How distressing is referral to colposcopy in cervical cancer screening?

A prospective quality of life study

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ABSTRACT

Objective: Referral for colposcopy because of abnormal Pap test results is likely to be distressing, but the extent and duration of these effects are unknown. We aimed to fill this gap.

Methods: We conducted a prospective observational study at two departments of Obstetrics and Gynecology (an academic and a non-academic setting). Women referred for colposcopy completed questionnaires before colposcopy, and at 1, 3, and 6 months afterwards. A reference group of 706 screen participants, aged 29-60 years old, was included and completed questionnaires once. Main outcome measures were generic health-related quality of life (HRQoL), assessed through the EQ-5D and the SF-12 physical and mental scores (PCS-12 and MCS-12); anxiety as assessed by STAI-6, and screen-specific anxiety as assessed by the Psychological Consequences Questionnaire (PCQ).

Results 154 women responded to the questionnaire, of whom 132 were included in the analyses. Histological results were CIN 1 in 17/115 women (15%) and CIN 2+ in 62 (54%). In 36 women (31%) there was no histologically confirmed neoplasia. Before colposcopy physical HRQoL scores were similar or slightly better than in the reference group, while mental HRQoL (MSC-12) and (screen-specific) anxiety were worse ($p<0.001$). Irrespective of CIN-grades, anxiety washed out during follow-up ($p<0.001$), with changes being clinically relevant.

Conclusions Referral for gynecological evaluation because of abnormal PAP-test results was distressing. Anxiety - and not the physical burden of management - seemed to be most bothersome to women. For all CIN-grades, distress disappeared over six months following colposcopy, suggesting a reassuring effect of gynecological management.

Key words

- Cervical cancer;
- Longitudinal;
- Quality of life;
- Screening;
- Distress;
- CIN;
- cervical dysplasia;
- abnormal Pap

Introduction

Screening for cervical cancer aims to reduce disease-specific mortality by early detection and treatment of pre-invasive (cervical intraepithelial neoplasia, CIN) or early invasive disease. Screen participants with abnormal Pap tests are generally referred for gynecological evaluation including colposcopy. Previous studies found that colposcopy was stressful for most women. (1) Not the procedure itself but the prospect of having cancer and risk of dying were the biggest sources of distress. (2)

Cervical cancer screening is aimed at preventing the disease by finding and treating precursor lesions, but these precursors are known to often regress. (3) The number of treated precursors will thus be considerably larger than the number of prevented cases of cervical cancer. Screening policy thus requires balancing the benefits of preventing cancer by treatment of lesions that are likely to resolve against the harms of screening. Distress and anxiety due to screening are such harms. Until 2004 there had been little research on how short-term effects of screening interventions affect quality of life. (4) While roughly half of the adult women in Europe are invited to have a smear test at least once every 5 years, of whom between 0.8 and 4.4% are referred to colposcopy every screening round, (5) the extent and duration of adverse quality of life effects after abnormal Pap test results are still unknown.

We aimed to prospectively assess the effects of colposcopy referral on women's generic health-related quality of life (HRQoL) and on (screen-specific) anxiety levels. A female reference group of screen participants was included as a proxy of HRQoL levels preceding referral. We compared HRQoL and anxiety outcomes of the study group, referred to as "colposcopy group", to those of the reference group.

Methods

Cervical cancer screening in the Netherlands

In the Dutch national cervical cancer screening program, women aged 30-60 are invited once every 5 years to have a Pap test. Participation does not entail costs. At the time this study was conducted, the national uptake rate was 65%, (6) and neither primary HPV screening nor HPV vaccination had been introduced. In 2009, 96.7% of women who participated had normal cytological smear results and in one percent Pap tests were of inadequate quality requiring repeat smears. High-grade cytological abnormalities, including moderately dyskaryotic (Pap 3a2 (7)) or worse, were found in 0.5% to 0.7% and low grade abnormalities, including borderline or mildly dyskaryotic (Pap 2/3a1) smear results, were found in 1.8% of screen participants. (6-8)

Women can be referred to gynecological evaluation through two different routes. Following the screening protocol women whose smear results are moderately dyskaryotic (Pap 3a2) or worse are immediately referred for colposcopy by a gynecologist. Women with borderline or mild dyskaryotic smear results (Pap2/3a1) are advised to have triage smears made by their GP. (7) If these are once again abnormal women are also referred for colposcopy.

If histology results of biopsies taken at colposcopy indicate CIN-grade 2 or worse further treatment is performed. A more conservative approach is recommended for women diagnosed with CIN 1 since the majority of these lesions will regress. After two or three consecutive negative smears women with CIN 1 will return to the national screening program.

Study design

Between February 2006 and April 2008 a prospective longitudinal cohort study was conducted in two Dutch hospitals. We aimed at including all women who were referred for gynecological

evaluation because of abnormal Pap test results in the screening program. Women whose patient files later showed that they were ineligible were excluded (see Figure 1.)

Women scheduled for colposcopy after abnormal smear results were sent a letter, in which they were asked for written informed consent to participate in the study, which involved completion of the attached questionnaire (see below), and 3 following ones after 1, 3 and 6 months (return envelopes were provided). Women were also asked for permission to consult their patient files and/or the gynecologist for clinical data about colposcopy follow-up. They were assured that not completing the questionnaires would not have any consequences for their medical care. No reminders were sent after the initial questionnaire. Once women had consented in participation in the study we sent reminders for follow-up questionnaires. A group of screen participants was included as a reference (see below). Both groups were 29-60 years old.

This study was part of a comprehensive evaluation of the Dutch cervical cancer-screening program. The medical ethics review committees of the Erasmus University Medical Center Rotterdam (MEC-2004-099) and of Medical Center Alkmaar (M04-051) approved the research protocol.

Respondents' characteristics

Questions on education, employment, marital status, and having children or not were part of the initial questionnaire. Educational level was classified as low (primary school or lower technical education), intermediate or high (college/university degree).

Information about Pap results at referral for gynecological evaluation and about CIN-grade was available conditional on women having granted permission to consult their patient files and/or gynecologist.

In this paper all colposcopy results worse than CIN 1 will be referred to as CIN 2+. The most severe grade of CIN in the first biopsy after inclusion in this study was used to define the respondents' CIN-grades. (9)

Reference group

We compared HRQoL and anxiety scores of the intervention group to those of a reference group of 706 screen participants, who had been recruited through the regional screening organization in Maastricht (10). Data were collected after screening but before women knew their test result. Reference and study group completed similar measures (see below).

Content of the questionnaires

Questionnaires included validated measures on generic HRQoL (11), generic anxiety (12), and screen specific anxiety (13). Generic HRQoL was assessed through the EuroQol classification (EQ-5D) and the 12-item Short-Form Health Survey (SF-12). The EQ-5D consists of 5 items (mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression). Scores can be linked to a utility score with 0 indicating 'death' and 1 'full health'. (14) The EQ-5D is complemented by a visual analogue scale on current health, the Valuation of Own Health, which is anchored by 'worst imaginable health state' (0) and 'best imaginable health state' (100). The SF-12 consists of 12 items in the physical and mental domain. Based on these item scores summary measures for the physical and mental component (PCS-12 and MCS-12) are constructed, (11) using norm-based methods with a mean of 50 and a standard deviation (SD) of 10. Age- and sex-adjusted SF-12 norm scores from the Dutch population, including women who do not participate in the screening program, are available from Statistics Netherlands. (15)

Generic anxiety was assessed through the STAI-6 containing 6 items on e.g. feeling at ease or upset. Higher scores (20-80) indicate higher levels of generic anxiety. (12, 16) STAI-State scores of over 44 define an individual as highly anxious. (17)

Screen-specific anxiety was measured through the Psychological Consequences Questionnaire (PCQ), which was developed to assess the consequences of breast screening on emotional, physical, and social functioning. Corresponding subscales contain 5, 4, and 3 items, respectively. (13) Ratings for symptoms within each dimension vary from 0 (not at all) to 3 (quite a lot of time). The overall PCQ score ranges from 0-36; (18) higher scores indicate more dysfunction. We used the Dutch version as adapted by Rijnsburger and colleagues. (19)

Statistical analyses

In accordance with guidelines, (20) missing items in the STAI-6 and the PCQ were imputed by respondents' own average score if they had completed at least 50% of the items. Differences between the colposcopy and reference groups considering background variables were assessed using t-tests for continuous variables and Chi-square tests for categorical ones. Differences considering HRQoL and anxiety scores were assessed using linear regression, controlling for differences in age. A condition for linear regression is a normal distribution of residuals. However, this condition is often not met when HRQoL measures are used. Therefore we inspected the residuals and compared them with the normal distribution. The deviations we found led us to perform a bootstrap analysis (21) (1,000 replicas) in the program R, (22) while controlling for differences between groups in age.

Friedman tests were used to assess changes in HRQoL scores in the study group across multiple measurements. Friedman tests are based on data from those who completed all assessments. For each measure we report how many women completed it at all four time points, and we report on the HRQoL and anxiety scores of just those women. We hypothesized

that more anxiety would be reported at baseline if the initial Pap result was more serious. Therefore we assessed HRQoL and anxiety by Pap result (Pap2/3a versus Pap 3b or worse), using t-tests to assess the significance of the differences between groups. We also hypothesized that the more serious the CIN-grade turned out to be, the more anxiety and screen specific anxiety would be reported at follow-up assessments, and therefore we assessed HRQoL and anxiety per CIN group (i.e. no CIN was found versus CIN 1 versus CIN 2+). We used ANOVA to assess the statistical significances of differences in HRQoL and anxiety scores between CIN-groups. Statistical analyses were performed using SPSS for Windows, version 17.

The minimal important difference (MID), indicating clinical relevance, was operationalized as a difference of at least half a SD. (23)

Results

154 women completed questionnaires after being referred for gynecological evaluation. Three of them were too young to have participated in the screening program. We excluded them from further analyses. After consulting patient files or gynecologists (if women had given us permission to do so), we found that another 19 women were ineligible since they had not been referred to the gynecologist after routine Pap tests (n=15) or they had already been having gynecological check-ups for at least a year (n=4). Thus, 132 women were included for analysis (see Figure 1, Table 1). Pap test results had been communicated to them by their GP (69%), or by their GP's assistant (29%). In two cases the hospital informed these women. Women had been contacted by telephone (74%), in person (22%) or by letter (5%). There is no protocol specifying how abnormal PAP results should be communicated to women.

Histological results were known in 115/132 women and were CIN 1 (n=17), CIN 2 (n=32), CIN 3 (n=29), or carcinoma stage 1 (n=1). In 36 women there was no histologically confirmed neoplasia. These women had been referred with Pap 2 (n=21), Pap 3a (n=13), or Pap 3b (n=2). In two women CIN-grades were unknown and fifteen women did not grant us permission to access their patient files or gynecologist. Since their HRQoL and anxiety scores were similar to those who had routine cervical smears, we included them in the analyses. Management was known in 117 women. Forty-six out of these women did not receive therapy, , 60/117 were treated once and 11 women were treated more than once (11/117), e.g. by LLETX excision and conisation or they had conisation twice. Table 2 presents the most invasive therapy per woman, reported per CIN-grade.

Overall, questionnaire response rates were 114 (86%), 110 (83%), and 108 (82%) at 1, 3, and 6 months follow-up.

Comparison colposcopy group and reference group

Background variables differed significantly between the colposcopy and the reference group (Table 1). As expected, women referred for colposcopy (n=132) were younger (40.6 vs. 45.6 years), because low grade CIN is more prevalent in younger age groups. Compared to the reference group they had more often paid jobs and less often children.

The crude PCS-12 scores of the colposcopy group were significantly higher – which indicates better physical functioning - than those of the reference group (54 versus 51, Table 3) and than the age adjusted norm score of 51 for the female Dutch population (Statistics Netherlands). The MCS-12 scores of the colposcopy group, however, were lower – which indicates poorer mental functioning - than those of the reference group (47 versus 53, Table 3) and than the Dutch norm scores of 52 (Statistics Netherlands). Differences remained significant after controlling for age (Table 3).

Average crude STAI-6 and PCQ scores were higher in the colposcopy group than in the reference population, indicating more generic and screen specific anxiety in women with abnormal smear results. Differences in STAI-scores and in two PCQ subscale scores exceeded the Minimal Important Difference (MID), indicating that the differences between the colposcopy group and the reference population were of clinical relevance (Table 3).

For all scale scores bootstrap analyses resulted in similar conclusions considering statistical significance and clinical relevance as the linear regression analyses.

Generic HRQoL and anxiety: results over time

Changes over time in the EQ-5D utility score, the EQ-5D 'rating of own health', and the sum score for physical function (PCS-12) were neither statistically significant nor clinically relevant. The scores for mental health score (MSC-12), generic anxiety (STAI-6), and screen-specific anxiety (PCQ) improved over time ($p<0.001$). Overall, changes over time indicated improved functioning towards the end of the follow up period. Changes in generic anxiety and in two

subscales of screen-specific anxiety indicated clinical relevance (Table 4). At baseline, 32% of the colposcopy group (41/130) reported high anxiety levels (i.e. STAI-6 scores of over 44). This decreased to 18% (20/112) at 1 month follow-up, and to 14% at 3 and 6 months follow-up (15/110 and 15/108, respectively). High anxiety was reported by 10% of the reference group. The significance of the difference between the groups decreased from $p<0.001$ at baseline to 0.24 at 6 months follow-up.

At 6 months follow-up, HRQoL and generic anxiety scores of the colposcopy group were similar to those of the reference group, while screen-specific anxiety scores remained worse.

Generic HRQoL and anxiety over time by initial Pap test result

HRQoL and anxiety were similar in women referred for colposcopy with Pap 2/Pap 3a (at most moderately dysplastic, n=90) versus women with Pap 3b or worse (at least severely dysplastic, n=21), data not shown.

Generic HRQoL and anxiety over time by CIN-grade

In 115 cases CIN-grades were known. Regardless of CIN-grade, generic HRQoL remained at similar levels throughout follow-up and (screen specific) anxiety decreased over time (Figure 2). With two exceptions, HRQoL and anxiety scores differed significantly between the 3 CIN-groups.

Discussion

We assessed the HRQoL and anxiety in a cohort of women with abnormal Pap test results who were referred for gynecological evaluation. At baseline, the colposcopy group reported more anxiety than the reference group, with differences being clinically relevant. We found that during follow-up, overall, HRQoL improved in the colposcopy group and their anxiety decreased over time, irrespective of CIN-grade.

The availability of clinical data, which enabled us to discriminate between varying degrees of abnormalities, is one of the strengths of this prospective study. Also, as recommended for quality of life research, we used both generic and screen-specific health measures that had been validated in similar groups as the currently described population. To enable interpretation of the HRQoL and anxiety scores we included a reference group, which is recommended but not often done (4). Limitations of this study are the lack of data about the length of the interval between the receipt of the Pap test results and the colposcopy results, the response rate being unavailable, and the relatively low number of respondents who were diagnosed with CIN 1.

CIN grade 2+ was found in 62 out of 115 women and the positive predictive value (PPV) was thus 54%, which is comparable to the 49% PPV of a moderately dyskaryotic Pap test in the Dutch screening program (5).

In 36 women in our cohort (31%) only normal Pap tests and histology results were observed during follow-up. These so-called false positive test results are inherent to screening programs; an abnormal test result leads to additional tests and hospital visits and may cause anxiety or worry, while no abnormalities are found in the end. This group of women, of whom four received treatment, reported similar HRQoL and higher anxiety levels as who were found to

have CIN2+, while in the latter group 59 out of 62 women received treatment. Anxiety - and not the physical burden of management - seemed to be most bothersome to women. In a review of 210 papers Cullen et al. concluded that affected domains in women with false-positive screening results include distress, fear and worry about having or getting cancer. (4) This issue becomes even more relevant with the introduction of HPV-screening, since the specificity of HPV screening is expected to be considerably lower in younger age groups (24). Twenty years ago most women interpreted the term precancer as 'early cancer'. (25) Also more recently, mildly abnormal smear results were misinterpreted as actually having cancer (26, 27) which will lead to more anxiety. (27) We therefore recommend to provide women who have abnormal smear test results with clear written information about the meaning of this result, stressing that the abnormal test result does not indicate that they have cancer, and to check in person or by phone whether this information was properly understood.

In a previous study, women not complying with follow-up protocols reported the highest anxiety scores. (28) Since we only included women who did participate in follow-up protocols, we probably arrived at an underestimation of women's anxiety, even more so because pathologically high levels of anxiety and worry apparently lead to low screening rates. (4)

The negative impact on mental health of abnormal smear results was found to be not of a lasting or serious nature in the majority of women. (29, 30) However, in a cross-sectional study among 270 women, addressed at 6-24 months after the initially abnormal Pap test result, our research group showed that borderline and mildly dyskaryotic smear results were consistently associated with considerable excess anxiety. (31)

CONCLUSION

We conclude that referral for gynecological evaluation after abnormal PAP-test results negatively impacted mental health. Anxiety - and not the physical burden of management - seemed to be most bothersome to women, which confirms earlier literature. Irrespective of CIN-grade, this negative effect on mental health diminished over time and had washed out at 6 months after baseline. Possibly, this indicates that management had a reassuring effect and led to reduced anxiety levels. We recommend carefully choosing cut-off strategies for referral to colposcopic evaluation. Also, clear communication about the meaning of false-positive test results is needed with women invited to participate in screening and with women who have abnormal test results, so they will understand what is going on – and especially what is *not.*

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Disclosure of interest

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Contribution to authorship

M. van Ballegooijen, D. Habbema and M.L. Essink-Bot conceived the idea for the study; M. van Ballegooijen and M.L. Essink-Bot designed the protocol; M.L. Essink-Bot supervised the execution of the study; I. Korfage, M. van Ballegooijen and M.L. Essink-Bot designed the questionnaire; I. Korfage, S. Westenberg and T. Helmerhorst organized the local data collection; I. Korfage was responsible for the database design and data entry; I. Korfage, M. van Ballegooijen, and M.L. Essink-Bot made the statistical design; I. Korfage performed the analyses; I. Korfage drafted the report; all the collaborators listed above contributed/edited the paper. I. Korfage is the guarantor of the study.

All authors have full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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345 **Details of ethics approval**

346 The medical ethics review committees of the Erasmus University Medical Center Rotterdam
347 (MEC-2004-099) and of Medical Center Alkmaar (M04-051) approved the research protocol.
348 All participating women gave written informed consent.

349

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355 **Legends of tables and figures**

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358 percentages, unless otherwise indicated, compared with a reference group of screen
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360 **Table 2** Most invasive treatment per woman, reported per CIN-grade

361 **Table 3** Generic Quality of Life scale scores (SD) in women referred to the gynecologist for
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364 adjusted.

365 **Table 4** Time trend analysis (repeated measures) of women with an abnormal Pap test result
366 (colposcopy group); starting before the first consultation with the gynecologist, plus

follow-up assessments at 1, 3, and 6 months later, and the statistical significance of changes over that time period.

Figure 2 Health-related quality of life and anxiety scores per CIN-stage at four assessments.

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Table 1 Background characteristics of the colposcopy group, observed scores in numbers and percentages, unless otherwise indicated, compared with a reference group of screen participants.

	Colposcopy group n=132	Screen participants n=706	*p*-value
Age (years)			<0.001
Average (SD)	40.6 (8.2)	45.6 (9.3)	
Median	40.2	45.1	
Range	29-60	29-60	
Missing	*4*	*1*	
Education (%)			0.06
Low education	21 (17)	144 (23)	
Medium	77 (62)	323 (50)	
High	26 (21)	174 (27)	
Missing	*8*	*65*	
Employment status (%)			0.03
Paid job	92 (81)	419 (67)	
Housewife/unpaid job/student	16 (14)	142 (23)	
No job	6 (5)	49 (8)	
Retired	0	13 (2)	
Missing	*18*	*83*	
Marital status (%)			0.03
Married/cohabiting	92 (72)	567 (81)	
Living without partner	36 (28)	137 (20)	
Missing	*4*	*2*	
Children (%)			0.002
No	40 (32)	130 (20)	
Yes	84 (68)	528 (80)	
Missing	*8*	*48*	
Average no. of children	2	2	
Country of birth (%)			<0.001
the Netherlands	120 (92)	627 (99)	
otherwise	11 (8)	4 (1)	
Missing	*1*	*64*	

Table 2 Most invasive treatment per woman, reported per CIN-grade

	Most invasive therapy per woman, n (%)					
	Cryotherapy	**LLETZ excision**	**Conisation**	**Uterus extirpation**	**No therapy**	**Total**
CIN-grade						
No neoplasia found	1 (1%)	0 (-)	1 (1%)	2 (2%)	32 (27%)	36 (31%)
CIN=1	4 (3%)	2 (2%)	1 (1%)	0 (-)	10 (9%)	17 (15%)
CIN2+	20 (17%)	29 (25%)	7 (6%)	3 (3%)	3 (3%)	62 (53%)
Unknown CIN-grade	0 (-)	1 (1%)	0 (-)	0 (-)	1 (1%)	2 (2%)
Total	25 (21%)	32 (27%)	9 (8%)	5 (4%)	46 (39%)	117 (100%)

Table 3 Generic Quality of Life scale scores (SD) in women referred to the gynaecologist for colposcopy, shortly after their abnormal test results and in a reference population of screen participants. Statistical significance of differences between groups was age-adjusted.

	Colposcopy group n=132	Screen participants n= 706	*p*-value
Generic health-related quality of life			
EuroQol utility, **EQ-5D** (0-1)	0.90 (0.14)	0.90 (0.18)	0.85
EuroQol , **Rating of own health** (0-100)	80 (12)	81 (13)	0.46
SF-12 (0-100)			
Sumscore physical (PCS-12)	54 (8)	51 (10)	0.04
Sumscore mental (MCS-12)	47 (12)	53 (9)	<0.001
Generic Anxiety			
STAI-6 (20-80) *	41 (12)	33 (10)	<0.001
Range	20-73	20-77	
Highly anxious (STAI score >44), n (%)	41 (32%)	70 (10%)	<0.001
Screen-Specific Anxiety			
PCQ			
Emotional Scale (0-15)	4 (4)	1 (2)	<0.001
Physical Scale (0-12) *	2 (2)	0 (1)	<0.001
Social Scale (0-9) *	2 (2)	0 (1)	<0.001
Total Score (0-36) *	8 (7)	2 (4)	<0.001
Range Total Score	0-29	0-30	

EuroQol and SF-12: higher scores indicate *better* functioning

STAI-6 and PCQ: higher scores indicate *worse* functioning.

* differences exceeded the minimal important difference (MID), indicating clinical relevance

Table 4 Time trend analysis (repeated measures) of women with an abnormal Pap test result (colposcopy group); starting before the first consultation with the gynaecologist, plus follow-up assessments at 1, 3, and 6 months later, and the statistical significance of changes over that time period.

	Shortly after suspicious smear n=132	At 1 month follow-up n=114	At 3 months follow-up n=110	At 6 months follow-up n=108	*p*-value*	No. of women who completed measure all 4 times	*Inter-pretation*
Generic health-related quality of life							
EuroQol utility, **EQ-5D** (0-1)	0.91 (0.14)	0.90 (0.15)	0.93 (0.15)	0.90 (0.21)	0.16	95	Similar
EuroQol **Rating of own health** (0-100)	81(12)	77 (18)	80 (17)	78 (18)	0.08	95	Similar
SF-12 (0-100)							
Sumscore physical (PCS-12)	54 (9)	53 (9)	53 (8)	53 (10)	0.27	77	Similar
Sumscore mental (MCS-12)	50 (10)	49 (11)	52 (10)	53 (9)	<0.001	77	Improved
Generic Anxiety							
STAI-6 (20-80) *	40 (11)	37 (13)	33 (9)	34 (10)	<0.001	96	Improved
Screen-specific Anxiety							
PCQ							
Emotional Scale (0-15)	4 (4)	3 (3)	2 (3)	2 (3)	<0.001	96	Improved
Physical Scale (0-12) **	2 (2)	2 (3)	1 (2)	1 (2)	<0.001	96	Improved
Social Scale (0-9) **	2 (2)	2 (2)	1 (2)	1 (2)	<0.001	96	Improved
Total Score (0-36) **	7 (7)	6 (7)	4 (6)	3 (6)	<0.001	96	Improved

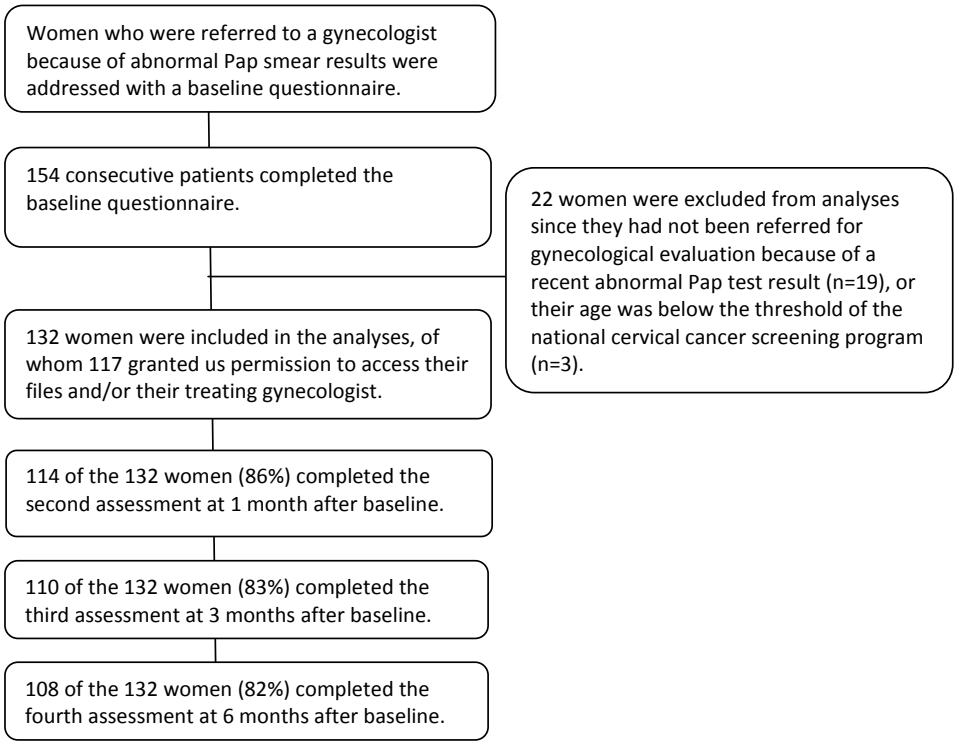
***** Statistical significance of differences was calculated using Friedman tests, including only respondents that completed all four assessments. HRQoL and anxiety scale scores are reported of those who completed that specific scale at each assessment.

****** Differences between first and fourth assessment exceed the minimal important difference (MID), indicating clinical relevance

EuroQol and SF-12: higher scores indicate *improved* functioning

STAI-6 and PCQ: higher scores indicate *poorer* functioning.

Figure 1. Flowchart of study population



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