Squamous intraepithelial lesion – microinvasive carcinoma of the cervix during pregnancy

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Summary

Objective: The objective of this work was to assess proper management of squamous intraepithelial lesion (SIL) and microinvasive carcinoma during and after pregnancy, to assess risks of punch biopsy and conization in pregnancy and to assess regression, persistence and risk of progression with low-grade (L) and high-grade (H) SIL.

Methods: We carried out a prospective study of 167 pregnant women from our colposcopic unit who were referred to us for abnormal cytological findings between 1997 and 2002. The diagnosis of precancerosis was verified in all of the women by punch biopsy, suspect microinvasive carcinoma needle or LETZ conization up to the 20th week of pregnancy. All women were followed-up during the pregnancy and 24 months after their deliveries.

Results: In 23 women with suspect early invasion we performed conization during the pregnancy (weeks 13-23). There were six cases (26.1%) of microinvasive carcinoma and 17 cases (73.9%) of HSIL. One pregnancy aborted two days after the conization. No other obstetrical complications were recorded and there were no premature deliveries.

Sixty-two women with HSIL were only followed-up during their pregnancy. We observed complete regression of HSIL during the study in 14 patients (22.6%), regression to LSIL in 17 patients (27.4%), persistence in 25 patients (40.3%) and progression to microcarcinoma in six cases (9.7%).

Eighty-two patients were followed up for LSIL. Complete regression of LSIL was observed during the study in 40 cases (48.8%), persistence in 24 cases (29.2%) and progression to HSIL in 18 cases (22.0%).

Conclusion: For LSIL and HSIL during pregnancy the above follow-up is a sufficient and safe protocol. Suspect microinvasive carcinoma should be treated by conization, which is a safe procedure until the 24th week of pregnancy.

Key words: Squamous intraepithelial lesion; Microcarcinoma; Pregnancy; Conization; Punch biopsy.

Introduction

Abnormal cytological findings can be obtained in 5% of pregnancies, which corresponds with the incidence in a normal population. In the Czech Republic, cytology is routinely performed in the first trimester of pregnancy. Abnormal cytological findings indicate that a colposcopy should be performed. The technique of a colposcopic examination during the first trimester is the same as in non-pregnant women, but due to pregnancy changes of the cervix, it becomes more difficult after the first trimester, and is especially difficult during the third trimester. Colposcopy during pregnancy affords the advantage of eliminating an unsatisfactory colposcopy examination because of the eversion of the transformation zone of the cervix. Punch biopsy can be used to enhance the precision of the diagnostics in case of a precancerous lesion. If one of the prebioptic methods indicate suspect microinvasion, it is desirable to perform an expert colposcopy. And in case of persisting suspect microinvasive carcinoma, it is desirable to perform conization up to the 24th week of pregnancy. Our study focused on histologically verified low-grade and high-grade squamous intraepithelial lesions and microinvasive carcinoma of the cervix during pregnancy and the management of these lesions during pregnancy and after the delivery. Our objective was to assess the risks of the follow-up protocol, to assess the occurrence (in %) of regression and progression of a low-grade lesion (LGL) and high grade lesion (HGL) after the delivery and to assess the degree of safety of the punch biopsy and conization techniques we employ in pregnant patients.

Materials and Methods

The prospective study we performed between 1997 and 2002 included 185 pregnant women with abnormal cytological and/or colposcopic findings who were referred to our colposcopic unit. In this group of women with abnormal findings of suspect cervical lesion we diagnosed 18 normal findings in which the precancerous lesions were not confirmed, and two invasive carcinoma findings. These women were subsequently excluded from our study which then finally covered 167 women. We have histologically confirmed LSIL (CIN I) in 82 women and HSIL (CIN II, CIN III) or microinvasive carcinoma (Stage IA1) in 85 women. In our study we included only patients up to the 20th week of pregnancy who signed an informed consent including their participation for a three-year follow-up study and biopsy. All patients underwent an expert colposcopy with the use of 3% acetic acid. Colposcopic findings were placed in one of the following categories: normal findings, low-grade lesion (LGL), high-grade lesion (HGL), suspect microinvasive carcinoma and suspect invasive carcinoma. Controled cytological examinations

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in our colposcopy unit were also performed in all patients, and the evaluations were done by the Bethesda nomenclature. Punch biopsy under colposcopy (one to three) was performed in all cases in which we expected LGL or HGL. Punch biopsy was performed without the application of local anesthesia, vasoconstrictive substance or coagulation and the patients were not hospitalized. Following the biopsy, a small vaginal packing was inserted which would be removed by the women four to six hours later. In case of suspect microinvasive carcinoma (from one of the diagnostic methods), conization was performed. The cone biopsies were performed under general anesthesia between the 13th and 23rd week of pregnancy. After disinfection and fixation of the cervix, a vicryl ligature was placed on the descendent branch of the uterine artery. An injection of 4 ml of terlipressine solution followed intracervically (localization clockwise in the numbers 3, 6, 9, 12). Three minutes later, a Lugol solution was applied to visualize the lesion, followed with laser (CO_2 laser -50W), needle conization or LETZ. The base of the cone was coagulated after the extirpation. Vaginal packing was then applied for 12 hours. An infusion consisting of 2g of $MgSO_4$ was applied intravenously during the procedure, and Mg lacticum was given for the remaining period of the hospitalization, which was on average of 5.1 days (4-7 days).

The follow-up protocol was the same for all women included in the study. This included colposcopic and cytological check-ups between the 22nd to 25th week of pregnancy (with women after conization, the first check-up consisted of only colposcopy without cytology), between the 32nd to 35th week of pregnancy, six weeks after their delivery and then every four months for a period of two years.

Results

High-grade SIL and microinvasive carcinoma: 85 patients with a median age of 28.2 (range between 20-37 years) having either HSIL or microinvasive carcinoma were diagnosed. Twenty-three patients underwent conization because of suspect microinvasive carcinoma. Sixty-two patients with HSIL were only followed-up after punch biopsy.

Twenty-three patients (27.1%) underwent conization between their 13th and 23rd week of pregnancy. Histopathological examination found six cases (26.1%) of microinvasive carcinoma and 17 cases (72.9%) of HSIL. Twelve cone biopsies (52.1%) had tumor-free margins (10 HSIL and 2 Stage IA1). No recurrence or persistence of precancerous lesions was detected two years after the delivery in these patients. Eleven biopsies (47.9%) (7 HSIL and 4 Stage IA1) had lesion involving the margins of the cone. Women with positive margins of the cone were followed-up during their pregnancy and four of them had normal colposcopy and cytology diagnosed six weeks after their deliveries and for the following two years. Six women were treated with repeated conization after the delivery (eight weeks to eight months). Histopathological findings in this group revealed one case of microinvasive carcinoma, four cases of HSIL and one case of LSIL. One woman with microinvasive carcinoma and CIS in the proximal margin disappeared from the follow-up and returned eight months after the delivery with cervical carcinoma Stage IB1 and concurrent breast cancer Stage III. In the final histology of the Wertheim operation, no positive lymphatic nodes (IB1, N0, M0) were detected in the carcinoma with invasion of 8 mm and 15 mm in the biggest diameter.

Only one pregnancy complication was observed after conization. A patient who had been hospitalized before for six weeks for retroplacentar hematoma had a spontaneous abortion two days after a LETZ biopsy in the 17th week of pregnancy. The histopathological finding was microinvasive carcinoma Stage IA1. All 22 women after conization delivered at term (37th to 41st week of pregnancy), two women (9.1%) delivered by caesarean section due to obstetrical indications, and the remaining 20 women (90.9%) delivered spontaneously without complications.

Sixty-two patients (72.9%) with HSIL confirmed by punch biopsy were followed-up during pregnancy. Fourteen patients' (22.6%) lesions regressed, eight patients (12.9%) had normal cytological and colposcopic findings up to one year after their delivery and then for another following year. Six patients' (9.7%) lesions regressed to LSIL and in the second year regressed to a normal finding. Nine patients' (14.5%) lesions regressed to LSIL and in the second year five were treated by conization (four cases with histology – CIN I, and one condymomatous lesion), four patients with LSIL did not wish to be further treated or continue with the follow-up after the period of the study. Thirty-nine patients (62.9%) were treated by conization after the delivery because of persisting HGL or progression of the lesion. The conizations were performed two weeks to 14 months after delivery depending on the findings and wishes of the patient. We indicated conization in six cases of suspect microinvasive carcinoma two to ten weeks after delivery. The histopathological findings consisted of five microinvasive carcinomas (Stage IA1) and one HSIL. In the remaining 33 cases, the decision was taken with regard to the patients' wishes (usually after the termination of breast feeding – 4 to 14 months after delivery). Histopathological examinations revealed eight cases of LSIL, 24 cases of HSIL (one patient had HSIL and adenocarcinoma in situ – AIS) and one case of microinvasive cancer Stage IA1. The summary results for the 62 women followed-up for HGL are shown in Table 1. In the course of the study, 14 women (22.6%) regressed to a normal finding and 17 women (27.4%) regressed to LSIL. In 25 women (40.3%) the findings remained unchanged. In the cases of six women, early invasive carcinoma (Stage IA1) was detected during conization (Table 1).

Table 1. — *HSIL - 62 cases followed during pregnancy, outcome after delivery and 24-month follow-up.*

Regression of the finding		
Normal finding	14 (22.6%)	
LSIL – follow-up	4 (6.4%)	31 (50%)
LSIL – conization	13 (21.0%)	
No regression of the finding		
HSIL + 1xAIS – conization	25 (40.3%)	31 (50%)
Mica - IA1 – conization	6 (9.7%)	

Microcarcinoma

In the group of women with follow-up, all deliveries took place at term: four delivered (6.5%) by cesarean section due to obstetrical reasons, one delivered (1.6%) by cesarean section due to Stage IA1 carcinoma, and 57 women (91.9%) delivered spontaneously.

Low-grade SIL: Eighty-two women with a histopathological diagnosis of LSIL with an average age of 26.4 years (range between 19-36 years) were followed-up during pregnancy. The patients were referred to us, on average, in the 15th week (range between the 9th - 20th week) of pregnancy. Regression in the first year after delivery was observed in 36 cases (43.9%). Thirty-six conizations (43.9%) were performed because of persistency or progression of the finding more than one year after delivery. Histopathological findings revealed LSIL in 19 cases, HSIL in 17 cases. In ten cases (12.2%) with persistent LGL, we respected the patients' wishes not to be treated by conization and to continue with the follow-up. In this group, three women got pregnant in the second year, two cases of LSIL regressed and the colposcopic and cytological findings were normal after the delivery, and in one case we performed conization after the delivery following an HSIL finding. In the cases of five women, the LGL finding persisted even after two years of follow-up. With two women, the LSIL finding regressed in the second year of the follow-up and the colposcopic and cytological findings were normal. The final results for 82 women followed-up for LGL in the course of the study are shown in Table 2. Forty women (48.8%) regressed to normal findings in the course of the study. The LGL finding persisted in the cases of 24 women (29.3%) and with 18 women (22%) the findings progressed to lesions HSIL. None of the women were diagnosed during the study for early invasison (Table 2).

Table 2. — *LSIL - 82 cases, outcome after delivery and 24-month follow-up.*

Group	Number of cases	%
Spontaneous regression - normal findings	40	(48.8%)
LSIL - persistent	24	(29.2%)
HSIL - progression	18	(22%)

Discussion

The follow-up of HSIL during pregnancy is a safe procedure in cases where colposcopy is performed by an expert colposcopist with a quality cytological background. We check patients every ten weeks - usually between the 12th and 14th, 22nd and 24th, and 32nd and 34th weeks of pregnancy. We have not found, in concordance with the available literature, any major complications after punch biopsies [1, 2]. The combination of expert colposcopy and cytology can be sufficient for the diagnosis of HGL, if both methods concur with each other. We reserve punch biopsy for cases of discord between colposcopy and cytology. The literature describes spontaneous regression of HSIL after delivery in 25%-33% of cases. In our study, 14 patients (22.6%) experienced complete regression, and in 17 patients, (27.4%) lesions regressed to LSIL up to two years after delivery. Other authors conclude that there is no difference in the regression rate of HSIL after spontaneous delivery or cesarean section [4, 5]. Because of the small number of cesarean sections in our group, it was highly difficult to obtain such data from our patients. In the group of 62 women with HG lesions that we followed-up on, only six patients (9.7%) progressed during their pregnancy and the post-delivery period, and during the subsequent conizations, we detected microinvasive carcinoma Stage IA1. Up to now, unfortunately, it has been impossible to predict which lesions would regress and which would persist or progress. Possibly immuno-histochemical or genetic parameters would help us in our predictions. According to current knowledge, regression or persistence/progression is due to the immune status and smoking preferences of women.

The most important topic of the management of suspect HG lesions in pregnancy is the recognition of microinvasion or invasion in lesions. Cytological and colposcopic diagnostics of microinvasion during pregnancy are very difficult, as our group also confirmed 23 conizations suspect for microinvasion of Stage IA while the histopathological examination confirmed the diagnosis in only six women (26.1%). Since colposcopy is difficult during pregnancy, an examination by two expert colposcopists is considered very important before conization is indicated. In order to properly estimate early invasion, it is necessary to remove the whole suspect lesion by conization rather than by punch biopsy, which is not considered satisfactory [3, 6]. Conization during pregnancy is more of a diagnostic than therapeutic procedure because we do not perform conization to the same extent as in non-pregnant patients. In pregnancy we always want to remove the most colposcopically suspected lesion. In our experience the least serious changes have been on the periphery of large lesions and we have usually detected a lower degree of precancerous lesions in the margins of conization. The literature reports residual SIL in 43-53% of cases [7-9]. In our cohort of 23 conizations during pregnancy 11 women (47.9%) had precancerous lesions reaching the margins of conization and residual findings were found after the deliveries of six women (26.1%). One woman (4.3%) failed to appear for the check-up after conization. Her findings progressed and 14 months after the conization she presented with invasive carcinoma Stage IB1 and breast carcinoma Stage III. In the cases of 12 women after conization with unaffected margins and four women whose precancerous lesion penetrated the border of the smear, we performed conization for therapeutic reasons and further follow-up did not confirm a precancerous lesion. The literature reports 5-15% blood loss following conization and a 25% chance of spontaneous abortion [7, 9, 10]. We did not observe any great blood loss after conization which would have required treatment. The only spontaneous abortion occurred in the case of the high-risk pregnancy. We assume that our method and technique described above is safe

between the 13th and 24th weeks. We recorded no increases in the rate of premature deliveries or cesarean sections. No premature delivery occurred in the group of patients after conization during pregnancy or in the follow-up group. This seemed to correspond with increasing the care for our patients. All our patients with HSIL were followed-up at the risk pregnancy clinic more often than normal women and we treated all vaginal infections in a timely fashion. In our study we had only one adenocarcinoma in situ with exocervical HSIL. Pre-adenocarcinoma in pregnancy is a very rare diagnosis.

Low-grade intraepithelial cervical lesions are the most common abnormal findings of the cervix. The combination of cytology and colposcopy is safe and sufficient for the follow-up. Progression of the lesion to invasive carcinoma is very unlikely during pregnancy. Progression takes many years; the literature describes only a 1% chance of progression during pregnancy [11]. Regression of LSIL is usually seen in more than 50% of women. We recorded regression in 48.8%. We found conservative management sufficient and we recommend at least two years of follow-up after delivery.

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