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Cervical dysplasia during pregnancy - Effects on oncological and psychological outcome: a case control study

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Summary

Pregnant patients with cervical intraepithelial neoplasia Grade 3 (CIN 3) are monitored in 8- to 12-weekly intervals unless invasive carcinoma is suspected. The aim of this case-control study was to evaluate differences in regression and healing rates as well as post-traumatic stress levels. *Materials and Methods:* Treatment and outcome were analysed retrospectively. Stress levels were measured using the standardized German version of the Impact of Event Scale-Revised (IES-R) questionnaire. *Results:* Spontaneous regression was seen in 26.9% of cases. Progression to invasive cancer was not detected. 88.2% of all pregnant and 88.3% of all non-pregnant women were regarded as healed. Stress level was not significantly higher in non-pregnant patients. *Conclusion:* Cervical dysplasia in pregnancy shows high spontaneous regression potential. Regression is associated with long-time healing of dysplasia. An observant approach in patients with CIN3 during pregnancy does not cause higher stress levels.

Key words: HSIL; CIN; Cervical dysplasia; Pregnancy; Post-traumatic stress levels.

Introduction

Cervical cancer is the third most common cancer diagnosis and the fourth leading cause of death in women worldwide, responsible for 9% (529,800) of all new cancer cases and 8% (275.100) of cancer deaths in women in 2008 [1]. Cervical cancer is the most common malignancy diagnosed in pregnancy [2, 3]. Cervical intraepithelial neoplasia (CIN) as a cancer precursor lesion has a ten-fold higher incidence than cervical cancer with a peak in women aged 25-29 years [4]. CIN is distinguished in three degrees of severity. Non-pregnant patients with CIN 3 are treated surgically by cervical conisation. Management guidelines for CIN 3 for pregnant patients recommend cytologic and colposcopic examinations every 8 to 12 weeks. Cervical conisation is only recommended when invasive carcinoma is suspected. In case of postpartum persistence CIN 3 is managed with loop electrosurgical excision like in non-pregnant women [5]. The data situation regarding conservative management in pregnant patients is still sparse and further evaluation regarding safety is needed. Furthermore there is no knowledge about psychological effects in women who are treated conservatively when a cancer precursor lesion is diagnosed in pregnancy. The purpose of this investigation was to perform a case control study of pregnant women with severe dysplasia and non-pregnant matched controls in order to compare postpartum regression, progression, and long-time healing rates. In addition this study furthermore assesses the emotional impact of the event and compares the emotional distress in pregnant and non-pregnant patients with CIN.

Materials and Methods

The authors performed a retrospective case control study of consecutively treated pregnant women with severe dysplasia, defined as cytologic high-grade squamous intraepithelial lesion (HSIL) and/or histologic CIN 3. Patients were treated during the time period from January 2000 to June 2011 in the Dysplasia Unit of the Ludwig-Maximilians-University of Munich. Control patients with severe dysplasia were matched for the year of diagnosis and date of birth ± four years. Regression of dysplasia was defined as a spontaneous improvement of high-grade dysplasia to < CIN 3 or a negative for intraepithelial lesion or malignancy (NILM) smear at the time of first postpartum control, progression as worsening CIN 3 to an invasive carcinoma. In order to evaluate long-time healing rates all patients were invited to the Dysplasia Unit for a follow-up pap smear and HPV screening at the time of study initiation. If a patient was not able or willing to attend, data was obtained from the attending gynecologist after written consent. Long-time healing was defined as a NILM smear. Cytology smears were classified according to the Munich nomenclature II and subsequently adapted to the Bethesda system (Table 1).

To calculate the time from the first abnormal pap smear to the diagnosis of severe dysplasia, cytology results were requested from the patient's attending gynecologist after written consent. Pregnant dysplasia patients were additionally given a questionnaire concerning obstetrical data (date of birth, delivery mode, birth weight, and complications during pregnancy).

To evaluate the subjective psychological distress caused by the

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Table 1. — *Comparison of Bethesda classification and Munich nomenclature II.*

Bethesda classification	Munich nomenclature II
Negative for intraepithelial lesions and malignancy (NILM)	Pap I, Pap II
Atypical squamous cells of undetermined significance (ASC-US)	Pap IIw
Atypical squamous cells – cannot exclude HSIL (ASC-H)/ Atypical glandular cells not otherwise specified (AGC-NOS)	Pap III
Low grade squamous intraepithelial lesion (LSIL)/ High grade squamous intraepithelial lesion (HSIL)	Pap IIID
High grade squamous intraepithelial lesion (HSIL)	Pap IVa, Pap IVb

traumatising event of the diagnosis, all patients were asked to complete the Impact of Event Scale-Revised (IES-R) questionnaire [3] in a German adapted version [6].

The questionnaire is composed of 22 questions and determines the actual stress caused by an extreme event, enabling the objective comparison of different levels of stress. The patients were asked to select one out of four possible answers for each question. The answer "not at all" was counted with 0, "a little bit" with 1, "moderately" with 3, and "frequently" with 5 points.

The questions are divided into three subscales: Intrusion, Avoidance and Hyperarousal in which the values of the given answers are simply summarized. The suspected diagnosis of posttraumatic stress disorder is calculated as followed: X = (-0.02 * Intrusion) + (0.07 * Avoidance) + (0.15 * Hyperarousal) – 4.36. When X > 0 the suspicion of a post-traumatic stress disorder can be raised. The minimum possible value for X is -5.06 and the maximum value 3.69.

All women participating in the case control study signed a written informed consent form. Protocols were approved by the local ethical review board of the Ludwig-Maximilians-University.

For patient demographics, risk factors, progression parameters, and the evaluation of the questionnaire descriptive statistics were used. Metrical normally distributed variables are represented as mean ± standard deviation, non-normally distributed ones are depicted as median (quartile 1; quartile 3). $P < 0.05$ was considered statistically significant, the confidence interval was defined as 95%. In order to compare metrical variables of two independent groups, the Mann-Whitney U-Test was performed, in case of a normal distribution the *t*-test was applied. The chi-square test was used to assess statistical differences between the two groups concerning given answers in the IES-R questionnaire. All statistical tests were performed using SPSS version 19.

Results

One hundred thirteen pregnant patients with CIN 3 or HSIL cytology were identified, of whom 52 were participated. 104 non-pregnant patients were eligible for the control group, matched by year of diagnosis of severe dysplasia and date of birth ± four years. 44 women in the control group took part in the study. The median patient age of both groups was 32 years (29-35). There was no difference regarding the risk factors tobacco use and duration of intake of contraceptives between the two groups (data not shown). In the case group the initial diagnosis of dysplasia was in 42.3% before pregnancy and in 57.7% during pregnancy, whereas 70% (n=21) were diagnosed within the first trimester and 30% (n=9) in the second one. There was no initial diagnosis in the last trimester.

Table 2. — *Pap smear and histology results at time of initial diagnosis.*

Group	Pap smear				
	ASC-US/ ASC-H	ASC-H/ ASC-NOS	LSIL/ HSIL	HSIL	Summary
Case					
Histology					
CIN1	0	0	1	0	1
CIN2	0	0	1	0	1
CIN3	0	0	2	5	7
No biopsy	2	4	15	22	43
Total	2	4	19	27	52
Control					
Histology					
CIN1	0	0	0	0	0
CIN2	0	0	0	1	1
CIN3	0	0	1	2	3
No biopsy	4	3	22	11	40
Total	4	3	23	14	44
Both					
Histology					
CIN1	0	0	1	0	1
CIN2	0	0	1	1	2
CIN3	0	0	3	7	10
No biopsy	6	7	37	33	83
Total	6	7	42	41	96

The initial diagnosis in both groups mainly occurred as an abnormal Pap smear. Most patients in both groups had an initial diagnosis of dysplasia in the course of a LSIL/HSIL or HSIL Pap smear (Table 2). In 40 pregnant patients (76.9%) severe dysplasia was diagnosed by biopsy, 12 women (23.1%) had cytological severe dysplasia. Almost all patients (n= 40, 90.9%) in the control group had a biopsy. HPV screening was performed in 98.1% of pregnant women and in 95.5% of controls, respectively; all tested participants were HPV high risk positive.

80.8% (n=42) in the pregnant group were managed by loop electrosurgical excision eight to ten weeks after delivery while in the control group a conisation was performed in every patient (n=44). One pregnant patient was lost to follow-up. There was no need for loop electrosurgical excision in nine patients of the pregnant group (17.3%) due to spontaneous regression. In these patients the diagnosis of regression was confirmed by biopsy in five cases, showing CIN 1 in two cases and a benign result in three cases, whereas the remaining four women had cytologic regression (NILM) with no biopsy performed. In five postpartum patients with loop conisation, regression

Table 3. — *Regression rates.*

Group	n	Spontaneous regression					No regression	
		NILM	Benign	CIN1	CIN2	Total	CIN3	total
Case								
Conisation	42	0	4	0	1	5	37	37
No conisation	9	4	3	2	0	9	0	0
Lost to follow-up	1							
Total	52	4	7	2	1	14	37	37
Control								
Conisation	44	0	1	0	0	1	43	43
No conisation	0	0	0	0	0	0	0	0
Total	44	0	1	0	0	1	43	43

Table 4. — *Healing rates.*

Group	NILM	ASC-US/ ASC-H	ASC-H/ ASC-NOS	LSIL/ HSIL	HSIL	Lost to follow-up
Case						
n	45	3	1	0	0	3
in %	88.2	6.7	2.2	0	0	6.7
Control						
n	38	3	1	1	0	1
in %	88.3	7.9	2.6	2.6		2.6

was seen in the cone specimen, showing CIN 2 in one case and a completely benign result in four cases (Table 3). Overall 14 women in the pregnant group turned out to have a spontaneous regression of high-grade dysplasia, 12 patients in the postpartum period, and two even antepartum. There was no statistical significant difference in the regression rates with regards to the mode of delivery (data not shown).

Only one patient in the control group showed spontaneous regression with a benign histology in the conisation specimen, while all of the remaining 43 women had a CIN 3 in the conisation specimen (Fisher's exact test: $p = 0.01$). There was no progression to invasive carcinoma within both groups.

After a median follow-up of 41.61 (22.67–98.14) months the healing rate, defined as a NILM Pap smear, was 88.2% in the case group. Four women still appeared to have an abnormal cytology result, with no patient showing LSIL or HSIL cytology. Three patients were lost to follow-up. Twelve of 14 patients with postpartum regression were healed of dysplasia and two remained with ASC-US/ASC-H Pap smear. The control group showed a healing rate of 88.3% after a median follow up of 36.39 (18.33–61.68) months. Five patients remained with an abnormal Pap smear, whereas no patient had HSIL cytology and only one patient showed LSIL/HSIL cytology. One control patient was lost to follow up (Table 4). Twenty-seven women of the case group had a current HPV test, of which 88.9% were high risk negative. 81.8% of the 33 tested women in the control group were HPV high risk negative. There was no significant difference between the two groups (Fisher's exact test: $p = 0.442$).

Table 5. — *Calculations of the posttraumatic stress disorder value.*

IES-R	Pregnant group N=46 Median (Quartiles)	Control group N=44 U Test	Statistics Mann-Whitney U-Test
Intrusion	1.0 (0.0; 7.75)	6.5 (0.0; 17.0)	$p = 0.016$*
Avoidance	3.0 (0.0; 10.0)	6.5 (0.0; 20.0)	$p = 0.047$*
Hyperarousal	0.0 (0.0; 5.0)	3.0 (0.0; 13.0)	$p = 0.039$*
Distress-value X	-4.1 (-4.4; -3.1)	-3.4 (-4.4; -1.7)	$p = 0.037$*
	Mean (±SD)		
	-3.6 ± 1.2	-2.8 ± 1.7	

*$p < 0.05$.

88.5% (46/52) of IES-R questionnaires sent out to the group of pregnant women were sent back completed; the control group returned 100% (44/44). Twenty-four women, 14 cases and ten controls, crossed out the questionnaire meaning that they were not stressed anymore. The following incidents were named as the primary endpoint of not feeling distressed by the dysplasia any longer: "After the first non-pathological pap smear" (cases: n=5/35.7%; controls: n=3/30%), "I never felt distressed by the incident" (cases: n=1/7,1%; controls: n=1/10%), and "After the cone biopsy" (cases: n=1/7.1%; controls: n=0). Seven cases (50%) and six controls (60%) crossed out the questionnaire but made no statement.

All three subscales showed statistically significant differences between the two compared groups. Intrusion in total showed significantly different answers (Mann-Whitney U-Test: $p = 0.016$), notably to the questions 3, 9, 14, and 20 (Chi²-Test q3: $p = 0.033$; q9: $p = 0.005$; q14: $p = 0.024$; q20: $p = 0.009$). The group of non-pregnant women compared to the group of pregnant women was less able to overcome the occurrence of high-grade dysplasia, with pictures popping into their minds, dreaming about it, and being reminded of it by other things. The subscale Avoidance also showed a significant difference between the two groups (Mann-Whitney U-Test: $p = 0.047$). The control group in particular tried not to talk or think about it, in comparison to the pregnant women (Chi²-Test q11: $p = 0.003$; q22: $p = 0.038$).

Controls showed higher values of Hyperarousal than cases (Mann-Whitney U-Test: $p = 0.039$). Particularly questions 19 and 21 ("Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a heart palpitations"; "I felt watchful and on-guard") display a significant difference between the groups (Chi²-Test q19: $p = 0.017$; q21: $p = 0.019$).

Calculations of the posttraumatic stress disorder value X show a total mean of -3.2 ± 1.5 and a median of -3.9 (-4.4; -2.4). Cases have a significantly different median compared to the controls (Mann-Whitney U-Test: $p = 0.037$) (Table

5). Six patients showed a posttraumatic stress disorder value of X > 0 (Cases: 1; Controls: 5). Calculated values were between 0.10 and 0.72. Except for one control, all women with elevated distress values were cured from cervical dysplasia until the end of data collection.

Discussion

In this retrospective case-control study, the authors analysed oncological safety in pregnant and non-pregnant patients with either cytologically or histologically proven high-grade dysplasia. The present data support the thesis that non-surgically management in pregnant patients is safe since no progression to cervical cancer occurred.

Several reasons justify a conservative approach in pregnant patients with CIN 3. First of all, surgical manipulation of the cervix can result in preterm contractions followed by premature birth. Higher rates of preterm birth after cervical conisation are well known even if surgery is performed in non-pregnant patients [7-10]. Secondly, existing data suggest a high spontaneous regression rate of cervical dysplasia in postpartum patients and progression rates to cervical cancer are low [11].

In this study 41 (78.8%) pregnant patients received a conisation eight to ten weeks after delivery showing regression in five patients. In nine women regression was confirmed by biopsy or cytology without a need for operation, showing a total regression rate in the pregnant group of 26.9%. Similar results were published in a prospective study for CIN 1 in pregnant and non-pregnant patients [12], as well as for patients with carcinoma in situ during pregnancy [13]. Other groups published even higher postpartum regression rates between 47.2% and 70.0% 6 to 12 weeks after delivery [12, 14-16]. Partially in these studies CIN 2 and 3 patients were evaluated together. Considering higher regression rates of CIN 2 lesions [17] could be part of the difference in overall higher regressions rates.

Long-time healing rates of dysplasia are high in both groups showing no differences between pregnant and non-pregnant patients. Even in patients with spontaneous regression, 12 out of 14 women show a regular smear result and two display only minor changes in their final cytological result. These results are further supported by a high elimination rate of high-risk HPV types in both groups (88.9% case group, 81.8% control groups). A negative high risk HPV test after conisation is a known test of cure [18] and generally regarded as evidence of successful treatment. The negative predictive value for a negative HPV test after a cone biopsy is between 92% [15] and 100% [19-23] and successful treatment usually leads to an elimination of the virus [24-27].

In anticipation of high emotional stress in pregnant patients diagnosed with CIN 3 and consecutive serial controls, the present authors were surprised that in this study the burden of dysplasia was not higher in the case group. Surprisingly there is even a higher number of patients with elevated post-traumatic stress values in the control group (n=5 control, n=1 case group). Still there are only 30.4% of the cases and 22.7% of the controls who denied an actual burden of dysplasia.

Limitations of the present study include its retrospective design and the numeric dimension of the study population. A high percentage of patients did not participate in the study (42% control group/ 46% pregnant group) mainly due to avoidance of recurrent emotional stressors, which could have biased the results as well. Since questionnaires were sometimes completed a long time after the initial diagnosis of severe dysplasia, results are difficult to interpret and probably do not reproduce the actual "real" stress after confrontation with the diagnosis in all cases.

The study confirms that an expectative management of high-grade cervical dysplasia in pregnancy is safe, as no progression to invasive cancer occurred. This is congruent with other data [12, 15, 28] and in accordance to official guidelines and recommendations [5].

Taking into account the high postpartum regression rates, a prolongation of the postpartum observation period could represent a reasonable option. Prospective data to answer this question is needed. The authors suggest histological confirmation in every postpartum patient before planning a conisation, since 12.2% of pregnant patients already showed regression in their conisation specimen. The exact mechanisms for higher postpartum regression rates are not entirely understood. There are different theories existing like the induction of viral activation in women already latently infected with HPV due to hormonal changes in pregnancy leading to cervical dysplasia which then regresses after pregnancy. Additionally an impaired immune system during pregnancy could be reactivated postpartum [29-31]. Concerning the influence of vaginal birth on regression rates, there are different opinions in the literature [32-34]. In the present study the authors could not detect a statistically significant relation between mode of delivery and regression rates.

Conclusion

The present study supports the expectant management of pregnant patients with dysplasia. It might even be considered to wait longer than 8 to 12 weeks postpartum before a loop electrosurgical excision procedure is performed. Since distress levels are low in general and surprisingly even lower in pregnant patients, a prolongation of the observational period seems to be feasible also from a psychological point of view. From the present authors' knowledge, these are the first published data of a long-time follow-up of severe dysplasia in pregnancy.

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