THE JOURNAL OF
Obstetrics and Gynaecology Research
The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology

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Journal:	*The Journal of Obstetrics and Gynaecology Research*
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Yamazaki, Hiroyuki; Hokkaido University, Gynecology Mitamura, Takashi; Hokkaido University, Gynecology Ihira, Kei; Hokkaido University Endo, Daisuke; Hokkaido University, Gynecology Sakurai, Manami; Hokkaido University, Gynecology Konno, Yosuke; Hokkaido University, Gynecology Watari, Hidemichi; Hokkaido University, Gynecology
Keywords:	3.118 Cancer and Pregnancy < 3 Gynecologic Oncology, 3.122 HPV infection and CIN < 3 Gynecologic Oncology, 3.123 Cancer of the Cervix < 3 Gynecologic Oncology

Original article

The difficulty to diagnose cervical cancer developing in the perinatal period with the first-trimester cytology: A retrospective study

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Runnning title:
Perinatally developing cervical cancers

Abstract

Aim: Most Japanese pregnant women undergo a first-trimester cervical cytological screening because of the low rates of HPV vaccination and routine cytological screening for young women. We aimed to investigate obstetric and oncologic outcomes of perinatally diagnosed invasive cervical cancer (ICC) and whether cytological screening during pregnancy was useful for detecting ICC.

Methods: We retrospectively reviewed the clinical data on ICC diagnosed during pregnancy or within one year after delivery from 2010 to 2018 at Hokkaido University Hospital.

Results: We identified eighteen ICC patients, and the median follow-up period was 46.5 months. Among eight patients with NILM, the mean duration to reach ICC diagnosis was 10.7 months, seven had stage IB1 or worse, and one was dead. On the other hand, among ten women with abnormal cytology, the mean duration for diagnosis was 1.4 months, and six had stage IB1 or worse, and one was dead. In terms of the timing of the final diagnosis, eight were during pregnancy and ten in the postpartum periods. Among eight pregnant patients, three resulted in a preterm delivery (33, 34, and 35 gestational weeks), and four terminated their pregnancies. One decided to continue the pregnancy until the term period. We performed conization in one patient and hysterectomy in seven.

Conclusion: These results suggest that temporary cytological screening during the first trimester of pregnancy might not be useful, and Japanese clinicians should vigorously promote HPV vaccination for schoolgirls and routine cancer screening for women of reproductive age.

Keywords: Cancer screening; Cervical cancer; Cytology, Human papillomavirus; Pregnancy

INTRODUCTION

Malignant tumors that develop during pregnancy are among the leading causes of maternal death in developed countries where perinatal management is widely available [1-5]. The number of cases has increased worldwide as the age of pregnant women increased, and is recently about 1 case per 1,000 deliveries [1-2]. Breast is the most reported organ in which a malignant tumor develops during pregnancy in Europe and North America [4], and in South Korea [5]. However, in Japan, 71.4% of all malignant tumors during pregnancy are cervical cancer, excluding CIN3 (cervical intraepithelial neoplasia; CIN), and this morbidity is higher than that in ovarian cancer (7.0%) and breast cancer (6.6%) [3]. The current guidelines describe that the screening cytology during pregnancy plays a vital role in early detection for cervical cancers and recommend it [6-7]. In Japan, they estimated that almost all pregnant women undergo cervical cancer screening because Japanese women generally see a doctor when perceiving pregnancy, and 99.9% of birth are in hospitals or clinics [8]. Also, the standard screening procedure for cervical cancer is cytology alone in Japan. When they obtain a result of ASC-US, clinicians consider HPV-DNA tests, biopsies with colposcopy when >LSIL, and HPV typing tests when CIN1-2 by biopsies.

We retrospectively analyzed ICC cases perinatally diagnosed and discussed the effectiveness of the first-trimester cytological screening and how we could improve their outcomes.

METHODS

We reviewed medical records of patients with cervical cancer in Hokkaido University Hospital from January 2010 to May 2018, and eligible cases were those diagnosed and treated during pregnancy or within a year after delivery. We collected information concerning age, gestational weeks, the result of screening cytology, reasons for having an examination, time to diagnose, histological type, disease stage, tumor size, treatment, HPV types if available, and follow-up period. We regarded NILM as normal cytology and the other as abnormal results [9]. HPV tests were routinely performed to diagnose cervical neoplasms using the multiplex PCR method (PapiPlex) at the GeneticLab Co., Ltd. (Sapporo, Japan) [10]. We measured tumor size by magnetic resonance imaging (MRI) or pathologically in microscopic cases. We used Fisher's exact test to compare frequencies, and Welch's t-test to continuous variables analyzed by R version 4.0.2: A language and environment for statistical computing (R core team 2020). We obtained informed consent for participation from the subjects. If we could not obtain informed consent face to face, the candidates were allowed to opt-out at Hokkaido university hospital. The institutional review board approved this study's publication in December 2020 (#020-0275).

RESULTS

We diagnosed eighteen patients with ICC during the perinatal period. We show their clinical characteristics in Table 2. All patients underwent screening cytology in the first trimester, and the results were NILM in eight (44.4%) and positive in ten (55.6%), as shown in Table 3. The cytological screening showed 55.6% of the sensitivity for cervical cancer developing within two years, and that did not differ between the devices used for cytology sampling. Table 4 shows the patients with NILM tended to have more advanced disease and non-squamous histology. For the patients with NILM, we diagnosed seven (87.5%) as stage IB1 or worse, and the median maximum size of tumors was 30 mm (range 0-50). In the positive cytology group, six of ten (60%) had stage IB1 or worse, and the median tumor size was 10 mm (range 0-50), which did not reach statistical significance to those of the NILM group. Positive cytology hastened confirmation of diseases, resulting in significantly shorter periods from screening to diagnosis than that of the NILM group (median 1.4 vs. 10.7 months, p=0.033). In 15 patients receiving the HPV-DNA test, 14 (93.3%) showed positive results, of which 12 (80.0%) were type16 or 18. We showed each result of HPV in Table 3.

We showed obstetric and oncologic outcomes sorted by the periods of diagnosis in Table 4. Eight patients were pregnant, and we diagnosed ten patients within a year after delivery. The mean age was 32.1 years (range 27-37 years) during pregnancy and 35.9 years (range 31-41 years) after delivery. In the pregnant group, four (50.0%) decided to continue their pregnancies and had live births, in which one (12.5%) was term birth, three (37.5%) were preterm, and all underwent cesarean section because of their tumors. The others had to undergo artificial abortions for immediate treatments, and we finally performed hysterectomy in seven patients (87.5%) and conization in one patient to preserve fertility (12.5%). During the follow-up period of median 72 months (range 42-114 months), seven patients (87.5%) revealed no evidence of disease, and one (12.5%), who was the patients No.4 diagnosed at 12 weeks of gestation by screening cytology but already had a bulky tumor with lymph node metastasis, developed a recurrence to die of the disease. All (100%) had live births in the postpartum group, and 8 of them (80.0%) were the full term of vaginal delivery. Two (20.0%) were preterm twin deliveries, and we had performed an elective cesarean section. We performed a hysterectomy in seven patients, concurrent chemoradiotherapy in two patients, and conization in one patient, which resulted in the fertility spared in one (10.0%). During the follow-up period of median 43 months (range 20-98 months), nine patients (90.0%) revealed no evidence of disease. However, one patient (10.0%, patient No.12) with NILM at the first trimester had a recurrence to die of the disease in whom we found a bulky cervical tumor and lymph node swelling a month after delivery.

DISCUSSION

Japanese women are strongly encouraged to undergo cervical cytology during their pregnancy, but these results suggest that a temporary screening might not be useful for improving either obstetric or oncologic outcomes of ICC, and other types of efforts are needed. What to learn from the relapsing cases is the earlier diagnosis would improve their outcomes, which results from a proper biopsy, though oncologic outcomes in our study would not be inferior to those generally reported [11]. Patient No.6, one of the two relapsing cases, did not undergo a biopsy during pregnancy because of the negative cytology at the first trimester instead of detecting a polypoid lesion of the cervix at nine gestational weeks. The previous report suggested that abnormal cytology's accuracy during pregnancy was equal to that of non-pregnant women regardless of used devices, i.e., brush or swab [12]. However, during pregnancy, vaginal bleedings would not strongly make clinicians consider a biopsy, especially in the first trimester, because the symptom is common and usually not a serious cause. Embryonal implantation, cervical erosion, threatened premature labor, or abortion, endometrial polyps may cause bleedings. Four patients No.4, 5, 6, and 10 were observed without cytology or biopsy for more than one month, especially half a year in No.6, from the presentation of vaginal bleeding or polypoid lesion. Normal screening cytology relieves us to keep away from intensive inspection, though clinicians highlight the importance of a coloscopy guided biopsy for abnormal cytology, which means colposcopy alone is insufficient to distinguish premalignant from invasive lesions [7, 13]. In our study, four of ten who had positive cytology did not undergo biopsy, which resulted in their postpartum diagnosis. Clinicians should consider repeating a biopsy or at least cytology when genital bleeding continues or polypoid lesion is detected.

HPV testing is more sensitive, less harmful than cytology, and independent of the inspector’s device or skill and could encourage biopsy even with normal cytology. In our study, we could detect all lesions in the first trimester if we performed both cytology and HPV test. A systematic review showed the sensitivity of the HPV test alone for detecting >CIN2 is 96.1%, in which the sensitivity of cytology was 53.0% and highly variable between areas. However, HPV positive rate has a peak between age 20-30. The specificity for >CIN2 ranged 76.5-95.5%, which was relatively lower in studies, including more young populations [17]. Women who have positive HPV with normal cytology could be encouraged to undergo regular screenings during the pregnancy and after the delivery, contributing to rapid diagnosis in perinatal periods.

Though it is important to detect lesions on the first-trimester screening, patient No.17 already had an advanced disease when we diagnosed her in the first trimester. First-trimester screening might help early diagnosis,

as shown in Table 3 because tumor diameters tended smaller in the positive cytology group (median 10 mm vs. 30 mm, p=0.19). However, that could be too late to cure, also, without giving up a child. Pre-pregnant screenings would reduce newly diagnosed carcinomas during pregnancy. Japanese Ministry of Health, Labour, and Welfare already recommends every two-year cytology to those aged 20 and above [14]. However, the rate of receiving gynecologic screenings was 17.5%, 36.5%, 45.4%, 50.6% in 20-24, 25-29, 30-34, 35-39 years old women, respectively [15]. Also, the older age at first marriage and first childbirth, average 29.4 and 30.7 in 2017, respectively [16], may increase the number of cases developing ICC in the perinatal period.

Cervical cancer is one of the preventable malignant tumors. The World Health Organization announced we could eliminate cervical cancers by 90% coverage of HPV vaccination and 70% coverage of screening [18]. However, in Japan, the vaccination coverage dropped from 70% to less than 1% after 2013 when the Japanese ministry of health, labor, and welfare suspended the proactive recommendation because of adverse events reports, which are finally revealed to have little relation with vaccination. They predict additional 24,600-27,300 cervical cancer cases over the lifetime of cohorts born from 1994 to 2007, which is more than double the number of cases newly diagnosed in a year [19]. We did not investigate the vaccination history in this study because nobody was expected to be vaccinated at the appropriate age when the vaccines for cervical cancer were not used in Japan.

During pregnancy, patients developing ICC would be suffering from three types of loss: lives of themselves, present fetuses, and children in the future. Trachelectomy could be a curative treatment option without giving up present pregnancy or reproductive function, though nobody in this study chose it. Non-pregnant women would consider radical trachelectomy (RT) with pelvic lymph node dissection, and oncologic outcomes are acceptable in the limited conditions, which are tumor diameter < 2 cm, not neuroendocrine histology nor gastric type adenocarcinoma [20]. Previous studies reported the obstetric complications of women who underwent RT, the pregnancy rates were 36-74%, and the term birth rates were 24-55% [20-23]. Though several reports show the operative safety in a few cases [25-27], RT could not be a standard procedure for the time being. These facts show the difficulty of continuing the pregnancy and preserve fertility without curative deterioration.

This study has limitations from the retrospective and single-center research, but few government surveys in Japan result in no accurate information about how many cases are developing cervical cancers in their perinatal periods and treated. The epidemiological investigation also would encourage HPV vaccination and general cytology for schoolgirls.

In conclusion, first-trimester screening plays a vital role in detecting cervical neoplasms. However, to decrease the number of perinatally diagnosed ICC, we should immediately improve the coverage of HPV

vaccination and general cytological screening before pregnancy. Also, our study revealed HPV test with cytology could increase the screening sensitivity and encourage early diagnosis during pregnancy.

Acknowledgements:

The authors want to thank Dr. Tatsuya Kato, Dr. Mahito Takeda, Dr. Noriko Kobayashi, for useful discussions.

Disclosure

All the authors declare no conflict of interest.

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Tables

Table 1. Clinical characteristics of all patients

Table 2. The diagnostic process for each cytological result

SCC: Squamous cell carcinoma, SIL: Squamous intraepithelial lesion

Table 3. Comparison of characteristics between negative or positive result groups from screening cytology

*Statistically significant difference

Table 4. Outcomes of all patients

SCC:Squamous cell carcinoma, CT:Chemotherapy, CCRT:Concurrent chemoradiotherapy , NED:No evivence of disease, DOD:Dead of disease

† Before the pregnancy and delivery in which cervical cancer diagnosed

Age: median (range)	33.5 y.o. (27-41)
Parity: median (range)	0 (0-2)
Follow-up period : median (range)	46.5 months (21-114)
Histology	
SCC	9 (50.0%)
Adenocarcinoma	6 (33.3%)
(Mucinous)	(4)
(Endocervical)	(1)
(Endometrioid)	(1)
Adenosquamous carcinoma	3 (16.7%)
(Glassy cell)	(2)
Stage (FIGO 2008)	
IA1	4 (22.2%)
IA2	1 (5.6%)
IB1	7 (38.9%)
IB2	4 (22.2%)
IIIB	2 (11.1%)
Treatment	
Conization	2 (11.1%)
Hysterectomy	14 (77.8%)
(+adjuvantCT)	(2)
CCRT	2 (11.1%)

No	Age	First trimester screening	Stage (FIGO 2008)	Histology	Occasions for diagnosis	Months from screening to diagnosis	Maxium tumor diameter	HPV type	Devices used in screening
1	37	NILM	1A1	SCC	Annual general checkup	16.9	<1 mm	High-risk (non 16,18)	Spatula
2	33	NILM	1B1	Glassy cell	Cervical tumor detected at postpartum examination	11.2	7 mm	Not examined	Brush
3	41	NILM	1B1	Mucinous	Cervical tumor detected at postpartum examination	8.1	8 mm	16	Cotton swab
4	37	NILM	1B1	Mucinous	Cytology at 24 weeks, polipoid lesion was detected at 19 weeks on the admission of threatened premature delivery	5.6	25 mm	Not examined	Brush
5	30	NILM	1B2	Mucinous	Polypectomy at 18 weeks, genital bleeding from 13 weeks	2.4	44 mm	18	N/A
6	31	NILM	1B2	Glassy cell	Polipoid lesion spontaneously dropped, detected from 9 weeks on the admission of threatened premature delivery	10.3	45 mm	18	Brush
7	33	NILM	3B	SCC	Genital bleeding	15.5	50 mm	31	Spatula
8	33	NILM	3B	SCC	Lower abdominal pain	18.9	35 mm	16	N/A
9	34	ASC-US	1A2	SCC	Postpartum screening	7.7	3 mm	Not examined	Brush
10	41	ASC-H	1B1	SCC	Cervical tumor detected at postpartum examination, colposcopy without biopsy during pregnancy	8.1	10 mm	Negative	Cotton swab
11	39	ASC-H	1B1	SCC	Follow up for SIL	17.7	11 mm	16	Brush
12	37	ASC-H	1B2	SCC	Postpartum screening	7.7	41 mm	16	Brush
13	33	HSIL	1A1	SCC	First trimester screening	1.3	<1 mm	16	Brush
14	29	HSIL	1A1	SCC	First trimester screening	1.5	4 mm	16	Spatula
15	34	HSIL	1B1	Adenosquamous	First trimester screening	1.1	13 mm	18	Cotton swab
16	35	AGC	1A1	Endocervical	First trimester screening	0.7	4 mm	18	Brush
17	27	AGC	1B2	Endometrioid	First trimester screening	1.2	50 mm	18	N/A
18	32	AIS	1B1	Mucinous	First trimester screening	1.2	10 mm	16	N/A

SCC: Squamous cell carcinoma, SIL: Squamous intraepitherial lesion

	Results of first trimester screening		
	Negative(n=8)	Positive(n=10)	
Diagnosed period			p=0.19
During pregnancy	2	6	
Postpartum	6	4	
Stage			p=0.31
1A1+1A2	1	4	
≥1B1	7	6	
Histlogy			p=0.64
SCC	3	6	
non-SCC	5	4	
Months from screening to diagnosis			p=0.03*
median	10.7	1.4	
range, SD	2.4-18.9, 5.7	0.6-17.7, 5.5	
Tumor size (mm)			p=0.19
median	30	10	
range, SD	0-50, 19.6	0-50, 16.9	
HPV types			p=0.14
16/18	4	8	
Other high risk	2	0	
Not detected	0	1	
Not examined	2	1	
Treatments			p=0.41
Hysterectomy	5	9	
CCRT	2	0	
Connization	1	1	
Devices			p=0.76
Brush	2	5	
Spatula	2	1	
Cotton swab	1	2	
N/A	2	2	

*Statistically significant difference

No	Age	Parity†	Gestational age at diagnosis	Periods after delivery to diagnosis	Stage (FIGO 2008)	Histology	Obstetric outcome	Treatment	Oncologic outcome	Follow-up period (months)
13	33	0	7 weeks		IA1	SCC	Induced abortion at 7weeks	Conization	NED	114
18	32	2	10 weeks		IB1	Mucinous	Moderate to late preterm delivery at 35weeks	Hysterectomy	NED	113
14	29	1	12 weeks		IA1	SCC	Early term delivery at 37weeks	Hysterectomy	NED	94
17	27	1	12 weeks		IB2	Endometrioid	Induced abortion at 15weeks	Hysterectomy + adjuvant CT	DOD	42
16	35	0	13 weeks		IA1	Endocervical	Moderate to late preterm delivery at 34weeks	Hysterectomy	NED	18
15	34	0	14 weeks		IB1	Adenosquamous	Induced abortion at 21weeks	Hysterectomy	NED	50
5	30	0	19 weeks		IB2	Mucinous	Induced abortion at 21weeks	Hysterectomy	NED	112
4	37	0	28 weeks		IB1	Mucinous	Moderate to late preterm delivery at 33weeks	Hysterectomy	NED	46
10	41	2		1 month	IB1	SCC	Moderate to late preterm delivery at 36weeks (twin)	Hysterectomy	NED	41
2	33	0		1 month	IB1	Glassy cell	Full term delivery at 38weeks	Hysterectomy	NED	24
3	41	2		1 month	IB1	Mucinous	Full term delivery	Hysterectomy	NED	47
6	31	0		1 month	IB2	Glassy cell	Full term delivery	Hysterectomy	DOD	20
12	37	0		1 month	IB2	SCC	Full term delivery at 40weeks	Hysterectomy + adjuvant CT	NED	31
9	34	2		2 months	IA2	SCC	Early term delivery at 37weeks (twin)	Hysterectomy	NED	21
7	33	0		6 months	IIIB	SCC	Full term delivery at 39weeks	CCRT	NED	52
1	37	0		8 months	IA1	SCC	Full term delivery	Conization	NED	45
8	33	1		8 months	IIIB	SCC	Full term delivery	CCRT	NED	59
11	39	0		10 months	IB1	SCC	Full term delivery at 39weeks	Hysterectomy	NED	98

† Before the pregnancy and delivery in which cervical cancer diagnosed

SCC:Squamous cell carcinoma, CT:Chemotherapy, CCRT:Concurrent chemoradiotherapy , NED:No evivence of disease, DOD:Dead of disease