently reported, and these advanced cervical cancers were missed because of the negative results of their cervical cytology screening during pregnancy.[13] Therefore, we are conducting several studies focusing on cervical cancer screenings during pregnancy.

The percentage of women with ACC results in our study (3.0%) was equivalent between the primipara group (3.1%) and multipara group (3.0%) and was similar to the percentages in several other reports. In January 2021, a large-scale Japanese study in which 238,743 pregnant women underwent cervical cytology screening was performed, and the overall frequency of ACC results was 3.3%.[14] The 2015 Odawara Cervical Cancer Screening Program for women of reproductive age (20–49 years) showed that the rate of women with ACC results who required a detailed examination was 2.4%.[15] One report described the cervical cancer screening uptake rate and cytological abnormalities in the adolescent and young adult population.[16] The rate of cervical cancer screening was 15.1% in the 20- to 24-year age group, 36.6% in the 25- to 29-year age group, and 49.4% in the 30- to 34-year age group. The rate of ACC was 4.5% in participants in their 20s and 3.2% in those in their 30s. The rate of ACC was similar to that in our study, suggesting that the detection rate of abnormalities reflects the background of the population that has not undergone screening. Regarding the low rate of cervical cancer screening in Japan, one survey of attitudes toward cervical

cancer screening cited the following factors: lack of time, high cost, participants' belief that they are healthy and do not need screening, and lack of knowledge about screening.[17]

In this study, we revealed the postpartum courses of patients with ACC diagnosed during pregnancy. In 11% of patients with newly detected cytological abnormalities during this pregnancy, those in whom the lesions developed after delivery required surgery. The postpartum follow-up results showed the risk of underestimation during pregnancy. In total, 7.2% of women discontinued follow-up of their own accord from delivery to 6 months post-delivery, even when diagnosed with ACC as a result of the pregnancy. Therefore, providing an ongoing consultation environment and raising awareness among pregnant women and medical professionals are important.

The Japanese Guideline for Gynecological Practice 2020 states that "a systematic review of cervical cytological sampling instruments has indicated that using a spatula or brush is preferable, and using only a cotton swab is generally not recommended."[18] However, using a cotton swab, which is less invasive, for sampling in pregnant women is acceptable despite the disadvantage of having fewer cells available for sampling. A study in Japan surveyed the detection rates of endocervical cells using different sampling instruments in pregnant women, premenopausal non-pregnant women, and postmenopausal women.[19] For pregnant women, cotton swabs had the lowest results. Because the purpose of cervical cytology in pregnant women is early detection of intraepithelial lesions, selecting instruments that can reliably sample endocervical cells, such as a brush, is preferable. A clinical inquiry in the United States revealed no serious adverse reactions when a nylon brush was used for sampling in 1900 pregnant women.[20] A spatula collects more endocervical cells than does a cotton swab.[21] In this study, although samples were collected with a spatula from 67.2% of the women, no women required treatment for bleeding. No major adverse events were observed after cervical cytology using a spatula during pregnancy, and the rate of concordance with the histologic findings tended to be high. These results suggest that spatula collection is preferable to cotton swab collection.

This study had some limitations. First, it was a retrospective study. Therefore, the infectious disease screening items and cervical cytology collection protocols differed among the patients. Second, this study was performed at a single institution, and the target area was limited. However, the positivity rate of the cervical cytology results did not significantly differ from those of a large-scale study in Japan[14] that was thought to reflect the current situation in Japan. Third, many cervical cytology reports did not state the collection instruments used, and these cases were excluded.

In Japan, where less than 5% of women have been vaccinated for HPV,[22] the low cervical cancer screening rate presents a major hurdle for preventing cervical cancer. In this study, approximately 20% of women underwent a regular cervical cytology screening before pregnancy, and this rate is lower than the normal screening rate in Japan.[2] The rate of new cervical cytological abnormalities was 3.0%, and the rate of diagnosing CIN1 or higher was 1.6%. In some cases, surgery was required after delivery. Therefore, cervical cytology screening should still be performed during pregnancy, although the accuracy is lower than that during non-pregnancy. Additionally, women should be informed of the importance of regular screenings after delivery.

Conclusions

Our study confirmed the importance of screening for ACC during pregnancy. Cervical cytology at the time of pregnancy for both primipara and multipara women

will remain important in Japan until the screening rate and prevalence of HPV vaccination are improved.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of conflicting interests

The authors have no conflicts of interest to declare.

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Author contributions

YM and AS: provided the concepts for the discussion and contributed to the finalization of the manuscript. HY, YI, SN, and TK: contributed to the original draft preparation and data collection. YS, TM, and TH: designed and supervised the study. KK: contributed to the statistical analysis and review of the manuscript. EM: provided the concepts for the discussion and review of the manuscript.

ORCID iD

Yasuyo Maruyama https://orcid.org/0000-0001-8136-1016

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