Arch Gynecol Obstet (2014) 289:1071–1077
DOI 10.1007/s00404-013-3076-5

GYNECOLOGIC ONCOLOGY

Clinical management of cervical intraepithelial neoplasia in pregnant and postpartum women

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Received: 4 July 2013 / Accepted: 24 October 2013 / Published online: 7 November 2013

Abstract
Objective To evaluate the clinical management of cervical intraepithelial neoplasia (CIN) and cervical microinvasive squamous cell carcinoma in pregnant and postpartum women.
Methods This prospective study enrolled 27,230 pregnant women undergoing routine gestational examinations between August 1, 2007 and July 31, 2010 in the Beijing Obstetrics and Gynecology Hospital, Capital Medical University. Colposcopy and cervical biopsy were performed for patients with abnormal Thin Prep® Papanicolaou test (TCT) results. Periodic colposcopy was performed every 8–12 weeks and cervical biopsy was performed if progression was suspected. Cervical cold knife conization was recommended to patients diagnosed with CINIII or microinvasive cervical carcinoma 6–12 weeks after delivery.
Results A total of 2,260 patients had abnormal TCT results (8.12 %). Colposcopy and cervical biopsy were performed for 369 patients. Fifteen patients had microinvasive squamous cell carcinoma, 116 patients had cervicitis, and the number of CIN patients with histological grades I, II, and III were 124, 49, and 65, respectively. Tumor progression during pregnancy was found in 253 patients (CINI or above). Prognosis varied depending on the highest grade of pathological diagnosis results during pregnancy or initial pathological diagnosis results performed 6–12 weeks after delivery by cervical biopsy under colposcopy. Treatment and follow-up were carried out according to diagnoses, state of progression, and reversion (if any).
Conclusion These findings underline a need for cervical lesion screening for all women during pregnancy, and colposcopy should be performed for pregnant women who have abnormal TCT results. Appropriate treatment and follow-up were recommended according to different diagnosis of CIN.

Keywords Pregnancy complication · Cervical intraepithelial neoplasia · Cervical carcinoma · Colposcopy · Clinical management · Treatment · Follow-up · Progression · Regression

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Introduction

Cervical cancer originates from cervical intraepithelial neoplasia (CIN), and the link between cervical cancer and human papillomavirus (HPV) infection is well established [1]. The World Health Organization ranks cervical cancer as the second most common cause of death in women worldwide. Worldwide incidence is currently set at

500,000 new cases every year, and mortality is set at 280,000 deaths per year [2]. Disease incidence has increased dramatically in women 35 years or younger, the proportion of women 35 years or younger accounting for all patients with cervical cancer has been from 3.4 % in the 1960s to 24.9 % in 2008 [3]. Moreover, the incidence of cervical cancer in pregnancy is estimated between 1.5/100,000 and 12/100,000 pregnancies. It is the most common malignancy detected during pregnancy [4, 5]. Of these, most patients (69–83 %) are diagnosed with cervical cancer at stage I [6]. Given that most CIN and stage I cervical cancers are asymptomatic, regular clinical screening is critical for detection of lesions at an early stage. During the last 50 years, screening programs based on conventional cytology have significantly reduced cervical cancer morbidity and mortality [7].

Studies investigating the medical management of cervical cancer during pregnancy are limited. Current diagnosis and management of cervical precancerous lesions in Western countries range from observation, cryotherapy, and/or conization. For the safety of pregnant women and fetuses, physicians are more reluctant to perform invasive procedures such as cryotherapy, loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) during pregnancy; endocervical curettage (ECC) for evaluation of invasion of the canal is not recommended during pregnancy. Most of research support conservative management for patients with CIN during pregnancy [8, 9].

In China, the cervical cancer cytological screening test is not widely employed during routine gestational examinations. There is lack of a standard medical strategy for cervical cancer screening that includes diagnosis, treatment, monitoring, and evaluation for pregnant and postpartum women. The objective of the current study was to evaluate the safety and feasibility of diagnosing and managing microinvasive cervical cancer and CIN during pregnancy in China, and ultimately to facilitate the establishment of a screening system. We tested the efficacy of this screening as part of a routine gestational examination to detect cervical precancerous lesions. We performed a prospective study with a large patient cohort using the Bethesda three-tier CIN classification system [10] for pregnant women examined in the outpatient obstetrics department at our hospital. Close clinical monitoring and follow-up examinations were performed for the patients diagnosed as CIN or cervical cancer at an early stage with biopsy under colposcopy. Procedures were carried out after delivery.

These findings underline a need for cervical lesion screening for all women during pregnancy, and colposcopy should be performed for pregnant women who have abnormal Thin Prep® Papanicolaou test (TCT) results. Appropriate treatment and follow-up were recommended according to different diagnosis of CIN.

Materials and methods

Patients

A total of 27,230 pregnant women underwent TCT screening enrolled in this prospective study were examined in the outpatient obstetrics clinic of the Beijing Obstetrics and Gynecology Hospital and Capital Medical University in Beijing, China, between August 1, 2007 and July 31, 2010. The quality of ThinPrep slides from 27,174 pregnant women was satisfactory. Of the 2,260 pregnant women with abnormal TCT results, 1,891 patients who voluntarily rejected biopsy under colposcopy could not be enrolled and followed up in our study. A total of 369 pregnant women underwent a first time colposcopy and cervical biopsy, 253 pregnant women diagnosed with CIN or cervical microinvasive squamous carcinoma by cervical biopsy under colposcopy were enrolled in our research, with 14 pregnant women lost to follow-up. The study was approved by the hospital Ethics Committee, and informed consent on all procedures was obtained from all patients prior to the examination. The patients underwent a routine gestational examination between 13 and 34 weeks gestation. Inclusion criteria for this study were women with uncomplicated pregnancies at 13–34 weeks gestation who agreed to continue pregnancy with the acknowledged diagnosis of cervical microinvasive squamous cell carcinoma at a histological grade of CINIII (invasion depth $\leq$3 mm, no lymph or blood vascular invasion) according to the American Society of Gynecologic Oncology. Exclusion criteria were the following: the patient had received a TCT within the last year, a history of miscarriage(s), pregnancy complications (placenta previa, vaginal bleeding) psychological disease, transplanted embryo, precious pregnancy, cervical lesions history within 1 year before pregnancy or not available for following up. Individual profiles were set up for each enrolled patient. Profiles included TCT screening results, colposcopy, and cervical pathological diagnosis. Based on the pathological diagnosis, patients were followed up every 8–12 weeks, and were provided with recommendations concerning delivery mode and timing. The follow-up examination after delivery was performed by the same gynecologist every 3 months until 1 year postpartum.

TCT screening

All patients underwent a routine gestational examination and TCT screening was carried out using a ThinPrep 2000 Processor (USA), an automated slide preparation unit that performs liquid-based cytology tests. The slides were examined by specialists with at least 10 years experience. The cervical cytological diagnostic criteria were adopted

from the Bethesda three-tier system [9]. Atypical squamous cells (ASCUS), possible high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC) were regarded as the abnormal TCT results. Patients with ASCUS underwent a second TCT 8 weeks later, and a postpartum TCT was recommended if the result was cervicitis. Colposcopy and cervical biopsy were performed if the second TCT confirmed ASCUS, ASC-H, LSIL, HSIL, or SCC, with the consent of the pregnant women.

Colposcopy

Colposcopy was performed by two attending physicians using a Leica MZ6 stereomicroscope (Leica Camera AG, Barnack, Germany). The physicians had at least 5 years experience with colposcopy examination, performing 500 procedures each year. A standard colposcopy protocol was adopted in the current study, including the acetic acid test and Lugol's iodine experiment [11]. The classification and initially diagnosis of abnormal colposcopy were described according to 2003 International Federation for Cervical Pathology and Colposcopy (IFCPC) terminology.

Cervical biopsy

Cervical biopsies of the most suspicious lesion under colposcopy were analyzed by two consultant pathologists, and 5 % of the total number of slides were reviewed and double checked every 3–6 months. The WHO classification of tumors pathology and genetic tumors of the breast and female genital organs was used for pathological diagnosis [12], and a cervical cancer clinical stage was assigned according to the criteria set by the International Federation of Gynecology and Obstetrics (FIGO) [13].

Statistical analyses

SPSS 11.5 software (SPSS Inc., USA) was used to perform statistical analysis. Continuous data were expressed as mean values ± SD. The categorical data were analyzed using the χ^2 test. P values <0.05 were considered statistically significant.

Results

TCT screening

A total of 27,230 pregnant women underwent TCT screening in the outpatient obstetric department of our hospital between August 1, 2007 and July 31, 2010. The average age was 29.8 ± 4.1 years, ranging between 17–49 years; and the gestational age was between 13–35.7 weeks. The quality of ThinPrep slides from 27,174 pregnant women was satisfactory, providing a satisfaction rate of 99.79 %. TCT abnormalities were detected in 2,260 women, with an incidence rate of 8.12 %; this included patients with SCC, HSIL, LSIL. LSIL in combination with atipical glandular cell (AGC), ASCUS-H, ASCUS, AGC and ASC in combination with AGC (see Table 1). Most of the pregnant women enrolled in our study suffered from slight vaginal bleeding secretion after TCT screening during pregnancy, and stopped itself in 24 h.

Detection rate of cervical lesions

A total of 369 pregnant women, including two with SCC, 121 with HSIL, 198 with ASCUS-H, and 48 with LSIL, underwent a first time colposcopy and cervical biopsy at the outpatient obstetrics department as part of initial gestational examination. The average gestational age was 16 ± 3 weeks, and satisfactory colposcopy images were obtained from 92.41 % (341/369) of the patients. Histological examination confirmed that there were 238 confirmed cases of CIN (65 confirmed cases of grade III, 49 of grade II, and 124 of grade I or CGIN I), 15 cases of cervical microinvasive squamous cell carcinoma, and 116 cases of cervicitis, respectively. Secondary cervical biopsies under colposcopy were conducted for the 253 patients with CIN diagnoses CINI or above. The average gestational age when the secondary biopsy was conducted was 27 ± 2 weeks, and satisfactory colposcopy images were obtained from 90.12 % (228/253) of the patients. In total, cervical biopsy of the most suspicious lesion was performed for 622 person-times, and 723 cervical tissue blocks (1–4 blocks/person-time) were obtained, with an average of 1.6 ± 0.6 cervical biopsies/person-time.

Of the 622 pregnant women who performed cervical biopsy under colposcopy, vaginal bleeding volume of 18 cases (2.89 %) was more than menstrual bleeding volume after cervical biopsy under colposcopy, including 7 cases after 24 weeks of pregnancy, 6 cases with cervical biopsy 2–3 blocks per times, 9 cases with pathological CINIII and above. Of the 18 pregnant women suffering vaginal bleeding, 8 cases successfully stopped vaginal bleeding by twice gauze packing, 10 cases suffered wound suture to hemostasis. The remaining pregnant women had slight vaginal bleeding that stopped by itself in 1–3 days, without obvious abdominal pain. All the pregnant women underwent colposcopy and cervical biopsy without any colposcopy and biopsy-related complications of infection, premature rupture of fetal membranes, abortion, premature delivery, within a week.

Table 1 Satisfactory TCT screening

GD	ASC		LSIL	HSIL	SCC	AGC			Total (no.)
	-US	-US-H				/	&ASC	&LSIL	
AB no. (%)	1,325 (4.876)	198 (0.729)	507 (1.866)	121 (0.445)	2 (0.007)	45 (0.166)	50 (0.018)	12 (0.004)	2,7174
N (no.)	24,914 (91.889)								

GD grade, *AB* abnormal, *N* normal, *No.* number

Table 2 Progression of patients diagnosed with CIN during pregnancy

Initial pathological diagnosis	Progression in pregnancy					
	CINI & CGIN I (no.)	CINII (no.)	CINIII (no.)	Invasive carcinoma at early stage (no.)	Progression rate (%)	Total (no.)
CINI & CGIN I	120	3	1	0	3.23	124
CINII	0	49	0	0	0	49
CINIII	0	0	63	2	3.08	65
Cervical microinvasive squamous carcinoma	0	0	0	15 (one progressed to Ia2)	6.67	15

Pathological conversion of CIN and cervical microinvasive squamous cell carcinoma during pregnancy

Fifteen patients were diagnosed with cervical microinvasive squamous cell carcinoma (invasion depth $\leq$3 mm) through a three-tiered screening test. One patient developed cervical invasive carcinoma stage Ia2 at gestational week 34, and a preterm cesarean section was conducted to terminate the pregnancy. The other 14 patients' conditions remained stable. The total CIN progression rate in pregnancy was 2.77 % (7/253) (see Table 2).

Prognosis and treatment of CIN and cervical microinvasive squamous carcinoma during pregnancy and postpartum

Of the 253 pregnant women diagnosed with CIN or cervical microinvasive squamous carcinoma, a total of 239 patients with CIN and microinvasive squamous carcinoma were followed up 6–12 weeks after delivery, and underwent cervical biopsy by colposcopy. 14 were lost to follow-up (5.53 %, 14/253); these included 11 patients initially diagnosed with CINI and 3 patients initially diagnosed with CINII. Cervical microinvasive squamous carcinoma was detected in 17 pregnant women, including two who were initially diagnosed with CINIII, the other 15 patients developed cervical microinvasive squamous cell carcinoma, or suspected minimal deviation adenocarcinoma (MDA), or were initially diagnosed with cervical microinvasive squamous carcinoma during the screening tests. These 17 patients were reviewed after delivery by colposcopy and a cervical biopsy test, and underwent CKC if necessary (Patients underwent CKC for further diagnosis and treatment of pregnant women diagnosed with CINIII or cervical microinvasive squamous carcinoma by colposcopy and a cervical biopsy 6–12 weeks after delivery) (see Table 3).

Table 3 Prognosis of patients diagnosed with CIN after delivery

The highest grade of pathological diagnosis during pregnancy	6–12 weeks after delivery		
	Progression	Stable	Reversion
SCC ($n = 17$)	0	12 (12/17)	5 (5/17)
CINI ($n = 113$)	10 (8.9 %)	44 (38.9 %)	59 (52.2 %)
CINII ($n = 46$)	4 (8.7 %)	15 (32.6 %)	27 (58.7 %)
CINIII ($n = 63$)	2 (3.2 %)	31 (49.2 %)	30 (47.6 %)

Discussion

Cervical cancer is the second most common cause of death for women worldwide, and the incidence of disease in young women of child-bearing age has increased markedly over the last 50 years. At present in China, TCT is the cost-effective method for CIN and early-stage cervical cancer screening and following up. The total price is about $20 per case. Owing to the state-medical insurance paying for part of the treatment cost, patients nearly bear the cost of $6. The price of TCT in The United States is about $9.75 per case. It is one of the cost-effective and small traumatic

screening methods, and has been widely applied to large-scale screening of cervical disease [14]. We conducted a prospective study on a large patient cohort of 27,230 pregnant women to test the efficacy of cervical cancer screening during routine gestational examinations at the obstetrics outpatient clinic of our hospital. The percentage of patients with abnormal TCT results was 8.12 % during pregnancy which concurred with previously published findings 7 % higher than the non-pregnant patients [15], may be caused by the effects on cytology of estrogen levels and the number of reproductive tract infective women increasing during pregnancy. Of these patients, 369 underwent additional screening with standard colposcopy and cervical biopsy procedures. We confirmed that 0.05 % of the patients had early-stage cervical cancer and 0.87 % had CIN. This incidence concurs with previously published findings in China and elsewhere [15–18]. Given our results, we recommend that TCT screening be performed at the first routine examination of pregnancy in patients who have not undergone a cervical cytological test within the last year.

None of patients with pathological CINI diagnoses developed cervical invasive squamous carcinoma during pregnancy or up until 12 weeks post-delivery. Only ten (8.9 %) of the patients progressed to CINII (7.1 %) or CINIII (1.8 %), 38.9 % remained stable, and 52.2 % of the patients reverted to cervicitis 6–12 weeks after delivery. In our previous study, we did not detect cervical squamous carcinoma in pregnant women that had twice ASCUS or LSIL TCT results were eventually diagnosed by colposcopy with cervicitis and CINI in both the first and second screenings during pregnancy [19]. We suggested that cervical biopsy might not be necessary for patients who had been diagnosed with cervicitis or CINI by colposcopy. Our current study confirms these results. These data also suggest that a thorough evaluation of a patient with ASCUS or LSIL should be conducted by a physician with vast colposcopy experience. In addition, we recommend that colposcopy and cervical biopsy be performed 12 weeks after delivery if the initial diagnosis was CINI or cervicitis during pregnancy.

None of the patients enrolled in this study that were diagnosed with CINII progressed to cervical invasive cancer during pregnancy. However, 8.7 % of these patients progressed to CINIII 6–12 weeks after delivery, 15 (32.6 %) patients remained stable, and 27 (58.7 %) patients reverted to CINI or below. Therefore, we recommend that patients initially diagnosed with CINII undergo cervical biopsy and pathological testing post-delivery to avoid a missed diagnosis during pregnancy. If colposcopy confirms CINII by pathological study, there is no need of follow-up with a colposcopy during a subsequent pregnancy, which concurs with Fader's previously report [20].

It is widely accepted that pregnancy can promote the progression of cervical cancer [21]. In addition, it has been reported that the risk of developing to cervical invasive cancer in pregnant patients with CINII or CINIII is 2- to 5-fold greater than that of normal cohorts [22]. During pregnancy, the blood supply and lymphatic circulation are flushed into the reproductive organs under the effects of estrogen and progesterone commencing at gestational week 10. This could be but one factor promoting the tumorigenesis, especially in combination with the robust growth of cervical squamous epithelium and endocervical glands, which might form papillary-like proliferations and result in decidualization. However, most studies concluded that pregnancy might not be a risk factor for the aggressive progression of CIN observed in pregnancy. Furthermore, most cervical lesions go into spontaneous remission or remain stable after delivery. Only 6–7 % patients progressed to an advanced stage [23].

There were 65 patients diagnosed with CINIII by cervical biopsy in our study; 2 (3.08 %) progressed to cervical cancer stage Ia1 during pregnancy. Of the 63 patients 6–12 weeks after delivery, 2 patients (3.2 %) progressed to cervical cancer stage Ia1, 31 patients (49.2 %) remained stable, and 30 patients (47.6 %) reverted to CINII or below. Therefore, the progression rate of CINIII in pregnancy was low, and some patients reverted to a less advanced grade [8], with the recommendation that they stay under close surveillance and follow-up with colposcopy every 8 weeks. A cervical biopsy might not be needed if there is no obvious alteration under colposcopy 6–12 weeks postpartum, unless an invasion is suspected. Appropriate management should be undertaken according to the pathological test results.

There were 15 patients diagnosed with suspected cervical cancer at early stage at the first gestational examination, and one patient developed cervical cancer stage Ia2, she underwent a premature caesarian section to terminate the pregnancy. CKC was performed on one patient with cervical squamous cancer at stage Ia2 diagnosed by final pathology 6–12 weeks postpaetum, 11 patients with cervical squamous carcinoma stage Ia1, and four patients with CINIII. Our findings suggest that the progression rate of cervical invasive squamous carcinoma at early stage is not high. However, these cancers may be unable to revert to a less advanced grade. For these patients, we recommended close surveillance and follow-up with colposcopy every 8 weeks. Again, a cervical biopsy might not be needed if there is no obvious progression under colposcopy 6–12 weeks post-delivery, unless progression is suspected.

Overall, the progression rate of CINIII was low, and some patients reverted to less advanced grade. For cervical

invasive squamous carcinoma, the progression rate was not high in the pregnant women, but the patient's conditions did not usually revert to a less advantaged grade.

In conclusion, colposcopy is essential and safe for pregnant women who have abnormal cytological examination results. A complete evaluation and cytological study should be conducted by physicians with abundant colposcopy experience. In 2012, the American Society of Colposcopy and Cervical Pathology (ASCCP) [24] published revised guidelines based on consensus; the society concluded that in pregnant women who had ASC variant or LSIL cytology diagnosis, colposcopy and subsequent management could be postponed until 6 weeks postpartum, as these abnormalities were likely to regress spontaneously with expectant management and unlikely to harbor occult invasive malignancy. There have been a lot of researches supporting these recommendations [20, 25]. In patients diagnosed with HSIL cytology during pregnancy, the ASCCP guidelines recommend [21, 24] that antepartum colposcopic assessment be performed by experienced clinicians who are familiar with pregnancy-induced cervical changes that may confound colposcopic impressions. Furthermore, if the impression is CINII/III or invasive cancer, cervical biopsies, and serial colposcopies during pregnancy are acceptable in this setting. It also has been reported [20] that patients should be evaluated initially by an experienced colposcopist for features suggestive of invasive disease; if none exist, most patients may avoid antepartum cervical biopsies and repeat evaluations during pregnancy, and may safely undergo expectant management until postpartum.

Our study suggested it may not be necessary to perform a cervical biopsy on patients with an initial diagnosis of CINI by colposcopy. A cervical biopsy under colposcopy should be conducted between gestation weeks 13 and 28 for patients with an initial diagnosis of CINII. There is no need of colposcopy follow-up for patients with a diagnosis of CINI or CINII until 6–12 weeks postpartum. We recommend close surveillance and follow-up by cervical biopsy under colposcopy for patients with a diagnosis of CINIII or suspect cervical cancer at stage Ia1. A second biopsy should be performed if progression is suspected. Pregnancy should be terminated once the progression is confirmed. Otherwise, disease management may be continued 6–12 weeks postpartum. Therefore, these findings underline a need for cervical lesion screening for all women during pregnancy.

Acknowledgments This study was supported by grants from the Beijing Municipal Science and Technology Commission.

Conflict of interest The authors declare that they have no conflict of interest.

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