

Abnormal Cytology during Pregnancy – A Retrospective Analysis of Patients in a Dysplasia Clinic

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Abstract. *Background:* The incidence of abnormal cytological results in pregnant women is as much as 7%. Often there is need to advise pregnant women with an abnormal cervical cytology result and monitor them throughout pregnancy, without endangering the mother or child. *Patients and Methods:* We retrospectively analyzed all pregnant women with an abnormal cervical cytology or condyloma in our dysplasia clinic between 01/2008 and 12/2011. Classification of the cervical cytological results was performed according to the Munich II nomenclature and a biopsy was obtained from most patients. Groups were defined in order to assess regression, persistence and progression. Particular attention was paid to the mode of delivery and the postpartum consultation. *Results:* A total of 65 pregnant women were treated in the dysplasia clinic. The reason for referral was Pap IIID in 46.2%, Pap IVa in 40% and Pap III or Pap II with condyloma in 6.2% patients. Only one patient presented with a Pap IVb finding. The pregnancy was continued in all but one cases. Postpartum, a total of 40% of cases, were in remission. A partial remission occurred in 4.6%. Persistence of the abnormalities was observed in 26.2%. Progression was documented in 3% and 71.1% were able to have a vaginal delivery. A caesarean section was performed in 22.2%. A total of 4.4% suffered a miscarriage, which was not caused by the colposcopy. *Discussion:* The distinctive feature of the present study is the high number of follow-up examinations, which showed that even women with highly dysplastic changes in pregnancy, who are regularly monitored can be advised to continue pregnancy. Vaginal delivery is possible in most cases.

Human papilloma virus (HPV) infections are especially common in young women and occur in up to 25% of the 20-30 year age group (1). The incidence of dysplastic changes is about 100-times higher than the incidence of cervical cancer. High-grade dysplasia occurs in 1% of cases (2). The prevalence of abnormal cytological results in pregnant women is as much as 7% (3). Consequently, we are often presented with the challenge of having to advise a pregnant woman with an abnormal cervical cytology result and of monitoring it during pregnancy, without endangering the mother or the unborn child. The primary aim during the care of a pregnant patient should be the exclusion of the development of an invasive lesion in order to prolong the pregnancy up to the point of viability of the child. The Cervical Pathology and Colposcopy Committee (AGCPC), the Germany Society of Gynaecology and Obstetrics (DGGG) and the German Cancer Societies (DKG) recommend the following course of treatment: A Pap IIID result should be followed-up with cytology and colposcopy in three months. Careful cytological and colposcopic testing should be performed for a Pap III result, possibly with an HPV test; Colposcopy and a specific colposcopy-guided biopsy in the 16th to 20th week of pregnancy are recommended for Pap IVa; Biopsy should not be performed during early-pregnancy because of the increased risk of spontaneous miscarriage. Cervical curettage is not possible at any time during pregnancy; Conization is obsolete during pregnancy; the only exception is a very strong and clear finding of an invasive lesion (1, 4). The indication for conization and, in the presence of proven invasion, the termination of a pregnancy, is always an individual case decision which should be made by an interdisciplinary team consisting of the responsible gynaecologists, oncologists, neonatologists and possibly radio-oncologists. In the case of a proven higher-grade dysplasia, the pregnant patient is followed-up every 8-10 weeks with cytology and colposcopy. Presentation for the final assessment and clearance of the abnormality takes place six weeks postpartum. The American guidelines are comparable to those listed above (5, 6).

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In the present study, we evaluated data from the dysplasia clinic at the Tuebingen University Hospital for Women from pregnant patients with suspicious cervical cytology results who were under our care in the period between 2008-2011. A summary of cytological, colposcopic and histological results are presented.

Patients and Methods

We retrospectively analyzed data for all pregnant patients who presented at the dysplasia clinic at the Tuebingen University Hospital for Women with an abnormal cervical cytological result during the period between January 2008 and December 2011. Patients with condylomas during pregnancy, which led to presentation at the clinic, and in whom a Pap IIID or dysplasia was diagnosed with colposcopy and cytology were also included. The age of the patients and the week of pregnancy were recorded, as were the cytological and histological results at the first presentation, during the course of the pregnancy, the mode of delivery and the postpartum consultation, as well as any necessary treatment. Particular attention was paid to a possible remission or progression of findings, as well as to pregnancy progress. Classification of the cervical cytological results was performed according to the Munich II nomenclature: I: Normal cell profile, age-appropriate, including mild inflammatory and degenerative changes as well as bacterial cytolysis; II: Clear inflammatory changes to the squamous epithelium and endocervical columnar epithelium. Epithelial cell regeneration, immature metaplastic cells, more significant degenerative cell changes, para- and hyperkeratotic cells. Normal endometrial cells, also after the menopause. In addition, specific cell profiles such as follicular cervicitis. Cellular changes with intrauterine device, signs of HPV infection without significant nuclear changes. Signs of herpes or cytomegalovirus infection; IIID: mild to moderate cell dysplasia; IVA: severe cell dysplasia or carcinoma *in situ*; IVb: severe cell dysplasia or carcinoma *in situ*. Invasive carcinoma cannot be excluded; V: malignant tumour cells. The following groups were defined to assess the regression, persistence or progression: Remission: I: improvement of a Pap IIID/ cervical intraepithelial neoplasia I-II (CIN I-II) with inconspicuous histology and cytology; II: remission of a CIN II with inconspicuous histology and cytology after colposcopy and/or postpartum conisation; III: remission of an adenocarcinoma *in situ* is defined as inconspicuous cytology and inconspicuous histology after conization. Partial remission: IV: partial remission is considered as an improvement in the histological classification from CIN III to CIN I-II after conisation; persistence: V: CIN I-II also confirmed as CIN I-II postpartum; VI: CIN III, which was removed as CIN III in the conisation; VII: cervical cancer after surgery. Progression: VIII: progression of a CIN II to a CIN III; IX: progression of a CIN III to an early cervical cancer. All patients were examined in the dysplasia clinic of the Tuebingen University Hospital for Women using standardized colposcopy and cytology methods. A portio biopsy was taken if the colposcopy was abnormal, especially in the 16th to 20th week of pregnancy. Cervical curettage was not considered. Most patients were followed-up every 8-10 weeks with colposcopy and cytology and a repeat biopsy was only performed if the results deteriorated, in accordance with the guidelines. The final assessment was performed 6-8 weeks postpartum. Medical histories from gynaecologists for example, referring to the mode of delivery, were also included.

Results

Between 01/2008 and 12/2011, a total of 65 patients were treated in the dysplasia clinic at the Tuebingen University Hospital for Women because of an abnormal cervical cytology result and/or condylomas. The mean age at first presentation was 30.1 (± 4.7) years. The mean week of pregnancy at the first visit was 14.2 (± 6.3).

Cytology results at presentation. The reason for referral was a Pap IIID result in 30 (46.2%) patients, Pap IVa in 26 (40%) of the pregnant patients, and a Pap III result or Pap II with condyloma in four (6.2%) patients respectively. Only one patient (1.5%) presented with Pap IVb findings.

Histology at first presentation. Histology showed a cervical intraepithelial neoplasia grade I (CIN I) in four patients (6.2%), 8 (12.3%) of the pregnant patients had a grade II (CIN II) cervical intraepithelial neoplasia, 23 patients (35.4%) had a cervical intraepithelial neoplasia grade III result (CIN III) and one patient (1.5%) was found to have an adenocarcinoma *in situ* (ACIS). Cervical cancer was histologically-diagnosed in only one patient (1.5%). In addition, one condyloma was found (1.5%), and histology was found to be inconspicuous in 19 cases (29.2%). No histology was attained in eight patients (12.3%), either because the stage of pregnancy was too early, the transformation zone was not visible, or, in one case, because an abortion had been planned.

Course of pregnancy and delivery. Pregnancy was only terminated in one patient (1.5%) for medical reasons. This was only performed after the couple had received extensive interdisciplinary counselling. Advanced cervical cancer was diagnosed in this patient at her first presentation in the 16th week of pregnancy (pT2a (5 cm) G3 pN0 (0/28) M0, L1, V1, R0, G3). A Wertheim's procedure was performed with *sectio parva*. The pregnancy continued in all other patients (98.5%). Four patients (6.2%) decided to undergo a termination during early-pregnancy for personal reasons. No data on the birth was collected for three patients (4.6%), as postpartum follow-up did not take place. Thirteen patients (20%) were still pregnant at the time of data collection. Excluding the patients who decided to undergo a termination and those who were still pregnant, the pregnancy outcome was evaluated in 45 patients. Thirty-two patients (71.1%) were able to have a vaginal delivery; 28 (62.2%) were spontaneous, and four (8.9%) were vacuum-assisted deliveries. A Caesarean section was performed in 10 cases (22.2%). The indications for this were two cases of breech position in a primipara, one patient who was HIV-positive, two cases of failure to progress, in three cases a section was performed after an individual risk assessment, and the reason

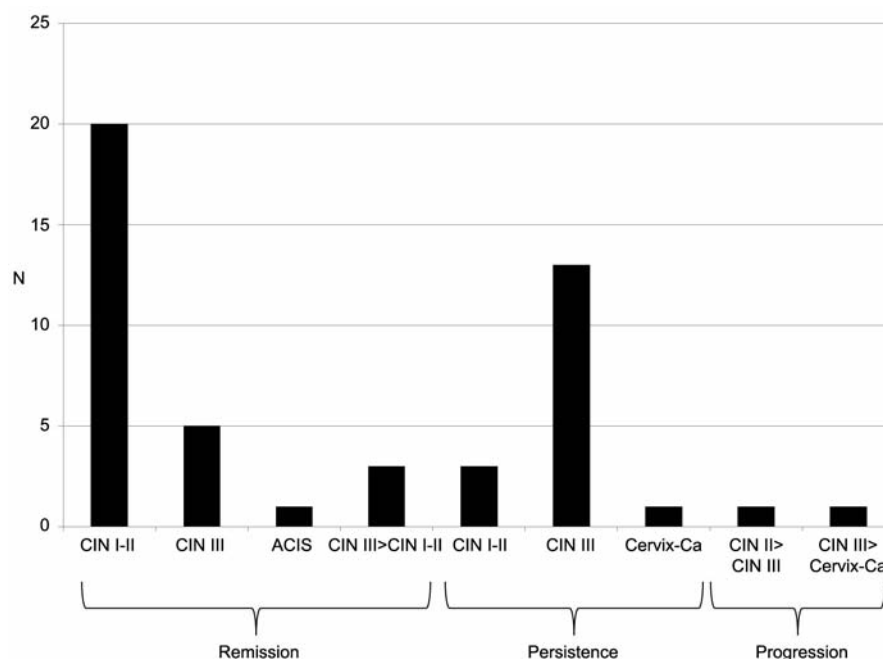


Figure 1. Remission/persistence and progression of dysplasia.

was not identified in one case. Two patients (4.4%) suffered a miscarriage which was not associated with the timing of the colposcopy, although these were twin pregnancies, which are associated with an increased risk of miscarriage *per se*.

Dysplasia progression (see Figure 1). Evaluation with regard to remission/persistence and progression postpartum showed that lesions in a total of 26 (40%) women were in remission, 20 patients (30.8%) had a remission from a mild-to-moderate grade dysplasia to an inconspicuous cytology and histology – this remission had already occurred during the pregnancy in 12 of these patients. There was even remission of a CIN III in five patients (7.7%) and remission of an ACIS in one pregnant patient (1.5%) shown by an inconspicuous cone histology result. A partial remission from CIN III to CIN I-II occurred in three patients (4.6%). Persistence of the findings was observed in 17 of the pregnant patients (26.2%). Three of these patients (4.6%) had a persisting CIN I-II, 13 (20%) had a persisting CIN III and one patient (1.5%) had cervical cancer. One patient (1.5%) was found to have progressed from a histologically-diagnosed CIN II to CIN III, and early cervical cancer (pT1a1 G2) was found after conization in another patient. It should be added that this patient's treatment was delayed because of repeatedly postponed postpartum follow-up appointments; therefore the conization could only be performed nine months postpartum. A total of 13 (20%) patients were still pregnant at the time of data collection, and no further data could be collected for four patients (6.2%).

Discussion

A pregnant woman with an abnormal cervical cytological result poses a great challenge for the gynaecologists responsibility for her care. On the one hand, it is necessary to preserve the life of the unborn child, and on the other hand, to also protect the health of the mother. Interventions such as tissue biopsy during early pregnancy, as well as conisation, should be avoided where possible (1, 4). Repeated biopsies should only be performed if the colposcopy findings worsen, and colposcopic and cytological follow-up should take place at a minimum of six weeks postpartum (5). Colposcopy and tissue biopsy appear to be the safest methods of assessing an abnormal cytological smear test during pregnancy (7). The aim of care of a pregnant patient with an abnormal cytological result is to continue the pregnancy and to exclude an invasive abnormality, so that it can first be eradicated after the pregnancy is complete. The option of conservative care of dysplastic changes during pregnancy has also been shown in other studies (8-10). A retrospective analysis by Yost *et al.*, which examined 153 women with CIN II and CIN III showed a high regression rate of 68% and 70%, respectively, and a persistence rate of 25% and 30%; 7% of the CIN II lesions tended to progress towards CIN III, but no patients developed a carcinoma (8). The concern with this study is that of the 269 patients in whom a CIN II or CIN III was diagnosed during pregnancy, 126 (47%) were lost in follow-

up. Therefore, no safe conclusions can be made regarding the progress, the pregnancy or the dysplasia. The retrospective study of 58 patients by Murta *et al.* also showed that high-grade cervical dysplasia during pregnancy can be conservatively managed throughout (9). Another retrospective analysis by Kaplan *et al.* showed a mostly stable course during pregnancy, where three women were diagnosed with a microinvasive carcinoma after a postpartum conization. The mode of delivery was not investigated in that study (10). The distinctive feature of the present study is the high number of follow-up examinations, which showed that women with dysplastic changes in pregnancy, who are monitored regularly can be advised to continue the pregnancy. It also showed a remission and partial remission rate of 43.1%; remission of severe dysplasia and an ACIS even occurred in 9.3% of cases. Persistence was observed in 26.2% of patients. Progression of CIN II to CIN III was seen in one patient (1.5%), which had no therapeutic consequences for the patient, as a CIN II result as well as a CIN III result can be treated with postpartum conization. No invasion occurred in this case. Progression of a CIN III to microinvasive cervical cancer was only observed in one patient. However, it should be noted that this patient refused postpartum follow-up for a long period of time and the conization was first performed nine months postpartum. Therefore this patient cannot be compared to an otherwise regular progression with clearance of the abnormality 6-8 weeks postpartum. Furthermore, it was shown that a vaginal delivery is possible in many cases (71.1%). The Caesarean sections mentioned were performed for other reasons, such as foetal breech position, secondary to labour progression, or after individual risk assessment unrelated to the dysplasia. Patient information and explanation is important for the care of pregnant women, as is a gynaecology-colposcopy link, especially postpartum. The management of a patient with histologically confirmed cervical cancer in pregnancy is a further therapeutic challenge. In the present study, in this patient with a pT2a G3 tumour, the lesion was advanced cervical cancer in a very early week of pregnancy. After the couple had undergone detailed counselling, a Wertheim's procedure was performed with *sectio parva*. At the time of data collection, the patient had fortunately been relapse-free for 2.5 years. A conization/trachelectomy with cerclage where indicated would be performed for a microinvasive carcinoma in pregnancy before the 20th to 22nd week, with additional pelvic lymphadenectomy for stage pT1a2 (2, 4). A vaginal delivery can be considered after an R0 resection; a primary Caesarean section is recommended after an R1 resection. If a microinvasive cervical cancer is diagnosed in a later week of pregnancy, one should initially wait, accelerate foetal lung maturation and perform a planned Caesarean section according to the individual diagnostic findings. Stage-appropriate treatment then follows. In the

case of advanced cancer in pregnancy, further treatment planning and determination of procedures must always be performed by an interdisciplinary team after the patient and couple have been extensively counselled. Based on individual case reports, pregnancy can be prolonged with chemotherapy given during the pregnancy if necessary, and thereby a viable and/or mature age can be attained for the child. Depending on the feasibility, the aim would be prolongation until the 25th week of pregnancy. Chemotherapy during the second or third trimester is likely not associated with the incidence of congenital malformations (11). Prolonging the pregnancy does not appear to have any negative effects on the prognosis (12). In summary, the monitoring and treatment of cervical cancer during pregnancy is an interdisciplinary challenge, and it should be performed at an experienced clinical centre. Dysplasia during pregnancy should be regularly monitored in a dysplasia clinic in order to detect any possible invasion. According to review of the existing literature and after evaluation of the present data, this risk can be classified as low.

Conflicts of Interest

The Authors state that they have no conflicts of interest to declare.

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