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Original Articles

'See and treat' approach for high-grade squamous intraepithelial cervical lesions

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Summary

Purpose of investigation: Evaluation of the over-treatment percentage when choosing a 'see and treat' approach in patients with deviant cervical smear test results. *Materials and Methods:* The authors performed a retrospective chart review among women who were treated for cytological low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL) from January 2009 until December 2010. All patients who were treated for deviant Pap-smears were analyzed. Patient characteristics were taken into account when performing the analysis. Data were analyzed using SPSS. Logistic regression was performed to determine the influence of age, smoking, and the reason to perform the Pap-smear. *Results:* A total of 723 patients with deviant Pap-smear results were analysed. High-grade cervical intraepithelial neoplasia (CIN) was found in 70.3% of the patients with a Pap 3A average dysplasia (low-grade squamous intraepithelial lesion). This indicates that 29.7% of the patients would be over-treated with a 'see and treat' approach. For Pap 3B (high-grade intra-epithelial lesion) or higher the over-treatment percentage was 6.7% or less. *Conclusion:* Potential risks of a loop electrosurgical excision procedure (LEEP) on future pregnancies and fertility should be taken into account when treating fertile patients for potential CIN. This should be part of the counseling process of patients with a Pap 3A average dysplasia. A 'see and treat' approach can and probably should be proposed to patients with a Pap 3B or higher.

Key words: Cervical smear; Colposcopy; Cervical intraepithelial neoplasia; Treatment; Loop electrosurgical excision procedure.

Introduction

Patients with abnormal cervical smear tests are managed according to Dutch guidelines by a so called 'three-step approach'. This 'three-step approach' withholds assessing that a patient has an abnormal cervical smear, followed by outpatient colposcopic evaluation with directed biopsies and if high-grade cervical intraepithelial neoplasia (CIN) is found, a third visit to provide treatment with a loop electrosurgical excision procedure (LEEP) [1-6]. This approach is cost and time consuming. Furthermore it is possible that colposcopists miss small lesions or microinvasive disease. This depends on the reliability of punch biopsies and the ability of the colposcopist to identify high-grade cervical intraepithelial disease [7].

A 'see and treat' approach, in which diagnosis and treatment of CIN takes place in a single visit, can be a good alternative for patients with cytological high-grade squamous intraepithelial lesion (HSIL). Advantages of a 'see and treat approach' are reduction of appointments and therewith higher compliance of patients, reduction of fear, and reduction of expenses [1-4, 8]. Disadvantages of this approach are potential over-treatment (treatment of patients without histologically confirmed cervical intraepithelial neoplasia grade II or III), the potential influence of the LEEP on future pregnancies and fertility, and chance of complications after a LEEP, such as bleeding, infection, cervical stenosis or cervical insufficiency [7-15].

The purpose of the present study was to evaluate the potential over-treatment percentage in a 'see and treat' approach and to determine from which abnormal cervical smear test a 'see and treat' approach is justified.

Materials and Methods

The authors performed a retrospective chart review in the Medical Centre Haaglanden in The Hague from January 1st, 2009 until December 31st, 2010. Informed consent was not necessary because the study was performed retrospectively. Treatment was not different for the included patients. The institutional review board of the Medical Center Haaglanden gave an exemption for ethical approval for this study. All patients who were treated for an abnormal cervical smear test were analyzed. Patients either had a colposcopy followed by a LEEP or merely a colposcopy or LEEP depending on the choice of the attending gynecologist. For the final analysis the highest grade of CIN, found in either the biopsy during colposcopy or the pathological diagnosis from the LEEP, was taken.

Pap-smears were investigated in the pathology department of the present hospital by specialized and trained assistants. If a

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Table 1. — *Outline of Dutch Pap classification system*

Pap	Description	Bethesda 2001
0	Inadequate	Unsatisfactory for evaluation
1	Normal	Negative for intraepithelial lesion or malignancy
2	Borderline dyskaryosis	ASC-US/ASC-H
3a1	Mild dyskaryosis	ASC-H/LSIL
3a2	Moderate dyskaryosis	HSIL
3b	Severe dyskaryosis	HSIL
4	Carcinoma in situ	HSIL
5	Carcinoma	Squamous cell carcinoma

ASC-US: atypical squamous cells of undetermined significance;
ASC-H: atypical squamous cells cannot exclude HSIL;
LSIL: low-grade squamous intraepithelial lesion;
HSIL: high-grade squamous intraepithelial lesion.

deviation was found, the Pap-smear was checked by the pathologist. Biopsies or LEEP tissue were directly examined by one of the pathologists. Statistical analysis was performed using SPSS statistics 20. Logistic regression was performed to determine the influence of age, smoking, and the reason to perform the Pap-smear.

Results

In the Netherlands the cervical smear test results are subdivided from Pap 0 until Pap 5. Table 1 gives an outline of the interpretation of the Dutch Pap classification system.

A total of 723 patients were analyzed. Patient characteristics are displayed in Table 2 and the results in Table 3; 434 patients underwent the 'three step approach' and came for colposcopic evaluation and biopsies after an abnormal cervical smear was found, followed by a LEEP excision procedure; 279 patients underwent colposcopic evaluation and biopsies only. These were mainly patients with low grade abnormal cervical smears and low-grade CIN, after which it was decided that LEEP was not necessary. Ten patients who had CIN 3 at colposcopic evaluation did not undergo a LEEP. Eight patients underwent cold knife conisation. One patient chose to undergo an uterus extirpation and one patient never showed up for the LEEP procedure. In one patient a cervical carcinoma was found during colposcopic evaluation. She was referred to a tertiary oncological center for Wertheim surgery. Eleven patients underwent immediate LEEP. Four patients had a

Table 2. — *Patient characteristics of 723 patients with abnormal cervical smears referred to the Medical Centre The Hague between January 1st, 2009 until December 31st, 2010.*

	Patients (n = 723)	No dysplasia (n = 106)	CIN 1 (n = 192)	CIN 2 (n = 146)	CIN 3 (n = 260)	Ca in situ (n = 4)	Cx-ca (n = 5)	No pathology result (n = 10)
Age (years)								
0-29	158 (21.9%)	21 (13.3%)	59 (37.3%)	34 (21.5%)	43 (27.2%)	0	0	1 (0.7%)
30-39	279 (38.6%)	43 (15.4%)	66 (23.7%)	57 (20.4%)	104 (37.3%)	2 (0.7%)	3 (1.1%)	4 (1.4%)
40-49	201 (27.8%)	29 (14.4%)	46 (22.9%)	38 (18.9%)	83 (41.3%)	2 (1%)	0	3 (1.5%)
50-59	64 (8.9%)	12 (18.8%)	15 (23.4%)	11 (17.2%)	23 (35.9%)	0	1 (1.6%)	2 (3.1%)
> 60	21 (2.9%)	1 (4.8%)	6 (28.6%)	6 (28.6%)	7 (33.2%)	0	1 (4.8%)	0
Smoking	212 (29.3%)	28 (13.2%)	51 (24%)	48 (22.6%)	81 (38.2%)	0	1 (0.5%)	3 (1.5%)
HPV positive	226 (31.3%)	47 (20.8%)	71 (31.4%)	46 (20.4%)	60 (26.5%)	0	2 (0.9%)	0
Reason for pap-smear								
Screening program	391 (54.1%)	56	88	80	155	3	2	7
Blood loss	138 (19.1%)	15	46	32	40	1	2	2
Other complaints	100 (13,8%)	13	31	17	34	0	1	1
Follow-up after CIN	57 (7.9%)	15	16	10	33	0	0	0

Table 3. — *Histologic results of 723 patients.*

Pap-smear result	Patients (n = 723)	No dysplasia (n = 106)	CIN 1 (n = 192)	CIN 2 (n = 146)	CIN 3 (n = 260)	Ca in situ (n = 4)	Cx-ca (n = 5)	No pathology result (n = 10)
Pap 1	5 (0.7%)	0	3 (60%)	1 (20%)	1 (20%)	0	0	0
Pap 2	28 (3.9%)	7 (25%)	15 (53.6%)	4 (14.3%)	2 (7.1%)	0	0	0
2x pap 2	105 (14.5%)	38 (36.2%)	35 (33.3%)	17 (16.2%)	12 (11.4%)	0	0	3 (2.9%)
Pap 2 + pap 3a1	84 (11.6%)	19 (22.6%)	26 (30.9%)	23 (27.4%)	15 (17.9%)	1 (1.2%)	0	0
Pap 3a1	79 (10.9%)	17 (21.5%)	32 (40.5%)	15 (19%)	13 (16.4%)	0	1 (1.3%)	1 (1.3%)
2 x pap 3a1	80 (11.1%)	10 (12.5%)	36 (45%)	18 (22.5%)	15 (18.8%)	0	0	1 (1.2%)
Pap 3a2	189 (26.1%)	14 (7.4%)	37 (19.6%)	49 (25.9%)	83 (43.9%)	1 (0.5%)	0	5 (2.7%)
Pap 3b	119 (16.5%)	1 (0.8%)	7 (5.9%)	16 (13.5%)	91 (76.5%)	1 (0.8%)	3 (2.5%)	0
Pap 4	30 (4.1%)	0	1 (3.3%)	2 (6.7%)	25 (83.4%)	1 (3.3%)	1 (3.3%)	0
Pap 5	4 (0.6%)	0	0	1 (25%)	3 (75%)	0	0	0

Table 4. — *Percentage of over-treatment if chosen for a 'see and treat' approach.*

	Over-treatment (%)
Pap 1	60%
Pap 2	78.6%
2x pap 2	72.4%
Pap 2 + pap 3A minor dysplasia	53.5%
Pap 3A minor dysplasia	63.3%
2x pap 3A minor dysplasia	58.7%
Pap 3A average dysplasia	29.7%
Pap 3B severe dysplasia	6.7%
Pap 4	3.3%
Pap 5	0%

HSIL abnormal cervical smear or higher. For the other patients, it was not clear why immediate LEEP excision was performed.

Three hundred forty-two patients (47.3%) had a cervical smear test result of Pap 3A2 or higher and 133 patients (70.3%) of the 342 patients had a high-grade CIN. This indicated that 29.7% of the patients would be over-treated if a 'see and treat' approach was performed. From a abnormal cervical smear test of Pap 3B and higher, the over-treatment percentage is 6.7 % or less. Age, smoking, HPV status or the reason for taking the Pap-smear had no influence on the results. The over-treatment percentages for each cervical smear test result are displayed in Table 4.

Discussion

In the present study the authors found an over-treatment percentage of 6.7% in patients with a Pap3b cervical smear result. Due to the retrospective character of the study, not all patients underwent a 'three-step approach' in this study. Some patients were treated with colposcopic evaluation and biopsies or LEEP procedure only, based on the choice of the attending gynecologist. This might have caused a bias in the found over-treatment percentages. In patients with a Pap3A average dysplasia, the authors found an over-treatment percentage of 29.7%. There have been few publications that analyzed a three-step approach versus a 'see and treat approach'. Most studies published so far included less patients than the present study. A retrospective study performed in Israel on 144 patients with cytologic HSIL described an over-treatment percentage of 29% [4]. A prospective evaluation of a 'see and treat' approach in 51 patients with cytological HSIL described an over-treatment percentage of 16% [3]. A retrospective chart review from China on 348 patients with cytological HSIL found an over-treatment percentage of 7.8%. The authors performed this research in a low-resource country and recommended a 'see and treat' approach, especially in patients who might have had problems with coming to a hospital [2]. A recent study from the Netherlands evaluated 3,192 patients who underwent a 'see and treat' approach. Patients could have had low-grade or high-grade cervical smear results at referral. When colposcopic evaluation was suggestive of a high-grade CIN, immediate treatment with LEEP was given. The authors found an over-treatment percentage of 18.1%. The lowest over-treatment percentage was found in patients with both a high-grade cervical smear result and a high-grade colposcopic impression [8]. The present study results are comparable to these previously published ones [2-4, 8].

The main problem of performing a direct LEEP after HSIL cervical smear test is the risk of over-treatment and the potential consequences of the LEEP procedure. The LEEP procedure might have a negative influence on fertility and pregnancy outcome. Possible complications of the LEEP procedure are cervical stenosis, bleeding, and urinary tract infections. There have been varying publications regarding the influence of a LEEP on pregnancy outcome, especially on the risk of preterm delivery. A meta-analysis published in 2006 about obstetric outcomes after treatment for CIN demonstrated an increased risk after LEEP of preterm delivery (< 37 weeks, RR 1.70, 95% CI 1.24–2.35), preterm premature rupture of membranes (PPROM, RR 2.69, 95% CI 1.62 – 4.46) and low birthweight (< 2,500 grams, RR 1.82, 95% CI 1.09–3.06). The authors performed further analysis with respect to the amount of the removed tissue during the LEEP procedure. In this analysis a significantly increased risk of preterm delivery was found if the depth of the LEEP procedure was more than ten mm. The authors recommend caution in the treatment of young patients with mild cervical abnormalities [11]. A meta-analysis from 2008 about adverse pregnancy outcomes after treatment of CIN found no increased risk of preterm delivery before 32 or 34 weeks after LEEP (RR 1.20, 95% CI 0.50–2.89) [9]. A retrospective cohort study from Finland, published in 2009, found a 2.61-fold (95% CI 2.02–3.20) increased risk for preterm delivery (< 37 weeks) with a mean gestational age for preterm delivery of 33.3 weeks. The main cause was PPROM (45.3%) [10]. A study from 2010 from Texas found no association between LEEP and preterm delivery [12]. Recently a systematic review and meta-analysis on LEEP and the risk of preterm birth was published. The authors compared 6,589 women who did and 1,415,015 women who did not undergo LEEP. Women who did undergo LEEP had an increased risk of premature delivery (pooled relative risk 1.61, 95% CI 1.35–1.92), but no increased risk was found in a second analysis, where the authors compared women who did undergo LEEP with women with a history of cervical dysplasia but no LEEP (pooled relative risk 1.08, 95% CI 0.88–1.33) [16]. Consequently, the results of the influence of LEEP on pregnancy outcome differ, but especially the risk of premature delivery seems increased. Taking these results into account, caution for performing a LEEP procedure should be considered in fertile women.

Potential complications of a LEEP procedure are bleeding complications, urinary tract infection, and cervical stenosis. The reported incidences of these complications differ between 0.7%–5% [3, 4, 17, 18].

The interpretation of the present results depends on which over-treatment percentage is considered acceptable when taking possible complications into account. The present authors consider the over-treatment percentage found in patients with a Pap3B severe dysplasia or higher, acceptable to execute a 'see and treat' protocol. For patients with Pap 3A average dysplasia, age, and desire to become pregnant should be taken into account before deciding on a treatment protocol (Table 3).

Hence, although results are variable, potential risks of LEEP on future pregnancies and fertility should be taken into account when treating fertile patients for possible high-grade CIN. When performing a LEEP procedure in patients with desire for future fertility, the depth of the LEEP should preferably be kept less than ten mm.

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