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Health-related quality of life in women after colposcopy: Results from a longitudinal patient survey

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Running title: Health-related quality of life in women after colposcopy

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Abstract

Background: Information concerning the health-related quality of life (HRQoL) consequences of colposcopy is limited, particularly over time. In a longitudinal study, we investigated women's HRQoL at 4, 8 and 12 months post-colposcopy and the factors associated with this.

Methods: Women attending colposcopy at two large hospitals affiliated with the national screening programme in Ireland were invited to complete questionnaires at 4, 8 and 12 months post-colposcopy. HRQoL was measured using the EQ-5D-3L and compared across a range of socio-demographic, clinical and attitudinal variables. A mixed-effects logistic multivariable model was employed to investigate associations between these variables and low HRQoL.

Results: Of 584 women initially recruited, 429, 343 and 303 completed questionnaires at 4, 8 and 12 months, respectively. The mean overall HRQoL score for the sample across all time points was 0.90 (sd=0.16). Approximately 18% of women experienced low HRQoL at each of the three time points. In multivariable testing, over the entire 12-month follow-up period, non-Irish nationals (OR=8.99, 95% CI 2.35-34.43) and women with high grade referral cytology (OR=2.78, 95% CI 1.08-7.13) were at higher odds of low HRQoL. Women who were past (OR=0.20, 95% CI 0.07-0.58) or never (OR=0.42, 95% CI 0.16-1.12) smokers were at lower odds of low HRQoL than current smokers. As women's satisfaction with their healthcare increased their odds of experiencing low HRQoL fell (OR per unit increase=0.51, 95% CI 0.34-0.75).

Conclusions: Women's HRQoL did not change over the 12 months post-colposcopy, but some subgroups of women were at higher risk of experiencing low HRQoL. These subgroups may benefit from additional support.

Keywords: Health-related quality of life, colposcopy, cervical screening, longitudinal study design

Introduction

Cervical cancer screening is effective in reducing incidence and mortality from cervical cancer among target populations [1]. To ensure effectiveness of screening, women who receive positive cytology test results require follow-up investigation, usually a hospital-based colposcopy. Colposcopy is a very common procedure with 171,874 women undergoing colposcopy for the first time in England in 2018[2].

Colposcopy and its related interventions (e.g. biopsies of any areas of the cervical transformation zone that appear abnormal, or treatment to remove abnormal cervical cells) are associated with distress and anxiety in women before and during the procedure(s) [3]. Concerns around cancer, sex and fertility can also persist after coloscopy and relatedinterventions [4-8].While an extensive body of literature exists on these dimensions of quality of life, there is considerably less evidence on validated health-related quality-of-life (HRQoL) measures, particularly those that are typically used to impute quality-adjusted life years (QALYS) in health economic evaluations, such as the widely-used EuroQol EQ-5D instrument [9]. Information is also limited on factors associated with HRQoL in women following colposcopy and related procedures and how colposcopy related HRQoL varies over time [10]. What evidence does exist, particularly from longitudinal studies, is often based on small samples [6, 11, 12] or includes only women with low-grade abnormal cytology [13]. While it could be hypothesised, given the relationship between anxiety and undergoing colposcopy, that the procedure would negatively impact HRQoL, it is difficult to draw such conclusions from the existing literature with some studies finding little to no relationship between receipt of colposcopy and HRQoL [6, 11], others a modest positive relationship [13] and still others a negative relationship, albeit short-term [12].

The discovery of the causal relationship between infection with certain high-risk strains of human papillomavirus (HPV) and cervical neoplasia [14]has transformed cervical cancer prevention. Many screening programmes have introduced (or intend to introduce) HPV testing as their primary screening tool instead of cytology-based testing and many countries offer vaccination against certain HPV types to young adolescents [15]. To determine how best to implement cervical cancer prevention in this changing context, the cost-effectiveness of these newer strategies are being assessed [16-18]. Consequently, new estimates of HRQoL for use in the calculation of QALYs would appear timely. Although primary HPV screening has been adopted by programmes, colposcopy is likely to remain a central pillar of follow-up of women with abnormal screening tests into the future.

The current study aimed to: (1) assess how women's HRQoL changes over the 12 months following colposcopy; (2) provide mean utility scores for different clinical and socio-demographic subgroups for use in (future) cost-effectiveness modelling; and (3) investigate the factors associated with low HRQoL in the year after colposcopy, as this may identify subgroups of women who could benefit from additional interventions or supports.

Methods

Setting

The study setting was Ireland, which has a mixed public–private healthcare system. The national cervical screening programme (CervicalCheck) was introduced in 2008, offering free cervical cytology tests and follow-up, if needed, to women aged 25–60 years. Women with two or more low-grade abnormal cervical cytology test results, or one high-grade result, were referred for colposcopy in a clinic affiliated with the screening programme located in one of 15 maternity hospitals throughout Ireland.

Participants and procedures

Women attending two large colposcopy clinics in Dublin, Ireland (The Coombe Women and Infants University Hospital and the National Maternity Hospital) were recruited to the study between September 2010-July 2011. Women were eligible if they were referred to colposcopy because of an abnormal cytology test result in the context of routine screening. They were eligible irrespective of the management they received at their initial clinic appointment (i.e. colposcopy only, loop excision, or another form of intervention or treatment) or subsequent follow-up. The exclusion criteria for the study were pregnancy at recruitment or treatment for previous cervical abnormalities. A member of the research team (CW) approached women at the clinics and invited them to participate in the study. For reasons relating to the clinical and operational circumstances prevailing in the two recruitment centres, it was not possible to consecutively approach all women attending clinics. The women were given a study information sheet with more details about the research. Interested women signed a consent form and returned it to the research team and were mailed questionnaire packs to complete at 4, 8 and 12 months after their clinic visit.

The women received no reward or payment for being recruited to the study, however, women who took part in the study and completed at least one of the questionnaires were offered the chance to enter into a prize draw to win one of two €150 high street shopping vouchers. Offering modest incentives such as these has been shown to be the most effective way of maximizing response rates [19]. Women were not be told about this incentive until they received their first (~4 month) questionnaire so that it did not affect their willingness to consent to the study. Ethical approval was obtained from the ethics committees of the Coombe Women and Infants University Hospital (ref:21-2006) and the National Maternity Hospital, Dublin (no reference number given).

Assessment of health-related quality of life

HRQoL was measured using the EuroQol EQ-5D 3L [9] included as part of the psychosocial questionnaire administered at 4,8 and 12 months after the women's initial colposcopy appointment. The EQ-5D is a widely used instrument for measuring HRQoL, particularly for health technology assessments (HTAs) and other economic evaluations. A broader description of the instrument can be found in the EuroQol Research Foundation's User Guide [20]. The EQ-5D consists of five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. Each of these dimensions has three response levels consisting of 1 'no problems', 2 'some problems' and 3 'extreme problems'. These responses can be linked to utility values ranging from 0-1 (death-full health). No Irish value set is available, consequently health states were valued using value sets for the UK [21].

142 The distribution of the HRQoL index values was discrete and non-normal. For modelling
143 purposes, therefore, we defined low HRQoL as a response of "3" in at least one dimension or
144 an answer of "2" in at least two dimensions.

145

146 *Assessment of potential predictors of health-related quality of life*

147 Information on potential predictors of low HRQoL was obtained from the four-month
148 questionnaire, which contained questions on a range of socio-demographic and lifestyle
149 factors [4, 7]. Women's satisfaction with life and general healthcare were assessed by means
150 of items adapted from McCaffery et al [22]. Colposcopy clinic records were used to provide
151 information on colposcopy referral cytology, initial colposcopic impression, initial
152 management and histology result. Clinical data were extracted from women's records at the
153 four month timepoint.

154

155 *Statistical Analyses*

156 Analyses were conducted in Stata 12. Mean HRQoL scores at each follow-up time point (i.e.
157 4, 8 and 12 months were computed overall and for a range of key socio-demographic and
158 clinical variables.

159 Because we had longitudinal data, a mixed-effects logistic multivariable regression model
160 was used to explore associations between socio-demographic, clinical and attitudinal
161 variables and low HRQoL. This allowed inclusion of all observations across all points [23].
162 Variables that were significant at the 5% level in univariate logistic analysis were included in
163 initial multivariable analysis and Wald tests used to determine which remained significant

once other independent variables were included. The final model only included variables that remained statistically significant. Time-point was included in all models, in order to test for a temporal trend in low HRQoL.

As sensitivity analyses, we re-ran the final model with utility scores as a continuous dependent variable in a mixed-effects linear model. We also changed the specification of "low" HRQoL so that it included women in the bottom three quartiles and re-ran the final model. These alternative analyses did not change the variables that attained statistical significance, nor the direction of their relationship with "low" HRQoL (data not shown).

Our study conformed with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [24]. A copy of the completed STROBE checklist for this study is available in supplementary file [Online Resource 1].

Results

Characteristics of participants

Of 584 women who consented to participate in the study: 429 (73%); 343 (59%) and 303 (52%) completed questionnaires at 4, 8 and 12 months post-colposcopy respectively. Women's socio-demographic, clinical lifestyle and attitudinal characteristics at four months are summarised in Table 1.

Temporal trends in HRQoL post-colposcopy

Mean overall HRQoL was static at 0.90 across all three time points (standard deviation (SD)=0.16 at 4 and 8 months and 0.14 at 12 months). Table 2 details the mean HRQoL scores

over time by several key clinical and socio-demographic characteristics. While broadly HRQoL appeared similar across groups, those without tertiary education had lower mean HRQoL than those who had. Those who had undergone large loop excision of the transformation zone (LLETZ) had lower HRQoL than those who had not and those with a medical card (which is available to those with limited means and provides free healthcare in the public system) had lower HRQoL than those who did not.

75 (18%) women were classified as having "low" HRQoL at four months post colposcopy. This percentage was unchanged at 8 months (n=57;18%) and 12 months (n=50;18%) post-colposcopy.

Factors that influence HRQoL over 12 months post colposcopy

The results of univariate analysis of associations between socio-demographic, clinical and attitudinal variables and low HRQoL testing are presented in Table 3. In the multivariable model (Table 4), nationality, the woman's referral cytology, smoking status and satisfaction with healthcare were significantly related to low HRQoL. The odds of having low HRQoL in non-Irish women were almost nine times higher than for Irish women (adjusted OR=8.99, 95% CI 2.35-34.43). Odds of low HRQoL was also more than two and half times higher for women referred for colposcopy on the basis of a high-grade cytology result (OR=2.78, 95% CI 1.08-7.13). Conversely, women who were either past smokers or who never smoked were at significantly lower odds of experiencing low HRQoL compared to current smokers (past vs current smoker: OR=0.20, 95% CI 0.07-0.58; never vs current smoker: OR=0.42, 95% CI 0.16-1.12). Higher levels of satisfaction with general healthcare received were associated with a lower odds of low HRQoL; with every unit increase in satisfaction on a Likert scale of 1-10 (where 10 indicated complete satisfaction), the odds of experiencing low HRQoL were reduced by approximately one half (OR=0.51, 95% CI 0.34-0.75).

Discussion

In this longitudinal study we found no discernible change in women's HRQoL over the 12 months post colposcopy; mean HRQoL values were identical at each time point as was the proportion of women with low HRQoL. In multivariable analysis, we identified two subgroups of women at higher odds of experiencing low HRQoL: (1) non-Irish women and (2) women with high-grade abnormal referral cytology. We also found that women who were not current smokers were less likely to experience low HRQoL and that as women's satisfaction with their healthcare increased, their odds of experiencing low HRQoL decreased.

Temporal trends in HRQoL post-colposcopy

Over the course of the three follow-up time points, mean HRQoL remained stable and high at 0.90. It is likely that the high index score reflects the relatively young age distribution of our study population; EQ-5D Index scores have been shown to decrease with age and younger respondents report better health statusn [25]. The pattern of little change over time is in keeping with most of the (limited) literature in this area. Korfage et al [12] found that both EQ-5D and EQ-VAS (a visual analogue scale running from 1-100) scores were similar at 1, 3 and 6 months post-colposcopy. Similarly, while Whynes et al [13] found some differences across time, none of these were greater than the minimum important difference for the EQ-VAS [26]. Heinonen et al [11] found that HRQoL was worse at 12 months than at baseline, but this may, in part, be because they used a more sensitive instrument to assess outcomes [27-29]. The issue of (lack of) sensitivity with respect to the EQ-5D-3L, has been documented before [28, 29]; this may also be an issue in the context of investigation and treatment of abnormal cervical cytology [30].

Factors that influence HRQoL over 12 months post colposcopy

Women whose referral cytology indicated moderate or severe dyskaryosis (i.e. "high-grade") were more likely to be report responses on the EQ-5D consistent with low HRQoL than women referred to colposcopy with (multiple) low-grade results. This finding appears new to the literature. Neither Heinonen et al [11] nor Korfage et al [12] found evidence of a relationship between HRQoL and women's original cytological abnormality. However, in both of these studies the numbers of women in the groups with different referral cytology were substantially smaller than those in our study. In a study of women with low-grade referral cytology, Whynes et al [13] found a relationship between colposcopy plus LLETZ management (compared to colposcopy only and colposcopy plus punch biopsies) and lower HRQoL at some follow-up time points. This association suggests that it is possible our finding reflects women with high-grade cytology being more likely, than those with low-grade cytology, to have underlying cervical intraepithelial neoplasia (CIN) grade 2/3 and undergo LLETZ. Women with high-grade cytology are also more likely to have undergone additional follow-up procedures. We did not have information on any interventions or procedures after the initial colposcopy appointment, and this is a limitation of the study.

We and others have shown that colposcopy itself, and attending for follow-up, can have an adverse psychological impact on women with high grade findings, causing significant anxiety, distress and worries which may be long lasting [31-33]. It is possible that these adverse psychological effects translate into decrements in HRQoL. For example, Whynes et al. [34] found the EQ-5D to be responsive to differing degrees of HADS-assessed anxiety and depression among a large sample (n=3119) of UK women with low grade cervical abnormalities detected through screening. In that study, a higher likelihood of HADS-identified anxiety and/or depression was associated with significantly lower EQ-5D index.

This suggests that our observed association between high grade dyskaryosis and low HRQoL may reflect more worries, distress or anxiety in that group.

In a previous study analysing this population, non-Irish women were found to be at increased risk of anxiety after colposcopy [4] and our analysis here finds the same pattern with HRQoL (i.e. non-Irish women were significantly more likely to be considered to have low HRQoL in the 12 months after colposcopy than Irish women). To the best of our knowledge, our study is the first to show this relationship with HRQoL after colposcopy. Disparities in cervical screening participation among immigrants compared with general population women (e.g. in Finland and England) have been well documented [35-37], but less is known about the impacts of screening participation in migrants compared to native populations. The previous cervical screening history of the women included in our study (both Irish and non-Irish) was not available. However, it seems unlikely that lack of previous access to screening among non-Irish women would explain our findings, as all but seven of the thirty-nine non-Irish women were from another OECD country, and would likely have had some access to smear tests. Referral cytology was not associated with nationality (p=0.581), and the model was adjusted for this, so this cannot explain the finding either. The number of non-Irish women in our study population was broadly in line with the number expected based on the nationality of people resident in Ireland [38]. Historically, the largest group of non-Irish nationals were UK citizens, but more diverse migration patterns mean that increasingly, non-Irish women may not speak good English. This may impede them in navigating the healthcare system and limit their understanding of information about their colposcopy. The Irish cervical screening programme has produced information leaflets in 11 languages, but these do not include information about colposcopy and follow-up, nor is information in a suitable language likely to be the only thing needed to enable a migrant to understand and navigate, and feel confident within, an unfamiliar healthcare system. More culturally appropriate screening and follow-up

literature for non-Irish women is needed for women who have limited English. In addition, more support, and assistance with patient navigation, for non-Irish women, could help reduce the risk of low HRQoL in such women following colposcopy.

Satisfaction with healthcare also determined whether women reported EQ-5D responses considered to indicate low HRQoL in the 12 months post colposcopy. While evidence on the relationship between satisfaction with healthcare and HRQoL is comparatively sparse, a review by Bamm et al. [39] and colleagues of people living with chronic conditions found a generally positive relationship between HRQoL and satisfaction with care, consistent with our findings.

In terms of our final predictor of HRQoL, the observed association between current smoking and low HRQoL measured by the EQ-5D is consistent with relationships in the general population [40-42], though it is possible that this finding reflects uncontrolled confounding by comorbidities; smokers have higher prevalence of comorbidities than non-smokers [43]. However, given the young age profile of participants (approximately 70% of participants were aged forty or younger) and the exclusion of women managed for previous cervical abnormalities, it is likely that the number of women with significant comorbidities would be small. There was a greater proportion of current smokers among women with high-grade disease compared to those with low-grade disease in our study (44% vs 29%) and smoking status and referral cytology result were significantly associated (p=0.018). Previous studies have observed an association between being a current smoker and low HRQoL [41,42]. However, in our model the effect of smoking was adjusted for referral cytology, so this cannot account for the observed association with smoking. The likelihood of regression of cervical precancerous lesions is significantly lower among women who smoke than in never-smokers [44] and women who smoke are more likely to require follow-up visits to

colposcopy clinics and require further treatments to remove cervical abnormalities compared to non-smokers [45]. This may explain our findings.

HRQoL, colposcopy and the implications for cost-effectiveness modelling

Many healthcare systems are re-evaluating the cost-effectiveness of cervical cancer screening protocols. Accurate estimates of HRQoL are of great importance to this process. The numbers of women involved in screening and follow-up are large, meaning that it is arguably more important to have robust HRQoL data for these health states than for states for which HRQoL might be lower, but which affect fewer women (e.g. cancer). To the best of our knowledge, our study represents one of the very few longitudinal studies on HRQoL of follow-up and which provides QALY weights for use in economic analyses. We have reported weights both by treatment received and also by histological finding. Ours is one of the few studies to do both. With respect to treatment received results are largely in keeping with the available literature. Whynes et al [13], for example, found mean QALY weights for women who had received a colposcopy (0.906), a colposcopy with biopsy (0.912) and LLETZ (0.919). These values are close to our own (0.92-0.89, 0.91 and 0.86-0.89 respectively). Our QALY weights by histology are also similar to those found in other studies [12, 46]. While there were not a sufficient number of women in our sample who had developed a cancer to report reliable weights for cervical cancer, we feel that these weights will be of use to cost-effectiveness modellers.

Strengths and limitations

Our study is one of only a handful to examine the predictors of low HRQoL in the year after colposcopy employing a longitudinal study design. With the exception of one UK trial [47], which only included women with low-grade cytology, our study is also the largest to have investigated HRQoL after-effects of colposcopy and related interventions. As a generic questionnaire, the comparative lack of sensitivity of the EQ-5D-3L (and potential ceiling/floor effects) [48] might mean some factors that concern women following colposcopy, such as worries about fertility, sex and cancer [4, 49, 50], are not adequately captured by the instrument. In terms of the explanatory variables considered in the study, women's clinical data (e.g. initial management received) was extracted from colposcopy clinic records at 4 months and we lacked information on any procedures that happened between then and 12 months. The other variables explored for associations with HRQoL also related to the 4-month time point; if these changed during follow-up the results may be impacted by some non-differential misclassification. Related to this, although life events have been shown to have a modest impact on HRQoL [51], we did not collect information on these or some other variables that influence HRQoL (such as social support) [52], meaning there is a possibility of some uncontrolled confounding.

Women were recruited from only two colposcopy clinics, both were part of the CervicalCheck screening programme. However, the hospitals in which they were located serve large numbers of patients from diverse backgrounds. For logistical reasons related to running a research study within busy hospital clinics, we were not able to systematically approach every woman in every clinic. It is possible that some particular groups of women were not approached (e.g. those visibly upset). While the way the women who took part in the study were recruited may affect overall estimates of HRQoL (i.e. we may have overestimated this), internal comparisons within the study population will not necessarily be

impacted. Women who completed and returned at least one of the three questionnaires were offered the chance to enter into a prize draw to win one of two high street shopping vouchers. While modest incentives such as these are effective in improving questionnaire response rates [19], we cannot entirely preclude the possibility that they influenced (directly or indirectly) HRQoL as measured in the study participants However, the authors are unaware of any empirical evidence to support this; indeed most studies show that incentives have no effect on quality of response, sample composition or response distributions [53].

Conclusion

While mean HRQoL the proportion of the sample considered to have low HRQoL, remained static over 12 months following colposcopy, some subgroups of women were at greater risk of low HRQoL. In particular non-Irish women and women whose referral cytology was high-grade had a significantly greater chance of low HRQoL. As well as providing information to inform cost-effectiveness analyses, our findings may aid policymakers, service providers and patient advocacy groups to better target supports and advice for women who have received a colposcopy thereby minimising the risk of them experiencing low health-related quality of life.

Declarations

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Author contributions

AÓC analysed the data and wrote the paper. MOC conducted the survey, analysed the data and wrote the paper. KOB analysed the data and wrote the paper. JOL, CM, TD and GF conceived and designed the experiments and wrote the paper. JM conducted the survey and wrote the paper. WP and CR conceived and designed the experiments and wrote the paper. CW conducted the survey and wrote the paper. LP conceived and designed the experiments and wrote the paper. LS conceived and designed the experiments, analysed the data and wrote the paper. All authors read and approved the manuscript

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Compliance with ethical standards

Conflict of interest

The authors have no conflicts of interest relevant to this manuscript.

Ethical approval

Ethical approval was obtained from the ethics committees of the Coombe Women and Infants University Hospital (ref:21-2006; approval granted 27 April 2010) and the National Maternity Hospital, Dublin (no ref. number given; approval granted 26th October 2010).

Informed consent

Written informed consent was obtained from women interested in partaking in the study.

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