Vaginal symptoms of unknown aetiology: a study in Dutch general practice

JANNY H DEKKER
A JOAN P BOEKE
JANNES JANSSENS
JACQUES Th M VAN EIJK

SUMMARY. Vaginal symptoms are frequently presented by women to general practitioners. In many cases, the aetiology of these symptoms remains unknown. This study focused on the factors associated with microbiologically unexplained vaginal symptoms, the course of symptoms and signs in these cases, and factors modifying this course. In a group of 810 women presenting to their general practitioner with vaginal symptoms (itching, irritation, abnormal but non-bloody discharge) the distribution of diagnoses was studied and factors associated with symptoms of unknown aetiology were identified using logistic regression analysis. During a three month follow up, the course of symptoms and signs was studied in 139 women with unexplained vaginal symptoms, using survival analysis methods. It was found that 25% of all the women had symptoms of unknown aetiology. A larger number of these women, compared with women with other diagnoses, were Caucasian, married, more highly educated, used oral contraceptives and reported psychological distress. During the follow-up period, a specific infection was diagnosed in less than 20% of the women with unexplained vaginal symptoms. Over half the women (54%) recovered within three months. Short duration of symptoms before presentation was associated with a higher probability of recovery. From the study, it was found that many women visiting the general practitioner for vaginal symptoms had no demonstrable microbial disorder. Often these symptoms were transient and disappeared without intervention. Persistent symptoms may call for further examination where somatic, as well as psychosocial, factors should be taken into account.

Keywords: vaginal disorders; vaginal discharge; differential diagnosis; diagnostic techniques.

Introduction

VAGINAL symptoms (itching, irritation and abnormal but non-bloody discharge) are a common reason for consulting the general practitioner. Though not a cause of great morbidity and, therefore, considered to be trivial at times, they can be the source of much distress. For this reason, an accurate diagnosis is recommended, based on knowledge of the epidemiology of lower genital tract infections, careful physical examination, consistent application of laboratory tests and, where needed, microbiological culturing. Vaginal trichomoniasis, candidiasis and bacterial vaginosis, as well as cervical infections with Neisseria gonorrhoeae and Chlamydia trachomatis, can be diagnosed in this way. Appropriate therapy can then alleviate much of the suffering from vaginal symptoms and prevent complications from, and spread of, sexually transmitted diseases.

Even after careful evaluation, a substantial proportion of all women consulting their general practitioner for vaginal symptoms will fail to be diagnosed: their symptoms cannot be explained microbiologically. Studies in family practices indicate that this is true for about one third of all women presenting with vaginal symptoms. Before the 1950s this proportion was even greater: bacterial vaginosis was not yet identified as a separate syndrome and tests for C trachomatis were yet to be developed, which meant that ‘vaginal symptoms of unknown aetiology’ included everything except yeasts, trichomiasis and gonorrhoea. This group has now been narrowed by excluding those with chlamydial cervicitis or bacterial vaginosis.

The origin of symptoms in women with no infective cause could be somatization, allergy or irritation, false negative cultures, bacteria belonging to transient flora which have become pathogenic, viruses, or a large cervical ectropion. Pre-carcinomatous lesions of the cervix are rare in women consulting their general practitioners with non-bloody discharge.

It is important to know whether a wait-and-see policy is appropriate for women with unexplained vaginal symptoms who have had a microbiological evaluation or whether the problem should be investigated more thoroughly. One approach to answering this question is to follow symptoms and signs over time, without intervening. Therefore, an explorative study was carried out aimed at finding a more effective approach to treating women with unexplained vaginal symptoms. The questions posed were:

how many women, consulting their general practitioner for vaginal symptoms, cannot be given a definite diagnosis; what patient characteristics, symptoms and signs are associated with vaginal symptoms of unknown aetiology, and how does the course of symptoms, signs and diagnoses in women who fail to be diagnosed as having a microbial problem progress over time, and what factors affect this course?

Method

Study population

The study population comprised of women aged between 15 and 54 years consulting their general practitioner between November 1987 and May 1990 with vaginal symptoms (itching or irritation in or around the vagina, or non-bloody discharge abnormal in its amount, colour or odour). The symptoms focused on were not related to retained foreign bodies, pointed condylomas or anogenital dermatoses such as lichen, psoriasis or eczema, nor suspected of being related to pre-carcinoma of the genital tract. The women were seen by 14 general practitioners in Amsterdam and seven in the east of the Netherlands.

To study the distribution of diagnoses and factors associated with these diagnoses, consecutive women presenting with vaginal symptoms in the Amsterdam practices only were included.
From all practices, women in whom no microbial disorder could be found, either by examination by the general practitioner or by microbiological culturing of the discharge, were asked to participate in a prospective study. They were followed up for three months. As a wait-and-see approach would not be appropriate when signs suggested pelvic inflammatory disease, women with these signs were not considered eligible. Those who were unable to complete a questionnaire in Dutch were also ineligible.

Women could be enrolled for a second time if they returned to the general practitioner with vaginal symptoms more than six months after their last visit, within the framework of the study. Participation in the study took place only after informed consent. The study was approved by the ethical committee of the teaching hospital of Vrije Universiteit in Amsterdam.

**Clinical evaluation**

After inspection of the genital area, the general practitioners performed a speculum examination, paying specific attention to the amount, colour and consistency of the discharge. The external os of the cervix and the posterior vaginal fornix were swabbed. After removing accumulated secretions, a swab was rotated firmly in the cervical canal to obtain cells for an enzyme linked immunosorbent assay (ELISA) test for *C trachomatis*. The pH value of the discharge was measured using pH-indicator paper and two drops of vaginal fluid were put on a glass slide where they were mixed with 10% potassium hydroxide and normal saline, respectively. After smearing the potassium hydroxide preparation for a fishy odour (amine test), cover slips were placed on the slide and the preparations were examined at 100x and 400x magnification, using a light microscope. The saline wet mount was examined for trichomonads, clue cells and leucocytes. The potassium hydroxide mixed wet mount was examined for the presence of pseudohyphae of yeasts.

In order to reduce inter-doctor variation in interpreting diagnostic tests, the general practitioners were trained in evaluating the discharge, taking material for culture, performing the laboratory tests and working according to the study protocol. The doctors recorded the symptoms, signs, results of laboratory tests and demographic data on standardized forms.

**Questionnaire**

Immediately after the clinical examination, all women completed a self-administered, pre-coded, baseline questionnaire addressing the type, duration and severity of symptoms, reasons for attendance, sexual activity, menstrual hygiene and contraceptive methods used. This questionnaire had been validated in a pilot study. Psychological state and personality traits possibly related to illness behaviour were also assessed. In order to identify psychological distress the general health questionnaire was chosen. The 28-item version, with scales for somatic symptoms, anxiety and insomnia, social dysfunction and depression was used. Personality traits were evaluated with the 18-item version of the health locus of control scale. This refers to the degree to which individuals perceive the events that happen to them as dependent on their own behaviour or as a result of luck, chance, fate or influence of people in a position of power.

**Laboratory evaluation**

The swabs from the vagina and cervix were placed in a transport medium and taken to the microbiological laboratory where they were processed within six hours after collection. The material was cultured for *N gonorrhoeae*, *Trichomonas vaginalis* and *Candida albicans*. All cultures were evaluated according to standard microbiological methods. The swab for *C trachomatis* was transported in a tube with buffer-fluid to the laboratory where an ELISA test was performed on the material.

**Follow up**

Women participating in the prospective study were seen two weeks, four weeks and three months after the baseline consultation. At each visit a speculum examination and tests on the vaginal discharge were carried out by the general practitioner in accordance with the baseline consultation. Cultures were taken at the second follow-up visit (after four weeks). Each time, a short questionnaire was completed by the patient, addressing the current symptoms and the course of the symptoms since the previous visit. Consultations in the intervening period for vaginal symptoms were registered in the same way as were planned visits during the follow-up period. When specific infections occurred during the study period, women were treated if necessary.

**Definitions**

Vaginal symptoms of unknown aetiology were defined as the absence of specific infections and of any sign of a disturbance of the vaginal flora where disturbance is pH>4.5, clue cells in the wet mount preparation or a positive amine test. The diagnosis of bacterial vaginosis was based on the presence of at least three out of four criteria: the occurrence of homogeneous vaginal discharge (not clot-like or curd-like), pH>4.5, clue cells and a positive amine test (Amsel criteria) in the absence of any specific infection.

Specific infections were defined in terms of a positive result of the microbiological examinations. When no culturing was done (in the prospective study two weeks and three months after the baseline visit), the general practitioner’s microscopic evaluation of the discharge was used to identify specific infections. *Herpes genitalis* was diagnosed if herpes lesions could be identified by inspection of the genital region.

**Outcome and statistical analysis**

Frequency distributions were studied to estimate the proportion of women with symptoms of unknown aetiology in those consecutively attending with vaginal symptoms.

Multiple logistic regression analysis was used to analyse the data on the variables that were possibly associated with vaginal symptoms of unknown aetiology compared with all specific diagnoses combined. This was done stepwise with backward deletion of variables based on statistical significance (threshold value $P<0.1$). Most variables were introduced as indicator variables. Age, the scores on the general health questionnaire and the health locus of control scale (health locus of control score after factor analysis with varimax rotation and forced two factor extraction), the consultation rate and the duration of symptoms were treated as interval variables.

At all three observation times, frequency distributions were studied to estimate the proportion of women with specific infections or bacterial vaginosis. Multiple logistic regression analysis was used to try to identify variables measured during the baseline observations, possibly related to infections later on.

At every consultation during the follow-up period, women had to state in the questionnaire if their symptoms had disappeared, improved, worsened or were the same. If their symptoms had ceased they were asked to specify the first day of disappearance. Survival analysis (Kaplan-Meier’s product limit method) and the proportional hazards method (Cox regression model) were used to estimate the proportion of women who continued to have symptoms as a function of time and the effect of potential modi-
fiers on this function, respectively. The variables introduced in the Cox regression model were the same as those in the logistic regression analysis. Recurrence of symptoms was also recorded.

**Results**

**Study population**

For the study of the distribution of diagnoses 642 out of 652 women from the practices in Amsterdam agreed to participate. Because of language problems, data were incomplete for the 32 women of Mediterranean origin so they were not included in the regression analysis, leaving 610 women for the cross-sectional study.

For the follow-up study, 157 women from all practices with symptoms of unknown aetiology were eligible, 15 of whom refused to participate (9.6%), mostly because they considered the study too demanding. Three forms were incomplete, leaving 139 women for the prospective study.

In the cross-sectional study three women were enrolled twice because they presented again with vaginal symptoms more than six months after their first enrolment; in the follow-up study this did not occur.

The ages of the women in both the cross-sectional and follow-up study ranged from 15 to 54 years, the largest group in the cross-sectional study being the 20 to 24 years age group (29.1%), and the largest group in the follow-up study being the 25 to 29 years age group (28.1%). In the cross-sectional study, 80.3% of the 610 women were Caucasian, 16.4% were Surinam or Dutch Caribbean, and 4.1% were of other ethnic origins. In the follow-up study, 89.2% were Caucasian, 8.6% Surinam or Dutch Caribbean and 2.2% from other ethnic origins. None of the women was pregnant.

**Diagnoses of women with vaginal symptoms**

There were between six and 18 missing cases for the different diagnoses but it was found that 227 women (37.6%) had a candida infection, 110 (18.3%) had bacterial vaginosis, 82 (13.8%) had a sexually transmitted disease (chlamydia 47 (7.9%), trichomonas 37 (6.1%) and gonorrhoea five (0.8%) and 152 (25.3%) had vaginal symptoms of unknown aetiology. If this last group was added to the women who showed some disturbance of the vaginal ecosystem, but no bacterial vaginosis or infection (43 women, 7.2%), the proportion of women with unexplained symptoms increased to 32.4%. No herps infections were observed. Double or triple infections were found in 2.5% of cases.

**Factors associated with unexplained vaginal symptoms**

In order to identify variables associated with unexplained vaginal symptoms, a logistic model was fitted. For each factor an odds ratio was calculated, reflecting the weight of the variable corrected for the influence of other variables. The confidence interval reflects the precision of the estimation.

The variables reaching significance are shown in Table 1. Symptoms showing a negative association (itching or irritation, recorded by both doctor and the patient) reduced the probability of unexplained symptoms, as did increased or malodorous discharge. Longer duration of symptoms before presentation made it more probable that the aetiology of the symptoms would remain unknown. The probability of this condition also increased if the woman was married, Caucasian, more highly educated, used oral contraceptives or had a higher score on the general health questionnaire. Of the variables reflecting information from the general practitioners’ observations during the speculum examination, a white or clear vaginal discharge or a discharge of

<table>
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<th>Table 1. Results of logistic regression analysis showing significant variables associated with unexplained vaginal symptoms.</th>
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<td><strong>Variable</strong></td>
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<td><strong>Symptoms mentioned spontaneously</strong></td>
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<tr>
<td>Vulvovaginal itching or irritation (absent versus present)</td>
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<td>Malodorous discharge (absent versus present)</td>
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<tr>
<td><strong>Demographic factors, behaviour and medical history</strong></td>
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<tr>
<td>Level of education (high versus low)</td>
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<tr>
<td>Ethnic origin (Caucasian versus other)</td>
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<tr>
<td>Marital status (married versus unmarried)</td>
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<tr>
<td>Vulvovaginal itching (absent versus present)</td>
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<tr>
<td>Amount of discharge (normal versus increased)</td>
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<tr>
<td>Previous duration of symptoms (&gt;3 months versus 1–3 months versus 2–4 weeks versus 1–2 weeks versus &lt;1 week)</td>
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<tr>
<td>Contraceptive methods (oral contraceptives versus other)</td>
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<td>Psychological distress (for every increase of GHQ score by 4, maximum 28)</td>
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<td><strong>Speculum examination</strong></td>
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<td>Amount of discharge (normal versus increased)</td>
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<td>Colour of discharge (white/clear versus coloured)</td>
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GHQ = general health questionnaire. *Total number of patients in analysis was 610, 25.3% of whom were women with vaginal symptoms of unknown aetiology. Comparison is between cases without a diagnosis and the others. Number of cases with one or more missing variable is 97. As the threshold value for keeping variables in the logistic model was 0.1, the 95% confidence interval may include unity.

normal quantity was more frequently associated with symptoms of unknown aetiology.

The variables which were not significant in the category of spontaneously mentioned symptoms included increase in vaginal discharge, pain in or around the vagina and abnormal colour of discharge. Non-significant variables in the demographic, behavioural and medical history category included age, socioeconomic status, duration of discharge, colour of discharge, painful micturition, hygiene of vulvovaginal region, tampon use, parity, frequency of sexual intercourse, number of sexual partners, reason for attendance (possibility of sexually transmitted disease, troublesome symptoms or fear of serious disease), consultation rate and internal–external orientation on health locus of control scale. In the speculum examination category, consistency of discharge was non-significant.

**Follow-up study**

Of the 139 women with vaginal symptoms of unknown aetiology who participated in the prospective study, 114 (82.0%) were seen on the first visit after two weeks, 108 (77.7%) remained in the study after one month and 92 (66.2%) completed the three month follow up. Lost cases did not differ from those who completed the follow up, with regard to age and duration and severity of symptoms (t-test and Mann Whitney tests). The actual times between baseline observations and the three observation sessions

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was slightly longer than anticipated (means of 18, 37 and 104 days, respectively). Only two women had intercurrent vaginal symptoms. In both cases no microbiological abnormality could be found.

**Diagnoses during follow-up period**

At two weeks, the general practitioners diagnosed a specific infection in 12.3% of patients (14/114) (candida six women, trichomonas one woman, bacterial vaginosis seven women). Examination in the fourth week resulted in diagnoses in 7.4% of the women (7/95) who had not been diagnosed as having a microbial disorder until then (candida three women, chlamydia three, bacterial vaginosis one woman). At the end of the follow-up period, doctors were able to diagnose four new cases among 76 women (5.3%) (candida three women and bacterial vaginosis one woman).

Of the variables assessed at the baseline visit, only a yellow or green vaginal discharge observed by the general practitioner was related to the diagnosis of an infection or bacterial vaginosis later on (coloured discharge increased the probability of a specific infection or bacterial vaginosis: odds ratio 3.1; 95% confidence interval (CI) 1.2 to 8.5).

**Course of subjective symptoms**

Survival analysis of the time at which symptoms disappeared enabled the use of information on patients who did not complete the follow-up, who were diagnosed during the follow-up period as having a specific infection or bacterial vaginosis or who had reached the end of follow up before the end-point in the analysis (120 days). Analysis of the proportion of symptomatic women as a function of time showed that at the end of the three month follow-up period 46% of the 139 women were not relieved of their vaginal symptoms of unknown aetiology. The median time between onset of symptoms and recovery was 105 days and the time at which 25% of the women had recovered was 26.5 days. The data for 45 of the 49 women whose symptoms disappeared during the follow-up period were complete enough for studying recurrences. Reappearance of symptoms before the end of the follow-up period was reported by 22.2% of the women (10/45).

Using the proportional hazards method (Cox regression model), variables were identified that influenced the course of subjective symptoms. Duration of symptoms prior to presentation was the most important modifier of this course: the shorter this period, the more probable the disappearance of symptoms. For every stepwise increase in duration the hazard ratio increased by a factor of 2.1 (95% CI 1.6 to 2.7). Therefore, symptoms lasting less than one week gave an 9.3-fold better prognosis than symptoms lasting longer than one month (three steps on the scale of symptom duration (Table 1); 2.1^3 = 9.3; 95% CI 4.1 to 19.7). A less influential factor was an increase in the amount of vaginal discharge. This factor worsened the prognosis (hazard ratio 4.4; 95% CI 2.1 to 9.4). The other variables in the model (promiscuity, parity, consistency of discharge, barrier contraceptive devices), though significantly related to the course over time, were less important.

To study the effect of symptom duration in more detail a Kaplan-Meier analysis was carried out in order to compare the survival curves in two categories of duration of symptoms of unknown aetiology in the 139 women: symptoms lasting less than or more than one month before presentation (Figure 1). The curve for the women with a previous duration of symptoms of shorter than one month fell much more rapidly than the curve for

![Figure 1](image-url)

**Figure 1.** Probability of recovery from time of presentation in women with unexplained vaginal symptoms, by length of previous symptom duration, as a function of time (Kaplan-Meier method). n = number of women in group.
women with longer lasting symptoms, meaning that a much greater proportion of the first category of women were symptom free at every point in time. The striking divergence of the curves was reflected in the small P value for the Mantel-Cox test for the difference between the curves (P<0.001).

Discussion

Many women presenting with vaginal symptoms could not be diagnosed as suffering microbiological disorders even after careful evaluation. Twenty five per cent of these women showed no signs of vaginal or cervical pathology. This proportion increased to 32% when those who had signs indicating a disturbance of the vaginal flora without completely meeting the Amsel criteria for bacterial vaginosis were included.

Specific symptoms were strikingly absent in these women with vaginal symptoms of unknown aetiology: they were less likely to suffer from itching and secreted more frequently normal smelling discharge of normal amounts. The only positive finding from the medical history was longer duration of symptoms before presentation at the general practitioner. Furthermore, a greater proportion of them used oral contraceptives. An association between unexplained vaginal symptoms and women who were psychologically distressed, Caucasian, married or more highly educated was observed.

A small number of the women were given a specific diagnosis during the follow-up period, most of which were of mild conditions. The proportion of new diagnoses tended to decrease over the follow-up period. Coloured discharge as assessed by the general practitioner was the only baseline observation related to later diagnosis of a specific infection or bacterial vaginosis.

For most women the unexplained vaginal complaints were transient: they reported disappearance of their symptoms without any medical intervention. Symptoms of short duration before presentation were especially promising with regard to the prognosis.

It may be that women with unexplained vaginal symptoms are those remaining after all other diagnoses have been excluded.47 Theories about this category of women will be discussed in the light of the evidence from this study and from the literature.

Women with unexplained vaginal symptoms may be suffering from functional somatic symptoms. Factors such as personality traits or stress may be important in causing these symptoms or awareness and interpretation of genital sensations. Illness behaviour may be important. Some support for this hypothesis can be derived from the observation that women who failed to be diagnosed as suffering microbial disorders had a higher score on the general health questionnaire, and lacked specific symptoms and findings following the speculum examination. Women with the same symptoms, but not suffering stress, may not have consulted. On the other hand, these women showed neither fear of serious diseases nor higher expectations from medical intervention.

Apart from case reports, only two studies could be traced that examined the psychosomatic hypothesis in women who where not diagnosed as having a specific problem.11,12 In these studies, women with clinically unconfirmed vulvovaginitis were found to suffer greater emotional distress and reported greater interference with sexual intercourse. The researchers described the chronicity of the symptoms and consequently, this hypothesis should be considered especially in cases of long duration.11,13,14 Minor distress, such as uncertainty or ignorance of physiologic processes, might play a role in women with a shorter history of symptoms.

It may be that unexplained vaginal symptoms are caused by infectious processes, and tests for the recognized pathogens may be falsely negative. Viruses, especially the papilloma types, or bacteria normally present as commensals may become pathogenic and hence the cause of the symptoms.24,25,27,49 In the present study, a small proportion of women were diagnosed during the follow-up period as suffering an infection or bacterial vaginosis. It may have been that these infections were already present, but undetected, at the baseline visit. However, yeast infections are almost certainly acquired, as the sensitivity of the culture methods would indicate. The same is probably true of bacterial vaginosis, given the reasonable inter-observer reliability in assessing the diagnostic criteria in trained physicians.31,40,50,51 However, the result from the ELISA test for chlamydia may have been incorrectly found to be negative, though this is unlikely.52

Mycoplasma hominis is often isolated in association with genital pathogens, especially those that are sexually transmitted and cause cervicitis.24,53 However, the importance of this as an independent pathogen is unclear. Ureaplasma urealyticum has not been associated with cervicitis or vaginitis.24,53 Escherichia coli, Streptococcus aureus, Staphylococcus faecalis and β-haemolytic streptococci are rare causes of vaginal diseases. When cultured they are, in general, considered members of the transient, commensal flora.14

Herpes simplex infections of the genital region, if macroscopically visible, would have been diagnosed by the doctor. Less clear cut lesions might not have been noticed.26 The incidence of human papilloma virus infections, though increasing, is still lower than of gonorrhoea or chlamydia infections. The infection is, like herpes, related to sexual activity.29 Women with sharp condylomas, which indicate an infection with human papilloma virus, were excluded from the study. However, small or flat condylomas or intraepithelial lesions caused by papilloma viruses might have escaped attention. They may cause vulvar itching or burning sensations.28,54 Some cases of the vulvar vestibulitis syndrome may be caused by human papilloma virus infections.55 Management of these infections is still troublesome.54

Undetected infectious processes in the genital region may play a role, albeit only in a small minority of women with unexplained vaginal symptoms.

Another theory for vaginal symptoms of unknown aetiology is that physiochemical agents are responsible for microbiologically unexplained vaginal symptoms in some women. However, vulvo-vaginal hygienic methods, barrier contraceptive devices combined with use of spermicidal agents or tampons were not found to be associated with the symptoms of unknown aetiology. Women with forgotten tampons or other retained foreign bodies were excluded from the study. However, vaginal irritants, extreme hygienic routines or allergic phenomena cannot be excluded as causes of vaginal symptoms.16-18

Women whom the general practitioner can not diagnose as suffering from microbial disorders should be informed of the results of the tests that have been done and be given some information on the physiology of the vagina. In general, being informed of the functioning of the body and the meaning of bodily processes helps patients to discriminate between symptoms of disease and normal physiologic processes. The general practitioner should invite all patients to return if symptoms persist and may suggest an appointment for retesting when the probability of sexually transmitted diseases is greater. Thereafter, the best policy is one of non-intervention, as the risk of overlooking infection is small. Many women's symptoms will disappear after such consultations.

Women in whom symptoms persist or recur should be seen after two months for a second consultation. A detailed history is important to gain insight into psychosocial distress, effects on sexual behaviour and use of irritants, such as douches and spermicides, in the genital region. A physical examination, laboratory tests and (if necessary) cultures for bacteria should be repeated. This exploration, especially into the history of the symptoms,
will take some time, but may prevent ineffective and unsatisfactory treatment. Further investigations, such as referral for colposcopy or viral cultures, should be done only if a clear indication arises.

References


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Address for correspondence
Dr J H Dekker, Department of General Practice and Nursing Home Medicine, Faculty of Medicine, Vrije Universiteit, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.