CERVICAL CYTOLOGY DURING PREGNANCY
——Comparison with non-pregnant women and management
of pregnant women with abnormal cytology——

YUTAKA MORIMURA, KEIYA FUJIMORI, SHU SOEDA,
TOSHIHIRO HASHIMOTO, YOSHIMASA TAKANO,
HIDEKAZU YAMADA, KAORU YANAGIDA
and AKIRA SATO

Department of Obstetrics and Gynecology, Fukushima Medical
University School of Medicine, Fukushima

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Abstract: To clarify the clinical significance of uterine cervical cytology during pregnancy, we analyzed the incidence of cervical cytology and its accuracy. Of the 1,593 pregnant women who underwent cervical cytology, the patients with abnormal cytology were followed up and performed histological confirmation on colposcopic biopsy specimen. An incidence of abnormal cytology and cervical neoplasm during pregnancy were 1.63% (26 cases) and 0.82% (13 cases), respectively. The incidence of abnormal cytology in the pregnant women was significantly higher than that (0.9%) in mass-screened, non-pregnant 214,375 women under the age of 45 years ($P < 0.001$). There was no significant difference of the incidence of cervical neoplasm between in the pregnant women and in mass-screened, non-pregnant women (0.82% vs. 0.46%). The accuracy of cervical cytology during pregnancy was 45.0% and this was not significantly different from that (27.6%) in the mass-screened, non-pregnant women.

Since, cervical screening cytology for uterine cervical cancer in the pregnant women as shown in this study, has an equal effectiveness to that in the mass-screened non-pregnant women, routine cervical cytology is highly recommended to performed during pregnancy. In addition, management of pregnant women with abnormal cytology was discussed in this article.

Key words: Uterine cervical neoplasm, Pregnant women, Cervical cytology, Retrospective analysis, Incidence and Accuracy
INTRODUCTION

Mass screening for uterine cervical cancer has been reported to be effective in early detection of uterine cervical cancer and its precursor lesions\(^1\)\(^{—}\)\(^4\). Although governmental screening for uterine cervical cancer started in 1982 in Japan, women aged under 30 are not included\(^5\). Furthermore, the rate of examination of young women is generally low\(^6\)\(^,\)\(^7\). Thus, most Japanese women of reproductive age do not undergo uterine cancer screening. Pregnant women often visit obstetricians and gynecologists, and these visits would be a good opportunity to perform uterine cancer screening. However, routine uterine cancer screening of pregnant women is not popular in Japan\(^8\).

We have been performing cervical cytology on all pregnant women who visit our hospital for obstetrical management. We analyzed the incidence of abnormal cytology and its accuracy of diagnosis in pregnant women and compared the data with those for non-symptomatic women who had undergone cancer screening. We discuss the significance of cancer screening for pregnant women in this article.

MATERIALS AND METHODS

Cases selected

From 1993 to 1999, 1,593 asymptotic women visited the Obstetrics and Gynecology Hospital of Fukushima Medical University for obstetrical management. They were examined by routine cervical cytology for cancer screening. Smear sampling was performed using a cotton swab. The smears were quickly fixed in 95% ethanol and stained by the Papanicolaou method.

During the period 1993–1999, 759, 761 patients underwent uterine cancer screening in Fukushima Prefecture. To compare the data with those for pregnant women, we analyzed the result of cervical cytology performed a total of 214,375 women with age under 45 years and child-bearing activity.

Cytological criteria

Cytological diagnosis was based on the following criteria of the Association of Japanese Obstetrician and Gynecologists\(^9\): Class I suggesting normal: Class II suggesting reactive change: Class IIIa suggesting mild or moderate dysplasia by smear mainly confined to superficial and intermediate squamous cells with mild nuclear atypia (Fig. 1): Class IIIb suggesting severe dysplasia by smear mainly confined to parabasal squamous cells with severe nuclear atypia (Fig. 2): Class IV suggesting carcinoma in situ (CIS) by smear contained a few undifferentiated malignant cells (Fig. 3): Class V suggesting microinvasive carcinoma (MIC) or frank invasive carcinoma (IC) by smear contained a lot of pleomorphic malignant cells (Fig. 4). Histologic diagnoses were based on the classification in the General Rules for
Treatment of Uterine Cervical Carcinoma\textsuperscript{10}).

Statistical analyses

The chi-squared method was used for comparison of incidences of abnormal cytology and cervical neoplasm. The accuracy of cervical cytological diagnosis in pregnant women and in non-pregnant women who had undergone screening was compared using Fisher's extract test. $P$-values less than 0.05 were considered significant.
Fig. 3. Smear from pregnant woman at 6th week of gestation suggesting carcinoma in situ (Class IV). Undifferentiated malignant cells contain uniform, round nuclei with coarse chromatin. (Papanicolaou stain, ×535)

Fig. 4. Smear from pregnant woman at 13th week of gestation suggesting frank invasive carcinoma (Class V). Malignant cells with various sized, bizarre nuclei aggregate in necrotic background. (Papanicolaou stain, ×535)

RESULTS

Cytology and histology in pregnant women

The ages of the patients ranged from 17 to 43 years (average age, 29.5 years). Cytological abnormalities were found in 26 (1.63%) of the 1,593 pregnant women, including 16 patients with class IIIa cytology, 10 patients with class IIIb cytology, 2 patients with class IV cytology and 2 patients with class V cytology. Colposcopical biopsies were not performed in 6 of 16 patients with class IIIa cytology because of a few numbers of atypical cells in smears and well-visualized normal transformation
zones in colposcopy. Colposcopical biopsies were performed in the other 10 patients with class IIIa cytology and the results of histological examinations showed cervicitis in 5 cases, mild dysplasia in 2 cases, moderate dysplasia in 1 case, severe dysplasia in 1 case and CIS in 1 case. Six patients with class IIIb cytology included one patient with moderate dysplasia, 2 patients with severe dysplasia and 3 patients with CIS. Two patients with class IV cytology showed CIS. Two patients with class V cytology were confirmed IC.

Table 1 shows the results of cytology and histology in the pregnant women. The diagnoses in 2 patients with class IIIa cytology and 2 patients with class IIIb cytology were underestimated, and the diagnoses in 5 patients with class IIIa cytology and one patient with class IIIb cytology were overestimated. All of diagnoses of patients with classes IV and V were accurate.

*Cytology and histology of non-pregnant women*

Of the 214,375 mass-screened women with age under 45 years in Fukushima Prefecture, there were 1,949 patients (0.909%) with abnormal cytology. These patients included 1,516 patients (0.71%) with class IIIa, 258 patients (0.12%) with class IIIb, 96 patients (0.04%) with class IV, 79 patients (0.04%) with class V cytology. Of the 1,516 cases of class IIIa cytology, 895 cases of reactive change, 259 cases of mild dysplasia, 163 cases of moderate dysplasia, 89 cases of severe dysplasia, 76 cases of CIS, 29 cases of MIC and 7 cases of IC were confirmed. Of the 258 cases of class IIIb cytology, 58 cases of reactive change, 11 case of mild dysplasia, 38 cases of moderate dysplasia, 54 cases of severe dysplasia, 60 cases of CIS, 34 cases of MIC and 3 cases of IC were confirmed. Of the 96 cases of class IV cytology, 15 cases of reactive change, no case of mild dysplasia, 6 cases of moderate dysplasia, 12 cases of severe dysplasia, 31 cases of CIS, 27 cases of MIC and 5 cases of IC were confirmed. Of the 79 cases of class V cytology, 10 cases of reactive change, 2 cases of mild dysplasia, 2 cases of moderate dysplasia, 8 cases of severe dysplasia, 27 cases of CIS, 23 cases of MIC and 7 cases of IC were confirmed (Table 2).

*Comparison between pregnant women and mass-screened, non-pregnant women*

Table 3 shows the incidences of abnormal cytology in the pregnant women and in the mass-screened, non-pregnant women. There were no significant differences between classes of abnormal cytology except for the class IIIb group. The percentage of total cytological abnormalities in the pregnant women was significantly higher than that in the mass-screened women ($P < 0.001$). Table 4 shows the incidences of uterine cervical carcinoma and its precursor lesions in the pregnant women and in the women who underwent screening. There was no significant inter-group difference between all lesions or between each type of lesions.

Table 5 shows the accuracy of diagnoses of cytology in the pregnant women and in the women who underwent screening. There was no significant inter-group difference between overall accuracy or between accuracy of each class. The rate of
### Table 1.
Cytologic diagnosis versus histology in pregnant women

<table>
<thead>
<tr>
<th>Class</th>
<th>Reactive change</th>
<th>Mild dysplasia</th>
<th>Moderate dysplasia</th>
<th>Severe dysplasia</th>
<th>Carcinoma in situ</th>
<th>Microinvasive carcinoma</th>
<th>Frank invasive carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>10</td>
<td>5 (50.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IIIb</td>
<td>5</td>
<td>0 (0%)</td>
<td>1 (20.0%)</td>
<td>1 (10.0%)</td>
<td>1 (10.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

### Table 2.
Cytologic diagnosis versus histology in mass-screened, non-pregnant women aged under 45

<table>
<thead>
<tr>
<th>Class</th>
<th>Reactive change</th>
<th>Mild dysplasia</th>
<th>Moderate dysplasia</th>
<th>Severe dysplasia</th>
<th>Carcinoma in situ</th>
<th>Microinvasive carcinoma</th>
<th>Frank invasive carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>1.55</td>
<td>82.5 (62.5%)</td>
<td>32 (23.1%)</td>
<td>29 (19.5%)</td>
<td>29 (19.5%)</td>
<td>7 (5.0%)</td>
<td>7 (5.0%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>28</td>
<td>85.0 (60.0%)</td>
<td>15 (42.9%)</td>
<td>12 (34.2%)</td>
<td>12 (34.2%)</td>
<td>3 (1.2%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>IV</td>
<td>1.95</td>
<td>39 (66.7%)</td>
<td>10 (17.2%)</td>
<td>5 (8.5%)</td>
<td>5 (8.5%)</td>
<td>2 (3.4%)</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>V</td>
<td>3.25</td>
<td>8 (25.6%)</td>
<td>6 (18.8%)</td>
<td>6 (18.8%)</td>
<td>6 (18.8%)</td>
<td>2 (6.3%)</td>
<td>2 (6.3%)</td>
</tr>
</tbody>
</table>

*Note: percentages in parentheses.*
Table 3. Comparison of the incidence of abnormal cytology between in pregnant women and in mass-screened women aged under 45

<table>
<thead>
<tr>
<th>Number of examined women</th>
<th>Pregnant women</th>
<th>Mass-screened women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIIa</td>
<td>10 (0.63%)</td>
<td>1,516 (0.71%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Class IIIb</td>
<td>6 (0.38%)</td>
<td>258 (0.12%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Class IV</td>
<td>2 (0.13%)</td>
<td>96 (0.04%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Class V</td>
<td>2 (0.13%)</td>
<td>79 (0.04%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total of abnormal cytology</td>
<td>26 (1.63%)</td>
<td>1,949 (0.909%)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4. Comparison of the incidence of cervical pre-cancer and cancer lesions between in pregnant women and in mass-screened women aged under 45

<table>
<thead>
<tr>
<th>Number of examined women</th>
<th>Pregnant women</th>
<th>Mass-screened women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dysplasia</td>
<td>2 (0.13%)</td>
<td>280 (0.13%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>2 (0.13%)</td>
<td>209 (0.10%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>3 (0.19%)</td>
<td>163 (0.08%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>4 (0.25%)</td>
<td>198 (0.09%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Microinvasive carcinoma</td>
<td>0 (0%)</td>
<td>108 (0.05%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Frank invasive carcinoma</td>
<td>2 (0.13%)</td>
<td>21 (0.01%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total</td>
<td>13 (0.82%)</td>
<td>979 (0.46%)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Table 5. Accuracy of cervical cytology in each class between pregnant women and mass-screened women

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pregnant</th>
<th>Screening</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIIa</td>
<td>over</td>
<td>5/10 (50.0%)</td>
<td>893/1,516 (58.9%)</td>
</tr>
<tr>
<td></td>
<td>adequate</td>
<td>3/10 (30.0%)</td>
<td>422/1,516 (27.8%)</td>
</tr>
<tr>
<td></td>
<td>under</td>
<td>2/10 (20.0%)</td>
<td>201/1,516 (13.3%)</td>
</tr>
<tr>
<td>Class IIIb</td>
<td>over</td>
<td>1/6 (16.7%)</td>
<td>107/238 (41.5%)</td>
</tr>
<tr>
<td></td>
<td>adequate</td>
<td>2/6 (33.3%)</td>
<td>54/258 (20.9%)</td>
</tr>
<tr>
<td></td>
<td>under</td>
<td>3/6 (50.0%)</td>
<td>97/258 (37.6%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>over</td>
<td>0/2 (0%)</td>
<td>33/96 (34.4%)</td>
</tr>
<tr>
<td></td>
<td>adequate</td>
<td>2/2 (100%)</td>
<td>31/96 (32.3%)</td>
</tr>
<tr>
<td></td>
<td>under</td>
<td>0/2 (0%)</td>
<td>32/96 (33.3%)</td>
</tr>
<tr>
<td>Class V</td>
<td>over</td>
<td>0/2 (0%)</td>
<td>49/79 (62.2%)</td>
</tr>
<tr>
<td></td>
<td>adequate</td>
<td>2/2 (100%)</td>
<td>30/79 (32.3%)</td>
</tr>
<tr>
<td></td>
<td>under</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>over</td>
<td>6/20 (30.0%)</td>
<td>1,082/1,949 (58.9%)</td>
</tr>
<tr>
<td></td>
<td>adequate</td>
<td>9/20 (45.0%)</td>
<td>537/1,949 (27.6%)</td>
</tr>
<tr>
<td></td>
<td>under</td>
<td>5/20 (25.0%)</td>
<td>330/1,949 (16.9%)</td>
</tr>
</tbody>
</table>
overestimated diagnosis in women who underwent screening was significantly higher than that in pregnant women \((P < 0.05)\).

**Management of pregnant women with abnormal cytology**

The management was performed as follows: All patients with mild and moderate dysplasia were followed, and postpartum smears have developed to normal. Three patients with severe dysplasia were followed, and the results of postpartum cytology showed class II or IIIa. Six patients with CIS were underwent conizations at 12th to 17th week of gestations. None of the patients who received conization during pregnancy had massive bleeding or obstetrical complications such as abortion, preterm labor or prolonged delivery. Of 2 patients with IC, one underwent artificial interruption and subsequently radical hysterectomy in the 16th week of pregnancy and the other in her first visit in the 26th week of pregnancy was diagnosed as frank invasive cancer. The latter patient underwent cesarean section and radical hysterectomy in the 3th week of pregnancy. The baby's weight was 2,000 g and reveals intact survival.

**DISCUSSION**

Many authors have reported that the frequency of CIN in pregnant women is equivalent to that of non-pregnant women\(^{11-14}\). The incidence of cervical neoplasm has been reported to be from 0.64 to 1.28%\(^{13,15-20}\), which is similar to the incidence of 0.82% in the present study. Ueki \textit{et al.} reported that the rates of cervical neoplasms in pregnant and non-pregnant women who had been screened in Osaka Prefecture, Japan were similar (0.35 vs. 0.25%)\(^{21}\). They compared results of examinations of pregnant women with those of mass screening of women of all ages. The comparison of incidences in the present study was made between pregnant women and screened women with age under 45 years and child-bearing activity. No difference was found. The effectiveness of detection of cervical neoplasm in pregnant women is equal to that of screening in non-pregnant women.

Routine examination of cytologic screening of pregnant women has become widespread in Western countries\(^{13,14,22-25}\). The incidence of abnormal cytology in pregnant women has been reported to be 0.8 to 3.5%\(^{12,18-21}\). The incidence of 1.63% in our series is similar to these previously reported incidences. There have only been a few studies in which the incidences of abnormal cytology in pregnant and that in mass-screened, non-pregnant were compared. Ueki \textit{et al.} reported that the rates of cervical neoplasms in pregnant women and women who underwent screening were similar (0.8% vs. 1.1%)\(^{21}\). These findings suggest that effectiveness for early detection of cervical neoplasms in pregnant women is the same as that in screening of non-pregnant women. In Japan, governmental uterine cancer screening limits to women aged over 30 years\(^8\). Furthermore, the rate of screening of women aged under 45 is lower than that of women aged over 50 years\(^{6,7}\). Thus, for young
women, cancer examinations should be conducted during pregnancy for early
detection of cervical cancer.

Many authors have reported that accuracy of cytology of pregnant women is as
high as 82 to 100%\(^{15,19,22-27}\). Lurrain & Gallup\(^{18}\) reported worse accuracy (63%),
similar to the accuracy rate in our study. However, since the diagnostic criteria
used for cytological and histological diagnoses in previous studies are different, it is
difficult to compare the accuracies of cytologic diagnosis. Several authors have
pointed out that a low level of accuracy in pregnant women might result in a high
rate of underestimation\(^{14,23,25}\). Possible reasons for underestimation are: 1) sam-
pling of only a small number of cells due to the fear of bleeding, 2) the increase
of secretion and cytolytic degeneration associated change with pregnancy, and 3)
histological overdiagnosis caused by pregnant reaction. On other hand, it has also
been reported that accuracies in pregnant women are equal to those in mass-
screened, non-pregnant women\(^{12,20,28,29}\). In the present study, there was no
significant difference of accuracy of cytological diagnosis between in pregnant
women and in mass-screened, non-pregnant women.

Management of patients with abnormal cytology in pregnancy is controversial.
Colposcopic examination is important for evaluation of patients with abnormal
cytology. Since the squamo-columnar junction becomes visible during pregnancy,
colposcopic examination can be facilitated. Many authors purposed there is no
specific colposcopic findings during pregnancy. Many colposcopists experienced no
severe complications in colposcopic examination for pregnant women\(^{18,21,29,31}\).
These findings suggest that colposcopic examination during pregnancy is useful for
detecting cervical neoplasms and for determining appropriate therapeutic proce-
dures.

Although cervical conization is an excellent method of histologic evaluation and
a therapeutic method for early cervical cancer and its precursor, this procedure
during pregnancy has associated some difficulties\(^{19}\). An increase in vascularity and
softening of the cervix occur in the second and third trimesters. These physiologi-
cal changes increase the risk of postoperative hemorrhage, premature onset of labor,
cervical incompetence and cervical rigidity. We think that cervical conization in
pregnant women should be performed before 17th week of gestation. In this series,
all the patients who underwent conization in first trimester of pregnancy had no
massive hemorrhage or obstetrical complications. They underwent normal vaginal
delivery and had no recurrence of disease. Due to above-mentioned difficulty,
conization should not be performed the second and third trimester\(^{19,22,26,30}\). Patients
with abnormal cytology that had been found in the second or third trimester
underwent conservative management during pregnancy and then postpartum coni-
zation were performed. Their lesions had not progressed in pregnancy. Many
authors have reported that pregnancy itself does not change cervical lesions\(^{18,23,31,32}\).
On the other hand, patients with frank invasive carcinoma during pregnancy should
be treated immediately and adequately\(^{33-38}\). Fetal maturation should be considerd.
In conclusion, cervical cytology during pregnancy has excellent accuracy and effectiveness for detection of cervical neoplasms. Visits to the obstetrician for pregnancy would be favorable opportunities for uterine cancer screening. We should understand the significance of cervical cytology for pregnant women and perform routinely.

REFERENCES

CERVICAL CYTOLOGY DURING PREGNANCY


