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**PATIENTS' PSYCHOLOGICAL REACTIONS TO COLPOSCOPY AND LLETZ  
TREATMENT FOR CERVICAL INTRAEPITHELIAL NEOPLASIA**

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## **Condensation**

Women undergoing see-and-treat LLETZ experience greater psychological distress and pain than women undergoing colposcopy, and there is high acceptability among patients for interventions during colposcopy.

**PATIENTS' PSYCHOLOGICAL REACTIONS TO COLPOSCOPY AND LLETZ  
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**Abstract**

**Objectives:** To compare intra-procedural distress between colposcopy and see-and-treat LLETZ patients, and to assess patients' perceptions of possible non-pharmacological interventions to reduce distress.

**Study design:** Retrospective postal questionnaire survey. A total of 151 women aged 20-60 with high-grade cervical intraepithelial neoplasia (CIN), of which 86 had undergone colposcopy, and 65 had undergone LLETZ treatment, recruited from the Department of Obstetrics & Gynaecology, University Hospital Galway, Ireland. Colposcopy- and LLETZ-related distress and pain, and patient perceptions of helpfulness of suggested interventions.

**Results:** Respondents reported high levels of colposcopy-related anxiety and worry. Those who reported fear of cancer, and concerns about fertility, colposcopy procedure itself and embarrassment had higher anxiety levels than those not reporting these concerns. LLETZ treatment was perceived as distressing, and as more painful than colposcopy. Women's perceptions of certain interventions were associated, and distinct coping profiles were identified.

**Conclusions:** Colposcopy elicits high levels of anxiety, and see-and-treat LLETZ patients experience greater negative psychological consequences than colposcopy patients. Finding suitable interventions to reduce anxiety levels is recommended.

**Keywords:** anxiety, colposcopy, LLETZ, pain, intervention

## **Introduction**

Cervical cancer is the second most common cancer in women worldwide, and each year approximately 233 000 women die from the disease [1]. The aim of cervical cancer screening is to detect and treat squamous cell carcinoma before it progresses into invasive disease. It is, however, recognised that screening is unlikely to eradicate all cases of squamous cell carcinoma, as persistent defaulters exist [2]. Reported rates of non-adherence to treatment of abnormal cervical smear is between 10% and 40% [3, 4]. The screening process is associated with high levels of anxiety, especially for women with abnormal smear results [5, 6], who must attend for diagnostic investigation by colposcopy [7-9]. High levels of anxiety associated with cervical cancer screening may be one factor affecting adherence to treatment.

The present study was conducted in order to further extend understanding of women's psychological reactions to colposcopy and LLETZ treatment, by assessing and comparing levels of anxiety, worry, distress and pain elicited by colposcopic examination and LLETZ in first-time patients. All patients were treated at an outpatient basis, and all LLETZ treatments were see-and-treat procedures under local anaesthesia.

A secondary aim was to ascertain patient perceptions of usefulness of possible interventions in reducing anxiety during colposcopy examinations. Patients' opinions of perceived helpfulness of watching a DVD, listening to music, distraction, watching the colposcopy screen, nurse reassurance, and more information were assessed.

## **Methods**

### **Participants and Procedure**

A total of 200 first-time patients (women aged 20-60 years) who had undergone a colposcopic examination during a previous twelve-month period were randomly selected from the colposcopy clinic register at University Hospital, Galway, Ireland.

Selected participants were sent the study questionnaire with a cover letter explaining the study, and a stamped addressed envelope (SAE), with reminder letters sent after 2 weeks. Ethical approval was granted by the Research Ethics Committee of the Health Service Executive Western Area.

## **Questionnaire**

The questionnaire items were based on the existing literature regarding psychological reactions to colposcopy and patient concerns. Anxiety and worry were assessed with two items measured on a 7-point response scale, from 'not at all anxious/worried' to 'extremely anxious/worried'. Respondents were asked to indicate what specific concerns they had in relation to attending for colposcopy, and were requested to tick as many or as few of the concerns that was applicable to them. The specific patient concerns were the colposcopy examination itself; possibility of biopsy/treatment; embarrassment; pain during colposcopy; cause of abnormality; diagnosis; fear of cancer; that fertility would be affected. Items assessing pain, discomfort, unpleasantness and embarrassment associated with the colposcopy and LLETZ treatment were measured on 7-point response scales, ranging from 'not at all' to 'extremely'. Peak pain was measured with one item on a 7-point response scale, from 'no pain at all' to 'excruciating pain'. Six possible interventions were selected based on previous research; watching a DVD, listening to music, distraction, watching the colposcopy screen, nurse reassurance, and more information. Participants were asked to rate how helpful they would have thought each to be, if it had been offered, on a 7-point response scale from 'not at all' to 'extremely'.

## Statistical analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences, version 15.0 (SPSS, Chicago, IL, USA). Following the recommendations by Fife-Schaw [10] regarding ambiguity of scales of measurement, both non-parametric and parametric statistical analyses were conducted, and yielded similar results. Therefore, it was considered appropriate to proceed with parametric statistical analyses. Independent *t*-tests were used to compare means for parametric continuous data. Chi-squared tests were used to analyse associations between categorical variables.

The responses for the ratings of information received and perceived helpfulness of interventions were collapsed into three categories, 'not very helpful' (0-1), 'moderately helpful' (2-4), and 'very helpful' (5-6), to aid interpretation.

## Results

Three questionnaires were returned due to incorrect addresses, resulting in 197 women being available for assessment. One hundred and fifty one questionnaires were returned, yielding a response rate of 77%.

Of respondents, 86 (57%) had undergone colposcopy (mean age = 33.03, SD = 7.44), and 65 (43%) women had undergone LLETZ (mean age = 33.66, SD = 6.12). There were no significant differences in any of the demographic variables, which are presented in table 1.

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Insert Table 1 about here  
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Certain colposcopy-related concerns affected reported anxiety levels, see table 2.

Women who reported concern about the colposcopy procedure itself, had greater anxiety levels (mean = 4.71) than women who were not worried about the colposcopy procedure (mean = 3.87,  $P < .05$ ). In addition, women who were worried about embarrassment had greater anxiety levels (mean = 4.76) than women who did not have this concern (mean = 3.97,  $P < .05$ ). Furthermore, women who reported fear of cancer had greater anxiety levels than women who did not fear cancer (means = 4.70 versus 3.11, respectively,  $P < .001$ ). Finally, women who had concerns over future fertility had greater anxiety levels (mean = 4.71) than women who did not have this concern (mean = 3.96,  $P < .05$ ).

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Insert Table 2 about here  
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Eighty-seven percent of the sample reported at least moderate anxiety, and 28% of the sample reported experiencing extreme anxiety and worry in relation to the colposcopy. There were no significant differences in reported levels of anxiety and worry between the colposcopy group and the LLETZ group, all  $P$ s  $> .05$ .

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Insert Table 3 about here  
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Women who underwent LLETZ experienced greater pain intensities (mean = 2.56) than women who underwent colposcopy (mean = 1.48,  $P < .001$ ), see table 3. This is also reflected

in the significantly higher peak pain rating in LLETZ patients (mean = 2.60) compared to colposcopy patients (mean = 1.74,  $P < .001$ ). Furthermore, LLETZ patients reported experiencing significantly greater discomfort (mean = 3.25) than colposcopy patients (mean = 2.41,  $P < .01$ ). Finally, LLETZ patients also reported elevated levels of unpleasantness (mean = 3.16) than colposcopy patients (mean = 2.03,  $P < .001$ ).

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Insert Table 4 about here  
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Table 4 outlines the perceived helpfulness of suggested interventions. Chi-squared tests revealed associations between the reported perceived helpfulness of certain interventions, producing distinct coping profiles. There was an association between the perceived helpfulness of watching the colposcopy screen and more information ( $\chi^2 [4] = 12.14, P < .05$ ). Women who perceived the screen as unhelpful also reported perceptions of more information as unhelpful, and women who perceived the colposcopy screen as very helpful also tended to perceive more information as very helpful.

There was an association between perceptions of the helpfulness of distraction and more information ( $\chi^2 [4] = 9.3, P < .05$ ). Women who perceived distraction as moderately helpful also perceived more information as moderately helpful, and women who perceived distraction as moderately helpful also tended to perceive more information as unhelpful.

There was an association between the perceived helpfulness of distraction and watching the colposcopy screen ( $\chi^2 [4] = 17.50, P < .01$ ). Women who perceived distraction as unhelpful also tended to perceive the colposcopy screen as very helpful.

There was an association between the perceived helpfulness of watching a DVD and watching the colposcopy screen ( $\chi^2 [4] = 10.42, P < .05$ ). Women who perceived watching a DVD as very helpful also reported perceptions of the colposcopy screen as unhelpful.

## Discussion

The present questionnaire study examined the difference in psychological reactions in women who underwent a diagnostic colposcopy examination or see-and-treat LLETZ treatment. High levels of colposcopy-related anxiety and worry were found, supporting previous research [6, 8, 11, 12]. Anxiety interacted with pre-colposcopy concerns, which were not solely related to procedural points, but also to general health concerns. Thus, women who reported concern about the colposcopy procedure itself, or worry about experiencing embarrassment during the examination had greater anxiety levels than women not reporting these concerns. Similarly, women who reported fear of cancer, or concerns over their future fertility were significantly more anxious than women not reporting these concerns. From these results it is clear that women find colposcopy stressful, and experience high levels of anxiety and worry in relation to the examination, which may be exacerbated in women with specific worries.

Notably, a large percentage of women (65%) feared they had cancer on receipt of the abnormal smear result, which is in line with other findings [6, 13-15]. This can be partly explained by a substantial portion of women believing that the purpose of the smear test is to detect cancer [16]. Combined, these results suggest that women have little knowledge of the purpose of cervical screening, and are uncertain about associated terminology.

There were no differences in anxiety levels between colposcopy or LLETZ patients, and this is likely due to the fact that women had no prior knowledge of whether they would require treatment or not. These results differ from a prospective study of colposcopy and

LLETZ patients, which found greater anxiety and psychosocial distress in colposcopy rather than LLETZ patients [17]. However, in that study, all LLETZ patients had previously undergone colposcopy, and there are suggestions that anxiety levels are reduced with repeat colposcopy visits [8]. In addition, the colposcopy group included women who had previously been treated with LLETZ. It can be speculated that returning for colposcopic examination after previous treatment for CIN increased distress scores above the levels of those women who underwent their first ever LLETZ treatment.

Differences do emerge between colposcopy patients and LLETZ patients when asked to report on intra-procedural distress. LLETZ patients report experiencing significantly greater pain intensities, for both overall and peak pain intensities. In addition, LLETZ patients also report experiencing significantly greater levels of discomfort and unpleasantness than colposcopy patients. While pain intensity is generally accepted to reflect the sensory experience of a situation, unpleasantness is thought to reflect the affective interpretation of a situation. Thus, patients undergoing LLETZ experience more acute sensations than colposcopy patients, and they also view the experience with greater negative affect than colposcopy patients.

This is the first study to have examined patients' experiences of pain, discomfort and distress when undergoing LLETZ. There are other studies that have indirectly measured patients' perception of pain in colposcopy [18, 19]. Twenty-eight percent of patients in the present study reported that they found colposcopy 'very painful', indicating that patients may experience greater levels of pain and discomfort than has previously been reported.

The results from this study suggest that the psychological consequences of attending for colposcopy and LLETZ may be greater than previously thought. There is currently no agreement among researchers regarding the most suitable type of intervention to reduce anxiety in women undergoing colposcopy [20]. While it appears that women are concerned

about the colposcopy procedure itself, information-based interventions appears ineffective in reducing anxiety levels [11, 21-25]. Therefore, the present study wished to ascertain patients' perceptions of possible coping interventions for use during the colposcopic examination.

The results revealed categorical associations between certain interventions, suggesting the presence of distinct coping profiles. Specifically, it appears that the distraction-based interventions represented a distinct coping profile, and the information-based interventions represented a separate coping profile. For example, patients who endorsed more information were more likely to also endorse the colposcopy screen, and those who perceived watching a DVD as very helpful were more likely to consider watching the colposcopy screen as not very helpful. These two coping profiles can broadly be termed preference for distraction and preference for information to increase coping during colposcopy. This finding is consistent with research that has identified two distinct cognitive coping styles, monitoring and blunting, to deal with adverse medical situations [26]. Monitors scan for threatening cues and have better psychological outcomes when presented with detailed information, whereas blunners generally distract from threatening cues and have better psychological outcomes when presented with less information.

Previous research has found evidence for reduced anxiety and increased adherence to follow-up treatment in women who view the colposcopy video screen [8, 27]. Furthermore, listening to music during colposcopy reduced anxiety and pain reports compared to standard care [19], although contrary results have been reported [28]. The need for suitable interventions to reduce anxiety during colposcopy and LLETZ is great, as high levels of anxiety may result in adverse psychological consequences such as pain and discomfort [29, 30]. The results from this study suggest certain interventions during the colposcopy procedure itself may be acceptable methods of reducing levels of anxiety. When designing interventions,

considerations ought to be given to patients' preferred coping styles, as there is evidence of increased adjustment when there is a match between coping style and intervention [26].

### **Conclusion**

The present study demonstrates that LLETZ is associated with greater psychological distress than colposcopy, and that anxiety may be exacerbated in women with specific concerns. Those concerns that are associated with greater anxiety levels, such as the colposcopy procedure itself, or fear of cancer should be addressed, ideally before the first visit to the colposcopy clinic. Finding suitable non-pharmacological psychological interventions deserve further examination, as they could be implemented with low cost to clinics and patients.

## References

1. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001;37 Suppl 8:S4-66.
2. van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ, Boer R, Habbema JD. Cost-effectiveness of cervical cancer screening: comparison of screening policies. *J Natl Cancer Inst* 2002;94(3):193-204.
3. Khanna N, Phillips MD. Adherence to care plan in women with abnormal Papanicolaou smears: a review of barriers and interventions. *J Am Board Fam Pract* 2001;14(2):123-30.
4. Shinn E, Basen-Engquist K, Le T, et al. Distress after an abnormal Pap smear result: scale development and psychometric validation. *Prev Med* 2004;39(2):404-12.
5. Idestrom M, Milsom I, Andersson-Ellstrom A. Women's experience of coping with a positive Pap smear: A register-based study of women with two consecutive Pap smears reported as CIN 1. *Acta Obstet Gynecol Scand* 2003;82(8):756-61.
6. Jones MH, Singer A, Jenkins D. The mildly abnormal cervical smear: patient anxiety and choice of management. *J R Soc Med* 1996;89(5):257-60.
7. Bekkers RL, van der Donck M, Klaver FM, van Minnen A, Massuger LF. Variables influencing anxiety of patients with abnormal cervical smears referred for colposcopy. *J Psychosom Obst Gyn* 2002;23(4):257-61.
8. Walsh JC, Curtis R, Mylotte M. Anxiety levels in women attending a colposcopy clinic: a randomised trial of an educational intervention using video colposcopy. *Patient Educ Couns* 2004;55(2):247-51.
9. Tahseen S, Reid PC. Psychological distress associated with colposcopy: Patient's perceptions. *Eur J Obstet Gynecol Reprod Biol* 2008;139:90-94.

10. Fife-Schaw C. In: Breakwell GM, Hammond S, Fife-Schaw C, editors. *Research Methods in Psychology*. London: Sage; 2006.
11. Chan YM, Lee PW, Ng TY, Ngan HY. Could precolposcopy information and counseling reduce women's anxiety and improve knowledge and compliance to follow-up? *Gynecol Oncol* 2004;95(2):341-6.
12. Freeman-Wang T, Walker P, Linehan J, Coffey C, Glasser B, Sherr L. Anxiety levels in women attending colposcopy clinics for treatment for cervical intraepithelial neoplasia: a randomised trial of written and video information. *BJOG* 2001;108(5):482-4.
13. Juraskova I, Butow P, Sharpe L, Champion M. 'What does it mean?' Uncertainty, trust and communication following treatment for pre-cancerous cervical abnormalities. *Psychooncology* 2007;16(6):525-33.
14. Hellsten C, Sjostrom K, Lindqvist PG. A prospective Swedish cohort study on psychosocial factors influencing anxiety in women referred for colposcopy. *BJOG* 2007;114(1):32-8.
15. Kavanagh AM, Broom DH. Women's understanding of abnormal cervical smear test results: a qualitative interview study. *BMJ* 1997;314(7091):1388-91.
16. Walsh JC. The impact of knowledge, perceived barriers and perceptions of risk on attendance for a routine cervical smear. *Eur J Contracept Reprod Health Care* 2006;11(4):291-6.
17. Le T, Hopkins L, Menard C, Hicks-Boucher W, Lefebvre J, Fung Kee Fung M. Psychologic morbidities prior to loop electrosurgical excision procedure in the treatment of cervical intraepithelial neoplasia. *Int J Gynecol Cancer* 2006;16(3):1089-93.

18. Bennetts A, Irwig L, Oldenburg B, et al. PEAPS-Q: a questionnaire to measure the psychosocial effects of having an abnormal pap smear. *J Clin Epidemiol* 1995;48(10):1235-43.
19. Chan YM, Lee PW, Ng TY, Ngan HY, Wong LC. The use of music to reduce anxiety for patients undergoing colposcopy: a randomized trial. *Gynecol Oncol* 2003;91(1):213-7.
20. Galaal KA, Deane K, Sangal S, Lopes AD. Interventions for reducing anxiety in women undergoing colposcopy. *Cochrane Database Syst Rev* 2007(3):CD006013.
21. Somerset M, Baxter K, Wilkinson C, Peters TJ. Mildly dyskaryotic smear results: Does it matter what women know? *Fam Pract* 1998;15(6):537-24.
22. Byrom J, Clarke T, Neale J, et al. Can pre-colposcopy sessions reduce anxiety at the time of colposcopy? A prospective randomised study. *J Obstet Gynaecol* 2002;22(4):415-20.
23. Tomaino-Brunner C, Freda MC, Damus K, Runowicz CD. Can precolposcopy education increase knowledge and decrease anxiety? *J Obstet Gynecol Neonatal Nurs* 1998;27(6):636-45.
24. Howells RE, Dunn PD, Isasi T, et al. Is the provision of information leaflets before colposcopy beneficial? A prospective randomised study. *Br J Obstet Gynaecol* 1999;106(6):528-34.
25. Marteau TM, Kidd J, Cuddeford L, Walker P. Reducing anxiety in women referred for colposcopy using an information booklet. *Br J Health Psychol* 1996;1:181-89.
26. Miller SM, Mangan CE. The interacting effects of information and coping style in adapting to gynecologic stress: Should the doctor tell all? *J Pers Soc Psychol* 1983;45:223-36.

27. Takacs P, Chakhtoura N, De Santis T. Video colposcopy improves adherence to follow-up compared to regular colposcopy: a randomized trial. *Arch Gynecol Obstet* 2004;270(3):182-4.
28. Danhauer SC, Marler B, Rutherford CA, et al. Music or guided imagery for women undergoing colposcopy: A randomized controlled study of effects on anxiety, perceived pain, and patient satisfaction. *J Low Genit Tract Dis* 2007;11(1):39-45.
29. Rhudy JL, Meagher MW. Fear and anxiety: Divergent effects on human pain thresholds. *Pain* 2000;84(1):65-75.
30. Tang J, Gibson SJ. A psychophysical evaluation of the relationship between trait anxiety, pain perception, and induced state anxiety. *J Pain* 2005;6 (9):612-19.

**Table 1.** Demographic variables of colposcopy group ( $n = 86$ ) and LLETZ group ( $n = 65$ )

<b>Variable</b>	<b>Colposcopy %</b>	<b>LLETZ %</b>
<b>Marital Status</b>		
Married/living as married	43	58
Single	50	36
Separated/divorced/widowed	7	6
<b>Level of Education</b>		
Third level education	68	69
Second level education	18	22
Education 'other'	14	9
<b>Parity</b>		
No children	56	41
One child	8	23
Two children	16	19
More than three children	18	17

**Table 2.** Mean patient anxiety levels in relation to specific colposcopy concerns (possible range of anxiety score 0-6)

Colposcopy concern	Yes <sup>a</sup>		No <sup>b</sup>		<i>t</i>
	Mean (SD)	( <i>n</i> )	Mean (SD)	( <i>n</i> )	
Colposcopy diagnosis	4.20 (1.40)	105	4.02 (1.89)	46	.64
Fear of cancer	4.70 (1.27)	98	3.11 (1.54)	53	6.81**
Cause of the abnormality	4.11 (1.45)	76	4.19 (1.68)	75	.32
Colposcopy would be painful	4.15 (1.53)	61	4.14 (1.59)	90	.01
Colposcopy procedure	4.71 (1.21)	49	3.87 (1.65)	102	3.19*
Requiring biopsy or treatment	4.48 (1.42)	46	4.00 (1.61)	105	1.74
Fertility affected	4.71 (1.35)	38	3.96 (1.59)	113	2.64*
Embarrassment	4.76 (1.46)	33	3.97 (1.56)	118	2.59*

<sup>a</sup> Yes = Concern present

<sup>b</sup> No = Concern absent

\*  $P < .05$

\*\*  $P < .001$

**Table 3.** Mean ratings of distress in women undergoing colposcopy and LLETZ (possible range for all variables 0-6)

	<b>Colposcopy</b>	<b>LLETZ</b>	<b><i>t</i></b>
	<b>(<i>n</i> = 86)</b>	<b>(<i>n</i> = 65)</b>	
<b>Distress variables</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
Anxiety	4.01 (1.57)	4.32 (1.55)	1.21
Worry	4.02 (1.52)	4.12 (1.60)	.39
Pain	1.48 (1.46)	2.56 (1.87)	3.84**
Discomfort	2.41 (1.66)	3.25 (1.94)	2.89*
Unpleasantness	2.03 (1.72)	3.16 (2.04)	3.65**
Embarrassment	1.86 (1.82)	2.06 (1.91)	.66
Peak pain	1.74 (1.44)	2.60 (1.67)	3.38**

\**P* < .01

\*\* *P* < .001

**Table 4.** Patients' ratings of perceived helpfulness of suggested interventions (*n* = 151)

<b>Intervention</b>	<b>Not very</b>		<b>Moderately</b>		<b>Very</b>	
	<b>%</b>	<b>(<i>n</i>)</b>	<b>%</b>	<b>(<i>n</i>)</b>	<b>%</b>	<b>(<i>n</i>)</b>
Nurse reassurance	1	(2)	15	(22)	84	(127)
More information	18	(27)	48	(73)	34	(51)
Distraction	29	(44)	42	(63)	29	(44)
Watching colposcopy screen	34	(51)	39	(59)	27	(41)
Listening to music	31	(46)	46	(70)	23	(35)
Watching a DVD	50	(76)	39	(58)	11	(17)

**Conflict of interest**

None.

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None.